THE CLEVELAND CLINIC

Cardiology Board Review

SECOND EDITION

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BRIAN P. GRIFFIN
SAMIR R. KAPADIA
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The Cleveland Clinic Cardiology Board Review

SECOND EDITION

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CONTENTS

Contributors
Preface

SECTION I  FUNDAMENTALS

1 How to Pass the Cardiovascular Disease Board Exam
John Rickard and Benico Barzilai

2 Cardiac Physical Examination
Craig R. Asher and Cesar Augusto Bonilla Isaza

3 Cardiac Anatomy
Robert E. Hobbs

4 Cardiovascular Physiology: Flow–Volume Loops
Ashley M. Lewis and Michael D. Faulx

5 Basic Cardiac Electrophysiology
Sergio G. Thal and Patrick J. Tchou

6 Cardiac Biochemistry
Mosi K. Bennett and Marc S. Penn

7 Clinical Epidemiology and Biostatistics
Michael S. Lauer and Eiran Z. Gorodeski

SECTION II  CARDIOVASCULAR IMAGING AND STRESS TESTING

8 Chest Radiography for the Cardiovascular Medicine Boards
Andrei Purysko and Michael A. Bolen

9 Fundamentals of Doppler Echocardiography
Andrew C.Y. To and L. Leonardo Rodriguez

10 Electrocardiographic Stress Testing
Marwa A. Sabe and Julie C. Huang

11 Stress Echocardiography
L. Leonardo Rodriguez and Thomas H. Marwick

12 Nuclear Cardiac Imaging: A Primer
Richard C. Brunken

13 Nuclear Stress Testing
Richard C. Brunken and Santosh Oommen

14 Cardiac MRI and CT
Andrew C.Y. To and Milind Y. Desai

SECTION

III 

CONGESTIVE HEART FAILURE AND CARDIOMYOPATHY

15 Pathophysiology of Congestive Heart Failure
Miriam Jacob and W. H. Wilson Tang

16 Medical Treatment of Heart Failure
Andrew Grant and Mazen Hanna

17 Heart Transplantation
Arvind Bhimaraj, Celeste T. Williams, and David O. Taylor

18 Devices for Heart Failure
Sangjin Lee and Maria M. Mountis

19 Myocarditis and Dilated Cardiomyopathy
Andres Schuster and W. H. Wilson Tang

20 Pulmonary Hypertension
Matthias Dupont and W. H. Wilson Tang

21 Heart Failure with Normal Ejection Fraction
Andrew O. Zurick, III and Allan L. Klein

22 Hypertrophic Cardiomyopathy
Anthony J. Hart and Harry M. Lever

SECTION

IV  CONGENITAL HEART DISEASE

23 Congenital Heart Disease in the Adult
Richard A. Krasuski and David S.Majdalany

24 Essential Echocardiographic Images in Adult Congenital Heart Disease
Ellen Mayer Sabik

SECTION

V  CARDIAC ELECTROPHYSIOLOGY

25 Twelve-Lead Electrocardiography
Gregory G. Bashian and Curtis M. Rimmerman

26 Electrophysiologic Testing, including His Bundle and Other Intracardiac Electrograms
Edwin T. Zishiri and Mina K. Chung

27 Sudden Cardiac Death and Ventricular Tachycardia
Daniel J. Cantillon and Oussama Wazni

28 Atrial Fibrillation and Flutter
John Rickard and Mohamed Kanj

29 Supraventricular Tachycardias
Christopher P. Ingelmo and P. Peter Borek

30 Wide-Complex Tachycardia: Ventricular Tachycardia versus Supraventricular Tachycardia
Roy Chung and Walid Saliba

31 Pacemakers and Defibrillators
Khaldoun G. Tarakji and Bruce L. Wilkoff

32 Syncope
Fredrick J. Jaeger

SECTION

VI  VALVULAR HEART DISEASE

33 Aortic and Pulmonary Valve Disease
Amar Krishnaswamy and Brian P. Griffin

34 Mitral and Tricuspid Valve Disease
William J. Stewart

35 Infective Endocarditis
Peter Zimbwa and Steven M. Gordon

36 Prosthetic Valvular Disease
Lawrence Lazar and James Thomas

SECTION

VII CORONARY ARTERY DISEASE AND CARDIAC CATHETERIZATION

37 Evaluation of Chest Discomfort
Clay A. Cauthen and Donald A. Underwood

38 Coronary Artery Disease: Demographics and Incidence
Michael Jolly and Leslie Cho

39 Stable Angina: Diagnosis, Risk Stratification, Medical Therapy, and Revascularization Strategies
Kellan E. Ashley and Conrad C. Simpfendorfer

40 Unstable Coronary Syndromes
Gus Theodos, Anthony A. Bavry, and A. Michael Lincoff

41 Acute Myocardial Infarction
Venu Menon and Christopher M. Huff

42 Complications of Myocardial Infarction
Olcay Aksoy and E. Murat Tuzcu

43 Risk Stratification and Post–Myocardial Infarction Therapy
Willis M. Wu and Samir R. Kapadia

44 Radiation Safety in the Cardiac Catheterization Laboratory
Imran N. Ahmad, Kevin A. Wunderle, and Frederick A. Heupler, J r.

45 Hemodynamic Measurements
James E. Harvey and Frederick A. Heupler, J r.

46 Catheterization Laboratory Imaging and Functional Assessment
Sachin S. Goel and Samir R. Kapadia

47 Percutaneous Coronary Intervention
Matthew Cavender and Stephen G. Ellis

SECTION

VIII AORTA/PERIPHERAL VASCULAR DISEASE

48 Diseases of the Aorta
Gian M. Novaro

49 Venous Thromboembolism
Firas Al Solaiman and John R. Bartholomew

50 Peripheral Artery Disease
Siddharth A. Wartak and Heather L. Gornik

51 Carotid Disease
Amar Krishnaswamy and Mehdi Shishehbor

SECTION

IX CLINICAL AND PREVENTIVE CARDIOLOGY

52 Hallmarks of Essential and Secondary Hypertension
Mohamed A. Rafey, Martin J. Schreiber, Jr., and Joseph V. Nally, J r.

53 The Dyslipidemias
Adam W. Grasso and Michael B. Rocco

54 Preoperative Evaluation of Cardiac Patients for Noncardiac Surgery
Matthew C. Bunte and Richard A. Grimm

55 Pregnancy and Heart Disease
Amanda R. Vest, Anjli Maroo, and Russell E. Raymond

56 Women and Heart Disease
JoEllyn Moore Abraham and Ellen Mayer Sabik

57 Pericardial Diseases
Evan Lau and Allan L. Klein

58 Effects of Systemic Diseases on the Heart and Cardiovascular System
Jay Sengupta and Curtis M. Rimmerman

59 Cardiac Neoplasms
Michael Samara and Brian P. Griffin

SECTION

X 

PHARMACOLOGY

60 Pharmacokinetic and Pharmacodynamic Essentials
Michael A. Militello

61 Cardiovascular Medicine—Essential Pharmaceuticals
Katherine M. Greenlee and Michael A. Militello

62 Cardiovascular Drug Interactions
Michael A. Militello

Index

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PREFACE

This book aims to provide a comprehensive overview of cardiovascular medicine in a concise and readable format. As such, it was specifically written to meet the needs of those preparing for certification or recertification examinations in cardiovascular medicine and those seeking a comprehensive update. It is based on a review course that we have organized at Cleveland Clinic over the last 12 years. This course has proven popular not only with those preparing for examinations but also with clinical cardiologists, internists, and midlevel providers.

This book would not be possible without the input and support of many individuals, specifically the faculty and fellows in cardiovascular medicine and related disciplines at Cleveland Clinic who wrote the individual chapters and questions. We also wish to thank the Cardiovascular Graphics group at Cleveland Clinic who provided inestimable assistance to this book and to the course over the years. As with all of our endeavors, this book would also have been impossible without the support of our families, to whom this book is dedicated. We hope that you enjoy the book and that you find it useful.

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SECTION I ■ FUNDAMENTALS

CHAPTER

How to Pass the Cardiovascular Disease Board Exam

John Rickard and Benico Barzilai

GENERAL INFORMATION

The American Board of Internal Medicine (ABIM) Certifying Examination in Cardiovascular Disease takes place each year in the fall. Applicants with special conditions who require longer testing durations generally take the exam over a 4-day period starting approximately 2 weeks after the general exam. Registration for the board examination begins in early March and lasts until early May. There is a late registration period, which incurs a late fee (generally around $400), which lasts from early May until early June. After the late registration fee deadline has passed, registration is no longer possible. Once registered, the opportunity to cancel registration (for an 85% refund) lasts until early September. After this deadline, cancellation is still possible up until 1 day prior to the exam at a 50% refund. At the Web site, www. abim.org, applicants can register for the exam online. Other valuable information such as coding sheets and a simulated computer question format for the exam are also found at this site. As registration test centers often fill up rapidly, early registration is key to assure the ability to take the exam at a nearby test center. Test results are typically first available on the ABIM Web site in early February.

For those recertifying, the test is offered twice annually, once in early April and again in early November. The deadlines to register for each test administration are in mid-February and mid-August, respectively. Board certification in internal medicine is not needed to recertify for the cardiology boards. In addition to passing the board exam, those seeking recertification must also have a valid and unrestricted license to practice medicine and obtain 100 points of self-evaluation via modules available on the ABIM Web site.

FORMAT

The cardiovascular diseases board exam is taken over the course of 2 days for first-time takers and 1 day for those taking it to recertify (those recertifying are exempt from the ECG and imaging sections). The first day is a full day consisting of four 2-hour blocks consisting of 200 multiple choice questions. The second day is a half-day consisting of an ECG section of 35 to 40 tracings lasting 2 hours 15 minutes and an imaging section lasting 2 hours consisting of 35 to 40 video images that include echocardiograms, ventriculograms, aortograms, and angiograms. Table 1.1 delineates the weighted subject content for the exam. Many cardiology trainees do not have sufficient exposure to peripheral vascular disease, pharmacology, and congenital heart disease during their training and must overcome this deficiency during their preparation for the examination. For the ECG section, a brief one- or two-line clinical vignette is provided with each ECG tracing. The test taker then must code relevant findings using a coding sheet, available in advance for review at the ABIM Web site. Similarly, for the imaging section, coding sheets are provided to capture the various findings. Of note, the coding sheet for the imaging section was updated for the 2011 exam. Test takers must make sure they review the updated coding sheet prior to the test. For the 2011 exam, coding sheets could be found at http://www.abim.org/pdf/cert-related/cvd_sample_cases.pdf.

TABLE
1.1 Breakdown in Content of the Cardiology Board Exam

Medical Content Category	Relative Percentage/Number of Questions
Arrhythmias	13.0%/22–25
Congestive heart failure	13.0%/22–26
Coronary artery disease	12.5%/20–23
Acute coronary syndromes/acute myocardial infarction	12.0%/21–25
Valvular disorders	12.0%/21–23
Aorta/peripheral vascular disease	9.0%/21–23
Hypertension/pulmonary disorders	7.0%/ 12–14
Physiology/biochemistry	6.0%/10–11
Pharmacology	5.0%/8–10
Congenital disorders	5.0%/8–10
Pericardial disease	4.0%/6–8
Miscellaneous	1.5%/2–3

HOW YOU ARE SCORED

For scoring, traditionally the multiple choice section and the imaging section have been combined. Starting in 2011, the imaging section was joined with the ECG section to

form one component, while the multiple choice section comprises a separate component. For a passing score, both components need to be passed. While the imaging section can be challenging, due to the combination of scoring with the ECG section, a poor performance on the imaging section can be balanced out by a stronger score on the ECG section. While there is no penalty for guessing on the multiple choice section, there is on the ECG and imaging sections such that overcoding leads to point deductions. First-time taker numbers and pass rates for the exam from 2006 to 2010 are listed in Table 1.2.

TABLE
1.2 First-Time Taker Pass Rates

Year	Number of Examinees/ Percentage Passing
2006	767/86%
2007	783/88%
2008	759/87%
2009	861/91%
2010	820/90%

TIPS

A 3-month study period prior to the test is a reasonable amount of time to prepare for the exam. Reviewing information in a scheduled way over this time period is important. The examination encompasses a large quantity of information making a last-minute approach ill advised. Fellows who are enrolled in busy advanced fellowship programs such as electrophysiology and interventional must be realistic about the need to study for the examination. Too often, these trainees do not allow themselves sufficient time to prepare. They may consider signing up for a dedicated course, which would force them to focus on the material covered on the examination.

The multiple choice section of the boards is structured such that a clinical vignette is presented with up to five answer choices provided. While the clinical vignettes are often long, each block of 50 questions is allotted 2 hours of time (2.4 minutes/question). Very few questions on the boards simply ask a question on a medical fact. The large majority of questions make the test taker read through a patient scenario complete with a past medical history, current symptomatology, in-depth physical examination findings, and imaging and laboratory data prior to asking how to proceed with the patient's management. In addition, the exam will often challenge the test taker to determine the most likely condition from the physical examination and then determine the treatment options based on other information given. Therefore, knowing the physical examination

findings of common cardiovascular conditions is imperative.

The board exam will not ask questions on any areas that are controversial or not supported by evidence. The majority of questions will focus on information obtained from guidelines—most notably class I and III recommendations. In preparing, it is important to focus on common therapeutic and diagnostic conditions rather than rare conditions. Anticipate questions regarding common conditions structured in complex ways. In addition, the results of major, practice-changing clinical trials are favorite board topics. Some board questions may strike the test taker as strange or potentially even unfair. It is important not to get stressed out by such questions as the board pilots new questions every year. These new questions will not be included in the final score. Lastly, the imaging section of the boards can be difficult due to variable image quality. One should ensure not to waste time overcoding but simply code the major findings that are clearly identifiable. It is also critical to make sure that all the available images have been viewed.

It is vitally important not to underestimate the ECG section. The majority of patients who failed the boards in the past have done so by failing this section. Knowing the coding sheet cold prior to sitting for the test is vital (the coding sheet is available online from the ABIM). Many test takers run into time issues with this section. Searching for the correct codes on the sheet can waste a significant amount of time and may cause some examinees not to finish. Secondly, the board exam commonly tests clinical syndromes on the ECG section. The test taker should be very familiar with the clinical syndromes on the code sheet and be able to identify such conditions rapidly. While electronic calipers are provided, they are rarely required to obtain the correct answer. Overuse of calipers can waste valuable time. It is also important not to overcode the ECG portion of the test. The board examiners want to ensure that the examinee can identify the major findings on each tracing. Taking time to code small, somewhat questionable ECG findings will waste time and possibly cause point deductions.

Lastly, it is important to get a good night sleep prior to the exam as the test is lengthy and can be very fatiguing, especially toward the end of the examination session. Taking the exam at the first opportunity after completion of your fellowship is strongly advised as the material learned in training will be the freshest at that time. Finally, and as mentioned previously, early registration is important to secure a nearby test location. Having to travel large distances or staying in a hotel prior to the test will only cause unneeded stress and distraction.

TEN PITFALLS TO AVOID

1. Underestimating the ECG and imaging sections
2. Not being familiar with the coding sheets for the ECG and imaging sections prior to the test

3. Not being able to identify common cardiovascular conditions based on physical exam findings
4. Overcoding the ECG and imaging sections
5. Spending a disproportionate time on one or two questions at the expense of other easier questions
6. Getting upset by what appears to be very strange, “out of left field”-type questions that are probably pilot questions that are not factored into the final score
7. Wasting too much time with the electronic calipers on the ECG section
8. Cramming for the test at the last minute
9. Registering late forcing the test to be administered a distance away from home
10. Not reviewing the sample questions on the ABIM Web site

CHAPTER

Cardiac Physical Examination

Craig R. Asher and Cesar Augusto Bonilla Isaza

INTRODUCTION TO PHYSICAL EXAMINATION

Over the years, the bedside skills of the cardiologist have diminished, due in part to the readily available access to echocardiography. However, the cardiology boards expect a high level of understanding of physical diagnosis. Most of the testing of physical diagnosis is indirect. Many of the questions are structured with a brief history and physical exam that provide clues about the diagnosis or answer. Often these are subtle hints that will not be appreciated by the unprepared. This chapter provides many of the pearls of physical diagnosis that are important for taking the boards.

INSPECTION

Basic principles (these descriptors may correlate with specific diagnoses):

- General appearance: Distress, diaphoresis, tachypnea, cyanosis, pallor
- Posture: Orthopnea, platypnea/orthodeoxia (dyspnea and O_2 desaturation in the upright position such as seen in patients with patent foramen ovale (PFO) and atrial septal defect (ASD) with R-to-L shunt), trepopnea (dyspnea lying on one side but not the other such as with large pleural effusions)
- Stature: Tall (Marfan syndrome, Acromegaly), short (Turner and Noonan syndrome, Down syndrome), dwarfism (Ellis–van Creveld syndrome associated with ASD)
- Nutritional status: Obese (sleep apnea, metabolic syndrome), cachexia (end-stage systolic heart failure, chronic disease, malignancy), athletic or muscular (anabolic steroid use)
- Abnormal movements: Chorea (Sydenham chorea as seen with rheumatic fever), ataxia (Friedrich ataxia associated with hypertrophic cardiomyopathy [HCM] or tertiary syphilis associated with aortic aneurysms), head bobbing (aortic

regurgitation [AR] or tricuspid regurgitation [TR]), Cheyne–Stokes respirations

See Table 2.1 for additional associated conditions and specific diseases found with various skin, head and neck, eye, chest and abdomen, extremity findings.

TABLE
2.1 Physical Examination Findings with Associated Conditions and Disease States

Physical Finding	Associated Conditions (Specific Diseases)
Eyes	
Roth spots, conjuctival petechiae	Endocarditis
Xanthelasmas	Dyslipidemia (Familial hypercholesterolemia)
Blue sclerae	(Osteogenesis imperfecta with aortic disease, AR, MVP)
Icteric sclerae	Cardiac cirrhosis
Ectopia lentis (upward displacement)	(Marfan syndrome)
Ectopia lentis (downward displacement)	(Homocystinuria and premature CAD, stroke, PVD)
Conjuctivitis	(Reiter syndrome with aortic disease, AR)
Corneal opacities	(Fabry disease with HCM)
Arcus senelis	(Coronary artery disease)
Retinal occlusion	Embolic disease
Chest and abdomen	
Pectum excavatum (funnel chest)	(Marfan syndrome with aortic aneurysm, MVP)
Pectum carinatum (pigeon chest)	(Marfan syndrome; Noonan syndrome)
Straight back syndrome	(MVP; Ankylosing spondylitis with AR)
Intercostal arteries collaterals	(Coarctation of the aorta and bicuspid aortic valve)
Extremities	
Rudimentary or absent thumbs	(Holt–Oram syndrome with ASD)
Osler nodes, Janeway lesions, splinter hemorrhage	Endocarditis
Hyperextensible joints	(Ehlers–Danlos syndrome)
Raynaud phenomenon	Connective tissue disorder; Vasculitis
Skin	
Jaundice	Right heart failure; Hemolysis
Xanthomas	Dyslipidemia (Familial hypercholesterolemia)
Central Cyanosis	Right-to-left shunts (Eisenmenger syndrome); Metahemoglobinemia
Differential Cyanosis	Right-to-left shunt with (PDA)
Peripheral Cyanosis	Cardiogenic shock, severe peripheral vascular disease
Telangiectasias (dilated blood vessels)	(Hereditary hemorrhagic telangiectasias with pulmonary AV fistula; Scleroderma)
Lentigines (brown skin lesions)	(LEOPARD syndrome; Carney syndrome with atrial myxomas)
Lupus pernio (purple skin lesion), erythema nodosum	(Sarcoidosis with pulmonary HTN, arrhythmias, myopathic disease)
Angiofibromas (shiny papules—on face adenoma sebaceum)	(Tuberous sclerosis with rhabdomyomas)
Striae atrophicae	(Marfan syndrome with aortic aneurysm, MVP)
Bronze pigmentation	(Hemochromatosis with supraventricular arrhythmias, cardiomyopathy)
Hyperextensible skin, bruising, fragile	(Ehlers–Danlos syndrome with aortic aneurysm)
Malar rash	(Lupus erythematosus with endo-, myo-, pericarditis)
Erythema marginatum	(Rheumatic fever with valvulitis)
Erythema migrans	(Lyme disease with heart block)
Head and Neck	
Elfin facies	(William syndrome with supravalvular AS, branch PS)
Moon facies	(Down syndrome with AV canal defects, ASD, VSD)
Broad nasal bridge, narrow palpebral fissures, and micrognathia	(DiGeorge syndrome with Tetralogy of Fallot, Truncus arteriosus, VSD)
Webbed neck, hypertelorism, low set ears, short stature	(Noonan syndrome with HCM, PS; Turner syndrome with BAV and coarctation)
Bifid uvula	(Loeys–Dietz syndrome with aortic dissection)
Macroglossia	(Amyloidosis; Down syndrome, Myxedema)

ARTERIAL PULSE

Basic Principles

- Described by upstroke, magnitude, and contour
- Composed of percussion (ejection, mid to later portion) and tidal waves (reflected wave from periphery, midlater portion)
- Graded 0 to 4. Grade 0 is absent; Grade 1 is barely palpable; Grade 2 is easily palpable; Grade 3 is normal; and Grade 4 is bounding.
- Normal pulse pressure approximately 30 to 40 mm Hg (systolic minus diastolic blood pressure)
- Anacrotic notch is present at the systolic upstroke in the arterial pulse (ascending limb).
- Dicrotic notch is present in the diastolic downstroke in the arterial pulse (descending limb) at aortic valve closure.

Disease States

See Figure 2.1.

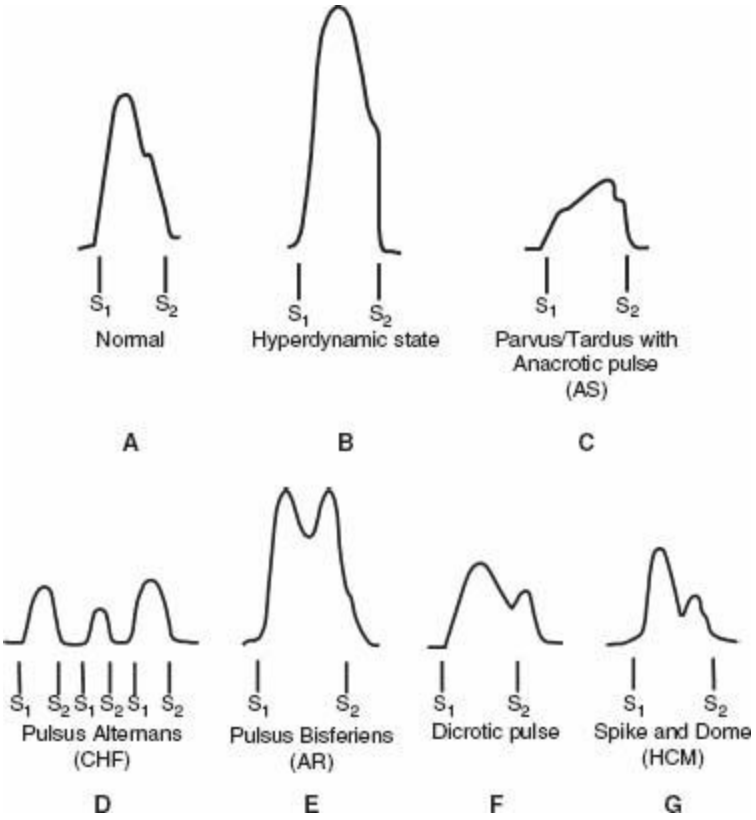

FIGURE 2.1 Carotid pulse findings in normal and disease states. **A:** The normal carotid pulse. There is a rapid ascending and descending limb. The descending limb is slower than the ascending limb and has a dicrotic notch that occurs during aortic valve closure. The dicrotic notch is generally not palpable on examination. **B:** Hyperdynamic pulse. There is a rapid, high volume ascending and descending limb. **C:** Parvus/tardus pulse with anacrotic notch refers to a small-amplitude pulse with a delayed systolic peak associated with AS. The anacrotic notch on the ascending limb may be appreciated on examination. D: Pulsus alternans is the beat-to-beat variation in the arterial pulse amplitude that is seen with left ventricular dysfunction and low stroke volume. **E:** Pulsus bisferiens is characterized by two systolic peaks during systole. The amplitude of the pulse is high. The initial peak is due to the ejection or percussion wave, and

the second peak is due to a reflected or tidal wave in the periphery. This type of pulse is most often seen with isolated AR or combined AR and stenosis. **F:** Dicrotic pulse is another form of double-peaked pulse where the dicrotic notch is present in diastole just after S_2. The dicrotic pulse usually occurs in patients with hypotension due to low CO or low SVR. **G:** Spike and dome pulse is another form of double-peaked pulse that occurs with HOCM. There is an initial delayed systolic peak followed by a lower-amplitude systolic peak.

Pulsus Alternans

- Alternating beat to beat strong and weak pulsations in sinus rhythm
- Reflects myocardial dysfunction due to alterations in preload, afterload, and contractility with each beat

Pulsus Paradoxus

- Exaggeration of normal inspiratory fall of systolic blood pressure (SBP) > 10 mm Hg
- Causes include cardiac tamponade, chronic lung disease/acute asthma, pulmonary embolism (PE), right ventricular infarction, congestive heart failure, tension pneumothorax, pregnancy, obesity, and rarely constrictive pericarditis (only effusive form)
- Major mechanisms include (a) ↑ venous return to the right heart during inspiration with shift of the septum to the left resulting in ↓ left ventricle (LV) stroke volume and therefore ↓ SBP and (b) ↑ pulmonary venous reservoir with inspiration resulting in ↓ left-sided filling (lower pulmonary vein to left ventricular gradient).
- Cardiac tamponade may occur without pulsus paradoxus due to loss of interventricular dependence with high LV enddiastolic pressure (AR or LV dysfunction), ASD (volume of shunted blood exceeds volume of blood between inspiration and expiration), or right ventricular hypertrophy (RVH) and pulmonary hypertension (PH).
- The paradox is that heart sounds can be heard during inspiration, while the pulse weakens and may not be palpable.
- Reversed pulsus paradoxus may occur with HCM or in mechanically ventilated patients.

Double-Peaked Pulse

- ↑ amplitude pulse with two systolic peaks
- Results from accentuated percussion wave and tidal wave
- Most common cause is severe AR (bisferiens) with or without aortic stenosis (AS), though may also occur with hypertrophic obstructive cardiomyopathy (HOCM, bifid or “spike and dome”)and hyperdynamic states (patent ductus arteriosus [PDA],

arteriovenous malformations).

Pulsus Tardus and Parvus

- Tardus (slow upstroke) and parvus (low amplitude)
- Caused by AS, though may be absent even in the setting of severe AS in elderly with noncompliant carotid vessels
- Associated with an anacrotic pulse

Anacrotic Pulse

- Notch on the upstroke of the carotid pulse (anacrotic notch) may be palpable.
- Two distinct waves can be seen (slow initial upstroke and delayed peak, which is close to S_2).
- Present in AS

Dicrotic Pulse

- Accentuated upstroke with second peak after dicrotic notch in diastole (after S_2)
- Second peak in diastole differentiates the dicrotic pulse from a bisferiens pulse.
- Occurs in patients with low cardiac output (CO) and high systemic vascular resistance (SVR) or high CO and low SVR (in both cases the systolic pressure is low)

Other miscellaneous signs/findings related to arterial pulse include the following:

Osler Sign

- Obliteration of brachial pulse by BP cuff with sustained palpable and rigid radial artery
- Invasive BP measurements may not correlate with cuff pressures and pseudohypertension may be present.
- Due to atherosclerotic, calcified blood vessels

Pulse Deficit

- Difference in the heart rate by direct cardiac auscultation and the distal arterial pulse rate when in atrial fibrillation (AF)
- Due to short diastoles with short RR interval, the contraction may not be strong enough to generate enough stroke volume to the periphery and thus the peripheral pulse may underestimate the heart rate.

Radial-to-Femoral Delay

- Generally radial and femoral pulse occur at nearly the same time (femoral slightly earlier).
- Due to obstruction of arterial flow due to coarctation, the femoral pulse may be delayed.
- Confirmed by ↓ in lower-extremity pressure compared to upper-extremity pressure in the supine position

Asymmetric right greater than left pulses and pressures:

- **Supravalvular AS:** The pool of blood is directed toward the right side of the aorta in greater proportion than to the left (due to the Coanda effect) resulting in a disparity in pulses and pressures, including inequality of carotid pulses.

Pressure/Pulse Difference in Two Arms (>10 mm Hg Systolic)

- Due to obstruction involving the aorta, innominate and subclavian arteries due to the following etiologies: congenital, arteriosclerosis, embolism, arteritis, dissection, postsurgical (subclavian flap repair for coarctation) or external obstruction (thoracic outlet syndrome).

Historical signs of severe AR due to high stroke volume detected by pulse abnormalities include the following:

Hill Sign

- Extreme augmentation of systolic BP in the femoral artery compared with the brachial artery (>40 mm Hg)
- Seen with severe AR
- Results from a summation of waves traveling distally in the aorta

Mayen Sign

- ↓ in diastolic BP with arm elevation of >15 mm Hg

Traube Sign "Pistol shot"

- Loud systolic sound heard over the femoral artery

Corrigan Pulse: "Water-Hammer" Pulse

- Large-amplitude upstroke and collapse of the carotid artery pulse due to high CO and low resistance

Duroziez Sign

- Systolic and diastolic bruit heard over the femoral artery with gentle compression

JUGULAR VENOUS PULSE

Basic Principles

- Pressure and waveforms should be evaluated.
- Adjust level of head/torso until pulsations optimally visualized. Generally around 45 degrees.
- Internal jugular preferable to external jugular and right internal jugular preferable to left
- Jugular venous pulse (JVP) ↓ with inspiration in normal patients

Jugular Venous Pressure

- Measured as the vertical height above the sternal angle or angle of Louis (junction of manubrium and sternum), which is considered to be 5 cm above the right atrium (RA) in all positions
- 9-cm H_2O is considered elevated.
- Conversion: 1.36 cm H_2O = 1 mm Hg
- Abdominojugular reflux (previously referred to as the hepatojugular) can be performed to confirm or determine elevated venous pressure. Application of pressure >10 to 30 seconds over the right upper quadrant (RUQ) results in sustained elevation of jugular pressure ≥4 cm above the sternal angle for >10 seconds following release of pressure. Straining (Valsalva maneuver) must be avoided since it will cause a false reading.

  - **A wave: RA filling durig RA systole**
  - **C wave: Upward motion tricuspid valve in systole / carotid artery deflection**
  - **X descent: RA relaxation (during RV systole)**
  - **V wave: RA filling during RV systole**
  - **Y descent: Fall in RA pressure when tricuspid valve opens (RV diastolic filling)**

Jugular Venous Waveforms

See Figure 2.2.

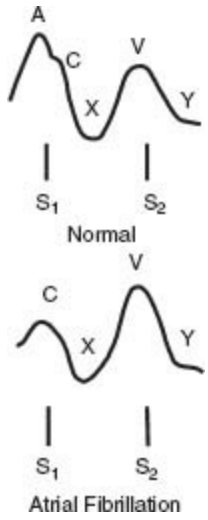

FIGURE 2.2 Internal jugular pulsations in normal individuals and during AF. The physiology attributed to each wave is noted. Typically, there are two positive waves ("a" and "v" waves) and two negative waves ("x" and "y" descents) in normal individuals. The "a" wave is lost with AF. The "c" wave is not appreciable on physical examination. RA, right atrium; RV, right ventricle.

Disease States

See Figure 2.3.

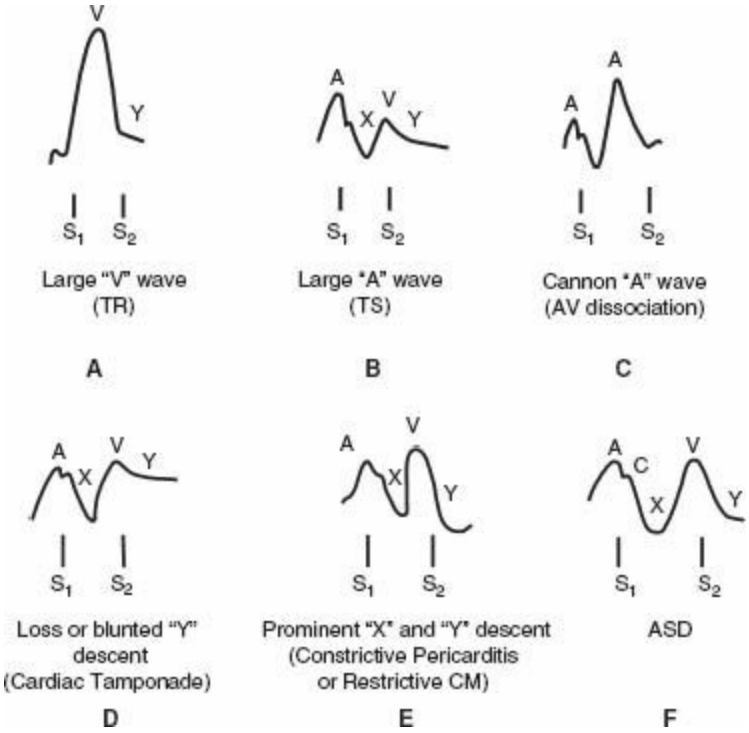

FIGURE 2.3 Internal jugular pulsations during various disease states. **A:** Large "v" or "cv" wave characteristic of TR along with a rapid "y" descent. **B:** Large "a" wave as seen with obstruction to right ventricular filling with TS. The "y" descent is slow when TS is present. A large "a" wave without a prominent "y" descent may occur with RVH or PH. **C:** Cannon "a" waves are present with AV dissociation and describe the presence of intermittent prominent "a" waves that occur during contraction against a closed AV valve during ventricular systole. It should not be confused with a prominent "v" wave. **D:** Loss or blunting of the "y" descent is an important feature of cardiac tamponade that

corresponds with impairment of diastolic filling. **E:** A prominent "x" and "y" descent is present with either constrictive pericarditis or restrictive cardiomyopathy. The rapid "y" descent is a marker of early rapid filling due to an abnormality of compliance that is seen with both of these conditions. **F:** The "x" descent and "y" descent with an ASD are equal in amplitude.

- AF—loss of "a" wave resulting in just one major positive wave
- Complete heart block or atrioventricular (AV) dissociation— cannon "a" wave due to contraction against a closed tricuspid valve
- Tricuspid stenosis (TS), RVH, PH, severe left ventricular hypertrophy (LVH)—giant "a" waves
- Severe TR—large "v" wave and rapid "y" descent
- ASD -prominent and equal "a" and "v" waves
- Constrictive pericarditis—prominent "y" descent (predominant filling during early diastole) and sometimes prominent "x" descent giving "w" shape waveform along with elevated jugular venous pressure and Kussmaul sign
- Restrictive cardiomyopathy—prominent "x" and "y" descent may also be present similar to constrictive pericarditis.
- Cardiac tamponade—prominent "x" wave and loss of the "y" descent representing loss of filling in diastole along with elevated jugular venous pressure
- Superior vena cava (SVC) obstruction—elevated but nonpulsatile JVP

Other Miscellaneous Signs/Findings

- Kussmaul sign—paradoxical rise in JVP during inspiration due to increased resistance of RA filling during inspiration. The opposite of the normal fall in JVP with inspiration.
- Classical finding in constrictive pericarditis. May also occur with RV infarct, severe TR or TS, PE, and restrictive cardiomyopathy but is absent with cardiac tamponade except for the effusive constrictive form.

PRECORDIAL MOTION

Basic Principles

- The normal apex moves toward the chest wall in early systole and is best palpated in the fourth or the fifth left intercostal space just medial to the midclavicular line.
- It is 1 to 2 cm in size and lasts less than one-third of systole.
- The apical pulsation is not always the point of maximal impulse (PMI) (e.g., in rheumatic mitral stenosis (MS), the PMI may be produced by the right ventricle).

Hypertrophy

- LVH results in an apical impulse that is sustained and not diffuse.
- RVH or PH results in a left parasternal heave or lift that is sustained and not diffuse.

Dilation

- LV enlargement results in a diffuse, laterally displaced apical impulse.
- RV enlargement results in a diffuse impulse occurring in the parasternal region.

Disease States

- LV aneurysms may produce diffuse outward bulging and a rocking effect.
- Constrictive pericarditis may be characterized by systolic retraction of the chest instead of outward motion (Broadbent sign).
- Hyperactive precordium occurs in volume overload (severe aortic and mitral regurgitation [MR], large left-to-right shunt).
- HCM causes a double systolic outward motion. This is due to a palpable "a" wave (increased atrial filling) and sustained outward movement of the apex. In some patients, there are two systolic motions as well as the motion during atrial systole resulting in a triple apical impulse.

FIRST HEART SOUND

Basic Principles

- Ventricular systole begins with closure of the mitral (first) and tricuspid (second) valves.
- S_1 is best heard with the diaphragm of the stethoscope at the apex for the mitral and the left sternal border for the tricuspid valve.
- Opening sounds of the mitral and tricuspid valves are pathologic sounds.

Intensity

- Mitral closure is generally louder than tricuspid closure.
- S_1 is generally louder than S_2 at the apex and the left sternal border and softer than S_2 at the left and the right second interspaces.

S_1 (particularly M_1) is ↑ with:

- Short PR interval (due to wide separation of leaflets at onset of ventricular systole)
- MS with mobile leaflets

- Hyperdynamic LV function or ↑ transvalvular flow due to shunts (↑ force of leaflet closure)
- TS or ASD (T_1 ↑)

S_1 is ↓ with:

- Long PR interval (leaflets close together at onset of ventricular systole)
- MS with immobile or calcified leaflets
- Severe AR (due to mitral preclosure from the jet hitting the mitral valve and high left ventricular end diastolic pressure [LVEDP])
- MR due to prolapse or flail (poor coaptation of leaflets)
- Severe LV dysfunction with poor CO (↓ force of leaflet closure)

S_1 is variable with:

- Atrial fibrillation
- Complete heart block and AV dissociation

Splitting

- Split S_1 must be differentiated from an S_4 gallop heard best at the apex with the bell of the stethoscope and an ejection sound (ES) (pulmonic or aortic) heard at the base of the heart.

Persistent splitting:

- Late T_1 closure due to severe TS, ASD or right bundle branch block (RBBB)
- Late T_1 closure due to Ebstein anomaly (S_2 also split) with associated multiple systolic and diastolic clicks "sail-like sounds"
- Early M_1 closure due to LV preexcitation

Reverse splitting (rare):

- Late M_1 closure due to severe MS (usually associated with TR), left bundle branch block (LBBB), RV pacing

SECOND HEART SOUND

Basic Principles

- Ventricular systole ends with closure of the aortic (first) and pulmonic (second)

valves.

- S_2 closure sounds are heard best with the diaphragm of the stethoscope in the second left and right intercostal spaces near the sternum.

Intensity

- Aortic closure heard best at the second right intercostal space adjacent to the sternum is generally louder than pulmonic closure heard best at the second left intercostal space adjacent to the sternum.
  - S_2 (A_2) is ↑ with hypertension (HTN), dilated aorta.
  - S_2 (A_2) is ↓ with AS.
  - S_2 (P_2) is ↑ with pulmonary HTN, dilated pulmonary artery (PA).
  - S_2 (P_2) is ↓ with pulmonary stenosis (PS).

Single S_2

- A_2 is absent with severe AS.
- P_2 is absent with chronic obstructive pulmonary disease (COPD) and obesity (inaudible sound due respiratory noise) or PS, pulmonary atresia, right ventricular outflow tract (RVOT) obstruction, and Tetralogy of Fallot.
- A_2-P_2 occur together with aging due to decreased inspiratory delay of P_2.

Splitting

Normally A_2 and P_2 separate during inspiration and come together during expiration (physiologic splitting) (Fig. 2.4). This occurs due to ↓ pulmonary vascular impedance and relatively longer RV ejection period relative to LV ejection period.

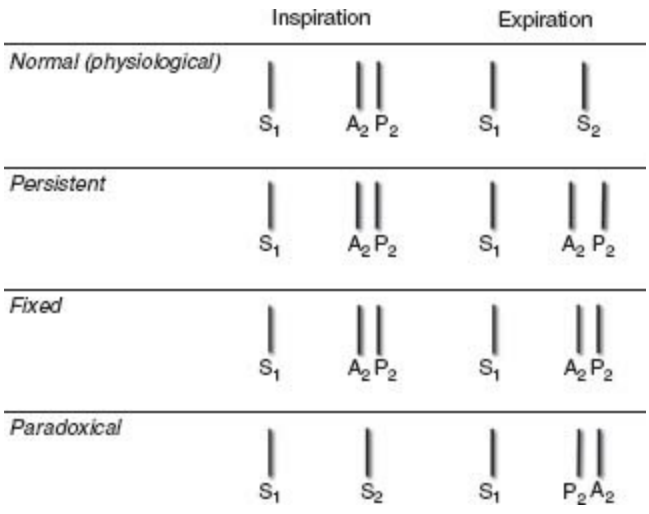

FIGURE 2.4 Illustration of normal S_2 (physiologic) splitting and pathologic S_2 splitting (persistent, fixed, paradoxical)

with the changes that occur as a result of the respiratory cycle. With normal physiologic splitting, P_2 closure occurs later than A_2 closure during inspiration with associated increased preload and a longer right ventricular ejection period. During expiration, a single S_2 sound is heard. With persistent splitting, A_2 and P_2 are heard throughout the respiratory cycle but separated by a wider distance during inspiration. This is due either to a delay in the closure of P_2 or an early closure of A_2. Fixed splitting may occur with hemodynamically significant ASDs and describes the equal and persistent separation of A_2 and P_2 during the respiratory cycle. Paradoxical splitting is the opposite of normal splitting (P_2 precedes A_2) during expiration, and a single sound is heard during inspiration. This is due to either a delay in A_2 closure or an early P_2 closure.

- Splitting of the S_2 may be physiologic or pathologic.

Pathologic splitting:

a. Fixed splitting—wide and persistent splitting that remains unchanged throughout the respiratory cycle

   Conditions—ASD (~70% secundum ASD when hemodynamically significant), RV failure (most common cause in adults), PS, Partial anomalous pulmonary venous return (usually with sinus venosus ASD), ventricular septal defect (VSD) with left-to-right shunt (A_2 closure is early)

b. Persistent splitting—splitting occurs with both inspiration and expiration but is not fixed with a further widening occurring with inspiration.
   - Conditions:
     1. P_2 delayed—RBBB, pulmonary HTN, RV dysfunction, PS, dilated PA
     2. A_2 early—severe MR, VSD, Wolf–Parkinson–White (WPW) (LV pre-excitation)

c. Paradoxical splitting—the normal sequence of A_2 followed by P_2 closure is reversed so that so that with expiration P_2 precedes A_2 and with inspiration the sounds come together.
   - Conditions:
     1. A_2 delayed—LBBB or RV pacing, AS, LV dysfunction, HCM, Dilated aorta or Ischemia
     2. P_2 early—WPW (RV preexcitation)

THIRD HEART SOUND

Basic Principles

- Physiologic sound in young adults though may disappear with standing. Almost all adults lose S_3 after 40 years old.

- It is normal during the third trimester of pregnancy.
- Best heard with light pressure of the bell of stethoscope (low frequency) in the left lateral decubitus position at the apex
- Right-sided S_3 can be heard at left sternal border and may ↑ with inspiration.
- Most commonly heard in conditions of high flow across an AV valves
- S_3 follows an opening snap (OS) and pericardial knock (PK) in timing.
- S_3 corresponds with the "y" descent of the central venous or atrial waveform or the Doppler E wave on an echocardiogram.
- An S_3 is not expected with severe MS.

FOURTH HEART SOUND

Basic Principles

- S_4 is usually pathologic (atrial gallop).
- S_4 is heard best with the bell of the stethoscope and occurs just before S_1, after the P wave on the EKG and is equivalent to the Doppler A wave on an echocardiogram.
- A left-sided S_4 is heard best in the left lateral decubitus position at the apex during expiration and a right-sided S_4 is heard at the left sternal border to midsternum best with inspiration.
- Common pathologic states associated with a left-sided S_4 include—AS, HTN, HCM, and Ischemic heart disease. A right-sided S_4 is heard with PH and PS.
- S_4 gallop is not heard with AF.
- When S_3 and S_4 are heard simultaneously such as may occur with tachycardia and prolonged PR intervals, a "summation gallop" (SG) is present.
- A quadruple rhythm with a distinct S_3 and S_4 may be heard with tachycardia.

EXTRA HEART SOUNDS

Diastole

See Figure 2.5.

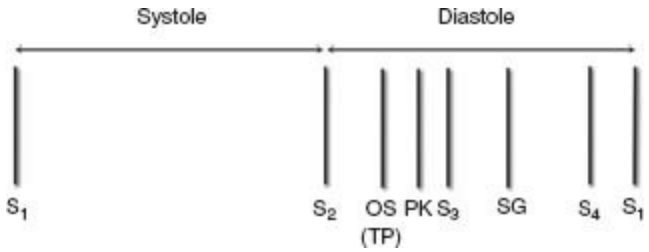

FIGURE 2.5 The relative timing of heart sounds heard during diastole is shown. The earliest sound audible is an OS. A TP related to atrial tumors such as an atrial myxoma occurs at the same time as an OS. A PK present with constrictive pericarditis occurs later than an OS but slightly earlier than an S_3 gallop. The PK can be distinguished from an S_3 since it is louder and higher pitched. An S_4 occurs before the onset of ventricular systole. Sometimes with rapid heart rates, there is a fusion of S_3 and S_4 to create an SG.

Opening Snap

- Pathologic sound generated by abrupt movement of the body of the mitral leaflets in early diastole due to MS or tricuspid stenosis (TS)
- OS is a high-pitched sound best heard medial to the apex with the diaphragm of the stethoscope.
- If the valve is not mobile or MR is present, an OS may not occur.
- An interval of <70 milliseconds is consistent with severe MS. However, this interval is affected by other factors such as left atrial and left ventricular pressure and compliance.
- S_2–OS interval may not be useful with rapid heart rates or with AS, AR, or MR.
- A tumor plop (TP) has about the same timing as an OS.
- A right-sided OS is best heard at the left sternal border and varies with respiration.

Other Diastolic Heart Sounds

- A tumor "plop" occurs at about the same time as an OS. It is due to the movement of a tumor such as a myxoma into the atrium during diastole.
- A PK is best heard with the diaphragm of the stethoscope at the apex and may vary with respiration. It is due to the rapid early left ventricular filling that occurs with constrictive pericarditis.

Systole

See Figure 2.6.

FIGURE 2.6 The relative timing of heart sounds heard during systole is shown. An ES is the earliest systolic sound audible and is heard just after S_1 but occurs before the carotid pulsation. Nonejection clicks are usually midsystolic or late systolic and are most commonly caused by MVP. MC, midsystolic click; LC, late systolic click.

Ejection Sounds

- ES occur in early systole following valve opening.
- ES occur before the upstroke of the carotid artery pulsation.
- ES are high pitched and heard best with the diaphragm.
- An aortic ES occurs most often with opening of a bicuspid aortic valve and may be heard at the sternum, LSB, or apex. It may also be heard with a dilated aorta.
- A pulmonic ES may be heard with PS. It will ↑ during expiration and ↓ during inspiration (the only right-sided sound that ↓ with inspiration). It may also be heard with a dilated PA.
- With increasing severity of PS, the time between S_1 and the ES shortens.
- With severe PS, S_1 and the ES may fuse (and therefore ES is not audible).

Nonejection Clicks

- Predominantly due to mitral valve prolapse (MVP) with myxomatous mitral valve
- Clicks due to MVP are due to tensing of the chordae during systole.
- Clicks are best heard with the diaphragm at the apex in mid to late systole.
- Other uncommon causes include atrial septal aneurysms, mobile tumors, HCM, and nonmyxomatous mitral valve disease.
- Clicks may be single or multiple and may vary over time.
- Maneuvers that ↓ LV volume or afterload move the click closer to S1 and maneuvers that ↑ LV volume or afterload move the click away from S_1 (Fig. 2.7).
- When the click is closer to S_1, the murmur becomes longer and may be louder.

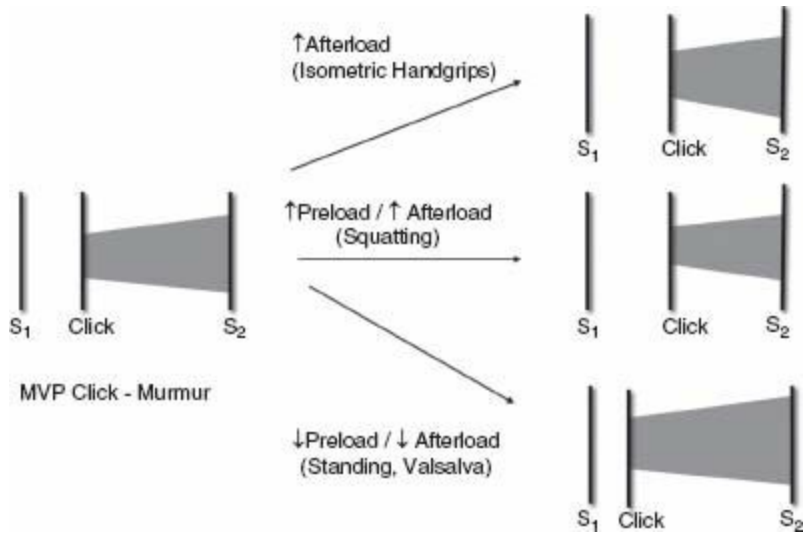

FIGURE 2.7 The systolic click-murmur associated with MVP. The click is dynamic in timing dependent on loading conditions. The murmur is a regurgitant type though not holosystolic starting after the systolic click. With an increase in preload and afterload with squatting, the click occurs later in systole (away from S_1) and the murmur is shortened. The intensity of the murmur is variable depending on the relative increase in afterload. With an increase in afterload with handgrips, the click occurs later in systole but the murmur may intensify depending on the relative increase in afterload. With maneuvers that decrease preload or afterload such as the Valsalva maneuver (phase 2) or standing the click moves closer to S_1 and the murmur is longer in duration and may be more intense.

Pericardial Friction Rubs

- Pericardial rubs are high-pitched, dynamic, and scratchy sounds.
- They are best heard with the patient leaning forward (or on elbows and knees) following forced held expiration or deep held inspiration.
- Three components may be heard, (a) atrial systole, (b) ventricular systole, and (c) rapid ventricular filling.
- Generally only one or two components will be heard. When one component is heard, it is generally the systolic component that can be confused with systolic murmurs.
- The presence of a pericardial rub does not correlate well with the volume of pericardial effusion. Pericardial rubs may occur with large pericardial effusions (several mechanisms contribute to generating the sound).
- A mediastinal crunch (Hamman sign) is due to air in the pericardium or mediastinum (as may occur after cardiac surgery) and may be associated with subcutaneous emphysema.
- Pleural rubs are accentuated during inspiration.

Prosthetic Heart Sounds

- The intensity of the opening and closing sounds varies according to the type and design of the prosthetic valve.

- With ball-cage valves (Starr–Edwards), the opening click (OC) is louder than the closing click (CC) for both aortic and mitral prostheses.
- With bileaflet or tilting disc valves, the CC is louder than the OC for both aortic and mitral prostheses.
- A decrease in the intensity of the OC or CC or a change in the relative intensity of the clicks for a given prosthesis should be considered abnormal.
- With aortic valve prostheses, any decrescendo AR murmurs should be considered abnormal.
- With mitral valve prostheses, any holosystolic MR murmurs should be considered abnormal.

Pacemaker Sounds

- High-frequency click sound heard in patients with either endocardial or epicardial pacemakers thought due to stimulation of skeletal muscle contraction (intercostal or pectoral muscles)
- A pacemaker sound is a presystolic click occurring immediately after the pacemaker stimulus and therefore may be confused with an atrial gallop or a loud S_1 sound.

HEART MURMURS

Basic Principles

- Heart murmurs are due to turbulence of blood flow either due to structural abnormalities or increased blood flow velocity.
- Heart murmurs are characterized in many ways including (1) timing (systolic, diastolic, or continuous) and (2) clinical significance (benign or pathologic).
- Systolic murmurs may be further classified based on timing of onset and termination as holosystolic, midsystolic, early systolic, and late systolic.
- Diastolic murmurs may be further classified based on timing of onset as early diastolic, middiastolic, and late diastolic.
- Heart murmurs are also described based on location heard, shape (e.g., crescendo-decrescendo, plateau), intensity (I–VI), pitch or frequency (e.g., high-pitched sounds like AR due to high-pressure gradient versus low-pitched sounds like MS due to low-pressure gradients), quality (e.g., musical, harsh), radiation, accompanying sounds, and response to maneuvers.
- Systolic murmurs are further characterized as (1) ejection and (2) regurgitant.
- Ejection systolic murmurs are diamond shaped, low or medium frequency, begin after S_1 and end before S_2, and increase in intensity after a long cycle length or PVC.

- Regurgitant systolic murmurs are often holosystolic, high frequency, begin with S_1 and or extend to and touch S_2, and do not change in intensity after a long cycle length or PVC.
- Ejection murmurs usually result from blood flow through a semilunar valve and regurgitant murmurs result from blood flow through an atrioventricular valve or a ventricular defect.

SYSTOLIC MURMURS

Systolic Murmurs: Ejection Type

See Figures 2.8 and 2.9.

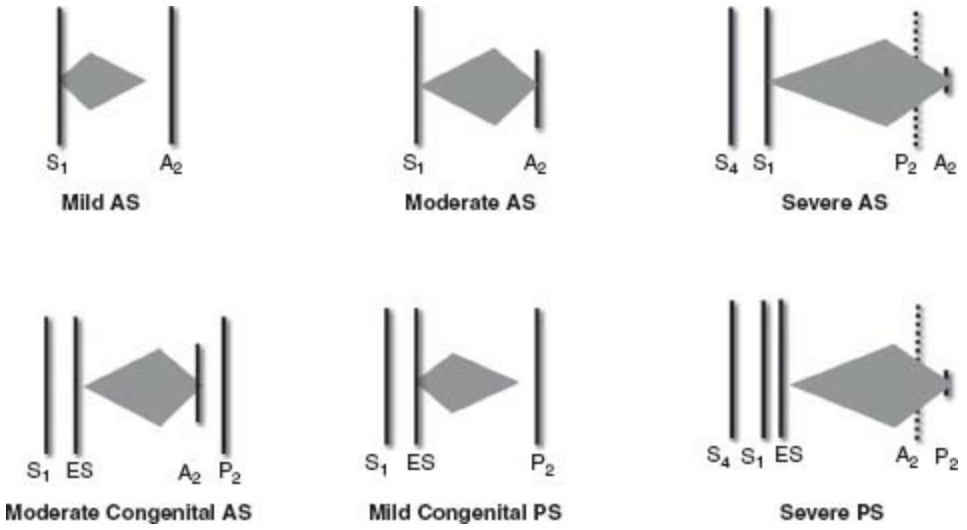

FIGURE 2.8 The systolic ejection murmurs due to AS and pulmonic stenosis (PS). The severity of stenosis is associated with the time to peak and the duration of the murmur as well as the associated findings. With severe AS, an S_4 gallop and paradoxical S_2 splitting may be present. With severe PS, a right-sided S_4 gallop and persistent S_2 splitting may be present. With congenital AS and PS, an ES may come before the murmur. With increasing severity of PS and AS, the corresponding P_2 and A_2 component of the second heart sound gets fainter.

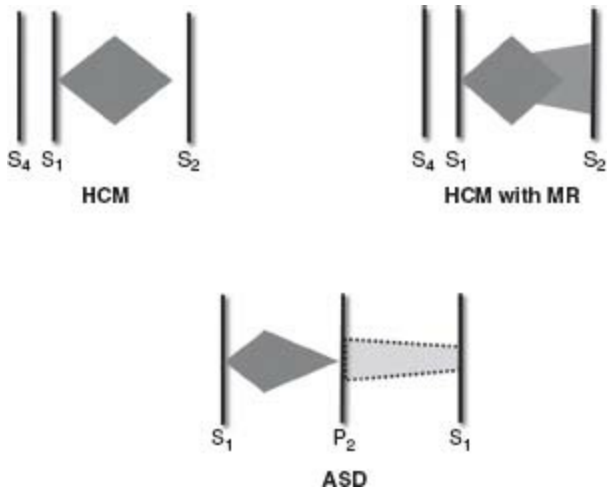

FIGURE 2.9 Systolic ejection murmurs due to HOCM and ASD. The murmur of HCM has a crescendo-decrescendo pattern. In some patients, LVOT obstruction resulting from systolic anterior motion of the mitral leaflet causes MR. This second systolic murmur is difficult to distinguish from the ejection-type sound. It has the qualities of a regurgitant murmur extending to the S_2 sound and extending to axilla. The murmur of an ASD typically is due to an ejection pulmonary outflow sound related to increased stroke volume. There also may be a diastolic rumble across the tricuspid valve related to increased flow entering the right ventricle.

1. Aortic valvular stenosis:
   - Location: heard best with the diaphragm at the aortic area
   - Description: mainly harsh, medium pitch with a crescendo/decrescendo configuration. In elderly, there is a high-pitched musical murmur that may be heard radiating to the apex (Gallavardin murmur). This may mimic an MR murmur.
   - Radiation: into the neck and great vessels though it may be toward the apex in elderly, but not beyond the apex
   - Intensity: related to stroke volume and severity and therefore may or may not reflect the severity of stenosis (e.g., mild AS with high stroke volume may be loud whereas severe AS with low stroke volume may be soft)
   - Severity: severe AS is characterized based on an ↑ in ejection time (longer duration and delayed peaking).
   - Maneuvers: AS murmur may ↓ following Valsalva and ↑ post PVC.
   - Associated findings:
     – Prominent "a" waves (↓ RV compliance because of septal hypertrophy—Bernheim effect)
     – "Parvus (reduced) and tardus (slow)" carotid upstroke with anacrotic pulse. Not always present in the elderly with stiff vessels.
     – Thrill over the carotid pulse (shudder)
     – Precordial thrill
     – Apical impulse is sustained, nondisplaced.
     – Early ES heard with congenital stenosis
     – A_2 intensity ↓ or absent with severe AS
     – Second heart sound is single (P_2) or may be paradoxically split.
     – Palpable and audible S_4
     – Reduced pulse pressure
   - Variations: Congenital supravalvular AS is heard best at the first or the second right interspace and is associated with radiation toward the right carotid artery with relatively ↓ left-sided pulses. A2 may be increased with this form of AS (Table 2.2).

2. Aortic sclerosis:
   - Location: right upper sternal border, heard best with the diaphragm
   - Description: soft
   - Radiation: does not radiate widely
   - Intensity and Severity: related to flow, early peaking
   - Associated findings: no associated findings of AS, normal S_2, and no radiation to the carotids
3. Hypertrophic cardiomyopathy:
   - Location: left ventricular outflow tract (LVOT) obstruction murmur is heard best along the mid and the lower left sternal edges.
   - Description: harsh
   - Radiation: LVOT obstruction murmur may be widely transmitted, although not usually heard at the neck.
   - Intensity and Severity: related to the degree of obstruction
   - Maneuvers: hemodynamic changes that affect LV volume, contractility, and vascular resistance help differentiate HOCM from AS:
     – Standing ↓ AS and ↑ HOCM
     – Valsalva (straining phase) ↑ the murmur of HOCM and ↓ or does not change the murmur of AS
     – Amyl nitrite ↑ the murmur of HOCM and AS.
     – Post PVC, the murmur of HOCM and AS is ↑.
   - Associated findings:
     – ↑ "a" wave (Bernheim effect)
     – Murmur of MR occurring in midlate systole may be present due to systolic anterior motion of the mitral valve.
     – Murmur of RVOT obstruction may be present at the left upper sternal border in rare circumstances.
     – Brisk carotid upstrokes sometimes bifid, "spike and dome." If carotid upstroke is reduced, contemplate an alternative diagnosis.
     – Sustained LV apical impulse, double or triple thrust
     – S_2 paradoxical split
     – S_4 gallop
4. Pulmonic stenosis:
   - Location: heard best in the pulmonary area
   - Description: harsh, medium pitch, crescendo/decrescendo
   - Radiation: directed to the left shoulder, back, lung fields, and neck

- Intensity: depends on stroke volume and severity
- Severity: characterized by the duration of murmur and time to peak
- Maneuvers: The murmur ↑ with inspiration.
- Associated findings:
  - ↑ "a" wave
  - Sustained sternal lift or heave
  - Normal S_1 followed by ejection click (EC) that may not be present in dysplastic leaflets
  - Absent or ↓ P_2
  - Widely persistent split S_2
  - Early pulmonic ES that ↓ with inspiration
  - Right-sided S_4 (atrial gallop ↑ with inspiration)
  - Murmur of TR
  - Elevated JVP

5. Innocent murmur in children: (Still murmur):
   - Location: left lower sternal border or apex
   - Description: low-medium frequency, vibratory or buzzing, short midsystolic
   - Radiation: usually none
   - Intensity and Severity: related to stroke volume but usually soft
   - Maneuvers: may change in intensity or disappear with different positions, such as standing
6. Innocent murmur in children to young adults: (Pulmonary ejection murmur):
   - Location: pulmonary area
   - Description: high frequency, early to midsystolic crescendo-decrescendo
   - Radiation: usually none
   - Intensity and Severity: related to stroke volume but usually soft

TABLE
2.2 Distinguishing Features between Left Heart Obstructive Conditions

Feature	Valvular	Supravalvular	Subvalvular	HOCM
Pulses				
Carotid pulse	Normal to ↓↓	Asymmetric	Normal to ↓↓	Brisk, Spike, and Dome
Pulse pressure after PVC	↑	↑	↑	↓ (Brockenbrough Sign)
Heart sounds				
Four heart sound	Common in severe disease	Uncommon	Uncommon	Common
Paradoxical splitting	Common	No	Rare	Common
Ejection click	Common with bicuspid valve without calcification	No	No	No
Murmurs				
Valsalva effect on murmur	↓	↓	↓	↑
Murmur of AR	Common	Rare	Sometimes	Rare

Systolic Murmurs: Regurgitant Type

See Figure 2.10.

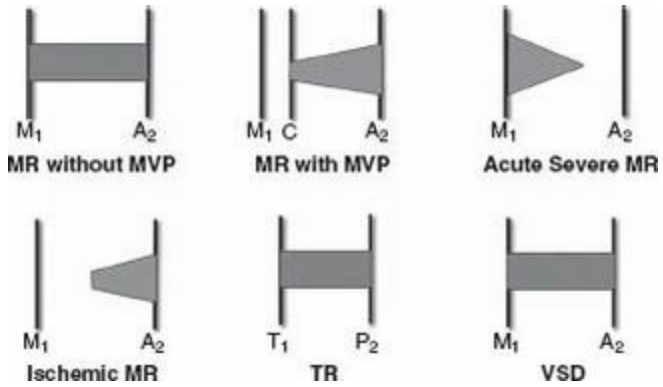

FIGURE 2.10 Regurgitant-type murmurs. The timing of the murmurs is shown with most regurgitant murmurs, MR, TR, and VSD extending from S_1 to S_2. However, some regurgitant murmurs are not holosystolic. Examples include acute severe MR where there is rapid equalization of the left atrial and ventricular pressures resulting in an early systolic murmur, the click murmur of MVP and ischemic MR associated with papillary muscle dysfunction.

1. Mitral regurgitation:
   - Location: usually heard best with the diaphragm at the apex
   - Description: blowing, high pitched
   - Radiation: typically into the left axilla unlike with AS
   - Intensity and Severity: variable related to BP, loading conditions, mechanism and acuity
   - Maneuvers: may ↑ with expiration and during isometric handgrip
   - Variations:
     – MR due to posterior prolapse may be anteriorly directed toward the left sternal border and neck
     – MR may not be holosystolic, following a click it may be mid or late systolic

and it may be early systolic with acute MR (rapid equalization of pressures)

- Associated findings:
  - Laterally displaced apical impulse
  - ↓ S_1
  - Mid to late systolic click, and late systolic murmur in patients with MVP
  - S_3
  - S_2 (P_2) may be ↑ when PH occurs.

2. Tricuspid regurgitation:
   - Location: heard best along the lower sternal border but also along right sternal border
   - Description: blowing, high pitched
   - Radiation: to the right side, not beyond the axilla as with MR
   - Intensity: may ↑ with inspiration (Carvallo sign), though sometimes even severe TR is not loud and may not ↑ with inspiration (RV failure when RV volume does not change)
   - Severity: may not be related to intensity though always with elevated JVP
   - Variations—if RV is severely dilated occupying the left precordium, then TR may be heard toward the apex.
   - Associated findings:
     - Left parasternal lift (due to RV hypertrophy)
     - Elevated JVP with large "v" or "cv" wave with rapid "y" descent with obliterated "x" descent.
     - Right-sided S_3
     - Diastolic rumble at the left sternal border, narrow split S_2, and ↑ P_2 if it is due to PH
     - Pulsatile liver
     - Right heart failure signs
3. Ventricular septal defect:
   - Location: around the lower sternum
   - Description: harsh and high pitched
   - Radiation: toward the sternum and not to the axilla
   - Intensity: generally loud but depends on the size of the shunt
   - Severity: usually accompanying thrill though the intensity of the murmur is not proportional to the degree of shunt (a loud, restrictive murmur is generally small, and a soft non-restrictive murmur is generally a large shunt)
   - Maneuvers: does not ↑ with inspiration as does TR

- Variations:
  - Depends of the relative compliance of the LV/aorta and RV/PA—may be early systolic when PH is present
  - If heard best in the first and second left intercostal spaces and radiating to the left clavicle, suspect supracristal defect or PDA.
- Associated findings:
  - Thrill
  - A_2 is usually normal.
  - P_2 is normal or ↑.
  - A diastolic rumble may be present due to increased flow across the mitral valve.

DIASTOLIC MURMURS

See Figures 2.11 and 2.12.

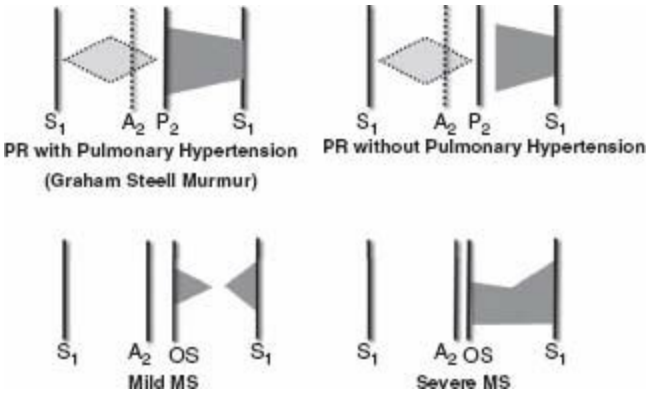

FIGURE 2.11 Diastolic murmurs. The diastolic decrescendo PR murmur associated with PH is called the Graham Steell murmur. The murmur follows a loud P_2 sound. In contrast, the PR murmur unrelated to PH starts after the P_2 sound. The murmur of MS usually occurs after a loud S_1 and may be decreased in intensity prior to presystolic accentuation due to atrial contraction. The severity of MS is determined largely by the duration of the S_2–OS interval and the duration of the murmur.

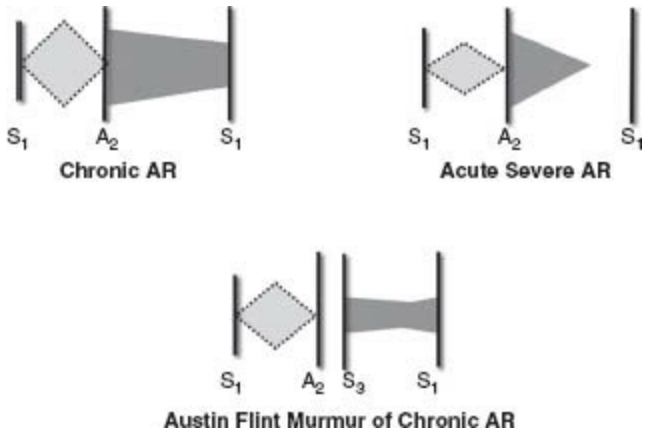

FIGURE 2.12 Diastolic murmurs of AR. The murmur of chronic AR is a decrescendo murmur beginning after S_2. There often is an associated loud systolic ejection murmur due to high stroke volume. The murmur of acute severe AR is decrescendo in configuration but is brief in duration due to rapid equalization between aortic diastolic and left ventricular diastolic pressure. The systolic ejection murmur in acute severe AR is generally less intense compared to chronic AR since the stroke volume is not able to increase acutely. The Austin Flint murmur is a diastolic flow murmur that occurs in patients with AR and mimics the diastolic rumble of MS. It begins after an S_3 gallop. Associated sounds (OS, S_1 intensity) and maneuvers aid to differentiate an Austin Flint murmur from an MS murmur.

1. Mitral stenosis:
   - Location: localized around the apex, heard best in left lateral decubitus position
   - Description: low-pitched diastolic rumble heard best with the bell and crescendo in late diastole
   - Radiation: none
   - Severity: related to duration of the murmur, not to the intensity. A_2–OS interval related to severity.
   - Maneuvers: ↑ with amyl nitrite and exercise due to tachycardia
   - Variations: early to mid diastolic rumble may be heard without stenosis due to ↑ flow (i.e., large VSD, PDA)
   - Associated findings:
     – S_1 may be ↑ if pliable leaflets.
     – OS present with ↓ OS to A_2 interval
     – ↑ P_2 and left parasternal lift if PH
     – AF is common
     – TR or MR murmurs may be present.
     – TS murmur may be present.
     – Elevated JVP with large “v” waves may be present with pulmonary HTN and associated TR.
2. Aortic regurgitation:

- Location: left or right sternal border
- Description: blowing, high-pitched decrescendo, heard best with the diaphragm, begins with A_2 and heard best sitting, leaning forward in expiration
- Radiation: if heard best with radiation to the right sternal border, suspect aortic root disease, and if heard best with radiation to the left sternal border or apex, suspect leaflet abnormalities.
- Intensity: related to the severity and acuity of the lesion dependent on the difference between the aortic and the LV diastolic pressure gradient
- Severity: in chronic AR, the duration of the murmur is associated with severity. In acute AR, a brief and soft early diastolic murmur may be present. The associated findings are important in determining severity.
- Variations: leaflet perforation may cause a "cooing" or musical sound.
- Associated findings:
  - Aortic systolic ejection murmur
  - Austin Flint murmur—a low-pitched rumbling apical diastolic murmur with presystolic accentuation that may mimic MS
  - Soft S_1 (premature closure).
  - Paradoxically split S_2
  - S_3
  - Laterally displaced hyperdynamic apical impulse
  - Wide pulse pressure with ↓ diastolic pressure
  - Large volume pulses
  - Bisferiens carotid pulse
  - Multiple peripheral signs may be present including those discussed in the arterial pulse section.
  - Diastolic MR may occur due to annular dilation.

3. Pulmonic regurgitation:
   - Location: pulmonary area
   - Description: high pitched and blowing, early diastolic decrescendo and generally brief beginning with P_2 if due to PH (Graham Steell) and lower pitched in the absence of PH beginning after P_2
   - Radiation: very localized
   - Intensity: ↑ with inspiration
   - Severity: "to-and-fro" murmur with severe PR and associated findings
   - Maneuvers: the murmur gets louder with inspiration.
   - Associated findings:

- Loud P_2
- Persistent split S_2
- Elevated JVP with a prominent "a" wave that may be masked by a large "v" wave if TR is also present
- TR murmur
- Parasternal lift due to RVH may be present.

4. Tricuspid stenosis:
   - Location: localized at the lower left sternal border or xiphoid area and best heard in the right lateral decubitus position
   - Character: not as low pitched as MS
   - Radiation: none
   - Intensity: ↑ with inspiration
   - Severity: related to the associated findings
   - Variations: a short, early to mid diastolic rumble may be heard without stenosis due to ↑ flow such as with an ASD.
   - Associated findings:
     - Large "a" wave and slow "y" descent
     - Tricuspid OS may be heard.
     - Splitting of S_1 and loud S_1/T_1 may occur.
     - Right heart failure signs may occur.

CONTINUOUS HEART SOUNDS

- They start in systole and encompass part or all of the systole and must extend through S_2 into diastole without discontinuation.
- Usually continuous murmurs peak near to or at S_2 but are not required to encompass all of systole and diastole.
- A holosystolic and holodiastolic murmur ("to and fro") together is not a continuous murmur since it does not go through the second heart sound.
- Continuous murmurs occur because of a continuous gradient between chambers or vascular structures (aorta–PA, artery–artery, artery–vein, vein–vein), during both systole and diastole.
- Benign continuous sounds include a venous hum and mammary souffle.
- A venous hum is heard mostly in children in the right supraclavicular area. It may have a "humming" quality. The intensity is variable depending on position (loudest sitting and with the head rotated contralaterally) and may be diminished by

compression.

- A mammary souffle is present in late pregnancy or during lactation. It may be primarily systolic heard in the third to fourth interspace on either or both sides. It may be abolished by compression.
- Pathologic continuous murmurs include PDA, coronary fistula, pulmonary arteriovenous fistulas, and coarctation of the aorta.
- Continuous murmurs radiated to the back are usually pathologic, and coarctation of the aorta, and pulmonary A-V fistulas should be suspected in first instance; rarely, the murmur of PDA is heard in the back.

Patent Ductus Arteriosus

See Figure 2.13.

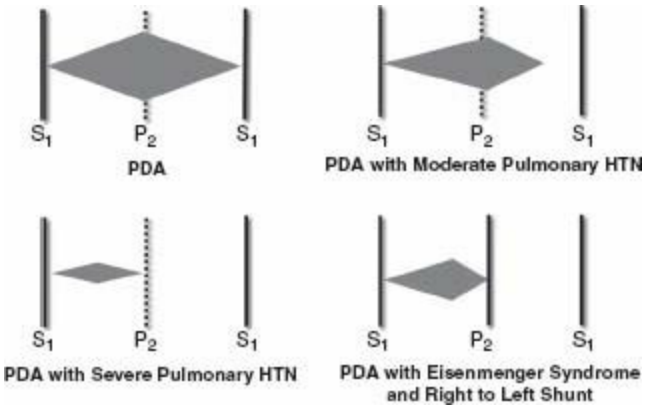

FIGURE 2.13 PDA murmur. The murmur of a PDA is a continuous murmur characterized by an increasing intensity in systole, extension through the S_2 sound, and then decreasing in diastole. Engulfing the S_2 heart sound is essential to distinguish a continuous murmur from a "to-and-fro" murmur. As the PA pressure goes up, the diastolic component of the murmur shortens and may disappear. With further increases in PA pressure, the systolic component diminishes and may also disappear. When Eisenmenger syndrome occurs with a right-to-left shunt, the continuous murmur will be altered and a short systolic murmur is all that remains.

- Heard best in the left second interspace near the sternum with radiation to the left clavicle
- Harsh, loud, machinery-like quality, sometimes associated with a thrill
- ↑ with peak intensity around S_2 and then gradually wanes and may not encompass all of diastole
- When PH develops, the diastolic portion gets shorter and softer. With severe pulmonary systolic HTN, the systolic component may also diminish and be absent.
- With large left to right shunt, an apical diastolic rumble may be heard.
- Associated findings:
  - Differential cyanosis when right to left shunting occurs (upper extremities with

normal oxygenation and lower extremities with cyanosis)

- Tachycardia
- Bounding peripheral pulses and wide pulse pressure
- Apical impulse displaced, diffuse

DYNAMIC AUSCULTATION

See Figures 2.14 and 2.15.

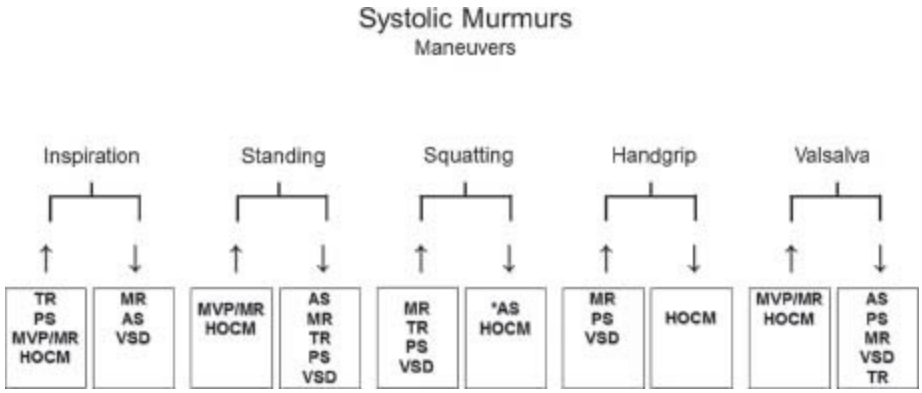

FIGURE 2.14 An algorithm demonstrating the effect of various maneuvers on systolic murmurs. TR, tricuspid regurgitation; PS, pulmonary stenosis; MVP/MR, mitral valve prolapse/mitral regurgitation; HOCM, hypertrophic obstructive cardiomyopathy; MR, mitral regurgitation; AS, aortic stenosis; VSD, ventricular septal defect. *The effect of squatting on AS may be variable (decreased, no change, or even increased) depending on the relative alteration of preload and afterload.

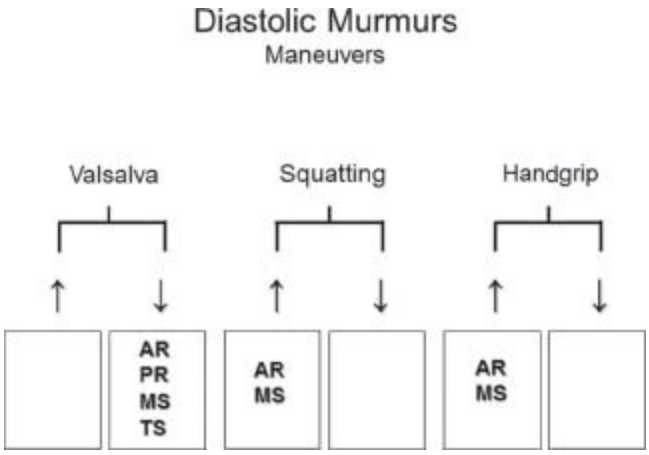

FIGURE 2.15 An algorithm demonstrating the effect of various maneuvers on diastolic murmurs. AR, aortic regurgitation; PR, pulmonary regurgitation; MS mitral stenosis; TS, tricuspid stenosis.

Respiration

- In general, right-sided murmurs and sounds ↑ with inspiration and left-sided murmurs and sounds ↓.

- Exceptions include
  - The ES of PS ↓ with inspiration.
  - The click of MVP moves closer to S_1 and the murmur may be longer and accentuated with inspiration.

Valsalva

- Obtained by performing an inspiration followed by forced exhalation against a closed glottis
- Phase II during straining is detected at the bedside—there is a ↓ in venous return and BP and reflex tachycardia.
- The opposite happens during phase IV where an ↑ in stroke volume results in an ↑ in BP, and a ↓ in HR. This phase has no utility in clinical practice but may lead to a diagnostic error (the overshoot).
- During the strain phase, the only murmurs that ↑ are those of HOCM and the MR murmur associated with MVP gets longer and may ↑ in intensity.
- Right-sided murmurs return to baseline levels within 2 to 3 beats after the Valsalva release.

Hemodynamic Maneuvers

- Raising legs while supine augments venous return and augments most right-sided heart sounds (after a few beats) and left-sided heart sounds (after 4 to 6 beats). The murmur of HOCM is ↓.
- Squatting results in ↑ venous return and systemic resistance. Most right- and left-sided murmurs ↑ such as AR, MR, and VSD. The murmur of HOCM is ↓.
- Hand grips ↑ BP and HR. AS murmur is unchanged or may ↓, most other left-sided murmurs↑. The HOCM murmur ↓ and click and murmur of MVP are delayed and usually ↓ in intensity.

Pharmacologic Agents

- Amyl nitrite results in marked transient preload and afterload (BP) reduction and subsequent ↑ in heart rate.
- This maneuver is best for distinguishing:

1) AS (↑) versus MR (↓)
2) MS (↑) versus Austin Flint (↓)
3) MVP click murmur gets longer.

- Innocent systolic murmurs are ↑.
- The intensity of the murmur of AR ↓.

Post PVC

- The murmurs of HCM, AS, and PS ↑.
- 2There is no change in the murmurs of MR and TR.
- The carotid upstroke ↑ in AS, and ↓, or remains unchanged in the HCM.
- The pulse pressure with HCM ↓ (Brockenbrough phenomenon) and that of AS ↑.

TYPICAL FINDINGS OF SPECIFIC MEDICAL CONDITIONS

Acute Myocardial Infarction

- Bradycardia or tachycardia
- Normotensive or hypotensive
- S_1 soft (associated with MR)
- S_2 paradoxically split
- S_3 gallop
- S_4 gallop (↓ LV compliance during ischemia)
- Late systolic murmur (crescendo) of MR (such as due to papillary muscle dysfunction)
- Early systolic murmur (decrescendo) of acute severe MR (such as papillary muscle rupture)

RV Infarction

- ↑ JVP with ↑ "a" and "v" wave
- Kussmaul sign
- Hypotension
- Right-sided S_3 or S_4 gallop (↑ with inspiration)
- Systolic murmur of TR
- Clear lungs

Dilated Cardiomyopathy

- ↑ JVP with ↑ "a" and "v" wave
- Low pulse amplitude, narrow pulse pressure, and pulsus alternans
- Diffuse apical impulse displaced laterally and downward
- S_2 paradoxically split (often due to LBBB)
- S_2 (P2) ↑ with pulmonary HTN.

- S_4, S_3, or SG with tachycardia
- MR or TR murmurs

Restrictive CM

- Macroglossia, purpura, bruising (amyloidosis)
- Cachexia
- Tachycardia
- Hypotension (including orthostatic hypotension)
- ↑ JVP with rapid "x" and "y" descent
- Kussmaul sign
- Narrow pulse pressure with decreased pulse amplitude
- S_3 gallop (less common S_4 gallop)
- MR or TR murmurs
- Right heart failure signs (hepatosplenomegaly, pulsatile liver, ascites, edema)

Cardiac Tamponade

- Hypotension (and signs of hypoperfusion)
- Tachycardia
- Pulsus paradoxus
- Elevated JVP with prominent "x" descent and reduced or absent "y" descent
- Quiet heart sounds
- Beck triad: (↑ JVP, quiet heart sounds, and hypotension)
- Ewart sign with dullness to percussion and bronchial lung sounds on the left side below the left scapula (due to compression of the left lower lobe by a large pericardial effusion)
- Pulmonary rales

Constrictive Pericarditis

- ↑ JVP with rapid "x" and "y" descent (Friedreich sign)
- Kussmaul sign
- Apical impulse may not be palpable.
- Systolic retraction of the apical impulse (Broadbent sign)
- Quiet heart sounds
- Pericardial knock
- Right heart failure signs (hepatosplenomegaly, pulsatile liver, ascites, edema)

- Pulsus paradoxus may be present with effusive-constrictive pericarditis.
- MR or TR murmurs

Pulmonary Hypertension

- Elevated JVP with prominent "a" waves
- Left parasternal systolic lift
- Loud P_2 (may be palpable)
- S_2 persistently split
- Right-sided S_4 or S_3 gallop
- Pulmonic ES
- Pulmonic regurgitation (Graham Steell murmur)
- TR murmur
- Right heart failure signs (hepatosplenomegaly, pulsatile liver, ascites, edema)

Type A Aortic Dissection

- Normotensive, hypertensive, or hypotensive
- Unequal upper-extremity BP
- Unequal or absent pulses
- New high-pitched diastolic decrescendo murmur (short duration and may be soft)
- Systolic ejection murmur (associated with severe AR and ↑ stroke volume)
- S_3 gallop
- Pericardial rub (if rupture into pericardial sac)
- Shock or cardiac tamponade
- Absence of peripheral signs seen with chronic AR
- Neurologic findings (including Horner syndrome and stroke)

Atrial Septal Defect

- Elevated JVP with equal size "a" and "v" waves
- RV systolic heave
- Palpable pulsation of the PA
- P_2 ↑
- S_2 fixed split
- Midsystolic ejection murmur (increased flow across the pulmonary outflow tract)
- Early low-pitched diastolic rumble (due to flow across the tricuspid valve)

- MR can be heard with an ostium primum ASD (with associated mitral valve cleft)
- Association with the Holt–Oram syndrome (upper limb deformities)

Ventricular Septal Defect

- Normal or ↑ intensity S_2
- Persistent split S_2
- S_3 gallop
- Diastolic rumble (due to ↑ flow across the mitral valve)
- Regurgitant holosystolic high-pitched murmur heard best along the left side of the sternum
- Palpable thrill
- With a supracristal VSD, the murmur is associated with AR.
- With a muscular VSD, the murmur may be decrescendo in shape (the defect becomes smaller as the muscle contracts).

Expected "Normal" Findings during Pregnancy

- Tachycardia
- Normotensive with a tendency toward ↓ diastolic BP
- Mildly ↑ or normal JVP with prominent "a" and "v" waves
- Brisk carotid upstrokes
- Laterally displace apical impulse
- ↑ S_1 and S_2/P_2
- Splitting of S_1
- Persistent splitting of S_2
- S_3 gallop
- Grade 1 to 2 ejection murmur (due to ↑ blood flow through the pulmonary outflow tract)
- Peripheral edema
- Venous hum
- Mammary souffle

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QUESTIONS AND ANSWERS

Questions

1. A 20-year-old man is referred for a cardiology consult due to an episode of nonexertional syncope associated with palpitations (his mother who is a nurse took his apical pulse and it was >200 bpm and irregular during the event). An electrocardiogram is reported as abnormal but not available. An echocardiogram was normal. Which of the following examinations suggests a cause for syncope in this patient?
   a. Normal S_1 and physiologic split S_2
   b. Normal S_1 and persistent split S_2
   c. Physiologic split S_1 and normal S_2
   d. Normal S_1 and fixed split S_2

2. A 31-year-old woman is 6 months pregnant. She has no significant medical or cardiac history. Her pregnancy has been uncomplicated except that now she is experiencing dyspnea with exertion. Which of the following examinations would be considered pathologic?
   a. Normal S_1 and S_2 with a 2/6 early systolic ejection murmur and 1/6 diastolic rumble. No extra sounds.
   b. Normal S_1 and S_2 with a S_3 gallop
   c. Normal S_1 and S_2. No extra sounds. Continuous murmur heard under the left breast.
   d. Normal S_1 and decreased S_2. An ejection sound (ES) decreases with inspiration.

3. A 25-year-old woman has a history of congenital heart disease. She was recommended to have a "corrective interventional procedure" several years earlier due to a continuous murmur, but she did not do it because she felt well. She now has developed the onset of dyspnea with a moderate level of exertion. Which of the following examinations would you expect to be present?
   a. Normal S_1, soft S_2/P_2, and continuous systolic and diastolic murmur
   b. Normal S_1, normal S_2/P_2, and continuous systolic murmur but short diastolic murmur
   c. Normal S_1 and loud S_2/P_2 with predominant systolic murmur. Pink hands and blue feet.
   d. Normal S_1 and S_2 with only a diastolic murmur. Pink hands and blue feet.

4. A 32-year-old woman has just returned from a year in India. She has a sore throat, fever, rash, arthralgias and is dyspneic. On examination, there is a soft S_1 and loud S_2. There is an S_3 gallop. She has 2 murmurs, a 3/6 apical holosystolic regurgitant systolic murmur and a 2/6 apical, short mid-diastolic rumble. What is the most likely explanation for her symptoms?
   a. Pulmonary stenosis (PS) and pulmonary regurgitation (PR)

b. Aortic stenosis (AS) and aortic regurgitation (AR)
c. Tricuspid stenosis (TS) and regurgitation
d. Mitral stenosis (MS) and mitral regurgitation (MR)

5. A 26-year-old woman is referred to cardiology clinic. She was told she had MVP 10 years earlier. A 2/6 regurgitant murmur is heard at the LSB with an associated midsystolic click. What is expected to happen when the patient changes from a standing to squatting position?
   a. The click moves toward S_2 and the murmur decreases.
   b. The click moves toward S_2 and the murmur intensifies.
   c. The click moves toward S_1 and the murmur decreases.
   d. The click moves toward S_1 and the murmur intensifies.

6. A 70-year-old man is seen in the hospital for preoperative cardiac clearance prior to hip surgery that is planned for today. Prior to falling and injuring his hip, he had no symptoms with >4 METS exertion. On examination, the intern hears a systolic murmur that is 3/6 in intensity. He is concerned that the patient has AS and would like to cancel the surgery and obtain an echocardiogram. Which of the following findings is not consistent with AS?
   a. Following a PVC, the intensity of the murmur is unchanged.
   b. The murmur starts after S_1 and ends before S_2.
   c. The murmur is intensified after a long cycle length in atrial fibrillation (AF).
   d. The murmur is typically crescendo/decrescendo in shape.

7. A 70-year-old man is day # 3 post inferior MI. He develops sudden hypotension. On examination, S_1 is decreased, S_2 (P_2) is increased. There is a decrescendo systolic murmur that begins with S_1 and ends in midsystole. There is a thrill along the left sternal border. What is the most likely diagnosis?
   a. Severe TR.
   b. Systolic anterior motion of the mitral valve with LVOT obstruction
   c. Pseudoaneurysm
   d. Ischemic MR

8. A 68-year-old man presents for evaluation of right heart failure. He has a history of coronary artery bypass graft (CABG) 10 years previously. He developed dyspnea with minimal exertion, orthopnea, palpitations, and lower-extremity edema in the past year. On examination, the jugular venous pressure is elevated to 15 cm H_2O with a prominent “x” descent and a “y” descent that is blunted. Kussmaul sign is absent and pulsus paradoxus is present. The heart sounds are soft. A PK is absent. Which of the following conditions is suspected?
   a. Restrictive cardiomyopathy
   b. “Classical” form constrictive pericarditis
   c. Effusive-constrictive pericarditis

9. A 47-year-old woman presents with dyspnea on exertion and episodes or presyncope. She has a history of rheumatic MS requiring a bioprosthetic MVR 10 years previously. On examination, JVP is 12 cm H_2O. S_1 is normal and S_2 is persistently split and accentuated. There is an early, long duration 3/6 blowing diastolic decrescendo murmur and a 2/6 early peaking SEM at the left upper sternal border. With expiration, both murmurs decrease in severity. What is the most likely diagnosis?
   a. Pulmonary regurgitation and stenosis
   b. PR with pulmonary hypertension (PH)
   c. AR and stenosis
   c. Prosthetic mitral valve stenosis

10. A 32-year-old man has a history of a heart murmur since childhood. He is asymptomatic but was told he could not play sports as a child. On examination, there are equal pulses. S_1 and S_2 are normal without a split. There is a 3/6 SEM. There is no ES. There is a 2/6 diastolic decrescendo murmur.

Following a PVC, the murmur increased in intensity as did the pulse pressure. Which is the correct diagnosis for this patient?

a. Subvalvular AS due to a subaortic membrane
b. Supravalvular AS
c. Hypertrophic cardiomyopathy
d. Bicuspid AS

Answers

1. Answer B: The patient has Wolf–Parkinson–White (WPW) syndrome with associated rapid AF that led to nonexertional syncope. With a manifest accessory pathway, left and right-sided WPW may be detected on auscultation due to abnormalities in the splitting of the second heart sound (S_2). With a left-sided pathway, the A_2 component of S_2 would occur early since the atrioventricular (AV) node is bypassed and electrical activation of the left heart and therefore completion of ejection would lead to an earlier A_2 closure sound. In expiration, A_2 and P_2 would be separated, and in inspiration, the separation would be increased. This is referred to as persistent splitting of S_2. When a right-sided pathway is present, the P_2 component of S_2 occurs early during expiration (P_2 before A_2) with a single sound during inspiration. This is referred to as paradoxical splitting of S_2. Physiologic splitting of S_1 or S_2 may be a normal variant and not associated with electrical or structural heart disease. A fixed split S_2 may be associated with a hemodynamically significant ASD, though this would not be an expected cause of syncope.

2. Answer D: The physiologic changes during pregnancy including increased HR, stroke volume and decreased systemic and pulmonary vascular resistance lead to expected variations from normal on cardiac physical examination. The intensity of the first heart sound (S_1) and S_2 may be increased and splitting of S_1 and S_2 may occur. An S_3 is common as is an early peaking, short systolic ejection murmur (≤2/6 intensity). These findings are all related to increased total volume and cardiac output (CO). Similarly, some women will have a very soft diastolic flow murmur related to increased flow across the AV valves. This may be physiologic if there are no other associated abnormal sounds (e.g., an opening snap [OS] of MS). Continuous murmurs such as a venous hum or mammary souffle may be heard. All other sounds including (1) reduced intensity S_1 or S_2, (2) paradoxical or fixed S_2 splitting, (3) ≥3/6 systolic ejection murmur especially if mid or late peaking and long in duration, (4) ≥2/6 regurgitant murmur, (5) continuous heart sounds other than the mammary souffle and venous hum, (6) S_4 gallop, or (7) ESs or extra sounds are considered pathologic. In this patient, a decreased S_2 sound and an ES that decreases with inspiration is consistent with PS. The other examples are acceptable in a normal pregnant woman.

3. Answer B: The clinical history and answers are consistent with a patent ductus arteriosus (PDA). Each choice suggests a different size of the shunt and level of pulmonary vascular resistance relative to systemic vascular resistance (SVR). See Fig. 2.13. Choice (A) is consistent with a small hemodynamically insignificant PDA characterized by a systolic and diastolic component that envelope the second heart sound. Choice (B) is consistent with at least a moderate-sized PDA with associated elevation of PA pressure. This results in shortening of the diastolic component of the murmur as the systemic and pulmonary vascular resistances in diastole begin to equalize. Remember that a continuous murmur is defined primarily by its extension through the second heart sounds and is not required to extend throughout all of systole and diastole. Choice (C) is consistent with a right-to-left shunt due to PH and resultant Eisenmenger physiology. In the setting of a PDA and Eisenmenger physiology, the upper extremities remain well oxygenated and pink since they do not receive shunted blood whereas the lower extremities do not—and therefore are blue. Choice (D) is an unlikely examination for a PDA.

4. Answer D: The history and clinical findings suggest acute rheumatic fever, which is manifest as a pancarditis. The endocardial lesion is an active valvulitis that most commonly involves the mitral valve followed by the aortic valve in frequency. In the acute phase of mitral valvulitis due to rheumatic fever,

there is both a functional MS and regurgitation due to inflammation of the leaflets. The diastolic murmur is known as the Carey Coombs murmur and distinguishable from chronic rheumatic MS due to the absence of an OS, loud S1, and presystolic accentuation of the diastolic murmur. The associated MR may be severe. Aortic valve involvement is manifest as AR. The examination described is most consistent with a predominant MR murmur with mild functional MS.

5. Answer A: The mitral valve click and associated mitral regurgitant murmur is dynamically affected by changes in preload and afterload. Since the leaflets and chordae are redundant and elongated, there is effectively a mismatch between the leaflets and the left ventricular cavity size. When the cavity is smaller (as with decreased preload or afterload), the leaflets prolapse earlier in systole. This results in the mitral click moving closer to S_1; therefore, the duration and intensity of the regurgitant murmur are increased. In contrast, when the cavity is larger (as with increased preload or afterload), the leaflets prolapse later in systole. This results in the mitral click moving away from S_1 and closer to S_2; therefore, the duration and intensity of the regurgitant murmur are decreased (see Fig. 2.7).

6. Answer A: Distinguishing between a systolic regurgitant and an ejection-type murmur is important to characterize the etiology of a murmur. Regurgitant murmurs result from abnormalities of the atrioventricular valves and shunts (MR and TR, ventricular septal defect [VSD]). Ejection murmurs result from abnormalities of flow through the semilunar valves or outflow tract (aortic and PS, HOCM). Regurgitant murmurs typically start with S_1 or at least extend to S_2, or both. They are typically high pitched and do not increase with a long diastole of AF or post PVCs since the relative gradient between the upstream and the downstream chambers do not change significantly. Ejection-type murmurs typically start after S_1 and end before S_2 and are generally medium pitched and crescendo/decrescendo in shape. With a long diastole of AF or post PVC, ejection murmurs increase in intensity.

7. Answer D: Acute ischemic MR following myocardial infarction may be due to organic or functional etiologies. The timing and intensity of the murmur are related in part to the mechanism and the severity as well as loading conditions. In the setting of organic MR due to papillary muscle rupture, the murmur is typically early systolic and then fades in later systole. This occurs because of rapid equalization of the left atrial and ventricular pressures in systole. In contrast, the functional etiologies of MR including papillary muscle dysfunction tend to occur later in systole.

8. Answer C: Constrictive pericarditis should be suspected in any patient with prior coronary artery bypass graft (CABG) and signs or symptoms of right heart failure especially if left ventricular function is preserved. The clinical findings in the patient are most notable for elevated JVP with a blunted “y” descent and pulsus paradoxus. The presence of a blunted “y” descent and pulsus paradoxus is not typical of classical form of constrictive pericarditis where there is typically a prominent “x” and “y” descent and the presence of Kussmaul sign. However, this constellation of findings is present with the effusive form of constrictive pericarditis. Effusive-constrictive pericarditis is due to an elastic pericardial visceral restraint with a tense pericardial effusion resulting in the clinical and hemodynamic features consistent with cardiac tamponade that subsequently revert to that of constrictive pericarditis following pericardiocentesis. Most patients with effusive-constrictive pericarditis ultimately require pericardiectomy. A PK is not expected in effusive-constrictive pericarditis and Kussmaul sign is generally absent.

9. Answer B: The patient has a Graham Steell murmur that is due to PR in the setting of PH. (See Fig. 2.11.) It is usually the result of longstanding MS. It differs from the findings seen with PR unrelated to PH where S_2 is not accentuated and the murmur is not heard immediately after S_2. Intensification of the murmur with inspiration and reduction of the murmur with expiration characterize this as a right-sided murmur, thus excluding AR and prosthetic MS. PS is a rare finding in rheumatic heart disease and would be associated with a reduced S_2.

10. Answer A: The patient has a subaortic membrane resulting in subvalvular AS and AR. Subvalvular membranes are usually due to fibrinous membranes or tunnels that result in fixed stenosis. Several mechanisms lead to associated AR including the effects of a jet lesion on the aortic leaflets and retraction of the leaflets due to the membrane. Supravalvular AS is rarely associated with AR and

typically has unequal pulses with right > left due to the streaming of the flow jet along the right side of the aorta. Bicuspid valvular AS is unlikely since the S_2 sound is preserved and there is no ejection click (EC). Finally, with HCM, the murmur post PVC is increased due to decreased preload resulting in increased systolic anterior motion of the mitral valve and increased obstruction. In addition, the pulse pressure (difference in pressure between the systolic and diastolic blood pressure) post PVC with HCM is decreased. With all other forms of AS (valvular, subvalvular, and supravalvular), the pulse pressure post PVC is usually increased.

CHAPTER

Cardiac Anatomy

Robert E. Hobbs

The heart is a muscular organ, pyramidal in shape, consisting of two parallel-valved pumps, located within the middle mediastinum, two-thirds to the left of the centerline. The base of the heart is oriented superiorly, whereas the apex points leftward, anteriorly, and slightly inferiorly. The cardiac apex is located at the fifth intercostal space near the midclavicular line. The heart is enclosed by the fibrous pericardium, which is bordered by the diaphragm inferiorly; the sternum and ribs anteriorly; the pleurae laterally; and the esophagus, descending aorta, and vertebrae posteriorly.

The average adult heart measures 12 cm from base to apex, 8 to 9 cm in width, and 6 cm in depth, approximating the size of a clenched fist. The heart weighs approximately 325 ± 75 g in men and 275 ± 75 g in women, accounting for 0.45% of body weight in males and 0.40% in females.

Viewed from the front, visible structures include the superior and the inferior vena cavae draining into the right atrium, the right ventricle (the most anterior chamber of the heart), the main pulmonary artery that courses superiorly and posteriorly before bifurcating, the left atrial appendage, a small portion of the left ventricle visible to the left of the left anterior descending coronary artery, and the ascending aorta (Fig. 3.1). The right heart forms the largest part of the anterior surface, whereas the left heart is largely posterior. The epicardial surface of the heart usually is covered with fat, proportional to age and the amount of body fat. Beneath the epicardial fat, the interventricular grooves separate the right and left ventricles and contain arteries, veins, nerves, and lymphatics. The atrioventricular (AV) grooves, which separate the atria from the ventricles, are located at the base of the heart. The interatrial grooves mark the borders between the atria. Posteriorly, the crux (“cross”) is the intersection of the AV, interatrial, and interventricular grooves. The acute cardiac margin is the junction of the inferior and anterior walls of the right ventricle. The obtuse margin is the rounded lateral wall of the left ventricle.

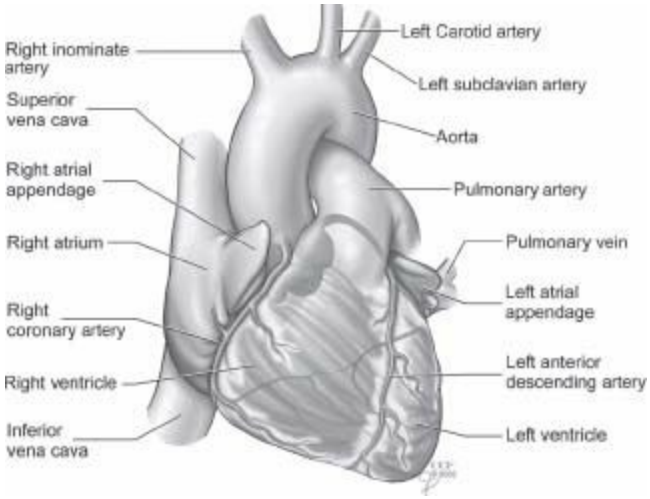

FIGURE 3.1 Frontal view of the heart and great vessels.

The heart is composed of four chambers. The right and the left atria are weakly contractile reservoirs that receive blood from the body and the lungs. They are positioned above the ventricles and are separated by the AV (tricuspid and mitral) valves. The right and left ventricles are muscular pumping chambers separated from each other by the interventricular septum. The ventricles eject blood through the semilunar (pulmonic and aortic) valves to the pulmonary artery and aorta, respectively.

The shape of the heart and the position of the valves are maintained by an internal fibrous skeleton. The cardiac skeleton consists of four valve annuli (or rings), the membranous septum, and the right and left fibrous trigones. The right fibrous trigone, also known as the central fibrous body, is located between the aortic, mitral, and tricuspid valves. It houses the His bundle and is the strongest component of the cardiac skeleton.

THE PERICARDIUM

The pericardium is a fibrous sac surrounding the heart and great vessels and containing 10 to 50 mL of pericardial fluid (Fig. 3.2). It maintains the position of the heart within the mediastinum, lubricates the cardiac surfaces, and provides a barrier against infection. Inferiorly, the pericardium is anchored to the central tendon of the diaphragm. Anteriorly, it is attached by ligamentous connections to the posterior sternum. Superiorly, the pericardium extends to the level of the second intercostal space, and laterally it is attached to the pleurae. The pericardium encloses the heart, portions of the vena cavae, most of the ascending aorta, the main pulmonary artery, and the four pulmonary veins. The pericardium consists of two layers. The inelastic fibrous pericardium is the outermost layer. The serous pericardium forms a thin mesothelial layer on the cardiac surface (the visceral pericardium or the epicardium) and lines the inferior surface of the fibrous pericardium (the parietal layer). The visceral pericardium

covers the heart and contains the coronary arteries and veins, autonomic nerves, lymphatics, and fat. Posteriorly, the pericardium folds upon itself to create several distinct sinuses. The oblique sinus is a pericardial reflection along the vena cavae and the pulmonary veins. The transverse sinus is a pericardial reflection located between the aorta, pulmonary artery, and atria. The ligament of Marshall is a pericardial fold containing the remnant of the embryonic left superior vena cava.

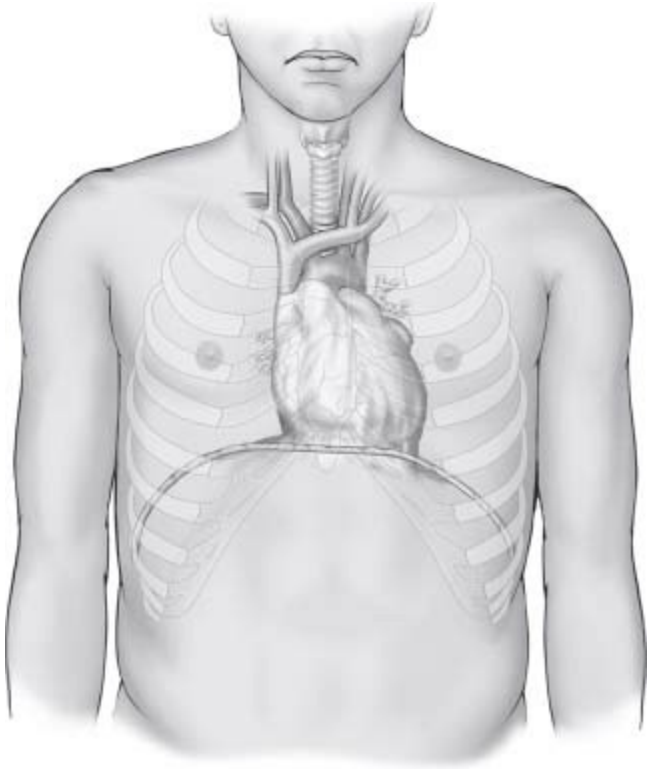

FIGURE 3.2 Frontal view of the pericardium.

CARDIAC CHAMBERS

Right Atrium

The right atrium is a low-pressure capacitance chamber that receives blood from the superior vena cava, inferior vena cava, and coronary sinus (Fig. 3.3). The right atrial volume is approximately 75 to 80 mL, and its free-wall thickness is 1 to 3 mm. The superior vena cava enters the superior aspect of the right atrium and directs its blood flow toward the tricuspid valve. The inferior vena cava returns blood from the lower body, and its eustachian valve directs blood flow toward the foramen ovale or the fossa ovalis. The coronary sinus returns most of the blood from the heart itself through an orifice partially guarded by the thebesian valve (valve of the coronary sinus). When the eustachian or thebesian valves are large and fenestrated, it is described as a Chiari net. Thebesian veins drain cardiac blood into the right atrium via multiple small orifices. The fossa ovalis, representing a closed foramen ovale, forms a 1.5- to 2.0-cm

depression on the interatrial septum. A patent foramen ovale is found in up to one-third of adults. The crista terminalis is a C-shaped muscular ridge on the right atrial free wall that separates the smooth posterior portion of the right atrium from the muscular anterior portion. The pectinate ("comb") muscles arise from the crista terminalis and course as bands anteriorly on the right atrial free wall. The right atrial appendage is a large triangular structure that overlies the right coronary artery and contains pectinate muscles. In the lower medial portion of the right atrium, Koch triangle overlies the AV node and the proximal His bundle. The tendon of Todaro is a fibrous band located between the valves of the inferior vena cava and the coronary sinus.

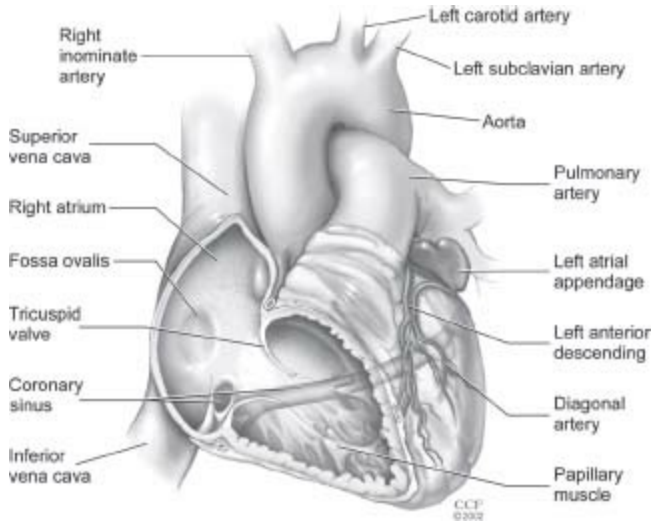

FIGURE 3.3 Frontal cutaway view of the right atrium and right ventricle.

Right Ventricle

The right ventricle is the most anterior chamber of the heart (Fig. 3.4). It is the smaller of the two ventricular chambers, separated from the left ventricle by the interventricular septum, which bulges into the right ventricle. It is triangular shaped when viewed from the right, and crescent shaped when viewed in cross section from the left. The right ventricular free wall is approximately 3 to 4 mm thick, or about one-third the thickness of the left ventricle. The right ventricle consists of an inlet portion, a trabeculated apical portion, and a smooth right ventricular outflow tract (infundibulum or conus portion). The walls of the right ventricle contain a latticework of muscle fibers called trabeculae carneae. The right ventricular apex is heavily trabeculated, more so than the left ventricle. The infundibulum (outflow tract or conus) portion of the right ventricle is smooth walled to the pulmonic valve. The right ventricle contains three papillary muscles, although the septal papillary muscle occasionally may be absent. Chordae tendineae (fibrous cords) extend upward from the papillary muscles and attach to the leaflet edges and to the ventricular side of the tricuspid valve. Chordae from one papillary muscle often attach to more than one tricuspid leaflet, and some chordae arise

from the septum. The crista supraventricularis (supraventricular crest) separates the inflow and outflow portions of the right ventricle. It consists of a septal band on the ventricular septum and a parietal band on the right ventricular free wall. The moderator band is an intracavity muscular bridge that connects the distal septum with the right ventricular free wall at the anterior papillary muscle. Blood enters the right ventricle via the tricuspid valve, turns upward at a 45- to 60-degree angle, and passes through the pulmonic valve into the main pulmonary artery.

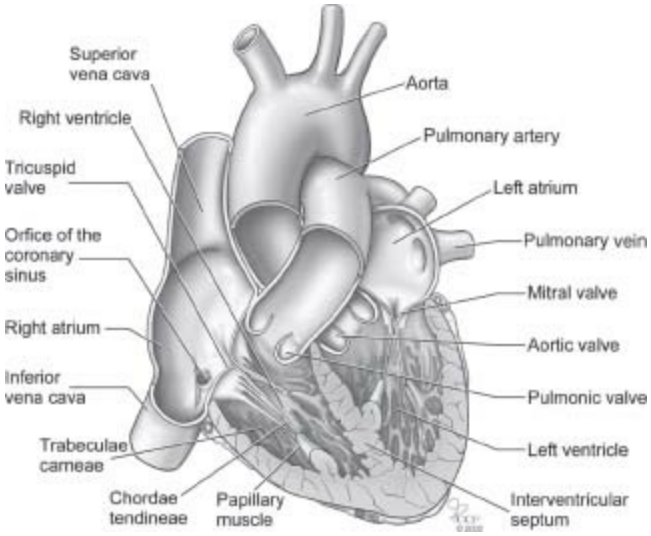

FIGURE 3.4 Coronal section of the heart and great vessels.

Left Atrium

The left atrium is the left upper posterior chamber of the heart (Fig. 3.5). It is cuboidal shaped, smaller than the right atrium (volume, 55 to 65 mL), but with thicker walls (3 mm) and higher pressure. It receives oxygenated blood from the lungs via four pulmonary veins (two from each lung). Unlike the right atrium, the left atrium has smooth interior walls and does not have bands of pectinate muscles except in the left atrial appendage. The left atrial muscle extends a variable distance within the pulmonary veins to prevent reflux during atrial contraction. The left atrial appendage, overlying the left circumflex coronary artery, is smaller, longer, more tortuous, and less triangular than the right atrial appendage, often containing two or more lobes. Left atrial contraction generates a stroke volume of 20 to 30 mL.

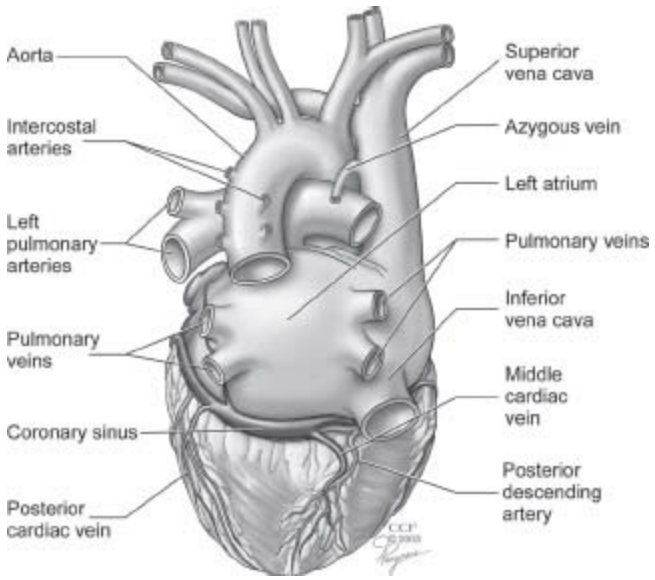

FIGURE 3.5 Posterior view of the heart and great vessels.

Left Ventricle

The left ventricle is a high-pressure, muscular chamber, 2.5 to 3 times thicker than the right ventricle (see Fig. 3.4). It is ellipsoid, or cone shaped when viewed from the right, and ring or doughnut shaped when viewed in cross section from the left. It is longer and narrower than the right ventricle, measuring approximately 7.5 cm in length and 4.5 cm in width. Structurally, the left ventricle consists of the inflow tract, the apical zone, and the left ventricular outflow tract. The anterior mitral leaflet separates the left ventricle into the posterior inflow tract and the anterior outflow tract. The septum consists of a large inferior muscular portion and a small superior membranous portion. The septum is thickest at the midportion and thinnest at the membranous portion near the aortic valve. The membranous septum has AV and intraventricular portions divided by the septal tricuspid leaflet. The His bundle is located within the interventricular portion of the membranous septum.

The left ventricular free wall measures approximately 8 to 12 mm and is thicker at the base than at the apex. It is composed of three layers: the endocardium, the myocardium, and the epicardium (or visceral pericardium). The outer two-thirds of the myocardium contains compact layers of muscle that twist and spiral inward from apex to base during contraction. The inner third of the myocardium consists of a latticework of trabeculae carneae that are more intricate than right ventricular trabeculations. The septal surface of the left ventricle is smooth.

Two papillary muscles, the larger anterolateral and the smaller posteromedial, arise from the free wall and have a variable number of heads. They anchor the chordae tendineae of the mitral valve, which are thicker than tricuspid valve chordae. Chordae tendineae restrict valve excursion during ventricular systole, thereby preventing the mitral valve leaflets from prolapsing into the left atrium. Most chordae arise from the

heads of the papillary muscles, but some arise from the free wall. Chordae from one papillary muscle may diverge and attach to both mitral leaflets. False chordae occur in half of normal hearts, and may connect walls, papillary muscles, and the septum, but are not attached to the mitral leaflets. They often cross the left ventricular outflow tract and can be identified by echocardiography. Many false chordae contain extensions of left ventricular conducting fibers.

Blood enters the left ventricle via the mitral valve and is ejected at a 90- to 120-degree angle through the aortic valve. The ejection phase is shorter in the left ventricle, but the pressure is greater compared with right ventricular contraction.

CARDIAC VALVES

Tricuspid Valve

The tricuspid valve is the largest of the heart valves and maintains forward flow of blood through the right heart (Fig. 3.6). The functional components of the tricuspid valve include the three leaflets, commissures, annulus, chordae tendineae, papillary muscles, and the right ventricle. The leaflets are named for their anatomic position: anterior, posterior, and septal. The anterior leaflet, which is the largest and the most mobile, partially separates the right ventricular inflow and outflow tracts. The posterior leaflet is the smallest, whereas the septal leaflet is the least mobile and is occasionally absent. The valve leaflets are attached to a discontinuous fibrous annulus that has a "D" shape. Chordae tendineae (tendinous cords) are attached to the edges and undersurface of each leaflet and are anchored by the papillary muscles and the interventricular septum.

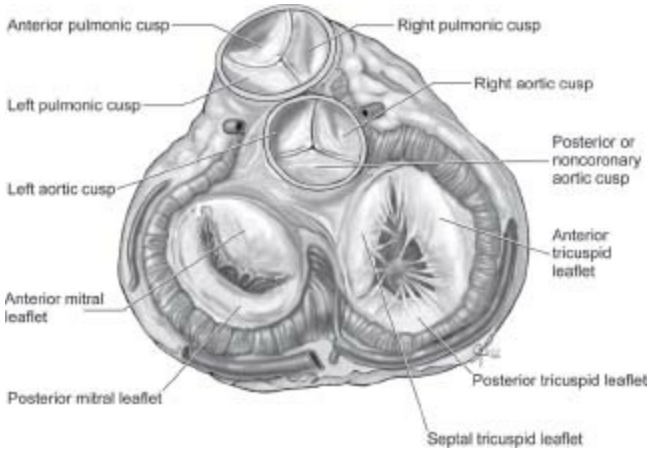

FIGURE 3.6 Cross-sectional view of the cardiac valves.

Pulmonic Valve

The pulmonic valve is the most anterior valve of the heart, located between the right ventricular outflow tract and the main pulmonary artery (see Fig. 3.6). It is the mirror

image of the aortic valve, containing right, left, and anterior cusps (or leaflets) that are thinner than those of the aortic valve. The pulmonary sinuses are partially embedded within the right ventricular infundibulum. During systole, the valve opens to form a rounded, triangular-shaped central orifice.

Mitral Valve

The mitral valve is named after the miter, a tall ornamental hat worn by bishops and abbots (Figs. 3.6 and 3.7). The valve, located between the left atrium and the left ventricle, maintains the forward flow of blood in the left heart. The mitral valve has six components: leaflets, commissures, annulus, chordae tendineae, papillary muscles, and left ventricle. When viewed from the side, the valve is funnel shaped, with the leaflets forming an apex protruding into the left ventricle. There are two mitral leaflets, the anterior and the posterior, which have similar surface areas but different shapes. The anterior leaflet is semicircular or oval shaped, broader but narrow transversely. It partially separates the left ventricular inflow tract from the left ventricular outflow tract. The posterior leaflet is crescent shaped, longer and narrower, half the height but twice the length of the anterior leaflet. It attaches over two-thirds of the posterior valve circumference. The posterior leaflet has two or more indentations forming three scallops (the middle usually is the largest). During atrial contraction, the valve forms an ellipsoid orifice. During ventricular contraction, the atrial side of the leaflets coapt, preventing regurgitation of blood into the atrium. Two commissures, the anterolateral and the posteromedial, separate the two leaflets. The chordae tendineae prevent the mitral valve from prolapsing into the left atrium during ventricular systole. Approximately 100 primary, secondary, and tertiary chordae attach to the free edge and underside of the valve and are anchored by two papillary muscles in the left ventricle. Some of the posterior leaflet chordae arise from the left ventricular free wall. Unlike the tricuspid chordae, mitral chordae do not have insertions into the septum. The mitral valve is surrounded by a saddle-shaped fibrous ring, the mitral annulus, which anchors the valve. It is connected to the tricuspid annulus by the right fibrous trigone (central fibrous body), forming part of the fibrous skeleton of the heart.

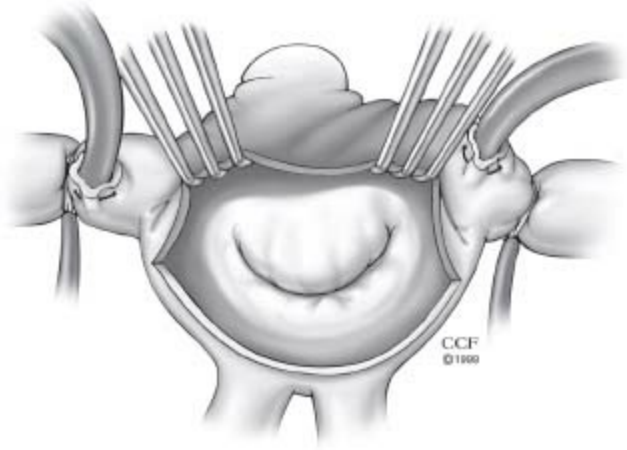

FIGURE 3.7 Surgical view of the atrial surface of the mitral valve.

Aortic Valve

The aortic valve, located between the left ventricle and the aorta, is thicker and stronger than the pulmonic valve (Figs. 3.6 and 3.8). It consists of three semilunar (half-moon) cusps located within the sinuses of Valsalva, three commissures, and an annulus. The three semilunar cusps, left, right, and noncoronary (or posterior), are pocket-like structures. The valve has a triangular-shaped central orifice when fully opened during systole. In diastole, blood fills the pocket-like cusps, causing the valve to close by coapting on the ventricular surfaces of the cusps. The nodules of Arantius are small fibrous mounds at the center of the free edge of each cusp. Three commissures radiate from the center of the valve, giving the appearance of a "peace sign." Approximately 1% to 2% of aortic valves are bicuspid.

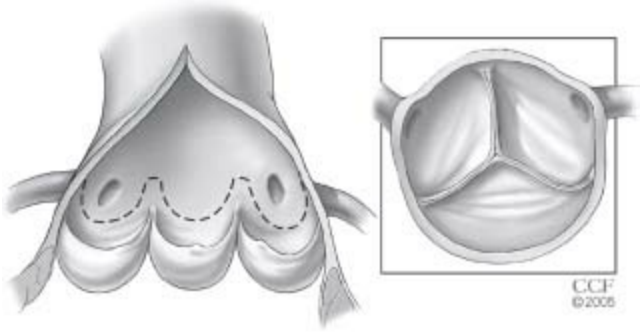

FIGURE 3.8 Side and top views of the aortic valve.

GREAT VESSELS

Vena Cavae

These large veins return blood from the body to the right atrium (see Fig. 3.1). The superior vena cava is formed by the juncture of the left and right innominate veins. The azygos vein enters the superior vena cava in the midthorax. Half of the superior vena

cava is contained within the pericardium. The superior vena cava enters the upper portion of the right atrium, where its blood flow is directed toward the tricuspid valve. The inferior vena cava is larger than the superior vena cava. It receives blood from the lower body and from the abdominal viscera via the hepatic veins. Only 1 to 2 cm of the inferior vena cava is enclosed by the pericardium. The inferior vena cava enters the right atrium on the lower lateral free wall, where its blood flow is directed by the eustachian valve toward the fossa ovalis.

Pulmonary Arteries

The main pulmonary artery is the most anterior cardiac vessel, located entirely within the pericardium (see Fig. 3.1). It arises from the base of the right ventricle, courses superiorly and posteriorly below the aortic arch, where it bifurcates into the left and right pulmonary arteries. The right pulmonary artery is slightly larger and longer than the left, dividing into a superior ascending branch and an inferior descending branch. The left pulmonary artery passes over the left mainstem bronchus and subdivides into a variable number of branches that parallel bronchial bifurcations. The left pulmonary artery is connected to the descending thoracic aorta by the ligamentum arteriosum (ductal artery ligament), a remnant of the ductus arteriosus.

Pulmonary Veins

Four pulmonary veins, the right and left, superior and inferior, return oxygenated blood from the lungs to the left atrium (see Fig. 3.5). Occasionally, five or six pulmonary veins may be found. Atrial muscle extends for 1 to 3 cm within the pulmonary veins and functions as a sphincter to prevent reflux of blood during atrial systole.

The Aorta

The aorta arises from the aortic fibrous ring and passes superiorly and to the right as the ascending aorta (Fig. 3.9). The proximal aorta (aortic root) is dilated and contains the aortic valve and the sinuses of Valsalva. The coronary arteries, the first two branches of the aorta, arise from the left and the right sinus of Valsalva, respectively. The aortic root measures approximately 3 cm at the annulus. The sinotubular junction, at the top of the sinuses of Valsalva, separates the aortic root (sinus portion) from the tubular ascending aorta. The proximal two-thirds of the ascending aorta is located within the fibrous pericardium. In the upper thorax, the aorta courses to the left and posteriorly, forming the transverse aortic arch. Three large vessels arise from the transverse aortic arch: the right innominate (brachiocephalic) artery, the left carotid artery, and the left subclavian artery. The aorta passes over the left pulmonary artery and then descends through the posterior mediastinum to the left of the midline. The ligamentum arteriosum (ductal artery ligament) is the remnant of the ductus arteriosus that is connected to the left

pulmonary artery. In the thorax, the aorta gives rise to 12 pairs of intercostal arteries, the anterior spinal artery, and several bronchial arteries. It passes through the diaphragm, where it narrows to approximately 1.75 cm, and bifurcates into the iliac arteries at the level of the fourth lumbar vertebra.

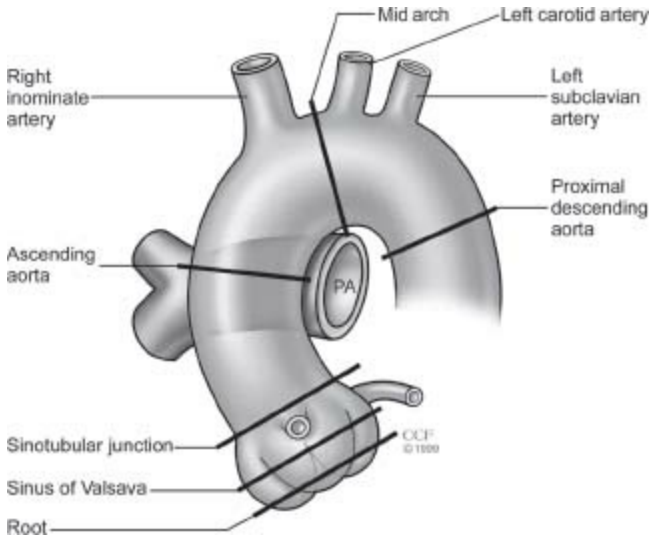

FIGURE 3.9 Aortic valve, thoracic aorta, and arch vessels.

Coronary Arteries

The coronary arteries are the first branches of the aorta, located on the surface of the heart in the AV and interventricular grooves between the cardiac chambers. They are often covered with fat, which is proportional to body fat and aging. The coronary arteries deliver oxygenated blood to the underlying heart muscle.

The right coronary artery is located in the right AV groove. It forms a C-shaped structure when viewed from the left, and an L-shaped structure when viewed from the right (Figs. 3.10 and 3.11). The right coronary artery bifurcates at the crux of the heart into a posterior descending branch and an AV branch. The posterior descending artery (PDA) follows the posterior interventricular groove and provides blood supply to the inferior (diaphragmatic) portion of interventricular septum. The AV branch passes beyond the crux of the heart, where it gives off branches that perfuse the posterolateral left ventricular myocardium. A dominant right coronary artery provides a posterior descending branch, an AV branch, and posterior ventricular or posterolateral branches. A codominant (balanced) right coronary artery provides a posterior descending branch but does not perfuse the posterior left ventricular myocardium. A nondominant right coronary artery is a small vessel that does not reach the crux of the heart and does not have posterior descending, AV, or posterior ventricular branches. The size of the right coronary artery is inversely proportional to the size of the circumflex branch. The first branch of the right coronary artery is the conus branch, which perfuses the right ventricular outflow tract. It has a “hook” or “question mark” shape when viewed from

the right. Fifty percent of hearts have a separate origin of the conus branch from within the right sinus of Valsalva. The second branch of the right coronary artery is the branch to the sinoatrial (SA) node. This thin vessel courses superiorly and posteriorly, supplying blood to the right atrium and the SA node. It has the appearance of a "tree branch" or an "antler" when viewed angiographically. The right coronary artery has a variable number of right atrial marginal branches and right ventricular marginal branches that arise perpendicularly from the main vessel. The AV nodal artery arises from the AV branch at the crux of the heart and courses superiorly.

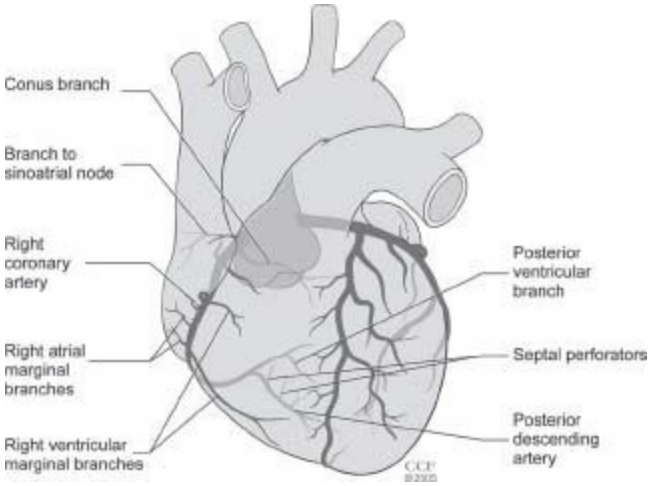

FIGURE 3.10 Right coronary artery, left anterior oblique view.

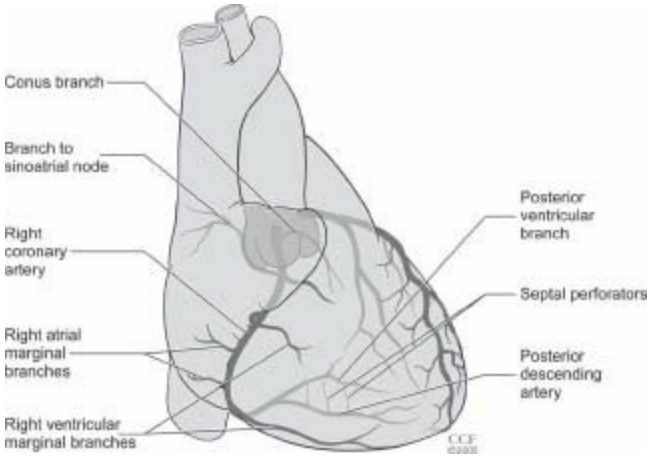

FIGURE 3.11 Right coronary artery, right anterior oblique view.

The left main trunk varies from 3 to 10 mm in diameter and from 1 to 4 cm in length (Figs. 3.12 and 3.13). Occasionally the left main trunk is absent, whereby the left anterior descending branch and the left circumflex branch arise from separate but adjacent orifices within the left sinus of Valsalva. The left main trunk trifurcates in 30% of hearts into the left anterior descending, a ramus branch, and the left circumflex branch.

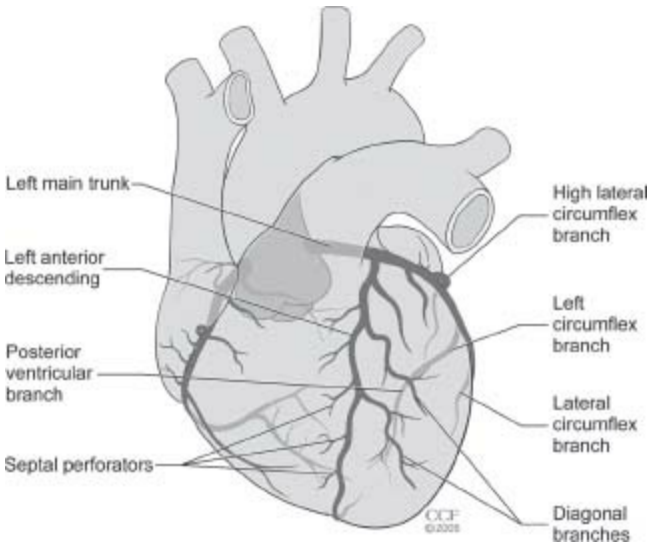

FIGURE 3.12 Left coronary artery, left anterior oblique view.

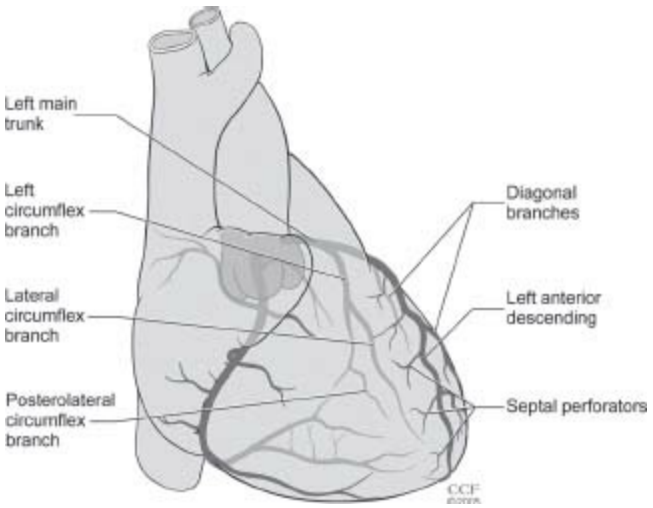

FIGURE 3.13 Left coronary artery, right anterior oblique view.

The left anterior descending branch, located in the anterior interventricular groove, supplies blood to the anterolateral wall of the left ventricle and most of the interventricular septum. It reaches the cardiac apex in 80% of hearts. The left anterior descending provides four to seven septal perforators, which supply blood to the anterior interventricular septum, and two to three diagonal branches, which perfuse the anterolateral wall of the heart.

The left circumflex coronary artery arises from the left main trunk and supplies blood to the lateral wall of the heart and to the left atrium. The branches of the circumflex sometimes are referred to as obtuse marginal branches. A different classification system describes these branches in relation to their position on the left ventricle: high lateral, lateral, posterolateral, posterior ventricular, and posterior descending. The size of the left circumflex is inversely proportional to the size of the right coronary artery.

Cardiac Veins

The venous system of the heart consists of the coronary sinus, cardiac veins, and the thebesian venous system (Fig. 3.14). The cardiac veins generally follow the anatomic course of the coronary arteries, and return blood to the right atrium via the coronary sinus. The great cardiac vein parallels the left anterior descending coronary in the anterior interventricular groove. It drains upward from the apex toward the base and then passes leftward and posteriorly, paralleling the left circumflex artery, and entering the coronary sinus at its origin. The posterior vein of the left ventricle drains into the distal end of the coronary sinus. The middle cardiac vein, located in the posterior interventricular groove adjacent to the posterior descending coronary artery, drains into the distal coronary sinus. The small cardiac vein parallels the course of right coronary artery and drains into the distal coronary sinus. There are 3 to 12 smaller anterior cardiac veins, some of which drain directly into the right atrium. Many small thebesian veins drain directly into cardiac chambers, most commonly the right atrium and the right ventricle. Venous anatomy is extremely variable, with multiple venous anastomoses. The coronary sinus is the largest cardiac vein, measuring approximately 2 to 5 cm in length and 3 to 5 mm in diameter. It is located in the posterior AV groove and drains into the right atrium.

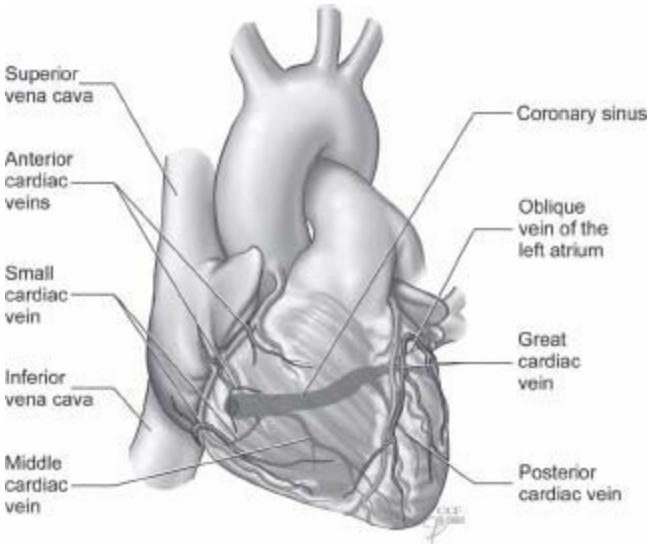

FIGURE 3.14 Frontal view of the cardiac veins.

Cardiac Lymphatic System

A plexus of lymphatic channels is located throughout the myocardium of all four cardiac chambers, draining outward from the endocardium toward the epicardium. Larger lymphatic channels follow the paths of the coronary arteries and veins and coalesce to forms a large lymphatic trunk that courses over the left main coronary artery and below the left pulmonary artery, where it drains into pretracheal lymph nodes and then into the

thoracic duct.

THE CONDUCTING SYSTEM

The conducting system consists of the SA node, the AV node, the His bundle, the right and left bundles, and the Purkinje fibers (Fig. 3.15). The components of the conducting system consist of modified myocardial cells that either have spontaneous automaticity or conduct electrical impulses throughout the myocardium to initiate contraction. The SA and the AV nodes have spontaneous automaticity, whereas the other components conduct electrical impulses rapidly.

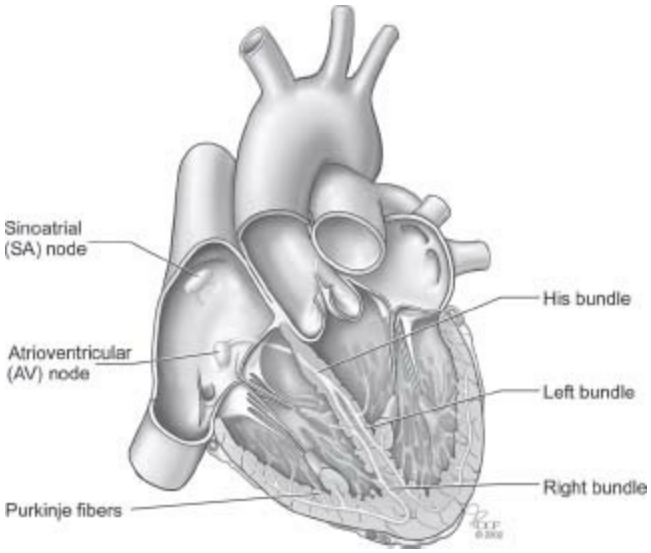

FIGURE 3.15 Cardiac conducting system.

The SA (sinus) node is a histologically distinct structure located in the roof of the right atrium between the superior vena cava and the right atrial appendage. It spontaneously depolarizes 60 to 90 times a minute, functioning as the heart's intrinsic pacemaker. Sinus node depolarization is more rapid in children and during exercise. The blood supply to the SA node consists of a central artery arising from the right coronary artery in 60% of hearts and from the left circumflex branch in 40%. There are no histologically distinct pathways between the SA and the AV nodes. Conduction spreads via ordinary atrial myocardium rather than specialized bundles of conducting fibers.

The AV node is located inferomedially within the right atrium, beneath Koch triangle, above the septal leaflet of tricuspid valve, and near the orifice of the coronary sinus. The AV node regulates the number of impulses that pass to the ventricles. It also has spontaneous depolarization, usually occurring at a rate of 40 to 60 per minute. AV nodal function is modulated by the autonomic nervous system, parasympathetics via the vagus nerve, and sympathetics via the sympathetic trunk. The AV node has a dual blood

supply arising from the AV branch of the dominant coronary artery and the first septal perforator of the left anterior descending. Impulses from the AV node pass to the His bundle located in the upper portion of the interventricular septum. Abnormal bypass tracks are strands of muscular tissue connecting the atrium and the ventricle, bypassing the AV node, originally described by Kent, Mahaim, and James.

The His bundle is a continuation of the AV node within the central fibrous body, which conducts electrical impulses rapidly. At the top of the muscular interventricular septum, the His bundle divides into the right and left bundles.

The right bundle courses down the septum, passes across the right ventricle within the moderator and septal bands toward the anterior papillary muscle, and extends upward to the right ventricular outflow tract. The left bundle courses down the septum and fans out into multiple conduction fibers to the papillary muscles and the rest of the left ventricle. False chordae may contain conduction fibers from the left bundle. The bundle branches have a dual blood supply arising from septal perforators of the left anterior descending and the posterior descending arteries.

Purkinje fibers are a terminal network of electrical conducting fibers, which initiate cardiac contraction in the myocytes. Muscular contraction starts in the papillary muscles and then spreads from the endocardial to epicardial segments of the apex upward to the outflow tract.

INNERVATION OF THE HEART

The heart receives parasympathetic and sympathetic afferent and efferent nerves. Preganglionic sympathetic nerves are located in upper thoracic spinal cord. Second-order neurons are found in cervical sympathetic ganglia. Postganglionic fibers terminate in the heart and great vessels. Parasympathetic fibers are located within the vagus nerves. They synapse with second-order neurons in ganglia located on the wall of the heart and great vessels. Sympathetic and parasympathetic fibers are contained within two cardiac nerve bundles. These nerve fibers course down the AV groove as the right coronary plexus and down the interventricular groove as the left coronary plexus.

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QUESTIONS AND ANSWERS

Questions

1. Which of the following structures are not found in the right atrium?
   a. Tendon of Todaro
   b. Moderator band
   c. Koch triangle
   d. Pectinate muscle
2. Which of the following statements about the pericardium is false?
   a. The pericardium contains 80 to 90 mL of pericardial fluid.
   b. It is connected to the diaphragm, sternum, and pleurae.
   c. It encloses the entire main pulmonary artery.
   d. The ligament of Marshall is a pericardial fold that contains the remnant of the embryonic left superior vena cava.
3. Which of the following statements about coronary arteries is true?
   a. The conus branch arises from a separate orifice in the aorta in 10% of patients.
   b. The left main trunk trifurcates into a left anterior descending, ramus branch, and left circumflex in 75% of patients.
   c. The sinoatrial (SA) nodal artery usually arises from an atrial branch of the left circumflex coronary artery.
   d. A dominant right coronary artery gives rise to a posterior descending artery (PDA), an atrioventricular (AV) branch, an artery supplying the AV node, and a posterior ventricular branch.
4. Which of the following statements about false chordae is true?
   a. False chordae are found in 1% of normal hearts.
   b. False chordae connect the upper septum with the mitral valve leaflets.
   c. False chordae often contain conducting fibers.
   d. False chordae are identified only at autopsy.
5. Which of the following statements about the tricuspid valve is true?
   a. It has three leaflets: anterior, lateral, and posterior.
   b. It is the largest heart valve.
   c. It is the most anterior heart valve.
   d. The posterior leaflet is the largest and most mobile.
6. A knife wound to the anterior chest is most likely to lacerate which cardiac structure?
   a. The left ventricle
   b. The right ventricle
   c. The left atrium
   d. The right atrium
7. Which statement about cardiac valves is false?

a. Approximately 1% to 2% of aortic valves are bicuspid.
b. The aortic valve normally leaks a small amount.
c. The pulmonic valve is the most anterior heart valve.
d. Approximately 100 chordae are attached to the mitral valve.

8. Which statement about the cardiac chambers is false?
a. The right atrium is smaller than the left atrium.
b. The right ventricle is smaller than the left ventricle.
c. The right ventricle is the most anterior chamber of the heart.
d. The left ventricle is thicker at the base than at the apex.

9. Which statement about the great vessels is false?
a. The main pulmonary artery is located entirely within the pericardium.
b. The pulmonary veins contain atrial muscle.
c. The ligamentum arteriosum connects the aorta to the left pulmonary artery.
d. The inferior vena cava is smaller than the superior vena cava.

10. Which statement about the cardiac conducting system is false?
a. There are no histologically distinct conducting pathways between the SA and the AV nodes.
b. The AV node is located in the upper interventricular septum just below the tricuspid valve.
c. The first site of electrical activation in the left ventricle is in the papillary muscles.
d. False chordae may contain conduction fibers from the left bundle.

Answers

1. Answer B: The moderator band, located in the right ventricle, is a muscular bridge that connects the distal septum and the right ventricular free wall at the anterior papillary muscle. The tendon of Todaro is a fibrous band located between the valves of the inferior vena cava and the coronary sinus in the right atrium. Koch triangle is located in the lower medial portion of the right atrium, overlying the AV node and the proximal His bundle. Pectinate muscles arise from the crista terminalis and course as bands on the right atrial free wall.

2. Answer A: The pericardium contains 10 to 50 mL of pericardial fluid. It is attached to the central tendon of the diaphragm, posterior sternum, and laterally to the pleurae. It encloses the heart, portions of the vena cavae, most of the ascending aorta, the main pulmonary artery, and pulmonary veins. The ligament of Marshall is a pericardial fold containing the remnant of the embryonic left superior vena cava.

3. Answer D: A dominant right coronary artery usually is a large vessel that crosses the crux of the heart to perfuse the posterolateral aspect of the left ventricle. The conus branch arises from a separate orifice in the aorta in 50% of patients. The SA nodal artery arises from the right coronary artery in 60% of patients and from the left circumflex in 40%. The left main trunk gives rise to a ramus branch in 30% of patients.

4. Answer C: Many false chordae contain extensions of left ventricular conducting fibers. They are found in 50% of normal hearts. False chordae may connect walls, papillary muscles, and the septum, but are not attached to mitral valve leaflets. They often cross the left ventricular outflow tract and can be identified by echocardiography.

5. Answer B: The tricuspid valve is the largest heart, whereas the pulmonic valve is the most anterior. The tricuspid valve consists of three leaflets, anterior, septal, and posterior. The anterior leaflet is the largest and the most mobile. The posterior leaflet is the smallest, whereas the septal leaflet is the least mobile and occasionally absent.

6. Answer B: The right ventricle is the most anterior chamber of the heart and the most likely to be injured by trauma. A small portion of the left ventricle is located along the left cardiac border. The right atrium occupies the right border of the heart and the left atrium is a left upper posterior chamber.

7. Answer B: All of the other valves leak a small amount but any regurgitation at the aortic valve is considered pathologic.

8. Answer A: The left atrium is smaller than the right atrium but has thicker walls and higher pressure.

9. Answer D: The interior vena cava is larger than the superior vena cava. It receives blood from the lower body and from the abdominal viscera via the hepatic veins.

10. Answer B: The AV node is located inferomedially within the right atrium, beneath Koch triangle, above the septal leaflet of the tricuspid valve, near the orifice of the coronary sinus.

CHAPTER

Cardiovascular Physiology: Flow–Volume Loops

Ashley M. Lewis and Michael D. Faulx

Understanding the factors that influence myocardial performance in normal and pathophysiologic states is essential for the cardiology boards. Myocardial performance is determined by the combined effects of ventricular preload, afterload, and contractility. A fourth factor, heart rate (HR), also plays a role in myocardial performance by influencing the duration of each cardiac cycle and the number of cardiac cycles per minute. Knowledge of how each of these factors responds to various disease states and therapeutic interventions provides the foundation upon which the practice of cardiovascular medicine is built.

DETERMINANTS OF MYOCARDIAL PERFORMANCE

Preload

Preload is the hemodynamic load on the myocardial wall (or the degree of stretch on the myocardial fiber) at the end of diastole, just prior to isovolumic contraction. The relationship between preload and myocardial performance was first described by physiologists Otto Frank and Ernst Starling over a century ago and is represented graphically by the Frank–Starling curve, which is discussed in greater detail in the next section. There are several experimental and clinical measures of left ventricular (LV) preload including (a) end-diastolic volume (EDV), (b) end-diastolic pressure (EDP), (c) wall stress at end diastole, and (d) end-diastolic sarcomere length. Conceptually, EDV is the most meaningful measure of ventricular preload. Clinically, EDP (by invasive measure of left ventricular end-diastolic pressure [LVEDP] or its surrogate, the pulmonary capillary wedge pressure, PCWP) is the most applicable.

Preload is predominantly determined by factors that influence venous return to the heart. Therefore, conditions that increase venous return such as volume resuscitation, supine body position, atrial contraction, skeletal muscle contraction, and decreased intrathoracic pressure (the result of deep inspiration) will increase preload, whereas

conditions that decrease venous return will decrease preload. Examples of such conditions include decreased intravascular volume (severe anemia, dehydration, diuresis), venodilators (nitrates), upright posture, loss of atrial contraction (atrial fibrillation), increased intrathoracic pressure (Valsalva maneuver, positive pressure ventilation), and increased intrapericardial pressure (pericardial tamponade or constriction).

Afterload

Afterload is the resistance that the ventricle must overcome during contraction in systole. At the cellular level, it may be described as the tension in a myocardial fiber during active contraction. The relationship between afterload and myocardial performance is predicted by the force–tension relationship and is discussed in greater detail in the next section. Although there are several surrogate measures of afterload, the most commonly used are (a) central aortic pressure, (b) systemic arterial pressure, (c) systemic vascular resistance (SVR), (d) arterial impedance, (e) myocardial peak wall stress (affected by LV geometry), and (f) LV pressure. Conceptually, myocardial wall stress is the most applicable measure of afterload because it accounts for the influence of LV geometry in addition to LV pressure (see below). Clinically, measures of systemic pressure or SVR are more practical.

Myocardial peak wall stress reflects the maximum force required for the myocardium to overcome resistance and effectively expel blood during systole. This depends on the intraventricular pressure and the geometry of the left ventricle. Wall stress (σ), expressed in force per unit area of myocardium, is related to intraventricular pressure according to Laplace law:

$$\sigma = \frac{P \times r}{2 \times h}$$

where P is ventricular pressure, r is ventricular chamber radius, and h is ventricular wall thickness.

SVR and LV geometry are the primary determinants of afterload. However, valvular pathology such as aortic stenosis can influence afterload. Afterload is increased by increased blood pressure (hypertension, vasoconstricting drugs), increased LV radius (LV dilatation), reduced arterial elastance (atherosclerotic “stiff” arteries), and decreased wall thickness (eccentric hypertrophy, advanced cardiomyopathy). Afterload is decreased by decreased blood pressure (vasodilator therapy), increased arterial elastance, and thicker, smaller LV cavities.

Contractility

Contractility refers to the intrinsic “vigor” of the cardiac muscle. When loading conditions (preload and afterload) remain constant, increased contractility results in

increased cardiac performance (stroke volume [SV]), whereas decreased contractility inhibits cardiac performance. The ejection fraction is a commonly used, though somewhat limited, surrogate for contractility. Contractility is a variable independent from loading conditions, whereas the ejection fraction can be affected by changes in preload and afterload. For this reason, the ejection fraction is really a better surrogate for SV, but since it does reflect contractility and has wide clinical availability, it remains the most popular surrogate for contractility. Contractility can be influenced by different drugs, and you are likely to encounter questions that are designed to assess your understanding of how drugs influence myocardial performance. Contractility (identified also as inotropy) is increased by drugs that alter the calcium/actin–myosin coupling mechanism. These drugs may be positive inotropes (catecholamines, phosphodiesterase inhibitors, digoxin) or negative inotropes (beta-blockers, centrally acting calcium channel blockers) (Table 4.1). The volume of myofilaments participating in the contraction process also has an effect on contractility. Contractility may increase in early aortic stenosis as the left ventricle hypertrophies, and it may decrease following the formation of scar after a myocardial infarction.

TABLE
4.1 Summary of Mechanisms of Action of Commonly Used Cardiovascular Drugs and Their Physiologic Effects

Drug	Receptors or Mechanisms of Action	Physiologic Effects
Phenylephrine	α	↑ afterload, usually no change in HR
Isoproterenol	β1 and β2	↑ contractility, ↑ HR, ↓ afterload
Norepinephrine	$\alpha > \beta$1 No β2	Marked ↑ afterload, modest ↑ CO
Epinephrine	β1, β2, and α ($\alpha > \beta$2 at high dose)	Low doses ↑ CO, ↓ SVR, Variable effects on MAP; higher doses ↑ SVR, ↑ CO
Dobutamine	β1 > β2, α	↑ CO, ↓ SVR, ↑ HR with or without a small reduction in BP
Dopamine (mcg/kg/min)	Dopa (low doses, <4) β1 (intermediate, 4–10) α (high doses, >10)	At moderate doses, ↑ contractility, ↑ HR ↑ CO; high doses (>10 μg/kg) cause vasoconstriction and ↑ SVR
Nitroprusside	Arterial, venous dilator	↓ preload, ↓ afterload
Nitroglycerin	Venous Ā arterial dilator	↓ preload Ā ↓ afterload
Hydralazine	Direct arterial vasodilator	↓ afterload, no effect on preload
Phentolamine	α antagonist	↓ afterload, ↑ contractility, ↑ HR
Furosemide	Diuretic	↓ preload
Milrinone	Phosphodiesterase inhibitor	Similar to dobutamine, no change in HR, ↓ pulmonary vascular resistance

HR, heart rate; CO, cardiac output; SVR, systemic vascular resistance; MAP, mean arterial pressure.

Heart Rate

HR is a contributor to myocardial performance by virtue of its influence on cardiac cycle length and the number of cardiac cycles per minute. The principal determinants of myocardial performance are preload, afterload, and contractility, reflected clinically in the SV, the volume of blood expelled from the heart during one cardiac cycle. However, global performance of the heart is generally measured by the ability of the heart to meet the metabolic demands of the body. This is reflected in the cardiac output (CO) or cardiac index, defined by the following:

$$\text{CO (L/min)} = \text{SV} \times \text{HR}$$

Cardiac index is simply the CO per unit of body surface area (BSA) (L/min/m^2).

Thus, for a given SV, a faster HR results in a higher cardiac index and a slower HR results in a lower cardiac index. Under certain circumstances, HR may also influence myocardial performance during a single cardiac cycle. For example, tachycardia in a patient with severe LV hypertrophy and abnormal relaxation might shorten diastolic filling time and prevent complete isovolumic relaxation, resulting in ineffective preloading. Conversely, bradycardia in a patient with severe aortic regurgitation may overload the left ventricle by allowing a greater volume of regurgitation during diastole. Both conditions may result in reduced cardiac performance and pulmonary congestion, though for different physiologic reasons.

Myocardial Performance

Myocardial performance reflects the ability of the heart to meet the metabolic demands of the body. There are many surrogate measures of myocardial performance, but CO is arguably the most complete. CO can be assessed both invasively (thermodilution, Fick calculation) and noninvasively (echocardiography, cardiac magnetic resonance imaging [MRI]). As mentioned previously, the ejection fraction is a reasonable measure of SV. On the cardiology boards, expect to see SV or CO used in reference to myocardial performance.

GRAPHIC ILLUSTRATION OF MYOCARDIAL PERFORMANCE

The concepts of preload, afterload, and contractility can be represented graphically by the use of Frank–Starling curves, force–tension curves, and pressure–volume (PV) loops, respectively. These graphics allow the reader to visualize the interplay between the components of myocardial performance and understand how individual disease states and interventions alter myocardial performance. Expect to see these on the cardiology boards.

Starling's Law and Frank–Starling Curves

Starling's law dictates that cardiac performance (defined by SV) increases as preload is increased. However, there is a nonlinear relationship between EDP (a measure of preload) and SV, as shown in Figure 4.1. When afterload and contractility are held constant, reduced preload (shift along the line to the left) will reduce SV while increased preload (shift along the line to the right) will increase SV. However, if optimal preloading conditions are exceeded, the SV will no longer increase in response to higher filling pressure, which is depicted by the plateau of the curve.

FIGURE 4.1 Frank–Starling curves. As preload increases, SV increases.

In addition to preload, ventricular contractility and afterload can influence Frank–Starling curves. When contractility is increased and preload is held constant, the SV increases (entire line shifts upward and to the left). When contractility decreases, the SV decreases in response (entire line shifts downward and to the right). When afterload increases while preload and contractility are held constant, the SV decreases (entire line shifts downward and to the right), while SV increases when afterload decreases (entire line shifts upward and to the left).

Force–Tension Curves

These curves describe the relationship between CO and afterload (Fig. 4.2). When preload and contractility are held constant, any decrease in afterload will produce an increase in SV (shift along the line to the left), whereas an increase in afterload will produce a comparable decrease in SV (shift along the line to the right). As with the Frank–Starling relationship, preload and contractility also influence the force–tension relationship. As preload increases for a given afterload, SV also increases (entire line shifts upward and to the right), whereas SV decreases if preload is decreased (entire line shifts downward and to the left). When contractility increases for a given afterload, the SV increases (entire line shifts upward and to the right). When contractility decreases, SV also decreases (entire line shifts downward and to the left).

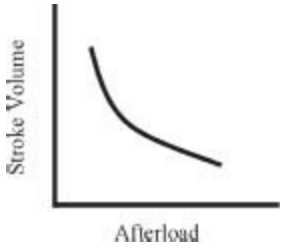


FIGURE 4.2 Force–tension curves. As afterload is reduced, SV increases.

Pressure–Volume Loops

If the ventricular volumes during one cardiac cycle are plotted against simultaneous pressures within the ventricle, a PV loop is constructed as shown in Figure 4.3. The PV loop is a rectangular illustration of the pressure and volume events that comprise a single cardiac cycle. The base of this rectangle is formed by the end-diastolic pressure–volume relationship (EDPVR), a line that describes the properties of the ventricle at the point of maximal diastolic relaxation. The EDPVR is nonlinear and analogous to the Frank–Starling curve since it illustrates the relationship between diastolic filling and myocardial performance. The end-systolic pressure–volume relationship (ESPVR) describes the systolic filling changes in the left ventricle. This curve is linear, beginning at the intersection of the pressure and volume axes, and touching the PV loop at the point of maximal end-systolic activation, when the aortic valve closes prior to isovolumic relaxation. Together these two pressure–volume relationships are the primary components of the PV loop.

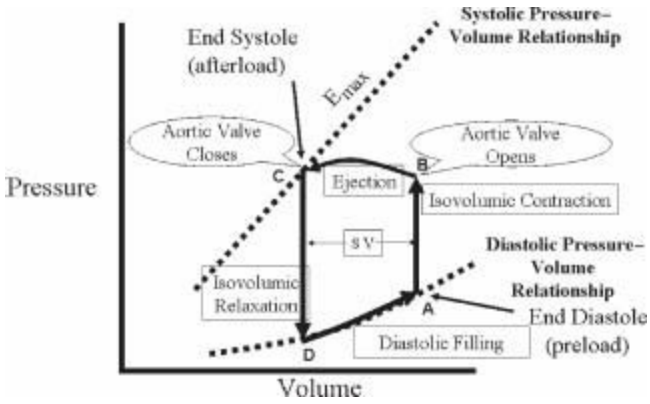


FIGURE 4.3 PV loops. Time A is the onset of systole, immediately following the closure of the mitral valve. This is followed by the period of isovolumic contraction (change in pressure with no change in volume). The aortic valve opens at point B, and the point of maximal ventricular activation is reached at point C, after which the aortic valve closes. This is followed by a period of isovolumic relaxation (change in pressure with no change in volume). The mitral valve opens at point D, followed by the filling of the LV. Systole includes the time period of isovolumic contraction and ejection (point A to C). Diastole includes the period of isovolumic relaxation and filling (point C to A). The dotted lines represent the end-systolic and EDPVR, which represent the boundaries of the PV loops.

INTERPRETING THE PRESSURE–VOLUME LOOP

Ventricular Volumes

The maximum volume in the ventricle during the cardiac cycle is the EDV, the point on the x-axis where the mitral valve closes and isovolumic contraction begins. The minimum LV volume is the end-systolic volume (ESV), the point on the x-axis at the end of isovolumic relaxation prior to the opening of the mitral valve. The SV is simply the difference between the two volumes:

$$SV = EDV - ESV$$

Intracardiac Pressures

As shown in Figure 4.3, point B represents the point at which the ventricle begins to eject blood into the vasculature (opening of the aortic valve). At this time, the ventricular pressure just exceeds aortic pressure. During the ejection phase, aortic and ventricular pressures are nearly equal, so the point of greatest pressure on the loop represents the greatest pressure in the aorta and is equal to the systolic blood pressure (SBP). End-systolic pressure (P_{es}) is the pressure on the PV loop at the end of systole and is only slightly less than the maximal pressure (SBP). Point D, following isovolumic relaxation, represents the pressure in the left atrium (LAP) at the time the mitral valve opens. EDP is represented at the end of diastole (point A) and is influenced by the compliance of the chamber.

Compliance

Compliance is the change in volume for a given change in pressure or, in mathematical terms, the reciprocal of the derivative of EDPVR. EDPVR is nonlinear and hence compliance varies with volume. Change in volume for a given change in pressure is greater at low volumes (greater compliance) than at higher volumes (lower compliance). Changes in compliance are related to structural and pressure changes of the heart, pericardium, and thorax.

Elastance and Contractility

Defined as the linear relationship between the change in pressure for a given change in volume at end systole on the ESPVR, elastance is represented by the slope, E_{max} or E_{es}. Elastance is a surrogate for contractility because it is independent of external conditions such as preload or afterload.

Stroke Work

Stroke work represents the work of the heart during each heart beat and is represented by the area of the PV loop.

SUMMARY OF THE ACTIONS OF THE AUTONOMIC NERVOUS SYSTEM ON THE COMPONENTS OF MYOCARDIAL PERFORMANCE

α1 stimulation: ↑ afterload, ↑ preload
β1 stimulation: ↑ contractility, ↑ HR
β2 stimulation: ↓ afterload

VALVULAR HEART DISEASE AND PRESSURE–VOLUME LOOPS

The PV loops in various valvular diseases are depicted in Table 4.2 and Figure 4.4.

TABLE
4.2 Valvular Heart Disease: PV Loops

Valve Condition	Afterload	Preload	Contractility (Early)	Contractility (Late)
Aortic stenosis	↑	↔	↑	↓
Aortic regurgitation	↑	↑	↔	↓
Mitral regurgitation	↓	↑	↑	↓
Mitral stenosis	↔	↓	↔	↔

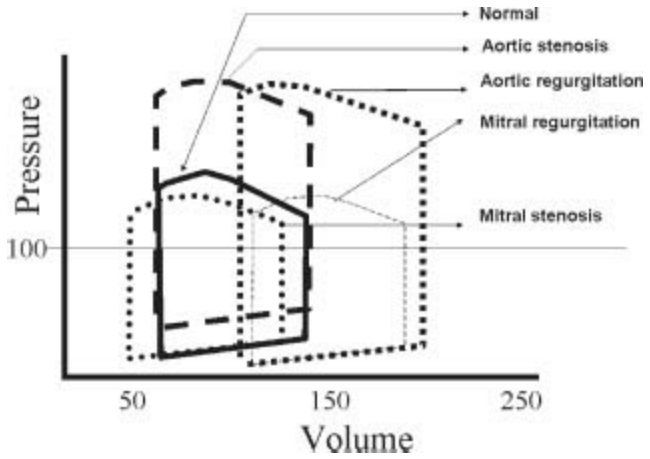


FIGURE 4.4 PV loops in various valvular disease states, with curves as depicted here for aortic and mitral regurgitation representing decompensated states.

CARDIOMYOPATHY AND PRESSURE–VOLUME LOOPS

The PV loops in various cardiomyopathies (CM) are depicted in Table 4.3 and Figure 4.5.

TABLE

4.3 Cardiomyopathy: PV Loops

Condition	ESV	EDV	Contractility
Dilated	↑	↑	↓
Hypertrophic	↓	↓	↑
Restrictive	↓ or ↔	↓ or ↔	↓ or ↔

ESV end-systolic volume; EDV, end-diastolic volume.

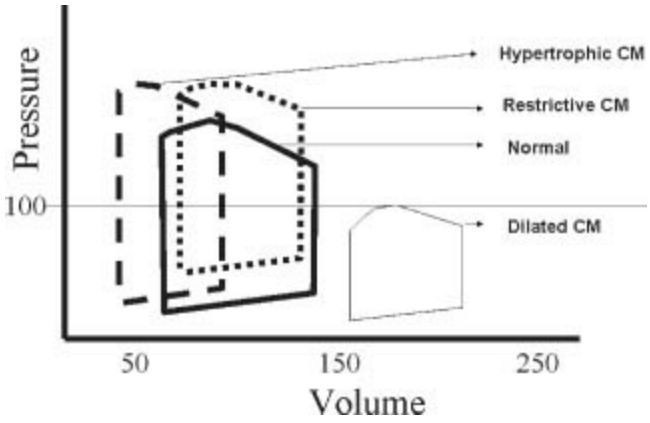
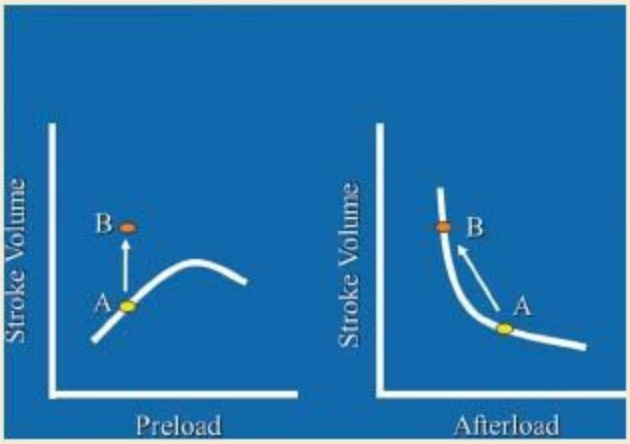


FIGURE 4.5 PV loops in various cardiomyopathies.

QUESTIONS AND ANSWERS

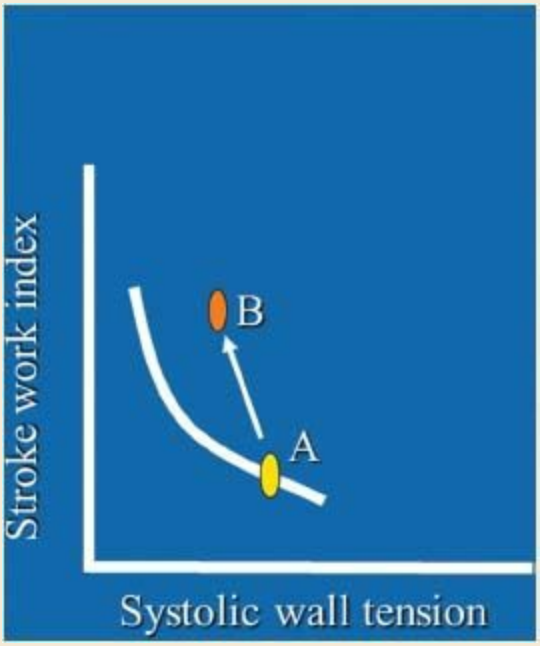
Questions

1. Which of the following medications will take this patient from point A to point B on the Frank–Starling and force–tension curves shown?



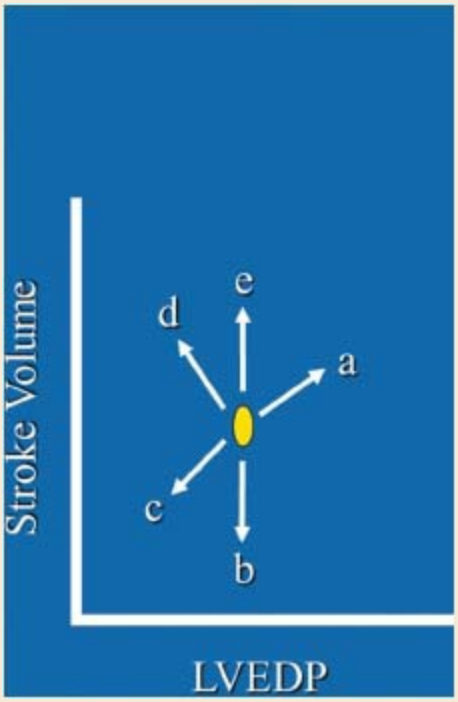
a. Propranolol
b. Norepinephrine
c. Hydralazine
d. Phenylephrine
e. Furosemide

2. Which of the following medications will take a patient from point A to point B on the force–tension curve shown?



a. Epinephrine
b. Phenylephrine
c. Furosemide
d. Isoproterenol
e. Digitalis

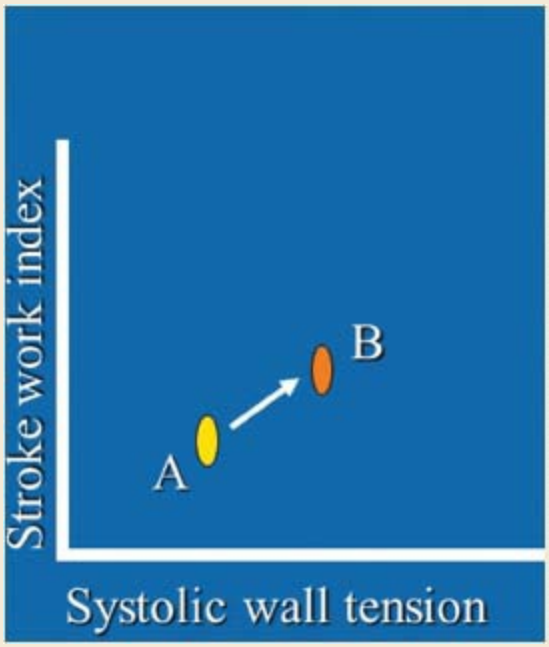
3. A patient with congestive heart failure is started on oral captopril. Which direction would this patient move on the Frank–Starling plot shown?



a.
b.
c.

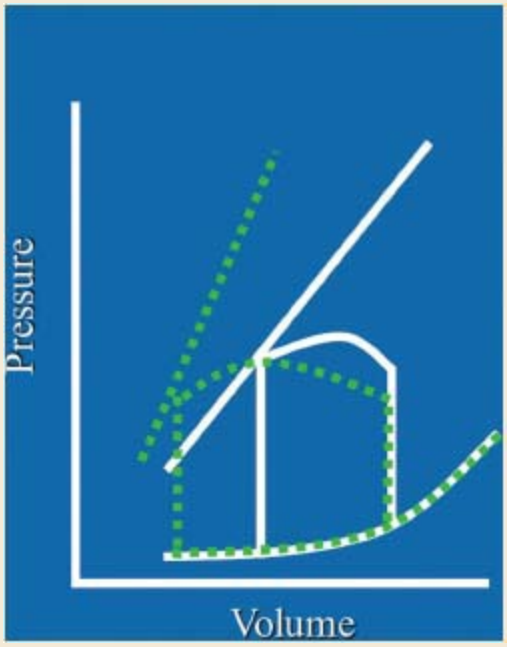
d.
e.

4. Which of the following medications will take the patient from point A to point B on the curve shown?



a. Norepinephrine
b. Phenylephrine
c. Furosemide
d. Isoproterenol
e. Digitalis

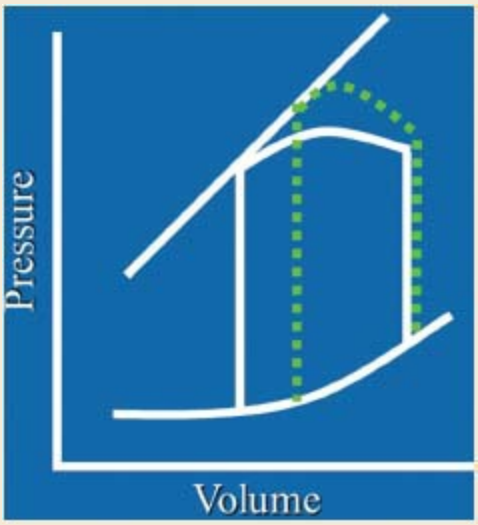
5. Which of the following medications will cause the indicated change (solid loop to dotted line) on the flow–volume loop shown?



a. Norepinephrine
b. Nitroprusside
c. Milrinone
d. Hydralazine

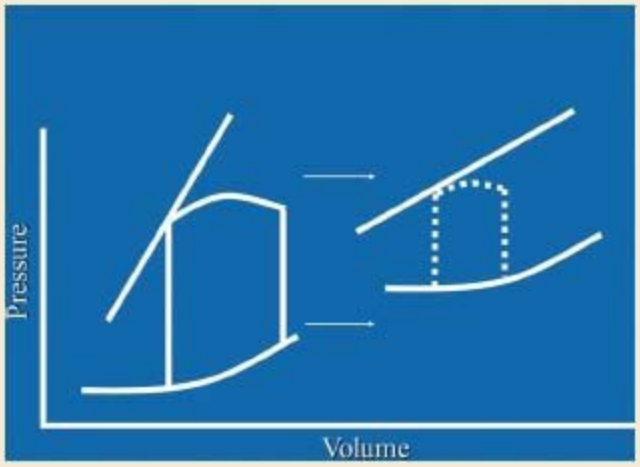
e. Phenylephrine

6. Which of the following medications, administered acutely, will shift the pressure–volume (PV) loop as outlined below (from the solid line to the dotted line)?



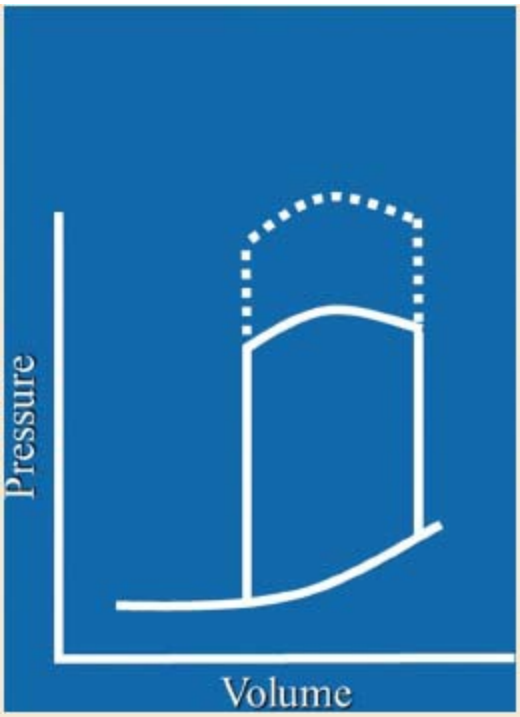
a. Phenylephrine
b. Captopril
c. Hydralazine + nitrates
d. Digitalis + Intravenous fluids (IVF)
e. Epinephrine

7. Compared to the normal PV loop shown (solid lines), the PV loop to the right (dotted lines) would best reflect which of the following conditions?



a. Hypertrophic cardiomyopathy
b. Restrictive cardiomyopathy
c. Dilated cardiomyopathy
d. Pericardial constriction
e. Mitral stenosis

8. Which of the following valvular disease states would change the PV loop in the manner shown (solid lines to dotted lines)?



a. Mitral regurgitation
b. Mitral stenosis
c. Aortic regurgitation (early)
d. Aortic stenosis (early)
e. Restrictive cardiomyopathy

9. What is not a determinant of myocardial performance?
a. Compliance
b. Heart rate (HR)
c. Preload
d. Afterload
e. Contractility

10. Which parameter is used in Laplace law to calculate left ventricular (LV) wall stress?
a. Left atrial radius
b. LV wall thickness
c. Left atrial pressure
d. Right ventricular wall thickness
e. Right atrial pressure

Answers

1. Answer C: Hydralazine reduces afterload and increases stroke volume (SV) without changing preload. Propranolol acutely reduces contractility and would not be expected to improve SV. Norepinephrine and phenylephrine both increase afterload. Furosemide reduces preload.

2. Answer D: Isoproterenol reduces afterload while increasing contractility. Epinephrine and phenylephrine both increase afterload. Furosemide does not affect afterload. Digitalis increases contractility but does not influence afterload.

3. Answer D: Captopril reduces both afterload and preload. At a given contractility, it would be expected to improve SV. Preload also decreases with c but so does SV (as in diuresis, nitrates). Preload is unchanged with b and e. The decreased SV with b could be seen with an agent such as phenylephrine. The increased SV of e could be seen with a pure afterload reducer like hydralazine. Preload and SV increase with a, which might occur with IV hydration.

4. Answer A: Norepinephrine increases afterload by its effects on α1 receptors while increasing

contractility by its action on β1 receptors. Phenylephrine increases afterload but should not improve SV. Furosemide does not increase afterload. Isoproterenol and digitalis can improve SV, but neither increases afterload.

5. Answer C: Milrinone increases contractility and decreases afterload, resulting in a greater SV. Norepinephrine may increase contractility but also increases afterload. Nitroprusside reduces afterload and preload but does not affect contractility. Hydralazine reduces afterload and improves SV but does not affect contractility. Phenylephrine increases afterload and does not improve SV.

6. Answer A: Phenylephrine increases afterload more than it increases preload and would be expected to reduce SV as shown. Captopril and hydralazine would reduce afterload and likely improve SV. Epinephrine would increase contractility and SV and can increase afterload at higher doses, but we would also expect to see increased contractility. Digitalis would also increase contractility, and IV fluids would increase preload as well.

7. Answer C: In dilated cardiomyopathy, the ventricle operates at higher filling pressures with greater afterload. SV and contractility are reduced, as depicted. Hypertrophic cardiomyopathy would be associated with a "spike and dome" pattern of early increased systolic pressure followed by abrupt decrease before return of systolic ejection in mid-late systole. There should be no major change in preload. Contractility is usually increased, and SV would be preserved or augmented. Restrictive cardiomyopathy and pericardial constriction can both result in lower SVs, but afterload is generally normal or reduced. There would also be early equalization of the diastolic pressure–volume curve. Mitral stenosis would be associated with reduced SV secondary to reduced preload; afterload and contractility would be unaffected.

8. Answer D: Early aortic stenosis is characterized by significantly increased afterload and increased LV systolic pressure with increased contractility and preserved SV, as shown. The increased contractility is the result of greater LV mass produced by compensatory hypertrophy. In later stages, the LV begins to dilate, increasing afterload more with a drop in contractility and SV. Preload eventually rises. Mitral regurgitation would be associated with increased diastolic filling pressure. Contractility is preserved or enhanced (at least initially) with decreasing LV systolic pressure that is proportional to the regurgitant volume. SV decreases as the regurgitant volume increases. Mitral stenosis would produce an underfilled ventricle with low SV and normal afterload. Early aortic regurgitation would greatly increase diastolic filling pressure with increased contractility and normal to increased SV. Over time, contractility would decrease and afterload would increase as the LV dilates.

9. Answer A: Myocardial performance is determined by contractility, HR, preload, and afterload. Although compliance does have an effect on preload, it is not a direct determinant of myocardial performance.

10. Answer B: LV wall thickness. The components that are used in Laplace law to calculate wall stress include LV pressure, LV radius, and LV wall thickness.

CHAPTER

Basic Cardiac Electrophysiology

Sergio G. Thal and Patrick J. Tchou

The aim of this chapter is to cover the main aspects of basic cardiac electrophysiology, developed in a review fashion for the Cardiovascular Medicine Board Examination. The information is organized as follows:

1. Basic action potential (AP) and ion channel implications
2. Electrical activity coupling mechanisms
3. Conduction system anatomy
4. Local electrophysiology characteristics of various conduction system components

MEMBRANE ACTION POTENTIAL

The initiation of the cell membrane AP is the first event in a process that ends with a cardiac contraction. Grossly, myocardial cells can be divided into those dependent on sodium ions (Na+) or calcium ions (Ca^{2+}) to drive AP depolarization.

Sodium-Dependent Cells

Each AP starts with net movement of ions across the cell membrane. In a steady state, the membrane is polarized near -90 mV. The transmembrane ionic current is the result of the balance between many inward and outward ionic currents. The sodium channel is voltage sensitive. This means that the probability of the channel being open for transport of the sodium ion increases with increase of transmembrane voltage (toward zero). When a cell receives depolarizing current, sodium channels open and increase the inward current. When the inward current exceeds the total outward current, a rapid opening of sodium channels occurs that overwhelms any outward current, resulting in the rapid upstroke portion of the AP termed Phase 0 (Figs. 5.1 and 5.2).

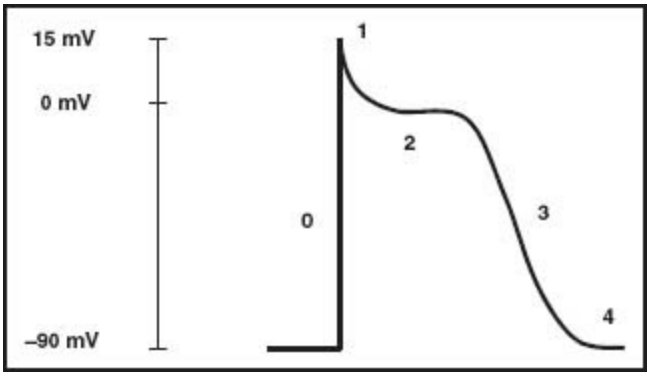


FIGURE 5.1 Action potential (sodium channel tissue). AP model of a sodium tissue. Numbers 0, 1, 2, 3, 4 delineate the different phases of the AP.

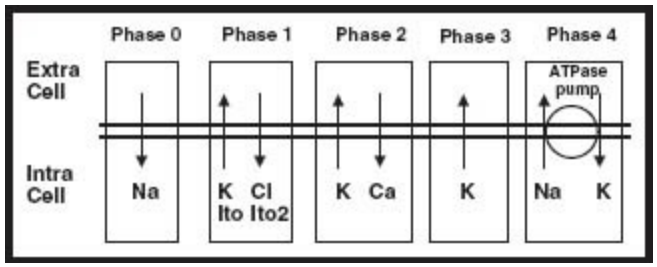


FIGURE 5.2 Main ion channel activities in AP phases. Na, sodium; K, potassium; Cl, chloride; Ca, calcium.

Sodium channels are characterized by a protein that works as a voltage-gated system. The active portion of this channel is the α subunit, which consists of a 2,000–amino acid glycoprotein. Properties of these channels include the following:

- Selective permeation
- Gating (activation and inactivation)
- Drug binding (local anesthetics)
- Susceptibility to many different neurotoxins

Levels of Na+ Channel Activity Regulation

1. Transcriptional regulation of Na^+ channel proteins is a mechanism to control Na^+ channel expression at a genomic level. This pattern of regulation can be influenced by feedback originating in the tissue electrical activity. The exact mechanism of this gene regulation remains incompletely understood.
2. Phosphorylation/dephosphorylation of the α subunit
3. Glycosylation. The regulation mechanism affects all channel subunits.

Abnormalities of the sodium channel can result in both the long QT syndrome and the Brugada syndrome.

Phase 1 (see Fig. 5.2) starts with the opening of a rapid outward potassium (K^+)

current called I_{to}. This determines a fast early repolarization with a prominent notch shape that approximates the membrane potential to 0 mV. These channels are characterized by outward movement of K^+ ions, which constitutes the principal source of membrane repolarization early during the AP. The channels inactivate soon after activation, although not as rapidly as the sodium current does. A dynamic interaction of four α subunits and an apparatus composed of a cytoskeleton and signaling complexes mainly form the K^+ pore. During the AP, these K^+ channels activate in response to membrane depolarization and inactivate in a timed manner. The channels are regulated by:

- Angiotensin II, which reduces I_{to} fast velocity
- α-Adrenergic stimulation, which reduces I_{to} fast velocity
- Hyperthyroidism, which increases I_{to} current density
- Aldosterone, which mediates a receptor-specific downregulation of I_{to}

In human pathophysiology, these channels provide an early repolarization current that can drive the transmembrane voltage toward resting membrane potential when the sodium current is dysfunctional. Thus, in Brugada syndrome, in which there is an abnormality in the sodium current that results in depressed sodium conductance, the I_{to} current may cause full repolarization in a portion of the myocardium early during the AP, resulting in a large voltage gradient between the repolarized part and parts that have more normal AP. Such gradients have been demonstrated in isolated tissue preparations to be capable of initiating reentrant wavefronts. These reentrant wavefronts can initiate polymorphic ventricular tachycardia or ventricular fibrillation.

The next portion of the AP, termed Phase 2 or the plateau phase (see Fig. 5.2), is the result of the balance of two different ion currents. During Phase 0, at the level of -40 mV, Ca^{2+} channels open, creating an inward Ca^{2+} current. This current, acting as an antagonist to the outward K^+ current, exerts its action by stabilizing transmembrane potential during the plateau phase. This phase concludes as the Ca^{2+} current declines by inactivation of L-type Ca^{2+} channels. These channels are also the critical initiators of cardiac excitation–contraction coupling through the initial increase in intracellular Ca^{2+}, which triggers the release of Ca^{2+} from the sarcoplasmic reticulum, which in turn provides a contraction signal to the cellular contractile elements. At a level of -40 mV of membrane potential, these channels rapidly activate, reaching a peak in approximately 2 to 7 milliseconds. Inactivation of the channel depends on time, membrane potential, and Ca^{2+} concentration.

Phase 3 (see Fig. 5.2), the repolarization phase, is dominated by the outward current of K^+ through the so-called “delayed rectifier” K^+ channels, which are responsible for

the return of the cell membrane to its resting polarized state. Two types of delayed rectifiers are important in the repolarization of human ventricular myocardium, a rapidly activating I_{Kr} and a more slowly activating I_{Ks} that peaks late in the AP, during Phase 3. Abnormalities in either of these two types of delayed rectifier K^+ channels can cause the long-QT syndrome.

Phase 4 (see Fig. 5.2) constitutes a stable polarized membrane. This stabilization of membrane AP after the descending Phase 3 is achieved mainly by the action of the voltage-regulated inward rectifiers (I_{K1}). These channels behave differently than the delayed rectifiers, which open in response to depolarization. The inward rectifier K^+ channels are opened at near-resting membrane potential, stabilizing the resting membrane potential near the K^+ equilibrium potential, but close in response to depolarization, facilitating the AP, hence the description of "inward rectifying."

Myocardial Tissues That Have Calcium-Dependent AP versus Tissues with Sodium Channels

The main differences between these two types of myocardial tissue can be found in Phases 4 and 0 of the AP. Calciumdependent tissues are the principal cellular component of the specialized conduction system and the sinus node. These cells have the ability to generate a spontaneous AP based on the differential characteristic of Phase 4. This difference is produced by ion currents that affect Na^+ and K^+ concentrations, called I_f, which activate at membrane potentials below -40 mV, and the K rectifier currents. These currents confer an unstable electrical property, causing these cells to develop spontaneous diastolic depolarization and automatic onset of APs in a rhythmic fashion. Once spontaneous diastolic activity raises the membrane potential to a value of -40 mV, opening of the slow Ca^{2+} channels results in an inward Ca^{2+} current (L-type Ca) that generates the slow AP upstroke (Phase 0). Na^+ channels possess a small, if any, role in the AP generation in these particular cells (Fig. 5.3).

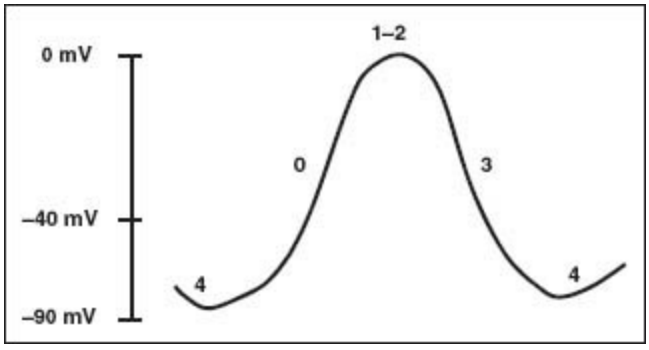


FIGURE 5.3 Action potential (calcium channel tissue). AP model of a calcium tissue. Numbers 0, 1, 2, 3, 4 delineate the different phases of the AP.

ELECTRICAL COUPLING CELLS (GAP JUNCTION)

GAP junction channels are the functional units that produce direct ionic communication between cardiac cells and play a major role in the propagation of the AP from one myocardial cell to the next. The molecular unit of the GAP junction is a protein called connexin. The oligomerization of six connexins forms a connexon, and two connexons form the final channel called the GAP junction. Among the 20 different subtypes of connexins identified in the human genome, connexin 43 is the most abundant in myocardial cells. Besides the genomic regulation of channel expression, they are also affected by the activity of protein kinase activity, low intracellular pH, and dephosphorylation.

GAP junction channels are not uniformly distributed within cardiac tissues. They are almost absent in the sinus node, are found in low concentration in various areas of the atrioventricular node (AVN), and demonstrate significant expression in the faster conducting atrial and ventricular muscle as well as His–Purkinje fibers. In these cells, the distribution of the connexons is not uniform. They are more concentrated along the ends of the myocytes than along the sides of the cell, thus giving a directional propensity for AP propagation. This gives rise to anisotropic propagation of depolarization, with faster conduction velocities along the muscle fiber orientation compared to the slower transverse fiber–orientated velocities.

CONDUCTION SYSTEM ANATOMY AND PHYSIOLOGY

The sinus node is located beneath the epicardial surface of the crista terminalis, at its junction with the high right atrium. It possesses a spindle-shaped structure and measures an average 10 to 20 mm in the long axis and 2 to 3 mm in the transverse axis. It is composed of a cumulus of small cells called P cells; the main component of the natural pacemaker. They are grouped in elongated clusters and are centrally located within the sinus node. Transitional cells called T cells surround the P cells and transmit the impulse generated by the P cells to the surrounding atrium. The final synchronized activity of the sinus node is achieved via the presence of GAP junctional channels that electrically couple the depolarization of P cells. At the periphery of the node, strands of nodal cells interdigitate with atrial cells, forming lateral connections and transferring the pacemaker impulse to the atrial cells. This organization is believed to be important to impulse propagation from a small source (the nodal cells) to a large reservoir (the atrial myocardium), preventing excessive dampening of the pacemaker current within the nodal cells by the large reservoir of atrial myocardium.

Cells within the sinus node demonstrate spontaneous diastolic depolarization, initiating APs in a repetitive fashion. These APs are calcium channel dependent and possess a similar morphology to those of the atrioventricular nodal cell, characterized by a slow Phase 0 upstroke velocity. Sinus node cells do not possess the GAP junction

protein connexin 43. Therefore, electrical coupling at the node center is poor, reflected as a low measured conduction velocity. The periphery is associated with an increase in conduction velocity. This characteristic is most likely important in isolating the sinus node from the potential suppressive hyperpolarizing influence of the atrial myocardium.

Normal sinus node function is affected by age. In the young, the intrinsic heart rate is faster, but vagal tone predominates at rest, causing slowing of the heart rate. In the elderly, resting autonomic tone tends to shift away from vagal predominance to sympathetic outflow. Thus, the extrinsic sinus rate at rest, the rate as modified by autonomic tone, tends to be similar within the ages of adulthood.

The impulse generated at the sinoatrial node is next transmitted to the AVN through atrial myocytes. There is anatomic evidence for the presence of three atrionodal pathways traversing the right atrium. A fourth pathway, called Bachmann bundle, derived from the anterior atrionodal pathway, directs impulse propagation to the left atrium via the interatrial septum. Anatomically, these so-called pathways do not demonstrate any specialized conduction tissue. Rapid conduction along these intra- and interarterial paths appears to be correlated with fiber size and orientation rather than the presence of specialized conduction tissue.

The AVN is a fusiform structure located subendocardially along the annular regions of the interatrial septum, with its distal end, the compact node, at the superior corner of the triangle of Koch. The triangle of Koch is defined by the insertion of the septal leaflet of the tricuspid valve, the tendon of Todaro, and the line that connect the os of the coronary sinus and the tricuspid annulus. The body and the proximal end (the tail) of the AVN are directed posteriorly along the tricuspid annulus. A second tail extends from the body of the AVN along the mitral annulus. The so-called slow pathway of the AVN corresponds to the tail of the AVN, whereas the fast pathway involves atrial inputs into the distal compact node. Similar to the sinus node, transitional cells surround this structure. Circulation to the AVN is provided in nearly 90% of individuals by branches of the right coronary artery extending superiorly from the crux into the trigone area along the AV annulus.

The His bundle is the anatomic structure that connects the compact AVN to the bundle branches. At the junction between the distal AVN and the proximal His bundle, the cells undergo a gradual change from possessing node-like APs to having His–Purkinje APs. That is the APs change from having slow upstrokes dependent on Ca^{2+} current to fast upstrokes dependent on Na^{+} current. The branches from the anterior and posterior descending arteries provide circulation to this portion of the conduction system and confer a better security margin for ischemic damage. The His bundle penetrates the AV ring at the central fibrous body and then arches anteriorly and inferiorly along the crest of the septal myocardium that forms the lower edge of the membranous ventricular septum. As it courses along the crest, left-sided fibers in the His bundle drop over the crest into the left ventricle, forming the posterior, septal, and

anterior fascicles of the left bundle branch. The His bundle then continues its course over the right ventricular septum as the right bundle branch. The right bundle brunch adopts a subendocardial trajectory over the right side of the interventricular septum and transmits the cardiac impulse to the Purkinje fibers located at the apical portions of the right ventricle. The bundle branches spread into a smaller Purkinje bundle and then into finer fibers that terminate at the myocardium. This branching structure of the His–Purkinje system facilitates a near-synchronous arrival of the sinus impulse at the myocardial endocardial surface.

Electrophysiologically, the AVN can be differentiated into three portions: atrionodal, compact node, and nodo-His. The compact node area presents a response characterized by an AP with a slow rate of rise during its upstroke and a low amplitude. The other two zones have transitional characteristics between the compact node zone and the atrial and His bundle potentials, respectively.

Calcium-type APs characterize the main AVN cellular type. Differentiating the AVN from the sinus node, GAP junctions play an important role in AVN conduction. Connexin 45 is present in this portion of the conduction system, though at a low level. It has also been demonstrated that the expression of connexin 45 constitutes the molecular basis of AVN dual pathways.

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QUESTIONS AND ANSWERS

Questions

1. Which of the following is not a characteristic of sodium channels?
   a. Selective permeation
   b. Pump electrolytes exchange mechanism
   c. Gating
   d. Drug binding
   e. Susceptibility to many different neurotoxins
2. Which of the following is not a characteristic of Phase 1 of the action potential (AP)?
   a. Phase 1 starts with the opening of a rapid outward K^+ ion current called I_{to}.
   b. These K^+ channels activate in response to membrane depolarization.
   c. These K^+ channels inactivate in a time-dependent manner.
   d. α-Adrenergic stimulation increases I_{to} maximum current.
   e. Aldosterone mediates a receptor-specific downregulation of I_{to}.
3. Which of the following is not a characteristic of calcium channels?
   a. During Phase 0, at the level of -40 mV, Ca^{2+} channels open, creating an inward Ca^{2+} current.
   b. This current acts as an agonist to the outward K^+ current.
   c. Phase 2 concludes as Ca^{2+} current declines by inactivation of L-type Ca^{2+} channels.
   d. Inactivation of the channel depends on time, membrane potential, and Ca concentration.
   e. Intracellular Ca^{2+} concentration acts as a critical initiator of cardiac excitation–contraction coupling.
4. Which of the following is the main mechanism by which resting membrane potential (Phase 4 of the AP) is maintained?
   a. Delayed rectifier K^+ channels
   b. Voltage-regulated inward rectifiers
   c. These channels open in response to depolarization.
   d. These channels open after reaching the resting membrane potential.
   e. These potassium channels stabilize the resting membrane potential near the sodium equilibrium potential.
5. Which of the following statements about GAP junctions is wrong?
   a. GAP junction channels are the functional units that allow direct ionic communication between cardiac cells.
   b. GAP junctions play a major role in the propagation of the AP.
   c. The molecular unit of the GAP junction is a protein called connexin.
   d. Connexin 43 is the most abundant in cardiac conduction system cells.
   e. Connexin 43 may be affected by the activity of protein kinase, low intracellular pH, and dephosphorylation.

Answers

1. Answer B: Sodium channels are characterized by a protein that works as a voltage-gated sodium channel. The active portion of this channel is the α subunit, which consists of a 2,000–amino acid glycoprotein. The other choices are all properties of these channels.

2. Answer D: Phase 1 starts with the opening of a rapid outward K^+ ion current called I_{to}. This determines a fast early repolarization. These K^+ channels activate in response to membrane depolarization and inactivate in a time-dependent manner. These channels may be regulated by the following means:

- Angiotensin II reduces I_{to} maximum velocity.
- α-Adrenergic stimulation reduces I_{to} fast velocity.
- Hyperthyroidism increase I_{to} current density.
- Aldosterone mediates a receptor-specific downregulation of I_{to}.

3. Answer B: During Phase 0, at the level of -40 mV, Ca^{2+} channels open, creating an inward Ca^{2+} current. This current act as an antagonist to the outward K^+ current. Phase 2 concludes as Ca^{2+} current declines by inactivation of L-type Ca^{2+} channels, letting the plateau phase subside. These channels are also the critical initiators of cardiac excitation–contraction coupling through the initial increase in intracellular Ca^{2+} concentration that triggers the release of Ca^{2+} from the sarcoplasmic reticulum, which in turn provides a contraction signal to the contractile elements of the cell. Inactivation of the channel depends on time, membrane potential, and Ca concentration.

4. Answer B: The stabilization of resting membrane potential after the descending Phase 3 of the AP is achieved mainly by the action of the voltage-regulated inward rectifiers (I_{K1}). These channels behave differently than the delayed rectifiers, which open in response to depolarization. The inward rectifier K^+ channels are opened near resting membrane potential, stabilizing the resting membrane potential near the K^+ equilibrium potential, but close in response to depolarization, facilitating the AP, hence the description as "inward rectifying."

5. Answer D: GAP junction channels are the functional units that allow direct ionic communication between cardiac cells and play a major role in the propagation of the AP from one cell to the next. The molecular unit of the GAP junction is a protein called Connexin. The oligomerization of six connexins forms a connexon, and two connexons form the final channel called the GAP junction. Among the 20 different subtypes of connexins identified in the human genome, connexin 43 is the most abundant in myocardial cells. Besides the obvious genomic regulation of the expression of these channels, they may also be affected by the activity of protein kinase activity, low intracellular pH, and dephosphorylation.

CHAPTER

Cardiac Biochemistry

Mosi K. Bennett and Marc S. Penn

The biochemistry of cardiac tissue involves tightly regulated interactions among ions, proteins, receptors, second messenger systems, and various cellular structures as well as extracardiac influences. Several abnormalities involving neurohormonal pathways as well as derangements of the contractile apparatus of the cardiac myocyte have been demonstrated in cells isolated from failing hearts. This chapter reviews some of the salient features of the biochemistry of the cardiac myocyte.

CARDIAC CONTRACTILITY AND CALCIUM HOMEOSTASIS

The cardiac myocyte is an interconnected network of myofibrils surrounded by sarcoplasmic reticulum (SR). Each myofibril comprises sarcomeres made up of thick myosin filaments and thin actin filaments that form the basic contractile unit of the cardiac myocyte (Fig. 6.1). The active sites of the actin filaments are covered in the resting state by two regulatory proteins, tropomyosin and troponin. Intracellular Ca^{2+} is the most important determinant of myocardial contractility and relaxation.[1] Once contraction ensues, calcium (Ca^{2+}) entry through L-type Ca^{2+} channels triggers an exponential release of Ca^{2+} from the SR through ryanodine receptors.[2] Calcium then binds troponin, leading to a conformational alteration of tropomyosin, exposing the actin active site, facilitating a "sliding" interaction between the actin filaments and the myosin heads as well as the hydrolysis of ATP (adenosine triphosphate), thus providing energy for contraction.[3] Following a cycle of excitation–contraction coupling, diastolic relaxation is initiated by cytosolic Ca^{2+} sequestration in the SR by the SR-Ca^{2+} ATPase (SERCA2a) pump (~75%) and exportation extracellularly by the Na^{+}/Ca^{2+} exchanger (~25%) located on the sarcolemmal membrane.[4,5] Abnormal cardiac SR function and Ca^{2+} signaling represent a characteristic of both systolic and diastolic Congestive Heart Failure (CHF).[6–8] There is good evidence that changes in either expression or function

of specific calcium-handling proteins lead to increased intracellular diastolic Ca^{2+} levels, decreased intracellular Ca^{2+} transients, delayed Ca^{2+} efflux, and depressed contractility.[9,10,11,26] For example, ryanodine receptors are upregulated and progressively activated by phosphorylation, contributing to the SR Ca^{2+} leak observed in CHF. Phospholamban is a regulatory protein that exerts an inhibitory effect on SERCA2a, limiting its ability to remove cytosolic Ca^{2+} following contraction. In failing hearts, phospholamban expression is altered and SERCA activity is decreased, resulting in diastolic and systolic dysfunction.[5,6,12,13,14–17] An understanding of the molecular mechanisms of heart failure is necessary to understand the potential for therapeutic targets. This fact is underscored by the recent clinical trial investigating whether the function of SERCA can be restored via gene transfer.[18]

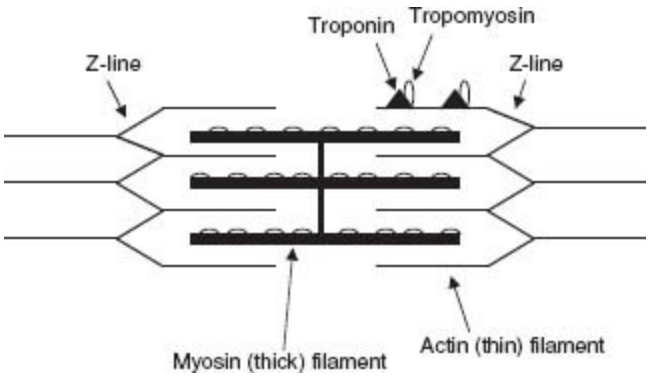

FIGURE 6.1 Sarcomere anatomy.

β-ADRENERGIC SIGNALING

Three β-adrenergic receptor (β-AR) subtypes have been characterized, β_1, β_2, and β_3. Catecholamines act to increase myocardial contractility primarily through β_1-adrenergic receptor stimulation leading to G protein–mediated adenyl cyclase activation and cyclic adenosine 3′5′ monophosphate (cAMP) generation, which triggers protein kinase A (PKA)–dependent phosphorylation of voltage-gated L-type Ca+ channels, ryanodine receptors, and phospholamban, which derepresses SERCA2a, leading to excitation–contraction coupling and positive inotropy (Fig. 6.2).[19–21] β_2-Adrenergic receptors as well as muscarinic cholinergic receptors, through an inhibitory G protein, provide negative control of adrenergic stimulation by inactivating adenyl cyclase, thereby limiting the generation of cAMP.[22] The role of β_3-adrenergic receptors is poorly defined, but there is some evidence that β_3-adrenergic receptors maintain coronary vasomotor tone through the nitric oxide (NO) pathway.[23] β-Arrestins also serve to restrict cAMP generation by increasing cAMP degradation and desensitizing the β-

receptor.[24] Derangements in chronic β-adrenergic signaling that have been implicated in the pathogenesis of CHF include β-AR downregulation, β-AR uncoupling from second messenger systems, upregulation of β-adrenoreceptor kinase (βARK1), and altered calcium trafficking.[25–30] β-Receptor blockade can restore calcium homeostasis and upregulate SERCA2a, ultimately improving cardiac performance with long-term treatment.[31]

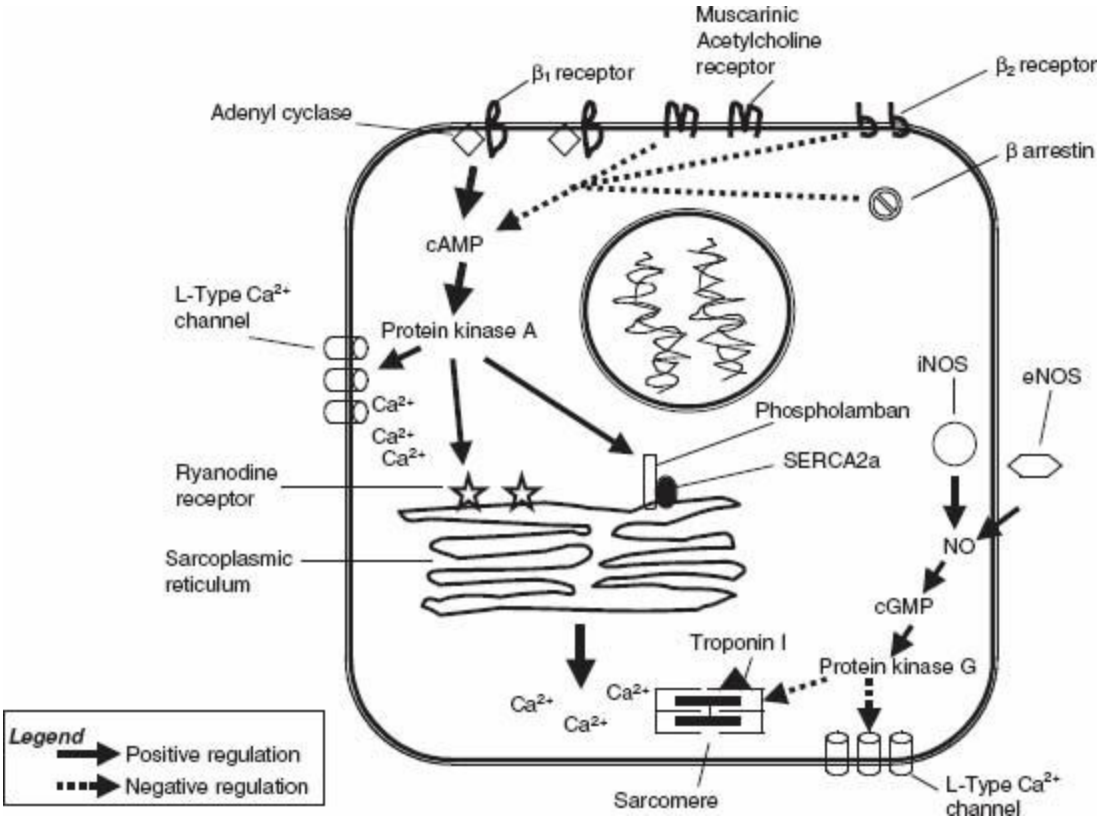

FIGURE 6.2 β-Adrenergic and NO regulation of the cardiac myocyte.

DIGITALIS AND THE NA^+-K^+ ATPASE

Digitalis, a cardiac glycoside derived from the foxglove plant, has been used for centuries to treat heart failure and atrial fibrillation. Digitalis functions by inhibiting the sodium pump (Na^+/K^+ ATPase) found in the cardiac cell membrane.[32,33] The Na^+/K^+ ATPase works constitutively, using energy from the hydrolysis of ATP to maintain a high intracellular K^+ concentration and a high extracellular Na^+ concentration.[34] Ca^{2+} is removed from the cytosol into the extracellular fluid by a sodium–calcium exchange (NCX1) pump driven by the preexisting Na^+ gradient.[35] Inhibiting the Na^+/K^+ ATPase promotes enhanced Na^+/Ca^{2+} exchange, leading ultimately to increased intracellular Ca^{2+} being available to the contractile apparatus, potentially leading to increased myocardial contractility.

PHOSPHODIESTERASE INHIBITION

Phosphodiesterase inhibitors (PDIs) such as milrinone affect contractility by inhibiting phosphodiesterase 3 (PDE3), increasing intracellular cAMP and Ca^{2+}, which leads to increased inotropy.[36] PDIs also have vasodilating properties that are important in unloading the failing ventricle.[37] Unfortunately, the gain in cardiac performance is tempered by increased arrhythmogenesis, myocardial oxygen consumption, and cardiac death, mitigating its usefulness beyond being a bridge to cardiac transplantation in end-stage CHE.[38,39]

RENIN–ANGIOTENSIN SYSTEM

The renin–angiotensin system (RAS) has a detrimental role in the pathogenesis of heart failure. Beyond its influences on blood pressure and salt and water regulation, it has stimulatory effects on the sympathetic nervous system, direct effects on myocardial hypertrophy, and indirect effects on myocardial contractility. Numerous large randomized clinical trials have demonstrated the symptom relief and survival benefit in patients with CHF treated with angiotensin-converting enzyme (ACE) inhibitors.[40–42] Angiotensinogen is cleaved to angiotensin I by the renally produced enzyme renin in response to renal hypoperfusion. Angiotensin I is then cleaved by ACE into the potent vasoconstrictor angiotensin II. Angiotensin II stimulates catecholamine release, increases cardiac hypertrophy, regulates blood pressure (angiotensin II receptors), and increases blood volume by stimulating aldosterone and vasopressin release, enhancing sodium and water retention (Fig. 6.3).[43] ACE inhibitors also increase the generation of bradykinin (thought to mediate the cough associated with ACE inhibitors), which is a nitric oxide synthase (NOS) agonist and may attenuate β-adrenergic contractility through NO signaling.[44] Bradykinin degradation may also have untoward effects on myocardial contractility that are offset by ACE inhibition.[45]

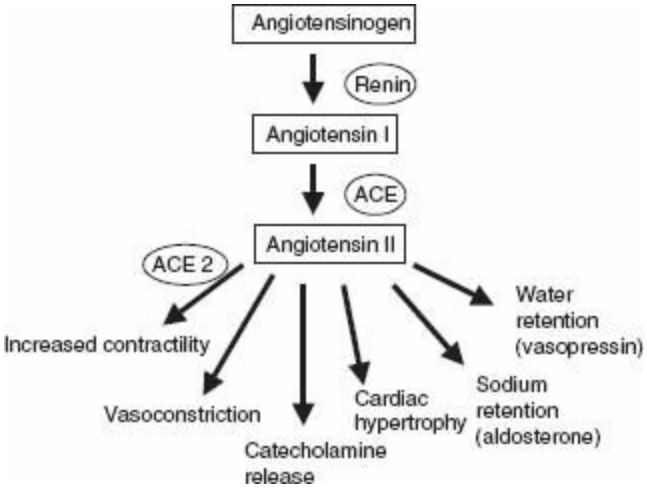

FIGURE 6.3 Renin–angiotensin system.

ACE-2 is an ACE isoform that is thought to be an important regulator of cardiac contractility. It catalyzes the cleavage of angiotensin I to angiotensin 1–9 and of angiotensin II to angiotensin 1–7. ACE-2 is not inhibited by ACE inhibitors, nor is bradykinin a by-product of its activity.[46–48] ACE-2 is upregulated within the myocardium with angiotensin II receptor blockade.[49] ACE-2 deficiency diminishes cardiac contractility and upregulates hypoxia-induced genes, suggesting its role in RAS modulation following ischemiamediated cardiac injury.[50]

NITRIC OXIDE

NO plays an important role in the endothelium-dependent functions of coronary vasomotor tone and thrombogenesis, but it also has direct effects on myocardial relaxation. NO is generated by the enzyme NOS, which has three isoforms: eNOS (endothelial), iNOS (inducible), and nNOS (neuronal). NO affects myocardial relaxation through effects on excitation–contraction coupling, regulation of adrenergic signaling, and mitochondrial metabolism.[51] Attenuation of β-adrenergic stimulation by NO (see Fig. 6.2) is mediated by cyclic guanosine 3′5′-monophosphate (cGMP)–dependent phosphodiesterase EII regulation of cAMP levels, protein kinase G–mediated downregulation of L-type Ca+ channels,[52,53] and the desensitization of troponin I to calcium.[54] NO may also influence myocardial relaxation by enhancing the activity of the delayed rectifier K^+ current[55] as well as cGMP-mediated inhibition of phospholamban and its negative control over SERCA2a.[56]

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QUESTIONS AND ANSWERS

Questions

1. Following a cycle of excitation–contraction coupling in cardiac muscle, cytosolic Ca^{2+} is sequestered in the sarcoplasmic reticulum (SR) primarily by what entity?
   a. Na^{+}/Ca^{2+} exchanger
   b. L-Type Ca^{2+} channels
   c. Phospholamban
   d. SERCA2a
   e. Ryanodine receptors
2. Downregulation of adrenergic signaling system in failure is due to all the following except:
   a. G protein-mediated adenyl cyclase activation and cAMP generation through β1 overstimulation
   b. Beta Adrenoreceptor Kinase (β-ARK) upregulation
   c. Beta Adrenoreceptor (β-AR) uncoupling from second messenger systems
   d. Altered Ca^{2+} trafficking
   e. Beta blocker therapy
3. Digitalis is a cardiac glycoside that does all of the following except:
   a. Indirectly activates a Na^{+}/Ca^{2+} exchanger found in the cardiac cell membrane
   b. Inhibits the Na^{+}/K^{+} ATPase found in the cardiac cell membrane
   c. Increases chronotropy by increasing intracellular Ca^{2+}
   d. Leads to a sodium gradient across the cardiac cell membrane that is favorable for Ca^{2+} influx
   e. Increases parasympathetic tone

4. Regarding the role of nitric oxide (NO) and cardiac function, which of the following is false?
   a. Bradykinin is a nitric oxide synthase (NOS) antagonist and may increase myocardial contractility.
   b. NO mediates endothelium-dependent coronary vasodilation.
   c. NO has three isoforms: iNOS (inducible), eNOS (endothelial), and nNOS (neuronal).
   d. NO leads to cyclic guanosine 3′5′-monophosphate (cGMP)-mediated attenuation of β-adrenergic stimulation and myocardial relaxation.

5. Regarding the renin–angiotensin system (RAS), which of the following is false?
   a. Chronic renal hypoperfusion leads to catecholamine release, hypertension, cardiac hypertrophy, and salt and water retention.
   b. Angiotensin-converting enzyme (ACE) inhibitors work by inhibiting angiotensinogen cleavage to angiotensin I.
   c. ACE-2 is not inhibited by ACE inhibitors.
   d. Bradykinin is thought to mediate the cough associated with ACE inhibitors.

6. Once contraction ensues, calcium entry through L-type Ca^{2+} channels triggers an exponential release of Ca^{2+} from the SR through what entity?
   a. Ryanodine receptor
   b. SERCA2a
   c. NA/K ATPase
   d. Na^{+}/Ca^{2+} exchanger
   e. Phospholamban

7. Catecholamines act to increase myocardial contractility through what type of beta-adrenergic receptor?
   a. Beta 2
   b. Alpha 1
   c. Beta 1
   d. Beta 3
   e. None of the above

8. Altered Ca^{2+} handling in heart failure is characterized by:
   a. Decreased reuptake of Ca^{2+} by the SR
   b. Increased diastolic cytosolic Ca^{2+} concentrations
   c. Decreased SERCA expression
   d. Upregulation of the expression of the RyR2 receptor
   e. All of the above

9. Under normal conditions, angiotensin II has which of the following effects?
   a. Arterial vasodilation
   b. Stimulates water retention through the release of vasopressin
   c. Decreases cardiac hypertrophy
   d. Inhibits aldosterone release causing causes sodium and chloride ions excretion and potassium retention.

10. Which of the following statements about cardiomyocyte Ca^{2+} handling in excitation–contraction coupling is false?
   a. Ca^{2+} enters the cell via the sarcolemmal Naþ/Ca2þ exchanger (NCX).
   b. Release of Ca^{2+} from the SR occurs through the ryanodine receptor.
   c. Ca^{2+} is pumped back into the SR via the cardiac SR Calcium-ATPase (SERCA2a).
   d. Ca^{2+} enters the cardiac muscle cell through L-type Ca^{2+} membrane channels.

Answers

1. **Answer D:** The active sites of the actin filaments are covered in the resting state by two regulatory proteins, tropomyosin and troponin. Intracellular Ca^{2+} is the most important determinant of myocardial contractility and relaxation. Once contraction ensues, calcium (Ca^{2+}) entry through L-type Ca^{2+} channels triggers an exponential release of Ca^{2+} from the SR through ryanodine receptors. Calcium then binds troponin leading to a conformational alteration of tropomyosin exposing the actin active site, which facilitates a "sliding" interaction between the actin filaments and the myosin heads as well as the hydrolysis of ATP providing energy for contraction. Following a cycle of excitation–contraction coupling, diastolic relaxation is initiated by cytosolic Ca^{2+} sequestration in the SR by the SR-Ca^{2+} ATPase (SERCA2a) pump (~75%) and exportation extracellularly by the Na^{+}/Ca^{2+} exchanger (~25%) located on the sarcolemmal membrane. Phospholamban, a regulatory protein, exerts an inhibitory effect on SERCA2a limiting its ability to remove cytosolic Ca^{2+} following contraction.

2. **Answer E:** Catecholamines increase myocardial contractility primarily through β-adrenergic receptor stimulation leading to G protein–mediated adenyl cyclase activation and cyclic adenosine 3′5′ monophosphate (cAMP) generation, which triggers protein kinase A (PKA)–dependent phosphorylation of voltagegated L-type Ca+ channels, ryanodine receptors, and phospholamban, which derepresses SERCA2a leading to excitation–contraction coupling and positive inotropy. Derangements in chronic β-adrenergic signaling that have been implicated in the pathogenesis of CHF include β-AR downregulation, β-AR uncoupling from second messenger systems, upregulation of β-AR kinase (βARK1), and altered calcium trafficking. β-Blocker therapy can restore calcium homeostasis and upregulate SERCA2a ultimately improving cardiac performance with long-term treatment.

3. **Answer C:** Digitalis inhibits the Na^{+}/K^{+} ATPase found in the cardiac cell membrane, which maintains a high intracellular K^{+} concentration and a high extracellular Na+ concentration. Ca^{2+} is removed from the cytosol into the extracellular fluid by a sodium-calcium exchange pump driven by the preexisting Na+ gradient. Inhibiting the Na^{+}/K^{+} ATPase promotes enhanced Na^{+}/Ca^{2+} exchange ultimately leading to increased intracellular Ca^{2+} available to the contractile apparatus increasing myocardial contractility. Chronotropy would not be increased with digitalis and in fact it is often used for the opposite effect of heart rate control in patients with atrial fibrillation.

4. **Answer A:** NO plays an important role in the endothelium-dependent functions of coronary vasomotor tone but also has direct effects on myocardial relaxation. NO is generated by the enzyme NOS, which has three isoforms: eNOS (endothelial), iNOS (inducible), and nNOS (neuronal). NO impacts myocardial relaxation through effects on excitation–contraction coupling, regulation of adrenergic signaling, and mitochondrial metabolism. Bradykinin is a NOS agonist, not antagonist, and may decrease myocardial contractility.

5. **Answer B:** Angiotensinogen is cleaved to angiotensin I by renin in response to renal hypoperfusion. Angiotensin I is then cleaved by ACE into the potent vasoconstrictor angiotensin II. Angiotensin II stimulates catecholamine release and cardiac hypertrophy, regulates blood pressure, and increases blood volume by stimulating aldosterone and vasopressin release enhancing sodium and water retention. ACE inhibitors also increases bradykinin generation, which is thought to mediate the cough associated with ACE inhibitors. ACE 2 is an ACE isoform thought to be an important regulator of cardiac contractility and is not inhibited by ACE inhibitors.

6. **Answer A:** Ca^{2+} entry and increase in intracellular calcium concentration activates the release of calcium from the SR through the ryanodine receptor (RyR2). Following a cycle of excitation–contraction coupling, diastolic relaxation is initiated by cytosolic Ca^{2+} sequestration in the SR by the SR-Ca^{2+} ATPase (SERCA2a) pump (~75%) and exportation extracellularly by the Na^{+}/Ca^{2+} exchanger (~25%) located on the sarcolemmal membrane. Phospholamban inhibits SERCA and limits its ability to remove cytosolic Ca^{2+} following contraction.

7. **Answer C:** Catecholamines act to increase myocardial contractility primarily through β_1-adrenergic receptor stimulation leading to G protein–mediated adenyl cyclase activation and cAMP generation. β_2-Adrenergic receptors as well as muscarinic cholinergic receptors, through an inhibitory G protein, provide negative control of adrenergic stimulation by inactivating adenyl cyclase, thereby limiting the generation of cAMP. The role of β_3-adrenergic receptors is poorly defined, but there is some evidence that β_3-adrenergic receptors maintain coronary vasomotor tone through the NO pathway. The α_1-adrenergic receptor primarily mediates arterial vasoconstriction.

8. **Answer E:** Abnormalities with Ca^{2+} handling are partly responsible for the systolic and diastolic dysfunction seen in congestive heart failure. There is a decrease in SERCA expression and activity, leading to decreased reuptake of Ca^{2+} by the SR and increased diastolic cytosolic Ca^{2+} concentrations. There is also upregulation of the expression and activity of the RyR2 receptor in failing hearts.

9. **Answer B:** Angiotensinogen is cleaved to angiotensin I by the renally produced enzyme renin in response to renal hypoperfusion. Angiotensin I is then cleaved by ACE into the potent vasoconstrictor angiotensin II. Angiotensin II stimulates catecholamine release, increases cardiac hypertrophy, regulates blood pressure (angiotensin II receptors), and increases blood volume by stimulating aldosterone and vasopressin release, enhancing sodium and water retention. ACE inhibitors block the conversion of angiotensin I to angiotensin II. Therefore, ACE inhibitors lower arteriolar resistance and increase venous capacity, increase cardiac output, lower renovascular resistance, and lead to increased excretion of sodium and potassium retention.

10. **Answer A:** Once contraction ensues, calcium (Ca^{2+}) entry through L-type Ca^{2+} channels triggers an exponential release of Ca^{2+} from the SR through ryanodine receptors. Calcium then binds troponin, leading to a conformational alteration of tropomyosin, exposing the actin active site, facilitating a "sliding" interaction between the actin filaments and the myosin heads as well as the hydrolysis of ATP (adenosine triphosphate), thus providing energy for contraction. Following a cycle of excitation–contraction coupling, diastolic relaxation is initiated by cytosolic Ca^{2+} sequestration in the SR by the SR-Ca^{2+} ATPase (SERCA2a) pump (~75%) and exportation extracellularly by the Na^+/Ca^{2+} exchanger (~25%) located on the sarcolemmal membrane.

CHAPTER

Clinical Epidemiology and Biostatistics

Michael S. Lauer and Eiran Z. Gorodeski

An ability to read the medical literature intelligently is an essential skill for the competent clinical practitioner. Acquiring this skill is challenging because of the high volume of medical articles published and the increasing sophistication of modern epidemiologic and statistical methods.

Topics that will be covered in this chapter include:

1. Exposures and outcomes
2. Types of clinical studies
3. Types of statistical errors
4. Data presentation: reporting of outcomes
5. Confounding and interaction
6. Multivariable regression and pitfalls
7. Bias and its consequences
8. External validity: assessments of causation and validity
9. Issues related to:
   - **a.** Randomized treatment/prevention trials
   - **b.** Studies of diagnostic tests
   - **c.** Prognostic (survival) studies
   - **d.** Case–control studies
   - **e.** Economics
   - **f.** Clinical prediction guides
   - **g.** Systematic review articles and meta-analyses

CURRENT CONCEPTS AND ESSENTIAL FACTS

Exposures and Outcomes

At the heart of virtually all clinical studies is an attempt to link an "exposure" with an "outcome." When reading an article, you should ask yourself what exactly the exposure and outcome variables are and whether their association is of interest to you.

For exposure, the "independent" variable, examples include:

1. A treatment strategy (or lack thereof)
2. A patient characteristic (such as age, gender, or cholesterol level)
3. A diagnostic test result (such as ejection fraction)

For outcome, the "dependent" variable, examples include:

1. A treatment outcome (such as death, myocardial infarction, need for revascularization)
2. A clinical event during follow-up (such as death or myocardial infarction)
3. A "gold standard" finding (such as evidence of coronary disease on an angiogram)

Types of Clinical Studies

Various types of clinical studies are reported in the literature, including the following.

Case Reports

Case reports, although they may be fun to read, rarely provide the kind of high-level evidence needed to influence clinical practice.

Case Series

Case series report on a group of patients who show a certain finding. Although there may be a clear-cut exposure and an outcome variable, the absence of a comparison group limits any conclusions that can be drawn. Case reports and case series are best thought of as hypothesis-generating studies.

Cohort Study

The cohort study is a fundamentally strong study design in which:

1. An inception cohort is clearly defined.
2. An exposure variable is defined.
3. The cohort consists of individuals with and without the exposure variable present at the time of inception.
4. The cohort is followed over time for the occurrence of a clearly and objectively defined outcome.

5. The occurrence of the outcome is compared in individuals with and without the exposure variable.

Case–Control Study

A case–control study (Fig. 7.1) is a somewhat weaker study design than a cohort study. In a case–control study:

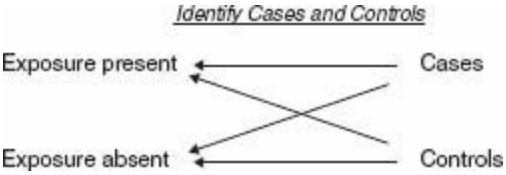

FIGURE 7.1 Case–control study diagram.

1. A "case" group of subjects with a given outcome is identified.
2. A "control" group of subjects, without the outcome, is identified.
3. The occurrence of an exposure variable is compared between the case group and the control group.

Studies of Diagnostic Tests

In studies designed to assess the value of a diagnostic test, a group of patients suspected of having a certain disease (outcome) undergo the diagnostic test, and then the results of the diagnostic test are compared against an accepted standard.

Cost-Effectiveness Studies

Cost-effectiveness studies usually take the form of a cohort study in which (a) the cost of an intervention is measured, (b) the outcomes of performing or not performing an intervention are compared, or (c) the cost of preventing an outcome is measured; typically, this last is recorded as dollars per year of life saved or dollars per quality-adjusted year of life saved (QALY).

Randomized Controlled Trials

Randomized controlled trials (Fig. 7.2) are the gold standard for assessing a treatment or a prevention measure. In these studies:

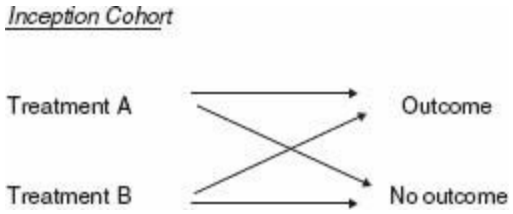

FIGURE 7.2 Randomized trial diagram.

1. A cohort of patients at risk for an outcome is defined.
2. Determination of which patients receive treatment or prevention is made entirely at random.
3. An outcome is measured after a predetermined follow-up period.

In effect, a randomized controlled trial is a kind of cohort study, except that the exposure variable is determined by the investigator, not by nature, using a randomization technique.

Prospective-versus-Retrospective Studies

In prospective-versus-retrospective studies, prospective data are obtained and coded at the time they are first available and, in the case of cohort studies, prior to the outcome. Retrospective data are obtained at a later time, often after the outcome has occurred.

Prospective studies are much less likely to be subject to observation bias or problems with missing data.

Meta-Analysis

Meta-analyses are systematic reviews of specific clinical questions with data pooled from multiple previously completed/published studies. Steps in a meta-analysis include:

1. Clinical hypothesis is defined.
2. Literature is searched.
3. Studies are selected based on prespecified criteria.
4. Consistent summary measures are collected from each identified study.
5. Pooled analysis is performed.

Most meta-analyses only pool randomized clinical trials, but meta-analyses can include cohort studies alone or mixed with clinical trials. Meta-analyses may suffer from publication bias as negative studies have traditionally been more difficult to publish.

Genome-Wide Association Studies

Genome-wide association studies (GWAS) are a contemporary form of case–control

studies that focus on genetic data. DNA from people with (cases) and without (controls) a disease is collected and placed on gene chips. These chips are read into computers that identify DNA variations between the two groups . DNA variations that are more frequently detected are "associated" with the disease and hint at chromosomal regions that may be responsible for the disease.

Statistical Tests

Statistics is the science by which observations made of a sample are assessed with respect to their likely validity in the entire universe.

Type I and Type II Errors

Commonly reported statistics include two types of statistical error analysis. In type I errors, an association between an exposure and an outcome is in fact a spurious one that has resulted from random chance. The "p value" refers to the likelihood that an observed association is due to chance alone. In type II errors, on the other hand, the lack of an observed association between an exposure and an outcome is in fact due to chance because the sample size was not large enough to detect an association if one in fact exists. This is one of the most common errors reported in clinical literature.

Hypothesis Testing

Statistical tests also aim to determine whether a "null hypothesis" should be rejected, where the null hypothesis is that no association exists between the exposure and the outcome. Today many clinical researchers are moving away from this sort of hypothesis testing and more toward estimation of effects along with confidence intervals, discussed below.

Comparisons of Continuous Variables

Continuous variables are variables that can have an infinite number of values, such as age, height, blood pressure, or cholesterol level. They are described using means, standard deviations, ranges, quartiles, quintiles, deciles, and so on.

When continuous variables are normally distributed (i.e., described by a Gaussian or bell-shaped curve), t tests are generally used to compare the means of two groups and ANOVA is used to compare means of three or more groups.

When the continuous variables cannot be assumed to be normally distributed, nonparametric testing, such as the Wilcoxon rank-sum, which compares median values and distributions of two groups, or the Kruskal-Wallis test, which compares medians and distributions of three or more groups, is often used.

To compare the strength of a presumed linear association between two continuous variables (e.g., left ventricle mass versus blood pressure), researchers often use tests of

correlation (r value), such as Pearson or Spearman tests. In these tests, the square of the r value describes how much the variability of one variable can be attributed to the other.

Comparisons of Categorical Variables

Variables that can only have a finite set of values (e.g., gender, presence or absence hypertension, use of a certain medication) are called categorical variables. For most samples, these kinds of variables are compared using the chi-square test. However, if the sample size is very small, researchers may instead use the Fischer exact test.

Data Presentation and Reporting of Outcomes

The statistical tests discussed above tell only part of the story. The strengths of associations can be described in a number of ways.

Number of Outcomes

Knowing the number of outcomes is essential to determining the strength of a study. In general, studies with <25 outcome occurrences are suspect. Studies with >100 outcomes may be compelling.

Absolute Event Rates

Absolute event rates are generally considered the most honest way to present data. How many outcomes were associated with exposures? How many outcomes occurred among those not exposed? Be suspicious if raw data are not provided. A careful reading of the raw data will enables a reader to distinguish between "statistical significance" and "clinical significance." It is the latter that we really care about.

Relative Risk or Risk Ratio

Relative risk or risk ratio (RR) is the proportion of event rates according to exposure, or

$$RR = \frac{O_E/N_E}{O_0/N_0}$$

where O_E is the number of patients with exposure who had the outcome. N_E is the number of patients with exposure, O_0 is the number of patients without exposure who had the outcome and N_0 is the number of patients without exposure.

A risk ratio of 1.0 implies no association; a value >1 implies an increased risk, and a value <1 implies a protective effect.

Relative Risk Reduction

Relative risk reduction (RRR) is defined as the proportional reduction in rates, or

$$\mathrm{RRR} = \frac{\left(\frac{O_0}{N_0} - \frac{O_E}{N_E}\right)}{\left(\frac{O_0}{N_0}\right)}$$

Absolute Risk Reduction

Absolute risk reduction (ARR) is the difference between absolute event rates, a more honest way of presenting data, or

$$\mathrm{ARR} = \frac{O_0}{N_0} - \frac{O_E}{N_E}$$

Number Needed to Treat

Number needed to treat (NNT) is the number of patients who would need to be exposed in order to prevent one outcome, or

$$\mathrm{NNT} = \frac{1}{\mathrm{ARR}}$$

Confidence Interval

The confidence interval (CI) is a measure of uncertainty; given a 95% confidence interval, we can be 95% sure that the true measure lies somewhere within the interval.

Odds Ratio

Odds are another way of describing the frequency of an event. For any given population in which O outcomes occur among N subjects,

$$\mathrm{Odds} = \frac{O/N}{1-(O/N)}$$

In effect, this is the probability of an event occurring divided by the probability that the event will not occur. The odds ratio compares odds between exposed and unexposed groups.

It is very important that you not confuse odds ratios with risk ratios (or relative risks). Generally, odds ratios and risk ratios are similar only if the outcome event rates are low (i.e., <10%).

Hazard Ratio

The hazard ratio is used specifically in survival studies. The hazard is the instantaneous probability of an event occurring given that a subject has survived for a certain period of time without experiencing that event. The hazard ratio compares the hazards of

exposed and unexposed groups.

Attributable Risk

Attributable risk measures the relative contribution of a given exposure to an outcome in a population. Thus, if we assume that the association is causal and we then remove the exposure, the attributable risk tells us by how much the outcome event rate should be reduced. Attributable risk (AR) is calculated as

$$AR = \frac{P(RR-1)}{P(RR-1)+1}$$

where P is the prevalence of exposure (or $N_E/[N_E+ N_0]$) and RR is the relative risk as described above.

Kaplan–Meier Event Rates

Kaplan–Absolute risk reduction Meier event rates are a graphical way of showing time free of an event. This method takes into account variable follow-up times (or censoring), an issue that is common in studies of outcomes of chronic diseases.

An example showing how these terms are calculated is now shown. Imagine a clinical trial in which 10,000 patients are randomized in a 1:1 manner to either drug A or drug B (i.e., 5,000 are assigned drug A and 5,000 are assigned drug B). Suppose that 2,500 of the drug A patients experience events, whereas 2,000 of the drug B patients have events. Thus, we have:

- Drug A: 5,000 patients
- Drug B: 5,000 patients
- Events with drug A: 2,500

Absolute event rate: 2,500/5,000 = 0.50

- Events with drug B: 2,000

Absolute event rate: 2,000/5,000 = 0.40

- Absolute rates, drug A and drug B: 0.50 and 0.40
- Risk ratio for drug B: 0.40/0.50 = 0.80
- Absolute risk reduction: 0.50 - 0.40 = 0.10
- Relative risk reduction: (0.50 - 0.40)/0.50 = 0.20
- NNT: 1/0.10 = 10
- Absolute rates, drug A and drug B: 0.50 and 0.40
- Odds for drug B: 0.40/(1 - 0.40) = 0.67

- Odds for drug A: 0.50/(1 - 0.50) = 1.00
- Odds ratio of drug B to drug A: 0.67/1.00 = 0.67

Terms Related to Studies of Diagnostic Tests

Studies of diagnostic tests often rely on 2 × 2 tables that relate diagnostic test findings to the presence or the absence of disease as assessed by a given standard. Figure 7.3 shows an example for which

	Disease Present	Disease Absent	Totals
Test Positive	A = true positives	B = false positives	T^+
Test Negative	C = false negatives	D = true negatives	T^-
	D^+ = prevalence (N)	D^- = (1– prevalence)(N)	N = total

FIGURE 7.3 A 2 × 2 table.

$$\text{Sensitivity (Sens)} = A/D^+ = \text{positive for disease}$$
$$\text{Specificity (Spec)} = D/D^- = \text{negative for health}$$

Thus,

$$A = \text{true positive} = \text{Sens}(D^+) = \text{Sens}(\text{prevalence})(N)$$
$$B = \text{false positive} = (1 - \text{Spec})(D^-)$$
$$= (1 - \text{Spec})(1 - \text{prevalence})(N)$$

Here, positive predictive value = true positives/all positives = A/(A + B), which is what we as clinicians really care about.

Substituting the above terms, we get the clinical version of Bayes theorem, namely,

$$\text{PPV} = \frac{\text{Sens}(\text{prevalence})(N)}{\text{Sens}(\text{prevalence})(N) + (1-\text{Spec})(1-\text{prevalence})(N)}$$
$$= \frac{\text{Sens}(\text{prevalence})}{\text{Sens}(\text{prevalence}) + (1-\text{Spec})(1-\text{prevalence})}$$

where PPV is the positive predictive value. Implications of Bayes theorem include:

1. PPV depends on sensitivity, specificity, and prevalence; the last is sometimes referred to as the pretest likelihood of disease.
2. PPV is most different from prevalence when the latter has a value near 0.50; that is, a diagnostic test is most useful the more uncertain one is of the diagnosis.

If one varies the cutoff point for a positive test, the specificity and sensitivity will vary in an inverse way. In other words, the better the sensitivity, the worse is the specificity, and vice versa.

A plot of sensitivity versus (1 − specificity) yields the receiver operating characteristic

(ROC) curve, where the area under the curve is a measure of the overall ability of the test to distinguish between patients with and without disease (Fig. 7.4).

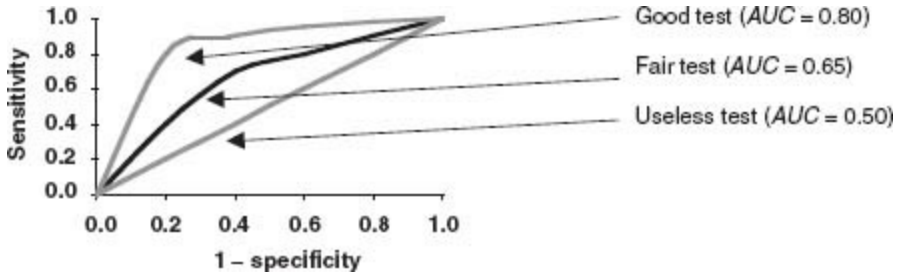

FIGURE 7.4 ROC curve.

The likelihood ratio (LR) enables us to relate pretest odds of disease to posttest odds:

$$LR+ = \frac{\text{Sensitivity}}{1-\text{Specificity}}$$

where LR+ is the positive likelihood ratio, and

$$\text{Odds}_{\text{post}} = LR\ (\text{Odds}_{\text{ple}})$$

where

$$\text{Odds}_{\text{pre}} = \frac{\text{prevalence}}{1-\text{prevalence}} \text{ and } \text{Odds}_{\text{post}} = \frac{PPV}{1-PPV}$$

In general, for a test to be clinically useful, the positive likelihood ratio (LR+) should be at least 10, whereas the negative likelihood ratio (LR-) should be <0.1.

In a similar fashion, the negative predictive value (NPV) is the ratio of true negatives to all negatives:

$$NPV = \frac{D}{D+C} = \frac{(\text{specificity})(1-\text{prevalence})}{(\text{specificity})(1-\text{prevalence})+(1-\text{specificity})(\text{prevalence})}$$

Analogously, LR− is

$$LR = \frac{\text{specificity}}{1-\text{sensitivity}}$$

The negative likelihood ratio relates the pretest odds of not having disease to the posttest odds of not having disease.

Confounding and Interaction

Even if an association between an exposure and an outcome is not due to random chance, it may not be a clinically meaningful one if confounding is present. A

confounding factor is said to exist if the factor has an association with both the exposure and the outcome but is not a causative link between them. As an example, consider alcohol intake as the exposure, lung cancer as the outcome, and smoking as the confounder. Smoking is a confounding factor with regard to the association between alcohol intake and lung cancer (Fig. 7.5).

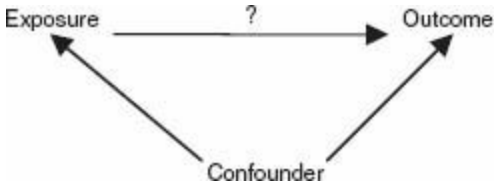

FIGURE 7.5 Confounding-factor diagram.

Researchers have several ways to deal with confounding.

Dealing with Confounding by Altering Study Design

The study design can be adjusted by:

- Restriction: Keep patients with confounders out of the study.
- Matching: Keep confounding factors balanced between those who are and those who are not exposed; this technique works better for cohort studies than for case–control studies.
- Randomization: If done properly and if sample size is large enough, randomization can assure balance of both observed and unobserved confounders.

Dealing with Confounding in the Analyses of the Study

Confounding can be avoided by:

- Restriction: Keep patients with confounders out of the analyses.
- Stratification: Assess the association between exposure and outcome according to the presence or the absence of possible confounders (discussed in more detail below).
- Multivariable methods: Discussed below.

Assessing Confounding by Stratified Analyses

Scenario A:

- Whole-population risk ratio (RR) = 3.0.
- Stratum with confounder C present, RR = 3.0
- Stratum with confounder C absent, RR = 3.0.

- No confounding is present.

Scenario B:

- Whole-population RR = 3.0.
- Stratum with confounder C present, RR = 1.0.
- Stratum with confounder C absent, RR = 1.0.
- Complete confounding is present.

Scenario C:

- Whole-population RR = 3.0.
- Stratum with confounder C present, RR = 1.5.
- Stratum with confounder C absent, RR = 1.5.
- Partial confounding is present.
- This is the most common scenario.

Interaction

> Interaction (also known as "effect modification") is an interesting situation in which the strength of an association between an exposure and an outcome is related to another factor. Such a scenario might be:

- Whole-population RR = 3.0
- Stratum with interaction factor I present, RR = 5.0
- Stratum with interaction factor I absent, RR = 2.0

Interaction can also be assessed using multivariable regression analysis by incorporating "interaction" terms into the analyses.

One of the most common errors in clinical research is failure to consider potential interactions.

Uses and Pitfalls of Multivariable Regression

Multivariable regression is used (a) to assess multiple confounders simultaneously, and (b) to estimate the likelihood of an outcome given multiple possible predictors.

Linear Regression

Linear regression is used when the outcome variable is continuous:

$$Y = \alpha + ß_1x_1 + ß_2x_2 + ß_3x_3 + \ldots + ß_ix_i$$

where $x_1$is the exposure of interest; x_2, x_3, ..., x_i are potential confounders; and the ß coefficients are parameter estimates of the associations between each covariate x and

outcome Y.

Logistic Regression

Logistic regression is used when the outcome variable is binary (yes/no):

$$\text{LogOdds} = \alpha + ß_1x_1 + ß_2x_2 + ß_3x_3 + ... + ß_ix_i$$

Cox Proportional Hazards Regression

Cox proportional hazards regression is used when the outcome is a hazard ratio, which is an assessment of time free of an outcome. Thus, the outcome includes not only whether an event occurs but also the length of observation before an event either does or does not occur. This is expressed as:

$$\text{Log hazard ratio} = h_0(ß_1x_1 + ß_2x_2 + ß_3x_3 + + ß_ix_i)$$

where h_0 is the theoretical hazard for subjects with all $x = 0$.

Common Errors in Using Multivariable Regression

- Model overfitting: more than one covariate per 10 outcome events—a very common and serious mistake
- Inappropriate linear assumption: when a logarithmic, inverse, or quadratic model would yield a better fit
- Violation of the proportional hazards assumption, which maintains that the hazard ratio between exposed and unexposed groups remains constant over time
- Failure to account for interactions
- Inappropriate variable selection: here knowledge of the biology of the question is really essential.
- Collinearity: covariates associated with one another
- Failure to look for and account for outliers and/or excessively influential observations

Bias and Its Consequences

Statistical bias is a systematic problem by which exposed and nonexposed subjects are either selected for study inclusion differently and/or have their outcomes assessed differently.

Selection bias occurs when the exposure of interest affects whether a subject is included in a study. A typical example is referral bias, under which patients with particularly severe illnesses are more likely to be studied at a tertiary care center. This

can lead to an invalid comparison with an unexposed group (a problem of internal validity) or difficulty generalizing results to the population at large (a problem of external validity).

Observation bias occurs when the exposure of interest has an effect, conscious or not, on how the outcome is measured. A way of avoiding this is "blinding" patients and investigators as to the nature of the exposure variable. Observation bias can result in an invalid comparison between exposed and unexposed patients, which is a problem of internal validity.

Recall bias may be a problem in case–control studies, in which patients with an outcome are more likely to recall an exposure than those without the outcome. A typical example is recall of pregnancy exposures among women who give birth to children with congenital defects.

Verification bias may be a problem in studies of diagnostic tests, in which the result of the diagnostic test directly affects the clinician's decision to refer a patient for the "gold standard" test. A typical example: patients with an abnormal stress study are more likely to be referred for coronary angiography. Verification bias results in an overestimation of sensitivity and an underestimation of specificity.

A key question to ask is "Are there differences in the way exposed and unexposed subjects are selected or evaluated?" If the answer is yes, then bias is likely to be present.

Causality and Validity

Randomized trials can establish causality, that is, that a particular treatment or prevention strategy specifically causes a certain outcome. Other types of clinical studies can only establish association, not cause.

Criteria have been established by which to judge whether an association is likely to be causal. These criteria include:

1. Strength of association
2. Dose–response relationship
3. Temporal relationship (exposure always precedes outcome)
4. Biologic plausibility
5. Consistency with other studies

Another important area to consider in evaluating research studies is validity. An observed association between an exposure and an outcome in a given population is likely to have internal validity if, after use of appropriate methods, it is not due to chance, confounding, or bias.

External validity refers to both the likelihood of a cause–effect association as noted above and the likelihood that the observed association is relevant to other populations

not studied.

Issues Related to Specific Types of Studies (From ACP Journal Club Criteria)

Randomized Trials

- Adequate randomization must be achieved. Look for "Table 1" and the type of randomization method used.
- Follow-up should include at least 80% of the study population.
- Consider the outcome measures chosen. Are they objective and clinically relevant? Are they subject to bias? For cardiology studies, all-cause death is the best outcome.

Studies of Diagnosis

- There should be a reasonable spectrum of patients.
- The "gold standard" should be interpreted without knowledge of the results of the test of interest (source of observation bias).
- Each participant should get both the test being studied and the gold standard test, with performance on the gold standard being independent of the results of the diagnostic test (i.e., no verification bias).

Studies of Prognosis

- The inception cohort should consist entirely of people who are free from the outcome.
- Follow-up should include at least 80% of the study population.
- Consider the outcome measures chosen.

Case–Control Studies

- The key to validity is how controls were chosen.
- Controls should come from the same person–time pool as cases.
- If a control had had the outcome, would he or she have become a case for the study?

Studies of Economics

- Comparisons involving real patients are best.
- Costs should be measured in terms of resources used, not charges.

- Incremental costs of one intervention over another should be included.
- Sensitivity analyses should be performed.

Clinical Prediction Rules

- Should be validated either in a different data set or by using modern validation techniques, such as bootstrapping
- Should consider treatment, diagnosis, prognosis, causation

Systematic Review Articles

- The article should identify the search methods used.
- Only quality source materials should be chosen.
- If the review includes meta-analysis, appropriate techniques to consider variations in study quality, sample sizes, and publication bias should be used.

CURRENT CONTROVERSIES IN RESEARCH

1. The peer review method: Issues include
   - **a.** Assessing reviewers
   - **b.** Dealing with bias and conflicts of interest
   - **c.** Creating uniform standards
2. Investigator concerns
   - **a.** Conflicts of interest
   - **b.** Drug and device company control over data and publication
   - **c.** Ethical issues, particularly regarding safety of human subjects
   - **d.** Informed consent and documentation
   - **e.** Complex regulations regarding research practice
3. Statistical and analytical methods
   - **a.** Getting away from p values
   - **b.** Equivalency trials
   - **c.** New types of databases (object-oriented, "meta-data," XML)
   - **d.** Controlling for bias and confounding with propensity analysis
   - **e.** Nonproportional hazards
   - **f.** Validation with bootstrapping and similar techniques
   - **g.** Optimal model selection methods; information theory
4. Public policy concerns

a. How to keep up
b. Proliferation of journal summary publications
c. Development of guidelines and their dissemination
d. Timing of publication and meeting presentations
e. The impact of the media
f. Associations between medical societies and editors; maintenance of editorial independence
g. Electronic versus paper information

SUGGESTED READINGS

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Guyatt G, Rennie D, eds. Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice. Chicago: American Medical Association; 2002.

Woodward M. Epidemiology: Study Design and Data Analysis. New York: Chapman & Hall/CRC Press; 1999.

QUESTIONS AND ANSWERS

Questions

1. A study finds that in the largely white community of Olmstead County, Minnesota, drug B is effective for controlling blood pressure compared to placebo. As a physician working in a practice caring mainly for African American patients, your concern is that this study may lack:
   a. Control for bias
   b. Internal validity
   c. Consideration of the effects of chance
   d. External validity
   e. Failure to consider interaction

2. A new diagnostic test for coronary disease is compared against cardiac catheterization among 100 patients who had both studies performed. Coronary disease is present in 50 patients, among whom 45 had a positive test. Among the patients without coronary disease, 25 had a positive test. Which of the following is true?
   a. The sensitivity is 90%.
   b. The specificity is 50%.
   c. The sensitivity is likely to be <90%.
   d. The sensitivity is likely to be <50%.
   e. The positive likelihood ratio is 2.

3. A study of 10,000 people without a history of myocardial infarction (MI) is done to see what effect a high uric acid level has on risk. An elevated level is present in 2,000, among whom 100 have an MI during 5 years of follow-up. Among the people without an elevated uric acid level, 200 have an MI during the same period. The odds ratio for an MI given an elevated uric level compared to those without an elevated level is:
   a. 0.50

b. 2.00
c. 0.25
d. 2.05
e. 5.25

4. In the above study, if we assume that there is a causative link between uric acid and MI, the attributable risk is:
   a. 0.13
   b. 0.17
   c. 0.25
   d. 2.00

5. A study of a new electrocardiograph (ECG) technology looks at the ability of the ECG finding to predict sudden death. Among 300 patients studied, 25 had sudden death. The unadjusted relative risk for the ECG finding for prediction of sudden death is 3.0. After adjustment for age, gender, left ventricular ejection fraction, nuclear findings, diabetes, hypertension, and cholesterol level in a multivariable Cox regression analysis, the adjusted relative risk is 2.5. Which of the following is true?
   a. The ECG finding is a valid, independent predictor of death.
   b. Confounding is present.
   c. Model overfitting occurred.
   d. The finding is statistically significant but not clinically significant.
   e. Bias was not adjusted for.

6. Recently published guidelines suggest that antibiotic prophylaxis prior to dental procedures is not indicated to prevent infective endocarditis in most cardiac patients. An investigator is designing a study to examine this further. Which of the following statements is true?
   a. A prospective cohort study design may prove that dental procedures cause infective endocarditis.
   b. A cross-sectional study design is appropriate to study the course of infective endocarditis.
   c. A meta-analysis of previously published observational studies will help quantify the summary data available about endocarditis prophylaxis.
   d. A case–control study is inappropriate when the goal is to study a rare disease.

7. What is a “p-value”?
   a. p-value is the probability that the relationship you are observing is pure chance.
   b. p-value is the probability that the null hypothesis is true.
   c. p-value is the probability of falsely rejecting the null hypothesis.
   d. p-value is the probability that replicating the experiment will yield the same result.

8. In the Randomized Aldactone Evaluation Study (N Engl J Med. 1999;341:709–717), the rate of death over a mean period of 24 months was 46% in the placebo arm, and 35% in the spironolactone arm. Approximately how many heart failure patients would need to receive spironolactone to prevent death in one person?
   a. 90
   b. 9
   c. 11
   d. Unable to calculate without knowing the incidence and prevalence of disease in the population

9. The RAPID trial (Circulation. 1995;91:2725–2732) was designed to test the hypothesis that bolus administration of one or more dosage regimens of reteplase was superior to standard-dose alteplase in achieving infarct-related artery patency 90 minutes after initiation of treatment. This was an example of a:
   a. Phase I study
   b. Phase II study
   c. Phase III trial
   d. Phase IV trial

10. A 65-year-old man is seen in clinic for evaluation of a murmur heard by his primary care physician. He is asymptomatic. On physical exam, he is found to have a systolic murmur. You estimate that he has a 40% chance of having aortic stenosis. You want to investigate this further with an echocardiogram, which is 90% sensitive and 95% specific. If the echocardiogram is positive, how sure can you be of the diagnosis?
    a. 90%
    b. 90% to 93%
    c. 93% to 95%
    d. 95%

Answers

1. Answer D: External validity. Just because the finding is true among Caucasians, it may not be true among African Americans.

2. Answer C: The sensitivity is likely to be <90%. This is an example of verification bias, in which sensitivity is overestimated and specificity is underestimated.

3. Answer D: 2.05. Remember, Odds = P/(1 -P). Thus, the odds for patients with an elevated uric acid level are 0.05/(1 -0.05) and the odds for patients without an elevated uric acid level are 0.025/(1 -0.025).

4. Answer B: 0.17. Attributable risk is Prev(RR -1)/[Prev(RR -1) + 1]. The prevalence is 0.2 and the relative risk is 2.0.

5. Answer C: Model overfitting occurred. There were only 25 outcome events, meaning that at most two or three covariates can be considered in a regression model.

6. Answer C: Meta-analyses of clinical trials or observational studies are a contemporary approach to pool and summarize existing studies. Cross-sectional studies may demonstrate the status of a disease in a point in time but cannot be used to study time-dependent processes. Cohort studies are the best study design for investigating the course or cause of a disease, but only clinical trials can be used to prove causation.

7. Answer A: The more formal definition is “the probability of obtaining a test statistic at least as extreme as the one that was actually observed, assuming that the null hypothesis is true.”

8. Answer B: Number needed to treat (NNT) = 1/absolute risk reduction (ARR). ARR=0.46–0.35 = 0.11, NNT = 1/0.11 = 9.

9. Answer B: Phase II studies evaluate whether an intervention has any biologic activity or clinical effect, and may also be used to estimate the rate of adverse events.

10. Answer B: Using clinical version of Bayes theorem, the probability of diagnosis is (0.90) (0.40)/[(0.90)(0.40) + (0.05)(0.60)] = 92.3%.

SECTION II ■ CARDIOVASCULAR IMAGING AND STRESS TESTING

CHAPTER

Chest Radiography for the Cardiovascular Medicine Boards

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Despite continuing advances that have greatly expanded the ability to assess cardiovascular anatomy noninvasively through an array of imaging modalities, chest radiography (CR) remains a very useful part of the initial cardiovascular evaluation. CR is widely available, can be acquired rapidly and inexpensively, and has a low associated ionizing radiation dose. With an organized approach toward interpretation, and insight into the strengths and limitations of CR, the cardiologist can maximize the use of this tool in clinical practice. This chapter focuses on the most important components of the CR with regard to cardiovascular disease, namely:

1. Pulmonary vascular patterns
2. Cardiomediastinal silhouette
3. Calcification patterns

The following radiographs illustrate the appearance of a variety of cardiac abnormalities. Whenever possible, tables are included to delineate the differential diagnoses for representative chest radiographic findings.

BASIC APPROACH AND PROJECTIONS

Understanding the strengths and weaknesses of CR techniques is helpful in both the selection and interpretation of exam. Standard CR techniques include erect posteroanterior (PA) and lateral projections. In patients unable to stand for an erect PA, an anteroposterior (AP) radiograph can be performed. Additional specialized CR

techniques exist, though their utilization is limited with widespread availability of tomographic imaging. The erect PA and lateral technique hold several advantages, as AP technique will magnify car- diomediastinal structures, and the ability to interpret pulmonary vasculature correctly is limited in supine patients. Additionally, more standardized techniques of acquisition are often used with PA radiographs, allowing for more reliable comparison between radiographs. Benefits of portable radiographs include the speed and convenience of obtaining a radiograph without transporting a patient.

Interpretation of radiographs can be aided by an ordered approach. Identification of the patient's name and date of the examination is a straightforward but important step and can save further confusion or wasted time when checked first. Visible medical devices (catheters, drains, and other support devices) should be assessed to confirm position and any associated complication. When prior CRs are available, they should be assessed concurrently to help detect new abnormalities or to confirm the stability of a long-standing finding.

The three aforementioned components, pulmonary vasculature, cardiomediastinal silhouette, and calcifications, can then be reviewed in any order. Changes in each of these central components are a direct manifestation of the underlying cardiovascular disorder; and taking all three of these components into account ensures an appropriate, systematic approach to the standard CR. Other elements of CR interpretation are important (such as appropriate technique, assessment of pulmonary parenchyma) and have important clinical implications; however, we focus our discussion toward the elements most helpful in depiction of cardiovascular disease.

PULMONARY VASCULAR PATTERNS

Pulmonary Vascular Patterns in Normal and Various Cardiovascular Disease States

1. **Normal**
   - In normal patients, the vessels in the upper zones are thinner than those at a similar distance from the hilum in the lower zones (normal ratio 1:3)
   - Pulmonary artery (PA)/pulmonic valve obstruction (no shunt or pulmonary hypertension)
   - Aorta/aortic valve (AV) obstructions (no shunt, left ventricular compromise, mitral valve disease)
   - Insignificant left-to-right shunt: $Q_p/Q_s < 1.5$
2. **Increased (overcirculation)**
   - Significant left-to-right shunt: $Q_p/Q_s > 1.5$ (acyanotic)

- Atrial septal defect (ASD)
- Ventricular septal defect (VSD)
- Patent ductus arteriosus
- Partial anomalous pulmonary venous return

3. **Decreased (undercirculation)**
   - Right-to-left shunt
   - Tetralogy of Fallot
   - Ebstein anomaly with ASD
   - Pulmonary oligemia
   - Ebstein anomaly (severe ± ASD)
4. **Admixture shunt (no pulmonic stenosis or atresia/cyanotic)**
   - Transposition complexes
   - Truncus arteriosis
   - Univentricular heart (single ventricle)
   - Total anomalous pulmonary venous return: types I and II
   - Tricuspid atresia + VSD
5. **High-output states**
   - Anemia
   - Pregnancy

Decreased Pulmonary Blood Flow (Fig. 8.1)

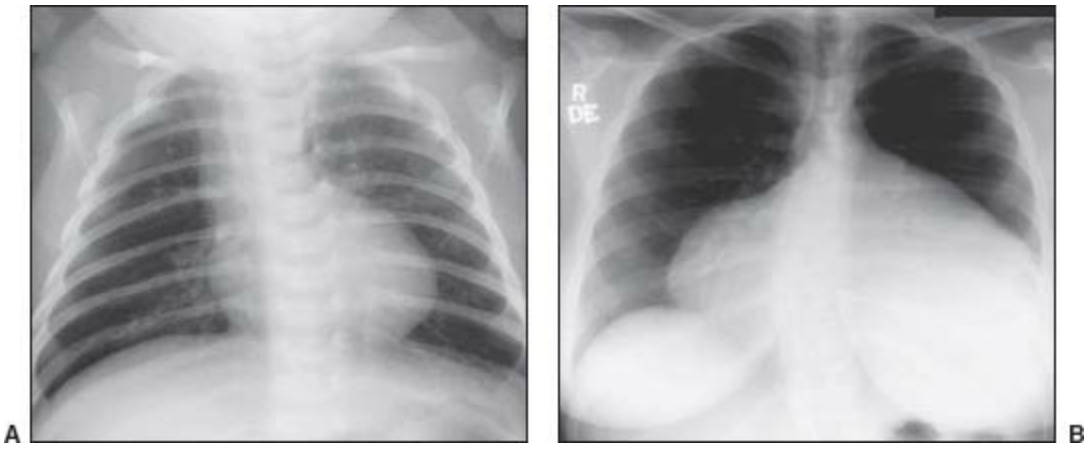


FIGURE 8.1 Decreased pulmonary blood flow. **A:** Tetralogy of Fallot. **B:** Ebstein anomaly.

Increased Pulmonary Blood Flow (Fig. 8.2)

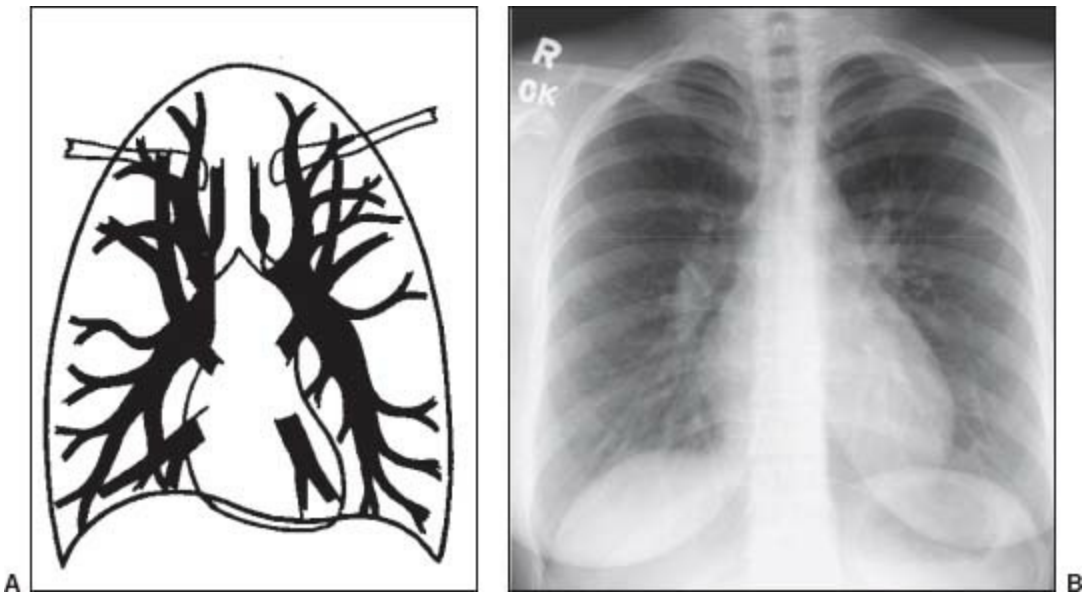


FIGURE 8.2 Increased pulmonary blood flow. **A:** Increased: balanced (overcirculation). **B:** ASD

Increased distributed (Fig 8.3)

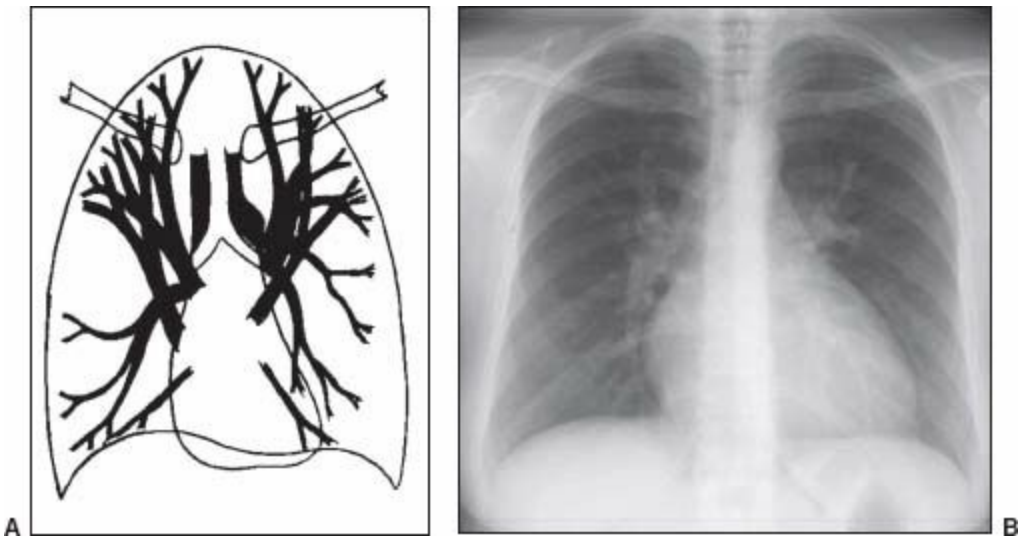


FIGURE 8.3 Increased: redistributed. **A:** Pulmonary venous hypertension (PVH). **B:** Hypertrophic cardiomyopathy (HCM) PVH.

Pulmonary Arterial Hypertension (PAH)

Causes of PAH

- Precapillary: pulmonary hypertension (both primary and pulmonary hypertension associated with hepatic disease, drugs/toxins, HIV), congenital cardiovascular disease, chronic thromboembolism, chronic alveolar hypoxia (COPD, interstitial lung disease, hypoventilation)
- Postcapillary: left sided cardiovascular disease, mitral stenosis, aortic valve

disease, cardiac tumors, extrinsic pulmonary venous compression, fibrosing mediastinitis, pulmonary venoocclusive disease

Increased: Central (Fig. 8.4)

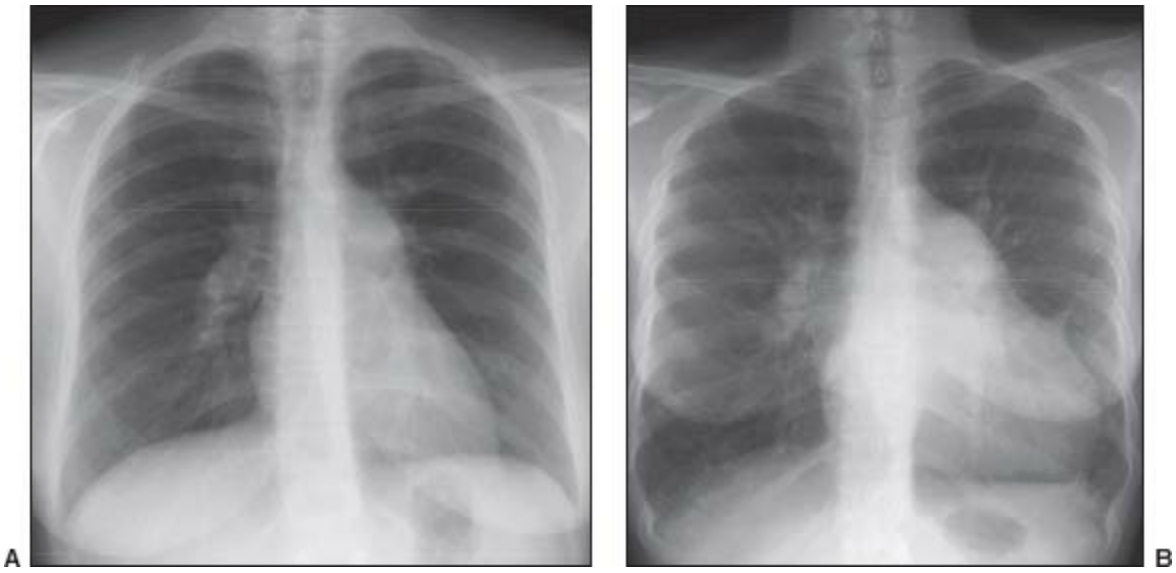


FIGURE 8.4 **A:** Idiopathic (pre-capillary) PAH; **B:** Post-capillary PAH.

Pulmonary Venous Hypertension

Stages of PVH

Stage 1: Pulmonary vascular redistribution

PCWP: Acute, 13 to 18 mm Hg; chronic, 18 to 22 mm Hg

Stage 2: Redistribution + interstitial pulmonary edema

PCWP: Acute, 18 to 25 mm Hg; chronic, 23 to 30 mm Hg

Stage 3: Redistribution + interstitial and alveolar pulmonary edema

PCWP: Acute, >25 mm Hg; chronic, >30 mm Hg>

Causes of PVH

Pulmonary venoocclusive disease

Pulmonary vein stenosis (postradiation therapy, post–atrial fibrillation ablation)

Left atrial/left ventricular obstruction

Myxoma or other tumors

Mitral valve disease

Mitral stenosis

Mitral regurgitation

Left ventricular compromise

Dilated cardiomyopathy
Acute or chronic myocardial ischemic disease
Restrictive cardiomyopathy
Pericardial disease
Constrictive pericarditis

Pulmonary Edema Patterns

Increased hydrostatic pressure gradient
Increased capillary permeability
Decreased osmotic pressure gradient
Lymphatic incompetence

TABLE
8.1 Radiographic Features of Different Types of Pulmonary Edema

	Cardiac Injury	Fluid Overload	Injury
Cardiac silhouette	Often enlarged	Normal or enlarged	Not enlarged
Pulmonary blood flow	Redistributed	Balanced	Normal
Pulmonary blood volume	Normal or Increased	Increased	Normal
Peribronchial cuffing	Very common	Not common	Not common
Air bronchograms	Not common	Not common	Very common
Lung edema	Even	Central	Peripheral
Pleural effusions	Very common	Very common	Not common

CARDIOMEDIASTINAL SILHOUETTE PATTERNS

Normal landmarks

- Central

  Tracheobronchial tree–PA relationship
  Early branching to middle lobe on right
  Right PA descends anterior to bronchus
  Left PA passes over and descends posterior to bronchus

- Right

  Right chambers
  Ascending aorta
  Superior vena cava/azygos vein

- Left

  Aortic “knob” (distal arch + isthmus)
  Descending aorta
  Main PA
  Descending aorta
  Left atrium
  Left ventricle

Normal Cardiac Silhouette (Fig. 8.5)

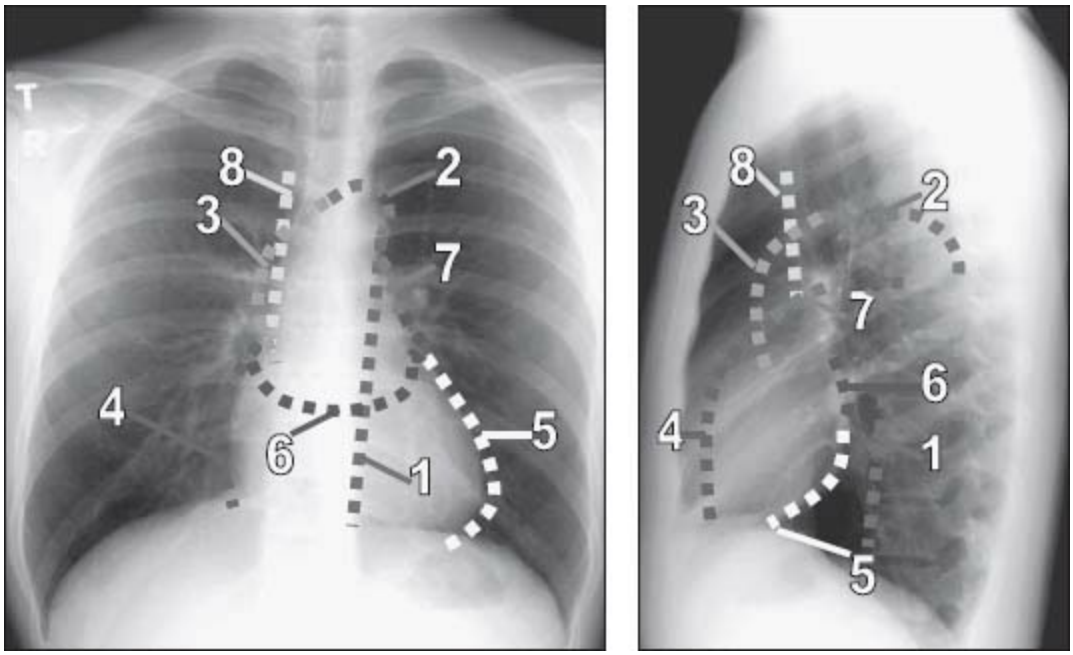


FIGURE 8.5 1, descending aorta; 2, aortic knob (distal arch and isthmus); 3, ascending aorta and proximal arch; 4, right ventricle; 5, left ventricle; 6, left atrium; 7, right atrium; 8, superior vena cava and azygous vein.

Normal Size

The most commonly used parameter for assessment of cardiac size is the cardiothoracic ratio, which corresponds to the maximum transverse diameter of the cardiac silhouette in relation to thoracic width. The accepted upper limit of normal is 50% in adults.

It should be emphasized that evaluation of individual cardiac chambers with CR is not reliable, with the occasional exception of left atrial dilation, which can be associated with a double density projecting over the right heart border as well as splayed central bronchi.

Interval changes in the size of the cardiac silhouette are of clinical interest, although this is always subject to variability in technique between CRs.

TABLE
8.2 Enlargement of Cardiovascular Structure: Basic Causes

Cause	Examples
Decreased integrity of wall	Post–myocardial infarction (MI) left ventricular true aneurysm
Volume overloading	Dilated left atrium in mitral regurgitation; dilated left ventricle in aortic insufficiency
Pressure overloading (differential response)	Atria dilate (dilated left atrium in mitral stenosis); ventricular hypertrophy (thick left ventricle in hypertension)

Pectus Excavatum (Fig. 8.6)

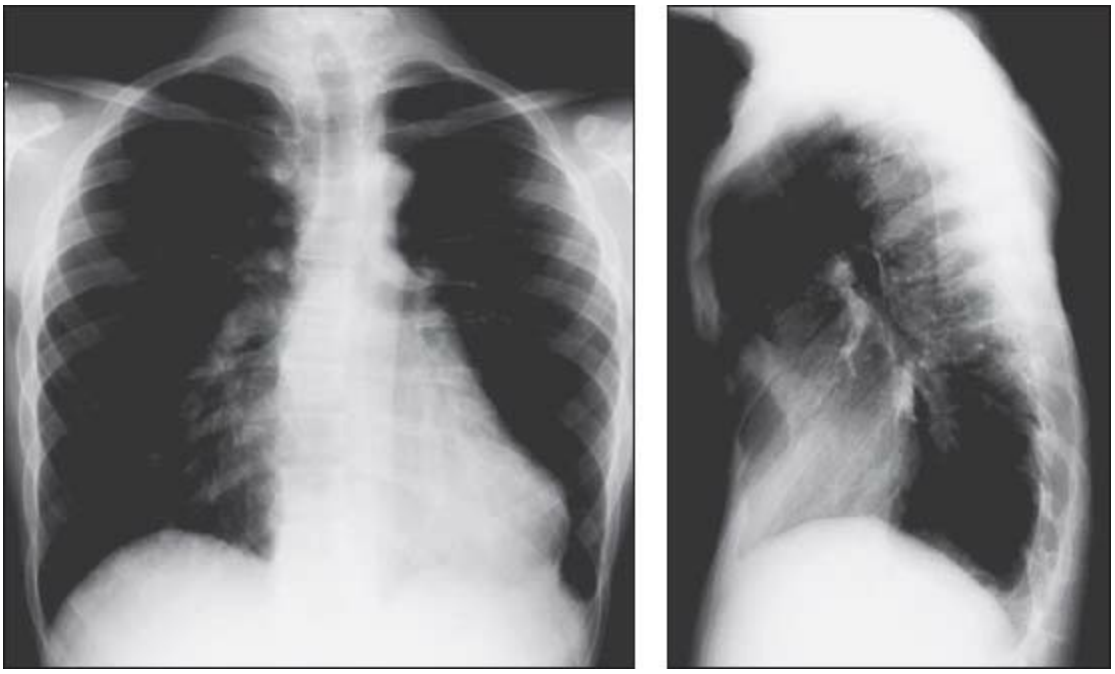


FIGURE 8.6 Pectus excavatum.

Findings

1. Pectus excavatum configuration of ribs
   - Straight or upsloping posterior ribs
   - Sharply downsloping anterior rib
2. Heart usually displaced to the left; right heart border not visible

Pericardial Cyst (Fig. 8.7)

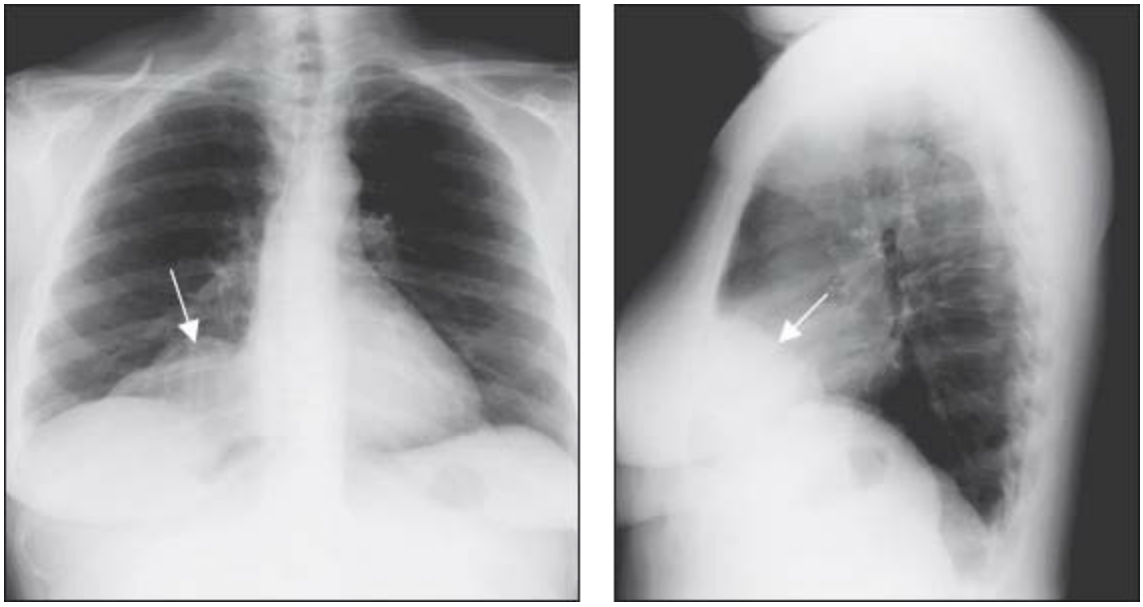


FIGURE 8.7 Pericardial cyst. Findings

Findings

1. The arrows mark the pericardial cyst

Aortic Stenosis (Fig. 8.8)

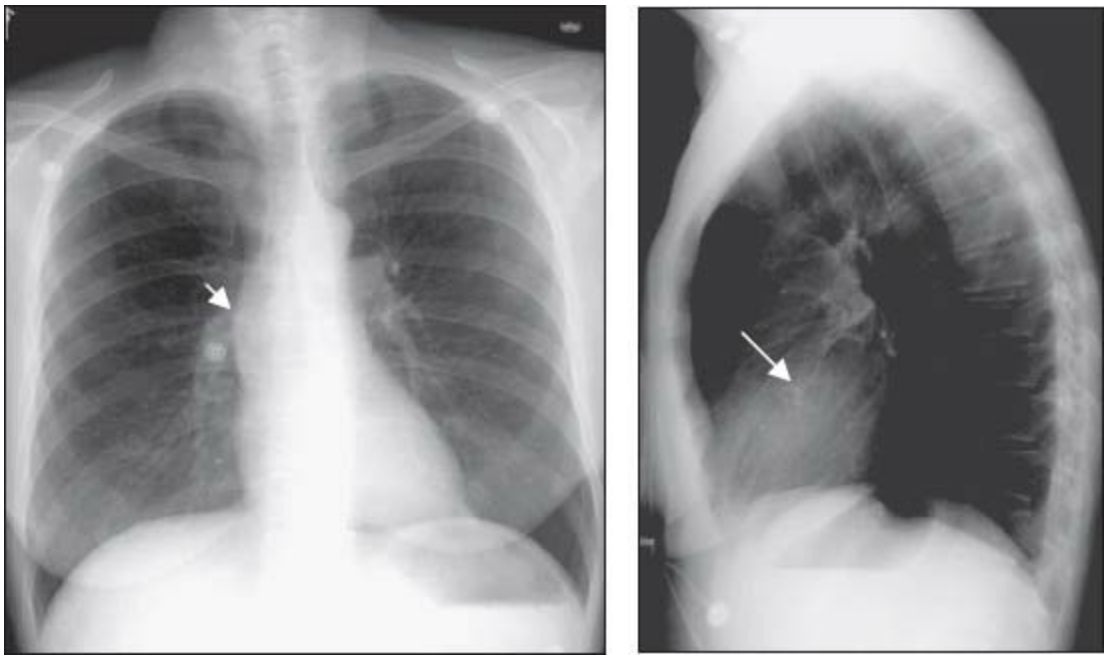


FIGURE 8.8 Aortic stenosis.

Findings

1. Calcified AV (long arrow)

2. Dilated ascending aorta beyond stenotic AV (short arrow)
3. Normal cardiac silhouette (because only pressure and not volume overload present)

Pseudocoarctation (Fig. 8.9)

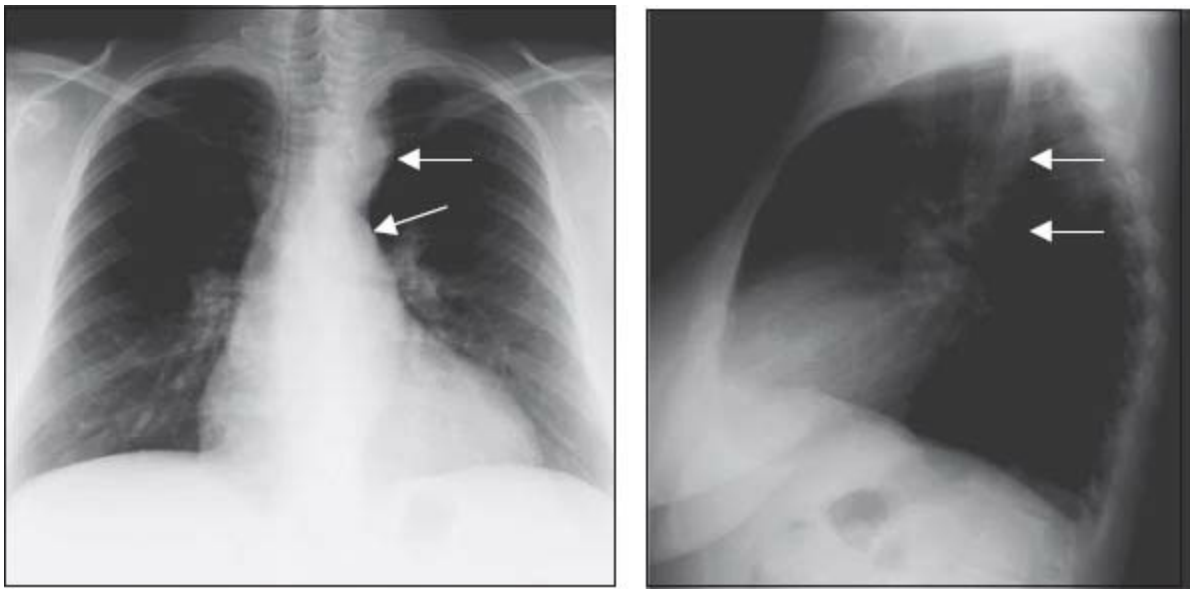


FIGURE 8.9 Pseudocoarctation.

Findings

1. "Double left aortic arch sign" (arrows mark the "2" arches)
2. Congenital elongation of the thoracic aorta associated with "kinking" of the aorta at the relatively fixed ligamentum arteriosum. There is no physiologic obstruction, so there is an absence of collateral vessel development and subsequent rib notching.

Coarctation (Fig. 8.10)

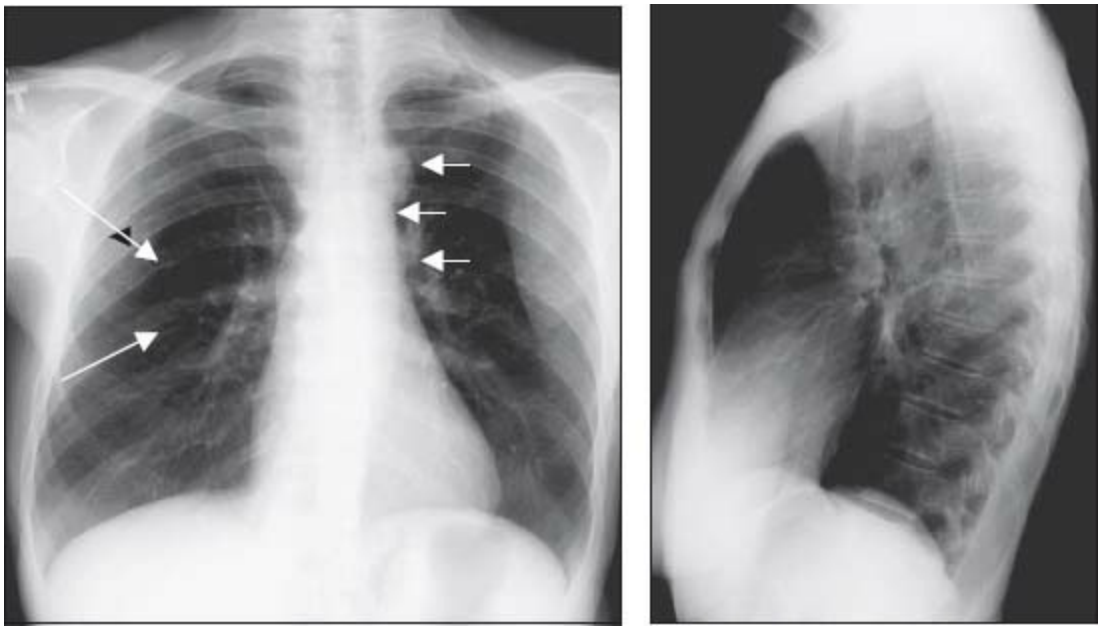


FIGURE 8.10 Coarctation.

Findings

1. Number "3" sign (short arrows)
2. Rib notching (long arrows) on the inferior portion of the posterior ribs (third to ninth) from pressure erosion by dilated intercostal arteries that serve as collateral blood flow between the internal mammary arteries and the descending aorta

Valvar Pulmonic Stenosis (Fig. 8.11)

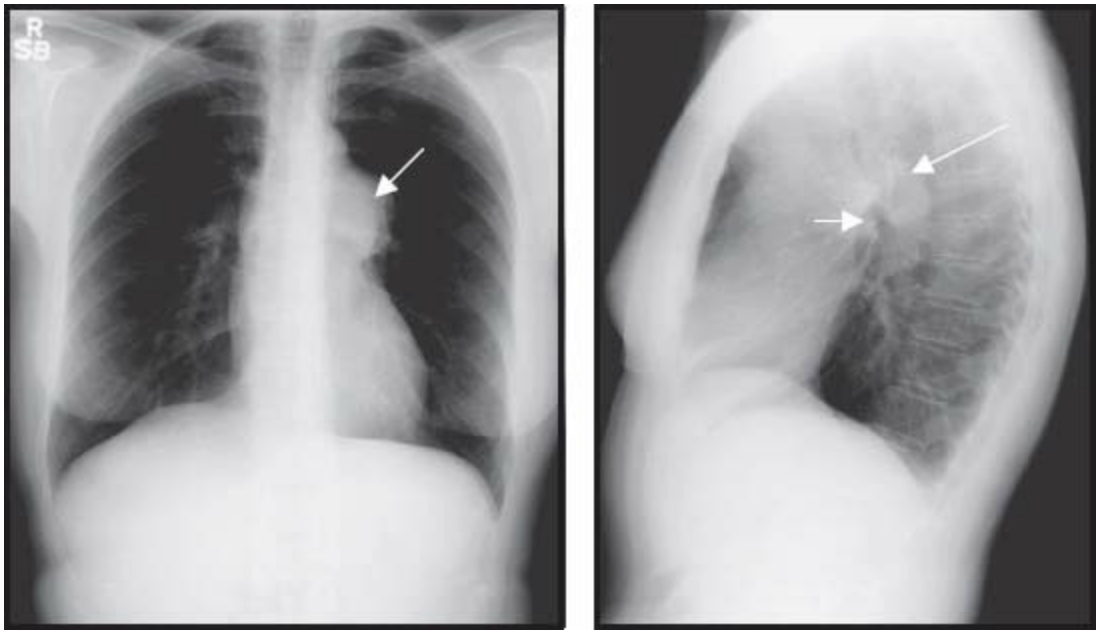


FIGURE 8.11 Valvar pulmonic stenosis.

Findings

1. Enlarged main PA, the degree of this enlargement does not predict the severity of stenosis
2. Selective enlargement of the left PA (long arrow) with normal-sized right PA (short arrow)
3. Normal cardiac silhouette and normal to decreased pulmonary vascular markings, depending on the degree of stenosis

Mitral Stenosis (Fig. 8.12)

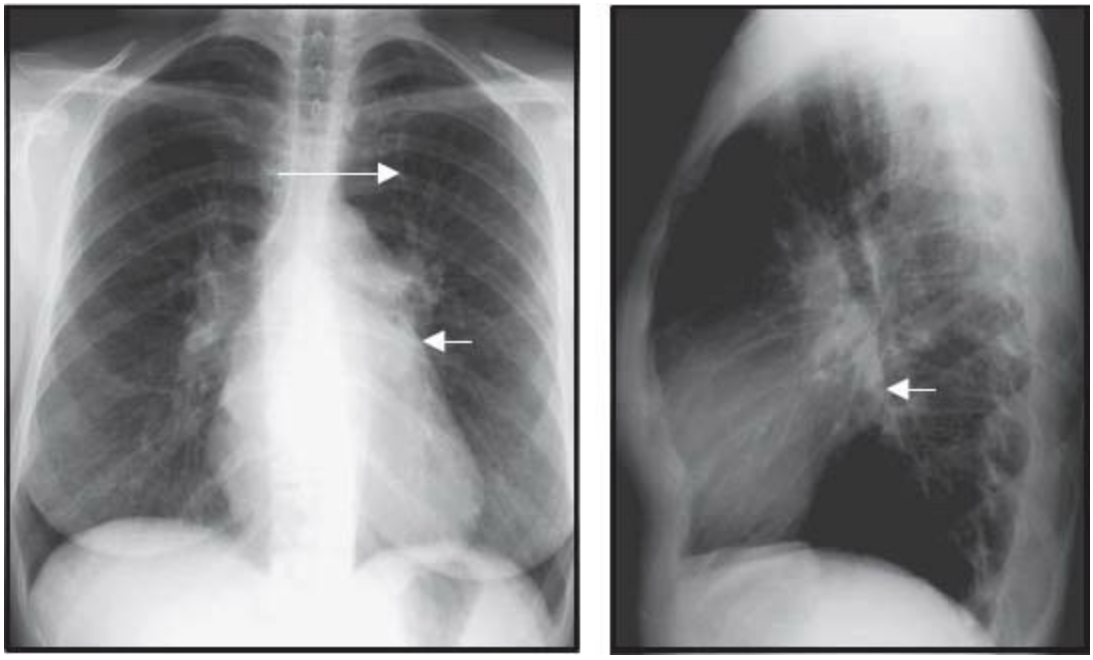


FIGURE 8.12 Mitral stenosis.

Findings

1. Increased pulmonary vascularity (long arrow)
2. Increased left atrial size (short arrows)
3. Normal-sized left ventricle

Mitral Regurgitation (Fig. 8.13)

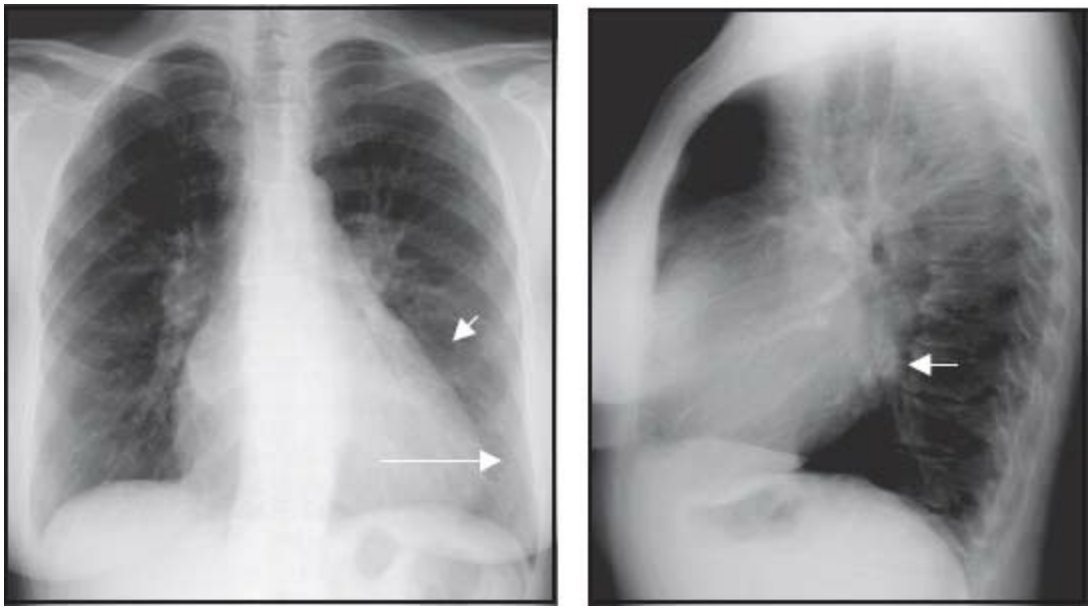


FIGURE 8.13 Mitral regurgitation.

Findings

1. Increased pulmonary vascularity
2. Increased left atrial size (short arrows)
3. Increased left ventricle size secondary to volume overload (long arrow)

CALCIFICATION PATTERNS

- Cardiac

  Left atrium
  Mitral annulus
  Mitral valve
  Aortic valve
  Coronary artery
  Myocardium (post-MI)

- Paracardiac

  Pericardium
  Thoracic aorta

Calcific Constrictive Pericarditis (Fig. 8.14)

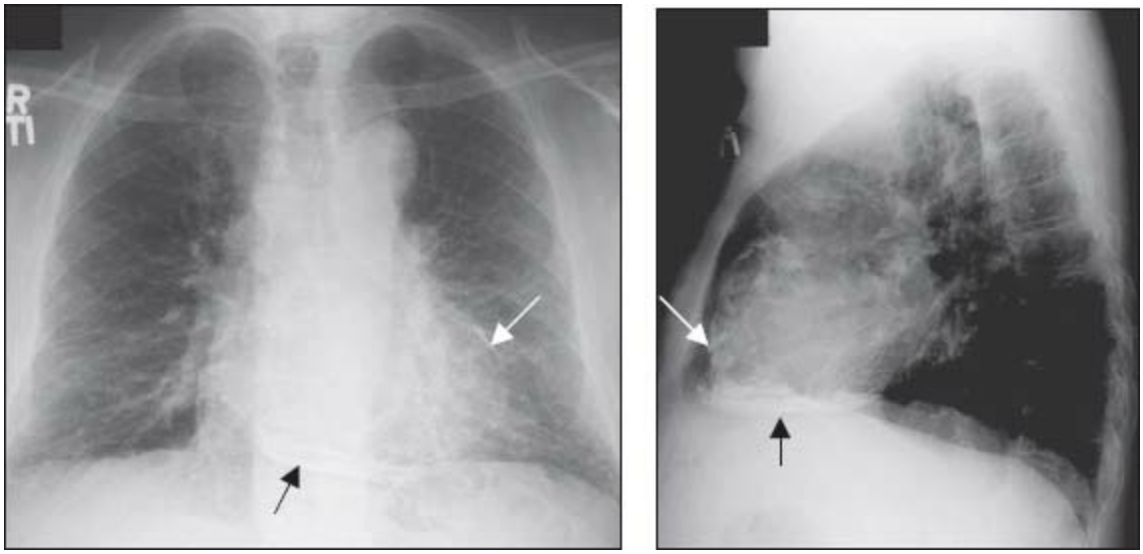


FIGURE 8.14 Calcific constrictive pericarditis.

Findings

1. Extensive pericardial calcification (arrows)
2. Calcifications along atrial surfaces suggest pericardium rather than myocardium origin.

Left Atrial Wall Calcification (Fig. 8.15)

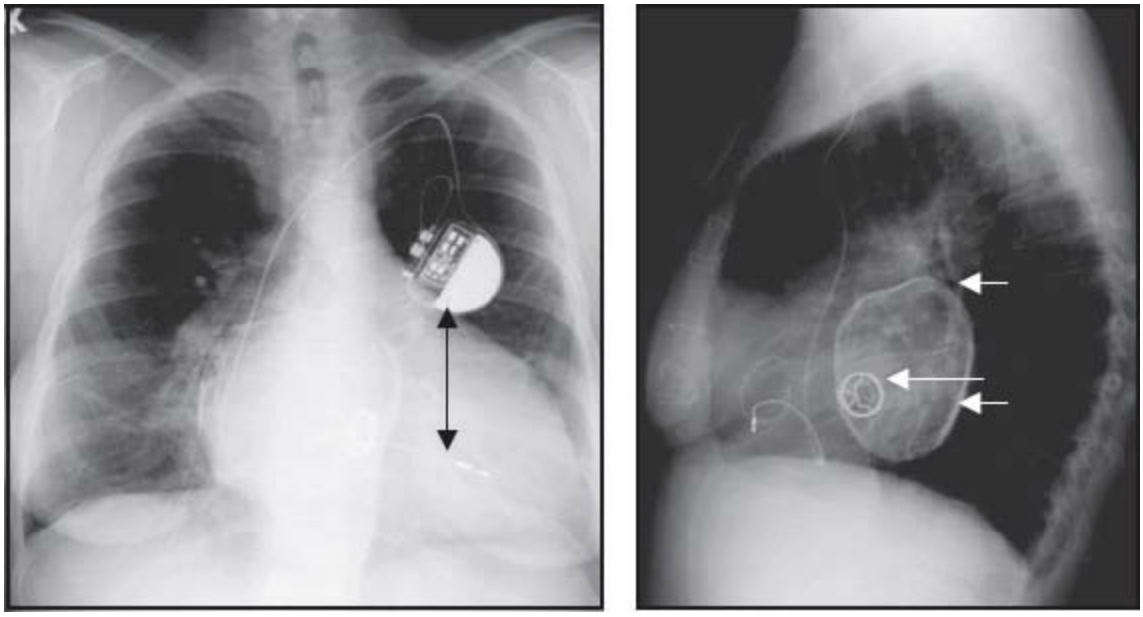


FIGURE 8.15 Left atrial wall calcification.

Findings

1. Severe diffuse calcification of the left atrium (short arrow)

2. Bjork–Shiley valve in the mitral position (long arrow)
3. Single right ventricular (RV)-lead pacemaker (black arrows)

Mitral Annular Calcification (Fig. 8.16)

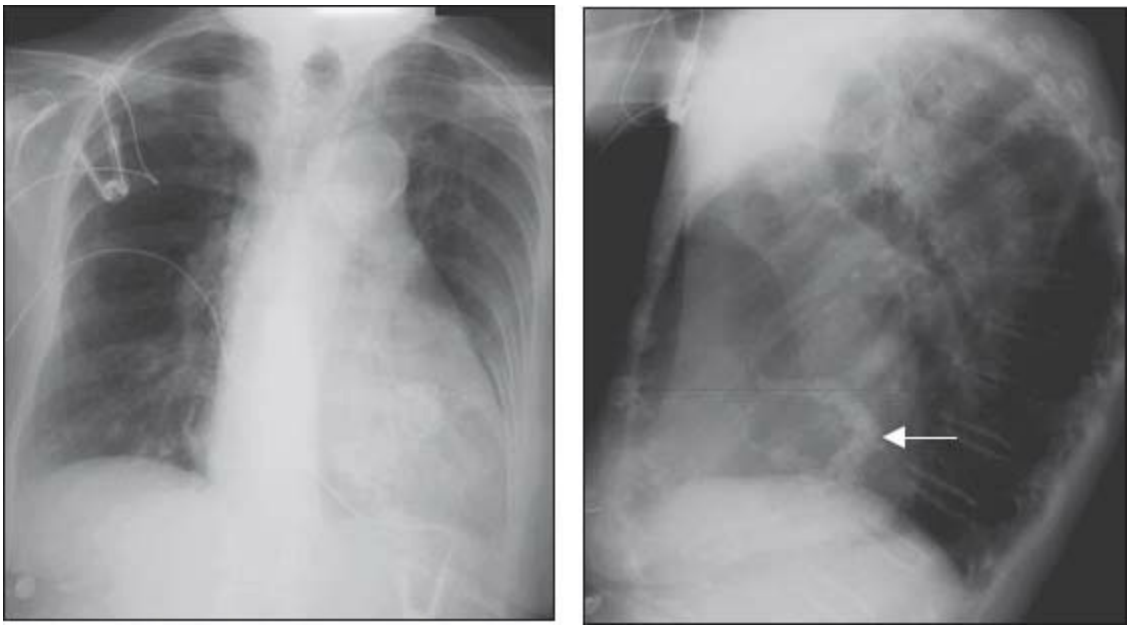


FIGURE 8.16 Mitral annular calcification.

Findings

1. Extensive mitral annulus calcification, seen best on the lateral radiograph as a large backward "C"

Calcified Post-MI Left Ventricular True Aneursym (Fig. 8.17)

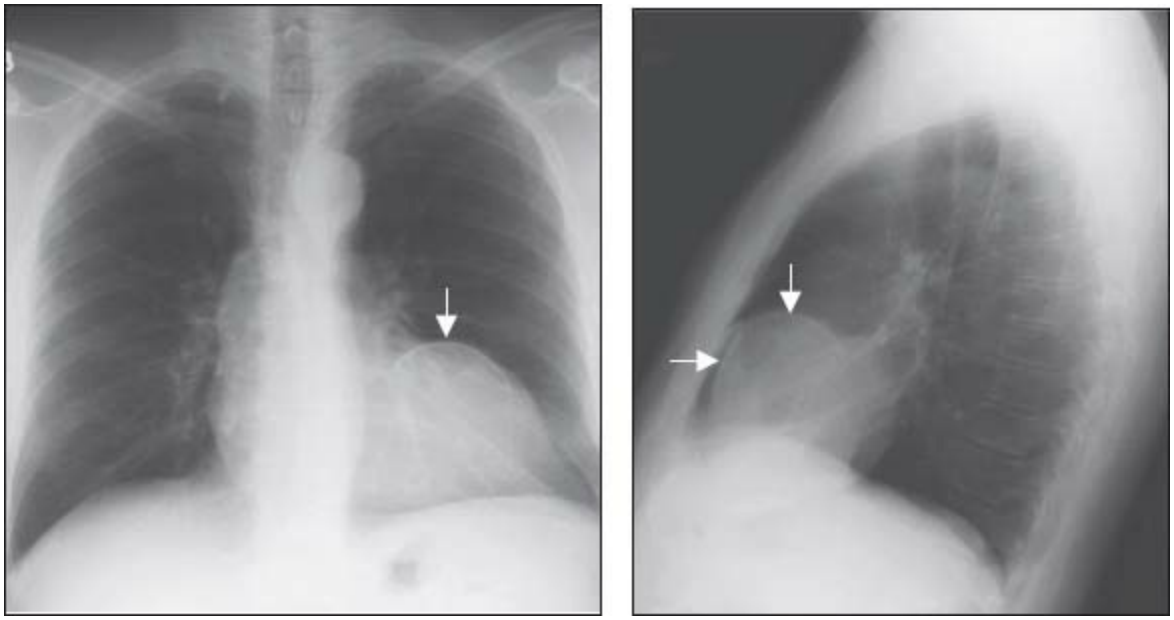


FIGURE 8.17 Calcified post-MI left ventricular true aneursym.

Findings

1. Calcified left ventricular aneurysm (arrows)

Coronary Artery Calcification (Fig. 8.18)

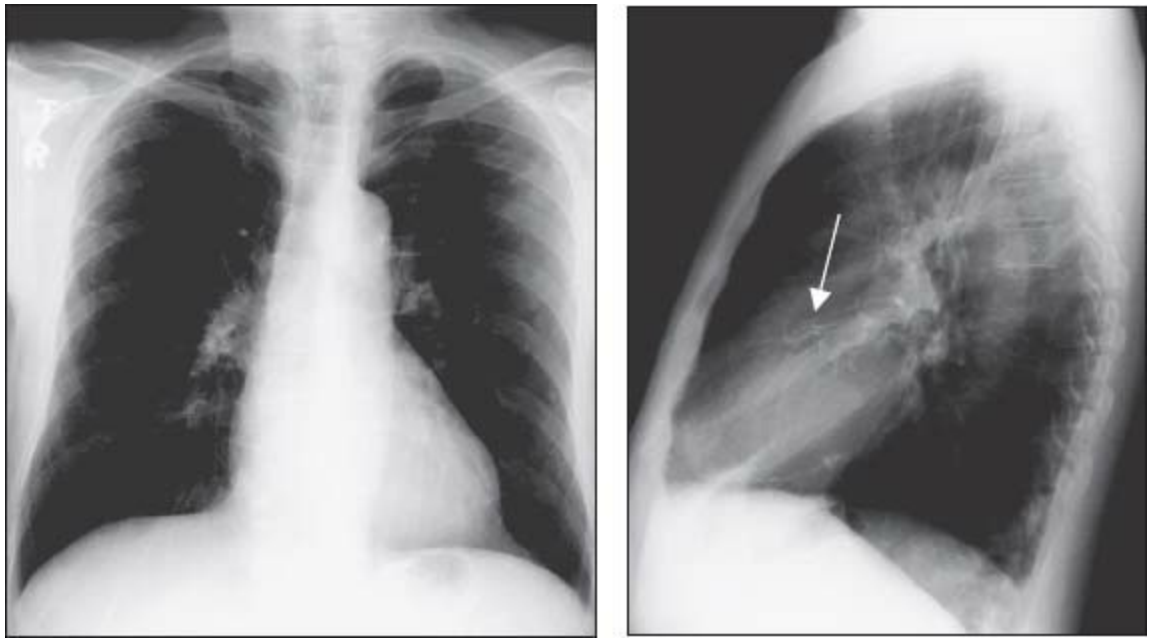


FIGURE 8.18 Coronary artery calcification.

Findings

1. Extensive coronary calcification of the left anterior descending artery (arrow), best

seen on the lateral radiograph.

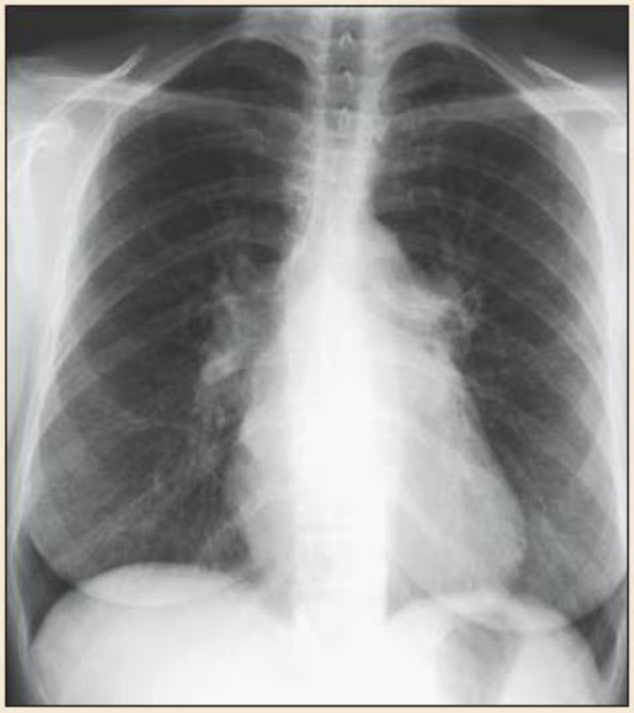
ACKNOWLEDGMENTS

The authors acknowledge Drs. Ross Downey, Richard White, and Richard Krasuski for their contributions to the first edition of this chapter.

QUESTIONS AND ANSWERS

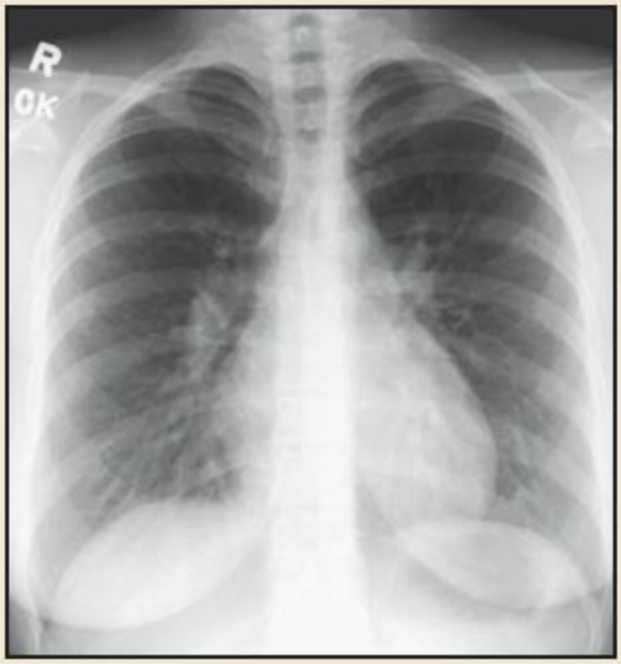
Questions

1. Ms. G. is a 28-year-old woman who immigrated to the United States from South America approximately 4 years ago. She has been told in the past that she has a heart murmur and recently noted the onset of exertional dyspnea. Her electrocardiogram (ECG) is notable for atrial fibrillation, and examination reveals a diastolic murmur best heard at the apex. Her chest radiograph is displayed below. Her atrial fibrillation is most likely secondary to:



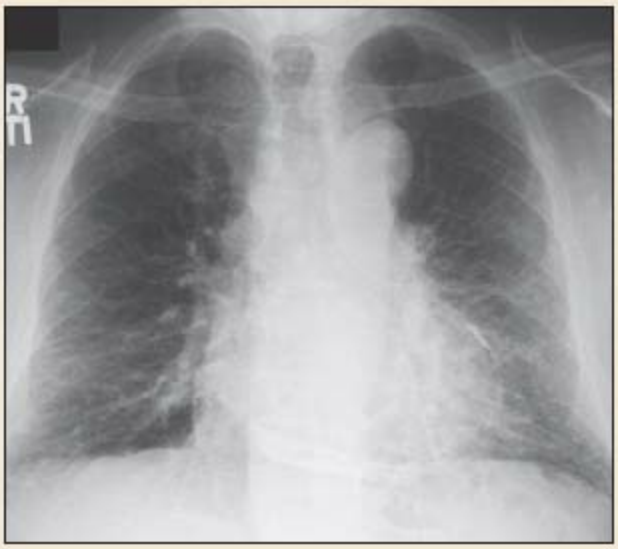
   a. Atrial myxomab.
   b. Increased transmitral gradient
   c. Idiopathic “primary” pulmonary hypertensiond.
   d. “Lone” atrial fibrillatione.
   e. Advanced left ventricular dysfunction

2. Mr. S. is a 38-year-old man with no prior medical history. Recently he has noticed a progressive reduction in his exercise tolerance. On examination he has a soft systolic murmur at the upper sternal border and a split second heart sound that does not appear to change with respiration. His chest radiograph is displayed below. The most likely explanation for these findings is:



a. Paroxysmal atrial fibrillation
b. Undiagnosed pulmonary stenosis
c. Undiagnosed ASD
d. Undiagnosed primary pulmonary hypertension
e. Left ventricular dysfunction with mitral regurgitation

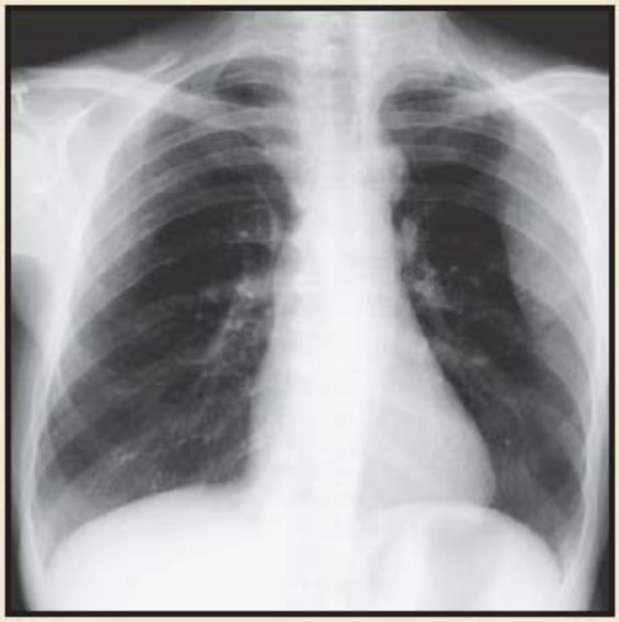
3. Ms. B. is a 74-year-old woman who immigrated to the United States from Southwest Asia 6 years ago. For the last 2 years she has noted progressive fatigue and lower-extremity edema. Her chest radiograph is displayed below. A right heart catheterization in this patient would be expected to show all of the following characteristics except:



a. Elevated pulmonary capillary wedge pressure
b. Diastolic equalization of pressures
c. Elevated RV pressure
d. A significant step-up in oxygen saturations
e. Normal to decreased cardiac output

4. Mr. N. is a 32-year-old man with recently diagnosed hypertension that has been refractory to medical

therapy. His exam is notable for a loud systolic murmur and weak peripheral pulses. His chest radiograph is shown below. The most appropriate surgical intervention for this patient is:



a. Resection and end-to-end anastomosis
b. Fontan procedure
c. Glenn shunt
d. Mitral valve repair
e. AV replacement

Answers

1. Answer B: Using the organized approach to radiograph interpretation, the pulmonary vascular pattern shows evidence of vascular redistribution suggestive of pulmonary venous hypertension. The left atrium is enlarged and the left ventricle is normal in size, suggesting possible mitral valve pathology. No chamber calcification is present to assist in the diagnosis. The case vignette describes a classical presentation for mitral stenosis. Though persistent inflammation may contribute to atrial fibrillation in this disorder, the primary mechanism in mitral stenosis is still felt to be elevated atrial pressure resulting in stretching of the atrial myocardium.

2. Answer C: Using the organized approach to radiograph interpretation, the pulmonary vascular pattern shows balanced overcirculation, and the pulmonary arteries are quite prominent. The right ventricle appears mildly enlarged. No significant calcification is present. The case vignette is notable for the physical exam, which is consistent with an ASD. Although this patient is certainly at increased risk for atrial fibrillation because of his congenital lesion, it is not the primary explanation for the findings. In pulmonic stenosis an oligemic pulmonary blood flow pattern is normally seen, and in left ventricular dysfunction with mitral regurgitation one expects to see a large left ventricle with pulmonary vascular redistribution suggestive of pulmonary venous hypertension. Primary pulmonary hypertension does not account for the physical findings in this case; additionally, a loud pulmonic closure sound would usually be present.

3. Answer D: Using the organized approach to radiograph interpretation, the pulmonary vascular pattern shows redistribution and pulmonary venous engorgement suggestive of elevated left heart filling pressure. There is chamber enlargement of both ventricles. The most notable feature of this radiograph, however, is the pericardial calcification, which appears circumferential. The vignette describes a case of constrictive pericarditis, possibly from old tuberculous infection. In this condition, one expects elevated filling pressure and a prominent Kussmaul sign (failure of the jugular venous pressure to drop with

inspiration). A pericardial knock is often present as well. A step-up in oxygen saturations (suggestive of an intracardiac shunt) would not be expected in this patient.

4. Answer A: Using the organized approach to radiograph interpretation, the pulmonary vascular pattern does not appear to be particularly prominent. The chambers of the heart also do not appear to be abnormal in size. There is, however, significant rib notching. This is due to the prominent collaterals that develop to bypass the circulation and allow adequate blood flow to reach the periphery. The presence of these collaterals combined with the case history suggests the aortic coarctation. The classical surgical correction of this abnormality is resection and end-to-end anastomosis of the aorta. Recently, percutaneous techniques have become more popular, not only for postoperative recurrence of coarctation, but also as primary therapy.

CHAPTER

Fundamentals of Doppler Echocardiography

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BASIC PRINCIPLES OF ULTRASOUND

Sound waves are mechanical vibrations produced by a source that are transmitted through a medium such as air. As sound waves travel through a medium, the particles of the medium are packed (compression), alternating with being spaced apart (rarefaction). Sound waves can be represented graphically as sine waves (Fig. 9.1). The wavelength (λ) is the distance between two similar areas along the wave path and is measured in millimeters. The frequency (f) is the number of wavelengths per unit time. Frequency is expressed in hertz (Hz), which is equivalent to cycles per second. Hence, the velocity of sound in a medium (c) is the product of wavelength and frequency; and wavelength and frequency are inversely related.

$$c = \lambda f$$

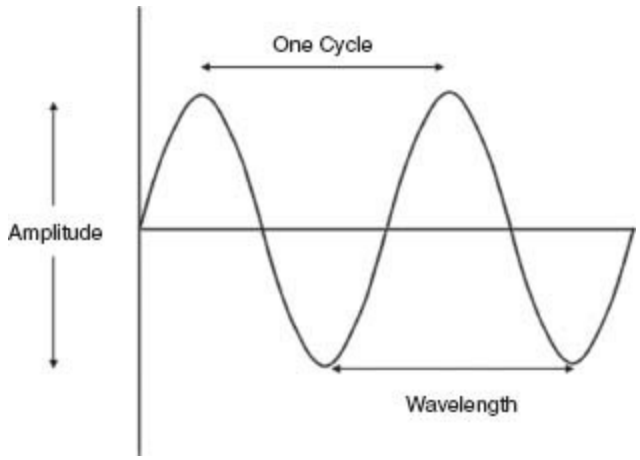

FIGURE 9.1 Figure of sound wave.

The amplitude of the sound wave (loudness) is measured in decibels (dB), which is in

logarithmic scale.

The propagation velocity of sound is determined by the stiffness of the medium and is also related inversely to its density. In human tissue, sound wave propagation velocity is 1,540 m/s (Table 9.1). Humans hear sound waves with frequencies between 20 Hz and 20 kHz; hence, ultrasound is defined as sound with frequencies higher than 20 kHz. Diagnostic medical ultrasound uses transducers with frequencies between 1 and 20 MHz.

TABLE
9.1 Velocity of Sound through Different Media

Material	Velocity of Sound (m/s)
Air	330
Fat	1,450
Water	1,480
Human soft tissue	1,540
Brain	1,540
Liver	1,550
Kidney	1,560
Blood	1,570
Muscle	1,580
Lens of eye	1,620
Bone	4,080

INTERACTION OF ULTRASOUND WITH TISSUE

Ultrasound beam travels in a straight line in a homogeneous medium; however, when the beam travels through a medium with two or more interfaces or in a heterogeneous medium, the path is altered. The interaction of ultrasound with tissue can be in the form of reflection, scattering, refraction, or attenuation.

When the ultrasound beam encounters a boundary between two different media, part of the ultrasound is reflected back toward the transducer and another part continues into the second medium. The amount of reflection depends on the difference in acoustic impedance between the two media. The amount of ultrasound reflected back is constant, but the amount received back at the transducer varies with the angle of the ultrasound beam to the tissue interface. Because the angles of incidence and reflection are equal, optimal return of the reflected ray occurs when the beam is perpendicular (90 degrees) to the tissue interface.

Scattering occurs when the ultrasound beam strikes smaller structures, less than one wavelength in the lateral dimension. This results in the ultrasound beam being radiated in all directions, with a minimal amount returning to the transducer. Scattering of

ultrasound produced from moving red blood cells is the principle behind Doppler echocardiography.

When the speed of sound differs in the two media, the acoustic impedance is different, and the ultrasound waves in the second medium are deflected from their original orientation. This is known as refraction. Because blood and most tissues have similar sound velocities, this is not a prominent effect in echocardiography.

When ultrasound travels through a biologic medium, part of the energy is absorbed and converted into heat. This process whereby ultrasound signal strength reduces is called attenuation. The degree of attenuation depends on the ultrasound frequency and on the differences in acoustic impedances between the two media. Lower ultrasound frequencies have a lower attenuation and penetrate deeper into tissues. Air has high acoustic impedance, which causes significant attenuation if there is any air between the transducer and the body tissue. Applying water-soluble gel on the transducer minimizes contact with air and hence attenuation.

TRANSDUCERS

The ultrasound transducer is the small hand-held probe that transmits acoustic energy and receives the returning echoes. Piezoelectric crystal converts electrical energy into sound energy and vice versa. Piezoelectric elements lack a center of symmetry and are anisotropic. When an electric current is applied, the polarized particles within the crystal are aligned, causing the crystal to expand and produce a mechanical effect. This is known as the direct piezoelectric effect. An alternating current causes the crystal to compress and expand alternately, which produces an ultrasound wave by compressions and rarefactions. Piezoelectric crystals generate an electric current when their shapes are altered while being struck by ultrasound waves. Therefore, the transducer functions both as a transmitter, transmitting a burst of ultrasound, and as a receiver, receiving the ultrasound signals reflected by internal tissue interfaces. A typical pulse lasts for only 1 to 6 μs.

The transducer frequency is determined by the nature and thickness of the piezoelectric element.

Image formation is based on the time interval between the ultrasound transmission and the arrival of its reflected signal. Deeper structures have longer flight times (Fig. 9.2). The time delay between transmission and reception is determined by the depth (d) of a certain structure and the speed of sound in blood:

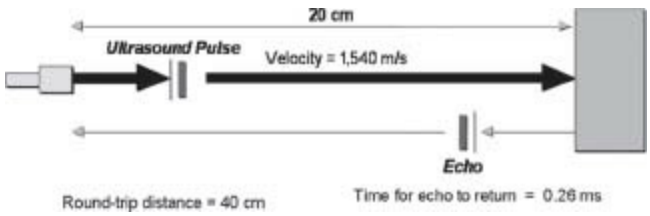

FIGURE 9.2 The time for the ultrasound beam to return to the transducer from a particular structure is a measure of the structure's distance from the transducer.

$$d = ct / 2$$

The factor 2 appears because t includes the time to and from the object. Knowing that the speed of sound in blood is 1,540 m/s,

$$d = 77t \text{ cm } (t \text{ in ms})$$

Resolution of the imaging system is defined as the smallest distance between two points that can be distinguished by the system as separate entities. Axial resolution refers to the ability to differentiate between points lying along the path or axis of the ultrasound beam. Lateral resolution refers to the ability to differentiate between points that are lateral to the beam, relative to the beam. Axial resolution is related to the ultrasound's wavelength, frequency, and the duration of the transmitted pulse. Lateral resolution is dependent on the distance of the specular reflector to the transducer and is a function of the beam width, which is defined as the diameter of the beam at a particular point. In the near field, the beam is maintained as a cylinder with a diameter comparable to the transducer. However, at points farther away from the transducer, the beam diverges and widens into a cone. This area is the far field. Beam width is a function of transducer size, shape, frequency, and focusing. The larger the transducer, the longer the near field is.

The lateral resolution is dependent on the gain of the system. Specular reflectors along the center of the beam produce stronger echoes than those that are at the beam margins. When the gain or sensitivity is set low, echoes from beam margins with lower amplitude may not be recorded, which makes the beam appear narrower. With higher gain, the echoes at the margins are recorded, and the beam width appears greater.

IMAGING MODALITIES

There are several imaging modalities in echocardiography. A and B modes have only historical importance. M mode (motion) displays axial information along a single scan line, displaying depth on the vertical axis and time on the horizontal axis. This provides high temporal resolution and rapid sampling rates, with the ability to visualize wall or valve motion. M-mode measurements have been the standard in echocardiography in quantifying chamber size and endocardial thickening (Fig. 9.3).

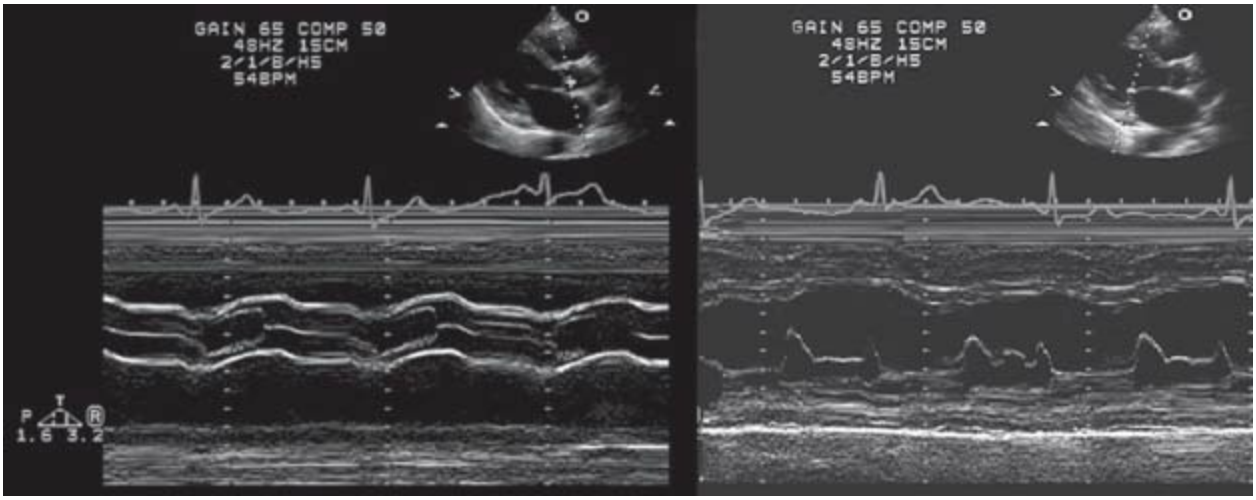

FIGURE 9.3 M-mode display.

Through parallel processing, the data from each scan line are analyzed separately, which increases the frame rate.

Two-dimensional (2-D) echocardiographic imaging is generated by sweeping ultrasound beam through an arc across a particular area of the heart. Electronic sweeping is accomplished by the use of phased array transducers. Transducer arrays are groups of individual transducers or transducer elements. Linear arrays are a group of transducers or transducer elements lined up next to each other in a straight row. The transducers are then pulsed individually or in groups. This requires a large window, which limits their use in cardiac imaging. Phased arrays contain multiple element transducers that sweep the ultrasound beam electronically through an arc. Exciting the transducers in sequence generates an ultrasound wave that propagates at an angle to the transducer and sweeps the beam from side to side.

A focused transducer is used to decrease diversion in the far field of the ultrasound beam. By placing a concave acoustic lens on the transducer surface or by altering the transducer curvature, the ultrasound beam is narrowed at a point away from the transducer. The focal zone is the area where the beam is narrowest and divergence is smallest. Phased array transducers can also focus the beam electronically by altering the shape of the wavefront according to the timing of firing of the individual transducer elements.

Two-dimensional echocardiography displays ultrasound data in a spatial orientation relative to time and localize depth by the reflected wave timing. This limits the amount of data that can be collected in a period of time and hence temporal resolution. The pulse duration (PD) is the time needed for the pulse to travel from the transducer to the tissue and back. This is dependent on the depth of the tissue and the speed of sound in that tissue:

$$PD = 2d / c$$

The pulse repetition frequency (PRF) is the rate at which individual pulses are transmitted (per second) and is equal to c/2d. Since the speed of sound in human tissue is 1,540 m/s, this translates to:

$$PRF = 77/d \text{ pulses/ms}$$

The number of lines per sweep depends on the time taken to produce one scan line and the time set for each sweep. The frame rate is the number of images acquired per second. In cardiac applications, the frame rate is typically >30 frames per second. A higher frame rate is preferred to visualize myocardial and valvular motion well. However, increasing the frame rate leads to fewer scan lines per frame, resulting in less data acquired per frame and therefore decreased image quality.

Echoes received by tissues produce vibrations within the piezoelectric crystal that translate into a small voltage. To form a final image, the electrical signal goes through complex signal processing that initially is amplified by a radiofrequency amplifier and compressed logarithmically in order to be displayed in varying shades of gray.

Serial processing occurs when one scan line is produced for each ultrasound pulse. This method limits the frame rate. With phased array transducers, it is possible to send out several scan lines simultaneously in different directions. Through parallel processing, the data from each scan line are analyzed separately, which increases the frame rate.

Dynamic range (expressed in decibels) refers to the amplitude ratio of largest signal displayed to the smallest signal detected above the system noise. Noise is a combination of all signals that reach the transducer from structures outside the ultrasound beam axis. These signal amplitudes are compressed into shades of gray, where the gray scale displays strong and weak echoes in various shades of gray. The dynamic range consists of the number of levels of gray in an image and can be adjusted.

Echo image data are obtained in a polar coordinate system and are converted into a video image by means of a digital scan converter.

Attenuation occurs when deeper structures produce weaker echoes than structures closer to the transducer. Electrical energy produced by these echoes is therefore less. Time gain compensation applies greater amplification for echoes returning at longer intervals from the initial pulse, which corresponds to the depth of the structure. As attenuation varies in individuals, time gain compensation can be adjusted by the user. Near-field gain can be set lower while far-field gain can be gradually increased to achieve better image quality.

HARMONIC IMAGING

When a sound pulse of frequency fo propagates through tissues, nonlinear interactions occur, generating a pulse with frequencies at multiples of the fundamental frequency fo:

2fo (second harmonic), 3fo (Fig. 9.4A,B). This is caused by minor distortions in the tissue, producing a very slight change in the shape of the wave as it propagates.

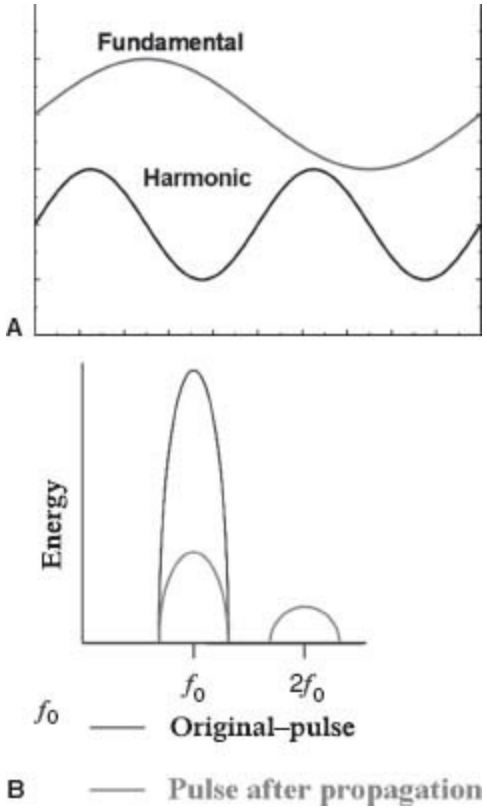

FIGURE 9.4 A: Tissue harmonic imaging utilizes pulse frequencies at multiples of the fundamental frequency f_0. **B:** Harmonic frequencies are of lower energy than the fundamental frequency.

The energy of these harmonic frequencies returning from the tissue is significantly less than the fundamental frequency. In order to benefit from harmonic imaging, the fundamental frequency needs to be filtered out, so that only the harmonic frequencies are passed to the demodulator.

Harmonic generation increases with the distance of propagation and that there is a nonlinear relation between fundamental and harmonic frequency energies. These aspects of harmonic imaging help to understand why it is useful in reducing near-field artifacts (low harmonic energy close to the transducer) and side-lobe artifacts.

Second harmonic tissue imaging is now used routinely in adult echocardiography. The benefits can be striking particularly in patients with difficult images. In general, there is an improved signal-to-noise ratio with brighter tissue and superior endocardial definition. Of note, valvular structures appear thicker when imaged using second harmonics compared to fundamental imaging. In some cases, it may be useful to turn harmonic on and off when evaluating valve leaflets.

Another use of harmonic imaging is contrast echocardiography. New contrast agents have been manufactured with very small (1- to 5-**μ**m) bubbles capable of crossing the

pulmonary capillary bed. The contrast effect is produced by microbubbles having different acoustic impedances than blood, causing the reflection and scattering of ultrasound. Ultrasound causes compressions and rarefactions of the microbubbles with a resonant frequency that is inversely related to the diameter of the microbubble. This ultrasoundmicrobubble interaction also generates harmonic frequencies. Compared to soft tissue, the microbubbles are strong reflectors, so tuning the ultrasound receiver to the second harmonic frequency displays the contrast agent preferentially within the image.

The approved indication for contrast imaging is left ventricle opacification. In patients with limited views, contrast significantly improves endocardial definition. Its main application is in suspected wall motion abnormalities at rest and after stress, or in suspected left ventricular (LV) thrombus. The use of contrast agents for myocardial perfusion, although promising, is still investigational. Myocardial perfusion and viability are potential uses of this technique, although they have not been approved for clinical use.

THREE-DIMENSIONAL ECHOCARDIOGRAPHY

Two-dimensional echocardiography is now the standard ultrasound imaging modality, although 3-D imaging is increasingly adopted as it provides a different imaging approach and several distinct advantages over 2-D echocardiography. Initially, 3-D images are constructed and displayed using conventional 2-D imaging with a multiplanar transducer. Tomographic slices of the heart are obtained and constructed into a 3-D image.

Image acquisition relies on matrix array transducer that replaces a single row of elements found in the conventional linear 1-D transducer with a 2-D grid of elements. As in a linear array transducer, the timing of individual transducer elements transmitting and receiving ultrasound energy controls the direction of the ultrasound beam. A matrix array transducer offers steering in both within a slice and elevation of a beam, allowing for interrogating the entire pyramid-shaped volume.

Parallel processing allows the volumetric device to receive multiple lines for any given transmit line to generate the 3-D volume. Real-time 3-D, “Live 3-D,” imaging can be performed at a lower temporal resolution (volume per second). Alternatively, a segmented “full-volume” 3-D dataset is obtained at higher temporal resolution by combining data from several cardiac cycles via ECG gating. The latter has the option of displaying images with color Doppler mapping. In the above 3-D image acquisition modes, datasets can be analyzed offline in either volumerendered or multiplanar reconstruction modes. Offline analysis tools are especially useful for accurately quantifying volume and mass, as well as visualizing complex anatomical abnormalities.

Three-dimensional echo is commercially available for both transthoracic and

transesophageal echocardiography. This technique has distinct advantage over 2-D echocardiography including chamber quantification, valvular heart disease especially mitral valve diseases, congenital heart disease, and intraoperative applications.

DOPPLER ECHOCARDIOGRAPHY

Doppler echocardiography utilizes the Doppler principle to determine the direction, velocity, character, and timing of blood flow within the cardiovascular system. The Doppler principle states that the frequency reflected on a moving object is a higher observed frequency than when it moves away from the observer. The Doppler shift (ΔF) is the difference in frequency between the received frequency (Fr) and the transmitted frequency (Ft):

$$\Delta F = Fr - Ft$$

Signal backscatter from small moving objects such as red blood cells produces a change in frequency of the signal, creating a Doppler effect. The Doppler shift is related to the velocity of the moving source (V):

$$\Delta F.\alpha.V = \Delta F = V / \lambda$$

Knowing that $\lambda = c/f$, and that the speed of sound tends to remain constant in tissue, change in the transmitted frequency will alter the wavelength. Therefore,

$$\lambda = c / Ft = V / \Delta F$$

Rearranging this expression produces:

$$\Delta F = V \cdot Ft / c$$

The ultrasound beam may be at an angle to the direction of blood flow. The true velocity is equal to the measured velocity divided by the cosine of the angle θ. Therefore,

$$\Delta F = F\,t \cdot V \cdot \cos\theta / c$$

where V is the true velocity of blood flow. As the sound path consists of the transmitted portion from the transducer to tissue and the reflected portion from the tissue back to the transducer, the equation is multiplied by 2, which produces the final Doppler equation:

$$\Delta F = 2Ft \cdot V \cdot \cos\theta / c$$

Since it is the velocity of the moving object that is of interest, rearranging the equation produces:

$$V = \Delta F \cdot c / (2Ft \cdot \cos\theta)$$

The angle the ultrasound beam makes with the direction of blood flow is important.

When the beam is parallel to the direction of flow, the angle is 0 degrees and cos 0 degrees = 1. When the beam is perpendicular to the direction of flow, the angle is 90 degrees and cos 90 degrees = 0, which means that there is no Doppler shift. Angles <20 degrees result in a <6% change in the recorded velocity. Thus, the effect of the beam angle on Doppler shift becomes more important when the angle is greater. For example, if the angle is 60 degrees, cos 60 degrees = 0.5, which leads to a 50% velocity error. This is important when calculating velocities in areas with abnormal blood flow, as in valvular stenosis.

The difference between transmitted and backscattered signals received by the transducer is determined by comparing the two waveforms. The frequency content is analyzed by fast Fourier transform. The display generated is known as a spectral analysis, with time displayed on the x axis and frequency shift or blood velocity on the y axis. Frequency shifts toward the transducer are displayed above the baseline, whereas frequency shifts away from the transducer are below the baseline. There are multiple frequencies for every given point in time, and each amplitude is displayed corresponding to its brightness (by gray or color scale). Therefore, the spectral display produces information on the direction of blood flow, the velocity (or frequency shift), and the signal amplitude.

Three different modalities are used in Doppler echocardiography: continuous-wave Doppler, pulsed-wave Doppler, and color Doppler flow mapping. Each modality is processed differently (Table 9.2).

TABLE
9.2 Comparison of Continuous Wave, Pulsed Wave, and Color Doppler

Continuous Wave	Pulsed Wave	Color Doppler
Ultrasound transmitted and received continuously	Ultrasound transmitted intermittently; two crystals; received after an interval (pulse velocities superimposed on a repetition frequency)	Doppler display color coded; one crystal; 2-D image
Records all blood velocities along beam	Records blood velocity at particular axis region of interest/sample volume	Useful for spatial mapping of Doppler signals (i.e., regurgitant jets or intracardiac shunt)
Records maximum velocity; useful for obtaining gradients	Useful for assessing low-velocity flow	Useful for quantification of regurgitant lesions
Smooth spectral signal defining onset and end of flow	Aliasing occurs when velocity of interest exceeds Nyquist limit	Aliasing appears as color reversal

In continuous-wave Doppler, sound beam is continuously transmitted and received. The transducer contains two crystals, one for continuous transmission and a second for continuous reception of the ultrasound signal. The spectral signal displayed is smooth in contour, showing the maximum velocity and defining the onset and end of flow. The Doppler profile is filled in because lower velocities are also recorded. This modality is useful for calculating high-frequency shifts or velocities encountered in stenotic or regurgitant lesions. The disadvantage is that continuous-wave Doppler simultaneously records all signals along the ultrasound beam. Thus, the detected Doppler shift may have occurred at any point along the scan line (Fig. 9.5A).

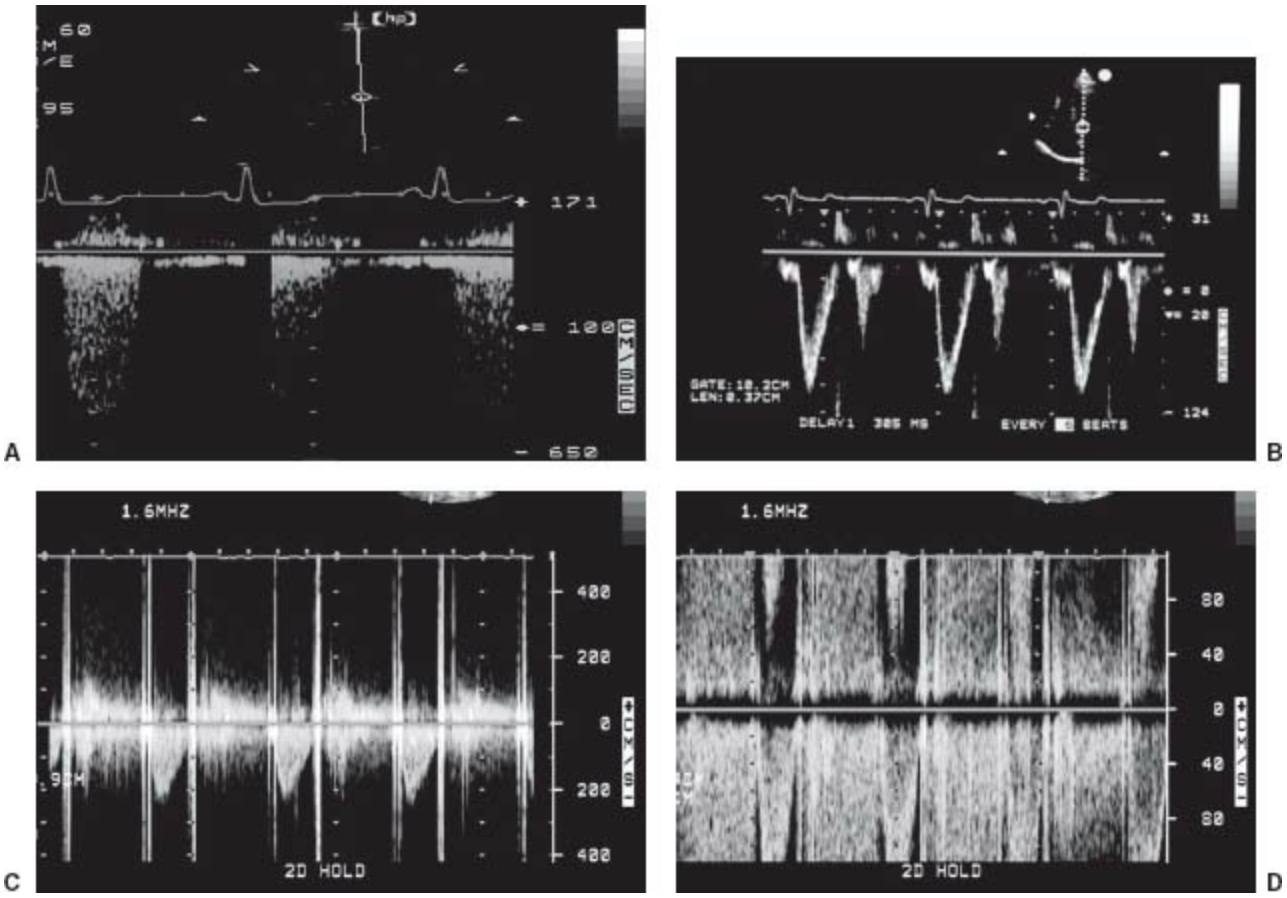

FIGURE 9.5 A: Continuous-wave Doppler. **B:** Pulsed-wave Doppler. **C,D:** High velocities—continuous wave **(C)** versus pulsed wave **(D)** Doppler with aliasing.

In pulsed-wave Doppler echocardiography, pulses of ultrasound are transmitted intermittently. This allows the pulse to traverse to a desired depth and, after a specific time delay, the backscattered signals are received by the transducer (Fig. 9.5B). As mentioned above,

$$d = ct/2 \text{ and } PD = 2d/c$$

The Doppler shift and velocity at the depth of interest is based on the time delay

measured. This is useful in assessing low-velocity flows such as in transmitral flow, although this may not be a reflection of the true maximum velocity. The PRF is the interval that the transducer waits after a signal before it sends out the next signal. The time interval is dependent on the depth of interest, and the PRF is also dependent on the depth. From earlier,

$$PRF = 77 / d$$

In pulsed-wave Doppler, the sample volume is the depth of interest. Pulsed Doppler echo samples the returning signal repeatedly, and there is a limit to the frequency shift (or velocity) that can be displayed unambiguously. The frequency of the ultrasound is determined by sampling the waveform for at least twice the wavelength. This requires sampling the pulse at twice the rate. The maximum detectable frequency shift is called the Nyquist limit, which is one-half the PRF.

When the velocity of interest is higher than the Nyquist limit, the signal wraps around into the reverse channel and then back to the forward channel. This is known as signal aliasing (Fig. 9.5D). Various methods can be used to resolve aliasing, including using continuous-wave Doppler ultrasound, shifting the baseline, increasing the PRF, or using a lower-frequency transducer.

Color Doppler flow mapping differs from pulsed Doppler echo in that multiple sample volumes (or multigates) are evaluated along each scan line. The 2-D image obtained from sweeping the scanning line across the echo sector is superimposed on color-coded velocity patterns. Flow toward the transducer is displayed in red, whereas flow away from the transducer is displayed in blue. The shade of color that is displayed indicates the velocity up to the Nyquist limit. As velocity increases, aliasing may occur. This is displayed by reversal of color.

STRAIN IMAGING

Strain imaging is a new echocardiography tool that has increasing use in clinical practice. Strain is a measure of tissue deformation and strain rate is the rate by which this tissue deforms. Ventricular contraction is characterized by myocardial shortening in the longitudinal and circumferential dimensions, that is, negative strain, and myocardial thickening in the radial direction, that is, positive strain. Strain is analogous to regional ejection fraction, where strain rate is analogous to regional contractility. Considering longitudinal strain, total systolic strain that occurs at end-systole and peak systolic strain rate are negative due to myocardial shortening in the longitudinal dimension. Myocardial relaxation during diastole results in positive longitudinal strain as the myocardium lengthens. Diastolic positive strain rate has two peaks, at early diastole and late diastole, coinciding with the E and A waves on pulse Doppler measurements at the mitral valve leaflets.

Echocardiography assesses strain by two major methods, tissue Doppler imaging and speckle tracking techniques. Tissue Doppler techniques display myocardial velocity of each pixel relative to the transducer. The instantaneous velocity gradient along a sample length can be quantified from the velocities from adjacent sites along the scan line that generate the strain rate data. Strain is subsequently derived by integrating the derived strain rate versus time curves. Such data are obtained at a high temporal resolution, which is the major advantage of this technique.

Speckle tracking techniques measure strain by another approach. Speckles are tissue ultrasound reflectors that are highly reproducible and can be tracked throughout the cardiac cycle. Regional deformation can therefore be derived by tracking speckles from frame to frame. The differential of the resulting strain versus time curves yields the instantaneous strain rate curves (Fig. 9.6). Compared to tissue Dopplerbased techniques, speckle tracking has a lower frame rate and higher noise, although this angle-independent approach made radial and circumferential strain measurements, as well as torsion, practical.

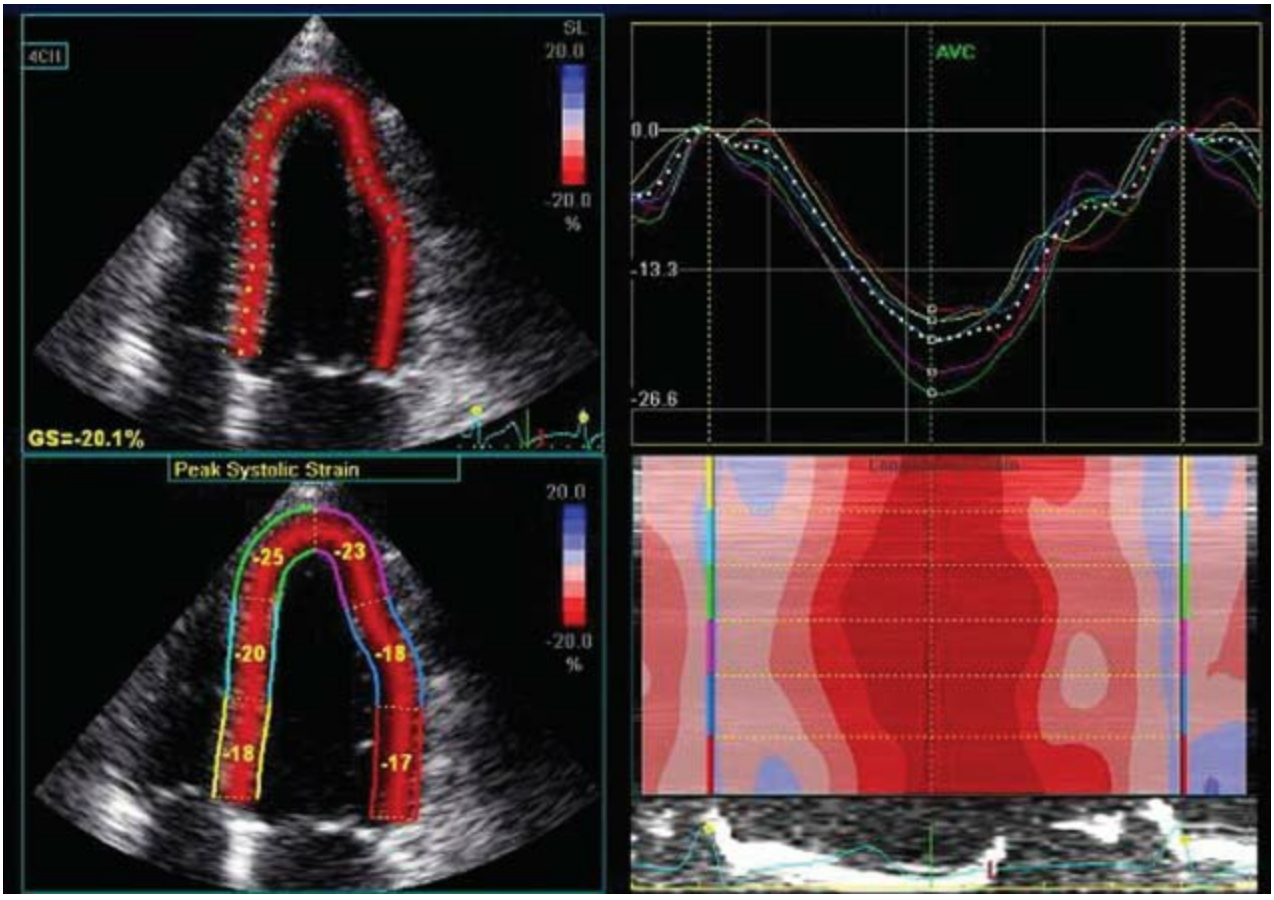

FIGURE 9.6 Speckle tracking strain measurements on transthoracic echocardiogram. Shown are the normal strain measurements from the apical four-chamber view. **Top left panel** illustrates the region of tracking; top right panel illustrates the derive strain versus time curve; **bottom right panel** illustrates the color-coded strain measurements with time according to LV segments on the y-axis; bottom left panel illustrates the peak systolic strain at aortic valve closure of the various LV segments.

IMAGING ARTIFACTS

Imaging artifacts can be produced from displaying structures that are not there, failing to display structures that are actually there, or forming an image of a structure that is different in shape or size from what it actually is. Side lobe artifacts occur when ultrasound energy disperses laterally from the main ultrasound beam and are produced from the edges of the transducer elements. The side lobes may reflect or backscatter signals and produce an artifactual image as though it were originating from the center of the ultrasound beam. The amplitude of these waves is generally much lower and as a result may not produce a strong image artifact. The extraneous beams produced from phased array transducers produce grating lobe artifacts that are more serious and affect the transducer lateral resolution.

Beam-width artifacts occur when structures that are in the far field of the ultrasound beam produce images that are superimposed on structures that are in the center of the ultrasound beam. This can produce artifactual images creating distorted images or the display of artifactual structures such as the appearance of vegetations on a valve leaflet, an intracardiac mass, or an aortic dissection. This also affects lateral resolution.

Reverberation artifacts are produced when ultrasound waves are being bounced back and forth between two or more highly reflective surfaces. This produces multiple linear echo signals that appear as parallel lines. This limits evaluation of structures in the far field.

Acoustic shadowing occurs when structures with high echo density block transmission of the ultrasound. This can be seen with calcified or prosthetic valves. This presents a problem in imaging structures that are distal to these dense structures because no reflected signals return to the transducer. In these cases, an alternate window is necessary to visualize structures of interest.

Range ambiguity occurs when an echo signal from a previous pulse reaches the transducer on the next pulse cycle. This causes deeper structures to appear as though they are closer to the transducer. Range ambiguity can be eliminated by increasing the depth setting and decreasing the PRF.

PRINCIPLES OF FLOW

Blood flow is defined as the volume of blood moved per unit time. Flow is related to the pressure, the vessel radius, and the blood viscosity. In steady flow, the fluid particles move along parallel lines to the vessel wall, described as laminar flow. Turbulent flow occurs when blood cells move in different directions at different velocities. This can occur in stenotic valves, regurgitant valves, or intracardiac shunts.

The velocity of blood flow changes when there is a change in size of the vessel diameter. This is expressed by the Bernoulli principle, which is based on the principle of conservation of energy (kinetic and pressure energy). The kinetic energy from the

blood flow is proportional to the density and the square of the blood flow velocity. When there is a change in the blood flow velocity, the kinetic energy (KE) also changes:

$$KE = {}^{1}/_{2}\,\rho v^2$$

Because total energy is conserved, the total energy at point 1 (P_1) must equal the total energy at point 2 (P_2).

$$\begin{aligned} &P_1 + KE_1 = P_2 + KE_2 \\ &\Rightarrow P_1 + \tfrac{1}{2}\rho(v_1)^2 = P_2 + \tfrac{1}{2}\rho(v_2)^2 \\ &\Rightarrow P_1 - P_2 = \tfrac{1}{2}\rho[(v_2)^2 - (v_1)^2] \end{aligned}$$

It is important to realize that some of the energy lost when going from point 1 to point 2 is due to energy required to overcome forces caused by changes in flow rate over time, that is, flow acceleration, as well as energy lost because of viscous friction. Therefore, the complete Bernoulli equation is:

$$\begin{aligned} \Delta P = {}&\tfrac{1}{2}\rho[(v_2)^2 - (v_1)^2] \\ &+ \rho(dv/dt)dx + R(v) \end{aligned}$$

The energy lost to viscous resistance (R(v)) and flow acceleration ($\rho(dv/dt)dx$) is negligible and can be eliminated from the Bernoulli equation. The velocity across stenotic lesions (such as valves) is much higher than the velocity proximal to the stenosis. The velocity proximal to the mitral valve is typically 0.2 m/s, and it is 0.8 m/s for the aortic valve. Because these numbers are small, $(\mathbf{v}_1)^2$ can usually be dropped from the equation, except when $\mathbf{v}_1 > 1$ m/s, such as in severe aortic regurgitation or subaortic obstruction. Using appropriate unit of measurements (m/s for velocity and mm Hg for pressure), ${}^{1}/_{2}\rho$ is approximately 4. Therefore, the simplified Bernoulli equation is often used to calculate the pressure gradient across the valve:

$$\Delta P = 4(\mathbf{v}_2)^2$$

Blood flow also must obey the principle of conservation of mass. The average velocity of blood at a particular point (V) is defined as the flow rate (Q) divided by the cross-sectional area (A) across the vessel at that point:

$$\mathbf{v} = Q / A$$

Knowing that the volume of blood entering the vessel is the same as the volume leaving (conservation of mass), the volume flow rate (Q) remains constant:

$$Q = v_1 \times A_1 = v_2 \times A_2$$

This equation is referred to as the continuity equation. Therefore, as vessel size increases, cross-sectional area increases, causing velocity to decrease and a resultant

decrease in kinetic energy. In stenotic lesions, the cross-sectional area decreases, causing the velocity to increase. The increase in velocity causes the parallel streamlines to converge and is called convective acceleration (Fig. 9.7).

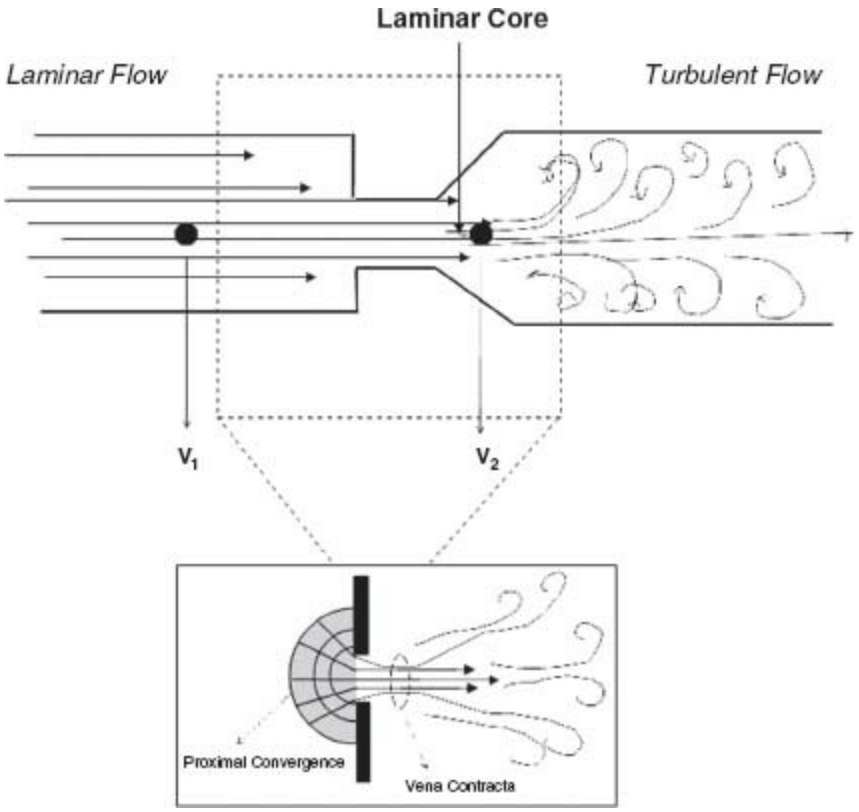

FIGURE 9.7 Flow through a stenotic lesion (e.g., valve).

Applying the continuity equation, the area across a stenotic lesion such as aortic stenosis can be calculated. This requires knowing the velocities proximal to the valve and across the valve in addition to the area proximal to the valve (r = radius, d = diameter at point 1).

$$\begin{aligned} A_2 &= A_1 \times (v_1 / v_2) \\ \Rightarrow A_2 &= \pi r^2 / 2 \times (v_1 / v_2) \\ \Rightarrow A_2 &= \pi d^2 / 4 \times (v_1 / v_2) \\ \Rightarrow A_2 &= 0.785 d^2 \times (v_1 / v_2) \end{aligned}$$

For example,

$$A_{\text{aortic valve}} = 0.785 d^2_{\text{LV outflow tract}} \times (V_{\text{LV outflow tract}} / V_{\text{aortic, valve}})$$

BASIC PRINCIPLES OF JETS

Flow accelerates as it approaches a restricted orifice, achieving maximal velocity at the orifice or slightly distal from the obstruction. The point of maximal velocity and

minimal cross-sectional area is called the vena contracta (Fig. 9.8). The location of the vena contracta depends on the geometry of the orifice and may occur downstream from the orifice. After exiting the orifice, flow remains laminar for about five orifice diameters before becoming turbulent. Downstream, the flow loses velocity and reattaches to the wall, recovering part of the pressure. This phenomenon of **pressure recovery** has implications in prosthetic valves and helps to explain some of the discrepancies between Doppler-derived gradients and those measured with catheters.

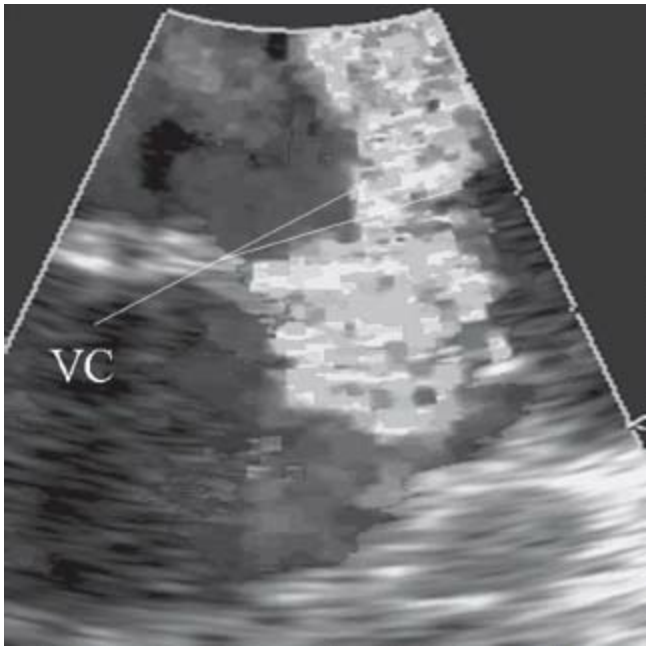

FIGURE 9.8 Vena contracta—the point of maximal velocity and minimal cross-sectional area.

Apart from the conservation of mass and energy, a jet also follows the conservation of momentum. Momentum equals mass multiplied by velocity. Jet momentum (M) is:

$$M = \rho \times Q \times v$$

where p = density, Q = flow rate, and v = velocity. Knowing that Q = A × V, where A is the orifice area,

$$M = p \times A \times \mathbf{v}^2$$

As jet flows into a receiving chamber, it will generate turbulent eddies entraining surrounding fluid. This phenomenon causes the jet to increase in size and decrease velocity, keeping the momentum constant. The momentum is the best predictor of jet appearance by color flow mapping. Jet flow can also be affected by the **Coanda effect,** which occurs when the jet attaches to and flows around nearby structures such as the atrial wall. These confined jets typically look smaller when imaged by color Doppler and may underestimate the severity of the regurgitation.

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QUESTIONS AND ANSWERS

Questions

1. All of the following statements regarding the Doppler equation are true except:
   a. In order to obtain the true velocity of blood flow at a certain point, the beam needs to be parallel to the direction of blood flow.
   b. The measured velocity of blood is overestimated when the beam is at a greater angle to the direction of blood flow.
   c. There is no Doppler shift when the beam is perpendicular to the direction of blood flow.
   d. The true velocity of blood flow is equal to the measured velocity divided by the cosine of the angle the beam makes with the direction of blood flow.
2. Continuous-wave Doppler echocardiography is useful for all of the following except:
   a. Determining peak velocity across the aortic valve
   b. Determining the pressure gradient across the aortic valve
   c. Determining precise location of flow obstruction
   d. Assessing the presence of dynamic left ventricular outflow tract obstruction
3. All of the following are used to resolve aliasing except:
   a. Decreasing the pulse repetition frequency
   b. Using continuous-wave Doppler ultrasound
   c. Using a lower-frequency transducer
   d. Shifting the baseline
4. Which of the following is true?
   a. The modified Bernoulli equation is used to calculate the area of a stenotic valve.
   b. The velocity of blood remains constant.
   c. The continuity equation is used to calculate the area of a stenotic valve.
   d. The continuity equation only requires knowing the velocities proximal to and across the valve.
5. Which of the following is true regarding contrast echocardiography?
   a. Harmonic imaging is used in contrast echocardiography.
   b. Contrast agents typically use microbubbles that are 50 mm in dimension.
   c. Commercial microbubbles are used for determining the presence of an atrial septal defect or a patent foramen ovale.
   d. Contrast echocardiography is a standard modality in determining myocardial perfusion.
6. Ultrasound wave propagation speed increases with:
   a. Higher stiffness and lower density
   b. Lower stiffness and higher density
   c. Higher stiffness and higher density
   d. Lower stiffness and lower density
7. Which of the following statements about the Bernoulli principle is incorrect?
   a. It relies on the principle of the conservation of energy.

b. The simplified Bernoulli equation may underestimate the true aortic valve area when used in patients with severe aortic regurgitation.
c. The simplified Bernoulli equation assumes that the effects of viscous resistance and flow acceleration are negligible.
d. The mean pressure gradient across a stenotic aortic valve is derived from $4v^2$, where v is the peak velocity recorded on Doppler echocardiography.

8. A 76-year-old patient with a loud systolic murmur undergoes echocardiography. The following parameters were measured:
LVOT diameter = 2.0 cm
LVOT peak velocity = 0.8 m/s
Aortic peak velocity = 4 m/s
Tricuspid regurgitation peak velocity = 3 m/s
Estimated right atrial pressure = 10 mm Hg
Which of the following calculations are correct?
a. Transaortic peak pressure gradient is approximately 65 mm Hg.
b. Estimated right ventricular systolic pressure is approximately 35 mm Hg.
c. Estimated right ventricular systolic pressure is approximately 65 mm Hg.
d. Transaortic peak pressure gradient is approximately 35 mm Hg.
e. Estimated right ventricular systolic pressure is approximately 25 mm Hg.

9. Which of the following statements about the interaction of ultrasound with tissue is incorrect?
a. Backscatter is the major source of ultrasound information used to create a two-dimensional (2-D) image.
b. Maximum amount of specular reflection is received by the transducer when the ultrasound beam is perpendicular to the tissue interface.
c. Refraction is a common cause of artifact in echocardiography.
d. Refraction is caused by ultrasound wave is deflected from the original direction due to difference in acoustic impedance.
e. Significant attenuation is observed at tissue–air interface due to high acoustic impedance of air.

10. What is the major disadvantage of continuouswave Doppler over that of pulsed-wave Doppler?
a. Aliasing
b. Range ambiguity
c. Angle dependence of velocity measurements
d. Signal processing

Answers

1. Answer B: The true velocity of blood flow is equal to the measured velocity divided by the cosine of the angle the beam makes with the direction of blood flow. The Doppler equation enables us to measure the velocity based on knowing the frequency shift, the transmitted frequency, and the speed of sound in blood. When the beam is parallel to the direction of blood flow, the angle is 0 degrees and cos 0 = 1; therefore, the true velocity is equal to the measured velocity. However, when the beam is perpendicular to the direction of blood flow, the angle is 90 degrees; cos 90 = 0, so there is no Doppler shift. The greater the angle between the beam and the direction of blood flow, the greater is the error in measuring the velocity of blood flow. In actuality, the measured blood flow will be underestimated in this scenario, and the true velocity will actually be higher than what is reported. Therefore, it is essential to keep the beam parallel to the direction of blood flow in order to minimize velocity errors because it is important to assess the velocity of blood flow in cases such as valvular stenosis. Angles that are <20 degrees may be acceptable because there is less velocity error.

2. Answer C: Continuous-wave Doppler is a useful modality for determining peak flow velocity and is used for high velocities such as in stenotic and regurgitant lesions. Therefore, it is used for determining peak velocity and pressure gradient across the aortic valve. It is also used in assessing whether there is

dynamic left ventricular outflow tract (LVOT) obstruction, which is observed in hypertrophic cardiomyopathy. Provocative maneuvers such as Valsalva or use of inhaled amyl nitrate increase the obstruction across the LVOT, which is manifested by a higher peak velocity and is determined by continuous-wave Doppler. Continuous-wave Doppler measures the highest velocity along the scan line but does not allow spatial location.

3. Answer A: Aliasing occurs when the signal wraps around into the reverse channel and then back to the forward channel. This occurs when the velocity of interest is higher than the Nyquist limit. The Nyquist limit is the maximum detectable frequency shift and is equal to one-half the pulse repetition frequency. To resolve aliasing, the Nyquist limit needs to be raised, which means increasing the pulse repetition frequency.

4. Answer C: The velocity of blood flow changes when there is a change in the size of the vessel diameter, as can occur across a stenotic valve. The Bernoulli principle is based on the conservation of energy, and the modified Bernoulli equation is used to calculate the pressure gradient across the valve. The continuity equation is based on the principle of conservation of mass, and that the volume of blood entering a vessel is equal to the volume leaving, implying a constant flow rate (area × velocity). As the vessel size increases, the cross-sectional area increases, causing the velocity to decrease. The continuity equation therefore allows us to measure the area across a stenotic valve and requires knowing the velocities proximal to and across the valve as well as the area of the vessel proximal to the valve (e.g., LVOT area [or diameter]) when calculating the area across the aortic valve.

5. Answer A: Contrast echocardiography is dependent on contrast agents that use bubbles that are small (1 to 5 mm) and are able to cross the pulmonary capillary bed, in order to better visualize the left ventricle. The main indication for using contrast is to improve endocardial definition to assess for wall motion abnormalities or presence of a left ventricular thrombus. Its use in myocardial perfusion is still investigational. The interaction between ultrasound and the microbubbles generates harmonic frequencies, so tuning the ultrasound receiver to the second harmonic frequency will preferentially display the contrast agent, which is a stronger reflector than tissue.

6. Answer A: Wave propagation speed is determined by the square root of the coefficient of stiffness, or bulk modulus divided by the density of the propagation medium. Hence, propagation speed increases with higher stiffness (e.g., bone) and lower density.

7. Answer D: The Bernoulli principle describes the phenomenon reflected by the conversation of energy. The simplified Bernoulli equation assumes that the effects of viscous resistance and flow acceleration are negligible, as well as that the velocity proximal to a stenosis is small compared to the velocity across the stenosis. This is not the case in severe aortic regurgitation where the proximal velocity can be elevated due to increased transaortic flow. This also applies to cases of subaortic obstruction. The equation $p = 4v^2$ describes the relationship between the peak pressure gradient and the peak velocity, not the mean pressure gradient. The latter is given by integrating the peak gradient over the duration of systole.

8. Answer A: By the simplified Bernoulli equation, transaortic peak pressure gradient is given by $4v^2$ where v = 4 m/s, that is, 64 mm Hg. The LVOT velocity of 0.8 m/s is <1 m/s, which makes the assumption of the simplified Bernoulli equation valid. The estimated right ventricular systolic pressure is given by the equation of $4v^2$ + estimated right atrial pressure, where v = 3 m/s, hence 46 mm Hg.

9. Answer C: Diffuse backscatter redirects sound energy in many directions, including back toward the transducer. The received sound waves are used to create an image; hence A is correct. The angle of incidence to the tissue interface directly determines the amount of reflected ultrasound beam toward the transducer. It is maximum when the beam is at 90 degrees to the tissue interface; hence B is correct. Attenuation at tissue–air interface is due to the significant acoustic impedance of air, hence causing significant attenuation; hence E is correct. Refraction occurs when there is a large difference in acoustic impedance at a medium interface. This does not occur prominently between blood and most soft tissues; hence refraction does not feature prominently in echocardiography.

10. Answer B: The major differences between pulsedwave and continuous-wave Doppler are aliasing seen in pulsed-wave Doppler and range ambiguity (inability to localize the identified velocity) in

continuous-wave Doppler. While range ambiguity can happen in pulsed-wave Doppler when the deeper structures are interrogated with high pulse repetition frequencies, it is a property that is always present in continuous-wave Doppler. Signal processing and the angle dependence of velocity measurements are identified in both techniques.

CHAPTER

Electrocardiographic Stress Testing

Marwa A. Sabe and Julie C. Huang

ESSENTIAL FACTS

1. With few exceptions, exercise stress testing is the test of choice for initial evaluation of suspected coronary artery disease (CAD).
2. Diagnosis of CAD using exercise stress testing is limited by verification bias and an uncertain "gold standard."
3. Exercise capacity is the most important prognostic factor derived from exercise stress testing; Duke treadmill score (DTS), heart rate recovery (HRR), chronotropic response, and ventricular ectopy during recovery also provide important prognostic information.
4. Exercise stress testing is most useful for intermediate-risk patients.

ESSENTIAL EVIDENCE/CURRENT GUIDELINES

The exercise electrocardiographic (ECG) stress test is one of the most commonly performed diagnostic tests in modern medicine and is the test of choice for the initial evaluation of suspected CAD. Its advantages include its low cost, general safety, noninvasive nature, and its usefulness in providing information regarding functional capacity. With the wide proliferation of imaging techniques, the "plain old treadmill test" has become increasingly underappreciated, despite its ability to predict short- and long-term risks. In fact, if a patient is able to exercise, has not been previously revascularized, and has a baseline ECG that is considered interpretable, ECG stress testing is the test of choice for the evaluation of suspected CAD.

Traditionally, the primary goal of exercise stress testing is the diagnosis of obstructive CAD and myocardial ischemia in patients with symptoms of angina or risk factors for heart disease. This goal, however, is hampered by verification bias; because

the majority of patients who undergo coronary angiography to confirm the diagnosis of CAD have had a positive stress test, it cannot be known for certain how sensitive or specific the stress test is—those who had a negative stress test are not evaluated similarly with angiography. Furthermore, the use of coronary angiography as the gold standard for the diagnosis of CAD is increasingly questioned, as more recent studies have suggested that, because of arterial remodeling, an angiographically normal-appearing artery can actually have a significant amount of atherosclerotic disease upon evaluation by other methods such as intravascular ultrasound. For these reasons, some cardiologists discourage the notion of exercise stress testing as a "diagnostic" tool, but instead consider it a "prognostic" tool.

Safety

Exercise treadmill testing is generally considered to be very safe, but can rarely be associated with serious complications. These may include myocardial infarction (3.5/10,000 tests), serious arrhythmias (4.8/10,000), and death (0.5/10,000). Exercise testing after myocardial infarction is also safe at as early as 3 to 5 days, though is usually limited to submaximal testing using endpoints of 70% age-predicted maximal heart rate (rather than the 85% on a standard exercise stress test) or a peak work level of 5 METs.

Indications and Contraindications to Exercise ECG Stress Testing

Most commonly, exercise stress testing is ordered for the diagnosis of obstructive or flow-limiting CAD; it is most useful in patients with an intermediate pretest probability based on age, gender, and description of chest pain. In a patient with a high pretest probability of CAD (e.g., a middle-aged male with typical anginal symptoms and multiple cardiac risk factors), a negative stress test does not sufficiently preclude a diagnosis of CAD and is more likely to be a false negative result. In contrast, in a patient with a low pretest probability of CAD (e.g., a young woman with atypical symptoms and no significant risk factors), a positive stress test is more likely to be a false positive result. The sensitivity and specificity of testing is therefore highest in patients with intermediate pretest probability. Patients must also have a baseline ECG in which ST segments and subsequent changes are interpretable.

Patients with left bundle branch block, paced rhythms, >1 mm of resting ST depression (e.g., digoxin therapy or left ventricular hypertrophy with strain pattern), and Wolff–Parkinson–White syndrome are therefore not recommended for exercise ECG testing without adjunctive imaging due to the difficulty in assessing ECG changes in these patients. In patients with underlying left bundle branch block on ECG, pharmacologic stress is preferred over exercise stress due to the risk of diagnosing false positive septal ischemia.

Stress testing can also be used to assess prognosis in patients with known or

suspected CAD. It is recommended after myocardial infarction for activity or exercise prescription, entrance into cardiac rehabilitation, and evaluation of medical therapy: and after revascularization to evaluate symptoms and as periodic monitoring of high-risk, asymptomatic patients. In patients with valvular heart disease, stress testing is used for evaluation of exercise capacity and may be very useful in determining the appropriate timing of surgery. Use of stress testing is also indicated for adjustment of pacemaker settings, assessment of suspected exercise induced arrhythmias, and evaluation of therapy in patients with suspected exercise-induced arrhythmias. Before a patient returns to work, testing may provide a comparison of peak workload achieved to that required in employment.

There are no class I indications for testing of asymptomatic patients, and routine screening is classified as a class III indication. However, patients who are asymptomatic but have multiple risk factors, those planning to start vigorous exercise or are engaged in occupations that may affect public safety (e.g., pilots, bus drivers), and those who are at high risk of cardiovascular disease because of comorbidities such as diabetes mellitus can still be referred for exercise stress testing though these are listed as class II indications (see Table 10.1 for class I indications for exercise stress testing).

TABLE
10.1 Class I Indications for Exercise Stress Testing

A. Diagnosis of Obstructive CAD

Adult patients (including those with complete RBBB or <1 mm of ST depression on resting ECG) with an intermediate pretest probability of CAD based on age, gender, and symptoms

B. Risk Assessment and Prognosis in Patients with Symptoms or a Prior History of CAD

1. Patients undergoing initial evaluation with suspected or known CAD (includes those with RBBB or <1 mm of ST depression on resting ECG)
2. Patients with suspected or known CAD, which has been previously evaluated, now presenting with a significant change in clinical status
3. Low-risk unstable angina patients 8–12 h after presentation who are now free of symptoms of ischemia or active heart failure
4. Intermediate-risk unstable angina patients 2–3 d after presentation who are now free of symptoms of ischemia or active heart failure

C. After Myocardial Infarction

1. Prior to discharge for prognosis, activity prescription, and evaluation of medical therapy (4–6 d)
2. Early after discharge for prognosis, activity prescription, evaluation of medical therapy, and cardiac rehabilitation if the predischarge exercise test was not done (14–21 d)
3. Late after discharge for prognosis, activity prescription, evaluation of medical therapy, and cardiac rehabilitation if the early exercise test was submaximal (3–6 wk)

D. Asymptomatic Persons without Known CAD

None

E. Valvular Heart Disease

In patients with chronic aortic regurgitation and equivocal symptoms, for assessment of functional capacity and symptomatic responses

F. Before and after Revascularization

1. To demonstrate ischemia prior to revascularization
2. To evaluate patients with recurrent symptoms that suggest symptoms after revascularization

G. Investigation of Heart Rhythm Disorders

1. To identify appropriate settings in patients with rate-adaptive pacemakers
2. For the evaluation of congenital third-degree heart block prior to starting competitive sports or increasing physical activity

H. Exercise Testing with Ventilatory Gas Analysis

1. In patients with heart failure being considered for cardiac transplantation for evaluation of exercise capacity and therapy response
2. Differentiation of cardiac vs. pulmonary causes of exercise-induced dyspnea or impaired exercise capacity.

Adapted from Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation. 2002;106:1883–1892.

Contraindications to exercise stress testing (Table 10.2) include testing of extremely low-risk patients and those with recent myocardial infarction (within 2 days), unstable angina or dynamic ECG changes, active or unstable arrhythmias or congestive heart failure, aortic dissection, severe aortic stenosis, or other acute cardiac or systemic processes. Relative contraindications are at the discretion of the physician: testing may proceed if the benefit outweighs the risk.

TABLE
10.2 Contraindications to Exercise Testing

Absolute contraindications
Recent significant change in resting ECG
Recent MI <2 days
Unstable angina not medically controlled
Uncontrolled arrhythmias causing hemodynamic compromise
Uncontrolled heart failure
Severe symptomatic aortic stenosis
Acute pulmonary embolism/infarction
Acute myocarditis or pericarditis
Suspected or known aortic dissection
Acute infection
Relative contraindications
Left main coronary stenosis
Moderate stenotic valve disease
Electrolyte abnormalities (K^+, Mg^{2+})
SBP > 200 mm Hg, DBP > 110 mm Hg
Symptomatic tachy- or bradyarrhythmias
Hypertrophic cardiomyopathy
Neuromuscular, musculoskeletal, or rheumatoid disorders that are exacerbated by exercise
High-degree AV block
Ventricular aneurysm
Uncontrolled metabolic diseases
Chronic infections (e.g., hepatitis, HIV)

MI, myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; AV, atrioventricular.
(Adapted from Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA guidelines for exercise testing: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). Circulation. 1997;96:345–354.)

Methods of Testing

Ideally, the exercise stress test should last 8 to 12 minutes; this provides a reasonable compromise for assessment of functional capacity without fatigue and attainment of anaerobic threshold. It is therefore important to choose the appropriate exercise protocol to suit the patient's projected ability to perform the test. For instance, the widely used Bruce protocol may be an appropriate test for most patients, but is likely too difficult for an elderly patient undergoing risk stratification before hospital discharge. A truncated test provides a less accurate assessment of functional capacity.

Although bicycle protocols allow for a more precise measurement of work capacity, most patients in the United States have more familiarity with treadmill methods and treadmill is therefore more commonly used. The disadvantage of treadmill is that work is only estimated and tends to be overestimated, depending on the degree of reliance (leaning) on handrails.

Placement of electrodes for ECG measurement differs in exercise testing compared

to standard 12-lead ECG and may result in rightward axis shift and false positive or negative inferior Q waves. Lead V_5 is often the best for assessment of ST changes. ECGs are obtained at rest, during each stage of exercise, at peak exercise, and every 1 to 2 minutes for at least 5 minutes of recovery. Other data obtained during testing include cardiac rhythm, heart rate, blood pressure, symptoms, and the patient's rating of perceived exertion. The test is completed when the patient attains 85% of the age-predicted maximum heart rate or cannot proceed because of symptoms. The age-predicted maximum heart rate is calculated as 220 minus the age in years.

Absolute indications for termination of stress testing (Table 10.3) include symptoms, drop in systolic blood pressure, sustained ventricular arrhythmias, and the development of ST elevation in leads without q waves. Relative indications for termination of testing are also listed.

TABLE
10.3 Indications for Termination of ECG Stress Testing

Absolute indications for terminating testing
SBP drop of ≥10 mm Hg in the presence of other signs of ischemia
Moderate to severe angina
Increasing ataxia, dizziness, and near-syncope
Pallor or cyanosis
Technical difficulties with ECG or blood pressure monitoring
Subject request
Sustained VT
ST elevation ≥1 mm in leads without pathologic Q waves
Relative indications for terminating testing
SBP drop of ≥10 mm Hg in the absence of other signs of ischemia
ST depression >2 mm
Arrhythmias other than sustained VT
Fatigue, dyspnea, wheezing, leg discomfort, and claudication
Development of bundle branch block or IVCD that cannot be distinguished from VT
Increasing chest pain
SBP > 250 mm Hg or DBP > 115 mm Hg

SBP, systolic blood pressure; VT, ventricular tachycardia; IVCD, intraventricular conduction defect; DBP, diastolic blood pressure.
(Adapted from Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA guidelines for exercise testing: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). Circulation. 1997;96:345–354.)

Diagnostic Interpretation

Interpretation of the ECG stress test primarily involves evaluation of the ST segment. The classic positive finding is ≥1 mm of horizontal or down-sloping ST-segment depression 80 ms after the J point, though many labs also consider up-sloping ST-segment depression ≥1.5 mm a positive finding. Ischemic changes tend to occur in leads I and V_4-V_6; the more widespread the ECG changes, usually the more severe the disease. ST-segment depression does not localize ischemia; however, ST-segment elevation in leads without Q waves does localize the distribution of ischemia and is an absolute indication for termination of the test. Markers of severe CAD during testing include a drop in systolic blood pressure below resting value, exercise-limiting angina, poor exercise capacity <5 METs, down-sloping ST depression in recovery, and ST depression at low work load.

Prognostic Interpretation

Of as much importance as evaluation of ST segments during stress testing is the contribution of other markers of risk to overall prognosis. Exercise capacity is the most important prognostic variable; it is widely accepted that patients able to perform >10 METs are in general at low risk for cardiovascular events (Table 10.4). The heart rate recovery (HRR), the difference in heart rate from peak exercise to 1 minute recovery, is known to be a very strong prognostic indicator. HRR of 12 beats or less predicts an increased relative risk of sudden cardiac death and all cause mortality independent of CAD severity. Normally, withdrawal of the sympathetic nervous system and reactivation of the parasympathetic nervous system lead to a drop in heart rate after exercise, that is, HRR > 12 beats. A reduction in vagal activity, which may be the mechanism of a low HRR, has been previously shown to have an adverse effect on mortality and may be the reason a poor HRR predicts mortality.

TABLE
10.4 Age and Gender Estimated Functional Capacity

	Estimated Functional Capacity (METs)				
Age (y)	Poor	Fair	Average	Good	High
			Women		
≤29	<7.5	8–10	10–13	13–16	>16
30–39	<7	7–9	9–11	11–15	>15
40–49	<6	6–8	8–10	10–14	>14
50–59	<5	5–7	7–9	9–13	>13
≥60	<4.5	4.5–6	6–8	8–11.5	>11.5
			Men		
≤29	<8	8–11	11–14	14–17	>17
30–29	<7.5	7.5–10	10–12.5	12.5–16	>16
40–49	<7	7–8.5	8.5–11.5	11.5–15	>15
50–59	<6	6–8	8–11	11–14	>14
≥60	<5.5	5.5–7	7–9.5	9.5–13	>13

The Duke treadmill score (DTS), a composite of exercise capacity and angina, also provides important information. It is calculated as:

$$\text{DTS} = \text{minutes of Bruce protocol} - 5 \times \text{ST deviation} - 4 \times \text{angina index}$$

where the angina index is 0 = no angina, 1 = angina, but not test limiting, and 2 = test-limiting angina. DTS interpretation is as follows:

Low (≥ + 5): mortality risk <1% per year

Intermediate (–10 to +4): mortality risk 1% to 3% per year

High (<–10): mortality risk >3% per year

The use of beta-blockers during stress testing may affect certain variables such as chronotropic incompetence and peak heart rate but has little if any effect on the DTS and its prognostic implications. The presence of ventricular ectopy during exercise recovery is a significant negative prognostic indicator.

Exercise ECG Stress Testing in Women

Women represent a special population when choosing stress test modality. Because of the lower prevalence of obstructive CAD in women, diagnostic tests that detect focal areas of stenosis, such as ECG exercise stress testing, are less sensitive and specific in women. One of the reasons for the decreased accuracy of the ECG exercise stress test in women is the difference of accuracy of ST-segment depression in men and women. Women are more likely to have ST and T-wave changes on baseline ECG and more ST depression with exercise testing that does not provide prognostic value. It has been proposed that estrogen may have a digoxin-like effect on ST segments during exercise as ST depression is more likely to vary with the menstrual cycle in premenopausal women, and postmenopausal women taking estrogen supplements are more likely to

have ST depression during exercise than women not taking these supplements. However, despite the decreased accuracy of exercise ECG stress testing in women, the 2005 Guidelines for the Role of Noninvasive Testing in the Clinical Evaluation of Women with Suspected Coronary Artery Disease recommends exercise ECG stress testing as the first diagnostic test of choice in intermediate risk, symptomatic women with normal baseline ECGs. In women who are asymptomatic, other parameters gained from the exercise stress test such as poor exercise capacity, low HRR, and failure to reach the target heart rate are more predictive of outcome than ECG changes associated with exercise.

Metabolic Gas-Exchange Analyses

Metabolic stress testing is indicated for the evaluation of exercise capacity and response to therapy in patients with heart failure being considered for heart transplantation as well as for differentiation of cardiac from pulmonary causes of exercise intolerance. It may also be used for the evaluation of exercise capacity when subjective measurement is unreliable, for the assessment of responses to specific therapeutic interventions, and for the determination of exercise intensity for a cardiac rehabilitation program. It is not indicated for routine evaluation of exercise capacity.

Several standard measurements are made in metabolic stress testing in addition to the above-mentioned variables used in routine ECG testing. The peak Vo_2 (oxygen uptake) defines the patient's aerobic capacity and is proportional to the cardiac output; a peak Vo_2 of <14 mL/kg/min identifies high-risk patients who are reasonable candidates for cardiac transplant despite ambulatory status. The respiratory exchange ratio (RER), calculated as Vco_2/Vo_2, where Vco_2 is the production of carbon dioxide, identifies the adequacy of the test, with RER > 1.09 suggesting adequate effort for reliable analysis of the test. Other important variable measurements include Vo_2 at anaerobic threshold, the VE (minute ventilation)/MVV (maximal voluntary ventilation) (proportion of ventilatory), and Vo_2 pulse or Vo_2/HR (measure of stroke volume).

SUMMARY

In modern medical practice with its large array of available diagnostic testing, there is still a role for exercise ECG testing in the evaluation of suspected ischemic heart disease. It should be used primarily for evaluation of symptoms, but it is also important for risk stratification in certain patients, as well as in evaluation of the effectiveness of therapy. In its use as a tool for diagnosis of CAD, it is best used in patients with an intermediate pretest probability based on patient characteristics and symptomatology. In this situation the sensitivity and specificity of the test are highest, generally reported as 68% and 77%, though these values are hampered by verification bias.

The prognostic information gained from stress testing is just as important, and includes exercise capacity, HRR, chronotropic competence, and the DTS.

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QUESTIONS AND ANSWERS

Questions

1. A 40-year-old asymptomatic man with no risk factors undergoes stress testing as part of an "Executive Physical" program. His resting electrocardiography (ECG) is normal and he is taking no medications. He has an exercise capacity of 14 METs (13.5 minutes on the Bruce protocol), no angina, a peak heart rate of 180, and 1 mm of down-sloping ST-segment depression noted in lead V5. His Duke treadmill score (DTS) is:
   a. 9
   b. 8.5
   c. 7.5
   d. 3.5
   e. 2

2. Given these test results, the next most appropriate step is:
   a. No further cardiac testing
   b. A stress imaging study
   c. A repeat stress test in 1 year
   d. Coronary angiography

3. A 55-year-old woman presents with intermittent substernal chest pain that radiates to the left arm. The pain is not clearly exertional and is not clearly relieved with rest. There is no history of gastrointestinal problems; her symptoms are not related to meals or body position. Her resting ECG is normal and she is taking no medications. She is referred for an exercise test and is found to have ST-segment depression. Assuming that the true, unbiased sensitivity of exercise ST-segment changes is 45% and the specificity is 85%, the likelihood that she has at least one 50% coronary artery stenosis is:
   a. 0.25
   b. 0.50
   c. 0.75
   d. 0.80
   e. 0.90

4. A 60-year-old man with chronic obstructive pulmonary disease (COPD) (FEV1 1.25) and chronic ischemic cardiomyopathy (EF 30%) is referred for metabolic stress testing, which shows the following: peak Vo2 15 mL/kg/min, peak Vco2 18 mL/kg/min, Vo2 at anaerobic threshold 10 mL/kg/min, peak VE 45 L/min. Which of the following is true?
   a. The test was submaximal.
   b. The primary limitation to exercise is cardiac.
   c. The primary limitation to exercise is pulmonary.
   d. The patient should be referred for cardiac transplantation.
   e. It is not possible to differentiate cardiac from pulmonary limitations to exercise in this patient.

5. A 60-year-old man presents with exertional pressure-like chest discomfort that is relieved with rest and that often radiates to the left arm and jaw. His resting ECG is normal. He is taking no medications. Which of the following is true?
   a. The patient should be referred for coronary angiography.
   b. The patient should have an exercise test to determine whether obstructive coronary artery disease (CAD) is present.
   c. The patient should be referred for an exercise imaging study.
   d. The patient should have an exercise test to determine his short- and long-term prognosis.
   e. The patient need not have any test; he should be started on a beta-blocker, aspirin, and a lipidlowering agent and then followed.

6. In which of the following patients is an exercise ECG stress test recommended by class I

indications?

a. A 45-year-old man with a past medical history of hypertension who presents with postprandial abdominal discomfort for the past few weeks
b. A 65-year-old female with a history of inferior myocardial infarction, status post percutaneous coronary intervention with stent placement in the right coronary artery and hypertension, who presents with worsening exertional, substernal chest pain for the past month, relieved with rest and nitroglycerin
c. A 50-year-old man with a family history of early CAD who presents for a routine physical exam and is noted to have left bundle branch block on resting ECG
d. A 60-year-old female with a history of 40-packyear smoking, hyperlipidemia, and diabetes mellitus, who presents with new symptoms of chest discomfort brought on with exertion for the past 2 weeks. Symptoms are relieved with rest. Her resting ECG has a right bundle branch block.
e. An 85-year-old man with exertional chest pain and shortness of breath. He has a harsh systolic murmur at the right upper sternal border with radiation to the carotids and a soft P_2 on exam.

7. A 55-year-old woman with a history of hypertension and hyperlipidemia presents to the ER with symptoms of substernal chest pain radiating to the left arm that started 2 days prior to presentation. ECG reveals no abnormalities and she is chest pain free after two sublingual nitroglycerin tablets. She is ruled out for acute myocardial infarction by three sets of biomarkers 8 hours apart. What is the next recommended step?
   a. Refer to the catheterization lab for immediate PCI.
   b. Order an exercise ECG stress test.
   c. Order a Persantine nuclear stress test because the exercise ECG test will likely show false positive ST depressions in female patients.
   d. Send the patient home with no further testing.

8. The patient in Question 7 undergoes an ECG exercise stress test with the following results:
   She completes 8 minutes of a modified Bruce protocol. She reaches a heart rate of 160 bpm, which decreases to 152 bpm after 1 minute of recovery. She has mild, nontest-limiting angina during the exam. Her ECG has no ST changes but does show occasional premature ventricular complexes (PVC's).
   Which of the following is a true statement based on these results?
   a. Based on her DTS score, she has a mortality risk of <1% per year.
   b. Her results cannot be interpreted because of the poor sensitivity and specificity of exercise ECG stress testing in women.
   c. She has an increased risk of mortality based on her heart rate recovery (HRR).
   d. PVCs have no prognostic value in stress testing.
   e. Her stress test should have been immediately terminated when she experienced symptoms of angina.

9. All of the following patients have contraindications to ECG exercise stress testing except:
   a. A 70-year-old man who had chest pain 48 hours prior to presenting to the ER. He is currently chest pain free. His ECG shows new q waves in V_1-V_3 that were not present on an ECG 1 month prior.
   b. A 45-year-old woman with postpartum cardiomyopathy who presents with decompensated heart failure.
   c. A 65-year-old man who presents with chest pain for the past few days brought on by exertion and deep breaths and relieved with rest. He was discharged 1 week prior after undergoing a right total knee replacement.
   d. A 55-year-old man with a history of hypertension who presents with complaints of exertional chest pain for the past month. His resting blood pressure is 160/100 and he has a heart rate of 65 with first degree AV block on resting ECG.
   e. An 85-year-old woman with recent history of syncope. On exam, she has a systolic ejection murmur with radiation to both carotid arteries. Her carotid pulses are delayed.

10. Which of the following parameters is a marker of severe CAD?
    a. Up-sloping ST depression in recovery
    b. 1-mm ST elevations in leads with q waves
    c. Exercise capacity of <6 METS
    d. ST depressions in leads V_1-V_3 in a patient with underlying RBBB
    e. A drop in systolic blood pressure below resting value during testing

Answers

1. Answer B: DTS = 13.5 minutes – 5 × 1 mm of ST depression – 4 × 0 angina = 8.5.

2. Answer A: A DTS ≥ 5.5 implies low risk of death (≤1% per year) and therefore no further testing is needed.

3. Answer C: This is the positive predictive value, where PPV = (Sens)(Prev)/[(Sens)(Prev) + (1 – Spec) (1 – Prev)]. The patients has atypical angina, and given her age and gender therefore has an intermediate-risk (0.50) pretest likelihood. Substituting values, the PPV is 0.75.

4. Answer C: The MVV is 40 × 1.25 = 50. Given his VE of 45, he used up 90% of his breathing reserve.

5. Answer D: The patient has typical angina and a very high pretest likelihood of disease. Exercise testing is appropriate to assess prognosis. If he is found to be at low risk, medical management will be appropriate.

6. Answer D: Class I indications for exercise ECG testing include patients with an intermediate pretest probability of CAD based on sex, age, and symptoms. These include patients with RBBB. Class II indications include patients with low (the 45-year-old man) or high risk of CAD. Class III indications include patients with baseline ECG that is not interpretable (LBBB, LVH with strain pattern, 1-mm ST depressions at rest, preexcitation, and paced rhythms), documented myocardial infarction, or established diagnosis of CAD based on angiography. The 85-year-old man likely has severe symptomatic aortic stenosis, which is a contraindication to exercise stress testing.

7. Answer B: This patient has an intermediate risk of CAD based on age, sex, and symptoms, thus an exercise ECG test is indicated. Although in this woman, false positive ST depressions are possible, this is not a reason to order a pharmacologic stress test before an exercise ECG test in a patient who can exercise and has an interpretable baseline ECG.

8. Answer C: Her DTS score is 8 – (5 × 0) – (4 × 1) = 4. A DTS score of −10 to +4 predicts a mortality risk of 1% to 4% per year. Although exercise ECG stress testing has a lower sensitivity and specificity in women, it is still recommended as the first test of choice to assess CAD in women with an interpretable ECG who can exercise. Her HRR is calculated as 160 – 152 = 8; HRR < 12 is predictive of an increased risk of mortality. Ventricular ectopy during testing is also a significant adverse prognostic indicator. Mild angina is not a reason to terminate testing; stress testing should be terminated for moderate to severe angina.

9. Answer D: Contraindications to exercise ECG stress testing include the following: MI in the past 2 days, recent significant change in resting ECG, uncontrolled heart failure, acute pulmonary embolus, and severe aortic stenosis.

10. Answer E: Markers of severe CAD during testing include a drop in systolic blood pressure below resting value, exercise-limiting angina, poor exercise capacity <5 METS, down-sloping ST depression in recovery, and ST depression at low work load. ST elevation in leads with preexisting q waves is not predictive of disease severity. ECG changes in leads V_1-V_3 in patients with RBBB are not interpretable.

CHAPTER

Stress Echocardiography

L. Leonardo Rodriguez and Thomas H. Marwick

Stress echocardiography (SE) is one of the main diagnostic modalities used in the evaluation of patients with known or suspected coronary artery disease (CAD). Stress echo permits an integral evaluation of global and regional ventricular function, valvular integrity, and, most important, myocardial response to stress. The Class I indications for SE in chronic ischemic heart disease are diagnosis of ischemia in symptomatic individuals and the assessment of myocardial viability (hibernating myocardium) for planned revascularization (dobutamine echo). In addition, the referral base to the test is being augmented by situations when the effects of increasing cardiac reserve are sought in patients with valvular heart disease, diastolic dysfunction, pulmonary hypertension, and hypertrophic cardiomyopathy.

The accuracy of SE is superior to stress electrocardiography (ECG) and comparable to that of nuclear stress testing. In general, SE is less sensitive for single vessel CAD but more specific than perfusion imaging.

Numerous studies have validated the prognostic significance of SE, with a negative test carrying a very low risk (<1%) of major cardiac events over the subsequent 4 to 5 years. SE can also distinguish viable from scarred myocardium. The ability to predict which patients with left ventricular (LV) dysfunction will benefit from modern revascularization techniques is an important piece of information that may facilitate the discussion of benefit and risk for intervention that may carry significant risk. Although the accuracy and prognostic implications of dobutamine stress echocardiography (DSE) in the detection of viability are comparable to the more contemporary modalities of positron emission tomography (PET) imaging and magnetic resonance imaging (MRI), the role of dobutamine-induced augmentation in predicting functional recovery has been challenged by the recent results of the STICH trial. Within the realm of valvular heart disease, SE has an increasing role in predicting the functional significance of a variety of valvular lesions. Compared to other noninvasive modalities, SE is safe, widely available, relatively inexpensive, and avoids radiation exposure. However, its

interpretation remains subjective and requires a considerable learning curve with substantial interobserver variability. Much effort has been devoted toward quantitation —for example using strain—but this remains challenging.

SE detects ischemia earlier in the ischemic cascade than ECG and before symptoms appear by identifying new regional wall motion abnormalities (RWMA) (Fig. 11.1). SE adds to exercise ECG particularly when the baseline ECG limits ST-segment assessment such as in left bundle branch block (LBBB), intraventricular conduction delay, paced rhythms, left ventricular hypertrophy (LVH), and digitalis effect.

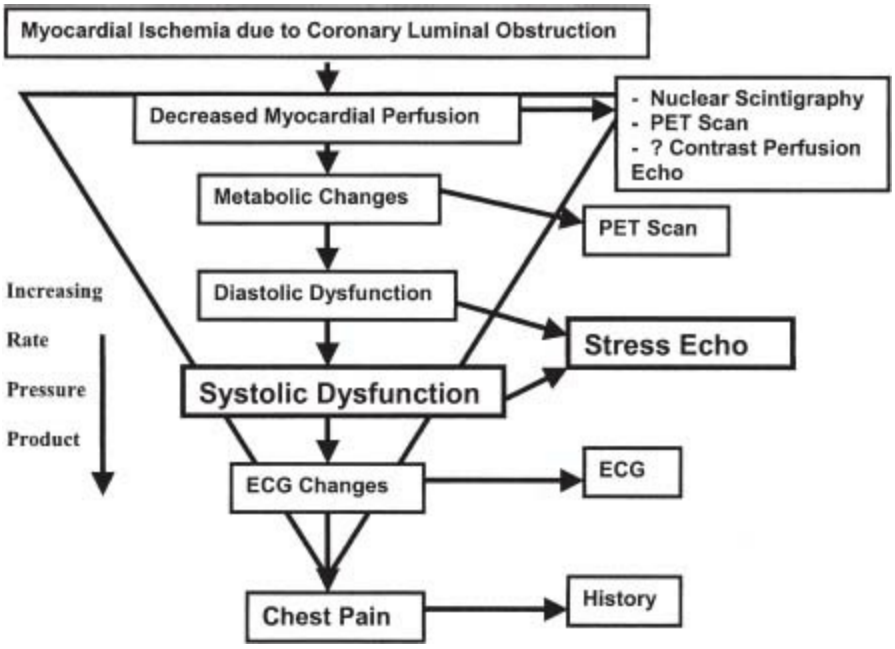

FIGURE 11.1 Ischemic cascade. (From Daly RP. Stress Echocardiography. In: Griffin BP, Topol EJ, eds. Manual of Cardiovascular Medicine, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2009:633, with permission from Wolters Kluwer Health.)

FORMS OF STRESS

Exercise Echocardiography

The most physiologic form of stress testing remains exercise. In addition to the echocardiographic data, exercise provides important physiologic information for prognosis and risk stratification. Exercise echo can be done using a treadmill or bicycle. The advantage of bicycle exercise is that imaging can be performed during stress. For treadmill exercise, patients must be taken off the treadmill and the echo images acquired within 1 minute of peak exercise. However, bicycle exercise is more effort dependent and therefore less reliable in reaching a target heart rate. Exercise is also preferred for noncoronary indications such as valvular heart disease or hypertrophic cardiomyopathy.

Pharmacologic Stress Echocardiography

Approximately 30% of patients are unable to exercise for reasons such as peripheral vascular disease, obstructive lung disease, or musculoskeletal problems. For these patients, pharmacologic SE can be performed. There are three options for pharmacologic SE: (a) sympathomimetic agents such as dobutamine, (b) vasodilator agents such as adenosine, and (c) atrial pacing.

Of the sympathomimetic agents, dobutamine has the largest clinical experience. It produces stress through an increase in myocardial oxygen demand via its positive inotropic and chronotropic effects. At low doses, it has positive inotropic effects mediated through cardiac α and β_1 receptors. At high doses it possesses chronotropic effects through the β_2 receptor. Dobutamine can be combined with atropine to achieve a target heart rate of 85% of age-predicted maximum heart rate. Contraindications to atropine use include angle-closure glaucoma and severe benign prostatic hypertrophy. In patients who are morbidly obese without other viable noninvasive options for risk stratification, dobutamine has been combined with transesophageal echo to avoid the potential morbidity of cardiac catheterization. When assessing viability, dobutamine is preferred for assessment of contractile reserve at low doses.

Vasodilators, such as adenosine or dipyridamole, induce ischemia via a coronary steal effect that preferentially shunts blood away from myocardial segments supplied by stenotic coronary arteries. Adenosine has a short half-life, and both have fewer side effects than dobutamine. However, the intensity of ischemia is also less, so the echo findings are also less pronounced, resulting in a lower sensitivity of approximately 50% to 60% and a decreased ability to detect small amounts of ischemia in patients with single-vessel disease. Atropine is required in all subjects in order to gather equivalent data. Vasodilator stress is commonly used in Europe and when myocardial perfusion data are sought with myocardial contrast echocardiography.

Atrial pacing, either by transvenous or transesophageal routes, has been used to achieve stress. The small increases in rate/pressure product and general poor tolerability of pacing have prevented this method from having general acceptance.

IMAGING TECHNIQUE

The typical treadmill protocol involves acquiring a series of resting images: parasternal long-axis, parasternal short-axis (including apical), and apical four-, three-, and two-chamber views. These images are stored digitally and then compared side by side with similar views acquired immediately poststress. During bike stress echo testing, images are recorded at rest and after each increment of load.

The dobutamine echo protocol starts with resting images in the same parasternal and apical views already mentioned. The infusion is started at 10 μg/kg/min, and this dose

is increased every 3 minutes to 20, 30, and 40 µg/kg/min. Atropine is administered if the patient does not achieve >85% of predicted maximal heart rate (PMHR) and handgrip can also be added.

Harmonic imaging is now used routinely for better endocardial definition. LV opacification has an important role for patients with suboptimal images to improve visualization of endocardial thickening, as this is the most specific marker for ischemia.

INTERPRETATION OF STRESS ECHO

At rest, akinesis (excursion <2 to 3 mm) and dyskinetic segments are often believed to be consistent with a transmural infarct—certainly, this is more likely if the wall is also thinned (<6 mm). Hypokinetic segments demonstrate a partial infarct or viable myocardium.

Responses to stress echo and their interpretations are summarized in Table 11.1. Results are reported graphically in bull's-eye form (Fig. 11.2), with segments assumed to correspond to a particular coronary distribution (Fig. 11.3). The traditional 16-segment ASE model has been supplanted by a 17-segment AHA model that includes the apical cap, although it needs to be acknowledged that the apex is often not visualized at 2-D echocardiography. Each wall segment is graded subjectively as normal, mildly hypokinetic, severely hypokinetic, akinetic, or dyskinetic in both the rest and stress images. A normal response to stress echo involves a global increase in contractility and hyperdynamic wall motion, and a gradual increase in heart rate. This is manifested by increased wall thickness, increased endocardial excursion, and a reduction in cavity size with stress.

TABLE
11.1 Stress Echocardiography Responses and Interpretation

Interpretation	Resting or Baseline Function	Response to Low-Dose Pharmacologic Stress	Peak and Poststress Function
Normal	Normal	Normal	Hyperdynamic
Ischemic	Normal	Normal; decreased in severe ischemia (new wall motion abnormality)	Decreased (new wall motion abnormality); LV dilatation (severe ischemia)
Scar	Decreased	Decreased	Decreased
Viable and ischemic (hibernating)	Decreased	Improved	Decreased (biphasic response)
Viable and not ischemic (stunned)	Decreased	Improved	Improved
Nonspecific	Decreased	Decreased	Improved

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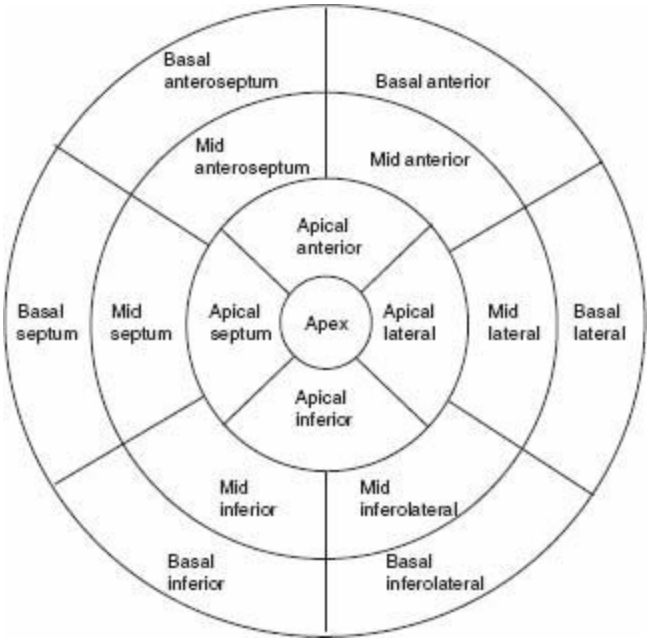

FIGURE 11.2 Typical bull's-eye representation used for reporting the 17 myocardial segments model. (From Daly RP. Stress Echocardiography. In: Griffin BP, Topol EJ, eds. Manual of Cardiovascular Medicine, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2009: 639, with permission from Wolters Kluwer Health.)

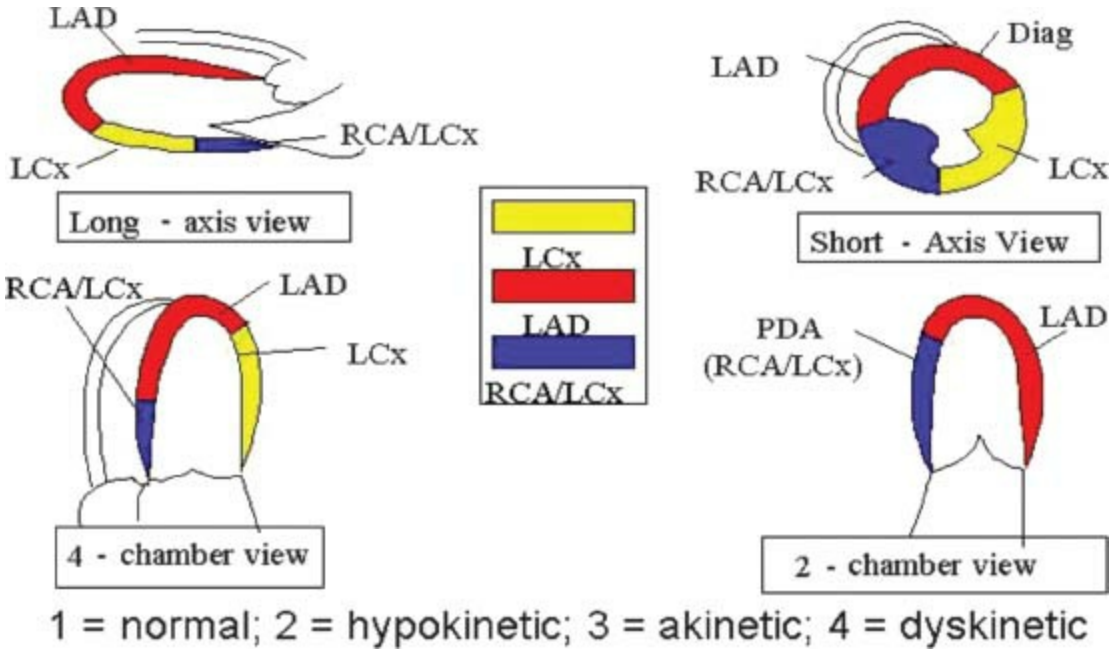

FIGURE 11.3 Relationships among the 17 myocardial segments in the American Heart Association (AHA) classification system and their coronary artery supplies. The four standard views are used to delineate the associations between coronary artery distribution and the segments. (From Daly RP. Stress Echocardiography. In: Griffin BP, Topol EJ, eds. Manual of Cardiovascular Medicine, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2009: 638, with permission from Wolters Kluwer Health.)

A decrease in overall ejection fraction (EF) with LV dilation poststress is an abnormal response that usually represents global ischemia. There are, however, other causes of global hypokinesis, such as a hypertensive response and severe valvular regurgitant lesions.

The use of modern display systems for dobutamine stress echo enables comparison of gradation of function at multiple stress levels—typically at rest, low-dose, prepeak, peak, and recovery. The recovery image is a valuable addition as the normal response to dobutamine involved not just an increase in endocardial thickening but also a marked reduction in cavity size, which may reduce wall stress. Because of this, wall motion abnormalities (WMA) may become apparent or more apparent as the LV fills after stress—the same effect can be derived with the use of beta-blockade. Systolic cavity obliteration is not uncommon—although prognostically reassuring, it decreases the sensitivity of the test. Another finding with little clinical significance during dobutamine stress is the development of systolic anterior motion of the mitral valve with a dynamic LVOT gradient.

Reproducibility of SE within centers is generally very good, yet concordance may be <80% between different centers, especially for technically difficult studies or mild CAD. Importantly, the prognostic implications of stress echo hold up across these differences.

USES FOR STRESS ECHOCARDIOGRAPHY

Traditionally, SE has been used for the diagnostic and prognostic assessment of CAD, but other uses include the assessment of myocardial viability with DSE, determining functional significance of valvular heart lesions, and provocation of subclinical disease —including inducible LVOT gradients, diastolic dysfunction, and inducible pulmonary hypertension.

Diagnosis of CAD

The diagnosis of CAD is made when RWMA are present. Ischemia is diagnosed when new or worsening areas of WMA develop with stress. The accuracy of stress echo for the detection of CAD is greater than that of ECG exercise stress testing alone and equivalent to that obtained with myocardial perfusion. The sensitivity ranges from 75% to 87%, and the specificity ranges from 74% to 80%, depending on disease prevalence. As with all noninvasive modalities, SE is less sensitive for single-vessel disease than for multivessel disease. Table 11.2 lists causes of false-positive and falsenegative SE.

TABLE
11.2 Causes of False-Positive and False-Negative Stress Echocardiographic Test Results

Causes of False Stress Echocardiographic Results	Factors Reducing Specificity or Sensitivity
False-Positive Results	
Abnormal septal motion (LBBB, after cardiac surgery)	Reduced or abnormal septal excursion with normal septal thickness
Nonischemic cardiomyopathy	May develop RWMAs (exact cause unknown)
Hypertensive response to exercise (SBP > 230 mm Hg, DBP > 120 mm Hg)	Nonischemic WMAs or LV dilatation
Poor image quality	
Overinterpretation	Observer bias may result in a lower threshold for calling a positive study; important to be blinded
Basal inferior or septal wall segments	Areas most likely to be overcalled; reduced excursion due to annular tethering effects
False-Negative Results	
Single-vessel disease	More likely to have subtle, rapidly resolving WMA than multivessel disease
Inadequate level of stress (more likely with beta-blockers)	Important to stress maximally; reach at least 85% of age-predicted maximum heart rate
LV cavity obliteration (more likely to occur with dobutamine)	Makes segmental wall motion analysis difficult
Poor image quality	
Left circumflex disease	Lateral wall drop-out; more likely to miss ischemia

DBP, diastolic blood pressure; LBBB, left bundle branch block; LV left ventricular; SBP, systolic blood pressure; WMAs, wall motion abnormalities.
From Daly RP. Stress Echocardiography. In: Griffin BP, Topol EJ, eds. Manual of Cardiovascular Medicine, 3rd ed. Philadelphia:
Lippincott Williams & Wilkins, 2009:641, with permission from Wolters Kluwer Health.

Compared to exercise ECG, SE is more sensitive and specific, as would be predicted based on the ischemic cascade in which RWMA occur prior to ECG changes (see Fig. 11.1). Compared to nuclear stress testing, SE is less sensitive, because perfusion precedes the development of WMA, but is more specific.

DSE has a sensitivity of 68% to 76% and a specificity of 80% to 85%, which is comparable to that of exercise echocardiography. Vasodilator SE demonstrates a significant decrease in sensitivity of 50% to 75%, but with slightly increased specificity of 80% to 100%.

Prognostic Role

Stress echo provides information about the two most important determinants of cardiovascular prognosis, LV function and the severity and extent of ischemia.

Exercise echo offers incremental prognostic information particularly in patients with intermediate risk probability. The total number of abnormal segments both at rest and exercise-induced is important in predicting mortality. In patients with known or suspected disease, a negative test pertains to a low risk of subsequent events (<1% per year), whereas a positive study has a 10% to 30% 1-year event rate of MI, PCI, CABG, or death.

Marwick et al.[1] demonstrated that exercise echo is an independent predictor of death and provides incremental evidence to the traditional Duke treadmill score. It is particularly useful in further stratifying yearly mortality in those with intermediate Duke treadmill scores. Patients with an intermediate Duke treadmill score but normal SE had a 5-year mortality of 1.7%. For those with single-vessel ischemia, the mortality was 3.6%, and for those with multivessel disease, it was 6.7%.

For DSE, ECG changes and hypotension are relatively insensitive markers of ischemia, but RWMA with stress are analogous to ischemia development with exercise. A risk score based on clinical and echocardiographic data may be used to quantify the risk of events in patients undergoing DSE given a lack of exercise data:

$$\begin{aligned}\text{DSE risk} = {} & (\text{age} \times 0.02) + (\text{heart failure} + \text{rate} \\ & - \text{pressure product} < 15{,}000 \times 0.4 \\ & + (\text{ischemia} + \text{scar}) \times 0.6\end{aligned}$$

Using cutoff values of 1.2 and 2.6, patients are classified into groups with 5-year event-free survivals of >95%, 75% to 95%, and >75%. This prognostic information may help facilitate rational decision making about medical management based on the likelihood of an adverse outcome, rather than a binary approach of whether the test is positive or negative.

Scar pertains to an intermediate prognosis between ischemia (high risk) and a normal study (low risk). In post-MI patients, the extent of LV dysfunction is more important than the extent of ischemic/viable myocardium, suggesting that with modern revascularization techniques, the long-term risk is more related to the inability to recover LV function.

For patients undergoing major noncardiac surgery, a positive DSE is associated with a risk of 7% to 25% for hard events (i.e., death and MI). The negative predictive value of DSE for this patient group is 93% to 100%. A meta-analysis concluded that nuclear stress testing and SE had comparable levels of accuracy for preoperative risk assessment, but that SE was significantly cheaper. Appropriate selection on the basis of pretest and operative risk is important as the use of stress echo in perioperative risk assessment is the most frequent source of inappropriate testing. Although questions remain as to whether preoperative revascularization can alter event rates, more exact knowledge of risk is certainly of value in the risk/benefit discussion in selected patients.

Role of DSE to Assess Viability

In patients with CAD and LV dysfunction, it is important to assess for myocardial viability. This is a Class I indication for the use of dobutamine echocardiography. For viability evaluation, the response to low-dose imaging is critical—continuous imaging is optimal (the period of augmentation can be brief), and an additional set of images is acquired at 5 μg/kg/min. The diagnosis of viability using this technique is based on the

presence of contractile reserve, defined as an increase in wall thickening at low-dose dobutamine (5 or 10 μg/kg/min, which should be extended to 20 μg/kg/min in patients on long-acting beta-blockers). Abnormal myocardial segments can respond to dobutamine in a variety of ways (see Table 11.1). A biphasic response (characterized by improvement at low dose and then worsening at peak) is a specific marker of regional recovery after revascularization, and if seen in >4 segments, has an 80% sensitivity and 80% specificity of recovery of global function (e.g., an EF increment >5%) after revascularization. A uniphasic response (improvement at low dose and continued improvement at peak) is a less specific marker of likely recovery. If the segment does not improve at all with low dose or peak dose it is considered irreversibly damaged, or a scar. The accuracy of DSE to predict recovery after revascularization is similar to that of PET, with less sensitivity but greater specificity. DSE is substantially more specific than thallium redistribution imaging for predicting viability. The accuracy of DSE compared to MRI is also similar.

Stress Echo in Valvular Heart Disease

SE helps determine the hemodynamic and functional significance of valvular lesions including aortic stenosis, mitral regurgitation, mitral stenosis, and hypertrophic cardiomyopathy.

DSE is useful in assessing the presence of contractile reserve in patients with aortic stenosis and severe LV dysfunction. Lack of LV function improvement with dobutamine suggests a poor prognosis even after aortic valve replacement. An increase in valve gradients with dobutamine infusion with no change in aortic valve area suggests that the aortic stenosis is the main contributor to low output, and that valve replacement may alter the patient's longterm prognosis. In some patients this technique may help to differentiate pseudostenosis from true aortic stenosis when severe LV dysfunction is present.

SE helps predict latent LV dysfunction in asymptomatic/minimally symptomatic patients with severe MR and normal LV function at baseline. Patients with increased LV size with stress present an increased risk of LV dysfunction postvalve repair. In patients with symptomatic moderate mitral stenosis or in those who are asymptomatic with apparent severe mitral stenosis, stress echo can evaluate the patient's functional response to exercise. SE can determine functional capacity as well as pulmonary arterial pressures at peak stress, which can assist with surgical timing. SE can help explain exertional symptoms in a patient with hypertrophic cardiomyopathy with mild or no resting gradients. Furthermore, important prognostic and hemodynamic information, such as hypotension with peak stress, can be gained from SE in this patient population.

CONCLUSIONS

The current era has brought a number of new technologies for the diagnosis of CAD. Nonetheless, SE is a remarkably versatile test, and its simplicity, ease of access, and inexpensiveness are likely to make it even more attractive in the coming era of bundled care.

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CHAPTER

Nuclear Cardiac Imaging: A Primer

Richard C. Brunken

Nuclear cardiac imaging contributes significantly to the care of patients with known or suspected heart disease. Recent innovations in instrumentation and the use of advanced image reconstruction techniques have permitted reductions in patient radiation doses and shorter imaging times, further enhancing the application of nuclear imaging techniques in the clinical arena. Measurements of absolute myocardial perfusion (in milliliter of blood flow per minute per gram tissue) and perfusion reserve obtained with positron emission tomographic (PET) imaging, once feasible only in research labs, can now be derived from clinical imaging studies using commercially available software. The information provided by noninvasive nuclear imaging studies is valuable for the detection and localization of coronary artery disease, risk stratification, and assessment of myocardial viability. This chapter describes the fundamentals of nuclear imaging and relates them to their specific clinical application.

OVERVIEW OF NUCLEAR IMAGING

A conventional nuclear imaging study employs a gamma camera to record the naturally occurring emissions of a radioactive tracer that is selected to visualize a physiologic process occurring in vivo. The ideal radioactive tracer permits visualization of the physiologic process of interest without disturbing it. The tracer must be nontoxic, emit energies appropriate for imaging, have a high target organ to background ratio, and impart as low a patient radiation dose as possible. It should be readily available and inexpensive to be practical for clinical use. Most radioactive tracers used for cardiac imaging are administered intravenously, but some used for PET imaging (below) may be administered as inhaled gases.

Radioactive tracers spontaneously decay by emitting packets of electromagnetic energy, or photons. The emitted photons are captured by the gamma camera and used to create an image of the physiologic process of interest. However, some of the emitted

photons will be attenuated (absorbed) before they leave the body and will not be used for image creation. The probability that a photon will be attenuated increases as the path length to exit the body increases.

A typical gamma camera has a lead collimator, a piece of metal with a "honeycomb" of openings that serves to focus the incident photons (Fig. 12.1). Most collimators used in cardiac imaging have holes that are parallel to each other (parallel-hole collimators). Photons traveling perpendicular to the camera pass through the holes and are used for image creation. Photons approaching the camera at an angle are stopped by the septa and are not used for imaging. Collimator performance depends on the length and diameter of its holes, as well as septal thickness. In general, spatial resolution improves as the ratio of the diameter of the hole to its length decreases. As spatial resolution improves, efficiency (the relative number of incident photons traversing the lead baffle) decreases. Collimator selection therefore reflects a trade-off between spatial resolution and count sensitivity. High-resolution collimators provide better spatial resolution but lower sensitivity than other collimators, because a larger proportion of photons are absorbed and do not reach the crystal. "General-purpose" or high-sensitivity collimators are capable of passing greater numbers of photons per unit of time, with somewhat poorer spatial resolution. "All-purpose" collimators have characteristics that are intermediate between these extremes.

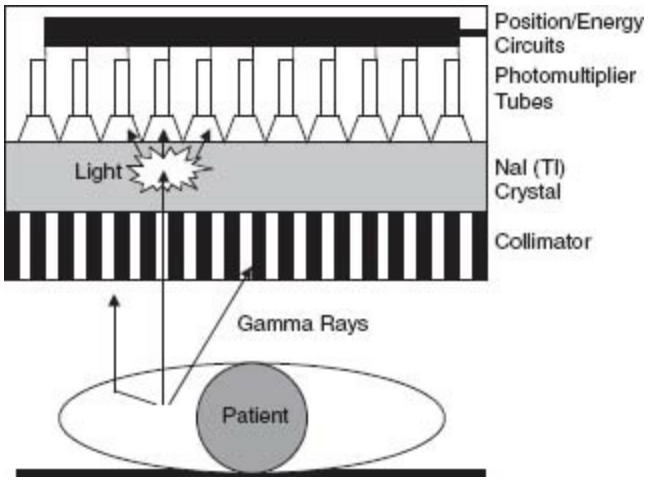


FIGURE 12.1 Schematic representation of a conventional gamma camera. Photons emitted by decay of the radiotracer of interest in the target organ can travel directly to the camera, or be scattered by interposed tissue. Photons that strike the lead collimator are absorbed and do not reach the crystal. The photons that pass through the collimator strike the crystal and interact with it, producing flashes of visible light. The photo-multiplier tube closest to the gamma-ray interaction receives the greatest amount of light, and comparison of the relative response from multiple photomultiplier tubes allows localization of the scintillation event. Light quanta strike the photo-cathodes of the photomultiplier tubes, causing the release of electrons. The electrical signal is amplified by the photomultiplier tubes and transmitted to the energy discrimination and positioning circuitry of the camera.

In a conventional gamma camera, photons exiting the collimator strike a sodium iodide crystal containing a trace amount of nonradioactive thallium. The crystal stops most of the photons and converts their energy into quanta of visible light. Photons that

are more energetic produce a greater number of light quanta than less energetic photons. A “light pipe” directs the light quanta to adjacent photomultiplier tubes. The photomultiplier tubes convert the energy of the light quanta into an electrical current and then amplify the strength of the current by several thousandfold. Special electronic circuitry is used to locate the x and y positions of the initial light impulse and to analyze the energy of the incident photons.

Some photons originating in the heart may be deflected from their initial path, or scattered, before entering the camera. Photons that are scattered in tissue generally lose energy when they are deflected. Scattered photons degrade the image because they do not travel in a direct path to reach the camera. Some scattered photons are deflected toward the camera at an oblique angle and are prevented by the collimator from reaching the crystal. However, other scattered photons do traverse the collimator and strike the crystal with an energy that is less than that of the photons that are not scattered. The contribution of scattered counts to the image can be minimized by setting an optimal “energy window” on the camera. Photons that strike the crystal with energies that are outside of the “energy window" are rejected, thereby improving image quality.

A nuclear image gradually emerges as increasing numbers of photons (scintillation events) are recorded by the camera. Image quality improves nonlinearly as the number of counts (scintillation events) in the picture increases. Thus, it is important to use a high enough radiotracer dose and/or to image for a long enough period of time to acquire a sufficient number of counts to achieve satisfactory image quality. State-of-the-art gamma cameras are capable of imaging about 200,000 counts per second, and some multiwire cameras are capable of even higher count rates. A camera witn a high count rate capability is needed for high-quality first-pass imaging (imaging performed as the tracer is administered intravenously).

Nuclear images can be obtained using planar or single photon emission computed tomographic (SPECT) acquisition techniques. Planar images are obtained with the gamma camera positioned in a fixed location. Usually, planar images are acquired in anterior, left anterior oblique, and left lateral projections. On occasion, planar images may also be obtained from a right anterior oblique projection. Planar images may be acquired for a specific period of time, for a specific number of counts, or for a given number of cardiac cycles (radionuclide ventriculography).

CARDIAC SPECT IMAGING

In SPECT imaging, pictures are obtained from multiple angles (projections) about the body. Conventional SPECT devices employ between one and four camera heads that rotate about the patient. Images are acquired over 180- or 360-degree arcs, usually by “stepping and shooting” an image every 3 or 6 degrees. Information from the raw projection images is then reconstructed using either filtered back-projection or iterative

reconstruction techniques. The reconstructed images are used to define the three-dimensional (3-D) distribution of the tracer in space. Image sets orthogonal to the long axis of the heart (vertical long axis, horizontal long axis, and short axis) are then generated for review.

SPECT images can be acquired with electrocardiogram (ECG) gating to permit assessment of ventricular function. The R–R interval of the ECG is usually divided into 8 or 16 equal time bins (frames) prior to study acquisition (Fig. 12.2). Each bin depicts a different portion of the cardiac cycle. At each step, the SPECT camera acquires 8 to 10 ECG gated images over multiple cardiac cycles. Gated image sets are reconstructed in the same cardiac axes as the nongated images, providing functional information for each of the "slices" in the image sets. Current software packages can also display the gated information as a 3-D rendering, permitting the study interpreter to visualize a graphical representation of the beating heart. Gated SPECT images provide information about regional wall motion and systolic thickening, as well as global left ventricular size and systolic function.

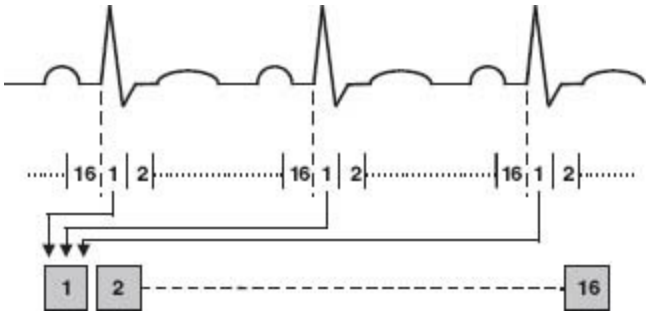


FIGURE 12.2 Graphic representation of the process of ECG gating. Using the R wave of the patient's ECG as a timing signal, image count data from multiple cardiac cycles are added to the time bin corresponding to the portion of the R–R interval in which they were acquired. Counts in each bin increase with each succeeding cardiac cycle, improving the quality of the image represented by that time bin. Usually, 8 or 16 images are acquired per R–R interval, each representing a time-averaged look at that portion of the cardiac cycle. Once the images are acquired, they can be displayed in a continuous ciné loop, depicting global and regional ventricular function.

Several advances in instrumentation have served to enhance the quality of SPECT nuclear cardiac studies. Correction for photon attenuation can be performed using a density map of the chest (a set of transmission images) obtained with either an external line source of activity or a low dose x-ray CT scan. The density map is used to correct for the loss of counts resulting from attenuation of myocardial activity by interposed tissue, reducing the likelihood that an attenuation artifact will be mistaken for a true perfusion defect. Solid-state cameras dedicated to cardiac imaging employ detectors made of cadmium–zinc–telluride (CZT) or cesium iodide (CSI) instead of conventional sodium iodide (Tl) crystals to detect emitted photons. Some solid state cameras employ L-shaped detector heads that are large enough to fit around the chest. This permits imaging of the heart without moving the camera. Semiconductors in the solid-state detectors of these cameras directly convert the energy of incident photons into an

electrical current. These instruments provide higher count sensitivity, improved energy resolution, and better spatial resolution than conventional gamma cameras. In some camera systems, the patient is imaged while seated in an upright or semiupright position. This improves patient comfort during imaging and helps to reduce movement artifacts. Accompanying the advances in instrumentation is the increasing application of iterative techniques for image reconstruction. Iterative reconstruction methods help to reduce noise and improve image quality in low-count studies. These developments have served to maintain image quality while permitting the use of shorter imaging times and/or lower radiopharmaceutical doses.

CARDIAC PET IMAGING

PET cardiac perfusion imaging is more sensitive and specific for the detection of coronary artery disease than conventional SPECT imaging. When PET imaging is performed with the metabolic tracer ^{18}F-2-fluoro-2-deoxyglucose (FDG), it provides important information about regional myocardial viability. Tracers used for PET imaging decay by ejecting a positron (a β^+ particle) from a proton-rich nucleus. Once ejected from the nucleus, the positron interacts with atoms in the surrounding medium, producing excitations and ionizations that slow its travel. As it slows, the positron eventually comes into close proximity with an electron in the surrounding medium. The electron and the positron are “anti-particles" and they mutually annihilate, liberating energy in the form of two 511-kiloelectron volt (keV) annihilation photons, which exit the annihilation site in opposite directions.

PET cameras employ circular banks of gamma-ray detectors to identify paired scintillation events occurring about 180 degrees apart (annihilation coincidence detection). If two detectors opposite each other simultaneously register photon hits in coincidence, then the annihilation event is localized to the volume between the two detectors (Fig. 12.3). If only a single photon is detected, the requirement for coincidence detection is not satisfied and the scintillation event is not used for image creation. Data from millions of annihilation events are reconstructed using standard filtered back-projection or iterative reconstruction techniques to create an image.

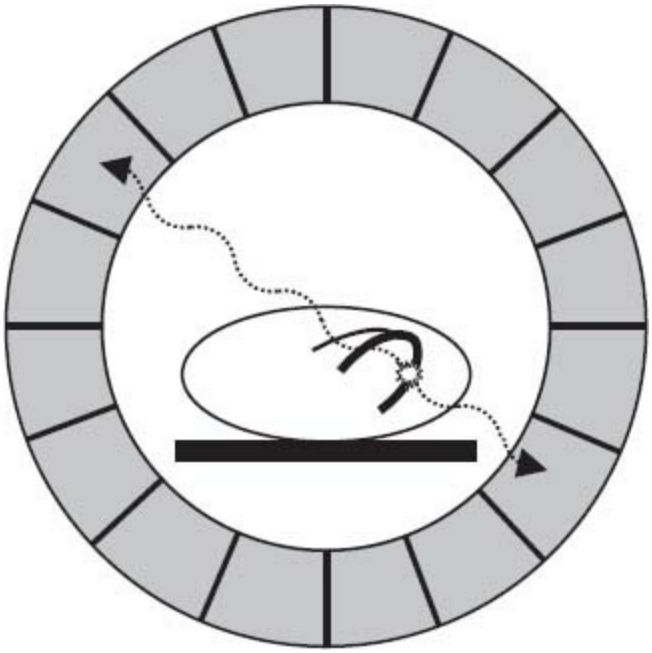


FIGURE 12.3 Schematic representation of PET imaging. When a PET radiotracer decays, it emits a positron, the antiparticle of the electron. The positron travels a short distance before interacting with an electron, resulting in their mutual annihilation. The annihilation event produces two 511-keV photons traveling in diametrically opposed directions. PET imaging relies on the detection of two photons "in coincidence" (arriving at opposite detectors at about the same time) to identify true annihilation events and localize them to the volume between the two detectors.

When a PET scanner operates in the two-dimensional (2-D) mode, each ring of detectors is separated from adjacent rings by lead or tungsten septa. An image is generated in the plane of each ring by using coincidence events occurring between detectors in that ring. A detector in one plane can also be in the "line of sight" and in coincidence with some of the detectors in the next higher or lower adjacent ring. By using interplane coincidences, an additional set of interpolated images is generated midway between the direct planes defined by the detector rings. The 3-D spatial distribution of the tracer is achieved by "stacking" images from multiple 2-D planes. When a PET camera operates in the 3-D mode, it operates without septa between the detector rings. Coincidences are identified between detectors lying in any ring combination. 3-D image reconstruction techniques are then used to define the tracer distribution over the entire volume that is imaged. The reconstruction techniques employed for a 3-D camera are more computationally demanding than those used for a 2-D camera. However, a PET camera operating in the 3-D mode is more sensitive for detecting annihilation events. This means that comparable image quality can be achieved using lower doses of radioactive tracers than those used for 2-D imaging.

PET images can be acquired at the moment of peak myocardial uptake of the tracer (static image acquisition), or a series of images can rapidly be acquired over time (dynamic list mode image acquisition). The images first acquired, the transverse images, are orthogonal to the body. Transverse images are reoriented into standard short-axis, and vertical and horizontal long-axis image sets analogous to those used in

SPECT imaging. ECG-gated PET images can be obtained to assess segmental wall motion and thickening, ventricular volumes and ejection fractions.

PET has several advantages relative to SPECT for cardiac imaging, including better temporal and spatial image resolution and more accurate correction for attenuation of emitted photons. Current PET instruments can acquire multiple cross-sectional images of the entire heart as rapidly as every 5 seconds. PET cameras have spatial resolutions on the order of 6 to 8 mm full-width, half-maximum (FWHM) in the center of the field of view, as compared to 12 to 15 mm FWHM for conventional SPECT cameras. In addition, the radiation dose imparted to the patient from rubidium-82 or nitrogen-13 ammonia is less than half that of a conventional rest-stress SPECT perfusion study performed with a technetium-99m labeled tracer.

Cardiac PET images are corrected for attenuation using transmission images depicting the density of the thorax. In conventional PET systems, transmission images are acquired using an external ring source of activity. In newer PET/CT systems, which are the instruments used most frequently in clinical practice for imaging, transmission images are obtained using a low dose x-ray CT of the thorax. The transmission images are acquired immediately before or after the nuclear images. If desired, the CT portion of the camera can be used for coronary CT angiography and/or calcium scoring at the same session.

On a PET camera that has been appropriately calibrated, counts on the images accurately reflect true tissue activity concentrations. Rates of myocardial perfusion and/or metabolism can be measured by examining the change in tissue tracer concentrations over time on dynamic PET images. Because the acquisition time of each image frame is operator-defined, it is possible to generate time-activity curves depicting changing tissue and vascular tracer activity concentrations over time. Cardiac count data from the time-activity curves are then fit using a mathematical model that describes the biologic behavior of the radioactive label. The parameter of interest (e.g., myocardial blood flow in milliliters per minute per gram of tissue or glucose consumption in micromoles per minute per gram of tissue) is then determined by the equation best fitting the patient's myocardial time-activity data. Commercially available software now permits noninvasive measurements of rest and hyperemic perfusion and myocardial perfusion reserves from dynamic rubidium-82 PET perfusion images.

INTERPRETATION OF NUCLEAR IMAGES

Myocardial perfusion images should be interpreted by an experienced physician. Care is taken to identify significant extracardiac activity that might impact image interpretation, to define cardiac chamber size, assess relative myocardial perfusion, and, where appropriate, examine regional and global myocardial thickening and wall motion. As a quality-control measure for the SPECT studies, the raw projection images are reviewed in a cinematic display. This enables the physician to look for motion and

displacement of the heart during imaging (which may create image artifacts), to identify interposed tissue that might attenuate the images, and to determine if the extracardiac distribution of the radioactive tracer is normal.

Once the projection images have been examined, the short axis, vertical long axis, and horizontal long axis images are reviewed (Fig. 12.4). The standard 17-segment left ventricular model is typically used for study interpretation. In this model each segment represents a near-equal proportion of the ventricular mass (0% for each segment except for the apical cap, which constitutes 4% of left ventricular mass) (Fig. 12.5).

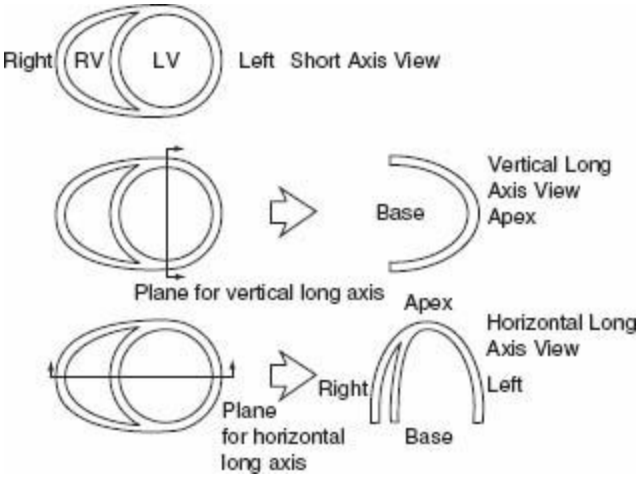


FIGURE 12.4 Cardiac plane definition. (From the Committee on Advanced Cardiac Imaging and Technology, Council on Clinical Cardiology, American Heart Association; Cardiovascular Imaging Committee, American College of Cardiology; and Board of Directors, Cardiovascular Council, Society of Nuclear Medicine. Standardization of cardiac tomographic imaging. Circulation. 1992;86:338–339, with permission from Wolters Kluwer Health.)

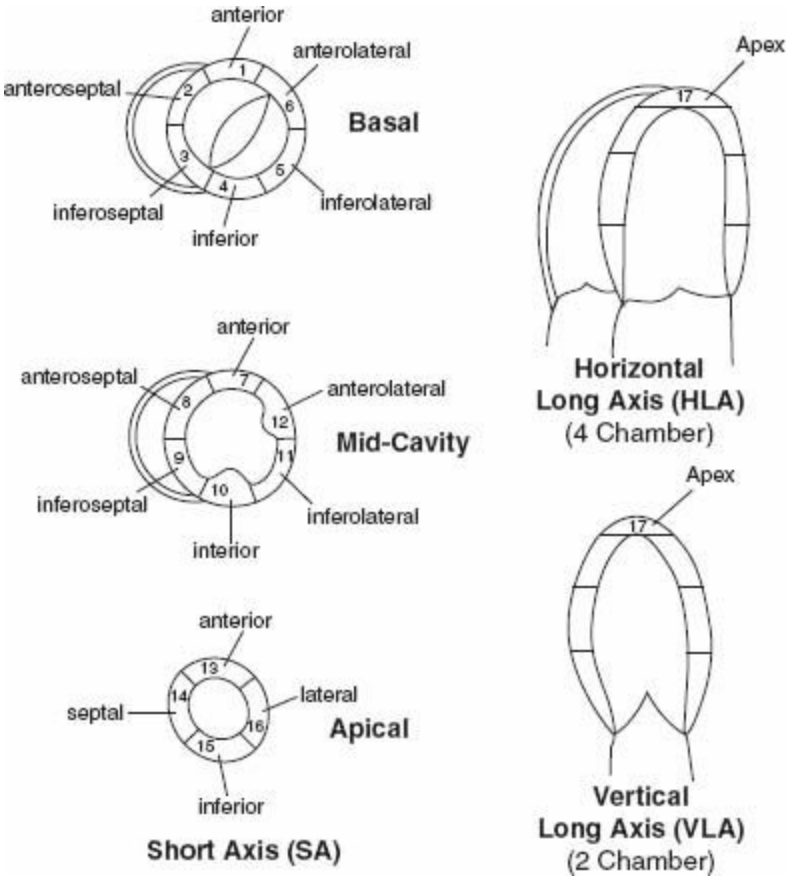
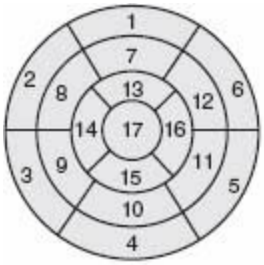


FIGURE 12.5 Regional wall segments. This diagram demonstrates how the left ventricle can be divided into standardized segments for cardiac imaging. Short-axis, horizontal long-axis, and vertical long- axis views are depicted. (From American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation. 2002;105:539–542, with permission from Wolters Kluwer Health.)

Segmental perfusion and function are scored based on a visual analysis of the images. One system assigns perfusion scores from 0 through 4; in this system, normal tracer uptake is scored as 0, a mild (equivocal) reduction in activity is scored as 1, a moderate definitive reduction in activity is given a score of 2, a severe reduction in activity is considered a 3, and a complete absence of activity is given a 4. Summing the scores generates an index that incorporates both the severity and the anatomic extent of a perfusion abnormality. For example, if the stress images demonstrate a perfusion defect involving three segments, with visual scores of 4, 3, and 2, the summed stress score is 9 (= [1 × 4] + [1 × 3] + [1 × 2]). Defects on the rest images are scored in similar fashion and added together to calculate the summed rest score. Rest and stress summed scores may be considered of low (0 to 4), intermediate (5 to 8) or high (>8) severity. The summed difference score is the sum of the differences between the stress and rest scores for each segment. The degree (or amount) of defect reversibility is considered low (summed difference score of 0 to 2), intermediate (summed difference score of 3 to 7) or high (summed difference score > 7).

Computer-generated analyses of the images are also used to aid in study interpretation. Relative tracer concentrations on the patient's images are compared to those of a database of gender-matched normal subjects, permitting rapid identification of image voxels with abnormal tracer concentrations. This analysis of the relative 3-D tracer distribution in the heart is usually displayed as a 2-D "polar map." In the polar mapping technique, the ventricle is considered to be composed of a group of short-axis slices. The apical short-axis slice is smallest in diameter, and as the slices get closer to the base of the heart the diameter of the slices gets larger. Imagine that the smallest short-axis slice is put inside the center of the next larger slice. Both slices are oriented as if the observer is looking up the ventricle toward the base: the septum is on the observer's left, the anterior wall is above, the lateral wall is to the observer's right, and the inferior wall is below (Fig. 12.6). If those two slices are put inside the center of the third slice, and these three slices are put inside the center of the fourth slice, and so on, the process can be continued until all of the short-axis slices are stacked inside the largest basal short-axis slice, each having the same orientation. Basically, the image slices form a "target" with concentric rings and the 3-D information has been mapped into a 2-D display. The parameter of interest (e.g., relative technetium-99m sestamibi activity) in each short-axis slice is expressed as a percentage of the maximal value over the entire heart ("normalized" to peak myocardial values). The normalized activity in each picture element (voxel) can then be displayed using either a gray or color scale to provide the viewer a map of the activity distribution over the entire left ventricle in a single image. Normalized patient data are referenced to gender-matched databases, and a second polar map is generated that displays the extent and the severity of the patient's abnormalities (e.g., two or three standard deviations from normal) on a voxel-by-voxel basis. A variety of parameters can be displayed using the polar mapping technique, including relative and absolute myocardial perfusion, relative systolic thickening (systolic change in counts on gated perfusion or metabolic images), segmental wall motion, thallium-201 redistribution, and PET perfusion-metabolism mismatches. These measurements provide an "independent observer" that assists in the interpretation of the images.



1) basal anterior
2) basal anteroseptal
3) basal inferoseptal
4) basal inferior
5) basal inferolateral
6) basal anterolateral
7) mid anterior
8) mid anteroseptal
9) mid inferoseptal
10) mid inferior
11) mid inferolateral
12) mid anterolateral
13) apical anterior
14) apical septal
15) apical inferior
16) apical lateral
17) apex

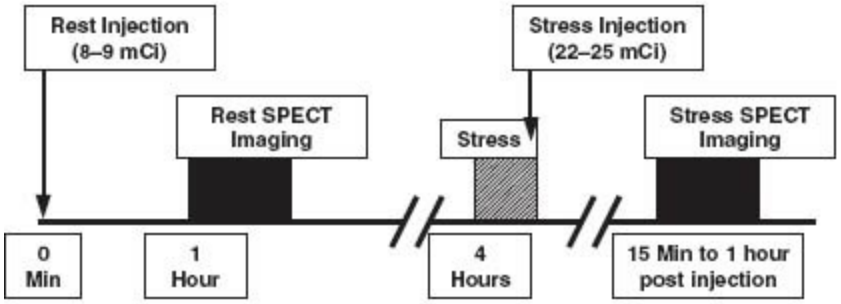
FIGURE 12.6 Left ventricular segmentation. A polar plot demonstrating the 17 myocardial segments and the recommended nomenclature. (From Port SC. Imaging guidelines for nuclear cardiology procedures, part II. J Nucl Cardiol 1999;6:G48–84, with permission of the American Society of Nuclear Cardiology.)

MYOCARDIAL PERFUSION IMAGING

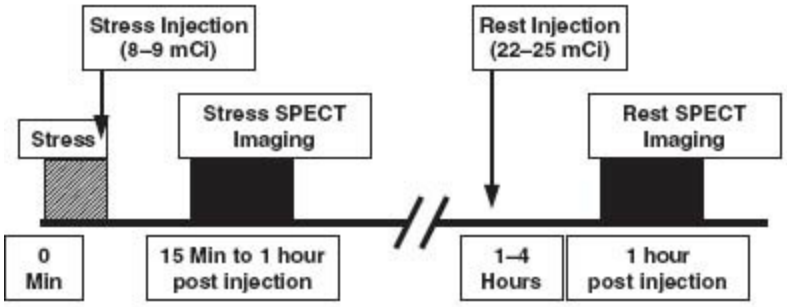
Perfusion imaging is used to show relative regional myocardial blood flow during physiologic states of interest, usually during stress (exercise, pharmacologic) and at rest. The ideal perfusion tracer localizes to the myocardium in direct proportion to blood flow, such that tissue counts increase linearly as blood flow increases. In practice, only two perfusion tracers come close to exhibiting this linear relationship: technetium-99m teboroxime (SPECT imaging) and oxygen-15 water (PET imaging). The other tracers used for clinical SPECT and PET perfusion imaging exhibit progressively smaller increases in tissue uptake as blood flows increase above about 2 mL/min/g tissue.

A summary of the various myocardial perfusion imaging protocols is given in Figure 12.7. Recent clinical studies indicate that use of a “stress only” image acquisition might be utilized in appropriately selected individuals (patients in whom the likelihood of a stress defect is considered low by their clinical presentation). Use of a “stress only" image acquisition protocol in appropriately selected patients reduces the time required for testing and patient radiation exposure. In individuals in whom exercise stress is not feasible, pharmacologic stress perfusion imaging is an acceptable alternative. As the severity of a coronary stenosis becomes more pronounced, the vessel loses its ability to increase blood flow in parallel with increases in tissue oxygen demand. In vascular territories supplied by a diseased artery, coronary flow reserve is impaired and a defect will be observed if images depicting myocardial perfusion during stress (exercise, hyperemia) are obtained. Unless the coronary stenosis is very severe, diseased vessels usually have a sufficient reserve to sustain blood flow under resting conditions, and perfusion images obtained in the basal state will not demonstrate a defect. A reversible defect (Table 12.1) is one that is present on stress images and not present on rest or redistribution images; it is the hallmark of stress-induced ischemia. Sometimes a coronary stenosis is severe enough to result in a perfusion defect if imaging is performed in a resting state. If a rest defect improves on redistribution or reinjection images, the segment is viable and likely to benefit from revascularization.

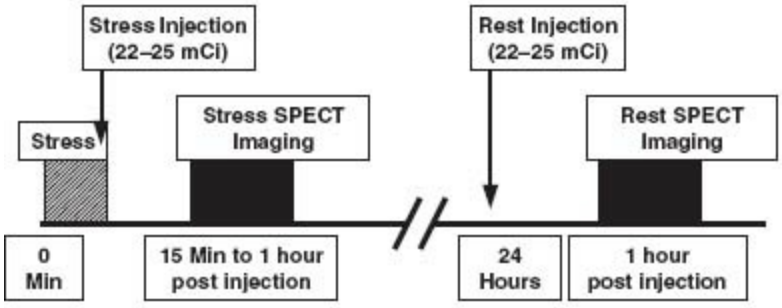
Same-Day Rest-Stress ^{99m}Tc Acquisition Protocol



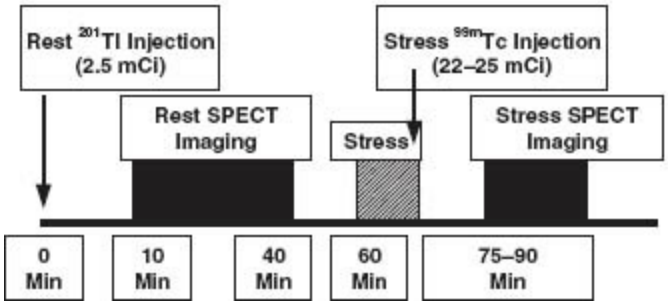
Same-Day Stress-Rest ^{99m}Tc Acquisition Protocol



Two-Day Stress-Rest ^{99m}Tc Acquisition Protocol



Separate Dual Isotope Acquisition Protocol



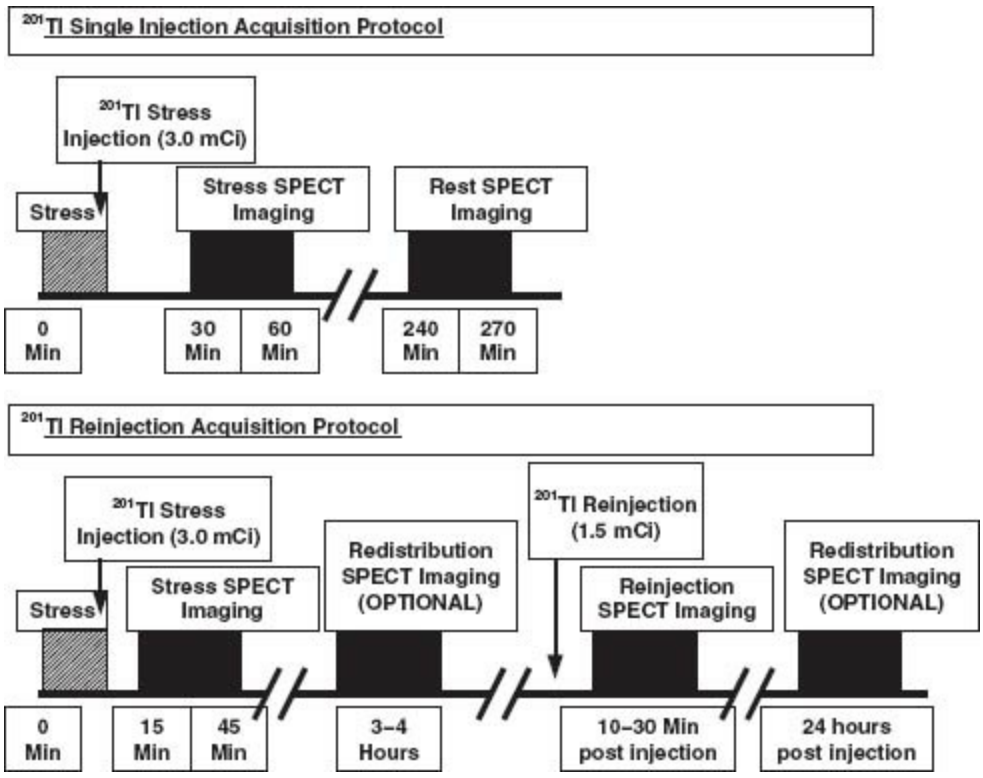


FIGURE 12.7 Schematic summary of various myocardial perfusion imaging protocols. (Adapted from DePuey EG. Updated Imaging Guidelines for Nuclear Cardiology Procedures, Part 1. J Nucl Cardiol. 2001;8:G1–G58. Additional in-depth information regarding myocardial perfusion imaging protocols can be found at www.asnc.org under Guidelines and Standards. Stress protocols and tracers.)

TABLE
12.1 Defect interpretation

Stress	Rest (or Early Redistribution)	Interpretation
Normal	Normal	Normal
Defect	Normal	Ischemia
Defect	Defect	Scar (or hibernation)
Normal	Defect	"Reverse redistribution"

A perfusion defect that persists on both stress and rest or redistribution/reinjection images, a fixed defect, may reflect myocardial scar or myocardial hibernation. Partially reversible defects are stress defects that improve but do not normalize completely on rest or redistribution/reinjection images; these likely reflect nontransmural scar with superimposable ischemia. A defect is said to exhibit reverse redistribution if it is present on rest or redistribution images and is absent or much less prominent on stress images. Reverse redistribution has been identified in patients with multivessel coronary artery disease and in patients with acute myocardial infarction; it may reflect a differential washout of the perfusion tracer. Reverse redistribution may also reflect a

technical artifact (oversubtraction of background activity on the rest/redistribution images).

The specific coronary artery affected by a stenosis is inferred by the anatomic location of a perfusion defect on the images. Typically, the left anterior descending (LAD) artery supplies the anterior wall, anterior septum, and apex. When it is dominant, the right coronary artery (RCA) usually supplies the inferior wall and the basal inferoseptum. The circumflex artery typically supplies the lateral wall when it is nondominant, and will additionally supply the inferior wall and basal inferoseptum when it is dominant (Fig. 12.8). Individual patient variations in the distribution of the coronary arteries do exist and may affect the patterns of myocardial perfusion identified on the nuclear images. In addition, observed perfusion patterns may be affected by the presence and adequacy of coronary collaterals.

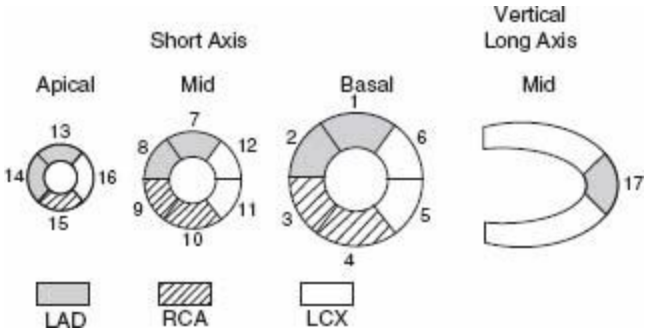


FIGURE 12.8 Coronary artery territories. Assignment of the 17 myocardial segments to the territories of the left anterior descending (LAD), right coronary artery (RCA), and left circumflex coronary artery (LCX). (From Port SC. Imaging guidelines for nuclear cardiology procedures, part II. J Nucl Cardiol 1999;6:G48–84, with permission of the American Society of Nuclear Cardiology.)

Myocardial perfusion imaging is utilized in clinical practice to identify coronary artery disease and to ascertain the physiologic significance of lesions of uncertain severity. It is used to stratify risk in patients following acute myocardial infarction and in patients with chronic coronary artery disease. The assessment of ventricular function from gated SPECT imaging provides incremental prognostic information beyond that provided by the pattern of myocardial perfusion alone. Myocardial perfusion imaging is also useful for risk stratification in patients prior to noncardiac surgical procedures, and in the follow-up of symptomatic patients with prior percutaneous transluminal coronary angio-plasty (PTCA) or coronary artery bypass grafts (CABG). It may also be useful for the differentiation of ischemic from nonischemic cardiomyopathies. In patients with ischemic cardiomyopathy, some have advocated late redistribution or reinjection imaging with thallium-201 to distinguish viable myocardium from scar.

PET METABOLIC IMAGING FOR MYOCARDIAL VIABILITY

In patients with ischemic heart disease, the presence of tissue glucose metabolism in

hypoperfused ventricular segments on PET metabolic imaging with FDG is a reliable marker of clinically important myocardial viability. This is manifest clinically by an improvement in regional contractile function in metabolically active myocardial segments following interventional restoration of blood flow. Ultimately, improvement in left ventricular ejection fraction (LVEF) and functional capacity are related to the anatomic extent and severity of the mismatch between perfusion and glucose metabolism on PET images obtained prior to coronary revascularization. Prior clinical studies indicate that individuals with the most extensive perfusion-metabolism mismatches derive the greatest functional benefit from revascularization and are most likely to exhibit an increase in global LVEF after the procedure.

RADIONUCLIDE VENTRICULOGRAPHY

Two types of nuclear imaging are used to assess ventricular function. In first-pass imaging, high-temporal-resolution sequential (or list mode) images of the central circulation are obtained as the radioactive tracer is administered intravenously. A camera with a high count rate capability and a "tight" bolus of the radioactive tracer are required to achieve a high-quality study. First-pass images are usually acquired from either anterior or left anterior oblique projections. The images derived from a first-pass study depict the movement of the radioactivity through the heart's chambers with a sufficient temporal resolution to permit measurement of ventricular ejection fractions on a beat-to-beat basis. Measurements from 5 to 15 cardiac cycles are usually averaged to calculate the ventricular ejection fraction. The formula used to calculate the LVEF is:

$$\text{LVEF} = \frac{(\text{end diastolic counts} - \text{end systolic counts})}{(\text{end diastolic counts})}$$

End-diastolic and end-systolic counts represent background-corrected counts in the left ventricle at end-diastole and endsystole, respectively.

First-pass studies can be used to assess the ventricular response to exercise stress. A tracer such as technetium-99m DTPA is employed, because the renal clearance of this radiopharmaceutical from the vascular space is rapid enough to permit sequential injections at baseline and during peak exercise stress. Counts in the right and left chambers of the heart are usually separated by a sufficiently long time interval so that it is possible to calculate both right and LVEFs at rest and at peak stress.

Ventricular performance can also be assessed with gated radionuclide ventriculography (multiple gated acquisition [MUGA]). In this technique, a radioactive tracer that remains in the vascular space, such as technetium-99m labeled red blood cells, is administered to the patient. Images over hundreds of cardiac cycles are acquired, using the R wave of the patient's ECG as the timing marker for image acquisition. The nuclear medicine technologist sets a "window," which defines the length of the cardiac cycles that are to be accepted for imaging. Only the cycles with

appropriate R–R intervals are incorporated into the imaging study, with rejection of shorter or longer cycles. Usually the R–R interval is divided into 16 to 24 frames of equal time duration. With each accepted cardiac cycle, counts from that portion of the cardiac cycle (each frame) are added to those of the corresponding frame from preceding cycles. Count data from about 400 to 600 cardiac cycles are allocated to 16 to 24 images representing different sequential portions of the cardiac cycle. Once the acquisition is completed, the images are played in a continuous cine loop to give a time-averaged estimate of ventricular function. The ejection fraction is calculated using background-corrected end-diastolic and end-systolic counts, employing the same formula as that for the first-pass studies. Unlike echocardiography, ejection fraction measurements made with this technique represent time-averaged values, and are not beat-to-beat measurements.

Gated cardiac images may be obtained from differing projections (anterior, right anterior oblique, left anterior oblique, left lateral). In some centers, tomographic (SPECT) gated radionuclide ventriculography is performed. Visual estimates of chamber size and regional wall motion are obtained from the images. If there is a clinical need, additional gated images may be acquired during intervention (stress, inotropic stimulation, sublingual nitroglycerin), to ascertain if there are regional or global differences in ventricular function elicited by the maneuver. A stable R–R interval is needed for gated radionuclide ventriculography. Patients with frequent ectopic beats, irregularly paced rhythms, and/or atrial fibrillation/flutter with an uncontrolled ventricular response rate benefit substantially by medical stabilization of the cardiac rhythm before referral for gated imaging.

Radionuclide ventriculography can be used to assess the severity of regional and global right and left ventricular dysfunction and to determine the effect of medical or interventional treatments on cardiac function. In conjunction with exercise stress, radionuclide ventriculography can be utilized to determine the presence and extent of stress-induced ischemia. Both rest and stress ejection fraction measurements provide useful prognostic information to the clinician. Because ejection fraction measurements obtained with this imaging technique are count based and are not dependent on assumptions about the shape of the ventricle, they are highly reproducible if the imaging study is performed properly.

RADIOACTIVE TRACERS FOR SPECT AND PET

Several different radioactive tracers are available for clinical imaging. Each has unique properties that may make it more or less suitable for a specific imaging task. Factors that influence the choice of tracer for an imaging study include (a) whether SPECT or PET imaging is to be performed, (b) the physiologic property to be visualized (e.g., perfusion, metabolism, neuronal innervation), (c) the patient's body habitus, (d) the

physical characteristics and the biologic behavior of the agent, and (e) the radiation dosimetry of the tracer. A brief overview of the radioactive tracers used for cardiac imaging in the United States is provided, to provide a basic understanding of the agents essential to the daily practice of nuclear cardiology.

SPECT Perfusion Agents

The most commonly used SPECT tracers of myocardial perfusion are technetium-99m sestamibi and technetium-99m tetrofosmin. Thallium-201 chloride is also used for myocardial perfusion imaging, but it imparts a significantly higher radiation dose to the patient than the technetium-99m labeled tracers.

Technetium-99m-Labeled Agents

Technetium-99m labeled sestamibi and tetrofosmin can be prepared locally using kits and technetium-99m eluted from a molybdenum-99 generator. They also are available as prepared unit doses from commercial radiopharmacies. Technetium-99m-labeled tracers result in better image quality than thallium-201 because the higher-energy, monochromatic, 140-keV photons are less subject to scatter and attenuation than the lower energy photons of thallium-201. In addition, the physical half-life of 6 hours permits administration of significantly higher activity doses than thallium-201. The higher count rates achievable with the larger doses yield better image quality and allow image acquisition gated to the patient's ECG. However, the extraction fractions of techne- tium-99m sestamibi and technetium-99m tetrofosmin (0.45 to 0.60) are lower than that of thallium-201. Therefore, net myocardial uptake of these tracers begins to plateau ("roll off") at lower tissue blood flow rates than thallium-201.

The technetium-99m labeled tracers are retained within myocardium predominantly by selective sequestration within the mitochondria of viable cells. Unlike thallium-201, technetium-99m sestamibi and technetium-99m tetrofosmin have minimal redistribution. As a result, these tracers are well suited for imaging of acute chest pain. Activity administered during chest pain can be imaged at a later time point with accurate depiction of the pattern of myocardial perfusion at the time the tracer was administered.

Thallium-201 Chloride

Thallium-201 is a cationic, metallic element with a physical half-life of 73 hours. Most of the photons emitted by thallium-201 are x-rays, with energies ranging from about 69 to 80 keV. The low energy photons are more susceptible to scatter and attenuation than the 140 keV technetium-99m photons. Because the longer half-life of thallium-201 results a higher radiation dose to the patient, thallium-201 doses are smaller than those of the technetium-99m agents. Thallium-201 images can therefore appear less distinct than technetium-99m images, due to lower image counts and lower photon energies.

Thallium-201 is a potassium analog that enters the cardiac myocyte via the Na^+/K^+-ATPase pump in the cell membrane. Although thallium-201 uptake by the myocardium is proportional to blood flow at lower blood flows, the amount of the tracer retained in the tissue at higher flow rates underestimates actual tissue perfusion. This “roll-off" of net tissue tracer accumulation at higher flows is common to all diffusible tracers; however, the “roll-off” begins at higher flow rates for thallium-201 than for technetium-99m-labeled agents, because of its greater first-pass extraction fraction.

Following its intravenous administration, blood levels of thallium-201 peak very rapidly, and there is a concentration gradient for the tracer from the vascular space to inside the cell. This gradient provides the stimulus for thallium-201 to enter the cell. As vascular tracer concentrations eventually decline, thallium-201 leaves the cell to go back into the circulation again. For myocardial regions with lower flows at stress (a perfusion defect), the flux of the tracer into and out of the area is slower than in normal tissue. As a consequence, initial images demonstrate a perfusion defect that appears to “fill in” or redistribute on delayed images. For areas with profound ischemia, a defect may be present on rest images, which then fills in on delayed images or on images obtained following the reinjection of a “booster” dose of thallium-201. The implication of redistribution on delayed or reinjection images is that there is viable tissue in that myocardial region, forming the basis for viability imaging with this tracer.

PET Tracers of Myocardial Perfusion

The perfusion tracers used for cardiac PET imaging include rubidium-82 chloride, nitrogen-13 ammonia, and oxygen-15 water.

Rubidium-82

Rubidium-82 has biologic properties similar to potassium. It is eluted directly off of a portable bedside strontium generator, obviating the need for an on-site cyclotron to perform PET perfusion imaging. The physical half-life of rubidium-82 is 75 seconds. Uptake by the cardiac myocyte is predominantly via membrane-bound Na^+/K^+-ATPase. Clearance from the blood pool is prompt and generally results in high-quality images. Like most other perfusion tracers, net myocardial uptake of rubidium-82 plateaus at higher myocardial blood flows.

Nitrogen-13 Ammonia

Nitrogen-13 ammonia is a perfusion agent that is produced via a cyclotron, and because of its short half-life of 10 minutes, it must be produced on site. In the vascular space, there is a dynamic equilibrium between $^{13}NH_4+$ and $^{13}NH_3$ and hydrogen ion. $^{13}NH_3$ diffuses across the membrane, and is trapped intracellularly via the glutamine synthetase

reaction. Like rubidium-82, net myocardial uptake of nitrogen-13 ammonia also decreases at higher blood flows. It has a high single-pass extraction fraction and long tissue retention, which permits ECG-gated image acquisition.

Oxygen-15 Water

Oxygen-15 is cyclotron produced, and its short half-life of 2.1 minutes requires it to be produced on site. Unlike rubidium-82 and nitrogen-13 ammonia, it is freely diffusible and net myocardial uptake of the tracer increases nearly linearly with increasing blood flows. Moreover, tissue retention of the tracer is largely independent of tissue metabolism. It is not rapidly cleared from the systemic circulation and image quality is lower because of relatively high background activity. As a result of these factors, oxygen-15 water is used less frequently for clinical imaging than either rubidium-82 or nitrogen-13 ammonia.

PET Tracers of Myocardial Metabolism

Positron-emitting tracers of myocardial metabolism play an important role in distinguishing between viable and nonviable myocardium in patients with impaired left ventricular function. The most commonly used PET agent for this purpose is FDG. (Other, less commonly used, PET agents used to assess other facets of myocardial metabolism include ^{11}C-palmitate and ^{11}C-acetate). FDG is a glucose analog that enters the cardiac myocyte by facilitated transport. Once within the cell, it competes with glucose for the enzyme hexokinase. FDG is phosphorylated to FDG-6-phosphate, which is then trapped within the cardiac myocytes and not further metabolized. FDG imaging is utilized with perfusion imaging to identify myocardium that is normal (with normal uptake of both the FDG and the perfusion tracer), hibernating (defect on the perfusion images, with preserved uptake of FDG), or scarred (defect on the perfusion images with matching defect on the FDG metabolic images).

SUMMARY

An understanding of the fundamentals of the instrumentation and radioactive tracers employed in nuclear cardiology forms the basis for the appropriate utilization of these advanced imaging techniques in clinical cardiology (see Chapter 25). Although SPECT myocardial perfusion imaging is still primarily performed using conventional gamma cameras, newer instruments with solid-state detectors dedicated to cardiac imaging are assuming a larger role in clinical practice. These advanced cameras, along with the use of iterative reconstruction techniques, permit myocardial perfusion imaging to be performed more rapidly using lower doses of the radioactive tracers. PET/CT perfusion imaging with rubidium-82 chloride or nitrogen-13 ammonia is more accurate for the

detection of coronary artery disease than SPECT imaging, imparts a lower patient radiation dose than conventional SPECT imaging, and can yield measurements of rest and hyperemic blood flows as well as flow reserves. If desired, CT angiography of the coronary arteries and/or coronary calcium scoring can be performed on the PET/CT camera in the same setting, providing both anatomic and physiologic information about the state of the heart.

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QUESTIONS AND ANSWERS

Questions

1. Which of the following statements is not true?
   a. Collimator selection for a gamma camera reflects a trade-off between spatial resolution and efficiency.
   b. Photons that pass through the collimator and strike the imaging crystal produce visible light that is then converted to electrical current and amplified by photomultiplier tubes.
   c. By setting a more narrow energy window around the isotope's photopeak, one can increase the sensitivity of a camera to include more scattered photons.
   d. Planar images are typically obtained from several fixed views, whereas SPECT images are obtained from multiple projections that are then reconstructed.

2. Assuming comparable biologic behavior, which of the following combinations of gamma-emitting isotopes and administered activity doses would result in the lowest absorbed dose of radiation to a patient?
   a. Short half-life, high dose
   b. Long half-life, high dose
   c. Short half-life, low dose
   d. Long half-life, low dose

3. Assuming a "right dominant" coronary artery distribution, match each of the ventricular segments (from the standard 17-segment model) with its most likely corresponding coronary arterial distribution.
   (1) Basal anterior
   (2) Basal anteroseptal
   (3) Basal inferoseptal
   (4) Basal inferior
   (5) Basal inferolateral
   (6) Basal anterolateral
   (7) Mid anterior
   (8) Mid anteroseptal
   (9) Mid inferoseptal
   (10) Mid inferior
   (11) Mid inferolateral
   (12) Mid anterolateral
   (13) Apical anterior
   (14) Apical septal
   (15) Apical inferior
   (16) Apical lateral
   (17) Apex
   a. Left anterior descending (LAD)
   b. Right coronary artery (RCA)
   c. Circumflex

4. Given the following simplified count data obtained during radionuclide ventriculography, what is the ejection fraction?
   End-diastolic counts = 1,000
   End-systolic counts = 650
   a. 54%
   b. 65%
   c. 35%
   d. 30%

5. Match the following combinations of stress and rest imaging findings with the appropriate

interpretation:

	Stress	Rest	Interpretation
a.	Defect	Normal	(i) Scar (or hibernation)
b.	Defect	Defect	(ii) Normal
c.	Normal	Defect	(iii) Ischemia
d.	Normal	Normal	(iv) Reverse redistribution

6. For which of the following myocardial perfusion imaging protocols would the radioactive tracer(s) utilized provide the lowest estimated effective radiation dose to the patient?
   a. Stress and 4-hour redistribution SPECT imaging, using 3.0 mCi of thallium-201 for the stress dose
   b. Dual isotope rest and stress SPECT imaging, using 2.5 mCi of thallium-201 for the rest dose and 25 mCi of technetium-99m tetrofosmin for the stress dose
   c. Stress only SPECT perfusion imaging with 25 mCi of technetium-99m sestamibi
   d. Rest and regadenoson stress rubidium-82 PET imaging with rest and stress doses of 30 mCi each

7. In which of the following patients would gated radionuclide ventriculography be expected to underestimate the left ventricular ejection?
   a. A 73-year-old woman with an inferobasal aneurysm
   b. A 43-year-old man with a nonrestrictive ventricular septal defect
   c. A 64-year-old woman with new onset atrial fibrillation and a poorly controlled ventricular response rate
   d. A 59-year-old man who is pacemaker dependent

8. Which of the following statements regarding cardiac positron emission tomography (PET) is true?
   a. Radioactive tracer doses used for a PET scanner operating in the three-dimensional (3-D) mode usually are less than for a comparable device operating in the two-dimensional (2-D) mode.
   b. Myocardial perfusion imaging must be performed using pharmacologic stress.
   c. An on-site cyclotron is necessary for myocardial perfusion imaging.
   d. ^{18}F-2-fluoro-2-deoxyglucose (FDG) imaging is used to assess local myocardial uptake of fatty acids in hypoperfused myocardium, distinguishing viable but hypoperfused tissue (preserved uptake) from myocardial scar (matching perfusion and metabolic defects).

9. Which of the following tracers of myocardial perfusion has the highest net tissue uptake at a myocardial blood flow of 4.0 mL/min/g tissue?
   a. Oxygen-15 water
   b. Thallium-201
   c. Technetium-99m sestamibi
   d. Rubidium-82

10. Which of the following isotopes liberates the lowest energy photons when it decays?
   a. Fluorine-18
   b. Rubidium-82
   c. Technetium-99m
   d. Thallium-201

Answers

1. **Answer C:** The purpose for setting a narrow energy window around the photopeak of an isotope is to exclude lower-energy photons, which are more likely to be photons that have been scattered and thus lost some of their energy. In doing so, some of the true photons are also excluded, thus decreasing the sensitivity.

2. **Answer C:** Assuming comparable biologic behavior for the gamma-emitting isotopes, the lower the administered dose, the lower the exposure, thus excluding choices a and b. For the same dose, the isotope with the shorter half-life will result in a lower absorbed dose of radiation because of the shorter duration of exposure.

3. **Answers:**
   a. (1), (2), (7), (8), (13), (14), (17)
   b. (3), (4), (9), (10), (15)
   c. (5), (6), (11), (12), (16)

4. **Answer C:** 35%, because LVEF = (end-diastolic counts - end-systolic counts)/(end-diastolic counts) = (1,000 - 650)/(1,000) = (350)/(1,000) = 0.35, or 35%.

5. **Answers:** a. (iii); b. (i); c. (iv); d. (ii)

6. **Answer D:** Because of the 73 hour physical half-life of thallium-201, the effective doses from protocols a and b are relatively high (22 and 23.5 milliSieverts, respectively). The estimated effective radiation dose from the stress only SPECT protocol with 25 mCi of technetium- 99m sestamibi is 7.3 milliSieverts, while that for the rubidium-82 PET study is 2.8 milliSieverts.

7. **Answer C:** The woman with poorly controlled atrial fibrillation will have widely varying R–R intervals over the period of image acquisition, adversely impacting allocation of counts to the appropriate frames (time bins). This usually results in an underestimation of the left ventricular ejection fraction (LVEF). Each of the other patients should have stable R–R intervals and the cardiac rhythm should therefore pose no problems in ECG gating of the study.

8. **Answer A:** PET scanners operating in a 3-D mode have a greater sensitivity than when operated in a 2-D mode. As a result, a smaller tracer dose is usually used for PET imaging in the 3-D mode as compared to the 2-D mode. While PET myocardial perfusion imaging is usually performed using pharmacologic stress, centers using nitrogen-13 ammonia for imaging can use treadmill exercise because this tracer's half-life is long enough to permit imaging following recovery from exercise. An on-site cyclotron is not required for PET myocardial perfusion imaging if generator-produced rubidium-82 is selected as the perfusion tracer. FDG imaging depicts regional myocardial glucose uptake, not fatty acid uptake.

9. **Answer A:** As myocardial blood flow increases, the net myocardial uptake of oxygen-15 water increases linearly. At a hyperemic blood flow of 4.0 mL/min/g, net myocardial uptake should be about four times that at 1.0 mL/min/g. For each of the other tracers listed, the incremental increase in tissue tracer uptake gets progressively smaller as blood flows rise much above 2.0 mL/min/g, that is, tissue uptake plateaus at hyperemic blood flows. For these tracers, net myocardial uptake at a blood flow of 4.0 mL/min/g will be appreciably less than four times that at 1.0 mL/min/g.

10. **Answer D:** When thallium-201 decays, most of the photons emitted are low energy x-rays (68 to 80 keV). Technetium-99m emits a 140 keV gamma ray when it decays. Fluorine-18 and rubidium-82 decay by positron emission, resulting in the production of 511 keV annihilation photons that are used for imaging.

CHAPTER

Nuclear Stress Testing

Richard C. Brunken and Santosh Oommen

Nuclear cardiac imaging has become an integral component of the clinical practice of cardiology over the last several decades. Myocardial perfusion imaging (MPI) facilitates the detection of coronary artery disease (CAD), permits assessment of the physiologic effects of equivocal coronary artery stenoses, and assists in the identification of patients who are likely to benefit from coronary revascularization. In individuals with known or suspected CAD, MPI provides incremental prognostic information beyond that afforded by stress electrocardiography alone and can be used for individual risk stratification for future cardiac events. The fundamentals of nuclear cardiac imaging and image interpretation are discussed in Chapter 10. This chapter focuses primarily on the clinical utility of MPI for patients with suspected or established CAD and how the information derived from these nuclear imaging studies can be used to assist in the care of the patient. The contribution of nuclear imaging to the management of patients with congestive heart failure (CHF) is also briefly discussed.

MYOCARDIAL PERFUSION IMAGING

Principles of Cardiac Nuclear Stress Testing

The usual goal of MPI is to compare the pattern of tissue perfusion in the resting state to that under stress conditions, in order to detect flow-limiting coronary artery stenoses. To understand how MPI is used for this purpose, it is helpful to recall certain aspects of cardiovascular physiology. In the basal resting state, oxygen extraction from myocardial capillary blood approaches 70% and is near maximal. Thus, there is little capacity to augment tissue oxygen delivery by increasing the myocardial extraction of oxygen from the blood when the ventricular workload increases. As a result, increases in the left ventricular workload must be accompanied by nearly proportional increases in myocardial perfusion, in order to meet the oxygen demands of the tissue. Healthy coronary vessels have flow reserves between three and six, meaning that they can

increase blood flows about three to six times above rest values during periods of stress.[1]

In most patients with CAD, autoregulatory changes in arteriolar vascular resistance are capable of maintaining normal tissue perfusion in the resting state. The left ventricular workload is low in the resting state, and the coronary circulation is usually capable of meeting basal myocardial oxygen demands. Thus, images of rest myocardial perfusion are typically normal in patients with CAD who have not had a prior infarction or an acute ischemic event. To detect an obstructive coronary stenosis, it is frequently necessary to use maneuvers that increase tissue perfusion, in order to distinguish between vessels with and without an impaired coronary flow reserve.

Detection of Coronary Stenoses

In an artery with an atherosclerotic lesion, coronary flow reserve decreases nonlinearly as the luminal narrowing increases. The ability of the coronary vessel to increase tissue perfusion during periods of stress becomes increasingly and progressively limited as the luminal stenosis becomes more pronounced.[1] During stress, perfusion in myocardium supplied by a coronary vessel with a limited flow reserve will be less than that in regions subtended by healthy arteries. Measurements of stress perfusion in affected areas (in milliliters of blood flow per minute per gram of tissue) typically will exceed resting values but remain less than the values in normal myocardium. Stenoses of 50% to 60% luminal cross- sectional area or greater are usually of sufficient magnitude to impair coronary flow reserve. However, other factors, such as the presence or absence of nonlaminar flow in the vessel, the presence or absence of collateral vessels, the presence of several stenoses in series, stenosis length, eccentricity of the lumen, absolute luminal cross-sectional area, heart rate, and the pressure gradient across the stenosis, may influence the physiologic effects of a coronary stenosis on tissue perfusion.

Images depicting myocardial perfusion during stress conditions show a reduction in the relative tracer concentration, or a stress perfusion defect, in the vascular territories supplied by the arteries with flow-limiting stenoses. The hallmark of stress-induced ischemia is a reversible perfusion defect, one that is present on stress perfusion images but absent on rest perfusion images. In studies in which measurements of coronary flow reserve made with intracoronary Doppler catheters have been compared to single photon emission computed tomography (SPECT) myocardial perfusion images, a strong correlation has been noted between stenosis flow reserves <2.0 and the presence of a reversible perfusion defect. Similarly, noninvasive measurements of myocardial perfusion reserve obtained with positron emission tomography (PET) in patients with CAD suggest that reversible SPECT defects are usually associated with perfusion reserves of 1.8 or less. In general, the more severe the luminal stenosis, the greater is the likelihood that it will be associated with a stress perfusion defect.

The anatomic extent of the stress perfusion defect and the magnitude of the reduction in the relative tracer activity within the defect provide objective information about the effects of a coronary stenosis on tissue perfusion during conditions of high oxygen demand. Commercially available computer programs can be used to compare the count data from a specific patient's images to those of a normal sexmatched population, to assist in the identification and quantification of myocardial perfusion defects (see Chapter 11). The relative tracer activity concentration within the stress defect provides an indication of the severity of the ischemia. Defect extent, or the amount of the left ventricle that is affected by the perfusion abnormality, can be expressed as the number of myocardial segments with an abnormal tracer concentration, or as the proportion (percent) of all myocardial voxels that have an abnormal tracer concentration. A proximal stenosis in a major epicardial artery will generally produce a stress defect that is larger and more readily detected than one resulting from a stenosis in a distal vessel or a smaller branch artery. The anatomic location of the perfusion defect can be used to infer which of the three major coronary vessels is (are) diseased (see Chapter 11). It may also be possible to deduce whether the stenosis is proximal, mid, or distal, based on the location and anatomic extent of the defect on the stress perfusion images.

Assessment of Relative versus Absolute Myocardial Perfusion

The SPECT or PET myocardial perfusion images used in routine clinical practice for CAD detection depict relative tissue perfusion. It is assumed that at least one area of the visualized myocardium is supplied by a vessel with a normal or near-normal coronary flow reserve. However, in some patients with multivessel CAD, there may be "balanced ischemia," a situation in which the coronary flow reserve of each of the three major coronary arteries is equally or nearly equally impaired. In balanced ischemia, the pattern of perfusion on the stress images appears relatively homogenous. A regional perfusion defect is not identified because me stress defect involves essentially all of the visualized left ventricular myocardium. This has stimulated additional clinical interest in the use of measurements of absolute myocardial blood perfusion (in milliliters of blood flow per minute per gram of tissue) and perfusion reserves from dynamic PET perfusion images. Computer programs used to calculate PET measurements of absolute myocardial perfusion and perfusion reserve are now "user friendly" and are commercially available for routine clinical use. If a patient's perfusion reserve measurements are abnormally low, this may result either from balanced ischemia from multivessel stenosis or from global microvascular dysfunction. The prevalence of balanced ischemia in CAD patients due to multivessel stenosis is not well defined and is likely to depend on each nuclear laboratory's specific referral pattern. In large cardiac referral centers, the prevalence of balanced ischemia is probably <5% of patients referred for nuclear stress testing, and it may be smaller in an office-based practice. Other observations from the stress test itself and either SPECT or PET

perfusion imaging can alert the nuclear cardiologist to the possibility of balanced ischemia. These include the onset of anginal symptoms with stress, a significant drop in systolic blood pressure with exercise, electrocardiographic ST-segment changes in response to stress, and acute ventricular dilatation and/or new systolic dysfunction on the gated stress perfusion images. When incorporating the results of a SPECT or PET perfusion imaging study into the management of the patient, the possibility of balanced ischemia should be considered—especially if there are other clinical observations that suggest this possibility—and further diagnostic testing should be pursued accordingly.

Resting Perfusion Defects

Perfusion defects on images acquired in the resting state may arise in several different situations. When a coronary stenosis is very severe (>90% to 95% area stenosis) or there is an unstable lesion with intermittent dynamic obstruction of the lumen, a defect can sometimes be identified on resting perfusion images. In this situation, the diseased vessel may be incapable of maintaining perfusion commensurate with the tissue's oxygen demands. A second set of perfusion images acquired at a later time may show redistribution, or "fill in" of the resting perfusion defect, as the tissue tracer concentration in this area equilibrates with that in adjacent normal myocardium. Sometimes, a supplemental dose of the perfusion tracer may be given prior to obtaining the late set of images, to assist in the "fill in" of the defect. The clinical implication of the filling in of a resting perfusion defect on redistribution or reinjection perfusion images is that the tissue is viable, and supplied by a vessel with a severe coronary stenosis.

A resting perfusion defect that persists on redistribution or reinjection images sometimes indicates a myocardial scar. In a scar, there is replacement of cardiac myocytes by relatively avascular fibrous tissue. Residual tissue perfusion in the segment with the scar is lower than in normal myocardium, resulting in a reduction in the relative tracer concentration on both the resting and redistribution/reinjection perfusion images. Because of the limited spatial resolution of current gamma cameras and PET tomographs, reductions in perfusion due to a nontransmural scar will be averaged over the minimum resolvable volume of the instrument (the partial volume effect). Thus, it is not possible to attribute an observed reduction in myocardial tracer activity to a scar specifically in the subendocardial, midmyocardial, or epicardial portion of the ventricular wall, as counts will be averaged over the entire thickness of the tissue. In studies of subjects with clinical myocardial infarction (MI), the extent and severity of persistent resting perfusion defects have generally paralleled the loss of viable myocytes, as measured by the size of the leak of cardiac enzymes or by the amount of tissue fibrosis on ventricular specimens.[2]

If a resting perfusion defect persists on redistribution or reinjection images, an alternative diagnostic possibility is myocardial hibernation, a state in which there is a

sustained downregulation of tissue perfusion, metabolism, and function. Although the mechanism by which human myocardium enters into a state of "hibernation" is not well defined, accumulating evidence suggests that multiple repetitive episodes of ischemia (repetitive stunning) may eventually result in myocardial hibernation.[3] Histopathologic studies of hibernating myocardium have identified structural and ultrastructural alterations in the tissue. These include a loss of myofibrillar protein, myocyte hypertrophy, accumulation of glycogen within the cytosol of the cardiac myocyte, and alterations in myocyte mitochondrial size and appearance. Modest increases in tissue collagen content have also been reported. As the name suggests, the clinical implication of hibernating myocardium is that the dysfunctional tissue is viable, and that it can be "awakened" by restoration of blood flow and benefit functionally by coronary revascularization.

In both hibernating tissue and myocardial scar, there is a persistent reduction in tissue perfusion. Because there is little or no capacity to increase tissue perfusion with stress in either situation, reductions in relative tracer concentration on resting perfusion images will also be present on stress perfusion images, and therefore appear as a fixed perfusion defect. Myocardial scar and hibernating tissue both exhibit systolic dysfunction, and may be indistinguishable from each other on conventional gated myocardial perfusion scintigraphy. Additional imaging studies are frequently needed in order to distinguish between hibernating (viable) tissue and myocardial scar. Low-dose dobutamine echocardiography, contrast magnetic resonance imaging, and glucose metabolic imaging with PET (below) are some of the methods that have been used to distinguish myocardial hibernation from scar.[4]

Stress Options for Myocardial Perfusion Imaging

Exercise is generally the preferred stress modality because it permits the simultaneous assessment of other parameters oi clinical interest including patient symptoms, functional capacity, vital signs, and the rate–pressure product as an indirect index of myocardial oxygen consumption. Graded exercise is most commonly performed on a treadmill, using one of several standard stress protocols (see Chapter 23). In order to optimize the examination for the detection of coronary stenoses, it is important to increase the ventricular workload high enough to elicit a significant increase in myocardial perfusion. In clinical practice, the usual goal is for the patient to achieve at least 85% of the maximum predicted heart rate (MPHR) for age. The radioactive perfusion tracer is administered intravenously about 1 to 2 minutes prior to the end of stress, to allow a long enough period of time for myocardial uptake of the imaging agent prior to the termination of exercise. SPECT is the most common imaging modality employed if a patient is undergoing exercise stress MPI, as the technetium and thallium tracers have a half-life long enough to be compatible with exercise testing protocols, as opposed to the 75-second half-life of rubidium-82, the tracer most commonly used in

PET cardiac imaging. However, if the testing facility has an on-site cyclotron, nitrogen-13 labeled ammonia (half-life = 10 minutes) can be used as a PET perfusion tracer with exercise stress MPI.

In some patients, an adequate level of exercise cannot be achieved because of orthopedic limitations, peripheral vascular disease, complicating medical illnesses, or the use of medications such as beta-blockers. Stress perfusion imaging is still feasible if a pharmacologic agent can be used to increase myocardial blood flow. About 40% of the MPI tests in the United States are performed using pharmacologic stress.[5] Two most commonly used pharmacologic stress agents, adenosine and dipyridamole, are potent coronary vasodilators. Another coronary vasodilator agent more recently approved for clinical use in radionuclide MPI is regadenoson, a selective A_{2A} receptor agonist.[6] These agents increase myocardial perfusion by directly dilating the coronary vasculature, thereby "uncoupling" myocardial perfusion from ventricular work. The fourth agent used for MPI is a synthetic catecholamine, dobutamine, which increases tissue perfusion primarily by increasing tissue oxygen demand through its positive inotropic and chronotropic effects. The pharmacologic agents used for stress perfusion imaging are summarized in Table 13.1.

TABLE
13.1 Agents for Pharmacologic Stress Testing

Drug	Mechanism	Dose	Risks	Comments
Adenosine	Coronary vasodilatation (binds to A_{2A} receptor, which results in arteriolar dilatation)	140 μg/kg/min by continuous IV infusion over 6 min	Bronchospasm, AV block (due to effects on A_1 and A_{2B}/A_3 receptors), ischemia/MI	Caffeine blocks. Short half-life of 2–10 s. Aminophylline reverses. Perfusion tracer injected midway during adenosine infusion.
Dipyridamole	Coronary vasodilatation (blocks cellular uptake of adenosine, increasing binding of adenosine to A_{2A} receptors)	0.142 mg/kg/min, by continuous IV infusion over 4 min	Bronchospasm, AV block (due to effects on A_1 and A_{2B}/A_3 receptors), ischemia/MI	Caffeine blocks. Reversed by aminophylline. Tracer injected 4 min after end of dipyridamole infusion.
Regadenoson	Coronary vasodilatation (via selective agonism of A_{2A} receptor)	0.4 mg in a 5 mL solution infused over 10 s, followed by saline flush	Bronchospasm, AV block (lower incidence than adenosine or dipyridamole), ischemia/MI	Caffeine blocks. Reversed by aminophylline. Longer half-life than adenosine (2 min for initial intravenous phase, 30 min for intermediate phase). Tracer injected 10–20 s after regadenoson and saline flush.
Dobutamine	Increases myocardial perfusion by increasing tissue oxygen demand	Incremental steps, beginning at 5–10 up to a maximum of 40 μg/kg/min. Can add isometric hand-rip or up to 1 mg of atropine if target heart rate not achieved	Ischemia/MI, arrhythmias, hypotension, hypertension	Useful for patients with asthma or other bronchospastic pulmonary disease who are unable to exercise. Unlike echocardiography, online monitoring of ventricular function is not possible during the period of stress. Beta-blockers are useful for treating side effects such as arrhythmias.

Adenosine is a small molecule that is produced by vascular smooth muscle and endothelial cells. Adenosine can also be generated by the extracellular dephosphorylation of adenosine triphosphate (ATP) and adenosine diphosphate (ADP). Free adenosine within the vascular space can reenter endothelial, vascular smooth muscle, or red blood cells by facilitated transport, or it can bind to specific receptors on the cell membrane. Adenosine induces coronary vasodilatation when it binds to A_{2A} receptors on the surface of the cell. (Adenosine binds to the A_1, A_{2B}, and A_3 receptors as well, explaining its accompanying effects of AV nodal blockade and bronchoconstriction.) Binding to the A_{2A} receptor causes an increase in intracellular cyclic AMP (cAMP) concentration via a coupled G-protein system that in turn results in coronary artery dilatation. Adenosine has a very short half-life (2 to 10 seconds), because it is rapidly cleared from the vascular space by uptake into endothelial and red blood cells. In normal coronary arteries, adenosine leads to increases in blood flows that are generally three to six times those in the resting state. Adenosine is usually administered as a continuous intravenous infusion at a rate of 140 μg/kg/min over a period of 6 minutes. The radioactive perfusion radiotracer is injected at 3 minutes, midway through the adenosine infusion. Some investigators have indicated that a 4-minute period of infusion of adenosine (with tracer injection at 2 minutes) is as efficacious for the detection of CAD as the 6-minute infusion protocol.

Dipyridamole blocks the cellular reuptake of adenosine. This causes more of the endogenous adenosine within the vascular space to bind to the A_{2A} receptors on the cell surface. Greater receptor binding by adenosine, in turn, promotes coronary vasodilatation. Dipyridamole has a significantly longer half-life than adenosine, inducing coronary vasodilatation that may persist for as long as 30 minutes following its administration. Dipyridamole is given by continuous intravenous infusion over 4 minutes, at a rate of 0.142 mg/kg/min. The radioactive perfusion tracer is injected about 4 minutes after the end of the dipyridamole infusion, to allow achievement of maximal myocardial hyperemia.

Regadenoson is a selective A_{2A} receptor agonist that was approved by the FDA for clinical use in MPI in 2008. Its coronary hyperemic effects have an onset within 30 seconds and usually last for 2 to 5 minutes. Regadenoson is administered intravenously as a single bolus dose of 0.4 mg, followed by a 5 mL saline flush. Two randomized double-blind multicenter trials—ADVANCE-MPI 1 and 2—demonstrated the safety of this agent in 1,871 patients, as well as an efficacy similar to adenosine for the detection of reversible perfusion defects on SPECT imaging.[6,7] Regadenoson has not been compared in a clinical trial with adenosine or dipyridamole as a stress agent for cardiac PET imaging.

The side effects of adenosine and dipyridamole are similar and include flushing, chest pain, dyspnea, headache, nausea, hypotension, bronchospasm, and AV block. Of

note, regadenoson appears to trigger fewer adverse events and has a favorable side-effect profile as compared to adenosine—a function of its selective agonism of the A_{2A} receptor. Side effects, especially AV block, are more commonly seen with adenosine but tend to be short-lived with this agent—dissipating within seconds of stopping the infusion. With regadenoson and dipyridamole, any side effects experienced tend to persist longer, and treatment with aminophylline (50 to 100 mg IV), a nonselective competitive antagonist, may be required. Clinical studies suggest that the side effects of all three vasodilator agents may be attenuated if the patient is capable of performing exercise in conjunction with the pharmacologic stress. Image quality may also benefit from the performance of adjunctive exercise. Contraindications to the administration of the vasodilator agents include asthma or a history of bronchospastic pulmonary disease, hypotension, unstable angina or acute MI within 2 days, high-degree AV block without a pacemaker, uncontrolled arrhythmias, and critical aortic or mitral valve stenosis. Unlike stress with exercise or IV dobutamine (below), the adequacy of the myocardial hyperemia induced by IV adenosine or dipyridamole cannot be inferred from the changes in heart rate or systemic blood pressure induced by the administration of these agents.

For adenosine, regadenoson, and dipyridamole stress, it is important that the patient refrain from the use of drugs such as aminophylline and theophylline prior to the test, as these medications are competitive antagonists of the adenosine membrane receptor.[8] These medications effectively blunt the hyperemia induced by these agents and may cause a falsely negative imaging study. Caffeine and caffeine-like substances such as theobromine, whose effects are similar to those of aminophylline, should also be avoided prior to pharmacologic stress testing with vasodilators. Current joint guidelines issued by the American Society of Nuclear Cardiology (ASNC) recommend that patients refrain from the use of caffeine for at least 12 hours prior to vasodilator stress testing.[9]

Dobutamine is a short-lived (half-life of about 2 minutes) β_1-adrenergic receptor agonist that is widely used for stress echocardiography. Unlike stress echocardiography, when dobutamine is used as the stress for nuclear perfusion imaging it is not possible to monitor ventricular function “online." Dobutamine stress should therefore be used with caution for nuclear imaging in patients with reduced left ventricular ejection fraction (LVEF), as new regional contractile abnormalities incited by ischemia could precipitate further deterioration in ventricular function. Dobutamine can be used in patients with bronchospastic pulmonary disease, in whom there is a relative contraindication to the use of the vasodilator stress agents described above. Dobutamine increases cardiac contractility and heart rate and is contraindicated in patients with recent MI, uncontrolled hypertension, or significant cardiac arrhythmias.

Dobutamine is administered as a continuous intravenous infusion, typically starting

at 5 to 10 µg/kg/min for 3 minutes and then increasing by 10 µg/kg/min every 3 minutes to a maximum dose of 40 µg/kg/min. If the patient does not achieve 85% of his or her age-related maximal predicted heart rate, he or she can be instructed to perform handgrip exercise and/or be given up to 1 mg of atropine IV to increase the heart rate. The perfusion tracer is administered intravenously 1 to 2 minutes before the end of the dobutamine infusion, to allow enough time for myocardial uptake of the imaging agent. Side effects of dobutamine include palpitations, chest pain, hypertension, hypotension, atrial fibrillation, and ventricular tachycardia. The side effects usually respond to stopping the infusion, or to the intravenous administration of a beta-blocker.

Indications for Myocardial Perfusion Imaging

The appropriate indications for MPI, as listed by the American College of Cardiology (ACC)/American Heart Association (AHA)/ASNC guidelines,[10] are summarized in Table 13.2.

TABLE
13.2 Appropriate Indications for MPI

Patient Group	Condition	Imaging Technique
ER patient with chest pain	For risk stratification in pt with *possible* ACS. Initial serum markers, enzymes, and ECG are nondiagnostic.	Rest perfusion imaging (with ECG gating, if possible).
	For CAD diagnosis in pt with *possible* ACS and nondiagnostic ECG. Negative serum markers and enzymes or normal rest perfusion scan.	Same-day rest/stress (ECG gated) MPI.
Acute MI/unstable angina	Assessment of LV function.	Rest MPI with ECG gating (rest gated radionuclide angiography is alternative option).
ST-elevation myocardial infarction (STEMI)	Measurement of infarct size and residual viable myocardium, in an unrevascularized asymptomatic stable patient after completion of the infarct.	Rest MPI with ECG gating, or with stress perfusion imaging with ECG gating.
	Thrombolysis without coronary angiogram, to identify inducible ischemia and myocardium at risk	Rest and stress MPI, with ECG gating whenever possible.
Non–ST-elevation myocardial infarction (NSTEMI)/unstable angina	In an unrevascularized stable asymptomatic patient after completion of the infarct, to determine the extent and severity of inducible ischemia, either in the distribution of the "culprit" vessel or in remote myocardium.	Rest and stress MPI, with ECG gating whenever possible.
	In individuals whose angina is stabilized on medical therapy, or in whom the diagnosis is uncertain, to identify the extent and severity of inducible ischemia.	Rest and stress MPI, with ECG gating whenever possible.
	To assess the functional significance of a coronary stenosis on angiography.	Rest and stress MPI.
CAD diagnosis in an individual with an intermediate probability of disease, and/or risk stratification in someone with an intermediate or high likelihood of disease *and* able to exercise to 85% MPHR or more	Those with preexcitation, LVH, on digoxin, or more than 1-mm ST-segment depression on resting ECG.	Rest and exercise stress MPI, with ECG gating whenever possible.
	Individuals with LBBB or ventricularly paced rhythm.	Rest and vasodilator stress MPI, with ECG gating whenever possible.
	Patients with an intermediate- or high-risk Duke treadmill score.	Rest and exercise stress MPI, with ECG gating whenever possible.
	In an individual with prior abnormal myocardial perfusion scan and new or worsening symptoms.	Repeat rest and exercise stress MPI, with ECG gating whenever possible.
CAD diagnosis in an individual with an intermediate probability of disease, and/or risk stratification in someone with an intermediate or high likelihood of disease *and* not able to exercise	To identify the extent, severity, and location of inducible ischemia.	Rest and vasodilator stress MPI, with ECG gating whenever possible. Rest and vasodilator stress MPI, with ECG gating whenever possible.
Detection of CAD in patients with ventricular tachycardia	Patients without known CAD or ischemic equivalent.	Rest and stress MPI, preferably exercise stress, with ECG gating whenever possible.

Detection of CAD in patients with syncope	Patients with intermediate- and high-risk for CHD, and no ischemic equivalent.	
Prior to intermediate- and high-risk noncardiac surgery	Initial diagnosis of CAD in those with at least one clinical risk factor for adverse perioperative CV events, and poor (<4 METs) or unknown functional capacity.	In those able to exercise, rest and exercise stress MPI, with ECG gating whenever possible. *or* In those unable to exercise, rest and vasodilator stress MPI, with ECG gating whenever possible.
	In individuals with established or suspected CAD and poor (<4 METs) or unknown functional capacity.	In those able to exercise, rest and exercise stress MPI, with ECG gating whenever possible. *or* In those unable to exercise, rest and vasodilator stress MPI, with ECG gating whenever possible.
	Diagnosis of CAD in patients with LBBB or ventricular-paced rhythm and at least one risk factor for adverse perioperative CV events.	Rest and vasodilator stress MPI, with ECG gating whenever possible.
	In suspected or established CAD, prognostic assessment of those with LBBB or ventricularly-paced rhythm on rest ECG.	Rest and vasodilator stress MPI, with ECG gating whenever possible.
Equivocal SPECT myocardial perfusion scan	Clinically indicated SPECT perfusion study is equivocal for CAD diagnosis or risk stratification purposes.	Rest and vasodilator stress PET myocardial perfusion study.
CAD patient with systolic dysfunction and CHF, with little or no angina	Prediction of improvement in regional/global LV function following revascularization.	Stress/redistribution/reinjection thallium-201 SPECT perfusion imaging *or* Rest/redistribution SPECT perfusion imaging *or* Myocardial perfusion plus FDG PET metabolic imaging *or* Resting sestamibi SPECT perfusion imaging.
	Prediction of improvement in natural history following revascularization.	Stress/redistribution/reinjection thallium-201 SPECT perfusion imaging *or* Rest/redistribution thallium-201 SPECT perfusion imaging *or* Myocardial perfusion plus FDG PET metabolic imaging.

Acute Chest Pain Syndromes

Prompt identification of individuals with acute coronary syndromes (ACSs) provides

the best opportunity to salvage viable myocardial tissue and save lives. In some who present to the Emergency Department with chest pain, elevated cardiac enzyme levels and an abnormal electrocardiogram (ECG) provide definitive evidence of an acute MI, and there is no need for imaging to establish the diagnosis. On the other hand, in those with chest pain that is clearly noncardiac in origin, there is little utility in pursuing an aggressive (and expensive) diagnostic imaging strategy to exclude coronary disease. There are, however, about 6 million patients who present to Emergency Departments each year in the United States with chest pain of uncertain etiology, who have normal enzyme levels and a nondiagnostic ECG. It is these patients, in whom an ACS remains a diagnostic possibility, that MPI has the highest clinical benefit.[11] Although the relative proportion of individuals with an ACS in this patient group is not large, the probability of an adverse outcome in those with a true coronary event is high if the diagnosis is missed. Reported mortality in Emergency Department patients with an ACS who are mistakenly sent home is as high as 5% to 6%. On the other hand, for those without an ACS who are admitted to the hospital for observation, there are substantial costs associated with the unnecessary utilization of health care services.

Rest SPECT MPI is useful for the evaluation of patients with suspected ACSs. Rest MPI can detect a regional perfusion abnormality in the absence of acute necrosis, especially if the radioactive tracer is injected during or shortly after an episode of chest pain. Reported negative predictive values of a normal rest myocardial perfusion scan in patients with suspected ACSs are as high as 99% to 100%, and up to 97% of patients who have a negative perfusion study in this setting will remain free of cardiac events over a short-term follow-up. Two randomized, prospective studies have shown that access to acute MPI has a beneficial effect on length of stay and hospital costs. It is the position of the ASNC that the evidence supports the use of acute rest MPI for the triage of selected Emergency Department patients with suspected ACSs.[11] However, rest perfusion imaging is less helpful in those with a history of prior MI because it is not possible to distinguish a resting perfusion defect due to an acute ischemic event from that of a preexisting scar.

Both thallium-201 and technetium-99m–labeled tracers have been used for rest myocardial imaging in Emergency Department patients. Thallium-201 begins redistributing shortly after its uptake by the myocardium, and images obtained later than 10 to 15 minutes following tracer injection may miss a regional perfusion abnormality. The technetium-99m-labeled tracers are preferred for imaging because they are rapidly trapped in the myocardium and permit imaging of tissue perfusion at the time of tracer injection up to 4 hours later. The sensitivity of acute rest MPI is highest if the radioactive tracer is injected during chest pain, or shortly thereafter. Ideally, the tracer should be administered within 2 hours of the episode of chest pain. In those without prior infarction, identification of a perfusion defect and/or a segmental wall motion abnormality on the rest gated SPECT perfusion images will ordinarily prompt hospital

admission and an aggressive work up for an ACS. By contrast, those who have normal scans can be discharged home with a low probability of sustaining an ischemic event in the immediate future.

Current imaging guidelines indicate that rest MPI is not appropriate for patients with definite acute MI.[10] However, some who have imaging because of an uncertain clinical picture at presentation will subsequently rule in for acute infarction, and the perfusion images can provide useful information about the anatomic site of injury. If the rest perfusion images are repeated prior to hospital discharge, a measure of the degree of myocardial salvage afforded by treatment can be achieved by subtracting the perfusion defect size on the resting images at discharge (final infarct size) from that on the early images (region at risk).

Risk Assessment after ST-Elevation Myocardial Infarction

Patients with acute STEMI who are suitable for primary percutaneous intervention are usually referred directly for angiography and coronary revascularization. However, current practice guidelines indicate that noninvasive risk stratification is appropriate for stable, low-risk patients (ejection fractions >40%) who have not received reperfusion therapy or who have been treated with fibrinolytic agents.[12] Final infarct size, the extent of inducible ischemia, and LVEF are the key elements of risk stratification for stable patients following ST-segment elevation myocardial infarction, and gated MPI is well suited for measurement of these parameters.[13]

Infarct size can be determined by measuring the amount of the left ventricle with a resting perfusion defect prior to hospital discharge. Clinical studies of patients with acute infarction suggest that resting perfusion defect size is a variable that contributes independently to cardiac risk. Patients with only small fixed perfusion defects generally have a good prognosis, whereas those with resting perfusion defects involving 20% or more of the left ventricle are at higher risk for cardiac events over the ensuing 24 months. The extent of inducible ischemia can be derived from the images by careful subtraction of the size of the rest perfusion defect from that of the stress defect. Inducible ischemia, whether in the clinical infarct zone or in other vascular territories, also contributes to cardiac risk. Patient risk increases as the percent of the left ventricle with stress-induced ischemia increases, with involvement of 10% or more of the ventricle by a reversible perfusion defect placing the patient into a highrisk group. Measurements of LVEF and ventricular volumes can also readily be obtained from the gated perfusion images. In general, as the LVEF declines to <40% there is a progressive and nonlinear increase in the risk of cardiac events. Other scintigraphic observations that have been associated with increased clinical risk in the post-MI patient include transient ischemic dilatation (TID) of the left ventricle on the stress images, and increased pulmonary tracer uptake (especially with thallium scintigraphy) on the stress

images.

Stress perfusion imaging with adenosine or dipyridamole can safely be performed as early as 2 days following an acute infarction,[14] while present guidelines suggest that submaximal exercise stress testing not be performed before 5 days after an acute event. MPI with vasodilator stress provides incremental prognostic information beyond that afforded by conventional clinical and stress electrocardiographic variables. Vasodilator stress perfusion imaging is more sensitive for the identification of ischemia than submaximal exercise stress testing and is more useful for risk stratification, probably because it is possible to safely achieve a greater degree of hyperemia without inducing frank ischemia using vasodilator stress (Fig. 13.1). Early risk stratification facilitates identification of the high-risk patient and appropriate referral for angiography.

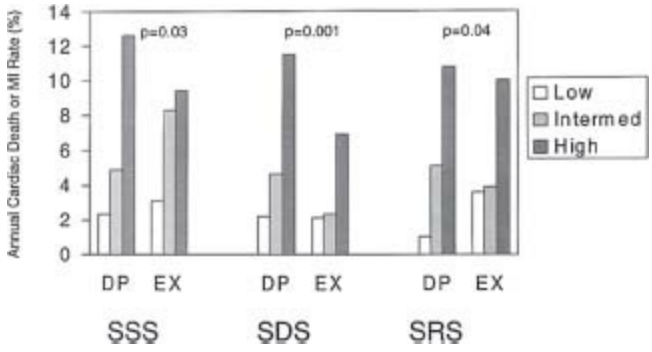

FIGURE 13.1 Annual rates of mortality/recurrent MI in patients with initial uncomplicated MI, according to the results of either dipyridamole (DP) or submaximal exercise (EX) myocardial perfusion scintigraphy. SSS, summed stress perfusion defect score; SDS, summed difference between stress and rest segmental scores; SRS, summed rest perfusion defect score. Low SSS and SRS values were defined by scores of 0-4; intermediate (Intermed) values by scores of 5-8; high values by scores >8. Low SDS values were defined by scores of 0-2, intermediate values by 3-7, and high values by scores >7. Higher perfusion defect scores were associated with higher event rates, and dipyridamole stress imaging provided better risk stratification than submaximal exercise perfusion scintigraphy. (From Brown KA, Heller GV, Landin RS, et al. Early dipyridamole ^{99m}Tc-sestamibi single photon emission computed tomographic imaging 2 to 4 days after acute myocardial infarction predicts in-hospital and postdischarge cardiac events. Comparison with submaximal exercise imaging. Circulation. 1999;100:2060–2066, with permission.)

Risk Assessment after Non-ST-Elevation Myocardial Infarction

Updated ACC/AHA guidelines for the management of patients with unstable angina and non–ST-elevation myocardial infarction (NSTEMI) recommend an early invasive approach for those with a high-risk profile who have no significant comorbidities.[15] However, the guidelines also suggest that stable patients without high-risk indicators might be managed using either a conservative or an early invasive strategy. Several studies have demonstrated the utility of MPI for the risk stratification of patients following NSTEMI. The presence of perfusion defects (fixed or reversible) on stress testing in stabilized NSTEMI patients is predictive of future events. In one study of 126

men who underwent a Tc-99m sestamibi stress SPECT myocardial perfusion study prior to hospital discharge, the event-free survival in patients with a normal scan was about 90% in the 18-month follow-up period, as compared to 55% in those with abnormal scans. Patients with reversible defects fared less favorably, with an event-free survival of only 30%. The rate of death and recurrent MI in this group was 40%, as compared to 20% for all patients with abnormal scans.

In those with unstable angina or NSTEMI, current AHA/ACC/ASNC imaging guidelines indicate that stress SPECT MPI is appropriate for the identification of inducible ischemia in (a) patients at intermediate or low risk for major adverse cardiac events, (b) patients whose angina is stabilized with medical therapy or in those in whom the diagnosis is uncertain, and (c) patients who have coronary stenoses of uncertain hemodynamic consequence on coronary angiography. Use of rest gated MPI can also be considered for determination of the left ventricular function.

Patients with Suspected or Established Chronic Coronary Artery Disease

Detection of Coronary Stenoses MPI has the highest clinical utility for the detection of flow-limiting coronary arterial stenoses in symptomatic patients with an intermediate pretest probability of disease.[10] In this scenario, regardless of whether the imaging study is negative or positive, the patient's posttest probability of disease has been substantially influenced by the results of the test.

In contrast, patients who have either a low or a high pretest probability of disease, MPI is less likely to provide meaningful additional diagnostic information and risk stratification. In those with a low pretest likelihood of disease, correlative angiographic studies indicate that the posttest probability of obstructive disease remains low. On the other hand, the patient with a high pretest probability of disease will continue to have high probability of disease regardless of MPI results.

The reported sensitivity of exercise myocardial perfusion SPECT imaging for detecting coronary stenoses of ≥50% ranges from 71% to 97% (average 87%), whereas specificity ranges from 36% to 100% (average 73%). For vasodilator (adenosine or dipyridamole) stress SPECT, reported sensitivity ranges from 72% to 93% (average 89%), whereas specificity ranges from 28% to 100% (average 75%). For MPI with PET, reported sensitivities range from 83% to 100% (average 97%), whereas specificities range from 73% to 100% (average 87%). In general, reported sensitivities and specificities of PET perfusion studies tend to be slightly higher than for SPECT studies, resulting in greater diagnostic accuracy.[16] The higher diagnostic accuracy likely reflects several factors, including the use of transmission images to correct the myocardial images for attenuation and the superior spatial resolution afforded by the PET imaging technique. Although it is not widely used in current clinical practice, recent studies suggest that the use of attenuation correction in conjunction with SPECT

myocardial perfusion might enhance its diagnostic accuracy. At the present time, studies directly comparing attenuation corrected SPECT versus PET for the detection of CAD are lacking.

MPI is especially useful for the detection of disease in individuals in whom the electrocardiographic changes with stress are nondiagnostic. These include patients taking digoxin, and those with left ventricular hypertrophy (LVH), ventricular pacemakers, left bundle branch block (LBBB), or Wolff–Parkinson–White syndrome. In those with LBBB, both reversible and fixed perfusion defects have been reported in the absence of obstructive disease on coronary angiography.[17] False positive perfusion defects are more common when exercise is used for stress, and for this reason pharmacologic stress imaging is preferred in those with LBBB.[18]. The perfusion defects are usually localized in the interventricular septum and may reflect actual abnormalities in regional blood flow. The cause of the septal perfusion defects is not clear, but it may reflect compression of perforating septal branch arteries due to the delayed onset of septal contraction resulting in a relative reduction in septal perfusion.

Identifying Disease Severity, Risk and Prognosis

Increasingly, MPI is being used to gauge the risk of cardiac events in symptomatic patients with known or suspected CAD. Some have argued that the use of prognostic endpoints is a better measure of the clinical utility of a test than a direct comparison with disease severity on angiography.

The factors associated with adverse outcomes on MPI studies include a large perfusion defect on the stress images (a summed stress score >8), a large fixed perfusion defect due to prior MI, a large area of reversible ischemia (especially if identified in multiple vascular territories), a LVEF <40%, stress- induced ventricular dyssynergy, TID of the left ventricle, and increased pulmonary uptake of the perfusion tracer.[19] An additional report indicates that there is an incremental prognostic value in assessing poststress left ventricular volumes on the gated SPECT perfusion images, with end systolic volumes >70 mL denoting a poorer prognosis.

Markers reflecting left ventricular function, such as the extent of myocardial scar, ventricular ejection fraction, and TID of the ventricle appear to be more predictive of cardiac death.[19] In contrast, markers of inducible ischemia, such as exertional symptoms, ECG changes, the extent and severity of a reversible perfusion defect, and associated inducible ventricular dysfunction, appear to be more predictive of an acute ischemic event, that is, the need for urgent coronary revascularization, progression from stable to unstable angina, and acute MI.

The patients most likely to benefit from MPI for risk stratification are those with an intermediate pretest risk of a cardiac event over the ensuing year. Low-risk, intermediate-risk, and high-risk categories have typically been defined as <1%, 1% to 2%, and >2% risk of a cardiac event per year, respectively. In general, patients with an

intermediate pretest risk who then proceed to have a normal cardiac SPECT scan have a low annual risk of cardiac events—on the order of 0.6% per year. Several more recent studies have suggested an even lower rate of cardiac death and nonfatal MI in those intermediate-risk patients with a normal cardiac SPECT scan, about 0.2% year. In these latter studies, individuals with an established history of CAD and a normal SPECT perfusion scan had an event rate about 0.9% per annum. In general, the absolute risk associated with a normal SPECT myocardial perfusion scan reflects the specific patient population under consideration. That is, stratification of patient risk depends on the anticipated pretest cardiac event rate in that specific population (Fig. 13.2).

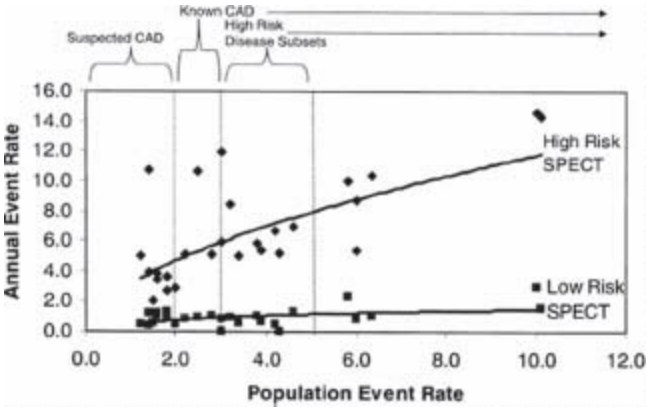

FIGURE 13.2 Meta-analysis of the posttest likelihood of a cardiac event, according to the findings on SPECT myocardial perfusion scintigraphy. The data points associated with a high-risk scan are shown by diamonds; those indicating a low-risk scan are shown by squares. The posttest event rate associated with a high- or low-risk myocardial SPECT perfusion scan reflects the pretest event rate in the population that best reflects the patient's clinical characteristics. A low-risk SPECT study in a patient from a population in which there is a larger naturally occurring pretest event rate (e.g., a diabetic patient) results in a posttest likelihood of a cardiac event that is somewhat higher than that in a patient from a pretest population with a low event rate. Conversely, a high-risk scan in a patient from a population with a low event rate is associated with a smaller absolute risk than that in a patient from a population with a higher frequency of cardiac events. (With kind permission from Springer Science+Business Media: Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. J Nucl Cardiol. 2004;11:171–185.)

For patients with abnormal scans, the risk of a cardiac event increases as the degree of the scan abnormality increases. This was demonstrated in a prospective study of 5,183 consecutive patients who underwent rest and stress MPI. In this investigation, patients with normal scans had a <0.5% annual rate of cardiac death and MI over the ensuing 642 ± 226 days. Those with mildly abnormal scans had a low risk of cardiac death but an intermediate risk of MI (0.8% vs. 2.7% per year), whereas those with moderately abnormal scans had an intermediate risk of cardiac death and MI (2.3% vs. 2.9% per year). The risk of cardiac death and MI was intermediate to high (2.9% vs. 4.2% per year) in the patients with severely abnormal scans.

Although individual authors may vary slightly in their definition of a high-risk myocardial perfusion scan, the annual rate of death or nonfatal MI is about 5.9% in those with high-risk scans. In an individual belonging to a population with a very high

pretest cardiac event rate (e.g., about 10% per year), a high-risk scan would stratify the patient to an even higher posttest risk of about 14% to 15% per year (see Fig. 13.2).

Other factors also modulate cardiac risk. For both low-risk and high-risk perfusion scans, the risk of cardiac death or nonfatal MI is higher for pharmacologic stress studies than for exercise studies. With exercise, a low-risk SPECT study nas about a 0.7% annual event rate, wnereas tnat for pharmacologic stress is about 1.2% per year. The annual event rate associated with a high-risk SPECT scan with exercise is about 5.6% per year, and is about 8.3% per year for a pharmacologic stress study.[19] Some authors therefore consider the necessity to use pharmacologic stress for MPI (a reflection of a poor functional class), an independent prognostic risk factor.

Gender also influences risk stratification. Although there is little difference between the sexes in the event rates associated with a low-risk SPECT scan, women with a high-risk SPECT scan have an annual cardiac event rate of approximately 6.2%, whereas that for men is about 5.3%. Diabetic patients also have higher event rates, for both low-risk (about 2% per year) and high-risk scans (about 9.5% per year). Therefore, diabetic women constitute the highest-risk patient cohort.

Specific Populations and Situations The use of MPI in selected patient populations and situations merits consideration.

Before and after Coronary Revascularization MPI before percutaneous coronary intervention (PCI). In a patient with atypical symptoms and an equivocal coronary lesion, the stenosis identified on angiography might not be the proximate cause of the individual's symptoms. Stress MPI is useful to characterize the physiologic effects of equivocal coronary lesions and thereby establish a link between the patient's symptoms and the angiographic findings.[10] MPI can also be used to identify the "culprit" vessel(s) in those with mild to moderate lesions in multiple arteries who have clinical evidence for stress-induced ischemia. Of note, evaluation for the functional significance of equivocal or moderate coronary stenoses identified during invasive coronary angiography may also be performed intraprocedurally using fractional flow reserve (FFR).

In order to adequately characterize the flow reserve characteristics of a coronary lesion on SPECT imaging, it is important to insure that adequate hyperemia has been achieved during stress (above). In patients who are unable to achieve at least 85% of their MPHR, pharmacologic stress testing is a practical alternative.

MPI after PCIs. In the first few months after PCI, routine MPI may be of diminished diagnostic value because of an increased incidence of false-positive perfusion defects secondary to endothelial dysfunction and abnormal flow reserve in the coronary bed distal to the site of intervention. Later following successful PCI, the main indication for MPI is recurrence of symptoms. In fact, per the most recent ACC/AHA appropriate-use

criteria for cardiac radionuclide imaging, stress MPI in patients who are asymptomatic and <2 years out from their PCI is considered inappropriate.[10]

MPI after coronary artery bypass graft (CABG). MPI can readily demonstrate the location, extent, and severity of rest and stress-induced perfusion defects in individuals with prior coronary artery bypass surgery. However, interpretation of the perfusion images should be performed considering the alterations in coronary anatomy resulting from the bypass procedure. Inducible ischemia might reflect obstructive disease in a bypass graft, a local problem with a graft anastamosis, or progression of a lesion in a native vessel distal to the insertion of a bypass graft. Ischemia can sometimes be identified in myocardial regions proximal to the insertion of a bypass graft. On gated perfusion images, abnormal septal motion is commonly noted in the post-CABG patient. This may reflect the loss of pericardial constraint as a result of the prior surgical procedure, rather than an intrinsic abnormality in contractile function, as systolic thickening is usually well preserved in those without prior injury.

MPI is most clearly indicated in post-CABG patients who have recurrent anginal or anginal-equivalent symptoms. The value of MPI in asymptomatic patients <5 years is currently listed as "uncertain" by current guidelines. However, in studies that included asymptomatic patients >5 years after CABG, several variables have been linked to an adverse outcome: the extent and severity of inducible ischemia (as measured by the summed reversibility score), perfusion defects in multiple vascular territories, the extent of fixed perfusion defects, and increased pulmonary uptake of thallium.[20] As such, stress MPI is also considered appropriate for risk assessment in asymptomatic patients more than 5 years after CABG, according to current guidelines.[10]

Preoperative Testing prior to Noncardiac Surgery MPI may be used prior to noncardiac surgery to help identify individuals at high risk for perioperative ischemia, infarction, and death.[21] Despite advances in medical care, reported mortality rates for perioperative MI are as high as 26%. Moreover, the costs of perioperative morbidity and mortality are of the order of $12 billion per year in the United States. Appropriate medical treatment can reduce perioperative morbidity and mortality, and improve the long-term prognosis of the patient. These facts underscore the need for identification of high-risk surgical patients.

Several clinical scoring systems have been utilized to assess cardiac risk in patients prior to noncardiac surgery. Most of these scoring systems, however, were derived from and applied to general surgical populations with a relatively low prevalence (<10%) of CAD. Use of these scoring systems in populations with a higher prevalence of coronary disease (as, e.g., in those with peripheral vascular disease, in whom the prevalence of CAD may be as much as 60%), underestimates the risk of cardiac events.

Noninvasive preoperative stress testing has its highest utility in patients with intermediate clinical predictors of cardiac risk. These include mild angina, a history of

prior MI, compensated CHF, and diabetes mellitus. Current practice guidelines suggest that the patients most likely to benefit from preoperative stress MPI are those with poor functional capacity (able to achieve <4 METs with exercise) who are scheduled to undergo intermediate (e.g., intra-abdominal surgery, carotid endarterectomy) or high-risk (e.g., abdominal aortic aneurysm repair) surgical procedures.[10,21]

The positive predictive value of MPI for perioperative cardiac ischemia is low (4% to 20%), but the negative predictive value is very high (96% to 100%). Patients with reversible defects have a greater risk of perioperative ischemia than those with fixed defects, and the relative risk increases in proportion to the extent of inducible ischemia on the perfusion imaging study. The evaluation of left ventricular function on gated SPECT perfusion images is important in patients with signs and/or symptoms of heart failure, because reduced ventricular systolic function is correlated with the risk of perioperative heart failure.

Nuclear Stress Testing in Women More women die of cardiovascular disease each year in the United States than from any other cause.[22] Although the prevalence of CAD in non-diabetic women <45 years of age is low, it increases significantly following menopause, and is similar to that in men by the seventh decade. Although deaths from CAD are declining in men, the same is not true for women. CAD claims the lives of more than 240,000 women each year in the United States and is a significant cause of morbidity and disability. Women are more likely to die from an acute MI than their male counterparts and are more likely to sustain recurrent infarction. Therefore, early identification of women with coronary heart disease (CHD) affords the best opportunity for intervention and, ultimately, a reduction in cardiovascular mortality.

Current guidelines rely on a Bayesian approach to gauge the relative value of stress testing for the detection of CAD in women. In asymptomatic premenopausal women, there is a low prevalence of coronary disease, cardiovascular risk is low, and the clinical utility of stress testing is generally of limited benefit. However, women with diabetes or peripheral vascular disease are the exception, because there is a higher risk of CAD. Stress testing in these women is appropriate according to current guidelines, even in the absence of symptoms, because of the greater pretest probability of disease. Symptomatic women, those with an intermediate or high pretest likelihood of disease (<50 years of age with typical angina, 50 years or older with typical or atypical chest pain, two or more cardiac risk factors), can be expected to benefit from stress testing.

The diagnostic accuracy of exercise stress electrocardiography for the detection of CAD in women is somewhat limited. ST-segment changes with stress have been reported to be less accurate for the detection of CAD than in men, as a consequence of a higher prevalence of ST–T-wave changes on the resting ECG, lower electrocardiographic voltages, and poorly understood hormonal effects on vascular tone.[22] Women are generally older when they present for evaluation, and may be limited

in their ability to achieve an adequate level of stress because of lower exercise capacity. Reported average sensitivities and specificities of stress electrocardiography for CAD detection in women are about 61% and 70%, respectively as compared to 72% and 77% for men. Current ACC/AHA guidelines suggest that stress electrocardiography be used as a first-line test for CAD detection in women with an intermediate pretest likelihood of disease who have a normal resting ECG and who are capable of achieving an adequate level of stress. In those with baseline ST–T changes on the ECG, or in those in whom an adequate level of stress is unlikely to be achieved, MPI provides an incremental benefit over the stress ECG, for both the diagnosis of CAD and risk stratification. Cardiac imaging is also suggested for women in whom the stress ECG is indeterminate or suggests an intermediate level of risk, as well as in those with an intermediate-risk Duke treadmill score.

In early clinical studies employing SPECT thallium-201 scintigraphy, reported sensitivities for the detection of single vessel disease in women were lower than in men. This was attributed to smaller left ventricular chamber sizes in women and to the physical characteristics of the isotope itself. In addition, breast attenuation often resulted in anterior wall defects and false positive tests. With the advent of technetium-99m–labeled tracers and gated imaging, the diagnostic accuracy of MPI has improved significantly in female populations. For example, adenosine sestamibi imaging has been reported to be 91% sensitive and 86% specific for the detection of coronary stenoses. Although the diagnostic accuracy of SPECT MPI in women may be slightly less than that in men, there is a substantial incremental benefit of MPI over the routine clinical variables and stress electrocardiography for risk stratification in female patients.

The Patient with Coronary Calcification on CT The presence of coronary calcification on electron beam CT (EBCT) or multidetector CT (MDCT) is related to the amount and extent of atherosclerotic plaque on coronary angiography. In general, the higher the CT coronary calcium score in a given patient, the poorer the prognosis. Coronary artery calcification has been shown to be an independent predictor of death relative to other clinical variables, with the mortality risk increasing linearly as the coronary artery calcium score increases.[23]

The information provided by CT and MPI is considered by some to be complementary. In general, the higher the coronary calcium score, the greater is the probability that a perfusion defect will be identified on SPECT MPI. For patients with coronary calcium scores <100, the prevalence of perfusion defects on MPI has been reported to be <1.8%.[24] For patients with scores between 100 and 400, the reported prevalence of SPECT perfusion defects is 5.2%, whereas that for patients with calcium scores >400 is 15% to 40%. Current ACC/AHA guidelines indicate it is appropriate to perform stress MPI in patients with Agatston scores >400, as well as for patients who have “high” CHD risk and a coronary calcium score between 100 and 400.

Further clinical studies are needed to determine if the extent of coronary artery calcification contributes to the risk stratification of those with normal myocardial perfusion studies.

The Patient with Severe Stenosis on Coronary CT Angiogram As the technical quality of coronary CT angiography continues to improve, this imaging technique is increasingly being utilized in clinical practice for the detection of obstructive coronary lesions. However, CT angiography is not well-suited for defining the functional significance of coronary lesions of indeterminate severity. Complementary information may be required to ascertain whether these lesions result in ischemia during stress. For this reason, stress MPI is considered appropriate by current ACC/AHA guidelines when noninvasive coronary angiography reveals coronary stenoses of uncertain significance.[10]

The Asymptomatic Patient with Diabetes Patients with diabetes mellitus are considered by Adult Treatment Panel (ATP III) criteria to have a CHD "risk equivalent," roughly equal in terms of risk of future cardiac events with patients with known stable CAD, peripheral arterial disease, and cerebrovascular disease. According to current ACC/AHA guidelines, it is considered appropriate to further risk-stratify asymptomatic diabetic patients using stress MPI. It is worth noting, though, that the most recent iteration of the appropriate-use guidelines for cardiac radionuclide imaging were published prior to the release of the 5-year follow-up data regarding cardiac outcomes in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study. In this study, 1,123 patients with adult-onset diabetes between the ages of 50 and 75 who had no known coronary disease or anginal symptoms were randomized to a baseline screening with adenosine stress MPI or no stress MPI. The trial demonstrated that 22% of patients screened at baseline with radionuclide imaging had silent myocardial ischemia.[25] At 5 years follow-up, however, there was no difference between the two randomization arms in terms of cardiac events and mortality.[26] Although there were significantly more coronary angiograms and revascularizations performed within the first 120 days in patients who underwent baseline screening MPI versus those that did not, these differences equilibrated over the course of the follow-up period—usually due to the development of symptoms and subsequent diagnostic testing in both groups. Interestingly, the event rate in the overall cohort was much lower than anticipated: 0.6% per year, instead of the 2% per year that the study design was based upon. As such, the study was underpowered to detect a 20% difference between the MPI-screened and nonscreened groups. However, the authors questioned whether a reduction in cardiac events from 0.6% to 0.5% per year—even if present—justified routine radionuclide cardiac imaging in asymptomatic diabetic subjects.

At present, ACC/AHA guidelines consider the use of stress MPI for risk

stratification in asymptomatic patients with high CHD risk (>20% over 10 years by Framingham risk score, or "CHD risk equivalents" such as peripheral vascular disease, abdominal aortic aneurysm, cerebrovascular disease, and diabetes mellitus) as "appropriate,"[10] albeit with a Class IIb indication in asymptomatic diabetics.[27] However, it is possible that these guidelines may be amended if further data corroborates lower-than-expected event rates in asymptomatic patients with CHD risk equivalents in an era of improved medical therapy for primary prevention of major adverse cardiovascular events.

NUCLEAR CARDIAC IMAGING IN HEART FAILURE

Role of Nuclear Imaging in Congestive Heart Failure

In individuals with CHF, nuclear imaging can assist in clinical management of the patient by (a) helping to define the etiology of the ventricular dysfunction, (b) characterizing right and left ventricular functions and volumes, (c) determining the relative contributions of myocardial stunning and scar to left ventricular dysfunction, and (d) distinguishing myocardial hibernation from scar in those with chronic ischemic heart disease. Although echocardiography has largely supplanted nuclear imaging for assessing diastolic ventricular function, and for characterizing cardiac performance in hypertrophic and valvular heart disease, nuclear imaging techniques remain extremely useful for the evaluation of patients with systolic heart failure. By the use of nuclear imaging, the clinician is afforded insights into the etiology and prognosis of heart failure in the patient, and perhaps more important, whether coronary revascularization in a high-risk individual is likely to improve symptoms and survival.

Etiology of Heart Failure: Ischemic versus Nonischemic Cardiomyopathy

In patients with impaired systolic function, it is crucial to distinguish myocardial dysfunction due to CAD (ischemic cardiomyopathy) from other causes of dilated heart failure (nonischemic dilated cardiomyopathy). In selected individuals with ischemic cardiomyopathy, coronary revascularization can provide both symptomatic and prognostic benefit, and noninvasive identification of these patients is key for optimal clinical management.[28] MPI is helpful for distinguishing between those with and without ischemic cardiomyopathy, and for the identification of those with ischemic cardiomyopathy who might benefit from coronary revascularization.

Generally, patients with left ventricular dysfunction due to CAD have either extensive fixed perfusion defects or a modest number of fixed defects with large reversible stress-induced perfusion defects (suggesting dysfunction on the basis of myocardial stunning). Six studies have shown that the sensitivity of MPI for the detection of CAD in heart failure patients is 100%, with a homogeneous pattern of

perfusion having a predictive value of 100% for a nonischemic cardiomyopathic process. However, a fixed perfusion defect does not preclude the possibility of a nonischemic cardiomyopatmc process, for patchy myocardial fibrosis can sometimes be manifest as a fixed defect. In addition, coronary flow reserve can be abnormal in nonischemic cardiomyopathy and reversible perfusion defects have also been reported in these individuals. The specificity of MPI for the identification of ischemic cardiomyopathy in dilated heart failure patients is therefore only about 40% to 50%.

Assessment of Ventricular Function

In addition to gated MPI, assessment of right and left ventricular function and volumes can also be achieved using radionuclide ventriculography. Right ventricular function can be evaluated using a first-pass imaging study, in which a series of images is obtained rapidly as a radioactive tracer is administered intravenously. It is useful for visualizing right ventricular function without the confounding influence of activity in other nearby vascular structures. Alternatively, tomographic equilibrium-gated blood pool imaging can also be used to assess right ventricular function.

Left ventricular function can be evaluated using equilibrium-gated blood pool radionuclide ventriculography. In this technique, an intravenously administered radioactive tracer such as technetium-99m pertechnetate is used to label the patient's red blood cells. Once the label is uniformly distributed throughout the vascular space, a set of images synchronized to the patient's ECG is obtained over multiple cardiac cycles. These images depict different times in the cardiac cycle (see Chapter 11). Because background corrected left ventricular counts are proportional to ventricular volume, the ejection fraction can be calculated by subtracting end-systolic counts from end-diastolic counts and dividing by the end-diastolic counts. Unlike echocardiography or contrast ventriculography, computation of the LVEF is independent of any assumptions about the shape of the ventricle.

Radionuclide ventriculography can be performed in nearly anyone with a stable cardiac rhythm, including those with obstructive pulmonary disease and marked obesity. Most of the available computer programs for the analysis of the gated images use automated edge-detection algorithms to define the border of the ventricular cavity in a consistent manner, resulting in LVEF measurements that are very reproducible. In patients wim CHF, the severity of global and regional systolic dysfunction can easily be defined with this imaging technique. Because of the high reproducibility of the LVEF measurements made with this imaging technique, it is also used to monitor the effects of cardiotoxic drugs such as doxorubicin. Serial LVEF determinations allow the clinician to maximize the dose of the chemotherapeutic agent given to the patient while minimizing the risk of CHF due to drug toxicity. The indications for radionuclide ventriculography are listed in Table 13.3.

TABLE
13.3 Indications for Radionuclide Ventriculography

- Determination of left ventricular function in STEMI and NSTEMI/unstable angina patients
- Initial evaluation of RV and LV function in patients with CHF
- Baseline measurement and serial monitoring of left ventricular function during therapy with cardiotoxic drugs (e.g., adriamycin)

Perfusion and Metabolic Imaging for Reversible Left Ventricular Dysfunction

In patients with ischemic cardiomyopathy, regional dysfunction associated with normal resting myocardial perfusion generally represents viable myocardium that is likely to benefit from coronary revascularization. These areas frequently demonstrate a perfusion defect with stress, suggesting that the regional dysfunction results from recent or repetitive myocardial stunning. Individuals with the largest amounts of ischemia may be expected to derive the greatest functional benefit from coronary revascularization.

For patients with regional left ventricular dysfunction and fixed perfusion defects, additional imaging is warranted to identify the presence or absence of viability (myocardial hibernation) in that region. Coronary revascularization can improve regional and global left ventricular function in those with viable but dysfunctional myocardial tissue, and thereby benefit heart failure symptoms and quality of life. Usually, an improvement in the global left ventricular ejection can be anticipated if the extent of hibernating myocardium exceeds 20% to 25% of the ventricle. Data based on meta-analyses of observational studies[28] have indicated that coronary revascularization in patients with myocardial viability benefits survival. More recent randomized trial data have been conflicting with regard to a mortality benefit of revascularization based on the presence or absence of viability, and this remains an active area of investigation.[29,30] A survival benefit could conceivably reflect factors besides an improvement in ventricular function, including prevention of ventricular remodeling and a reduction in ventricular arrhythmogenesis.

Several nuclear imaging options can be used to identify myocardial viability. Markers of viability that have been proposed include the fill-in of a perfusion defect on late (24-hour) thallium-201 redistribution or reinjection images, reversibility of a rest perfusion defect on 3- to 4-hour redistribution images, and demonstration of residual tissue glucose metabolic activity in hypoperfusion myocardial regions (a perfusion-metabolism mismatch) on PET images obtained using the glucose analog F-18 2-fluoro-2-deoxyglucose (FDG). Some have proposed that a relative perfusion tracer concentration >55% to 60% of maximal myocardial activity on rest perfusion images

can be used to identify myocardial viability. In a meta-analysis, radionuclide techniques and dobutamine echocardiography had similar positive and negative predictive values for identifying segments with improvement in wall motion following revascularization.[31] The nuclear imaging techniques appeared to be slightly more sensitive in identifying viability, as defined by an improvement in function following revascularization, whereas dobutamine echocardiography appeared to be slightly more specific.

SUMMARY

Nuclear cardiac imaging techniques have become an integral component of the practice of clinical cardiology. As with any diagnostic tool, the physician must have a working knowledge of the strengths and limitations of the imaging technology in order to utilize this technology for optimum clinical benefit. In appropriately selected patients, MPI is very useful for identifying obstructive CAD, for characterizing the functional significance of equivocal coronary stenoses, and for risk stratification. In those with CAD and systolic ventricular dysfunction, nuclear imaging techniques can be used to quantitate the severity of the ventricular dysfunction and to monitor the myocardial response to treatment noninvasively. Nuclear imaging techniques may also identify those individuals with ischemic cardiomyopathy who are likely to benefit functionally and prognostically from coronary revascularization.

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QUESTIONS AND ANSWERS

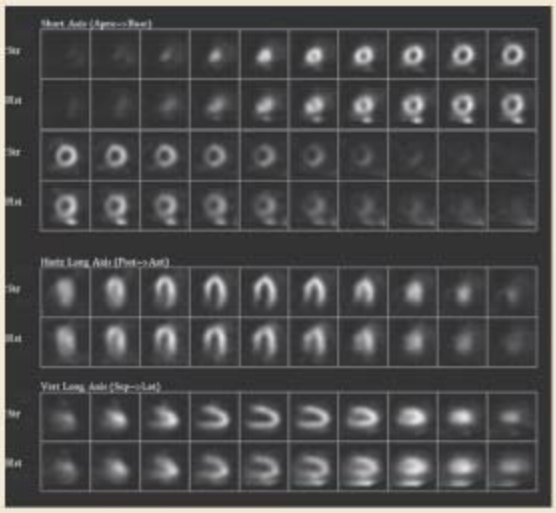
Questions

1. A 65-year-old man with a 45-pack-year smoking history, hyperlipidemia, intermittent claudication, and hypertension has been experiencing shortness of breath with exertion for 3 months. He is referred for an adenosine cardiac single photon emission computed tomography (SPECT) study for symptom evaluation. His medications include metoprolol, lisinopril, aspirin, theophylline, and simvastatin. During the adenosine infusion, the patient does not report any chest pain, nor are there any ST-segment changes on the electrocardiogram (ECG). High-degree atrioventricular (AV) block develops 30 seconds following the start of the adenosine infusion, prompting the cardiology fellow attending the stress test to stop the infusion. The SPECT perfusion images are interpreted as normal, with no regional ischemia. Despite continuation of medical therapy the patient's symptoms persist, and 6 weeks later he is referred for cardiac catheterization. At catheterization there is a proximal 75% right coronary artery stenosis, a 75% to 80% proximal left anterior descending artery stenosis, and a 70% to 75% stenosis of the proximal circumflex artery. Possible reasons for the absence of a reversible perfusion defect on the cardiac SPECT study include all of the following except:
   a. Ingestion of a chocolate bar 3 hours before the test was performed
   b. Right bundle branch block (RBBB) on the resting ECG
   c. Provocation of "balanced ischemia" by the adenosine stress
   d. Failure to withhold the patient's medications prior to the test
   e. Termination of the adenosine infusion at 30 seconds

2. Which of the following individuals is likely to benefit most from nuclear stress imaging?
   a. A 25-year-old man with midline chest pain, which is tender to the touch and intermittently responsive to ibuprofen
   b. A 30-year-old woman who gets chest discomfort after eating highly seasoned food but who has no trouble when she plays tennis three times a week
   c. A 39-year-old male smoker with shortness of breath on exertion and a mildly elevated low-density lipoprotein (LDL) cholesterol level. His father died suddenly at age 45, and his 42-year-old brother recently had two stents placed in one of his coronary arteries. The resting ECG shows nonspecific ST-T-wave changes.
   d. A 76-year-old man, former smoker, with hypertension and recent inferior wall myocardial infarction (MI) treated by placing two stents in the right coronary artery. He was awakened by an episode of chest pain that lasted almost 20 minutes and that has not responded to sublingual nitroglycerin.
   e. A 55-year-old female with hypercholesterolemia, hypertension, frequent heartburn, and increasing shortness of breath on exertion. On echocardiography, there is moderate left ventricular hypertrophy (LVH), and aortic valvular calcification with an estimated aortic valve area of 0.69 cm^2.

3. A 58-year-old male executive is seen for left-sided chest pain. He has a history of bilateral thumb pain for which he took a cox-2 inhibitor for 2 years before switching to naproxen. He works long hours and admits to fatigue and loss of libido. He has an elevated lipoprotein A (Lpa) level but an otherwise normal lipid profile. The hs-CRP level is normal and a cardiac SPECT study 3 years earlier was normal. He undergoes an exercise cardiac SPECT and exercises to 10 METs on the Bruce protocol, achieving 106% of his maximum predicted heart rate (MPHR). With exercise, he experiences fatigue

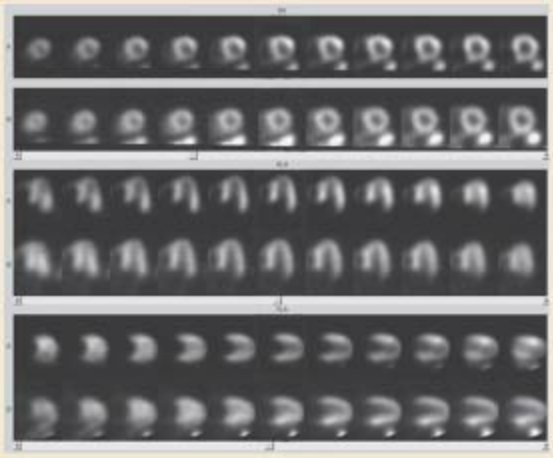
but no angina. No ST-segment changes are noted with stress. The myocardial perfusion images from the exercise study are shown (see figure).



Based on the results of this scan, his cardiac mortality over the next 3 years can be estimated as:

a. ≤1.5%
b. 3%
c. 5%
d. 6%
e. >9%

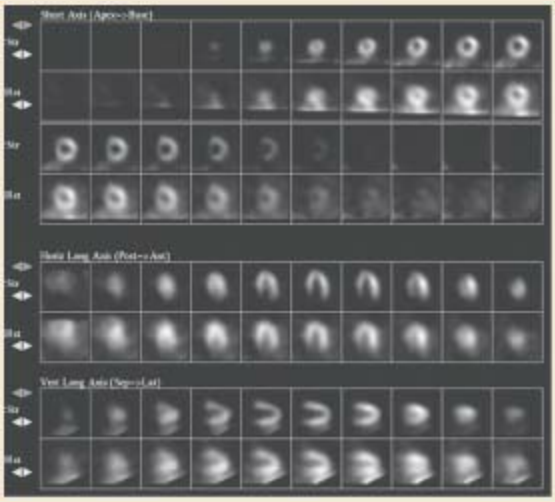
4. A 71-year-old man with a history of hyperthyroidism, hypertension, and remote pulmonary embolism is referred for treatment of new-onset atrial fibrillation. He underwent a rest rubidium/dipyridamole stress rubidium-82 perfusion study (see figure).



The myocardial perfusion images are most consistent with:
a. Inferior ischemia
b. Apical and inferior ischemia
c. Anterior wall ischemia
d. Diaphragmatic attenuation
e. Normal perfusion scan

5. A 36-year-old woman presents to the Emergency Room with atypical chest pain. She smokes and there is a family history of coronary artery disease (CAD). The ECG shows a normal sinus rhythm

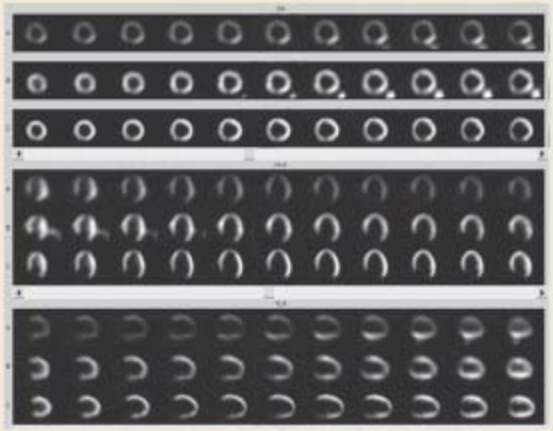
with early repolarization. Cardiac enzymes are negative and the patient is referred for stress myocardial perfusion imaging (MPI). The patient undergoes treadmill exercise using the Bruce protocol. She is able to complete stage 2 of the exercise protocol (7 METs), being limited by leg fatigue. She does not experience chest pain with exercise. She achieves 92% of her maximal age-predicted heart rate. During stress, the ECG shows a new left bundle branch block (LBBB). Rest thallium-201 and stress Tc-99m tetrofosmin images were obtained (see figure).



The myocardial perfusion images demonstrate:

a. Normal study with breast attenuation
b. A fixed septal perfusion defect
c. A reversible septal perfusion defect, indicating disease in the left anterior descending coronary artery
d. A reversible septal perfusion defect, reflecting the development of LBBB with exercise
e. A reversible septal perfusion defect of uncertain etiology

6. An 80-year-old man is referred for a second opinion regarding the need for cardiac surgery. He sustained an inferior MI 12 years ago. Over the last 4 years, he has had increasing shortness of breath, but no angina. Nine months ago he had an echocardiogram that showed mild calcific aortic stenosis, with a left ventricular ejection fraction (LVEF) of 60%. Three months prior to presentation he was hospitalized for congestive heart failure (CHF). Echocardiogram again showed mild aortic stenosis, with a LVEF of 25%. Cardiac catheterization confirmed mild aortic stenosis, and on coronary angiography, there was multivessel CAD. Rest and stress rubidium-82 perfusion images, and ^{18}FDG metabolic positron emission tomography (PET) images, were obtained (see figure).



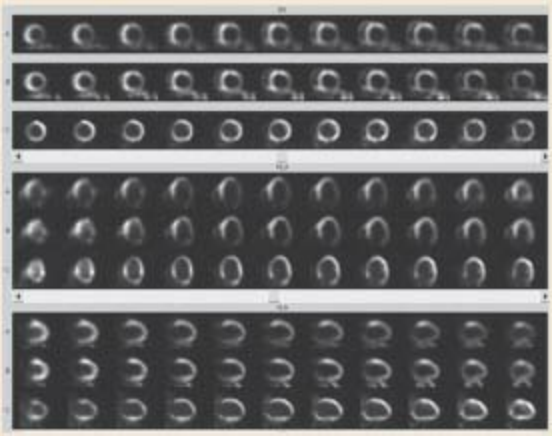
The PET scan demonstrates:

a. A small inferior scar
b. Extensive septal, anterior, apical, and lateral ischemia
c. A small inferior scar, with extensive septal, anterior, apical, and lateral ischemia
d. Extensive myocardial hibernation involving the septal, anterior, apical, and lateral regions, with a small inferior scar
e. Normal regional perfusion and metabolism findings suggest nonischemic dilated cardiomyopathy.

7. In a patient with ischemic cardiomyopathy, which of the following scintigraphic findings suggests that abnormal regional function is unlikely to improve if coronary revascularization is performed?

a. A defect on rubidium-82 PET images with preserved uptake on ^{18}F-fluorodeoxyglucose PET images in the same area
b. A reversible stress-induced perfusion defect in the same region on rest thallium-201/stress Tc-99m sestamibi SPECT images
c. The region exhibits a Tc-99m sestamibi SPECT perfusion defect with a relative tracer concentration of 55% of maximal myocardial activity. Relative tracer activity on PET images with ^{18}F-fluorodeoxyglucose is 95% of peak maximal myocardial activity.
d. A resting thallium-201 perfusion defect in which the relative tracer concentration is 40% of peak myocardial uptake, and which then increases to 90% of peak myocardial uptake on images obtained following thallium-201 reinjection
e. A matching defect on ^{13}N-ammonia and ^{18}F-fluorodeoxyglucose PET images

8. A 57-year-old man with a history of CAD, prior MI, and remote coronary artery bypass surgery was referred for evaluation for coronary revascularization because of recurrent angina and heart failure symptoms. There was a history of hyperlipidemia, hypertension, and deep venous thrombosis. An implantable cardioverter-defibrillator (ICD) had been placed 2 years before because of ventricular arrhythmias. Echocardiography confirmed global left ventricular systolic dysfunction, with an LVEF of 20%. Rest and stress rubidium-82 perfusion and ^{18}F-fluoro- deoxyglucose PET images were obtained (see figure).



Which of the following statements is true regarding the scintigraphic findings?

a. Left ventricular dysfunction is probably due to a nonischemic cardiomyopathy.
b. On contrast magnetic resonance imaging, pronounced late enhancement will probably be observed in the lateral wall.
c. A reversible perfusion defect is identified in the anterior wall.
d. Coronary revascularization would be unlikely to improve the patient's heart failure symptoms.
e. On histopathologic examination, extensive myocardial fibrosis would be expected if a biopsy of the lateral wall of the left ventricle were obtained.

9. Which of the following is not a contraindication to pharmacologic vasodilator stress testing with an adenosinergic agent?
   a. Severe reactive airway disease
   b. Severe symptomatic aortic stenosis
   c. LBBB
   d. High-grade AV block
   e. All of the choices are contraindications to adenosinergic agents.

10. Which of the following are acceptable options for postinfarct risk management in a patient with a permanent ventricular pacemaker who has been conservatively managed during an acute non–ST-elevation myocardial infarction (NSTEMI) and has not undergone coronary angiography prior to discharge?
   a. Optimal medical therapy including aspirin, thienopyridine, statin, beta-blocker, and ACE-inhibitor; no need for further diagnostic testing.
   b. Optimal medical therapy and resting echocardiogram
   c. Optimal medical therapy, resting echocardiogram, and symptom-limited exercise ECG testing
   d. Optimal medical therapy, resting echocardiogram, and symptom-limited exercise SPECT imaging
   e. Optimal medical therapy and vasodilator stress SPECT imaging with gated ejection-fraction estimate

11. A 63-year-old man is referred to you for the evaluation of exertional chest discomfort. His resting ECG is abnormal. In which of the following situations would MPI NOT be a necessary adjunct to the stress ECG to identify inducible ischemia?
   a. Wolff–Parkinson–White pattern on baseline ECG
   b. LBBB on baseline ECG
   c. LVH with secondary repolarization changes on baseline ECG
   d. RBBB on baseline ECG
   e. Digitalis effect on baseline ECG

Answers

1. Answer B: Appropriate patient preparation is crucial for successful nuclear stress imaging. Recent ingestion of chocolate and/or theophylline could have blunted the hyperemic effects of adenosine, resulting in a falsely negative study. A 30-second infusion of adenosine might not have delivered a sufficient amount of the drug to produce adequate myocardial hyperemia. Alternatively, in a patient with proximal stenoses of nearly equal severity in each of the major coronary vessels, “balanced ischemia” is also a consideration; in this situation, a regional disparity in myocardial perfusion on the stress images is not identified because the impairment in flow reserve is similar in each of the three vascular territories. Right bundle branch block itself would not be expected to cause a false negative perfusion study.

2. Answer C: The 39-year-old smoker has several cardiac risk factors and is in an intermediate-risk category for an adverse cardiac event. This patient is the one most likely to benefit from diagnostic testing, for a positive stress perfusion study will put him into a high-risk category, whereas a negative stress perfusion study will stratify him into a low-risk patient population. The young man and woman in a and b have noncardiac chest pain; they are in a low-risk population and are unlikely to derive a benefit from stress MPI. The patient in d has known CAD and an unstable clinical picture following recent coronary stenting, and would more appropriately be referred directly for repeat coronary angiography. The patient in e has moderately severe aortic stenosis, and would more appropriately be referred for cardiac catheterization and coronary angiography.

3. Answer A: The myocardial perfusion images in this middle-aged man with atypical chest pain and two cardiac risk factors (male sex, elevated lipoprotein a level) are normal. The risk of a cardiac event over the next 3 years in this patient is ≤ 1.5% (≤ 0.5% per year), according to one study.

4. Answer B: Reversible perfusion defects are identified involving the apical and inferior myocardial regions. In PET imaging, transmission images are used to correct the emission images for attenuation,

thus attenuation by the diaphragm should not influence the tracer concentration in the inferior wall.

5. Answer E: A reversible septal perfusion defect is identified on the myocardial perfusion images. The reversible defect could reflect either the onset of LBBB with stress or obstructive coronary disease in the left anterior descending artery or both. Therefore, the findings are equivocal for CAD. The patient had CT coronary angiography following the nuclear imaging study, and this did not reveal any coronary lesions.

6. Answer C: Extensive reversible perfusion defects are noted in the septal, anterior, apical, and lateral regions, and there is a small scar in the inferior region that is best identified on the short-axis images. Because of the extensive ischemia, the patient was referred for coronary revascularization.

7. Answer E: A matching defect on ^{13}N-ammonia and ^{18}F-fluorodeoxyglucose PET images is indicative of myocardial scar, and there is little chance that the region will exhibit improved function if revascularization is performed. Regions with perfusion-metabolism mismatches, or hibernating myocardium, as exemplified by the findings in a and c, are likely to improve functionally if revascularization is performed. Dysfunctional regions with reversible perfusion defects, whether in response to stress (b) or on rest/reinjection thallium-201 images (d), are also likely to benefit functionally from coronary revascularization.

8. Answer C: A reversible perfusion defect is identified in the anterior wall. On the rest rubidium-82 perfusion and ^{18}F-fluorodeoxyglucose images, there is an extensive perfusion-metabolism "mismatch" consistent with myocardial hibernation involving the anterolateral and inferolateral walls, as well as a portion of the inferior wall. There is a small inferior scar. The findings indicate that the patient would benefit from coronary revascularization. Prior histopathologic studies indicate that there is minimal fibrosis in areas with hibernating tissue, and therefore extensive late enhancement on contrast magnetic resonance imaging would not be anticipated.

9. Answer C: LBBB is a situation in which pharmacologic stress is preferred over exercise stress, due to an increased incidence of false-positive septal perfusion abnormalities on MPI with exercise stress. All of the other scenarios are relative contraindications to adenosinergic vasodilator stress.

10. Answer E: The current ACC/AHA guidelines regarding predischarge risk stratification in low-risk patients (i.e., those who are stable and without symptoms of ischemia or heart failure for 12 to 24 hours) who are admitted for unstable angina or NSTEMI—and who have not already undergone coronary angiography— recommend some form of noninvasive stress testing and assessment of LVEF prior to discharge.

This patient has a ventricular pacemaker, and so stress ECG testing alone would be nondiagnostic. Also, the ventricular-paced rhythm makes pharmacologic stress preferable to exercise, due to the increased incidence of false-positive septal perfusion abnormalities with exercise SPECT imaging in that situation.

11. Answer D: All of the other choices render ECGs nondiagnostic with respect to the presence of stress-induced ischemia.

CHAPTER

Cardiac MRI and CT

Andrew C.Y. To and Milind Y. Desai

Cardiac magnetic resonance imaging (MRI) and computed tomography (CT) are noninvasive imaging modalities with clinical utility in a wide array of cardiovascular diseases. Common indications, technical considerations, and specific clinical scenarios are reviewed, with attention to the essential knowledge base that might be expected of fellows completing a general cardiovascular medicine fellowship.

CARDIAC MRI

Recent advances in pulse sequence design and scanner hardware have permitted MRI to become a useful tool in the noninvasive assessment of cardiovascular diseases. MRI provides high-resolution anatomic images; quantitative assessment of ventricular function as well as myocardial mechanics, perfusion, and viability; quantification of intra- and extracardiac shunts; measurements of valvular velocities and gradients; and contrast-enhanced angiography without the use of ionizing radiation or nephrotoxic contrast agents. Table 14.1 summarizes the indications of MRI in cardiovascular medicine, in particular drawing attention to the advantages of MRI in the assessment of these conditions.

TABLE
14.1 Indications of MRI in Cardiovascular Diseases

Indications	Specific Conditions Where MRI Has Incremental Utility	Advantages of MRI in These Conditions
Myocardial diseases	Ischemic cardiomyopathy Nonischemic cardiomyopathy Restrictive cardiomyopathy Hypertrophic cardiomyopathy Myocarditis Inherited disorders of cardiac metabolism	Cardiac chamber size and function quantification Myocardial morphology Myocardial tissue characterization
Pericardial diseases	Acute pericarditis Constrictive pericarditis Pericardial effusion	Pericardial thickness Pericardial delayed enhancement Constrictive physiology assessment Myocardial tissue characterization
Congenital heart disease		Cardiac chamber size and function quantification Valvular stenosis and regurgitation evaluation *Qp*:*Qs* quantification Extracardiac vasculature imaging
Mass	Cardiac masses Paracardiac masses	Cardiac morphology Tissue characterization Extracardiac structural imaging
Aorta	Aortic aneurysm Aortic dissection	Aortic size Aortic wall morphology Branch vessel assessment

Technical Considerations

MRI Physics

The nuclei of all atoms are composed of one or more protons. Protons have a small positive electric charge and spin at a rapid rate. The rapid spinning motion of a positively charged proton produces a small but measurable magnetic field that in a sense is similar to a tiny bar magnet. Normally, the magnetic fields of these protons are randomly oriented throughout the body. When they are placed within an MRI scanner, however, protons within the body align themselves with the external magnetic field of the scanner, just as a compass aligns with the earth's magnetic field. By applying radiofrequency (RF) waves, a portion of these protons can be made to change their alignment to a more excited state. As these protons relax and return to their original alignment, they emit a signal that can be measured and used to generate a clinical image. Hydrogen (^{1}H) is the most abundant atom in the body and forms the basis of MRI imaging.

Basic Imaging Sequences

Imaging in MRI depends on using gradient coils within the scanner to send RF pulses in specific patterns to stimulate the ^{1}H protons within the body. As these protons relax, they emit signals that are detected by receiver coils placed over the body, perpendicular to the main magnetic field of the scanner. Signal localization within the body is achieved by applying varying frequency and phase gradients along orthogonal planes. Image contrast is determined by variations in relaxation time (T1, T2, and T2*) of the different atoms that make up the tissues or organs of interest.

Pulse sequences are combinations of different types of RF pulses that result in

different “weighting” toward one type of relaxation versus another (e.g., T1 weighting, T2 weighting). T1-weighted images are the basis of delayed enhancement imaging where contrast between fibrosed tissues with retained gadolinium and normal tissues are highlighted. T2-weighted images are useful for evaluation of tissue edema after a myocardial infarction, myocarditis or certain inflammatory conditions, such as Takayasu arteritis. T2* weighting, though rarely used, is helpful in iron overload conditions such as hemochromatosis or hemosiderosis.

The most common types of pulse sequences used in cardiac MRI are as follows:

- Spin echo or “black blood” images. These pulse sequences are designed so that flowing blood produces no signal and appears dark (Fig. 14.1). However, because of the time for the inversion pulses to saturate the signal of flowing blood and the T2 weighting, spin echo pulse sequences usually produce still images. These pulse sequences provide good tissue contrast and anatomic detail, making them useful for visualizing morphology. Myocardium has an intermediate signal intensity on spin echo images, whereas fat and cerebrospinal fluid have high signal intensity (i.e., they appear bright).

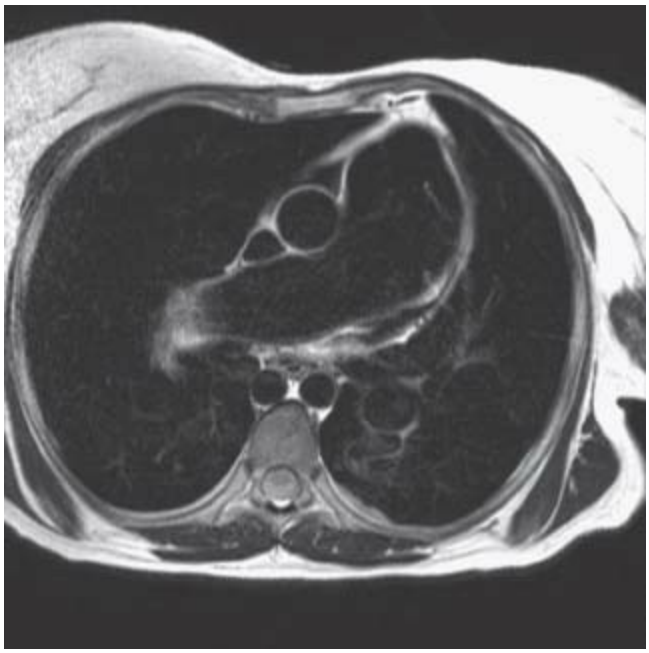


FIGURE 14.1 Axial spin echo image at the level of the pulmonary artery of a patient with an atrial septal defect (ASD) and Eisenmenger syndrome. Moving blood is black, whereas myocardium and fat have an intermediate and high-signal intensity, respectively. Note the prominence of the main and right pulmonary arteries, suggesting pulmonary arterial hypertension.

- Gradient echo or “white blood” images. Gradient echo sequences, including steady-state free precession (SSFP) sequences, are commonly used for cine sequences, as the short repetition times permit acquisition of sufficient data throughout the cardiac cycle with high temporal resolution, at 20 to 50 ms (Fig. 14.2). Flowing blood

appears bright on gradient echo sequences as fresh unsaturated spins of flowing blood have high signal intensities. White blood images are useful for visualizing cardiac function as well as turbulent flow due to valvular disease or intracardiac shunts.

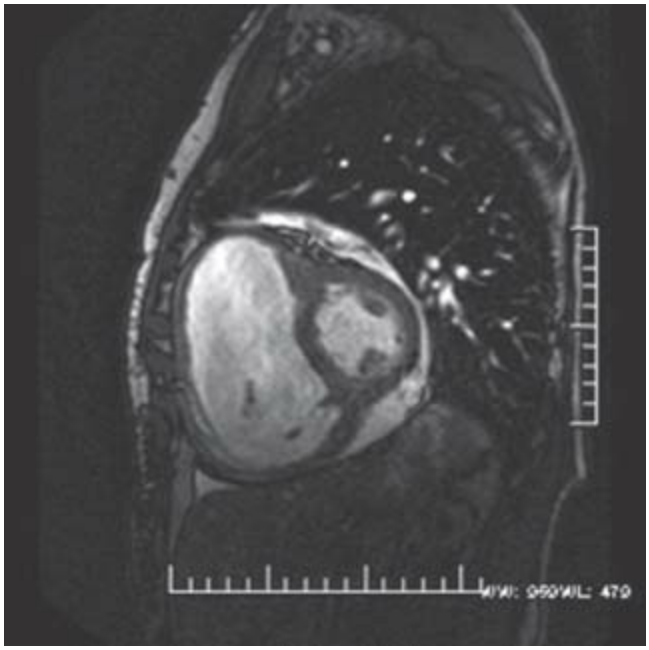


FIGURE 14.2 Still frame from a gradient echo short-axis cine loop of the same patient in Figure 37.1. Note the bright, "white blood" appearance of the blood pool within the left and right ventricular cavities. The RV is severely enlarged and, on cine images, has moderately reduced systolic function. In addition, a small pericardial effusion is present.

- Phase-contrast velocity-encoded imaging. As hydrogen nuclei move through a magnetic field gradient, they acquire a particular phase shift proportional to the velocities at which they are moving through the field gradient. Phase-contrast imaging is analogous to Doppler imaging in echocardiography and is used to quantify both the velocity and flow of blood through an area of interest. Blood flow is quantified by multiplying the cross-sectional area of a particular vessel (e.g., the ascending aorta) and the integral of the velocities in the region of interest. Accurate velocity and flow quantification allows the estimation of gradients across valves, regurgitant volumes, as well as shunt fractions such as Qp/Qs ratios (Fig. 14.3).

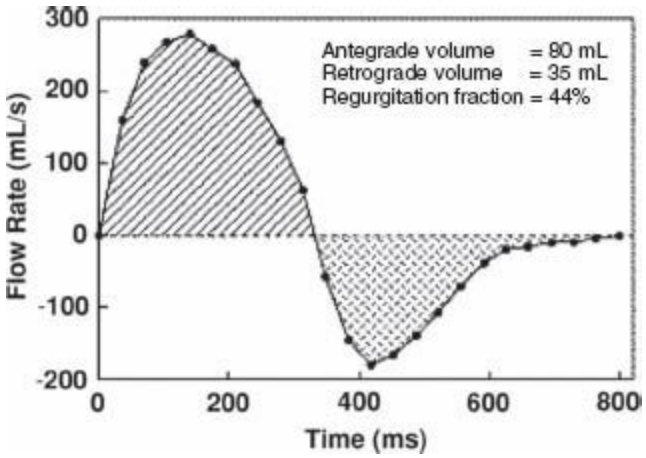


FIGURE 14.3 Flow curve obtained from phase velocity images of the pulmonary artery in a patient with surgically palliated tetralogy of Fallot. Forward and regurgitant volumes as well as regurgitant fractions can be calculated, which in this case suggests moderate pulmonic insufficiency.

- Magnetic resonance angiography (MRA). MRI gadolinium-based contrast (most commonly gadolinium DTPA) is an extracellular agent that influences the magnetic property of adjacent tissue. Contrast shortens the T1 relaxation times and appears bright on T1-weighted sequences. It allows better visualization of the cardiac and extracardiac vasculature. Gadolinium-based contrast agents have the advantage of being nonnephrotoxic and have a very low incidence of adverse events compared with contrast dyes used in x-ray angiography or CT. However, the concern over nephrotoxic systemic fibrosis limits the use of gadolinium based contrast in patients with chronic renal failure.
- Perfusion imaging. First-pass tracking of MRI contrast bolus allows the evaluation of myocardial perfusion. When performed with stress conditions, most commonly with vasodilator stress such as adenosine, but also dobutamine, ischemia and infarction can be assessed, similar to perfusion imaging protocols used in nuclear medicine.
- Delayed enhancement imaging. In areas of scarred or fibrotic myocardium, there is an expansion of interstitial space where gadolinium is retained, after the initial contrast injection. The delayed wash-out of gadolinium makes fibrotic areas appear as bright or "hyperenhanced" when myocardium is imaged 10 to 15 minutes after contrast injection (Fig. 14.4). A special inversion pulse is applied prior to main read-out sequence timed to "null" the signal intensity of normal myocardium, so that the contrast with fibrotic tissues is maximized. Specific patterns of hyperenhancement correspond with certain cardiovascular diseases, as described below.

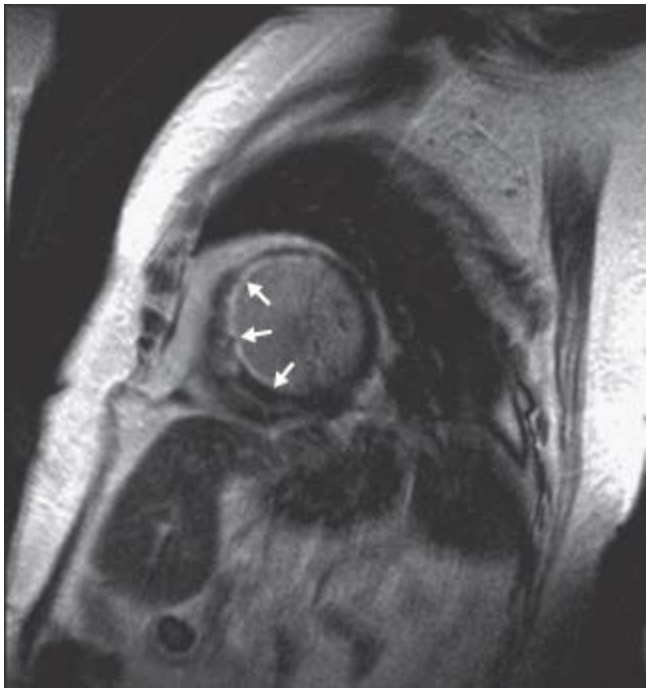


FIGURE 14.4 Delayed hyperenhancement short-axis image acquired 10 minutes after the injection of gadolinium DTPA in a patient with multivessel coronary artery disease. An optimal inversion time (TI) was used in this image to "null" (darken) normal myocardium and accentuate (white) areas where gadolinium has remained in the interstitium on a "delayed basis" (delayed hyperenhancement). Note the hyperenhanced area along the subendocardial anteroseptal wall (white arrow), as well as patchy areas of hyperenhancement in the midinferoseptal and inferolateral walls.

Cardiac MRI imaging is usually performed during periods of 10 to 15 second breath holds to minimize respiratory movement. Cardiac gating with electrocardiography is done using MRI-compatible electrodes, aggregating data from multiple cardiac cycles to generate a single image or a single cine loop. Respiratory gating or triggering can be used in pulse sequences that require data from more cardiac cycles than can be fitted within one breath hold. Free-breathing acquisitions are sometimes used for real-time imaging of the heart when patients are unable to hold their breath, although spatial and temporal resolutions are limited in these acquisitions.

MRI-compatible equipment is used for monitoring patient's blood pressure, heart rate, cardiac rhythm, respiration, and oxygen saturation inside the scanner.

Selected Clinical Applications

Viability Assessment

Delayed hyperenhancement imaging delineates of areas of acute and chronic myocardial infarction. Areas of both acute and chronic myocardial infarction appear bright (hyperenhanced) on delayed images postgadolinium administration. Such areas typically begin at the subendocardium and extend at a variable depth toward the epicardium, depending on the transmurality of the infarction. These hyperenhanced areas occur within a coronary distribution, unlike other causes of hyperenhancement such as

sarcoidosis or myocarditis.

Hyperenhancement in acute infarction is due to disruption of myocardial membranes, which permits the diffusion of contrast agent into the expanded extracellular spaces. Hyperenhancement in chronic infarction is the result of the expanded interstitial space from the collagenous scar tissue allowing contrast to accumulate with slow wash-out, thereby appearing bright on delayed images. Areas of acute infarction appear bright on T2-weighted spin echo images due to local tissue edema, permitting one to differentiate between an acute and chronic infarct.

In patients with coronary artery disease and left ventricular dysfunction, the distinction between viable and nonviable myocardium may be important in determining the strategy of revascularization. Patients with viable myocardium are more likely to have an improved left ventricular ejection fraction and survival after revascularization. The extent of transmural hyperenhancement by cardiac MRI has been shown to predict both improvement in myocardial contractility and survival after coronary revascularization in patients with ischemic cardiomyopathy, and is thus used as a measure of myocardial viability. Myocardial segments with 25% or less transmural hyperenhancement are considered viable, whereas segments with 75% or greater transmural hyperenhancement are considered nonviable. Segments with 25% to 75% of transmural hyperenhancement have an intermediate likelihood of functional recovery after revascularization. The likelihood of functional recovery of these intermediate segments is often determined by the number of adjacent segments with either nonviable (75% to 100% transmural hyperenhancement) or viable (0% to 25% transmural hyperenhancement) myocardium.

Coronary Artery Disease

Visualization of the coronary arteries by MRI is technically challenging because of the small size of the coronary arteries, vessel motion during ventricular systole, and limited acquisition time. Coronary imaging with either MRA or three-dimensional SSFP sequences is a useful tool in the assessment of anomalous origin of the coronary arteries (Fig. 14.5). However, due to the abovementioned limitations, assessment of coronary artery stenosis, smaller caliber vessels, and coronary stent patency remains difficult.

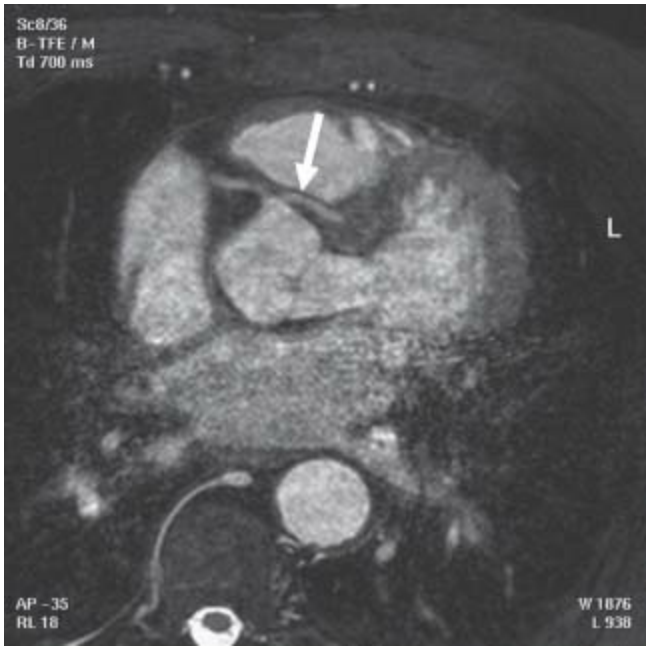


FIGURE 14.5 Gradient echo axial image of an anomalous left coronary artery arising off the right sinus of Valsalva (white arrow) and passing between the pulmonary artery and aorta. The right coronary artery (RCA) arises normally. Note the motion artifact in the lower half of the picture

Heart Failure

MRI is the "gold standard" technique for the evaluation of left and right ventricular volumes, mass, and ejection fraction. Standard gradient echo cine images accurately assess for volumes, systolic function, regional wall motion abnormalities, ventricular aneurysm, and pseudoaneurysm. Other MRI techniques including delayed enhancement and stress perfusion imaging differentiate between ischemic and nonischemic etiologies of heart failure.

Myocardial Disease

Dilated Cardiomyopathy MRI accurately quantifies the degree of ventricular dilatation and ventricular dysfunction in dilated cardiomyopathy. Typically, delayed enhancement images demonstrate either no fibrosis or midmyocardial fibrosis not fitting a coronary artery territory. Resting perfusion sequences are normal.

Hypertrophic Cardiomyopathy Hypertrophic cardiomyopathy is primarily assessed by echocardiography but MRI has definite incremental values because of its superior image quality and ability to demonstrate myocardial fibrosis. MRI excels in characterizing the morphology of the disease and quantifies the degree, extent, and distribution of hypertrophy. The complex relationship between the septal hypertrophy, left ventricular outflow tract, mitral valve leaflets, subvalvular apparatus, and papillary muscles is accurately demonstrated, so that atypical cases of hypertrophic cardiomyopathy with concurrent mitral valve leaflet abnormalities and papillary muscle abnormalities can be

identified. The accurate visualization of anatomical relationships also makes MRI crucial for premyectomy or preablation planning. In addition, MRI may also have a role in screening for preclinical disease because of the sensitivity of the technique.

Myocardial fibrosis demonstrated on delayed hyperenhancement imaging has potential prognostic value. A distinct pattern of midmyocardial hyperenhancement is noted in hypertrophic cardiomyopathy, affecting most commonly the hypertrophied septum, but also right ventricular free wall insertion points into the interventricular septum and other areas. The presence of myocardial hyperenhancement correlates with clinical markers of sudden cardiac death, as well as detection of ventricular arrhythmia on Holter monitoring. Recent longitudinal studies suggest an association between hyperenhancement and sudden cardiac death.

MRI helps in the differential diagnosis of cases that mimic hypertrophic cardiomyopathy such as physiologic hypertrophy of an athlete's heart and hypertensive heart disease. Fabry disease, an X-linked recessive disorder of lysosomal targeting enzymes, accounts for as much as 5% of all cases of presumed hypertrophic cardiomyopathy and can be identified by marked left ventricular hypertrophy and the distinct basal inferolateral delayed hyperenhancement with sparing of the subendocardium. Identification of these patients guides treatment, usually with intravenous α-galactosidase replacement therapy.

Restrictive Cardiomyopathy MRI can help distinguish among various etiologies of restrictive cardiomyopathy, as well as differentiate between restrictive cardiomyopathy and constrictive pericarditis.

- Cardiac amyloidosis. Spin echo and gradient echo images demonstrate increased thickness of the left and right ventricular myocardium, and occasionally of the atrial walls and atrioventricular valves. Systolic function is usually preserved or mildly impaired, although abnormal diastolic relaxation may be evident on myocardial tagging. Delayed hyperenhancement images demonstrate a diffuse enhancement of the left and occasionally right ventricle (RV). Such hyperenhancement may be predominantly subendocardial, but usually the global pattern of myocardial hyperenhancement distinguishes amyloidosis from coronary artery disease. In addition, appropriate nulling of the myocardium with an inversion recovery prepulse on delayed hyperenhancement images may be difficult with amyloidosis due to both the global shortening of T1 relaxation time in the amyloid affected myocardium and the early wash-out of gadolinium, from the bloodstream.
- Cardiac sarcoidosis. Cine gradient echo images may demonstrate normal or impaired left ventricular systolic function, often with regional wall motion abnormalities. The extent and distribution of sarcoid involvement of the heart vary. In the early stages of sarcoidosis, the myocardium may demonstrate patchy high

signal intensity on T2-weighted black blood images as a result of localized inflammation, along with focal patchy areas of hyperenhancement in a noncoronary distribution. Patchy hyperenhancement corresponds to areas of noncaseating granulomas that are the typical histologic findings of sarcoidosis. In more severe cardiac sarcoidosis, areas of hyperenhancement are also seen, along with ventricular wall thinning and aneurysms, most commonly along the basal anteroseptal wall.

- Hemochromatosis. These patients present as dilated cardiomyopathy on cine gradient echo images, with evidence of reduced myocardial contractility on cine-tagged images. Due to tissue iron accumulation leading to local field inhomogeneity, signal loss is seen in both the myocardium and the liver on T2*- weighted spin echo sequences.

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) presents with right ventricular enlargement and/or decreased right ventricular dysfunction. Right ventricular dysfunction can be diffuse in advanced ARVC, or limited to areas of "scalloping" or bulging of the right ventricular free wall with associated akinesis or dyskinesis. Small saccular aneurysms appear as nipple shaped projections off the right ventricular free wall and right ventricular outflow tract (RVOT). Fibrofatty infiltration can be seen on spin echo images as areas of high signal intensities, which suppresses fat-saturation sequences. These areas appear bright on delayed hyperenhancement images.

On the latest task force criteria on ARVC in 2010, cardiac MRI is one of the imaging modalities for documenting global/regional dysfunction/structural alterations (Table 14.2). While fibrofatty replacement of the myocardium is considered a major criterion for the diagnosis of ARVC if detected on biopsy specimens, diagnostic criteria for MRI have not been incorporated into task force recommendations as yet.

TABLE
14.2 Imaging Criteria for Diagnosis of ARVC

Global and/or Regional Dysfunction and Structural Alterations

Major
- By two-dimensional echo:
  - Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole):
    - PLAX RVOT 32 mm (corrected for body size [PLAX/BSA] 19 mm/m²)
    - PSAX RVOT 36 mm (corrected for body size [PSAX/BSA] 21 mm/m²)
    - or fractional area change 33%
- By MRI:
  - Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following:
    - Ratio of RV end-diastolic volume to BSA 110 mL/m² (male) or 100 mL/m² (female)
    - or RV ejection fraction 40%
- By RV angiography:
  - Regional RV akinesia, dyskinesia, or aneurysm

Minor
- By two-dimensional echo:
  - Regional RV akinesia or dyskinesia and 1 of the following (end diastole):
    - PLAX RVOT 29 to <32 mm (corrected for body size [PLAX/BSA] 16 to <19 mm/m²)
    - PSAX RVOT 32 to <36 mm (corrected for body size [PSAX/BSA] 18 to <21 mm/m²)
    - or fractional area change >33%–40%
- By MRI:
  - Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following:
    - Ratio of RV end-diastolic volume to BSA 100 to <110 mL/m² (male) or 90 to <100 mL/m² (female)
    - or RV ejection fraction >40%–45%

From Marcus FI, McKenna WJ, Sherill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation. 2010;121:1533–1541, with permission.

Constrictive Pericarditis

MRI is excellent for both the morphologic and functional assessment of constrictive pericarditis and other pericardial disease. T2-weighted spin echo sequences demonstrate pericardial thickening, as well as the presence of pericardial effusion. The normal pericardium is typically <2 mm in thickness and is often thickest over the right ventricular free wall. In constriction, pericardial thickness is usually >3 to 4 mm. Pericardial calcification is more difficult to demonstrate on MRI compared to CT, because of signal loss on MRI in areas of calcifications. Indirect signs of constriction can be seen in atrial enlargement, systemic and pulmonary vein enlargement.

Functional assessment of pericardial diseases by MRI demonstrates the presence/absence of constrictive physiology, which includes diastolic bounce of the interventricular septum, diastolic restraint, tubular or conical-shaped narrowing of one or both ventricles, and pericardial tethering. These can be seen in standard cine gradient echoes. Myocardial tagging images can also demonstrate pericardial tethering to the adjacent myocardium, rather than the normal free sliding of the myocardium over the pericardium in healthy hearts. In addition, ventricular interdependence can be demonstrated on free-breathing gradient echo cine sequences where the interventricular septum is seen to shift toward the left ventricle during inspiration. The characteristic septal shift is often most prominent on the first heartbeat that follows the beginning of inspiration.

Aortic Disease

Aortic Dissection Using a combination of spin echo, gradient echo, and contrast-enhanced MRA images, the thoracic and abdominal aorta can be evaluated for dissection flaps, location of the true and false lumens, entry and reentry intimal tears, involvement of aortic branch vessels, and associated complications (e.g., pleural effusion, cardiac tamponade, aortic regurgitation).

Compared to transesophageal echocardiography, MRI has a similar sensitivity for detection (98% to 100%) but a superior specificity (98% to 100% compared to 68% to 77%) for the diagnosis of aortic dissection. The sensitivity and specificity of MRI and CT are similar. However, an MRI study of the aorta takes much longer than CT, which makes it better suited for nonemergency imaging (e.g., chronic dissection) or in the follow-up of patients after surgical repair.

Intramural Hematoma Noncommunicating intramural hematomas of the aorta are thought to be a form of aortic dissection without intimal rupture or tear. Clinical presentation is similar to typical aortic dissection. On MRI, it appears as a smooth crescentic or circumferential area of aortic wall thickening without evidence of false lumen blood flow.

Aortic Aneurysm A combination of spin echo, gradient echo, and contrast-enhanced MRA images describe the size, location, and extent of a thoracic or abdominal aortic aneurysm. In addition, presence of thrombus, accompanying dissection, involvement of aortic branch vessels, and growth rate can also be accurately documented. MRA sequences can potentially underestimate the size of the aneurysm if there is significant thrombus formation. Effacement of the sinotubular junction may be seen in aneurysms of the ascending aorta and indicate annuloaortic ectasia, conferring a higher risk of aortic rupture. Mycotic aneurysms of the aorta or its branch vessels can be identified by the typical saccular appearance, as well as increased signal intensity of the aneurysm wall on T2-weighted spin echo sequences due to the presence of localized inflammation.

Limitations of Cardiac MRI

Despite its increasing versatility and robustness, important limitations still remain in cardiac MRI imaging. The electromagnetic forces created by the MRI scanner can induce important thermal and nonthermal effects in some patients. Contraindications to MRI imaging must be identified before the patient enters the scanner (Table 14.3). Nonferromagnetic metallic devices, such as mechanical heart valves, sternal wires, and retained pacing wires after cardiac surgery, are safe to image, although they are often a source of image artifact. Internal orthopedic prostheses (e.g., artificial hip joints) are safe to image.

TABLE

14.3 Contraindications to MRI

Contraindications	Concern
Absolute Contraindications	
Cerebral aneurysm clips	May become displaced by the strong external magnetic field of the scanner, causing severe local injury. Aneurysm clips that are "non-ferromagnetic" or "weakly ferromagnetic" may be safe to image.
Implanted neural stimulator, cochlear implant, implanted insulin, or other drug pump	Most implantable devices employ a strong internal magnet or utilize electronic circuitry that can be damaged by the strong external magnetic field of the scanner.
Cardiac pacemaker or defibrillator	Pacemakers/defibrillators are important contraindications to MRI imaging because of the potential for device malfunction. Small studies suggest that some non–pacer-dependent patients with pacemakers may be imaged, although the devices must be interrogated and potentially reprogrammed before and after imaging. MRI-compatible devices are in development.
Ocular foreign body, metal shrapnel, or bullet fragment	Metallic foreign objects within the body can become displaced by the strong external magnetic field of the scanner, causing severe local tissue injury.
Temporary pacemaker wires	Contain metallic tips that may become heated during MRI imaging, causing local tissue damage.
Relative Contraindications	
Intravascular stents, coils, and filters	Initial concerns that these objects may migrate after early exposure to MRI magnetic fields have been largely unfounded. Coronary stents have been safely imaged as early as several hours after implantation. However, most manufacturers recommend waiting 6 weeks after implantation so that these objects can endothelialized by the vessel wall.
Hearing aids	Same concerns as for cochlear implants; must be removed prior to entering the scanner.
Pregnancy	Considerable evidence suggests that exposure to MRI is safe. However, exposure during the first trimester, particularly to MRI contrast agents, should be avoided.
Claustrophobia	Some claustrophobic patients may have difficulty within the confines of an MRI scanner. Oral anxiolytics (e.g., alprazolam) may be useful in such patients.

Patient cooperation is critical to successful cardiac imaging. Patient movement during image acquisition results in degraded image quality, and anxious or claustrophobic patients may require oral or intravenous sedation. Breath holds of 10 to 15 seconds are used to limit respiratory movement artifact. Children and adult patients who are unable to breath hold can still be imaged, although acquisition times may be increased for signal averages, or spatial resolution is limited on free-breathing sequences. Arrhythmias are problematic due to image degradation and make flow quantification by phase velocity imaging unreliable.

Cost and availability are other limitations to the widespread use of cardiac MRI, although cost will decrease over time. Furthermore, MRI scanners are not portable, and acquisition times of 15 to 60 minutes make imaging of unstable patients difficult.

CARDIAC CT

Technologic advances have revolutionized the use of multidetector CT (MDCT) in cardiac imaging. Improvements in gantry rotation, increased detector rows, image acquisition protocols, and postprocessing algorithms have lead to vastly improved spatial and temporal resolution.

Indications

While there is considerable overlap in many of the clinical indications for cardiac MRI and CT, the techniques differ significantly. CT excels in superior spatial resolution and is the gold standard for assessing coronary artery stenoses and anomalous coronary arteries. Scan time is short and is more suited for emergency imaging. On the other hand, MRI excels in functional assessment with a higher temporal resolution, ability to quantify hemodynamics and characterize tissue, and is therefore more suited in imaging cardiomyopathy.

Technical Considerations

CT Physics

Data acquisition in CT depends on the measurement of transmitted x-rays after they pass through an object. An x-ray source is used to produce a collimated, fan-shaped x-ray beam. As this beam passes through a patient, photons are absorbed or scattered, thereby reducing transmission of x-ray to the detectors on the opposite side. This attenuation of x-ray correlates with the atomic composition and density of the objects through which the photons pass, as well as the energy of the photons themselves. Objects with a high attenuation, such as bone or metal, absorb most of the transmitted photons from the x-ray beam, whereas low-attenuation tissues such as lung allow most of these photons to pass through to the x-ray detectors.

X-ray detectors receive the attenuated signal and digitize the information so that a set of attenuation values can be calculated. From the x-ray measurements made as the x-ray tube rotates around the patient, specific mathematical reconstruction algorithms, most commonly filtered back-projection, generate the image. The raw data are "filtered" or preprocessed to minimize beam hardening and scattered radiation, after which "back-projection" is performed to create a set of axial images with specific density values from the raw data. Newer reconstruction algorithms have been increasingly employed, including iterative reconstruction, where a statistical model is employed to reconstruct the image from the raw data, with a relative insensitivity to noise.

CT densities are expressed as Hounsfield units (HU), which range in value from –1,024 to +3,071 HU. Although this full range of density values could be displayed as a gray scale from black (lowest) to white (highest), the human eye is incapable of distinguishing between small changes in densities within this scale. The image display is therefore adjusted using "window levels" and "widths" to optimize tissue contrast. The window level (or center) indicates the density value in the middle of the displayed gray scale. The window width determines the density values around the window level within the gray-scale display. Objects with a CT density above the window width are

displayed as white; objects below the window width are displayed as black. In effect, the window level determines the tissue types visualized and the window width determines the image contrast.

The density of water is defined as 0 HU. The value of nonenhanced (i.e., no contrast) tissues, such as muscle and blood, range from –100 to +200 HU. Fat tissue has lower density values, whereas bone and calcium have higher density. Contrast-enhanced arterial blood, such as the coronary arteries, has a density level of +200 to +400 HU. For cardiac imaging, the window level is usually set between +250 and +300 HU, with a window width of 600 to 1,000 HU.

Electron-Beam CT

Electron-beam CT (EBCT) scanners, although decreasing in popularity, were the first technique developed to evaluate coronary calcium scoring. EBCT images are generated by scanning an electron beam at four tungsten coils positioned below the patient. Because there is no mechanical motion within the gantry, temporal resolution is excellent (50 to 100 milliseconds). Although they are still used in a limited number of practices, EBCT scanners have largely been replaced by more advanced MDCT imaging.

Multidetector CT

The MDCT scanner is the most common type of CT scanner used today and consists of a rotating assembly of x-ray tube mounted opposite a series of detectors on a gantry around the patient. The x-rays form a "cone beam" flowing from the source on one side to the detectors on the opposite side of the rotating gantry. In most CT imaging, including cardiac imaging, the patient is moved at a fixed speed, or pitch, through a constantly rotating gantry (spiral acquisition). Multiple detector rows allow the acquisition of multiple simultaneous parallel slices per gantry rotation, which occurs at speeds between 300 and 400 milliseconds per rotation. Current MDCT scanners acquire the entire cardiac image during a single breath hold. In spiral acquisitions, electrocardiogram (ECG) gating is done retrospectively, which means that data are collected throughout the entire cardiac cycle, but image is reconstructed only in mid-late diastole, according to the ECG signal. Dose modulation algorithms reduce the x-ray tube current during systole when data are generally not used for image reconstructions.

Newer scanners have the option of acquiring data with prospective ECG gating, where the table moves sequentially through the long-axis of the body and data are acquired within just over half of a complete gantry rotation, triggered by the ECG signal. This acquisition mode minimizes radiation dose. In the new generation scanners, several innovations further improve image acquisition and quality. In the new 320-slice scanner, the axial sequential acquisition mode covers the entire heart in half a gantry rotation. Alternatively, a dual source scanner utilizes two x-ray sources so that data are

acquired within just over one-quarter of a gantry rotation, doubling the temporal resolution, hence minimizing motion artifact.

In cardiac CT, an additional data reconstruction technique known as multisegment reconstruction may be performed. This technique utilizes data from more than one cardiac cycle to construct a clinically useful image. Multisegment reconstruction improves temporal resolution at the cost of an increase in radiation exposure, because sampling occurs during more than one cardiac cycle.

Patient Selection and Preparation

Appropriate patient selection is an important part of maximizing the clinical utility of any diagnostic test. Coronary CT angiography (CTA), the most popular application for cardiac CT, is best suited for patients with an intermediate risk of coronary artery disease. Low-risk patients are better served with other noninvasive tests to avoid unnecessary contrast and radiation exposure. High-risk patients are better served by cardiac catheterization because of a high likelihood of significant coronary calcification that impact usefulness of the technique. In addition, patients with coronary stents or those with ongoing cardiac arrhythmias are not well suited for coronary CTA.

Unlike cardiac MRI, cardiac catheterization, or other imaging modalities, cardiac CT image acquisition cannot be easily repeated, because of radiation dose and limit in contrast administration. Appropriate patient preparation increases patient comfort and maximizes image quality. Each step of the scan should be explained to the patient, and breath holds should be practiced before the actual scan. Heart rate should be slowed to a target heart rate of 50 to 60 beats per minute prior to the scan—typically with oral Atenolol or Metoprolol (50 to 100 mg 1 hour prior to the scan) and intravenous Metoprolol (5 mg IV every 5 minutes up to a maximum dose of 30 mg) as tolerated. Calcium channel blockers can also be used to slow the heart rate in those intolerant of beta-blockers but are less efficacious. Finally, in patients undergoing coronary CTA, sublingual nitroglycerin spray or tablet is given immediately before the scan for coronary vasodilation.

Selected Clinical Applications

Coronary Artery Disease

Coronary CTA visualizes both luminal stenoses as well as wall abnormalities. Images are often interpreted in traditional orthogonal planes (axial, sagittal, and coronal) as well as oblique planes that follow the axis of the coronary arteries. Multiplanar reconstruction, MPR, uses straight or curved thin images from the three-dimensional volume of images to create a two-dimensional representation of a vessel. This technique is useful for following tortuous coronary artery segments and for visualizing an entire vessel simultaneously (Fig. 14.6). Maximum-intensity projection, MIP, selects the

brightest voxel (three-dimensional pixel) from a three-dimensional image stack and displays them in the specified projections, similar to the way angiographic images appear on cardiac catheterization (Fig. 14.7).

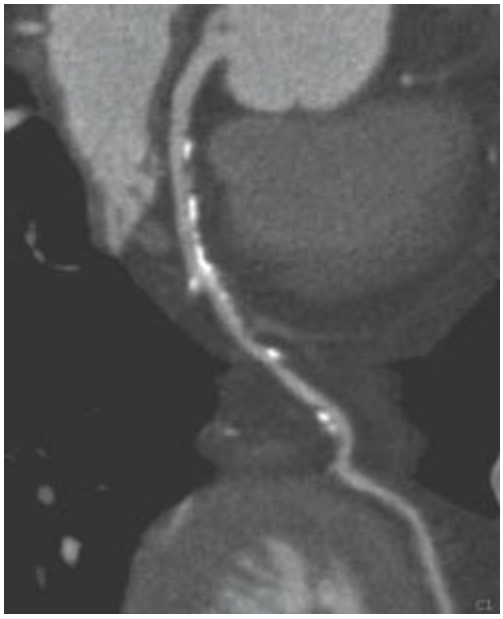


FIGURE 14.6 Multiplanar reformation (MPR) MDCT image of the left anterior descending (LAD) artery. The vessel is viewed from the beginning of the left coronary artery ostium, through the left main, to the distal LAD. The bifurcation of the LCX and diagonal arteries are not shown in this view. Note the calcified and noncalcified plaque in the proximal and midportion of the vessel, causing mild stenosis.

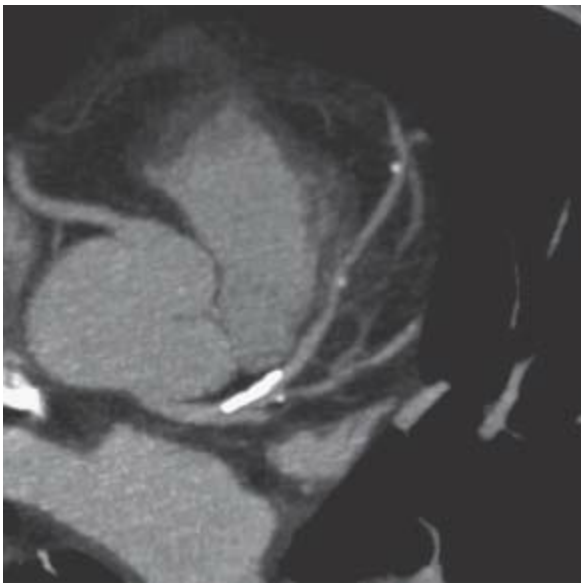


FIGURE 14.7 MIP of an oblique axial MDCT image of the LAD. Note the calcified plaque in the proximal portion of the vessel. It is not possible to accurately quantify the degree of stenosis behind the calcified plaque.

CT identifies coronary artery stenoses caused by calcified or noncalcified plaque. Noncalcified plaques have low to intermediate attenuation and appear as defects in the vessel wall as outlined by contrast. Calcified plaques appear as high attenuation (i.e.,

bright) lesions that are often associated with calcium blooming artifacts. Blooming may give the appearance that the stenosis is more severe than actuality due to attenuation of the x-ray photons by calcium. When vessel or plaque calcification is significant, it is often impossible to quantify the degree of vessel stenosis, as the x-ray attenuation precludes assessment of the full vessel lumen (see Fig. 14.7). Coronary stenoses are classified as mild (<50% diameter stenosis), moderate (50% to 70% stenosis), or severe (>70% stenosis). Spatial resolution of the advanced CT scanners is 0.4 × 0.4 × 0.4 mm or less. In comparison, invasive coronary angiography provides a spatial resolution of <0.2 mm. Despite the limitation of spatial and temporal resolutions, current scanners have >90% sensitivity and specificity for the detection of >70% coronary artery stenosis compared with cardiac catheterization. The negative predictive value of a normal coronary CTA is typically over 98%. Despite recent advances, coronary CTA remains an evolving field with several important limitations. Although contrast within a stent may suggest stent patency, in-stent restenosis cannot be reliably quantified because beam-hardening artifact from the stent material that obscures the vessel lumen. Coronary artery bypass grafts can be evaluated for patency; however, the distal anastomosis is often difficult to visualize due to a combination of small vessel size and artifacts from calcium and surgical clips.

Coronary Calcium Scoring

Coronary artery calcification is a reliable, albeit somewhat limited, sign of coronary atherosclerosis. The prevalence and extent of coronary calcium increases with age in both men and women, although the onset of calcification seems to be delayed by about 10 years in women compared with men. Men tend to have higher calcium scores than women. Individuals of either gender with diabetes or renal insufficiency have increased coronary calcification. Coronary calcium scoring uses noncontrast EBCT or MDCT to quantify coronary calcification. Several algorithms are available. The Agatston score, the most commonly used method, assigns a calcium score based on the maximal HU number and the area of calcium deposits. Only areas of calcification ≥1 mm^2 and >130 HU are included in this algorithm. Other algorithms quantify the volume and/or mass of coronary calcium. Coronary calcium scoring has been used to assess long-term cardiac risk, with incremental value over that of current risk assessment tools. The test is most useful in intermediate-risk populations, in whom a normal or abnormal score may reclassify individuals to a lower or higher risk group, respectively. However, it remains unclear how this score should be incorporated into current treatment pathways and the improvement of overall risk assessment over that of traditional risk factors remains small. Coronary plaque calcification does not correlate well with the degree of histopathologic stenosis, and the typical plaque rupture that leads to acute coronary syndromes does not always occur at the site of calcification. Some centers use calcium scoring prior to coronary CTA in elderly patients; patients with a calcium score >800

are thought to have excessive calcification and coronary CTA is aborted, saving the patient unnecessary contrast and radiation exposure. In addition, CT is widely used in patients undergoing sternotomy for repeat cardiac surgeries as it identifies structures such as coronary bypass grafts or the ascending aorta that may be adherent to the back of the sternum and therefore increase procedural risk.

Pulmonary Vein Assessment

Pulmonary vein isolation is an increasingly common treatment of atrial fibrillation. Cardiac CT is useful in preprocedural planning to delineate the number and location of pulmonary veins, as well as to evaluate for the development of postprocedural pulmonary vein stenosis, a known complication of the procedure. Pulmonary vein stenosis is often detected early as pulmonary vein wall thickening, sometimes with mediastinal lymph node enlargement; at a later stage, luminal narrowing or obstruction is present. Some centers incorporate the preprocedural anatomic data provided by cardiac CT into procedural left atrial electrophysiologic maps.

Aortic Disease

CT is well suited for the evaluation of aortic anatomy and pathology and is the test of choice for acute aortic dissection, transection, intramural hematomas, penetrating ulcers and aneurysmal diseases. Motion artifact of the aorta is uncommon because of its relative immobility, and most studies are adequate using older 16-slice scanners and 3-mm-thick slices. Imaging of the entire thoracic and abdominal aorta can be acquired in a single breath hold. Prospective or retrospective ECG gating can be utilized if anatomy of the aortic root and ascending aorta is important.

Limitations of Cardiac CT

Image Quality

A number of factors influence image quality by cardiac CT. Characteristics related to the MDCT scanner include detector row number and type, detector width, gantry rotation time, and tube output. Tube output varies according to the patient's body habitus (higher output for larger patients) or clinical condition (e.g., lower output for evaluation of prosthetic valve motion). Other factors that affect image quality are determined by the patient or clinical conditions at the time of image acquisition (Table 14.4). Finally, streak artifacts result from metallic objects within the thorax (e.g., bypass graft clips and pacemaker wires) or high contrast concentration in the right atrium or ventricle. The latter can be minimized by the use of a saline flush immediately following contrast bolus injection so that contrast is cleared from the right side of the heart.

TABLE

14.4 Factors Influencing Cardiac CT Image Quality

Factor	Concern
Patient size	Higher degree of x-ray beam attenuation in obese patients causes degraded image quality. Tube output can be increased to compensate, but results in a higher radiation dose exposure.
Patient motion	Failure to hold breath appropriately or patient movement during image acquisition leads to motion artifacts. Breath-hold training and practice prior to the actual image acquisition significantly increases patient cooperation. Inform patients to expect to experience a hot sensation during contrast injection.
Heart rate	Heart rates >70 beats per minute during image acquisition reduces the amount of time spent in diastole (when there is minimal coronary artery motion), resulting in degraded image quality. Oral and intravenous beta-blockade prior to image acquisition should be employed whenever possible.
Cardiac rhythm	Cardiac arrhythmia, premature atrial contractions, or premature ventricular contractions result in degraded image quality as a result of inappropriate ECG triggering.
Coronary calcification	"Blooming artifact" due to coronary calcium obscures the vessel lumen, rendering stenosis quantification unreliable.

Radiation Exposure

Cardiac CT uses ionizing radiation to image the heart and exposes the patient to a predictable amount of radiation depending on the body part and the protocol used (Table 14.5). The effective radiation dose is higher in women and obese patients because of their increased body fat. Radiation dose is also higher in patients with faster heart rates, which negates the effectiveness of dose modulation.

TABLE
14.5 Relative Radiation Exposure due to Medical Procedures

Diagnostic Procedure	Typical Effective Dose (mSv)	Equivalent Period of Natural Background Radiation
Natural background radiation	3–4 (range 1.5–7.5)	1 y
Chest x-ray (PA and lateral)	0.04	6 d
Transatlantic flight	0.03	5 d
Lung ventilation (81 mKR)	0.1	2–4 wk
Lung perfusion study (99m-Tc)	1	4–6 mo
Calcium scoring	0.8–2	3–6 mo
CT head	2	8 mo
Cardiac catheterization (diagnostic)	3–4	1 y
Coronary CTA		
■ Helical retrospective	4–12	1–3 y
■ Axial prospective and newer protocols	1–4	3–12 mo
Myocardial perfusion (201 Tl)	15–18	4–5 y
CT abdomen/pelvis	10–20	3–6 y
Cardiac positron emission tomography (PET)	14–20	4–6 y

"Dose modulation," or ECG-controlled tube current modulation, is a technique that limits radiation exposure while maintaining adequate image quality. The technique of ECG triggering adjusts the scanner tube current so that it is highest during ventricular diastole when cardiacmotion is minimized and imaging is desirable and lowest during systole when cardiac motion impairs image quality. Images acquired during systole are during periods of reduced tube output, resulting in noisier images, but often are

acceptable, as systolic frames are typically used only in reconstruction of cine loops. Dose modulation can reduce the effective radiation dose by 35% to 45% when used appropriately. Dose reduction is best at slower heart rates because of the relative increase in the duration of diastole and overall shorter scan time. The new iterative reconstruction algorithm shows promise in reducing image noise and hence reducing the overall dose needed in order to maintain similar image quality. In general, CT scanning should be avoided in pregnant women because of teratogenicity and potential increase in childhood malignancy. Breastfeeding is a relative contraindication to contrast exposure.

Contrast Exposure

Most cardiac studies currently require between 75 and 100 mL of contrast dye, followed by 30 to 50 mL of a saline flush. Iodinated contrast agents used in CT imaging carry a 2% to 4% risk of contrast allergy and a variable risk of renal dysfunction after contrast exposure. In general, contrast nephropathy risk is negligible in patients with a serum creatinine $\leq$1.8 mg/dL with no predisposing factors to renal dysfunction. Factors that increase contrast nephropathy risk include increasing age, elevated serum creatinine level or a history of renal dysfunction, volume depletion, heart failure, and diabetes. Because of the presence of multiple comorbidities in patients undergoing cardiac CT studies, most centers use low-osmolar nonionic contrast agents. Patients with a history of contrast dye allergy should be premedicated with steroids and diphenhydramine several hours prior to their study.

Gadolinium based contrast agent used in MRI can be substituted for traditional CT contrast agents in those patients with a history of anaphylaxis with iodinated contrast dye. Disadvantages include a reduction in contrast attenuation and the higher cost of gadolinium.

EVALUATION OF CARDIAC MASSES BY CT AND MRI

CT and MR are able to visualize not only cardiac anatomy but also the surrounding mediastinal, pulmonary, and chest wall structures. The wide field of view, coupled with high spatial resolution, make these imaging modalities useful techniques in the evaluation of cardiac and paracardiac masses.

Both benign and, to a lesser extent, malignant masses have various anatomic and tissue characteristics by CT and MR that help to narrow the differential diagnosis of a cardiac mass (Table 14.6). Findings suggestive of malignancy include right ventricular or right atrial involvement, infiltration into surrounding structures (e.g., penetration through the pericardium), irregular borders, pulmonary or mediastinal involvement, and hemopericardium. Findings suggestive of a benign tumor are left-sided involvement along the interatrial septum, smooth borders, and lack of pericardial effusion. Contrast

perfusion through the mass can be used to identify vascular tumors, both benign and malignant, and to differentiate tumors from thrombus.

TABLE
14.6 Evaluation of Cardiac Masses by MRI and CT

Mass	Location	MRI	CT
Myxomas	Left atrial cavity, attached to the interatrial septum at the border of the fossa ovalis (85%); posterior and atrial walls; atrial appendage	Variable composition of water-laden myxomatous tissue, fibrous tissue and calcification T2-W higher signal than myocardium	Calcifications evident
Lipomas	50% subendocardial, 25% subepicardial, 25% wall of cardiac chamber extending intracavitary	T1-W high signal intensity similar to subcutaneous fat; T2-W moderate signal intensity	Density of lipoma is similar to mediastinal fat
Thrombus	Posterolateral wall or left atrial cavity; left atrial appendage; apex of impaired left ventricle	T1-W fresh thrombus has higher signal intensity than myocardium; older thrombus may have increased signal on T1-W with decreased signal intensity on T2-W	Fresh thrombus has lower density, older thrombus may have calcifications
Angiosarcomas	Right sided, especially right atrium; pericardium with hemopericardium	Heterogenous mass with hemorrhagic areas appearing as hyperintense on T1-W	Hypodense nodular mass with inhomogeneous enhancement postcontrast
Rhabdomyomas	Myocardium or ventricles (right = left), large and may obstruct a valve or chamber; multiple sites involved in most cases and atria involved in 30% cases	Indeterminate signal on T1-W; slightly hyperintense on T2-W	Intracavitary low-attenuation mass postcontrast
Fibromas	Myocardium, particularly the anterior free wall and interventricular septum causing conduction abnormalities	Indeterminate signal on T1-W compared to skeletal muscle; lower signal intensity than myocardium on T2-W	Calcified areas of necrosis
Metastases	Nodular deposits or localized or diffuse pericardial thickening with hemorrhagic or serosanguinous pericardial effusion	Nonspecific	Nonspecific
Pericardial cyst	Typically right cardiophrenic angle	Simple fluid characteristics with intermediate signal intensity on T1-W and high signal intensity on T2-W	Well-circumscribed, low-attenuation, nonenhancing mass adjacent to pericardium

T1-W, T1-weighted spin echo images; T2-W, T2-weighted spin echo images.

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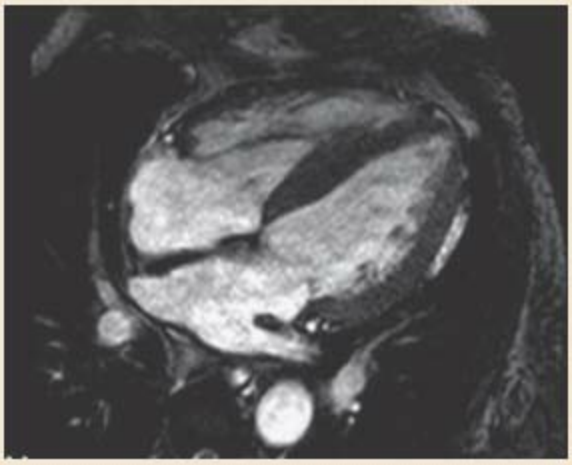
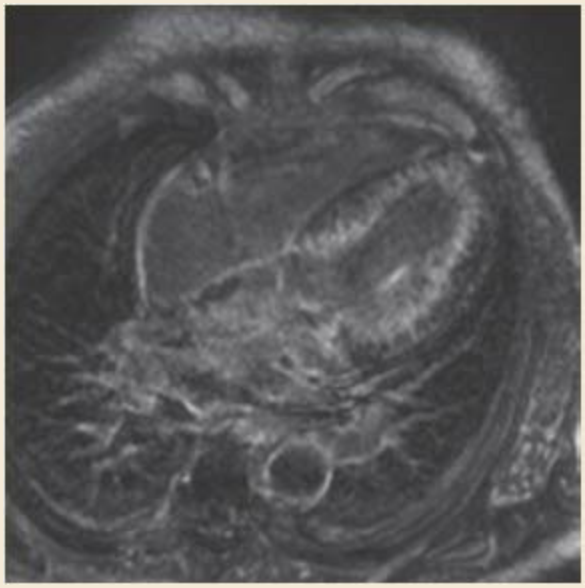
QUESTIONS AND ANSWERS

Questions

1. A 51-year-old man presents to your clinic for evaluation of progressive exertional dyspnea over the last 6 months. On physical examination, his heart rate is 85 beats per minute, his respiratory rate is 22, and his blood pressure is 108/65 mm Hg. His jugular venous pulse is visible 8 cm above the sternal angle at 45 degrees. The Point of Maximal Impulse (PMI) is sustained but normal in location. He has an S4 gallop and 1+ bilateral pedal edema. A PA and lateral chest x-ray are unremarkable. A transthoracic echocardiogram reveals normal left and right ventricular systolic function with mild left ventricular hypertrophy and abnormal diastolic function. A cardiac magnetic resonance imaging (MRI) with gadolinium contrast is obtained.



Still frame gradient echo image, four-chamber view.

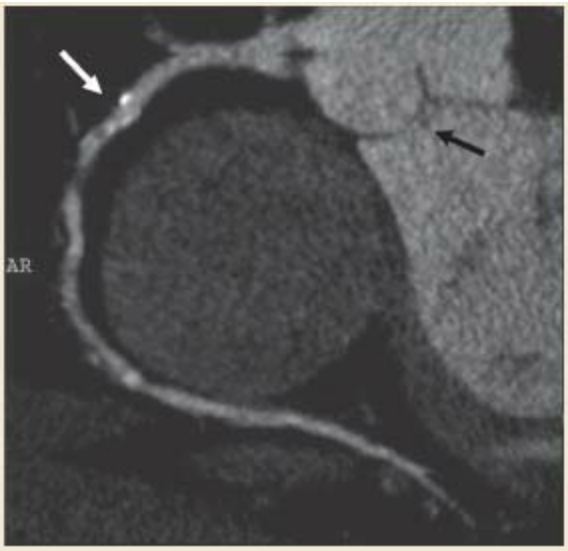


Corresponding delayed hyperenhanced image, four-chamber view.

Based on these images, the next most appropriate clinical step is:

a. Endomyocardial biopsy
b. Fat pad biopsy
c. Initiate corticosteroid therapy
d. Surgical pericardial stripping

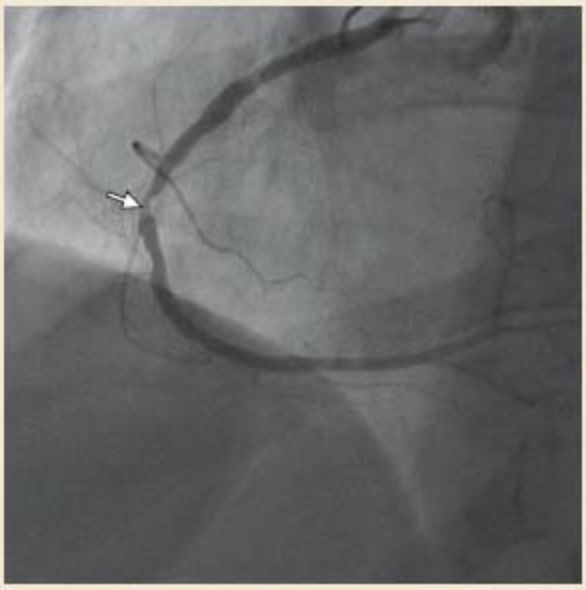
2. You are asked to see a 58-year-old woman in the emergency room who has presented with intermittent retrosternal chest pain without radiation lasting for <1 minute and a single episode of rest pain lasting 10 minutes today. She states she has been having these symptoms since shoveling snow 1 week prior to presentation. Her past medical history is significant for gastroesophageal reflux, for which she takes an over-the-counter H_2 blocker infrequently. She takes no other medications. She was told at a health screening fair a few months ago that her cholesterol levels were high, but she has not seen her family physician about it. Physical examination is unremarkable. Electrocardiogram (ECG) reveals normal sinus rhythm with no ischemic changes. Initial laboratory evaluation, including a portable chest x-ray and cardiac enzymes, are within normal limits. A cardiac CT angiography (CTA) is obtained to further evaluate the etiology of her chest pain.



Curved multiplanar reformatted (MPR) image of the aortic valve (black arrow) and right coronary artery (RCA) (white arrow).

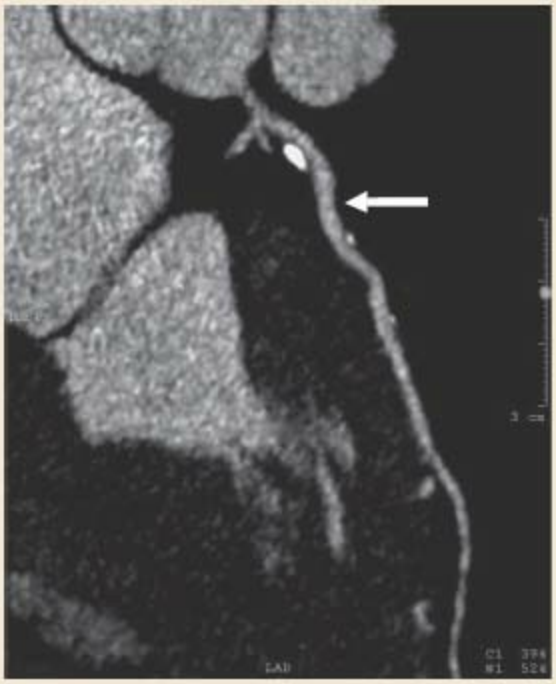
Based on this image, the next most appropriate step is:

a. Begin therapy with an angiotensin-converting enzyme (ACE) inhibitor, beta-blocker, and diuretic.
b. Begin therapy with a proton pump inhibitor.
c. Obtain a transthoracic echocardiogram to evaluate for aortic stenosis.
d. Refer the patient for a nuclear stress study.
e. Refer the patient for cardiac catheterization.



Left anterior oblique cranial projection of the RCA reveals a 60% to 70% stenosis in the midportion of the vessel (white arrow).

3. A 42-year-old man with diabetes and a family history of coronary artery disease undergoes coronary CTA after an equivocal exercise stress test. The following multiplanar reconstruction (MPR) image is obtained of the left main and left anterior descending (LAD) arteries

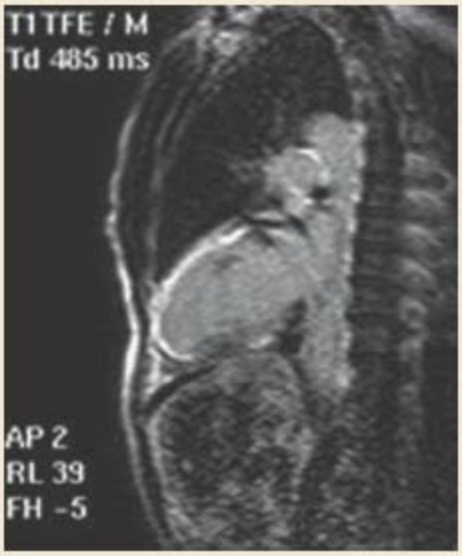


Curved MPR image of the LAD (white arrow).

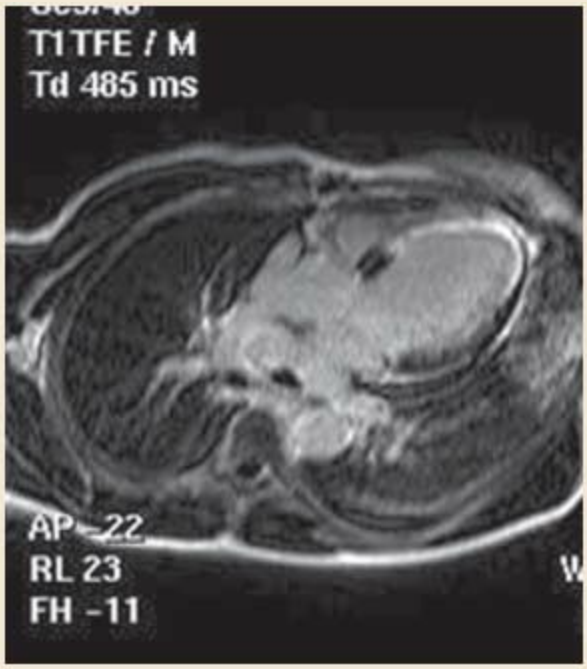
Which of the following statements is true regarding the calcified plaque seen in the proximal LAD in this image?

a. Additional postprocessing should be performed to remove the calcium blooming artifact.
b. Coronary calcification may occur in the presence of atherosclerosis but is a nonspecific finding.
c. Coronary calcification tends to overestimate coronary artery stenosis due to the blooming artifact.
d. The degree of coronary calcification correlates well with the severity of stenosis in the underlying vessel.

4. A 60-year-old man with a history of hypertension and dyslipidemia presents to the hospital in acute pulmonary edema approximately 72 hours after probable onset of an anterior myocardial infarction. The patient is stabilized and a cardiac catheterization is performed, which demonstrates a diffusely calcified 90% lesion of the ostial–proximal LAD that is not amenable to percutaneous intervention. The RCA and left circumflex (LCX) artery demonstrate mild to moderate diffuse disease. A transthoracic echocardiogram demonstrates a left ventricular ejection fraction of approximately 15%. He is referred for coronary artery bypass surgery and a cardiac MRI is obtained to assess for myocardial viability.



Delayed hyperenhanced image obtained 15 to 20 minutes after gadolinium DTPA, two-chamber view.

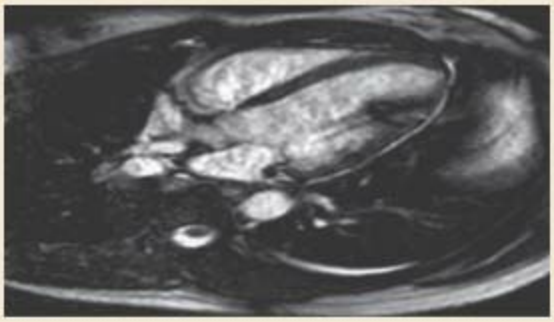


Delayed hyperenhanced image obtained 15 to 20 minutes after gadolinium DTPA, three-chamber view.

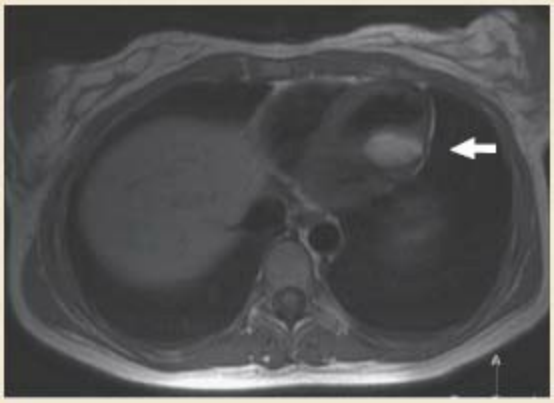
All of the following would be appropriate except:

a. Surgical revascularization of the LAD artery
b. Medical therapy with an ACE inhibitor, beta-blocker, and diuretic
c. Medical therapy with aspirin and a statin
d. Consideration for implantation of a defibrillator

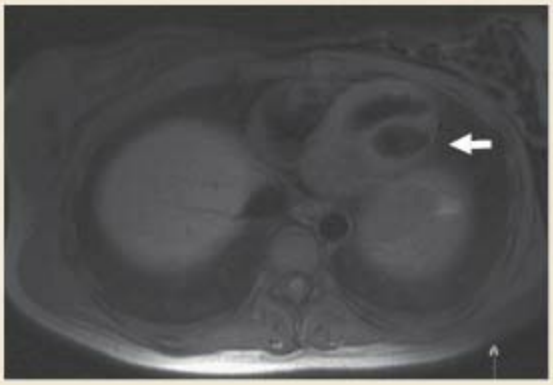
5. A 32-year-old woman is referred to your office for evaluation of occasional palpitations and increasing exertional dyspnea. She denies any history of fever, syncope, or neurologic deficits. Physical examination is unremarkable. A transthoracic echocardiogram demonstrates a poorly defined left ventricular mass, and a cardiac MRI is obtained for further evaluation of the lesion.



Still frame gradient echo image, three-chamber view.



Black blood (turbo spin echo) axial image depicting an intracardiac mass (white arrow).



Corresponding fat saturated black blood (T2-weighted STIR) axial image.

Both echo and MRI demonstrate normal systolic function and no valvular abnormalities. No other lesions are noted on the cardiac MRI study. A computed tomography (CT) scan of the chest, abdomen, and pelvis are otherwise normal. Given the signal characteristics on the above image, this lesion most likely represents:

a. Fibroma
b. Lipoma
c. Myxoma
d. Thrombus
e. Papillary fibroelastoma

6. In which of the following aspects is CT inferior to MRI?
   a. Spatial resolution
   b. Temporal resolution
   c. Typical scan time
   d. Characterization of calcium

e. None of the above

7. In which of the following does MRI not have incremental value over echocardiography in the evaluation of patients with hypertrophic cardiomyopathy?
   a. Quantification of left ventricular septal thickening and left ventricular mass
   b. Quantification of left ventricular outflow tract obstruction
   c. Mitral valve anatomy
   d. Papillary muscle anatomy
   e. Presence of myocardial fibrosis

8. All of the following CT scanning properties are employed to minimize radiation exposure except:
   a. Axial prospective ECG gating
   b. ECG gated tube modulation
   c. Iterative reconstruction
   d. Filtered back projection
   e. Alteration of tube voltage

9. A 77-year-old man with prior mitral valve repair with a C-shaped mitral annuloplasty ring and aortic valve replacement with a stented bovine bioprosthesis is referred for cardiac MRI to investigate for suspected ascending aortic aneurysm. He has a history of prior motor vehicle accident with a total right knee joint replacement, thoracic spinal fixation device. Which of the following is an absolute contraindication for him to undergo MRI?
   a. Mitral annuloplasty ring
   b. Bioprosthetic aortic valve
   c. Prosthetic knee joint
   d. Thoracic spinal fixation device
   e. None of the above

10. Retrospective or prospective ECG gating is commonly used in cardiac CT to freeze cardiac motion. In which of the following clinical indication(s) is/are ECG gating crucial for optimal image quality?
   a. Coronary artery stenosis
   b. Pulmonary vein stenosis
   c. Ascending aortic dissection/hematoma
   d. a and c
   e. a, b, and c

Answers

1. Answer A: Endomyocardial biopsy. Although the mildly thickened ventricular myocardium is consistent with several different etiologies of cardiomyopathy, the diffuse pattern of hyperenhancement throughout the left ventricle on delayed hyperenhanced black blood MRI images (second figure above) is typical of cardiac amyloidosis. Cardiac sarcoidosis, which might be an indication to begin corticosteroid or other immunosuppressive therapy, typically demonstrates patchy areas of hyperenhancement, along with ventricular wall thinning and aneurysms, most commonly along the basal anteroseptal wall. Cine gradient echo images in sarcoidosis may demonstrate normal or impaired left ventricular systolic function, often with regional wall motion abnormalities. Although there may be a role for immunosuppressive therapy in specific subtypes of amyloidosis, histologic diagnosis should be confirmed before therapy is initiated. There is no thickening of the pericardium, conical deformity of the ventricles, or atrial enlargement on these images to suggest constrictive pericarditis, making pericardial stripping inappropriate.

2. Answer E: Refer the patient for cardiac catheterization. The curved MPR image reveals a noncalcified atherosclerotic plaque in the mid-RCA associated with severe luminal stenosis, which can be compared to her corresponding coronary angiogram (see image below). The low attenuation characteristics of this lesion on coronary CTA suggest that it is a noncalcified plaque, unlike the higher-attenuation calcified plaque that occurs more proximally. Current CT technology does not allow precise

quantification of coronary stenoses as is done with invasive angiography. Therefore, most lesions are graded as mild (<50%), moderate (50% to 70%), or severe (>70%) stenoses. There is no evidence of heart failure that would suggest therapy with ACE inhibitors, beta-blockers, and diuretics. The aortic valve leaflets appear thin and noncalcified, making aortic stenosis less likely. Cine CT images of the ventricles and aortic valve could be reconstructed, if desired, to assess ventricular function and leaflet mobility. Additional noninvasive testing is not indicated in this patient because of the abnormalities seen on coronary CTA.

3. Answer C: Coronary calcification tends to overestimate coronary artery stenosis due to blooming artifact. This is due to attenuation (absorption) of the x-ray photons by deposits of calcium, which is relatively dense compared to its surrounding tissues. Currently, this artifact cannot be removed by postprocessing techniques. The presence of coronary calcification does correlate with an individual's overall atherosclerotic disease burden, but it does not predict the severity of stenosis of the underlying vessel. Calcification within an artery is a specific sign of atherosclerosis.

4. Answer A: Surgical revascularization of the LAD artery. Delayed hyperenhancement images demonstrate transmural scarring from the proximal to distal anterior and anteroseptal walls, as well as the apex and inferoapical segments. The transmural extent of hyperenhancement suggests a poor likelihood of recovery of myocardial function after revascularization (whether surgical or percutaneous), consistent with nonviable myocardium. Surgical revascularization would be high risk given his low ejection fraction, and unlikely to improve his long-term survival or ventricular function because of the nonviable myocardium in the infarctrelated territory. The other choices would be indicated given the clinical scenario.

5. Answer B: Lipoma. In the first and second images, an encapsulated mass is visible in the posterolateral wall of the left ventricle. In the third image, the mass has similar signal intensity as the nearby subcutaneous fat, suggesting a possible fatty nature. This is confirmed on the subsequent fat-saturated black blood axial image, in which a special pulse is given prior to acquisition of the image to suppress signal arising from fatty tissue. The mass now appears black due to loss of signal, as does the nearby subcutaneous fat, confirming the fatty nature of the mass.

The fatty content of the mass and the normal left ventricular systolic function are not consistent with a left ventricular thrombus. Papillary fibroelastomas do occur on the endocardium but most often (50%) occur on the aortic valve. They are not usually encapsulated and often demonstrate a "frond-like" appearance (similar to pompoms used by cheerleaders) and frequently have a stalk. Myxomas are most often located in the atria and are not characterized by this degree of fat content. Many myxomas have patchy, dark areas of low signal intensity on MRI because of calcification within the tumor.

6. Answer B: Comparing CT and MRI in cardiac applications, CT has clearly superior spatial resolution and canbe completed usually within one breath hold. MRI, on the other hand, excels in superior temporal resolution and tissue characterization. However, calcium appears in signal void areas on MRI, which makes it difficult to identify. Hence, "temporal resolution" is the correct answer.

7. Answer B: Cardiac MRI is an important adjunctive imaging modality for the evaluation of hypertrophic cardiomyopathy. It accurately quantifies the thickening of the left ventricular septum (a), as well as visualizes the mitral valve (c) and subvalvular anatomy (d) which are not uncommonly associated conditions that require surgical treatment at the time of myectomy. These are sometimes imaged sufficiently on echocardiography, although MRI has the definite advantage of not being limited by imaging planes and window. The presence of myocardial fibrosis (e) is associated with worse prognosis and is not characterized by echocardiography. Quantification of left ventricular outflow tract (b) obstruction, however, is best performed by Doppler echocardiography where real-time imaging and alignment with the left ventricular outflow tract at high temporal resolution enables the technique to obtain the most accurate gradient, which is at present difficult by MRI.

8. Answer D: Radiation dose exposure depends on the tube voltage (e), current, coverage, and pitch. In cardiac imaging, the window when full radiation is applied during the cardiac cycle is also important. Tube current modulation (b) reduces the amount of radiation applied during a portion of the cardiac cycle when data may not be used for reconstruction. Axial prospective ECG gating (a) restricts the tube current and data acquisition to a specified narrow window within the cardiac cycle, hence reducing the

amount of radiation. Iterative reconstruction (c) is a new method of image reconstruction from the raw data obtained, which has reduced image noise hence allowing for a lower tube current for similar image quality. Filtered back projection (d) is the name of the most commonly used image reconstruction algorithm, therefore not a strategy for radiation dose reduction.

9. Answer E: Most prosthetic valves and annuloplasty rings are made of nonferromagnetic materials and can be safely scanned with MRI. While the stented prosthetic valves can give rise to significant susceptibility artifact in some MRI sequences, the effect of annuloplasty rings on image quality tends to be minimal. Most orthopedic devices such as prosthetic hip and knee replacements as well as internal spinal fixation devices are made of titanium or cobalt–chromium alloy and have no significant ferromagnetic properties. While large image artifact from thoracic spinal fixation devices may affect the image interpretation due to artifact, they are usually safe.

10. Answer D: ECG gating freezes cardiac motion and is important for cardiac imaging. The coronary arteries move rapidly during the cardiac cycle, especially the RCA, making cardiac motion artifact problematic in patients with higher heart rate, even when ECG gating is employed. Ascending aortic anatomy is best assessed with ECG gating, especially in cases of suspected aortic dissection or hematoma, where aortic root and ascending aorta motion artifact can sometimes mimic the appearance of intramural hematoma. ECG gating becomes less of an issue when the suspected pathology is in the aortic arch or the descending aorta. Motion of pulmonary veins during the cardiac cycle is relatively less compared because of its location in the base of the heart. While many scanning protocols incorporate ECG gating, pulmonary veins can often be adequately imaged in atrial fibrillation where a nongated spiral scan is employed.

SECTION III ■ CONGESTIVE HEART FAILURE AND CARDIOMYOPATHY

CHAPTER

Pathophysiology of Congestive Heart Failure

Miriam Jacob and W. H. Wilson Tang

DEFINITION OF HEART FAILURE

There are multiple definitions of heart failure, but it is fundamentally a clinical syndrome. Similar to anemia or acute renal failure, heart failure is not a "standalone" diagnosis, but rather always possesses an etiology In some cases, however, the etiology cannot be determined. Virtually any form of heart disease can lead to heart failure. In general, heart failure is defined as a clinical syndrome characterized by shortness of breath and fatigue at rest or with exertion in the presence of underlying structural and/or functional heart disease. In advanced cases, salt and water retention are manifested by edema and organ dysfunction.

DEMOGRAPHICS OF HEART FAILURE

Heart failure is a common condition in the United States affecting more than 5 million people, with an overall self- reported prevalence of 2.4%. The incidence increases with age. At the age of 40, the lifetime risk of developing heart failure is one in five. In those older than 65, 10 per 1,000 people will have heart failure. The most common preceding diagnosis is hypertension (75%). Not only is it common in the general population, but it is also associated with high morbidity and mortality. There has been a 164% increasing hospitalization rate over the past 15 years, now accounting for almost 1 million hospitalizations and approximately 3.5 million outpatient visits, annually Heart failure accounts for about 7% of all deaths due to cardiovascular disease. Those who are diagnosed also have a shorter survival; 50% of those diagnosed with heart failure die in 5 years. In-hospital mortality is as high as 5% to 8% (Roger et al., 2011).

The morbidity associated with heart failure in an individual affects both ambulatory

and inpatient care. The average patient takes six medications. Seventy-eight percent of patients have at least two hospitalizations per year. Up to 30% are readmitted within 90 days of hospitalization (Schrier and Gheorghiade, 2011). In the Medicare population, 18% have heart failure, which translates to 6 billion dollars of Medicare payments. They average one hospitalization per year, with an average stay of 7 days. These patients use outpatient services often, with about 10 physical office visits per year (Schneider et al., 2009). The annual cost attributed to heart failure is approximately $46 billion (Schrier and Gheorghiade, 2011).

THE INDEX EVENT

The event may be obvious, such as a sudden loss of a large mass of contractile tissue (i.e., an acute myocardial infarction), or it may be completely silent, such as the early expression of a mutant gene. In many cases, such as familial cardiomyopathy and the onset of valvular heart disease or hypertension, heart failure occurs after a lengthy latency period, or it may develop acutely, such as from acute aortic insufficiency due to bacterial endocarditis. The index event could take the form of acute lymphocytic myocarditis and manifest as heart failure only many months or years later. There are infinite genetic and environmental influences, which is why the natural history of heart failure and the pace at which it unfolds is so variable among individual patients. Uncertainty about the index event or etiology also makes the prognosis for any individual patient unclear. Given the heterogeneity in the presentation of heart failure, the description includes the stage of heart failure from being at risk (stage A), asymptomatic with structural heart disease (stage B), symptomatic heart failure (stage C), and those with refractory heart failure (stage D) (Fig. 15.1; Hunt et al., 2009).

Identifying the underlying etiology of the heart failure is an important part of the evaluation as it may directly impact long-term prognosis. Common etiologies include:

- Hypertension
- Myocardial ischemia/infarction
- Genetic (familial or hereditary)
- Diabetes mellitus
- Myocarditis (infectious, giant cell)
- Infiltrative or restrictive (hemochromatosis, amyloidosis, sarcoidosis, Fabry disease)

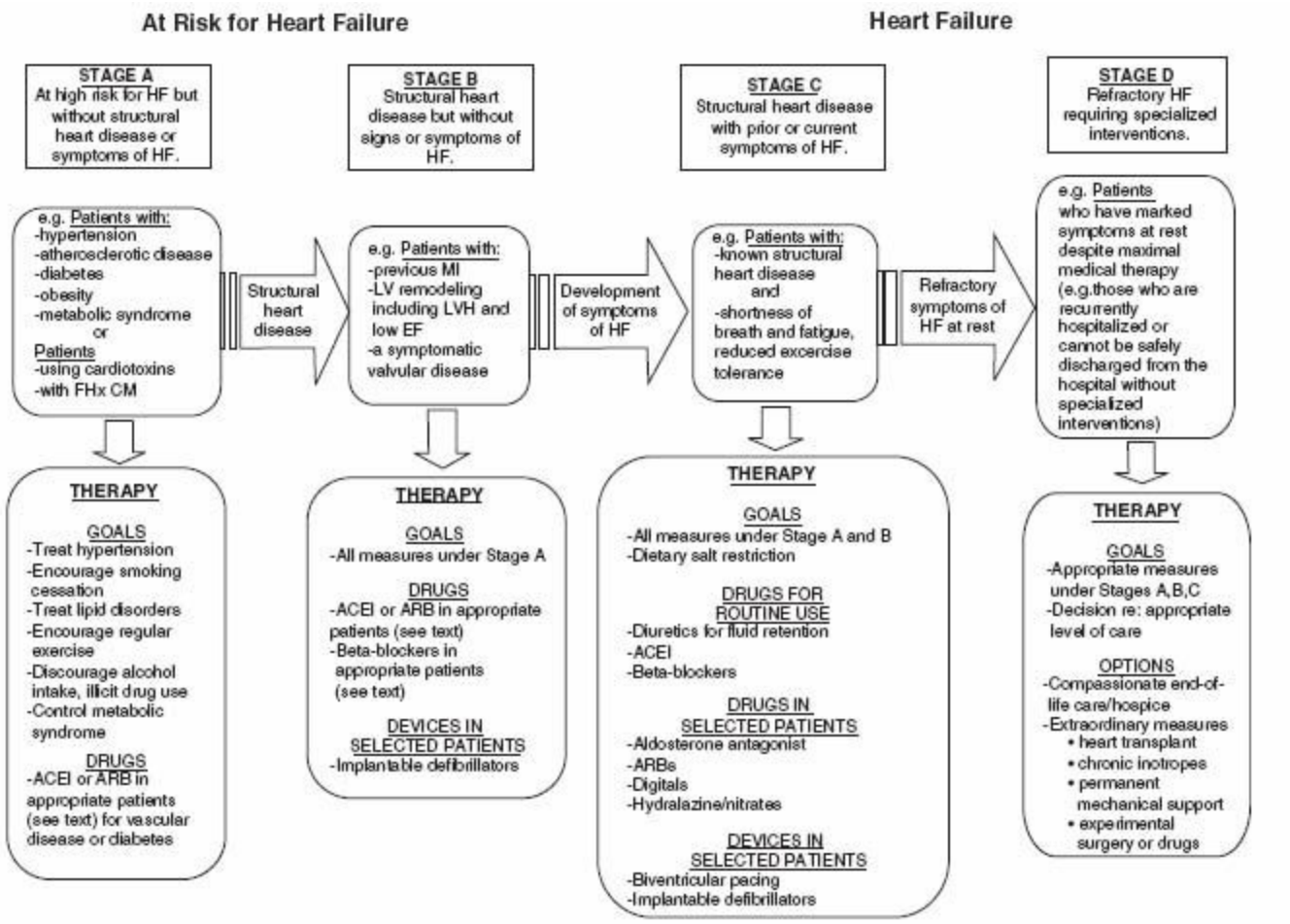


FIGURE 15.1 Stages in the development of heart failure/recommended therapy by stage. (Redrawn from Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration with the International Society for Heart and Lung Transplantation. J Am Coll Cardiol. 2009;53(15):e1-e90, with permission from Elsevier.)

- Substance use (alcohol, ephedra, cocaine)
- Peripartum cardiomyopathy
- Connective tissue disease
- Doxorubicin and other chemotherapy-induced cardiotoxicity
- Infectious—Chagas, HIV Echovirus, Coxsackie
- Valvular heart disease
- Other miscellaneous pathologies (e.g., pericardial disease)

ADAPTIVE RESPONSES TO THE HEART FAILURE SYNDROME

The circulation adapts to a perceived disruption in homeostasis with both short-term and long-term adaptations. Shortterm adaptations include activation of the Frank-

Starling mechanism and activation of the sympathetic nervous system (SNS). Long-term adaptations include heightened and alterations in the size and the shape of the heart (the so-called left ventricular [LV] remodeling). Although these adaptations may be somewhat protective in the short-term, over time they become counterproductive and contribute importantly to the pathogenesis of heart failure.

The Frank-Starling mechanism acts to increase the force of heart muscle contraction in response to an increase in end-diastolic volume (Fig. 15.2). In heart failure, however, this response is blunted, both at rest and during exercise. The force-frequency response is also attenuated in the failing heart, secondary to decreased norepinephrine (NE) stores and **β**-receptor density, which produces a decreased inotropic response to exercise so that less contractile force is generated in response to an increase in heart rate. Patients with heart failure can still call on the Frank-Starling mechanism, albeit at a reduced operational level. The inability to raise the stroke volume during exercise may be one of many reasons why patients have reduced exercise

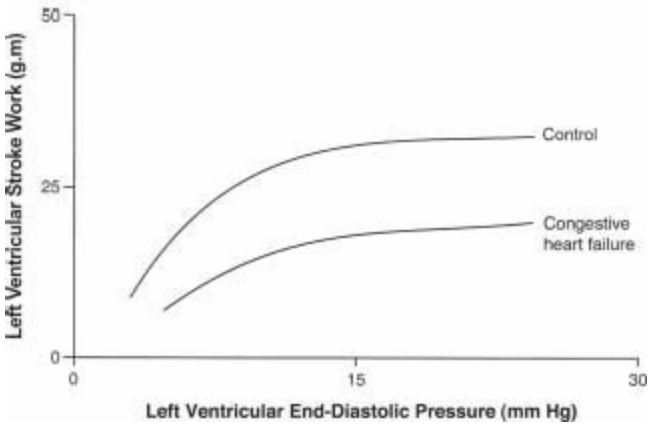


FIGURE 15.2 Heart failure is characterized by a diminished ability to increase the cardiac output or cardiac work in response to an increase in preload-Starlings law of the heart.

AUTONOMIC NERVOUS SYSTEM DYSFUNCTION

The SNS is activated early in the syndrome of heart failure, before overt signs and symptoms occur. Elevated plasma NE levels are observed and are an important marker of a poor prognosis. The mechanism that activates the SNS in heart failure is unknown. Increased local levels of synaptic NE in the heart increase the force of contraction and heart rate, offering early support for the failing heart. But this may also be the source of dysrhythmias and likely is responsible for the downregulation of β-adrenergic receptors. The failing heart tissue is itself also relatively depleted of NE, thus rendering the heart less responsive to sympathetic stimulation. There is less myocardial reserve in response to inotropic stimulation. The SNS also drives some of the increase in myocyte size, thus contributing to the LV remodeling process. Finally, the SNS activates the RAAS via β-receptors in the kidney, adding further to heightened peripheral resistance,

salt, and water retention, and LV remodeling. In summary, early activation of the SNS in heart failure is "protective" by increasing heart rate, force of contraction, myocardial mass, and by protecting blood pressure, but there is a price to pay in the long run. Ultimately, excessive SNS activity is directly toxic to the heart and contributes importantly to the pathogenesis of heart failure.

Reflex control mechanisms are abnormal in heart failure (Fig. 15.3). Peripheral vascular resistance is increased, and there is defective parasympathetic control, an abnormal response to orthostasis, a blunted heart rate response to exercise and to pharmacologic vasodilation, impaired heart rate recovery from exercise, reduced heart-rate variability, and altered baroreceptor function. These abnormalities may improve following heart transplantation, suggesting that these are functional and not structural changes. They are rarely normalized. The precise cause of these abnormal reflex control mechanisms is not clear, but they may be the result of evolutionary forces that are acting to redistribute blood flow to more vital organs.

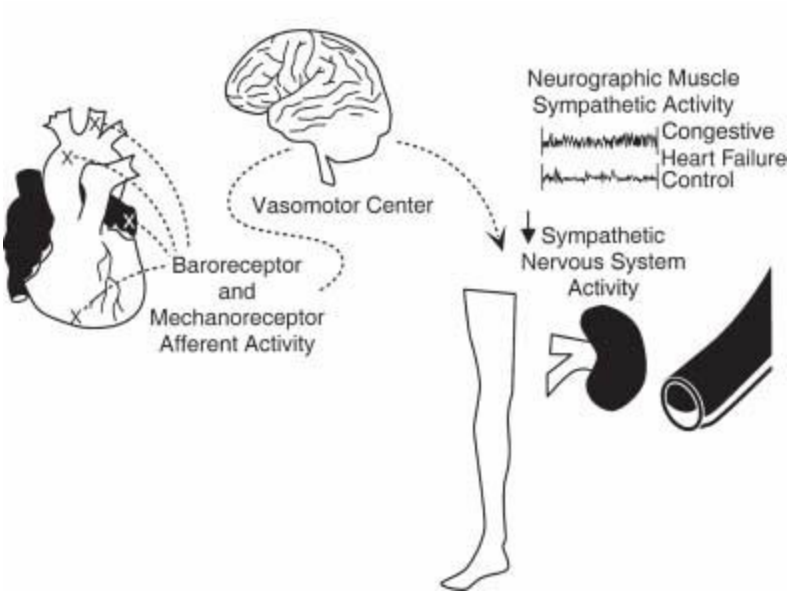


FIGURE 15.3 Baroreceptor and mechanoreceptor activation occurs when the heart is distended due to volume overload. This signal is processed by the brain and, in the setting of heart failure, fails to reduce sympathetic activity (the normal response). The result is enhanced sympathetic traffic to the periphery, vasoconstriction, and reduced renal blood

RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM

The RAAS is active in the circulation and in the tissue in heart failure. Probably 90% of the activity of the RAAS is embedded in the various tissues, including the heart, brain, and vasculature. This system, in conjunction with the SNS, plays a key role in the pathogenesis of the syndrome.

The RAAS is known to be activated by numerous mechanisms:

- Volume contraction
- Low cardiac output
- Decreased renal blood flow
- Hyponatremicperfusate to the macula densa
- β-Adrenergic stimulation to the kidney
- Diuretics
- Salt and water restriction

Angiotensin-II (Ang II) is a small, potent peptide produced by the cleavage of Ang-I by angiotensin-converting enzyme (ACE). Ang-II has a vast array of biologic activities, most of which contribute importantly to the pathogenesis of heart failure:

- Vasoconstriction
- Vascular and cardiac myocyte growth, hypertrophy
- Activation of fibroblasts with increased collagen production
- Facilitation of NE release
- Stimulation of aldosterone release
- Volume expansion
- Thirst stimulation
- Arginine vasopressin release
- Proinflammatory activity
- Direct toxicity to the myocardium when present in excessive quantities
- Mesangial hypertrophy in the kidney
- Increased intraglomerular hydraulic pressure via postglomerular efferent arteriole vasoconstriction

COUNTERREGULATORY SYSTEMS (NATRIURETIC PEPTIDES)

B-type natriuretic peptide (BNP) is released from the myocardium during heart failure in response to increased myocardial wall tension. It circulates in quantities relative to the severity of heart failure, and is widely used as a marker for the diagnosis and severity of heart failure. The biologically active moiety, BNP, is a modest vasodilator with some diuretic and natriuretic properties. It also has antigrowth activity and reduces collagen synthesis in vitro. BNP also tends to offset activity of the SNS and the RAAS. This endogenous counterregulatory peptide is not able to stem the tide of forces that drive the progression of severe heart failure, as very high levels of plasma BNP and NT-pro-BNP are observed in patients with acute decompensation. It is possible, however, that the release of BNP in the early stages of heart failure may forestall the

onset of more severe signs and symptoms particularly with its natriuretic effects and may be more counterregulatory toward the SNS and RAAS.

BIOMARKERS IN HEART FAILURE

In search of insight into heart failure physiology at the bedside, there are many research-based and clinically available biomarkers that have been studied in heart failure including markers of inflammation, oxidative stress, myocardial injury, myocardial stress, extracellular matrix remodeling, and neurohormones. For example, natriuretic peptides have been found to correlate with changes in ventricular volume and pressure load, while at more advanced stages correlated with renal impairment and overall congestion. Both atrial natriuretic peptide (ANP) and BNP are produced from the ventricles in response to increase volume and/or pressure, which can predict both short-term and long-term outcomes in chronic heart failure patients, including rehospitalization and mortality. It has been shown to predict all-cause mortality in patients with no evidence of LV systolic dysfunction. With treatment, BNP decreases in acute heart failure. Both the biologically active BNP and the N-terminal fragment (NT-proBNP) can be measured in the blood (Wright and Struthers, 2006).

NE has also been shown to be a biomarker of heart failure outcomes although not as powerful a predictor as BNP and possessing much more heterogeneity. With activation of the SNS, NE is thought to be a marker as well as being directly toxic to myocytes. Over time, an increase in BNP or NE is associated with increased mortality (Anand et al. 2003).

Hyponatremia (serum sodium < 135 mEq/L) is associated with poor prognosis in many medical conditions. Worsening hyponatremia goes along with worsening systolic function, decreased glomerular filtration rate (GFR), and Arginine vasopressin (AVP) dysregulation. About 25% of patients with heart failure have hyponatremia, which is caused by neurohormonal dysregulation and diuretics (especially thiazides). Hyponatremia is associated with increased mortality at 30 days and at 1 year. Persistent hyponatremia is most morbid with increased heart failure hospitalizations and increased mortality as compared to treated hyponatremia or patients with normal serum sodium (Jao and Chiong, 2010).

As in acute coronary syndrome and some chronic diseases (like chronic renal failure), increased cardiac troponin is associated with worse prognosis. Cardiac troponin (either T or I) in various studies is elevated in 10% to 50% of chronic heart failure and 6% to 84% of acute heart failure patients. The possible mechanisms linking elevated troponin to worsening heart failure include increased wall stress, subendocardial ischemia, inflammatory cytokines, oxidative stress, altered calcium handling, and neurohormonal activation. Even with adjustment for BNP, increased troponin T or I is associated with worsening mortality with a hazard ratio from 2 to 5. In

acute heart failure, as with hyponatremia, persistent troponin elevation is associated with a worse prognosis (Kociol et al., 2010).

INFLAMMATION AND OXIDATIVE STRESS

Inflammation has been implicated in the pathogenesis and progression of heart failure for many years. C-reactive protein (CRP) and proinflammatory cytokines (TNF-α, IL-1, IL-6, and IL-18) have been associated with worse outcomes. IL-6 has been associated with a hypertrophic response, while TNF-α (through activation of matrix metalloproteinases [MMPs]) is associated with ventricular dilation.

Oxidative stress results in an imbalance of reactive oxygen species and reactive nitrogen species, which exacerbates myocardial damage in heart failure. One must measure indirectly the effect of oxidative stress through oxidized low-density lipoprotein (LDL), myeloperoxidase (MPO), and urinary biopyrrins.

MPO is associated with endothelial dysfunction and seems to contribute to LV remodeling. Higher levels of MPO are seen in chronic heart failure and higher levels are seen with increasing severity of New York Heart Association (NYHA) class and predict increased mortality from heart failure. Several newer inflammatory markers have promising prognostic data, but all of these markers await validation of clinical studies and how to best link them to treatment strategies.

RENAL RETENTION OF SALT AND WATER

A hallmark of advanced heart failure is retention of salt and water. This leads to the well-recognized signs and symptoms of tissue congestion such as pulmonary edema, ascites, and leg edema. The mechanism of salt and water retention early in the natural history of heart failure is still not well understood and may be a result of underlying defect at the level of tubular function or response to salt and volume load. In the later stages, reduction in renal blood flow undoubtedly contributes to the problem. The kidney somehow perceives a reduction in effective circulating volume, and unleashes a host of mechanisms, including activation of the RAAS, to conserve and expand circulating volume. GFR is protected early in heart failure by vasoconstriction of the efferent glo- merular arterioles. This is due to Ang-II, which also stimulates the release of aldosterone from the adrenal cortex and contributes to sodium reabsorption and water retention. Eventually, this adaptation wanes, intraglomerular hydraulic pressure falls, and GFR is reduced. The development of renal insufficiency heralds the onset of a dwindling prognosis. Salt and water retention are further aggravated by intense activation of the SNS, causing edema and congestion. Increased release of arginine vasopressin diminishes free water clearance, leading to hyponatremia and more vasoconstriction. Eventually, the “goal” of volume expansion is met, but at the expense

of circulatory and tissue congestion. Circulatory homeostasis is not achieved.

LEFT VENTRICULAR REMODELING

Another hallmark of heart failure is that the heart gradually changes size and shape as the syndrome progresses. LV mass increases, cells drop out, myocytes slip away from each other, collagen increases, the heart becomes more stiff, the myocytes become larger and elongate, the chamber dimension increases, wall tension increases adding to reduced performance (the law of Laplace), and the heart simply becomes less efficient over time. The failing heart is exquisitely sensitive to higher afterload (Fig. 15.4), consistent with the notion that the dilated heart performs more poorly. In a sense, these changes define heart failure at the organ level. The remodeling process is due to a confluence of forces, including perverse loading conditions and unrelenting activity of various neurohormones. As the heart hypertrophies, capillary density is reduced, leading to a form of "energy starvation" from oxygen deprivation. High-energy phosphate use is altered. Eventually, myocardial contractility is reduced. The following processes, currently under intense study, contribute to the remodeling of the heart:

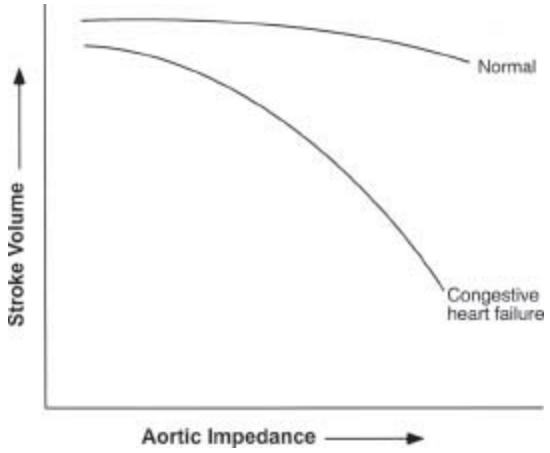


FIGURE 15.4 The failing heart is exquisitely sensitive to afterload. As impedance to ejection increases (increased vascular resistance, increased wall tension, etc.), the performance of the left ventricle diminishes proportionately. On the contrary, acute vasodilation with nitroprusside leads to a marked increase in cardiac output

- Increased myocardial mass (hypertrophy)
- Increased myocyte size (elongation and increased width)
- Cellular necrosis and apoptosis (cell dropout)
- Collagen deposition (reactive and replacement)
- Myocyte slippage (increased MMPs, decreased tissue inhibitors of MMPs or tissue inhibitors of metalloproteinases [TIMPs])
- Chamber enlargement

- Increased wall tension
- Decreased myocardial performance
- Impaired filling due to increased muscle and chamber stiffness
- Reversion to the "fetal genetic program" (enhanced BNP synthesis, progrowth)
- Activation of neurohormones
- Increased synthesis and release of counterregulatory hormones (i.e., BNP)

ABNORMAL CELLULAR MECHANISMS

Important changes occur at the cellular level in the setting of heart failure. These abnormalities undoubtedly contribute to reduced contractility, as they are imbedded in the contractile units, that is, the sarcomere and the myocyte itself. Many of these abnormalities have been observed in vitro, in the laboratory setting only, but some have been derived from failing human hearts extirpated at the time of heart transplantation. It is not entirely clear whether these molecular abnormalities are primary features that contribute quantitatively to the failing heart or whether they are secondary or the so-called epiphenomena that occur as a consequence or a result of the heart failure syndrome. Nevertheless, it is important to consider them:

- Decreased β-receptor density in the heart
- Increased G_i coupling protein in the heart
- **α-** to β-myosin heavy-chain transition (decreased myosin ATPase enzyme velocity) in the myocytes
- Defect in sarcolemma calcium uptake
- Defect in calcium-ATPase (SERCA) and phospholamban (Ca^{2+} exchange)
- Abnormal contractile proteins

These changes, observed at the molecular level, likely contribute to reduced inotropy and may serve as a substrate for rhythm disturbances. They may be a vestige of evolutionary forces that initially allow the heart to operate in a more economical manner in the face of excessive inotropic stimulation. Over time, these "adaptations" contribute to impaired organ function.

PERIPHERAL VASCULAR AND SKELETAL MUSCLE ADAPTATIONS IN HEART FAILURE

Profound changes occur in the periphery in the setting of heart failure, and these likely are responsible for the impaired exercise tolerance and fatigue that commonly plagues patients. In addition to exercise intolerance, sleep disturbances occur, often in the form

of obstructive and central sleep apnea. Blood flow is redistributed to the brain and skeletal muscles, away from the kidneys and the splanchnic beds. Abnormalities in reflex control underlie these changes. Skeletal muscles begin to atrophy, which contributes to fatigue. The causes of exercise intolerance are multiple and complex. On the cellular level, there is endothelial dysfunction with decreased nitric oxide in the periphery and decreased β-adrenergic myocardial receptor density. The skeletal myocyte switched from slow- to fast-twitch fiber with reduced mitochondrial size and enzymes and muscle atrophy. From the standpoint of cardiac physiology, there is chronotropic incompetence, reduced lung compliance, inability to increase stroke volume in response to exercise, and overall deconditioning.

PROGNOSIS

It is important to identify where an individual patient is situated in the natural history of heart failure, providing needed optimism for those in the early stages while allowing for advanced directives for patients in the end stages. However, data regarding prognosis are nearly always derived retrospectively from large databases and represent group data that may not apply to an individual patient. For example, a low "ejection fraction (EF)" is not a powerful risk factor in a group of patients with advanced disease, since the degree of compensation may influence the pace of disease progression. Physicians need to keep this in mind when interacting with patients and their families, who frequently ask about prognosis. Clearly, the overall prognosis has improved for heart failure over the past decades with many new and effective treatments. Nonetheless, heart failure is usually not "cured," but it can be managed as a chronic condition. Many prognostic factors associate with a poor prognosis, including those shown in Table 15.1.

TABLE
15.1 Prognostic Factors Associated with a Poor Prognosis of Congestive Heart Failure

Myocardial Factors	Symptoms/Signs	End-Organ Dysfunction
LV ejection fraction	Low peak VO_2 and/or high V_E/VCO_2	Acute/chronic kidney disease
LV dimensions	Increased NYHA class	Anemia
Right ventricular function	Ascites and elevated jugular venous distention	Depression
Elevated BNP	Pulmonary edema	Hyponatremia
Symptomatic VT	Cheyne–Stokes respiration	Pulmonary disease
Wide QRS	Syncope	Liver dysfunction
High NE	Cardiac cachexia	
Abnormal hemodynamics		

Several risk scores have been developed to stratify those at risk for heart failure and the survival with known heart failure. The Heart Failure Survival Score (HFSS) studied patients with severe heart failure and/or those being evaluated for cardiac transplant. It

sought to identify those with poor event-free survival including more than just the peak maximum oxygen capacity (peak VO_2). The score predicts event-free survival at 1 year—low risk approximately 93% and high risk 43%. The noninvasive HFSS model includes ischemic etiology, resting heart rate, EF, QRS ≥ 0.12 second (due to any cause), resting mean blood pressure, peak VO_2, and serum sodium. The invasive model includes the pulmonary capillary wedge pressure. More recently, the Seattle Heart Failure Model was developed to estimate 1-, 2-, and 5-year survival with heart failure. The model was derived and validated in patients with various grades of HF (NYHA class I to IV). This model adds the effect of medications and devices. The independent predictors are NYHA class, ischemic etiology, diuretic dose, EF, systolic blood pressure, serum sodium, hemoglobin, percent lymphocytes, uric acid, and cholesterol (Table 15.2). This complex model is available for free online.

TABLE
15.2 Heart Failure Risk Scores

	Heart Failure Survival Score	Seattle Heart Failure Model
Characteristics of HF	NYHA class Ischemic etiology LV ejection fraction	NYHA class Ischemic etiology
Vitals	Resting heart rate Resting mean blood pressure	Systolic blood pressure
EKG	QRS ≥ 0.12 s	
Laboratories	Serum sodium	Serum sodium Hemoglobin Lymphocytes (%) Uric acid Total cholesterol
Medications		Diuretic dose
Stress test	Peak VO_2	
Invasive hemodynamics	Pulmonary capillary wedge pressure[a]	

NYHA, New York Heart Association; LV left ventricular;VO_2, oxygen consumption. "Only in the invasive model of HFSS.

SUMMARY

Heart failure is a complex syndrome, and its pathophysiology is inherently complex. Nevertheless, there are some unifying features. There are signs and symptoms of dyspnea, fatigue, and sometimes tissue congestion. There are underlying structural and/or functional abnormalities of the heart. The heart "adapts" to an index event to maintain circulatory homeostasis in the short term, but over the long term, there is further progression of heart failure, in part driven by these "adaptive" mechanisms. The heart enlarges, becomes more globular, and more inefficient. Excitation contraction becomes abnormal. Rhythm disturbances occur. LV performance diminishes, and often mitral and tricuspid insufficiency occurs. Exercise tolerance is diminished, salt and volume are retained, renal function deteriorates, and signs and symptoms worsen. We

now have a much better understanding of how these events unfold, and treatment has improved markedly. However, the natural history of heart failure is highly variable in individual patients, making prognosis difficult to determine.

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QUESTIONS AND ANSWERS

Questions

1. Which of the following statements about heart failure is true?
   a. It is a clinical syndrome.
   b. It can be caused by any form of heart disease.
   c. It is diagnosed primarily by history and physical exam.
   d. All of the statements are true.

2. The principal features of heart failure include all of the following except:
   a. Activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS)
   b. Left ventricular (LV) remodeling
   c. The ability to mount a reflex tachycardia
   d. Downregulation of β-adrenergic receptors

3. The inability to exercise properly in heart failure is due to all of the following except:
   a. Reduced ejection fraction (EF)
   b. Skeletal muscle atrophy
   c. Endothelial dysfunction in peripheral vessels
   d. Inability to increase stroke volume and heart rate

4. Which of the following statements about the prognosis for heart failure is true? (Select the best answer.)
   a. It is fairly easy to predict in individual patients.
   b. It is commonly assessed by measuring peak VO_2 during exercise.
   c. It is closely coupled to EF in individual patients.
   d. It is commonly estimated by measuring neurohormones.

5. Which of the following characterizes heart failure?
   a. Downregulation of β_1- and β.-receptors
   b. Downregulation primarily of β-receptors, with little change in β-receptors
   c. Downregulation of G proteins and β_1- and β_2- receptors
   d. Increase in myocardial norepinephrine (NE) stores
   e. Intact baroreceptor function

6. All of the following neurohormones are associated with vasoconstriction, cell growth, hypertrophy, and sodium retention except:
   a. Angiotensin-II (Ang-II)
   b. Norepinephrine
   c. Brain natriuretic peptide
   d. Endothelin
   e. Arginine vasopressin

Answers

1. Answer D: Heart failure, like renal failure or anemia, is a clinical syndrome with a constellation of signs and symptoms. It has many possible etiologies, since virtually any form of heart disease can lead to heart failure. Patients must have signs and symptoms (i.e., a low EF does not equal heart failure) that usually consist of dyspnea and fatigue at rest or with exertion. There must be underlying cardiac structural and/or functional abnormalities. There is no laboratory test for heart failure (i.e., a history and physical exam are necessary), though a plasma BNP level may help facilitate the diagnosis in certain settings.

2. Answer C: Patients with heart failure have well-documented disturbances of the autonomic nervous system and are unable to mount a reflex tachycardia in response to upright tilt, orthostasis, intense vasodilation, or other volume-depleting stimuli. In fact, the extent of this blunted sympathetic response is coupled to the severity of heart failure and is predictive of a poor prognosis. Similarly, patients with heart

failure do not fully activate the parasympathetic arm of the autonomic nervous system in response to systemic pressor activity with phenylephrine (there is less vagal-induced slowing of the heart rate). Heart-rate variability is also blunted in patients with heart failure, and is also associated with a poor prognosis.

3. Answer A: There has been a very reproducible and consistently poor relationship noted between resting EF and exercise capacity (r = 0.20-25) in patients with chronic heart failure. This is likely because exercise capacity is limited in patients with chronic heart failure, not by abnormal central hemodynamics but by peripheral factors such as deconditioning and atrophy of skeletal muscles, changes in skeletal muscle oxidative enzymes, redistribution of blood flow away from skeletal muscles to more vital organs, and endothelial dysfunction in the peripheral vasculature due to a relative deficiency of local nitric oxide synthesis in blood vessels.

4. Answer B: There are almost as many "prognostic factors" in heart failure as there are stars in the clear night sky. Many of them are related to each other, and their independent contributions to prognosis are difficult to measure. Determining how much exercise the patient can do is perhaps the closest "factor" we have to a true "gold standard" for estimating prognosis. For example, the VO_{2max} should be < 14 mL/kg/min for a patient to be considered for heart transplantation. Preserved exercise tolerance is a very powerful predictor of a better prognosis in patients with chronic heart failure.

5. Answer B: In chronic heart failure, it is primarily the β_1-receptor that is downregulated. The density of cardiac β_2-receptors is much less than that of the β_1- receptors, and the β_2-receptors may be less important in modulating positive inotropy. In addition to relatively selective β_1-receptor downregulation that occurs in chronic heart failure, there is important uncoupling of the G-stimulating protein from the b-receptors, leading to a reduction in positive inotropic state.

6. Answer C: Natriuretic peptides modulate sodium and water (volume) regulation, vasodilation, natriuresis, antifibroblast proliferation, and anticollagen deposition, and have antiremodeling activity. Their biologic activities are nearly opposite to those of Ang-II, norepinephrine, endothelin, and arginine vasopressin

CHAPTER

Medical Treatment of Heart Failure

Andrew Grant and Mazen Hanna

The management of heart failure (HF) depends on the underlying mechanism. This chapter focuses on the treatment of HF related to left ventricular (LV) systolic dysfunction, the best understood and studied nonvalvular cause of HF. LV dysfunction is generally defined by a reduction in left ventricular ejection fraction (LVEF).

We briefly discuss lifestyle measures and then review established pharmacotherapy. Trial evidence is summarized where appropriate. Current guideline recommendations from the American College of Cardiology[1] and the Heart Failure Society of America[2] are cited in each section with some changes in wording for clarity. Where guidelines are quoted, the strength of the recommendation is given, followed by the level of evidence in parentheses (e.g., I,C refers to a class I recommendation with level of evidence C). Discussion of surgical treatments and device-based therapies for HF can be found elsewhere in this book.

LIFESTYLE MEASURES

Sodium Restriction

Retention of sodium is an important aspect of the pathophysiology of HF and occurs due to overactivation of the sympathetic and renin–angiotensin–aldosterone systems (see Chapter 15). It is felt for this reason that limitation of salt intake reduces HF symptoms. The typical recommendation is that patients adhere to a diet of <2 g/day of sodium from all sources.

ACC Guideline[1]

- Sodium restriction is indicated in patients with current or prior symptoms of HF and reduced LVEF who have evidence of fluid retention (I, C).

Fluid Restriction

Fluid balance is generally monitored closely during hospitalization for HF. This can be difficult to achieve in the outpatient setting. For those with serum sodium levels <130, however, a fluid restriction of 2 L/day (and sometimes 1.5 L) may be advisable.

HFSA Guidelines[2]

- Restricted fluid intake is recommended for HF patients with moderate hyponatremia (serum Na <130) (I equivalent, C).
- Restricted fluid intake should be considered among HF patients without significant hyponatremia who demonstrate fluid retention that is difficult to control with sodium restriction and diuretic therapy (IIa equivalent, C).

Exercise

HF patients are generally counseled to engage in regular physical exercise within the limits of their symptoms. For those with a recent myocardial infarction (MI) or high burden of coronary artery disease, the usual recommendations on cardiac rehabilitation and exercise should be followed.

Clinical Trials

Multiple small trials had suggested that exercise training is associated with improved functional capacity, decreased HF hospitalizations, and possibly a decrease in mortality.[3–5] In a meta-analysis, it has also been shown to have a favorable effect on LV remodeling.[6]

The HF-ACTION trial evaluated the effect of aerobic exercise in 2,331 patients with stable HF and LV dysfunction.[7] Patients randomized to regular exercise had a greater improvement in peak oxygen consumption and 6-minute walk distance. In contrast to previous smaller trials, there was no difference in all-cause mortality or hospitalization after a mean follow-up of 30 months.

ACC Guideline[1]

- Exercise training is recommended as an adjunctive approach to improve clinical status in ambulatory patients with current or prior symptoms of HF and reduced LVEF (I, B).

MEDICAL THERAPY IN CHRONIC HEART FAILURE

Neurohormonal Blockade

Activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system leads to adverse physiologic effects in HF. Medications that block or dampen these effects include beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, AT1 receptor blockers (ARBs), and aldosterone antagonists. These medications have become an important cornerstone of contemporary HF management. It is recommended that these agents, particularly ACE inhibitors and beta-blockers, be considered in all HF patients and that they be titrated to achieve the doses used in clinical trials or to maximal tolerated doses.

Beta-Blockers

Mechanism of Action There are a number of proposed mechanisms by which beta-adrenergic blockers have been theorized to be beneficial in HE. Over time, they improve the efficiency of beta-adrenergic signaling, and some agents in this class restore a more normal distribution of beta-receptors on the cell surface. Hemodynamic and cellular effects include reduced wall tension, inhibition of adverse remodeling, and prevention of myocyte apoptosis.[8] Beta-blockers have a favorable impact on ventricular remodeling in both ischemic and nonischemic cardiomyopathies.[9]

Clinical Trials Multiple large-scale RCTs have shown beta-blockers to improve symptoms and reduce mortality in HF (Table 16.1).[10]–[14] It should be noted that the nonselective beta-blocker bucindolol was also studied in the BEST trial, which showed no significant improvement in mortality.[15] This agent has a significant degree of intrinsic sympathomimetic activity.

TABLE
16.1 Landmark Trials Evaluating the Effect of Beta-Blockers on Clinical Outcomes in HF

	USC[10]	CIBIS II[11]	MERIT HF[12]	COPERNICUS[13]	COMET[14]
N	1,094	2,647	3,991	2,289	3,029
LVEF	<0.35	<0.35	<0.40	<0.25	<0.35
NYHA	II–IV	III–IV	II–IV	IV	II–IV
Beta-blocker	Carvedilol	Bisoprolol	Metoprolol succinate	Carvedilol	Carvedilol
Mortality in comparitor	8% placebo at 6–12 mo	17% placebo at 16 mo	16% placebo at 18 mo	19% placebo at 10 mo	40% metoprolol at 58 mo
Relative risk reduction	65%	34%	34%	35%	17%

Cautions

- Bradycardia can occur due to sinus node slowing and/or AV block.

- Initiation of beta-blockers during acute HF decompensation can worsen symptoms due to negative inotropy.

ACC Guidelines[1]

- Beta-blockers are indicated in patients with current or prior symptoms of HF and reduced LVEF (I, A).
- Beta-blockers are indicated in patients with asymptomatic LV dysfunction (I, A).
- Agents demonstrated to be beneficial in HF include carvedilol, bisoprolol, and metoprolol succinate.

Angiotensin Converting Enzyme Inhibitors

Mechanism of Action These agents block the ACE, preventing conversion of angiotensin I to angiotensin II (see Fig. 6.3). The role of angiotensin II in HF is discussed in detail in Chapter 15. By preventing the formation of angiotensin II, ACE inhibitors decrease vasoconstriction, increasing arterial compliance. The resulting decrease in vascular resistance unloads the failing left ventricle. ACE inhibitors reduce adverse structural changes such as ventricular hypertrophy and dilation, even among patients without overt HF.[16,17] At a microscopic level, they have also been shown to reduce fibrosis.[18]

Clinical Trials Numerous published trials have demonstrated reductions in cardiovascular endpoints including mortality using ACE inhibitors in patients across the spectrum of HF (Table 16.2).[19–23] ACE inhibitors have also been studied extensively in the setting of MI complicated by LV dysfunction or HF. Three key trials are summarized in Table 16.3.[24–26]

TABLE
16.2 Landmark Trials of ACE Inhibitors in chronic HF or LV Dysfunction

	CONSENSUS[19]	SOLVD Treatment[20]	SOLVD Prevention[21]	V HeFT II[22]	ATLAS[23]
N	253	2,569	4,228	804	3,164
LVEF	not reported	<0.35	<0.35	<0.45[a]	<0.30
NYHA	IV	II–IV	I	I–IV	II–IV
ACE inhibitor	Enalapril	Enalapril	Enalapril	Enalapril	Lisinopril 32.5–35 mg
Mortality in comparitor	36% Placebo at 12 mo	40% Placebo at 41 mo	16% Placebo at 37 mo	25% Hydral/ISDN at 24 mo	42% Lisinopril 2.5–5 mg at 46 mo
Relative risk reduction	31%	16%	No difference	28%	No difference

[a]Some patients were enrolled on the basis of increased LV end-diastolic diameter or cardiothoracic ratio; mean LVEF was 0.29. ISDN = isosorbide dinitrate.

TABLE
16.3 Landmark Trials of ACE Inhibitors in LV Dysfunction or HF Post-MI

	SAVE[24]	AIRE[25]	TRACE[26]
N	2,231	2,006	1,749
LVEF	<0.40	Not reported	<0.35
Other patient characteristics	Post-MI	Post-MI Symptomatic HF	Post-MI
ACE inhibitor	Captopril	Ramipril	Trandolapril
Mortality in placebo	25% at 42 mo	23% at 5 mo	42% at 24–50 mo
Relative risk reduction	17%	27%	18%

Cautions

- Angioedema is a rare but serious complication of ACE inhibitors.
- Hyperkalemia can occur, especially in combination with ARBs or spironolactone.
- Renal dysfunction can be exacerbated by ACE inhibitors.
- Known bilateral renal artery stenosis is a contraindication to ACE inhibitors.
- ACE inhibitors should not be used during pregnancy.
- ACE inhibition leads to increased levels of bradykinin—in some patients, this is associated with the development of dry cough.

ACC Guidelines[1]

- ACE inhibitors are indicated in patients with current or prior symptoms of HF and reduced LVEF (I, A).
- ACE inhibitors should be used in patients with reduced LVEF in the absence of symptoms (I, A).

Angiotensin Receptor Blockers

Mechanism of Action Angiotensin can be produced by other proteases besides ACE. Furthermore, although angiotensin II action on AT1 receptors leads to vasoconstriction and adverse remodeling, action on AT2 receptors may actually have beneficial antifibrotic effects.[27] These findings helped suggest the idea that using a selective ARB

may be beneficial in HF.

Clinical Trials—ACE Inhibitor-Intolerant Patients The CHARM Alternative trial enrolled 2,028 patients with HF who were intolerant of ACE inhibitors and randomized them to candesartan or placebo.[28] There was a significant reduction in the rate of the primary endpoint of death or HF hospitalization at 34 months in the candesartan group (33% vs. 40% with placebo).

Clinical Trials—Comparison to ACE Inhibitors The data from head to head trials comparing ACE inhibitors and ARBs in HF are mixed (Table 16.4). The ELITE I trial suggested a significant hard-endpoint benefit of using losartan rather than captopril in HF.[29] This finding was not reproduced in the larger follow-up ELITE II trial.[30] The OPTIMAAL study in post-MI patients showed the opposite result with a trend toward captopril being superior to losartan with respect to major cardiovascular events.[31] The VALIANT study compared the ACE inhibitor captopril, the ARB valsartan, and a combination of the two in post-MI patients with HF or LV dysfunction.[32] In this study, there was no difference between groups with respect to rates of death or HF hospitalization.

TABLE
16.4 Landmark Trials Comparing ARBS to ACE Inhibitors in HF

	ELITE I[29]	ELITE II[30]	OPTIMAAL[31]	VALIANT[32]
N	722	3,152	5,477	9,818[a]
Admission criteria	LVEF < 0.40 NYHA II–IV Age > 65 y	LVEF < 0.40 NYHA II–IV Age > 60 y	MI with Anterior Q or HF or LVEF <0.35 or EDD >65 mm[b]	MI with LVEF <0.40 or HF[c]
Ischemic etiology	68%	79%	100% Post-MI	100% Post-MI
ARB	Losartan	Losartan	Losartan	Valsartan
Comparitor	Captopril	Captopril	Captopril	Captopril
Mortality	46% RRR at 12 mo	No difference at 18.2 mo	No difference at 32.4 mo	No difference at 24.7 mo

[a]4,909 valsartan and 4,909 captopril; combination arm with 4,885 excluded here.
EDD=end diastolic diameter; LV LVEF <0.35 or EDD >65 mm present in only 13.6% of patients.
[c]28% had no symptoms and mean LVEF was 0.35.

Clinical Trials—Combination with ACE Inhibitors Several trials have tested the effects of adding ARB therapy to patients already stabilized on ACE inhibitors (Table 16.5). CHARM added randomized patients already taking ACE inhibitors to the

addition of candesartan or placebo.[33] This trial showed a significant reduction in death and HF hospitalization in patients receiving candesartan. The ValHeft trial randomized patients to valsartan or placebo in addition to regular HF therapy.[34] More than 92% of patients were on an ACE inhibitor at baseline which was continued. In the overall trial, there was no mortality difference between groups, but patients receiving valsartan had a significant reduction in HF hospitalization. As mentioned above, the VALIANT study compared the combination of valsartan and captopril to the use of either agent alone.[32] The 4,885 patients who received the combination of ACE inhibitor and ARB had mortality rates and HF hospitalization rates that were identical to those of the captopril alone group.

TABLE
16.5 Landmark Trials of the Addition of an ARB to an ACE Inhibitor in HF

	ValHEFT[34]	CHARM Added[33]	VALIANT[32]
N	5,010	2,548	9,794[a]
LVEF	<0.40	<0.40	<0.40 or HF[b]
NYHA	II–IV	II–IV	I–IV[b]
Ischemic etiology	57%	62%	100% post-MI
ARB	Valsartan	Candesartan	Valsartan
ACE inhibitor	93% on ACE	100% on ACE	100% captopril[a]
Mortality	No difference at 23 mo	No difference at 41 mo	No difference at 24.7 mo

[a]4,909 captopril alone and 4,885 combination; 4,909 patients on valsartan alone excluded here.
[b]Required either LVEF < 0.40 or overt HF; 28% had no symptoms and mean LVEF was 0.35.

Cautions

- Angioedema can occur with ARBs but much less commonly than with ACE inhibitors.
- Cough caused by ACE inhibitors is not seen with ARBs.

Otherwise, the side effect profile of ARBs is much like that of ACE inhibitors.

ACC Guidelines[1]

- ARBs are indicated for ACE inhibitor-intolerant patients with HF and reduced LVEF (I, A).
- In patients with reduced LVEF but no symptoms of HF who are intolerant of ACE inhibitors, an ARB should be used if the etiology is ischemic (I, B) and is

reasonable if the etiology is nonischemic (IIa, C).

- ARBs are a reasonable first-line alternative to ACE inhibitors in patients with HF and reduced LVEF (IIa, A).
- The addition of an ARB to an ACE inhibitor and beta-blocker can be considered in persistently symptomatic HF patients with reduced LVEF (IIb, B).

Aldosterone Antagonists

Mechanism of Action Spironolactone was originally used as a potassium-sparing diuretic. It blocks mineralocorticoid receptors in the kidney, preventing reabsorption of sodium and excretion of potassium in the distal convoluted tubule. Because aldosterone production is upregulated in HF (see Chapter 15), it becomes an obvious target for therapies. Spironolactone also has some androgen blocking activity, which can lead to adverse effects such as breast tenderness and gynecomastia. Eplerenone is more selective for the aldosterone receptor and does not have these same side effects.

Clinical Trials The RALES trial firmly established the benefits of aldosterone antagonism in patients with severe symptomatic HF and reduced LVEF[35] The EPHESUS trial studied only post-MI patients with resulting LV dysfunction.[36] In an effort to include higher risk patients, the investigators required patients to have either symptomatic HF or diabetes. The recently published EMPHASIS study may expand the use of these agents in patients with less symptomatic HF, although these findings have yet to be incorporated into national guidelines.[37] These three trials are summarized in Table 16.6.

TABLE
16.6 Landmark Trials of Aldosterone ALandmark Trials of Aldosterone and Post-MI LV Dysfunction

	RALES[35]	EPHESUS[36]	EMPHASIS[37]
N	1,663	6,632	2,737
LVEF	<0.35	<0.40	<0.30
Symptoms	NYHA III–IV	Post-MI HF or DM	NYHA II
Agent	Spironolactone	Eplerenone	Eplerenone
Mortality in placebo	46%	16.7%	15.5%
Relative risk reduction	30%	15%	24%

Cautions

- Caution should be used in patients with renal dysfunction.
- Hyperkalemia (Should not be prescribed if K > 5 mM)
- Spironolactone can be associated with breast tenderness and gynecomastia.

ACC Guidelines[1]

- An aldosterone antagonist is recommended in selected patients with NYHA III or IV symptoms of HF and reduced LVEF who can be monitored for preserved renal function and normal potassium concentration (I, A).
- Creatinine should be ≤2.5 in men or ≤2.0 mg/dL in women.
- Potassium should be ≤5.0 mEq/L.

Other Vasodilators

Afterload reduction of the LV in chronic HF decreases wall tension and improves forward stroke volume. Preload reduction with venous vasodilator therapy helps to decrease LV filling pressures and improve symptoms.

Hydralazine and Nitrates

Mechanism of Action Hydralazine increases intracellular cGMP promoting smooth muscle relaxation leading to vasodilation. It acts primarily in the arterioles, decreasing blood pressure and LV afterload. It is often given in conjunction with nitrates in HF because of a synergistic activity on the nitric oxide pathway and more sustained clinical effect. The combination of hydralazine and a nitrate leads to lower LV filling pressure and an increase in cardiac output.

Clinical Trials The original V-HeFT study compared a combination of hydralazine and isosorbide dinitrate (ISDN) with placebo in patients with HF and reduced LVEF.[38] It showed a significant mortality reduction to 26% at 2 years from 34% in the placebo arm.

V-HeFT II compared the same combination of hydralazine and ISDN to the ACE inhibitor enalapril.[22] Event rates in the hydralazine and ISDN arm of V-HeFT II were similar to those of V-HeFT, with a 2-year mortality of 25%. The enalapril arm, however, had an even lower mortality rate of 18% at 2 years.

In the V-HeFT II trial, there appeared to be less benefit of ACE inhibitor over hydralazine and nitrates among black patients. The A-HeFT trial enrolled patients self-described as African American to directly test the utility of adding hydralazine and ISDN when symptoms persisted on ACE inhibitors.[39] The trial was discontinued early after a mean follow-up of 10 months because of a significant reduction in mortality in the group treated with hydralazine and ISDN (6.0% vs. 10.2% in placebo).

Cautions

- Use of phosphodiesterase inhibitors such as sildenafil for erectile dysfunction in combination with nitrates is contraindicated because of the risk of hypotension.
- Methemoglobinemia is a rare but serious side effect of nitroglycerin.
- Headache is a common side effect of nitrates.

ACC Guidelines[1]

- Hydralazine and a nitrate could be considered in patients with HF and decreased LVEF who are intolerant of ACE inhibitors and ARBs (IIb, C).
- Hydralazine and a nitrate should be used in self-identified African American patients with HF and decreased LVEF who have persistent moderate or severe symptoms despite treatment with a beta-blocker, an ACE inhibitor, and a diuretic (I, B).

Calcium Channel Blockers

Mechanism of Action In general, calcium channel blockers are not recommended in HF and impaired LV function. The more cardioselective diltiazem and verapamil in particular are contraindicated because of their negative inotropic properties. The dihydropyridines, on the other hand, act more peripherally causing vasodilation and reducing blood pressure.

Clinical Trials The MDPIT trial evaluated the benefits of diltiazem in patients who had suffered a MI. Among patients with pulmonary edema on chest x-ray, use of diltiazem was associated with higher cardiac mortality.[40] The PRAISE-I study compared amlodipine to placebo in patients with HF and reduced LVEF[41] It showed a trend toward a decrease in the combined endpoint of death or CV hospitalization among patients randomized to amlodipine. This difference was significant among the subset of patients with a nonischemic cardiomyopathy. The subsequent PRAISE-II trial enrolled only patients with nonischemic-dilated cardiomyopathies and randomized them to amlodipine or placebo. There was no difference in outcomes found. Small randomized trials of amlodipine[42] and nifedipine[43] have shown mixed results with respect to exercise tolerance with these agents.

Cautions

- Nondihydropyridine calcium channel blockers diltiazem and verapamil have negative inotropic effects and are considered contraindicated in HF.
- Amlodipine and nifedipine can be associated with edema and increased fluid retention.

ACC Guidelines[1]

- Calcium channel blockers should not be used as routine treatment in patients with current or prior symptoms of HF and reduced LVEF (III, A).

Alpha-blockers

The ALLHAT trial showed increased rates of HF in patients randomized to the alpha-blocker doxazosin compared to other antihypertensives.[44] Alpha-blockers continue to be used as add-on therapy in patients with HF and refractory hypertension despite maximal doses of indicated drugs. The use of alpha-blockers in HF is not specifically mentioned in the ACC or HFSA guidelines.

Digitalis Glycosides

Preparations of digitalis have been used for centuries in the treatment of cardiovascular diseases. Digoxin is primarily used for rate control of atrial fibrillation, but it has an important role in the management of symptomatic HF in selected patients in sinus rhythm as well.

Digoxin

Mechanism of Action Digoxin acts via a number of different mechanisms. The primary effect has long been felt to be blockade of the Na/K ATPase in cardiac myocytes (see Chapter 6). This leads to an increase in intracellular calcium available for contraction and therefore to an increase in inotropy. Effects in other tissues lead to digoxin having sympatholytic and parasympathomimetic effects. It is now felt that the neurohormonal blockade activities of digoxin may play an important role in the long-term clinical benefits of its use.

Clinical Trials The Digitalis Investigation Group (DIG) trial studied the effects of digoxin in comparison to placebo in 6,800 patients with HF and decreased LVEF[45] There was no significant difference between groups in the rates of mortality at a mean follow-up of 37 months. There was, however, a significant decrease in hospitalization for worsening HF in the digoxin group (26.8% vs. 34.7% in placebo).

Withdrawal Trials Several trials have tested the effects of withdrawing digoxin from stable patients on more contemporary HF treatment. The PROVED study randomized 88 patients with symptomatic HF on digoxin to continuation or withdrawal.[46] Discontinuation of digoxin resulted in higher rates of treatment failure and decreased exercise tolerance. The RADIANCE study similarly randomized 178 patients to continuation of digoxin or withdrawal of the agent for 12 weeks and initiation of

placebo.[47] Patients in the placebo arm had higher rates of crossover to active treatment. In this study, they also showed significant worsening of symptoms and exercise tolerance.

Monitoring of Levels Digoxin toxicity is a major concern among HF patients, particularly the elderly and those prone to electrolyte disturbances. Digoxin toxicity is most common with serum levels >2.0, but can occur at lower levels. A post hoc analysis of the DIG trial demonstrated an interaction between serum digoxin levels and all-cause mortality.[48]

Cautions

- Digoxin toxicity is a life-threatening complication of treatment with numerous manifestations.
- Hypokalemia, hypomagnesemia, hypercalcemia, and acute renal failure can all precipitate digoxin toxicity.

ACC Guideline[1]

- The use of digoxin is reasonable in patients with current or prior symptoms of HF and decreased LVEF (IIa, B).

HFSA Guideline[2]

- Serum digoxin levels should be maintained <1.0 ng/mL (generally 0.7 to 0.9 ng/mL).

Investigational Agents

Many other agents have been tested or are under investigation for the treatment of HF. Several agents and classes with recent publications are briefly discussed below.

Phosphodiesterase Inhibitors

LV dysfunction with HF is a major secondary cause of pulmonary hypertension (type 2 by the current classification scheme). There are theoretical concerns that reducing pulmonary pressures in patients with left-sided HF could lead to increased pulmonary edema. Nevertheless, there is interest in using selective pulmonary arterial vasodilators in HF. Several small trials have shown hemodynamic benefit and increased exercise tolerance.[49,50]

Polyunsaturated Fatty Acids

Epidemiologic studies have linked consumption of polyunsaturated fatty acids (PUFAs)

with decreased rates of adverse cardiovascular events.[51] GISSI-HF randomized 6,975 patients with symptomatic HF (>90% of whom had LVEF < 0.40) to omega-3 PUFA or placebo.[52] At a follow-up of 3.9 years, there was a statistically significant reduction in allcause mortality (27% vs. 29% in placebo).

Ivabradine

This medication has selective inhibitory effects on the sinus node. It was postulated as the basis of the SHIFT study that controlling heart rate with such an agent in HF patients unable to tolerate maximal beta-blocker doses may be beneficial. SHIFT randomized 6,558 patients to receive ivabradine or placebo in addition to conventional HF therapy.[53] Although there was a significant reduction in cardiovascular death or HF hospitalization, the trial has been criticized for underdosing of beta-blockers. The argument is that slowing the sinus node rate may be beneficial but could have been achieved by uptitration of beta-blockers to maximal doses.

Treatment of Related Conditions

Anemia and Iron Deficiency

Anemia is commonly associated with HF, and normalization of hemoglobin may be associated with increased exercise tolerance. There is evolving evidence to suggest that there may be symptomatic benefit to treatment of iron deficiency in HF even in the absence of anemia.

Clinical Trials The STAMINA-HF trial examined the effects of darbapoetin alpha in 319 patients with HF and anemia.[54]
Treatment resulted in a significant increase in hemoglobin levels but had no significant impact on mortality or hospitalization rates.

FAIR-HF enrolled 459 patients with symptomatic HF and decreased LVEF who had iron deficiency defined as ferritin <100 μg/L (or <300 μg/L with transferrin saturation <20%).[55] Only half of the patients had anemia (defined as hemoglobin <12.0 g/dL). Randomization was to a regimen of intravenous iron to achieve iron repletion or placebo. Iron therapy was associated with improved self-reported quality of life and symptom status at 24 weeks, both among anemic and nonanemic irondeficient HF patients.

ACC Guidelines[1]

- Increasing erythropoiesis in HF patients with decreased LVEF is not well established (IIb, B).
- Iron supplementation therapy "is undergoing further investigation."

Rhythm Control for Atrial Fibrillation

Atrial fibrillation is a common arrhythmia in patients with HF and LV dysfunction. This topic is discussed in detail elsewhere in this text. The AF-CHF study of 1,376 patients with HF and EF <0.35 did not show any difference between ratecontrol and rhythm-control strategies with respect to mortality or worsening HF.[56]

ACC Guideline[1]

- It is reasonable to adopt either a rate control strategy or a rhythm control strategy in patients with HF and reduced LVEF who develop atrial fibrillation (IIa, A).

Anticoagulation for Prevention of Stroke

HF is a prothrombotic condition, associated with increased levels of fibrinogen, D-dimer, and antithrombin.[57,58] Stasis of blood within a poorly contracting left ventricle also contributes to the formation of clot. As such, rates of stroke and systemic embolus are higher in patients with LV systolic dysfunction.[59]

Clinical Trials The WATCH study compared ASA, clopidogrel, and warfarin in 1,587 patients with LV systolic dysfunction.[60] This study demonstrated a significant reduction in ischemic stroke among warfarin patients, but this was offset by an increase in rates of intracranial hemorrhage. It should be noted that the study was underpowered due to poor enrollment. The HELAS study enrolled 197 patients with HF and decreased LVEF.[61] Patients with nonischemicdilated cardiomyopathies were randomized to warfarin or placebo. Those with ischemic heart disease were randomized to ASA 325 mg QD or placebo. At 2 years of follow-up, there was no difference between the groups in rates of embolic events. The WARCEF trial comparing warfarin to placebo is ongoing.

ACC Guideline[1]

- Anticoagulation for prevention of stroke or systemic embolus is not well established in HF patients with reduced LVEF in the absence of other indications for anticoagulation (IIb, B).

MEDICAL THERAPY IN ACUTE HEART FAILURE

Supportive Treatment

HF decompensation is a spectrum from progression of exertional symptoms to cardiogenic shock with florid pulmonary edema. The general principles of Advanced

Cardiac Life Support apply to the initial stabilization of patients presenting with acute HF syndromes.

HFSA Guidelines[2]

- Supplemental oxygen should be administered for all patients with acute HF who demonstrate hypoxia (I equivalent, C)
- Positive pressure ventilation may be considered for severely dyspneic patients with pulmonary edema (IIb equivalent, A)

Admission to Hospital

The decision about when to admit a patient with decompensated HF is a complex one. The following lists of clinical parameters (modified from Table 12.1 of the HFSA 2010 guidelines)[2] is not meant to be exhaustive.

Features of acute decompensation for which admission to hospital is recommended:

- Hypotension
- Resting tachypnea or hypoxia
- Altered mentation
- Worsening renal function
- Hemodynamically unstable arrhythmia
- Acute coronary syndrome

Features of acute decompensation for which hospitalization should be considered:

- New diagnosis of HF with congestion
- Worsening pulmonary or systemic congestion
- Major electrolyte disturbances
- Pneumonia, pulmonary embolus, diabetic ketoacidosis, and stroke/transient ischemic attack
- Repeated defibrillator discharges

Invasive Hemodynamic Monitoring

Invasive hemodynamic assessment with a pulmonary artery catheter is performed for a number of different indications in HF patients, including assessment of pulmonary hypertension, and pretransplant workup. In the context of acute HF exacerbation, placement of a PA catheter can help distinguish HF from other causes of hypoxia or hypotension. It also allows careful titration of vasoactive medications to hemodynamic parameters.

Clinical Trials A large observational study in the medical intensive care unit (ICU) showed an increase in mortality in patients who received invasive monitoring with a pulmonary artery catheter.[62] A meta-analysis of small trials using PA catheter-guided therapy in the ICU showed no improvement in hospital stay or mortality with this strategy.[63] The ESCAPE trial randomized 433 patients with acute decompensated HF to invasive hemodynamic monitoring or usual care.[64] There was no significant difference between the two groups with respect to the primary endpoint of days alive out of hospital.

ACC Guidelines[1]

- Invasive hemodynamic monitoring should be performed in patients with respiratory distress or systemic hypoperfusion in whom intracardiac filling pressures cannot be adequately assessed clinically (I, C).
- Invasive hemodynamic monitoring is reasonable for HF patients with persistent symptoms despite initial therapy who have one of the following features: hypotension, worsening renal function, or need for IV vasoactive agents (IIa, C).
- Invasive hemodynamic monitoring is reasonable in HF patients being considered for advanced therapies such as cardiac transplantation or mechanical circulatory support (IIa, C).

Decongestion

A longstanding focus of acute HF management has been on the rapid shift of fluid from the pulmonary interstitial space. This improves symptoms of dyspnea and oxygenation. Following this stabilization phase, efforts are generally made to remove further salt and water targeting peripheral edema and ascites.

Loop Diuretics

Mechanism of Action So-called loop diuretics act by blocking the Na/K/2Cl cotransporter in the Loop of Henle. They are potent inhibitors of sodium reabsorption in the nephron. The commonly used loop diuretics are furosemide, bumetanide, and torsemide (Table 16.7).

TABLE
16.7 Commonly Used Loop Diuretics and their Relative Dosing in Acute HF

Agent	Initial IV Dose	Maximal Single IV Dose
Furosemide	40 mg	160–200 mg
Bumetanide	1 mg	4–8 mg
Torsemide	10 mg	100–200 mg

Modified from Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American college of Cardiology Foundation/American Heart Association task force on practice guidelines developed in collaboration with the International Society of Heart and Lung Transplantation. J Am Coll Cardiol. 2009;53:e1–e90, Table 16.5, with permission from Elsevier.

Route of Administration During acute exacerbations of HF, intravenous formulations of diuretic are generally used. This route of administration provides a more reliable bio-availability because edema in the bowel wall can interfere with absorption of oral diuretics, especially furosemide. The effective dose conversion of oral to intravenous furosemide is approximately 2:1.[65,66]

It has been suggested that continuous IV infusions of loop diuretics are superior to intermittent boluses. The DOSE study[67] compared these two strategies in a randomized, blinded trial of 308 patients. There was no difference between continuous infusion and intermittent bolus diuretics (every 12 hours) on dyspnea or renal function. The study was not powered for hard clinical endpoints, but there was no difference in death or rehospitalization at 60 days, nor was there a difference in length of initial hospital stay.

Sequential Nephron Blockade Addition of a diuretic from another class that acts more distally in the nephron is a well-established means of potentiating the effect of a loop diuretic.[68] The classical agents used in this way have been thiazide diuretics such as hydrochlorothiazide and chlorthalidone. Metolazone is now commonly used in this fashion, with a simple daily or twice daily oral dosing regimen. Metolazone acts in a very similar way to the thiazide diuretics.

Concerns

- Observational studies and retrospective analyses of randomized trials have shown a relationship between use of diuretics and increased mortality.[69,70]
- Electrolytes need to be monitored carefully due to risks of hyponatremia, hypokalemia, and hypomagnesemia.
- Prerenal azotemia can be precipitated by overdiuresis.

ACC Guidelines[1]

- Patients admitted for HF with significant fluid overload should be treated with intravenous loop diuretics (I, C).
- When diuresis is inadequate to relieve congestion, treatment should be intensified with higher doses of loop diuretic, addition of a thiazide or metolazone, or transition to a continuous infusion of loop diuretic (I, C).

Vasopressin Antagonists

Mechanism of Action Arginine vasopressin, or antidiuretic hormone, is a hormone released from the posterior pituitary that causes retention of free water and is important in regulation of serum sodium and osmolality. It also causes vasoconstriction (hence its name). Interest has emerged in targeting vasopressin as a potentially harmful upregulated hormone in HF. Tolvaptan is a selective vasopressin antagonist, blocking the V_2 receptor. Its use should result in diuresis of more hypotonic fluid than is seen with loop diuretics.

Clinical Trials EVEREST was a trial of 4,133 patients hospitalized for acute decompensated HF comparing tolvaptan with placebo in addition to usual care.[71] Patients treated with tolvaptan had more weight loss after 24 hours (1.8 kg vs. 1.0 kg with usual care) and at hospital discharge. At a mean of 10-month follow-up, there was no significant effect of tolvaptan on mortality or HF readmission rates. As expected, tolvaptan was associated with increased sodium levels among hyponatremic patients.

Adenosine Receptor Blockers

Mechanism of Action This class of medications blocks the adenosine receptor. Adenosine receptors are found in the afferent arterioles of the glomerulus and their stimulation has been posited to mediate worsening renal function in HF. There has been interest in the use of the selective A_1 receptor blocker rolofylline to treat HF with acute kidney injury.

Clinical Trials The PROTECT study randomized, patients with acute HF and renal dysfunction to rolofylline or placebo in a 2:1 fashion.[72] The primary endpoint, a composite of death, worsened HF, or renal dysfunction, was no different between the two groups. Rolofylline was associated with an increased risk of seizures.

Ultrafiltration

Mechanism of Action Ultrafiltration removes isotonic fluid from the circulation through an extracorporeal circuit. This can be carried out using standard central venous catheters or special peripheral IVs.

Clinical Trials The UNLOAD study compared veno-venous ultrafiltration to intravenous diuretics in 200 HF patients.[73] Ultrafiltration resulted in a significantly greater 4.6 L fluid loss at 48 hours (vs. 3.3 L in the diuretic group). Interestingly, with this modest increase in weight loss, there were important effects on the rates of clinical endpoints in the intermediate term. Specifically, there were decreased 90-day rates of HF rehospitalization and unscheduled physician visits. It has been argued that this is because ultrafiltration decongests patients without the use of diuretics, which themselves have deleterious neurohormonal effects.[74]

ACC Guideline[1]

- Ultrafiltration is reasonable in HF patients with refractory congestion not responding to medical therapy (IIa, B).

Vasodilators

Nitrates

Nitroglycerin has long been used for the treatment of acute decompensated HF. Nitroglycerin is biotransformed into nitric oxide, which activates guanylate cyclase and increases cGMP. This leads to smooth muscle relaxation and vasodilation. At low doses, nitroglycerin acts as a venodilator, at high doses as an arterial vasodilator. The benefits in HF are pulmonary decongestion and facilitation of diuresis. Large clinical trials comparing nitroglycerin to placebo in HF are lacking, however. The topical application of nitroglycerin can lead to skin irritation, and a rare complication of this drug is methemoglobinemia.

Nitroprusside is predominantly a systemic arterial vasodilator that decreases LV filling pressures by reducing the afterload imposed on the failing ventricle. Its use is more often limited by hypotension and the need for invasive monitoring in an ICU setting. There is also a theoretical risk of cyanide toxicity when nitroprusside is used at higher doses.

Nesiritide

Nesiritide is a recombinant form of human B-type natriuretic peptide. The VMAC study showed that nesiritide was associated with a greater reduction in LV filling pressures than nitroglycerin or placebo.[75] The ASCEND-HF trial tested the effect of this medication on symptoms and hard outcomes in acute decompensated HF.[76] It enrolled 7,141 patients with acute HF and randomized them to nitroprusside or placebo in addition to usual care. The study did not show a significant reduction in death or hospitalization at 30 days. Nesiritide seemed to have favorable effects on patient

dyspnea, but these trends did not meet the prespecified margin for statistical significance. Concerns about the safety of the agent were also not realized. Previous meta-analyses had suggested that nesiritide was associated with increased rates of worsening renal function.

ACC Guideline[1]

- In patients with severely symptomatic fluid overload unresponsive to initial treatment with diuretics, it is reasonable to add a vasodilator such as nitroglycerin, nitroprusside, or nesiritide (IIa, C).

Other Agents

Morphine

Morphine sulfate has been used routinely in the management of acute HF for decades. It is postulated that morphine provides symptomatic benefit by alleviating air hunger, but also has an early effect on LV end-diastolic pressures and facilitates pulmonary vasodilation. Analysis of observational data from the ADHERE registry has shown a correlation between use of morphine in acute HF and higher rates of mortality.[77] Morphine is not specifically discussed in the most recent ACC or HFSA guidelines.

Neurohormonal Blockade

As discussed earlier, the initiation of ACE inhibitor and beta-blocker therapy in chronic HF patients is usually deferred until a time of hemodynamic stability and (in the case of beta-blockers) relative "euvolemia." This raises the question of when it is appropriate to continue these therapies in the setting of acute decompensation.

HFSA Guidelines[2]

- Beta-blockers should be continued in most patients experiencing an exacerbation of HF unless they develop cardiogenic shock, refractory volume overload, or symptomatic bradycardia (I equivalent, C).
- A temporary reduction of beta-blocker dose (generally by one-half) may be considered in the setting of acute HF exacerbation (IIa equivalent, C).

Inotropes

Inotropes are agents that increase myocardial contractility. Unfortunately, although many such medications have demonstrated immediate hemodynamic benefits, they have not as a group been shown to improve clinical outcomes in acute or chronic HF. In fact, in many cases they have been shown convincingly to increase the risk of adverse cardiovascular events including arrhythmia and death. The main indication for

parenteral inotropes in HF is in the resuscitation of patients with cardiogenic shock. In this group, it is felt that end-organ dysfunction can be stabilized or improved by increasing cardiac output.

Dobutamine

Dobutamine is the prototypical inotrope of the adrenergic agonist class. By stimulating beta-1-receptors in the heart, it results in increased cardiac output. Effects on blood pressure are variable because beta-2-receptors and alpha-receptors in the vasculature are activated as well.

There are two studies comparing low-dose intermittent dobutamine with placebo in HF. One of these showed no significant impact on exercise tolerance, mortality, or time to HF readmission.[78] The other trial (which has been published only in abstract form) was stopped early due to an excess of deaths in the dobutamine arm.[79]

Dopamine

Dopamine has complex pharmacologic actions. At low doses, its primary action is on dopamine receptors. At moderate doses, it acts on adrenergic receptors including beta- and alpha-receptors in the heart and vasculature. This gives dopamine the sometimes desirable property of raising blood pressure. It is often used for patients in cardiogenic shock with severe or symptomatic hypotension. Higher doses of dopamine result in relatively greater alpha-stimulation such that the vasopressor properties dominate.

The DAD-HF trial compared low-dose furosemide and low-dose dopamine to high-dose furosemide in patients with acute HF.[80] The dopamine group had similar diuresis to the high-dose furosemide group, but with lower rates of renal dysfunction.

The SOAP II trial randomized 1,679 patients with shock to dopamine or norepinephrine as their initial vasopressor.[81] The overall trial showed no difference in mortality between the two agents, but dopamine use was associated with more arrhythmic events. In a subanalysis of the 280 patients with cardiogenic shock, mortality was higher with dopamine than with norepinephrine.

Milrinone

Milrinone is a phosphodiesterase inhibitor. It leads to decreased breakdown of cAMP in cardiomyocytes. This increases the amount of calcium available for contraction. Clinical effects include an increase in cardiac output and heart rate. Like dobutamine, this agent can cause hypotension.

In the OPTIME-HF trial, 48-hour intravenous infusion of milrinone or placebo was added to standard therapy in 951 acute HF patients.[82] In this study, milrinone was associated with higher rates of hypotension and arrythmias and no decrease was seen in

the number of days hospitalized for cardiovascular causes.

Oral milrinone in severe HF has been studied in the PROMISE trial of 1,088 NYHA functional class III or IV patients.[83] After a median follow-up of 6.1 months, there was a 34% relative increase in the rate of cardiovascular death. Rates of hospital admission, worsening HF, and drug discontinuation were also higher in the active treatment group.

Levosimendan

This agent binds selectively to troponin C and increases the response of myofilaments to calcium. This medication is not presently available for use in the United States.

The SURVIVE trial randomized 1,327 patients with acute decompensated HF requiring inotropes to dobutamine or levosimendan.[84] There was a significant reduction in B-type natriuretic peptide at 24 hours, but there was no significant difference in the primary outcome of mortality at 180 days. Levosimendan was associated with higher rates of atrial fibrillation, hypokalemia, and headache.

ACC Guidelines[1]

- Patients with hypotension and clinical evidence of hypoperfusion and elevated intracardiac filling pressures should be treated with a vasopressor or inotrope (I, C).
- Inotrope use might be reasonable in patients with hypotension and low cardiac output without congestion (IIb, C).
- Long-term continuous infusions of inotropes should not be used except as palliation for patients with end-stage HF (III, B).
- Continuous infusion of a positive inotrope may be considered for palliation of symptoms in patients with refractory end-stage HF (IIb, C).

MEDICATIONS TO AVOID IN HEART FAILURE

A variety of medications can worsen symptoms of HF or precipitate decompensation. This can occur through one or more of the following mechanisms:

- Direct toxicity to cardiac myocytes
- Decreased inotropy due to myocardial depression
- Increased sodium or fluid retention

Nonsteroidal Anti-inflammatory Drugs

Both nonselective and COX-2-selective nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with increased risks of HF exacerbation and

mortality.[85] Concerns have also been raised about the safety of using ASA in patients with HF. Early hemodynamic data suggested an interaction between ASA and ACE inhibitors. A meta-analysis of large trials did not show an impact of ASA use on the beneficial effects of ACE inhibitors.[86] It is generally felt now that HF is not a contraindication to the use of ASA.[1]

Calcium Channel Blockers

Diltiazem and verapamil are relatively contraindicated in HF with decreased LVEF because of their negative inotropic properties (see above).

Antiarrhythmic Medications

The SWORD study randomized 1,549 patients with reduced LVEF post-MI to sotalol or placebo.[87] The trial was discontinued early because of increased rates of death among patients receiving active treatment. In the ANDROMEDA study, dronedarone was associated with increased mortality in patients with NYHA functional class III or IV HF and LV dysfunction.[88] The only antiarrhythmic medications felt to be safe and appropriate for use in HF are amiodarone and dofetilide. Routine use of antiarrhythmic medications to prevent ventricular arrhythmias is not recommended.

Oral Hypoglycemics

The thiazolidinedione rosiglitazone has recently had restrictions placed on its use because of cardiovascular safety concerns. A large meta-analysis of trials of rosiglitazone showed a 43% increase in the risk of MI and a possible increase in mortality.[89] The use of pioglitazone has not been demonstrated to have similar associations with these outcomes.

Metformin is another common oral hypoglycemic that is often avoided in HF patients because of concerns about lactic acidosis. Although lactic acidosis has not been convincingly associated with metformin, it was a rare but serious adverse effect of phenformin, another drug of the biguanide class.

Chemotherapy Agents

Anthracyclines, cyclophosphamide and a variety of other chemotherapy medications have been shown to have direct cardiotoxic effects. Where possible, these drugs should be avoided in patients with known HF or depressed LV function.

HEART FAILURE WITH PRESERVED LVEF

The majority of clinical trials in HF management have specifically excluded patients with normal LV function and preserved LVEF. There is a growing recognition that a large percentage of patients admitted with a diagnosis of HF have no evidence of LV dysfunction.[90–93]

The main focus of treatment in these patients is control of factors that may precipitate HF such as myocardial ischemia, hypertension, and arrhythmia.[1]

Angiotensin Receptor Blockers

CHARM Preserved studied the use of candesartan in 3,025 patients with HF and LVEF > 0.40.[94] There was no significant difference between candesartan and placebo with respect to the primary endpoint of cardiovascular death or admission for HF A significant difference was seen in the secondary outcome of HF admission, however, with a relative risk reduction of 15%.

The I-PRESERVE study enrolled 4,128 patients with HF and LVEF >0.45. [95] The primary outcome was a composite of death or hospitalization for cardiovascular reasons. At a mean follow-up of 50 months, there was no significant difference between irbesartan and placebo in the primary outcome or in rates of HF admission.

MONITORING AND FOLLOW-UP

Disease Management Programs

There is a growing interest in the development and implementation of disease management programs for HF. These are generally multidisciplinary programs that involve formal guidelines for inpatient management, structured discharge planning, and close post-discharge follow-up. In a meta-analysis of small trials, disease management programs were associated with a reduction in mortality and readmission for HF.[96]

Implantable Hemodynamic Monitors

Direct measurements of right ventricular and pulmonary artery pressures with implanted devices have been trialed in very small studies. In one study, patients had decreased rates of HF readmission when data from the invasive monitor was available to physicians.[97] Certain implantable defibrillators have internal sensors that measure thoracic impedance as an estimate of lung water caused by cardiogenic pulmonary edema. The utility of monitoring such parameters is still being actively studied.[98]

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QUESTIONS AND ANSWERS

Questions

1. Which of the following lifestyle modifications has been demonstrated to decrease mortality in heart failure (HF) patients?
   a. Sodium restriction to <2 g/day from all sources
   b. Regular aerobic exercise 30 minute/day, 5 to 7 days/week
   c. Fluid restriction to <1.5 L/day
   d. Daily weights and blood pressure monitoring
   e. None of these modifications

2. A 50-year-old female with a nonischemic-dilated cardiomyopathy is being followed for HF with NYHA functional class II symptoms. Her current medications are carvedilol 6.25 mg BID, enalapril 10 mg BID, eplerenone 25 mg QD, and furosemide 20 mg QD. On physical examination, her HR is 70 bpm, blood pressure is 104/72 mm Hg, and oxygen saturation is normal on room air. Her JVP is not elevated, she has a normal chest exam, and there is no peripheral edema. Her complete blood count, electrolytes, renal function, and thyroid indices are normal.
   What is the recommended dietary fluid restriction for this patient?
   a. <3 L/day
   b. <2.5 L/day
   c. <2.0 L/day
   d. <1.5 L/day
   e. No specific fluid restriction is indicated

3. A 36-year-old male presents with an acute inferior wall myocardial infarction (MI). He is admitted to the CCU following primary angioplasty to a dominant right coronary artery. His chest x-ray shows mild pulmonary edema, and left ventricular ejection fraction (LVEF) is 46% by ventriculography.
   Following initial stabilization, his medications are metoprolol 25 mg twice daily, ASA 81 mg QD,

clopidogrel 75 mg QD, fondaparinux 2.5 mg QD, and atorvastatin 80 mg QD. His heart rate is 64 beats per minute, blood pressure is 108/78 mm Hg, and oxygen saturation is normal on room air. Complete blood count, electrolytes, urea, and creatinine are normal.

Which of the following changes to his therapy would be most appropriate prior to discharge?

a. Increase clopidogrel to 75 mg BID.
b. Discontinue metoprolol.
c. Start ramipril 2.5 mg daily.
d. Start spironolactone 12.5 mg daily.
e. Start hydralazine 25 mg TID.

4. Which of the following statements is correct regarding the use of angiotensin receptor blockers (ARBs) in HF?
   a. Side effects of angiotensin receptor blockers relate to increased levels of bradykinin.
   b. An angiotensin receptor blocker is a reasonable first-line alternative to an ACE inhibitor in patients with HF and reduced LVEF.
   c. An angiotensin receptor blocker should be considered in ACE inhibitor-intolerant patients with HF only in combination with an aldosterone antagonist.
   d. An angiotensin receptor blocker should be considered in ACE inhibitor-intolerant patients with HF only in combination with a continuous positive inotrope.
   e. An angiotensin receptor blocker should never be given to ACE inhibitor-intolerant patients because angioedema occurs with this class of agents as well.

5. Important side effects of the aldosterone antagonist eplerenone include all of the following except:
   a. Renal dysfunction
   b. Lightheadedness
   c. Gynecomastia
   d. Hypotension
   e. Hyperkalemia

6. Which of the following statements about digoxin is correct?
   a. Digoxin toxicity can be precipitated by hypokalemia, hypermagnesemia, or hypocalcemia.
   b. Digoxin has been demonstrated to decrease rates of repeat hospitalization in HF patients, but at the expense of increased mortality.
   c. During chronic therapy, digoxin levels should be monitored and maintained in the range of 1.5 to 2.0 ng/mL.
   d. Digoxin acts by downregulating the expression of the gene coding for the cardiac Na+/K+ ATPase.
   e. Digoxin has sympatholytic and parasympathomimetic properties.

7. A 46-year-old female is found to have an abnormal EKG at the time of a routine physical. She denies any symptoms, and has a normal physical examination. She has an echocardiogram performed that demonstrates an LVEF of 30%. A coronary angiogram is performed and is normal. She is diagnosed with a nonischemic-dilated cardiomyopathy. Based on the information provided, which of the following agents should be added to her medical regimen?
   a. Eplerenone
   b. Carvedilol
   c. Nitroglycerin
   d. Furosemide
   e. Warfarin

8. A 72-year-old female with severe LV systolic dysfunction has chronic symptoms of HF with NYHA functional class III symptoms. She is admitted to hospital with worsening breathlessness and leg swelling. On examination, she is grossly volume overloaded. Her current medications include ASA 81 mg daily, lisinopril 5 mg daily, furosemide 40 mg daily, spironolactone 25 mg daily, and simvastatin 40 mg at bedtime.

   What changes to her diuretic regimen would be most appropriate?

a. Increase furosemide to twice daily dosing.
b. Increase furosemide and change to intravenous formulation.
c. Add metolazone.
d. Discontinue furosemide and start hydrochlorothiazide.
e. No change

9. Which of the following statements regarding vasodilators in HF is correct?
   a. The combination of hydralazine and isosorbide dinitrate has equivalent effects on mortality and repeat hospitalization to those of an ACE inhibitor in HF.
   b. Nesiritide has been shown to lower intracardiac filling pressures in patients with decompensated HF but has not been shown to decrease mortality.
   c. A dihydropyridine calcium channel blocker such as amlodipine or nifedipine is a reasonable alternative to an ACE inhibitor in HF.
   d. Nitroprusside is a recombinant form of atrial natriuretic peptide.
   e. Nitroglycerin acts by binding to nitric oxide reductase, causing venodilation.

10. You are asked to see a 56-year-old female with a history of cardiac sarcoidosis and severe LV dysfunction. She is treated with lisinopril, metoprolol, spironolactone, and furosemide. One week ago, she developed an acutely painful swollen ankle. She was seen by her family doctor and treated with colchicine and naproxen. She returned to the same doctor after 2 days and was started on amoxicillin and clavulinic acid. She has since developed worsening exertional breathlessness and presents to the emergency department in decompensated HF.
    Which of her medications is most likely to have contributed to worsening HF?
    a. Naproxen
    b. Colchicine
    c. Amoxicillin
    d. Clavulinic acid
    e. Metoprolol

Answers

1. Answer E: Although some studies have suggested a reduction in hard endpoints with aerobic exercise in HF, the large HF-ACTION trial did not show any effect on mortality. Other lifestyle measures in HF have not been studied in large clinical trials.

2. Answer E: No specific fluid restriction is suggested in the care of HF patients without refractory volume overload or hyponatremia.

3. Answer C: An ACE inhibitor should be used in all patients with HF complicating a MI. There is good evidence to continue a beta-blocker in this case. In the absence of significant LV systolic dysfunction, there is no established role for spironolactone here.

4. Answer B: The ACC gives a IIa recommendation for the use of ARBs as a first-line alternative to ACE inhibitors in patients with HF and reduced LVEF. Side effects of these agents are not related to increased bradykinin levels; this is a potential mechanism of the side effects of ACE inhibitors such as dry cough. In ACE inhibitor-intolerant patients, use of an ARB is a class I recommendation without qualification regarding the use of other agents. Rates of angioedema are considerably lower with ARBs than with ACE inhibitors.

5. Answer C: Eplerenone differs from spironolactone in that it has higher specificity for the aldosterone receptor. As a result, gynecomastia is not an important side effect of eplerenone. Hypotension with or without symptoms such as lightheadedness can be a side effect of any antihypertensive agent. It remains important to monitor for hyperkalemia and renal dysfunction.

6. Answer E: The pharmacology of digoxin and its complications are important board exam subjects. Digoxin has both sympatholytic and parasympathomimetic effects, making statement E correct. Digoxin toxicity can be precipitated by a variety of electrolyte disturbances; these include hypokalemia,

hypomagnesemia, and hypercalcemia. Digoxin decreases rates of repeat hospitalization in HF; the effect on mortality is probably neutral. Target serum digoxin levels should be 0.7 to 0.9 ng/mL. The direct action of digoxin is blockade of the Na^+/K^+ ATPase, not downregulation of its gene expression.

7. Answer B: Beta-blockers have a class I indication in nonischemic (and ischemic) cardiomyopathies with asymptomatic LV systolic dysfunction. Eplerenone and spironolactone may soon have expanded indications to include functional class II patients, but current guidelines endorse their use only in functional class III and IV patients. Asymptomatic patients were not included in any of these trials. Nitroglycerin and furosemide would be indicated for symptoms acutely or chronically. There is no recommendation to routinely prescribe anticoagulation in this setting.

8. Answer B: Increasing diuretic dose and switching to intravenous formulation at the time of hospitalization for acute decompensation is the specific recommendation in the Heart Failure Society of America guidelines. Increasing furosemide to twice daily dosing and adding metolazone remain reasonable considerations, and discontinuing furosemide and starting hydrochlorothiazide, or no change, are clearly incorrect.

9. Answer B: Nesiritide is effective in lowering LV end-diastolic pressure, but the large ASCEND-HF trial did not show any difference in mortality. The VHeFT II study showed enalapril to be superior to the combination of hydralazine and isosorbide dinitrate. Calcium channel blockers are not recommended as first-line treatment for HF patients. Nitroprusside is a nitrate, not a natriuretic peptide hormone like nesiritide. Nitroglycerin is converted into nitric oxide which activates guanylate cyclase.

10. Answer A: Nonsteroidal anti-inflammatory medications are a common precipitant of HF exacerbations. Colchicine, amoxicillin, and clavulinic acid are not major contributors to HF decompensation. Metoprolol and other beta-blockers can worsen symptoms of HF at the time of initiation, but this is not a new medication for this patient.

CHAPTER

Heart Transplantation

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Though major advances in the therapeutic armamentarium have provided improvements in mortality and morbidity for heart failure patients, outcomes are far from optimal. The 1-year survival of patients with New York Heart Association (NYHA) functional class IV heart failure on optimal medical therapy averages 50% to 80%.[1] More than 100,000 individuals are estimated to be in end-stage heart failure, while only around 2,000 transplants have been performed annually in the United States for the last many years.[2] In contrast to the dismal prognosis of end-stage heart failure patients, the 1-year survival after transplantation averages 85% to 90% at most US centers.[2] Hence, heart transplants (and ventricular assist devices) are viable last resort options for heart failure patients to improve mortality and morbidity. Knowledge of the selection criteria and contraindications for heart transplant and timing for consideration of advanced therapies is necessary to provide the best care for heart failure patients. Many heart transplant patients continue to seek care from nontransplant cardiologists, and hence, basic concepts of rejection and immunomodulating pharmacology are necessary in order to suspect rejection and avoid effects of drug interactions. Recent recognition for the need of standardization of care for the cardiac transplant patients has led to development of guidelines by the International Society of Heart and Lung Transplantation (ISHLT).[3] The guidelines use categorization of recommendations similar to the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines and are referred to for certain topics thought to be relevant for a general cardiologist.

ORGAN ALLOCATION

There were 16,070 deceased organ donors in the United States during 2007 and 2008, and 28% of the time, a heart was recovered and transplanted.[4] The United Network for

Organ Sharing (UNOS) has the government contract for the procurement and distribution of cadaveric organs in the United States. UNOS operates through 11 geographic regions of the country with each region further divided into 58 organ procurement organizations (OPOs). The OPO's main responsibility is to communicate with local hospitals, identify potential donors, and coordinate the transplant process.

THE DONOR

The local OPO is responsible for the initial identification and screening of the potential donor. Once consent for donation is obtained, the primary screening consists of confirming brain death, age, body size, and ABO blood type of the potential donor. The initial evaluation also includes obtaining routine laboratory tests, serologic tests (hepatitis B and C, HIV), identifying the presence of active malignancies, clinical course, and the etiology of death. Cardiac screening includes an electrocardiogram, chest x-ray, transthoracic echocardiogram (if inadequate, transesophageal echocardiogram), and determination of prolonged hypotension or cardiopulmonary resuscitation. A cardiac catheterization may be performed, depending on the age and the presence of coronary artery disease risk factors. Generally, if the potential donor is male and >45 years of age or female and >50 years of age, a cardiac catheterization is recommended.

Once the screening is completed, the donor is entered into the UNOS database and a "rank list" is obtained for each organ. The OPO contacts the recipient transplant centers in order of rank on the list. Candidates are ranked by a variety of factors including ABO blood group compatibility, geographic proximity between donor and transplanting hospitals, priority status of the potential recipient (as detailed below in the recipient section), and length of time spent on the waiting list. In general, the allocation of hearts is first within the local OPO and then outside the OPO in 500-mile concentric rings with the donor hospital in the center of the rings.

The final screen is completed by the harvesting surgeon and involves a review of the locally obtained data as well as a visual inspection of the donor heart. The surgeon looks for contusions, palpates for any obvious atherosclerotic lesions in the epicardial vessels, and reassesses cardiac function.

After brain death has been established and up to the time the organ is procured, the goal of medical management is to maintain hemodynamic stability of the potential donor. Brain death is associated with a high adrenergic state causing fluctuation in blood pressure, arterial vasoconstriction, and end-organ under-perfusion. Therefore, continuous monitoring of arterial pressure, central venous pressure, and urinary output is essential. The targeted systolic blood pressure is >100 mm Hg, central venous pressure between 8 and 12 mm Hg, urinary output >100 mL/h but 300 mL/h, and hematocrit >30%. Close attention must be made to maintaining normal electrolytes,

acid–base balance, and oxygenation. The goal is to optimize cardiac output of the donor heart to achieve blood flow that promotes organ function with the least amount of vasoactive drug support. However, inotropic or vasopressor agents (dopamine, dobutamine, and epinephrine) may be needed. Recommendations on donor heart selection have been recently published by the ISHLT, the details of which are beyond the scope of this chapter.[3]

THE RECIPIENT

Due to disparity between the need and supply of donor hearts, the process of patient selection and allocation must be examined closely. It is crucial that transplant centers allocate organs to patients with the greatest need and the greatest chance to derive maximal benefit.

The current indications for cardiac transplantation are listed in Table 17.1. Potential recipients must undergo a thorough evaluation (Table 17.2) in an attempt to identify any condition that could potentially adversely affect the recipient's survival or quality of life after transplantation. Initial evaluation involves identifying comorbidities that might increase mortality and morbidity independent of heart failure and hence preclude from consideration for transplant.

TABLE
17.1 Selection Criteria for Heart Transplant Listing

Cardiogenic shock requiring either continuous inotropic support or mechanical support (IABP or ventricular assist device)
Persistent symptoms (NYHA III–IV) refractory to maximal medical therapy (including resynchronization); LVEF < 20% and a maximal (RER > 1.05) functional metabolic stress test showing a peak $VO_2 \leq 12$ mL/kg/min (If intolerant to beta-blockers ≤ 14 mL/kg/min)
Intractable or severe anginal symptoms with no revascularization options
Intractable life-threatening arrhythmias unresponsive to medical therapy, catheter-based intervention, or implantable cardioverter/defibrillator

TABLE
17.2 Recommended Evaluation Prior to Transplantation

- Complete history and physical examination
- Laboratory data:
  - Complete blood count (CBC) with differential, complete metabolic panel
  - Thyroid function studies
  - Liver function panel, creatinine clearance
  - Lipid profile, hemoglobin A1c, urinalysis
- Cardiovascular data:
  - Electrocardiogram, chest x-ray, echocardiogram
  - Exercise test with oxygen consumption
  - Right and left heart catheterization, myocardial biopsy[a]
- Immunologic data:
  - Blood type and antibody screen
  - HLA typing
  - Panel of reactive antibodies (PRA) screen
- Serology for infectious diseases:
  - Hepatitis HBsAg, HBsAb, HBcAb, HepCAb
  - Herpes group virus
  - Human immunodeficiency virus
  - CMV IgG antibody
  - Toxoplasmosis
  - Varicella and rubella titers
  - EBV IgG and IgM antibodies
  - Venereal Disease Research Laboratory (VDRL) or Rapid Plasma Reagin (RPR)
- Vascular assessment:
  - Carotid Dopplers
  - Peripheral vascular assessment
  - Abdominal ultrasound
  - Ophthalmology exam[a]
- Cancer screening:
  - Prostate-specific antigen[a]
  - Papanicolaou smear, mammography[a]
  - Colonoscopy[a]
- Psychosocial evaluation:
  - Support system
  - Substance abuse history
  - Psychiatric history
- Baseline:
  - Dental examination
  - Bone density scan
  - Pulmonary function tests

[a]If appropriate.

The patient also needs immunologic testing including ABO blood typing, tissue typing for determination of human leukocyte antigens (HLAs), and screening for existing anti-HLA antibodies (Panel Reactive Antigen test). It is imperative that a careful psychosocial evaluation be performed to identify patients with substance abuse, noncompliance, or any behavioral trait that would lead to adverse posttransplant outcomes.

The list of contraindications for transplant listing is evolving constantly. Mancini

and Lietz[5] published a general list in 2010 and is presented in Table 17.3. There is no consensus for certain relative contraindications and hence the list varies based on individual institution experience and preference.

TABLE
17.3 Exclusion Criteria for Cardiac Transplantation

Absolute Contraindications:

Any systemic illness with a life expectancy < 2 y:
- Active or recent solid organ or blood malignancy within 5 y
- AIDS with frequent opportunistic infections
- Active systemic lupus erythematosis, sarcoid and amyloid with multisystem involvement
- Irreversible renal or hepatic failure being considered for only heart transplant
- Significant obstructive pulmonary disease ($FEV_1 < 1$)

Fixed Pulmonary Hypertension:

- PASP > 60 mm Hg
- Mean TPG > 15 mm Hg
- Pulmonary vascular resistance > 6 Wood units

Relative Contraindications:

- Age > 65–70 y
- Active infection except device related infection in VAD patients
- Active peptic ulcer disease
- Severe diabetes with end organ damage (neuropathy, retinopathy)
- Severe peripheral arterial disease not amenable to intervention
- Morbid obesity (BMI > 35 kg/m^2) or cachexia (BMI < 18 kg/m^2)
- Creatinine > 2.5 mg/dL or creatinine clearance < 25 mL/min
- Bilirubin > 2.5 mg/dL, serum transaminases > 3× normal, INR > 1.5 off warfarin
- Severe pulmonary dysfunction with FEV_1 < 40% of normal
- Recent pulmonary infarction within 6–8 wk
- Difficult to control hypertension
- Irreversible neurologic or neuromuscular disorder
- Active mental illness or psychosocial instability
- Drug, tobacco, or alcohol abuse within 6 mo
- Heparin-induced thrombocytopenia within 100 d

A patient who qualifies for a cardiac transplant gets a priority based on the severity of illness. Hence, the patients on the transplant list are divided into Status 1A (highest priority), defined as patients limited to the intensive care units who are dependent on

mechanical circulatory support devices (mechanical assist device, intra-aortic balloon pump, extracorporeal membrane oxygenator) or high-dose intravenous inotropes plus Swan–Ganz catheter. Patients who are mechanically ventilated or have ventricular-assist device-related complications such as a thromboembolism or a device infection and those with a mechanical assist device for a 30 day period are also listed as Status 1A. Status 1B includes patients on continuous intravenous inotropes or patients with ventricular-assist devices once their 30 day 1A time has expired. A patient who does not meet criteria for Status 1A or 1B is listed as Status 2. Status 7 patients are those who are considered temporarily unsuitable to receive a transplant (Table 17.4).

TABLE
17.4 UNOS Status Definitions

Status 1A: A patient listed Status 1A has at least one of the following devices or therapies in place.
(A) Mechanical circulatory support that includes one of the following:
LVAD and/or RVAD (max 30 d)
Total artificial heart
Intra-aortic balloon pump
ECMO
(B) Mechanical circulatory support with objective medical evidence of significant device-related complications such as thromboembolism, device infection, mechanical failure, and/or life-threatening ventricular arrhythmias
(C) Mechanical ventilation
(D) High-dose single intravenous inotrope, or multiple intravenous inotropes, in addition to pulmonary catheter in place

Status 1B: A patient listed as Status 1B has at least one of the following devices or therapies in place.
(A) LVAD and/or RVAD after 30 day Status 1A time has expired.
(B) Continuous infusion of intravenous inotropes

Status 2: A patient listed as Status 2 is one who does not meet criteria of Status 1A or 1B.

Status 7: A patient listed as Status 7 is considered temporarily unsuitable to receive a transplant.

Inpatients in need of a transplant are more clinically obvious than ambulatory patients. Determining the appropriate timing for consideration for transplant listing for ambulatory patients can be complicated. A patient should be considered for transplant when the expected survival without transplantation is lower than after transplantation. Variables like ejection fraction, NYHA class, and etiology of heart failure do not predict outcomes in heart failure consistently. In ambulatory patients, one of the best

predictors of survival is peak oxygen uptake (VO_2) measured by a cardiopulmonary exercise testing, which is an objective measure of functional status. The patient should achieve maximal exercise, represented by respiratory exchange ratio (RER) > 1.05 in order for the VO_2 to accurately predict outcomes. In cases where a maximal threshold is not achieved, the carbon dioxide ventilator equivalent ratio (VE/VCO_2) >35 can be used as a cutoff to refer for transplant listing. The ISHLT guidelines recommend repeating the test every 6 to 12 months to objectively reassess the need to remain on the transplant list.[3] The goal is to list a patient for transplantation after all medical and surgical options have been exhausted, but before the patient becomes debilitated with end-organ damage that may compromise posttransplant survival. Figure 17.1 provides an algorithm for patient selection for transplant listing.

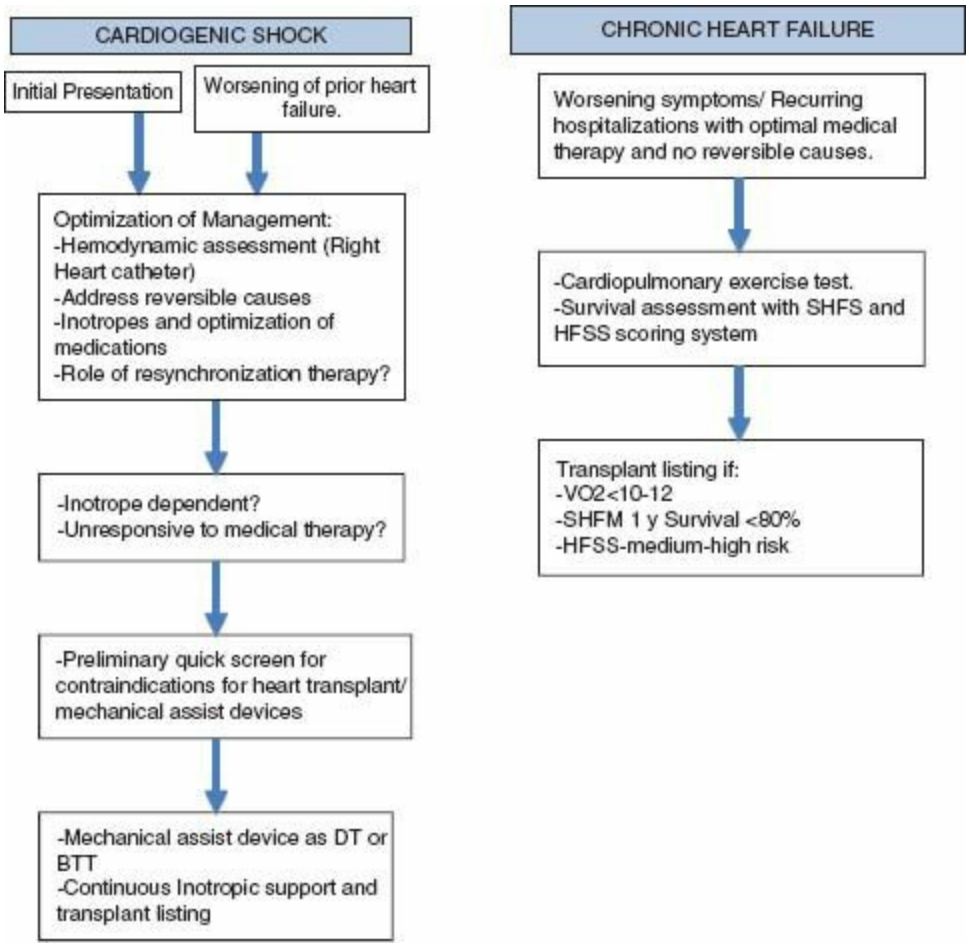

FIGURE 17.1 Steps in considering a patient for transplantation in the setting of acute decomposition **(A)** and in relatively stable **(B)** clinical situations. DT, destination therapy; BTT, bridge to transplant.

POSTTRANSPLANT MANAGEMENT ISSUES

Management of heart transplant patients broadly comprises monitoring for and management of the following: (a) allograft rejection, (b) complications and drug

interactions of immunosuppressive agents, (c) infections, and (d) malignancies.

Rejection

The transplanted heart is identified as foreign by the recipients' immune system and is subject to a constant attempt at immune destruction. Cellular identity of self and nonself for an organism is mediated primarily through a group of antigens called major histocompatibility complex (MHC) and expressed on cell surfaces. In humans, this group of proteins is named human leukocyte antigens (as they were first identified on leukocytes).

Rejection can involve both cellular and humoral (antibody-mediated) immune injury to the allograft and is often classified into four major types: hyperacute, acute cellular, antibody-mediated (humoral), and chronic (cardiac allograft vasculopathy [CAV]).

Hyperacute rejection is an antibody-mediated event, which occurs minutes to hours after transplantation and is caused by preexisting recipient antibodies against the donor's HLA present on the vascular endothelial cells. The histologic hallmark of hyperacute rejection is leaky capillaries, endothelial swelling, microthrombosis, polymononuclear infiltrate, and, subsequently, tissue necrosis. Immunohistochemical studies show deposition of immunoglobulin and complement within the vessel walls. Clinically, there is profound hemodynamic compromise and graft failure. Even with aggressive treatment, hyperacute rejection almost always leads to rapid graft loss. The catastrophic effects of hyperacute rejection can generally be prevented by PRA screening and by donor-recipient HLA and ABO blood- group cross-matching prior to transplantation. It is rarely seen in the current era.

Unlike hyperacute rejection, acute cellular rejection (ACR) is primarily a T-lymphocyte–mediated process, which can occur from the first week after transplantation up to many years out. Twenty to forty percent of transplant patients experience at least one episode of ACR in the first year posttransplantation.[6] A histologic grading system was developed in 1990 and updated in 2004 by the ISHLT. This grading classification is based on the amount of inflammatory infiltrate and presence or absence of myocyte necrosis[7] (Table 17.5) and helps guide immunosuppressive therapy. The consensus of most transplant centers is that rejection is considered significant when the biopsy is graded at least 2R or if there is any evidence of hemodynamic compromise regardless of grade. Many advanced grades of rejection may be present for prolonged periods (weeks) prior to the development of allograft dysfunction, thus the rationale for "surveillance" biopsies to detect rejection prior to the progression to significant allograft compromise.

TABLE
17.5 The 1990 and Revised 2004 ISHLT Pathologic Grading of ACR

Grade 0—No acute rejection	Grade 0R—No ACR
Grade 1A—Focal, mild acute rejection Grade 1 B—Diffuse, mild acute rejection	Grade 1R—Mild, low grade, ACR: interstitial and / or perivascular infiltrate with up to one focus of myocyte damage
Grade 2—Focal, moderate acute rejection	Grade 2R—Moderate, intermediate-grade, ACR: two or more foci of infiltrate with associated myocyte damage
Grade 3A—Multifocal moderate rejection Grade 3B—Diffuse, borderline severe acute rejection	Grade 3 R—Severe, high grade, ACR: diffuse infiltrate with multifocal myocyte damage ± edema ± hemorrhage ± vasculitis
Grade 4—Severe acute rejection	

Antibody-mediated rejection, also known as humoral rejection, is initiated by alloantibodies directed against donor HLAs on endothelial cells.[8] Antibody-mediated rejection is much less common than ACR. The biopsy reveals arteriolar, venular, and capillary endothelial swelling, nuclear enlargement, and infiltration of macrophages with or without lymphocytes (with B-cell predominance) early in the process. Once complement activation is initiated, there is recruitment of neutrophils, interstitial edema, and intravascular thrombosis with cell injury. Immunoflouresence microscopy shows complement components C3d, C4d, and C1q within the vessel walls. Episodes of antibody-mediated rejection are more severe than ACR and are usually associated with greater hemodynamic compromise, increased incidence of accelerated coronary artery vasculopathy at 1 year, and graft failure, with an overall poorer prognosis. Both AMR and ACR can coexist in 25% of acute rejection episodes.[9] Patients at the highest risk for developing humoral rejection include women, patients with high panel reactive antibodies and/or a positive donor-recipient cross-match, cytomegalovirus (CMV) seropositivity, and patients with sensitization to OKT3.[10] The 2004 ISHLT pathologic criteria classify AMR into present as AMR1 and absent as AMR 0. The criteria for AMR are (a) evidence of histologic features: myocardial capillary injury with endothelial swelling and intravascular macrophage accumulation with possible interstitial edema and presence of neutrophils and (b) positive immunofluorescence or positive immunoperoxidase staining for AMR (+CD68, C4d). Serologic evidence of donorspecific alloantibodies can be used as a supportive finding but is not required. Though immunoperoxidase staining can be used, immunofluorescence seems to be more sensitive.[11] With advancement in laboratory techniques, the concepts, diagnosis, and

therapeutics of AMR are evolving.

Monitoring for rejection primarily involves surveillance endomyocardial biopsies (EMBs). Because most rejection episodes occur within the first 3 to 6 months after transplantation, the frequency of biopsies is greater early on. A typical schedule might be weekly for 1 month, every other week for next month, every 3 to 4 weeks for next 1 to 2 months, every 4 to 6 weeks for 1 to 2 months, every 6 to 8 weeks until 1 year after transplant, and then every 3 to 6 months for the next 1 to 3 years while immunosuppression is being altered. Many programs stop routine surveillance biopsies after 3 to 5 years if the patient is stable on maintenance immunosuppression. It is reasonable to consider EMB for unexplained acute graft dysfunction regardless of time posttransplant or if major changes in the immunosuppressive regimen are required. Biopsies for the first 6 to 12 postoperative months and for patients at high risk for rejection beyond 12 months are considered reasonable. The utility of EMBs beyond 5 years is unclear. The current ISHLT guidelines [3] do not consider it necessary to perform routine immunostaining techniques screening for AMR, unless there is a suspicion on microscopy. Several centers, however, perform routine immunostaining.

Many studies have evaluated the utility of noninvasive tests such as ECG, signal-averaged ECG, heart rate variability, QT dispersion, echocardiogram, and MRI, but none have shown convincing strength to predict rejection. The only noninvasive technique currently utilized in allograft rejection surveillance is gene expression profiling (GEP). The Allomap test, which utilizes GEP, was approved by the FDA in 2008 for use after 2 months posttransplant. The GEP technique was validated in the Cardiac Allograft Gene Expression Observational (CARGO) study in which peripheral blood mononuclear cells were analyzed for upregulation of certain target genes (which are upregulated during allo- reaction).[12] A group of 11 discriminator genes were identified and validated to biopsy evidence of significant rejection (Grade 2R). A scoring system from 0 to 40 is used with the threshold suggesting no rejection varying with the duration from transplant: 3 to 6 months (<20), 6 to 9 months (<30), and >12 months (<34).

The Allomap testing tool can be used for its high negative predictive value in individuals at a low risk of rejection. It is not indicated to be used in those who are <2 months posttransplant, are still on high-dose steroids (≥20 mg prednisone or high dose of IV steroids), have undergone myeloablative therapy in the last 21 days, received blood products or hematopoietic growth factors in the last month, are pregnant, or are <15 years old. The IMAGE trial was undertaken to establish the utility of a clinical strategy of GEP-based rejection surveillance as a noninferior technique compared to the standard of surveillance EMBs.[13] In patients >6 months posttransplant, the trial showed that at 1 year, the use of GEP along with clinical and echocardiographic assessment was noninferior (HR 1.04, CI 0.67–1.68) compared with routine EBMs and decreased the number of biopsies per patient. A key question this study raised was the utility of

surveillance, irrespective of the type of test, as rejection episodes that were diagnosed prior to clinical graft dysfunction in either arm late after transplant was extremely low.

CAV, often called chronic rejection, remains a major limiting factor to long-term survival following cardiac transplantation. The incidence of CAV after transplant increases with the time from transplant: 8% at 1 year, 20% at 3 years, 30% at 5 years, and >50% at 10 years. It is an aggressive form of coronary artery disease that occurs months to years after transplantation and involves predominantly the entire length of the arterial vasculature with occasional involvement of the veins. Often the small intramyocardial vessels are severely involved. The histologic characteristics show concentric intimal thickening comprising of proliferative smooth muscle cells and extracellular matrix (ECM) with the vascular media and adventitia relatively unaffected. CAV is elicited by endothelial injury with a response from both cellular and humoral immune systems. Immune recognition to endothelial antigens leads to recruitment of inflammatory cells, of which the major effector cells are macrophages. These cells secrete proinflammatory cytokines and chemokines that influence proliferation of smooth muscle cells and deposition of ECM protein, causing luminal occlusion (5). Three stages of evolution of CAV have been suggested: (a) nonspecific endothelial injury (e.g., ischemia, trauma, and infection), (b) allo-response—recruitment of predominantly monocyte—macrophages and T-lymphocytes, and (c) arteriopathy—smooth muscle—like cell proliferation and ECM deposition.

ISHLT GUIDELINES[3]: REJECTION SURVEILLENCE:

Class IIa:

1. The standard of care for adult heart transplant recipients is to perform periodic endomyocardial biopsy (EMB) during the first 6 to 12 post operative months for surveillance of rejection. (Level of Evidence: C)
2. After the first postoperative year, biopsy surveillance for an extended period of time is recommended in patients at higher risk for late acute rejection, to reduce the risk for rejection with hemodynamic compromise and the risk of death in Africa-American recipients (who are at higher risk of rejection). (Level of Evidence: C)
3. Gene expression profiling can be used to rule out the presence of acute cellular rejection (ACR) of grade 2R or greater in appropriate low-risk patients, between 6 months and 5 years HT. (Level of Evidence: B)

Class IIb:

1. The use of routine EMB later than 5 years after HT is optional, depending on clinical judgment and the risk of for late allograft rejection. (Level of Evidence: C)

Class III:

1. The routine use of ECG parameters for acute allograft rejection monitoring is not recommended. (Level of Evidence: C)
2. The use of echocardiography as an alternative to EMB for rejection monitoring is not recommended (Level of Evidence: C)
3. The routine clinical use of MRI for acute allograft rejection monitoring is not recommended. (Level of Evidence: C)
4. The use of B-type natriuretic peptide (BNP), troponin I or T, C-reactive protein (CRP) levels for acute allograft rejection monitoring is not recommended. (Level of Evidence: C)
5. The use of systemic inflammatory markers for acute heart allograft rejection monitoring is not recommended. (Level of Evidence: C)

Both immune and nonimmune factors contribute to the pathogenesis of CAV The 2010 ISHLT report[3] looked at 5,677 transplants performed between July 1997 and June 2001 to determine that the risk of developing CAV within 8 years of transplant was influenced by donor and recipient age, donor diabetes/hypertension, donor body size, and donor/recipient characteristics. Early CAV risk factors include pretransplant coronary artery disease, increase in donor age, donor body mass index (BMI), and a history of donor hypertension, while lesser risks for developing early CAV were seen in female donors and recipients. Late CAV risk factors include donor hypertension, hospitalization during the first year posttransplant for rejection, pretransplant coronary artery disease, HLA-DR mismatch, decreasing recipient age, and increasing donor age.

Unfortunately, the clinical diagnosis of CAV is usually made after the disease is advanced. Many times, the first clinical manifestation of CAV is ventricular arrhythmias, congestive heart failure, or sudden death. The surgical denervation of the heart prevents the pain associated with myocardial ischemia or infarction, particularly in the first 5 to 10 years after transplant. Because of the absence of symptoms, annual angiograms are often performed to detect CAV Angiograms are somewhat insensitive because of the poor visualization of the concentric lesions that affect distal and small vessels before they become apparent in the main epicardial vessels. Coronary angiograms have been shown to underestimate the presence of disease as demonstrated by histopathol- ogy studies and intracoronary ultrasound (IVUS). Studies have shown

IVUS to be a more sensitive tool in detecting and following the progression of CAV by identifying maximal intimal thickness (an increase in ≥0.5 mm on serial IVUS examinations is considered significant); however, its increased cost, invasiveness, and lack of universal availability limit its use. An ISHLT consensus document proposes a new prognostically relevant nomenclature of CAV[14]

Angioplasty of CAV lesions, if discrete, may provide short-term palliation; however, restenosis rates are high and retrospective studies have shown DES to be better than BMS. Coronary artery bypass has limited use because CAV usually involves distal vessels and thus provides poor targets for bypassing. Retransplantation is an option, but the risk is higher than at the first transplant.

The mainstay of therapy for CAV is prevention and modification of coronary artery disease risk factors, including weight loss, lipid reduction, and controlling hypertension, and diabetes. These modifiable risk factors are thought to contribute to endothelial injury and the proliferation of smooth muscle cells and thus progression of CAV. Along with risk-factor modification, certain therapeutic modalities have been shown to be of some benefit in the prevention and progression of CAV. Statins not only lower cholesterol but also downregulate cytokine expression, lower plasma levels of C-reactive protein, and improve endothelial function and hence potentially decrease the onset of CAV. Calcium channel blockers have also been found to stabilize the endothelium and decrease platelet aggregation with a decrease in release of platelet-derived growth factor. Single-center studies have suggested that supplementation with vitamin C and E may retard early progression of transplant-associated arteriosclerosis. Two newer immunosuppressive agents, Sirolimus and Everolimus, have potent antiproliferative and antimigratory actions on vascular smooth muscle cells and have been shown in two multicenter prospective studies to decrease IVUS parameters of coronary vasculopathy. Furthermore, small single-center studies by Mancini et al.[15] and Segovia et al.[16] (RAPASTAT study) have suggested the benefit of Sirolimus in reducing adverse clinical outcomes and progression of IVUS parameters, respectively, in patients diagnosed with CAV. The clinical use of these proliferation signal inhibitors is limited by poor tolerability related to serositis and infections.

ISHLT GUIDELINES[3]: SCREENING FOR CAV

Class I:

1. Annual or biannual coronary angiography should be considered to assess the development of cardiac allograft vasculopathy (CAV). Patients free of CAV at 3 to 5 years after transplant, especially those with renal insufficiency may

undergo less frequent invasive evaluation. (Level of Evidence: C)

2. Follow-up coronary angiography is recommended at 6 months after a PCI (percutaneous coronary intervention) because of high restenosis rates in transplant recipients. (Level of Evidence: C)

Class II a:

1. Evaluation of Coronary Flow Reserve in conjunction with coronary angiography may be useful for the detection of small vessel coronary artery disease (CAD), which is a manifestation of CAV. (Level of Evidence: C)
2. Treadmill or dobutamine stress echo and myocardial perfusion imaging may be useful for the detection of CAV in heart transplant recipients unable to undergo invasive evaluation. (Level of Evidence: B)

ISHLT GUIDELINES[3]: CAV MANAGEMENT

Class I:

1. Primary prevention of CAV in heart transplant recipients should include strict control of cardiovascular risk factors as well as strategies for the prevention of cytomegalovirus (CMV) infection. (Level of Evidence: C)
2. In heart transplant recipients, statin therapy has been shown to reduce CAV and improve long-term outcomes regardless of lipid levels and should be considered for all HT recipients. (Level of Evidence: A)

Class IIa:

1. In HT recipients with established CAV, the substitution of mycophenolate mofetil (MMF) or azathioprine (AZA) with a PSI can be considered. (Level of Evidence: B)
2. PCI with drug eluting stents is recommended in both adults and children with CAV and offers short term palliation for appropriate discrete lesions. (Level of Evidence : C)
3. Surgical revascularization can be considered in appropriate individuals (Level of Evidence C)
4. Cardiac transplantation may be considered in patients with severe CAV and

absence of contraindications. (Level of Evidence C)

Immunosuppressive Strategies

Historically, during evolution of immunosupression for organ transplantation, a concept of induction was developed as a strategy to develop tolerance in the recipient to the donor organ. By attempting to wipe out the immune system during the pretransplant period it was thought that the donor antigen exposure and hence immune memory can be diminished leading to decreased chance of rejection on the long term. Though true tolerance is far from reality, such induction immunosuppressive strategies have proved beneficial in kidney transplants. Similar benefits were not realized in orthotopic heart transplant recipients when used routinely. Due to multiple reports of higher risk of infection and long-term risk of malignancy in patients receiving induction immunosuppressive therapy, some centers are reserving immune depletion agents to two clinical scenarios: (a) individuals at high risk of rejection and (b) in individuals with abnormal renal function as alternative potent immunosuppressive agents to delay initiation of calcineurin inhibitors giving time for the kidney function to recover from perioperative insult. Agents used are either lymphocyte depleting (antithymocyte globulins [ATG], Alemtuzumab, and Muromonab) or nonlymphocyte depleting (Daclizumab and Basiliximab).

While maintenance immunosuppressive agents are used to prevent significant rejection episodes, acute rejection episodes are treated with uptitration of the maintenance doses in either low-grade rejection, high-dose steroids in high grade cellular rejection, or combination of lymphocytedepleting or nondepleting agents with or without IVIG and plasmapheresis in antibody-mediated rejection.

The understanding of the pharmacodynamics of immunosuppressant agents is closely related to basic immunology of T-cell and B-cell activation and mounting a rejection episode. Figure 17.2 depicts the sites of action of immunosuppressant agents in relation to T-cell activation.[17]

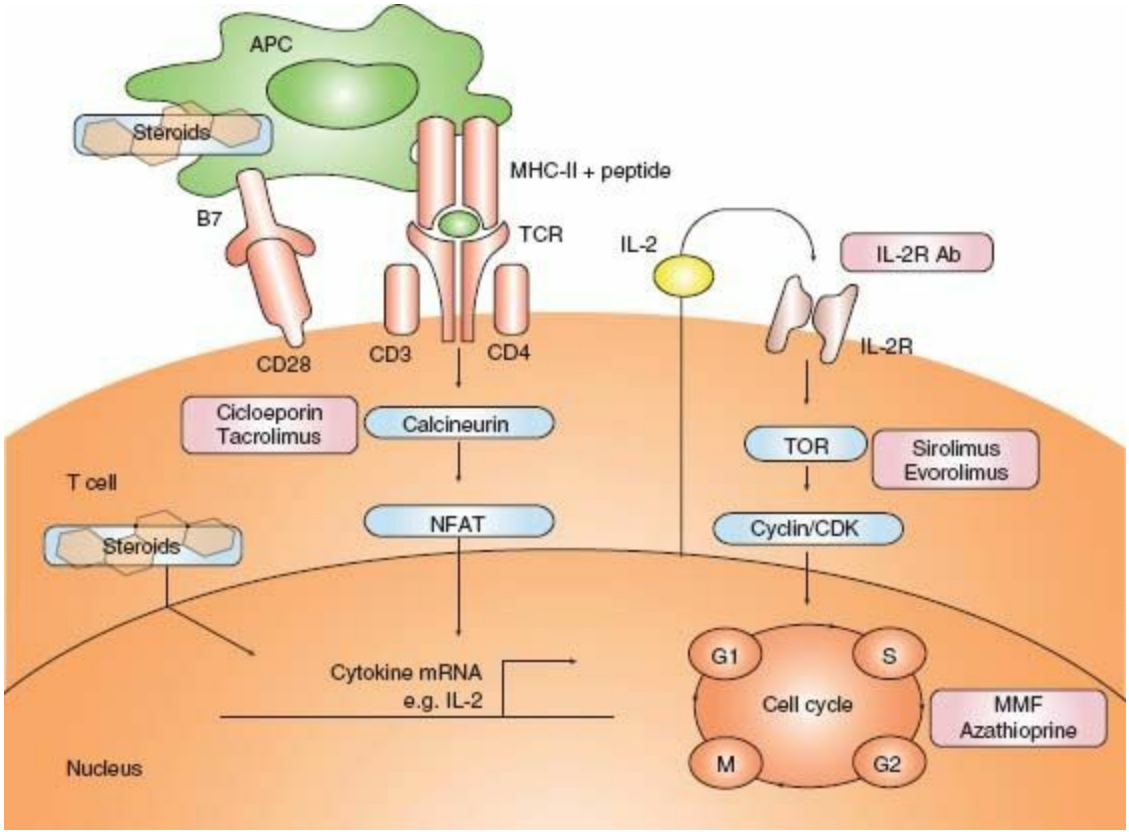

FIGURE 17.2 Schematic of mechanisms of action of immunospuressive drugs. (Reprinted from Halloran PF, Gourishankar S. Principles and overview of immunosuppresion. In: Norman DJ, Turka LA, eds. Primer on Transplantation. Mt Laurel, NJ: American Society of Transplantation; 2001:87–98, with permission.)

Individual Immunosuppresant Agents

Polyclonal Antibodies

Antilymphocyte antibodies are used immediately posttransplantation to treat rejection episodes refractory to high-dose steroids or in patients with rejection associated with hemodynamic compromise. Polyclonal antithymocyte antibodies are antibodies derived from horse (ATGAM) or rabbit (Thymoglobulin). These antibodies are directed against multiple hematopoietic cell surface antigens and bind to the surface antigens, leading to cell depletion. T-cell surface antigens (CD2, CD3, CD4, and CD8) and B-cell surface antigens (CD19, CD20, and CD21) are predominantly affected leading to depletion of these cells in both peripheral circulation and lymphoid organs. These agents are considered efficacious when the CD3/CD2 counts are reduced to <10% of the pretreatment values. Complications can include febrile reactions, which usually occur during the initial infusion, and rarely, serum sickness. A higher incidence of serum sickness in the horse-derived antibodies has made it a less-favorable choice. The development of leukopenia or thrombocytopenia may require a reduction in dose or termination of therapy. Studies have shown an increased incidence in viral infections (CMV) and perhaps posttransplant lymphoproliferative disease (PTLD) associated with

polyclonal antibody use.

Monoclonal Antibodies

Muromonab-CD3 (OKT3) is used for induction therapy in recipients with greater risk of rejection and for episodes of steroid-resistant rejection. OKT3 is an anti-CD3 monoclonal antibody that prevents the activation of the CD3-TCR receptor, which is required to generate the intracellular signals for T-cell activation. As the antibody remains bound to the receptor, further activation and proliferation of T cells are inhibited. However, OKT3 binding to the CD3-TCR complex on the surface of the T cell by itself can activate the T cell leading to cytokine release. Fever, chills, wheezing, chest pain, and hypotension characterize the cytokine release syndrome, which can be potentially life threatening. Symptoms are minimized by premedication with acetaminophen, intravenous steroids, and antihistamines. CD3+ T cells are generally undetectable during OKT3 therapy; however, within 12 to 24 hours after cessation of OKT3, CD3+ T cells reappear in circulation, unlike after treatment with ATG preparations, with which the lymphocyte depletion is present for weeks. There is an increased risk of developing HSV and CMV infections, especially in patients who are CMV donor positive and recipient negative (Table 17.6). Also, latent Epstein-Barr virus (EBV) may reactivate, leading to lymphoproliferative disorders including malignant monoclonal B-cell lymphomas. OKT3 is occasionally associated with aseptic meningitis or encephalopathy. Clinical studies have shown a significantly higher incidence of pulmonary edema, hypotension, and lymphomas compared to ATGAM. Due to these reasons, OKT3 has fallen out of favor as an agent for induction therapy.

TABLE
17.6 Risk of CMV Clinical Disease

Donor	Recipient	Immunosuppression	Risk (%)
+	–	Standard[a]	>50
+/–	+	Standard	15–20
+/–	+	Induction ALA[b] + standard	25–35
+/–	+	Antirejection ALA + standard	65
–	–	Any	0

[a]Cyclosporine or FK 506, azathioprine or mycophenolate-mofetil, and prednisone.

[b]Antilymphocyte antibody.

The interleukin-2 (IL-2) receptor (CD25) antibodies Basiliximab (Simulect) and Daclizumab (Zenapax) selectively inhibit T-cell proliferation by binding to the IL-2

receptor of activated T cells, preventing clonal expansion and activation of T cells. In heart transplant recipients, IL-2 receptor antagonists reduce the risk of rejection without increasing the incidence of infections during the early postoperative period. These monoclonal antibodies have been mostly used during induction to delay the introduction of calcineurin inhibitors. This approach creates a window to improve renal dysfunction exacerbated by ischemic-reperfusion injury. Basiliximab and Daclizumab are considered to be nondepleting induction agents because they do not affect resting lymphocytes. Basiliximab is a chimeric antibody (30% murine, 70% human protein), whereas Dacliximab is a humanized antibody (10% murine, 90% human protein), both designed to be less immunogenic than a fully murine monoclonal antibody. The IL-2 receptor antibodies appear to offer some advantage in heart transplant recipients, including the lack of the cytokine release syndrome and no reported increased risk of infections or malignancies. In 2009, most patients undergoing induction therapy received IL2R antagonist.[2]

A newer agent Alemtuzumab, a humanized murine monoclonal antibody against CD52 (cell surface protein expressed on lymphocytes, NK cells, monocytes, and thymocytes), is being studied in heart transplant recipients as an induction agent.

ISHLT GUIDELINES[3]: INDUCTION AGENTS

Class II a:

1. Immunosuppressive induction with polyclonal antibody preparations may be beneficial in patients at high risk of renal dysfunction when used with the intent to delay or avoid the use of a CNI (calcineurin inhibitor). (Level of Evidence: B)

Class II b:

1. Routine use of immunosuppressive induction in all patients has not been shown to be superior to immunosuppressive regimens that do not employ such therapy. (Level of Evidence: B)
2. classClass II b: Immunosuppressive induction with antithymocyte globulin (ATG) may be beneficial in patients at high risk for acute rejection. (Level of Evidence: C)

Calcineurin Inhibitors

In the early 1980s, cyclosporine (CsA), a lipophilic endacapeptide calcineurin inhibitor derived from a plant fungus, was first introduced as an immunosuppressant. Its use resulted in a dramatic reduction in the incidence of acute rejection in heart transplant recipients. Today, the calcineurin inhibitors are the cornerstone of therapy after heart transplantation, in conjunction with an antiproliferative agent and corticosteroids (CSs) (the so-called triple-drug therapy).

Calcineurin, a calcium-dependent serine-threoninephosphatase, is a vital enzyme in the transcription of IL-2 and other cytokine genes. The interaction of IL-2 with its receptor on activated T cells induces T-cell proliferation, which triggers the emergence of effector cells responsible for tissue destruction, resulting in clinical acute rejection. The T-cell receptor (TCR) is activated in response to alloantigens, causing an increase in intracellular calcium, which in turn activates the cytosolic protein, calmodulin. Ca^{2+}-calmodulin interacts with calcineurin, activating its phosphatase moiety. Calcineurin is then able to dephosphorylate the nuclear factor of activated T cells (NFAT). NFAT translocates into the nucleus and causes transcription of T-cell–dependent lymphokines, such as IL-2 (and its receptor), interferon-γ, and tumor necrosis factor-α.

The calcineurin inhibitors (cyclosporine and tacrolimus) exert their effects by binding to cytosolic proteins called immunophilins upon entry into the T cell. Cyclosporin binds to cyclophilin and tacrolimus binds to FK-binding protein-12 (FKBP-12). Binding of cyclosporine and tacrolimus to its respective immunophilin enhances the immunophilins affinity to calcineurin. The immunophilin–drug complex inhibits the phosphatase activity of calcineurin, thereby preventing translocation of NFAT into the nucleus and therefore preventing the transcription of IL-2 and other cytokine genes.

The early preparation of cyclosporine (Sandimmune) was oil based and its bioavailability was unpredictable due to variations in absorption and metabolism. Neoral, the new microemulsion formulation of cyclosporine, has demonstrated greater bioavailability and more predictable pharmacokinetics than Sandimmune and hence translated into less rejection episodes, lower required dose, and less treatment failures.[18] Cyclosporine is absorbed in the upper GI tract and the majority is eliminated through metabolism in the cytochrome P450 system. It also inhibits CYP3A4 enzymes altering metabolism of medications being processed through this enzyme.

The side effects and toxicities of cyclosporine include nephrotoxicity, hypertension, gingival hyperplasia, hirsutism, neuropathy, hyperlipidemia, and hyperkalemia. Drug-level monitoring is helpful in lessening the risk of toxicity while maintaining antirejection efficacy. Target CsA levels are measured trough levels. Because rejection is more prevalent early posttransplantation, higher levels of CsA are generally targeted (Table 17.7).

TABLE

17.7 Drug Therapy in Cardiac Transplantation

Drug	Target Level (ng/mL) [m]	Interactions	Toxicities
Cyclosporine	275–375 [0–1.5] 200–350 [1.5–3] 150–300 [3–6] 150–250 [>6]	↑ cyclo levels via cyt P450: erythromycin, ketoconazole, diltiazem, cimetidine ↓ cyclo levels: isoniazid, rifampin, phenytoin	Nephrotoxcity Hypertension Hypomagnesemia Hypertrichosis Gout Gingival hyperplasia Hyperlipidemia
Tacrolimus	10–15 [0–2] 8–12 [3–6] 5–10 [>6]	Same as cyclosporine	Nephrotoxicity Neurotoxicity HTN < cyclosporine ↑ lipids < cyclosporine Glucose intolerance Alopecia Diarrhea
Mycophenolate-mofetil	Routine levels not recommended. Trough <1.5 mg—considered low	↓ absorption in the presence of antacids containing magnesium or aluminum hydroxide	Anemia Diarrhea Nausea
Sirolimus Everolimus	4–12 3–8	Same as cyclosporine	Hyperlipidemia Thrombocytopenia Anemia Neutropenia Diarrhea
Azathioprine	Levels not monitored	Allopurinol—↑ levels	Myelosuppression, leukopenia Keep WBC >3,000/mL

Tacrolimus (Tac), formerly called FK506, is a highly immunosuppressive calcineurin inhibitor. Tac is about 100 times more potent than CsA. Like CsA, it is metabolized via the cytochrome p450 3A-4 system, and its intravenous dose is one-fourth to one-fifth of its oral dose. Toxicities include nephrotoxicity, neurotoxicity, hyperuricemia, hypomagnesemia, gastrointestinal (GI) symptoms, diabetes, hyperkalemia, hyperlipidemia, and alopecia. Drug monitoring is very important to lessen the toxic effects while maintaining efficacy (see Table 17.7).

Clinical trials have shown mixed results when the performance of Tac and conventional CsA was compared among heart transplant patients in conjunction to receiving azathioprine, mycophenolate mofetil (MMF), and steroids. Early studies showed no significant differences in outcomes between the two calcineurin inhibitors, while later studies revealed significantly lower 6 month rates of any treated rejection and ISHLT cellular grade 3A rejection episodes in the tacrolimus group.[19] Monotherapy with tacrolimus was recently evaluated in the TICTAC (Tacrolimus in Combination, Tacrolimus alone compared)[20] trial showing comparable rejection rates in comparison to using a combination of Tac/MMF. Several studies have also shown the effectiveness

of replacing CsA with Tac in cases of refractory rejection, gingival hyperplasia, or hirsutism. Patients treated with CsA have higher cholesterol and triglyceride levels, more hypertension, cholelithiasis, gingival hyperplasia, and hirusitism compared to patients on Tac, while the latter had more diabetes mellitus, tremor, and anemia.[19,21,22] The calcineurin inhibitor chosen is often dependent on the patient, the side- effect profile, and the institutional experience.

In view of the side effect profile of the CNIs and suggestive benefit of antiproliferative agents in regard to allograft coronary vasculopathy, newer trials are evaluating CNI sparing regimens.

ISHLT GUIDELINES[3]: CNI USE

Class I:

1. Lower levels of CNIs in HT should be sought when CNIs are used in conjunction with MMF because with this combination lower levels are safe and associated with lower rejection rates as well as improved renal function. (Level of Evidence: B)

Class IIa:

1. Calcineurin inhibitor-based therapy remains the standard in immunosuppressive protocols used after heart transplant. (Level of Evidence: B)

Class IIb:

1. The results of clinical trials suggest that TAC-based regimens may be associated with lower rejection rate but not superior survival after HT than cyclosporine based regimens. (Level of Evidence: B)
2. CNI monotherapy with early CS withdrawal may be considered in highly selected individuals. (Level of Evidence: B)

Antiproliferative Agents

Azathioprine (Imuran) is a purine analog that impairs DNA synthesis and acts as an antiproliferative agent. It suppresses both T- and B-cell synthesis. It is well absorbed in the upper GI tract and metabolized in the liver. Some of its metabolites are broken down

via xanthine oxidase. Hence, a xanthine oxidase inhibitor such as allopurinol can increase the azathioprine levels up to four times. The usual dose of azathioprine is 1 to 3 mg/kg/d, with the aim of keeping the white blood cell count >3,000 and the platelet count >100,000. Myelosuppression is the major toxicity, and it is generally dose dependent. Withdrawal of azathioprine usually reverses myelosuppression within 7 to 10 days. Other side effects include hepatotoxicity and pancreatitis. Malignancies, especially cutaneous malignancies, may be more common when compared to other, newer agents. Due to its side effect profile and available alternatives, the use of azathioprine has declined.[2] Randomized trials have also shown that MMF, evorolimus, and sirolimus have lower rates of CAV when compared to azathioprine.[23–25]

MMF (Cellcept), also an antiproliferative agent, blocks the de novo pathway of purine synthesis in T and B lymphocytes that lack a robust salvage pathway. Mycophesnolic acid (MPA), a product of a Penicillin fungus, is the active metabolite of MMF. It is readily absorbed across the GI tract; however, the absorption of MPA is decreased in the presence of antacids containing magnesium and aluminum hydroxides. Toxicities of MMF include GI symptoms (nausea, vomiting, and diarrhea) and myelosuppression. The incidence of these adverse events is higher in patients receiving >3 g/d. Most symptoms will resolve with reduction of dose. Though many centers have MPA serum levels available, the relationship between MPA levels and rejection remains unclear. Hence, the current guidelines recommend against routine monitoring of drug level to adjust dosing[3] (see Table 17.7). In specific situations where there is a suspicion of low-drug exposure leading to rejection, a trough level can be used to tailor dose adjustment. The serum levels of MPA are higher when this drug is administered with Tac compared to CsA, thus it is advisable to empirically reduce the dosage of MMF when switching from CsA to Tac. Comparing MMF to azathioprine on background of CsA and prednisone, there appears to be a 3-year survival advantage and a reduction of graft loss to rejection with MMF.[23] However, one trial showed more opportunistic infections, diarrhea, and esophagitis in the MMF group compared to AZA-treated patients. MMF has become the dominant antiproliferative agent used in clinical practice.

TOR Inhibitors

Rapamycin (Sirolimus) is a macrolide antibiotic with a similar structure to tacrolimus. It is in the class of immunosuppressants called target of rapamycin (TOR) inhibitors. The TOR enzyme is a cytoplasmic protein responsible for connecting signals from the surface of the T cell to the nucleus for stimulation of growth and proliferation of the T lymphocytes. Rapamycin binds to TOR and inhibits cell proliferation stimulated by growth factors. It is known to inhibit platelet-derived growth factor and basic fibroblast growth factors in the arterial smooth muscle cells and endothelial cells, respectively. Studies have shown a decrease in the incidence of coronary allograft vasculopathy in

heart transplant recipients receiving this immunosuppressant.[25] Common side effects include hyperlipidemia and thrombocytopenia. When rapamycin is used alone there appears to be no adverse effects on kidney function; however, when it is used in combination with calcineurin inhibitors, there is a potentiation of the calcineurin inhibitor–induced nephrotoxicity. Therefore, the dose and target levels of the calcineurin inhibitor must be reduced substantially.

Everolimus (RAD: Certican) is a derivative of sirolimus with an identical mechanism of action. RAD, like rapamycin, inhibits clonal expansion of T cells but does not inhibit T-cell activation. It exerts its affects by forming a complex with FKBP-12 to inhibit the cyclin-dependent kinases termed the TOR. This leads to G1 S-phase cell cycle arrest. When compared to sirolimus, everolimus has a shorter half-life (30 hours compared to rapamycin at 60 hours) as well as a relatively higher bioavailability. Like the calcineurin inhibitors, RAD and rapamycin are biotransformed through the cytochrome P450, 3A-4 system. Side effect profile is similar to Sirolimus and has also been associated with a significant reduction in allograft vasculopathy measured by IVUS at 1 year (7).

Corticosteroids

CSs are important for induction, maintenance, and treatment of rejection in heart transplant recipients. CSs have immunosuppressive and anti-inflammatory effects and affect the number, distribution, and function of T cells, B cells, macrophages, as well as endothelial cells. The usual treatment for moderate rejection (grade 2R) without hemodynamic compromise is pulse-dose steroids (250 to 1,000 mg solumedrol intravenously daily for 3 days). Most rejection episodes respond to initial therapy.

ISHLT GUIDELINES[3]: ANTIPROLIFERATIVE AGENTS

Class IIa:

1. MMF, EVL or SRL as tolerated should be included in contemporary immunosuppressive regimens because therapies including these drugs have been shown to reduce onset and progression of CAV (assessed with IVUS). (Level of Evidence: B)

ISHLT GUIDELINES[3]: CORTICOSTEROID USE

Class I:

1. CS withdrawal can be successfully achieved 3 to 6 months after HT in many low risk patients. (Level of Evidence: B)

Class IIa:

1. Corticosteroid avoidance, early CS weaning or very low dose maintenance CS therapy are all acceptable therapeutic approaches. (Level of Evidence: B)
2. If used, CS weaning should be attempted if there are significant CS side effects and no recent rejection episodes. (Level of Evidence: C)

Steroids are associated with many side effects including cataracts, diabetes, myopathy, osteopenia, growth retardation in children, aseptic necrosis, hirsutism, cushingoid appearance, and dermatologic problems. They also exacerbate hypertension and hyperlipidemia, and cause adrenal insufficiency. Thus, it is important to give stress doses of hydrocortisone when indicated (illness, surgical procedures) to patients on chronic CSs. Current practice favors withdrawal of steroids to minimal dosage or none at 6 months to 1 year posttransplant, provided there are no rejection episodes. Yet, data from the ISHLT registry between 2007 and 2009 shows that 89% of patients are still on steroids at the end of 1 year and 52% at 5 years.[2] Typically, serial EBMs are performed to monitor for rejection while CS are withdrawn.

Combination Regimen

Most transplant centers initiate triple therapy with a CNI, an antiproliferative agent, and a CS. Figure 17.2 reflects the idea of using medications acting on different pathways of T-cell activation in order to achieve effective immunosuppression. In general, the various clinical trials have not shown significant mortality benefit of one combination over the other. Tacrolimus, mycophenolate, and prednisone are currently the dominant immunosuppressive choices. The mTOR inhibitors are not used widely due to their side effect profile. Sirolimus and evorolimus are used in 11% of patients at 1 year and 23% at 5 years posttransplant.[2]

ISHLT GUIDELINES[3]: CHOICE OF IMMUNOSUPRESSION AGENTS

Class IIB:

1. The adverse events of immunosuppressive drugs observed in randomized

clinical trials underscore the need for individualization of immunosuppressant according to the characteristics and risks of the individual recipient. (Level of Evidence: C)

POSTTRANSPLANT COMPLICATIONS

Infection

Preventing allograft rejection with immunosuppressive agents increases the risk of infection posttransplantation. Infections continue to be one of the leading causes of death after cardiac transplantation. Knowing the timetable of common infections following solid-organ transplant will aid in formulating a differential diagnosis and determining the timing of the various preventative strategies.

A pretransplant infectious disease evaluation is used to identify any condition that would disqualify a potential recipient for transplantation, update immunizations, identify and treat active infections, and define the risk of infection in order to determine the strategy for preventing posttransplant infections.

During the first 30 days after transplantation, there are generally three types of infections that occur: (a) active infection transmitted with the allograft, (b) untreated pre-transplant infection in the recipient, and (c) nosocomial infections, which are commonly related to surgical wounds or indwelling catheters. More than 95% of the nosocomial infections during this period are bacterial or fungal (Candida species). In contrast, late infections that occur 1 to 6 months following transplantation are generally caused by opportunistic organisms such as Pneumocystis carinii (PCP), Aspergillosis species, Nocardia asteroids, and Listeria monocytogenes and viral infections such as CMV or EBV, which are by far the most common. After 6 months posttransplantation, most patients require decreasing levels of immunosuppression and thus their infectious disease risks become similar to those of the general population. The majority of patients require antiviral, antibacterial, and antifungal prophylaxis for 6 to 12 months posttransplantation. Approximately 5% to 10% of transplant recipients experience recurrent rejection episodes and thus are still at risk of developing opportunistic infections secondary to increased immunosuppressive therapy.

There are no specific guidelines for endocarditis prophylaxis in heart transplant patients. Although the incidence of endocarditis is low in this population, the mortality rate is approximately 80%. Individuals who develop valvular heart disease have a higher risk than those who do not. The use of antibiotic prophylaxis for dental procedures in heart transplant patients is considered reasonable.

Viral Infections

CMV remains the most important infection affecting the morbidity and mortality of heart

transplant recipients. The serologic (presence of antibody to CMV) status of the donor and the recipient is a predominant predictor of posttransplant CMV disease events. Donor seropositive (D+)/recipient seronegative (R-) bears the greatest risk of developing CMV clinical disease, which can present as leukocytopenia, pneumonia, colitis, gastritis, esophagitis, hepatitis, or myocarditis. With D+/R- status, there is an increased incidence of tissue-invasive CMV, recurrent CMV, ganciclovir-resistant CMV, and CAV. Patients at highest risk receive prophylaxis with oral valgancyclovir with or without CMV hyperimmune globulin (CMV–IVIG, Cryptogam). Active CMV disease must be treated with intravenous gancyclovir with or without CMV–IVIG, depending on whether or not invasive CMV is present.

Fungal Infections

Candida species and Aspergillosis are the most common fungal infections after transplantation. Oral clotrimazole or nystatin is used during the first 3 to 6 months or during periods of enhanced immunosuppression, when there is an increased risk of opportunistic infection.

Protozoal Infections

Trimethoprim-sulfamethoxazole (TMP-SMX) is highly effective against PCP and Nocardia infections. Prior to the institution of PCP prophylaxis, approximately 10% of cardiac transplant recipients developed PCP, with a mortality rate up to 40%. Nowadays, with TMP-SMX prophylaxis, PCP is exceedingly rare. Toxoplasmosis is also a concern in heart transplant recipients. A Toxoplasma-seronegative recipient of a Toxoplasma-seropositive donor is at highest risk of developing toxoplasmosis posttransplant. Prophylaxis with TMP- SMX is also effective posttransplantation and during episodes of increased immunosuppression therapy (steroid-resistant rejection). Active toxoplasmosis can present as myocarditis and is treated with pyrimethamine and sulfonamide.

Malignancies

Cutaneous malignant lesions are the most common tumors after cardiac transplantation and account for nearly 40% of de novo cancers.[26] Posttransplantation, the incidence of squamous cell carcinoma and basal cell carcinoma is increased, with basal cell carcinoma being the most common type (unlike the general population, in which squamous cell carcinoma is the most common type of skin cancer).

PTLD is a unique type of lymphoma that occurs in approximately 3.4% of all heart transplant recipients.[27] Approximately 90% of all PTLDs are associated with EBV These tumors are B-cell in origin and range from a benign polyclonal process to a highly malignant monoclonal lymphoma. Typically the tumor arises 12 to 18 months following transplant and is most commonly located intraabdominally. The patient may have a mononucleosis-like presentation. Risk factors for developing PTLD include

EBV-seropositive donor to EBV-seronegative recipient, type of organ transplanted (lung and heart have the highest incidence), preceding CMV infection, and the level and type of immunosuppression used posttransplantation. PTLDs have variable prognoses, with treatment strategies geared toward drastically decreasing background immunosuppressant drug therapy. This tactic may lead to a regression of PTLD in 23% to 50% of the patients.[27] Malignant lymphomas (even if EBV initiated) usually require cytotoxic chemotherapy as well, and despite aggressive therapy, have poor response rates (<50%).

Chronic immunosuppression and induction therapy have been implicated as risk factors for malignancy. A strategy of minimization of immunosuppression with acceptance of lower CNI levels and/or decreased MMF dose is important upon diagnosis of a lymphoid malignancy. Cancer screening recommendations are similar to the general population. Standard therapy is recommended for individual cancers. Certain cancers have a more malignant course in transplant patients compared to the general population.

Chronic Renal Dysfunction

Renal dysfunction remains an important complication. About 20% of patients have some degree of renal dysfunction 1 year following cardiac transplantation. By year 7, approximately 10% of survivors have a creatinine >2.5 mg/dL, while 4% are on chronic dialysis.[2]

Risk factors for late renal dysfunction include chronic administration of calcineurin inhibitors (cyclosporine and tacrolimus), preexisting renal dysfunction, diabetes, hypertension, and generalized atherosclerosis. The renal toxicity associated with calcineurin inhibitors includes early functional nephrotoxicity and late structural nephrotoxicity. The early form of nephrotoxicity occurs when calcineurin inhibitors are administered for the first time. The calcineurin inhibitors cause vasoconstriction of the afferent arterioles, resulting in a decrease in renal blood flow and a decrease in glomerular filtration rate. The late form of renal dysfunction is thought to be caused by a combination of the acute reno-vascular effects plus direct toxic effects on renal tubular epithelial cells. Cyclosporine has been shown experimentally to cause apoptosis in tubular and interstitial cells, potentially inducing tubular atrophy and subsequent fibrosis. Both early and late renal effects are dose related. The management of chronic renal insufficiency is to minimize the dosage of calcineurin inhibitors, which may or may not halt the progression of the renal dysfunction. Another alternative is to switch to a sirolimus-based regimen, which may have renalsparing effects if initiated before renal dysfunction is progressive. Kidney transplantation should be considered for end-stage renal dysfunction.

Hypertension

The majority of adult cardiac transplant recipients are diagnosed with arterial

hypertension. The use of cyclosporine is linked directly to the development of posttransplant hypertension. Three proposed mechanisms are direct sympathetic activation, increased responsiveness to circulating neurohormones, and direct vascular effects. A common endpoint of these proposed mechanisms is vasoconstriction of the renal vasculature, leading to sodium retention and an elevated plasma volume. Hypertension has been found to be less common in patients receiving tacrolimus than in those receiving cyclosporine. Steroids also play a role in the development of hypertension posttransplant. The mineralocorticoid activity causes sodium retention and also contributes to the increase in plasma volume. The denervated transplanted heart may not respond well to the increased after load, and persistent hypertension may lead to left ventricular hypertrophy and subsequent left ventricular systolic and diastolic dysfunction. Initial nonpharmacologic therapy should include sodium restriction. First-line pharmacologic agents include calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors. Calcium channel blockers are the most commonly used class of medications followed by ACE inhibitor. Diltiazem has the advantage of increasing the cyclosporine level by competing with cytochrome P450, thereby decreasing the required cyclosporine dose. Monotherapy is effective in <50% of patients posttransplantation and multiple agents are often needed to achieve adequate blood pressure control. Historically, beta-blockers have been avoided, secondary to concerns about excessive bradycardia or exercise intolerance in the denervated heart; however, if they are needed, they are effective antihypertensive agents.

Hyperlipidemia

Approximately 1 month after heart transplantation, recipients frequently demonstrate an increase in total cholesterol, low-density lipoprotein (LDL) cholesterol, apolipoprotein B, and triglyceride levels. The etiology of dyslipidemia in heart transplant recipients is multifactorial, including genetic predisposition, high-fat diets, and immunosuppressive agents. In particular, CSs and cyclosporine have been found to be important immunomodulating drugs that contribute to the development of hyperlipidemia posttransplant. Cyclosporine decreases bile acid synthesis from cholesterol and thus increases serum cholesterol levels. CSs increase acetyl coenzyme A (CoA) carboxylase activity and free fatty acid synthesis, which is a precursor to cholesterol synthesis. Statins have been found to reduce LDL cholesterol levels in heart transplant recipients. In particular, pravastatin has been shown to cause not only a significant reduction in cholesterol levels at 3, 6, 9, and 12 months posttransplantation but also a reduction in rejection episodes associated with hemodynamic compromise, a decrease in the incidence of CAV, and an increased overall 1-year survival.[28] Current recommendations are to prescribe a low-dose statins to all transplant recipients early after transplantation, regardless of their lipid levels, as long as liver function tests are normal. A critical interaction between the statins and cyclosporine or tacrolimus (via

cytochrome P450–3A inhibition) increases the risk of myositis and rhabdomyolysis. Thus, statins are started at lower doses in transplant patients and titrated up carefully.

Tricuspid Regurgitation

Tricuspid regurgitation (TR) is not uncommon in the transplanted heart. Mild TR is present in virtually all transplanted hearts, and moderate–severe TR is present in up to 50% of transplant patients who live >5 years. Mechanical torsion on the tricuspid annulus due to the biatrial anastamosis accounts for at least mild–moderate regurgitation. The more anatomically correct, bicaval anastamotic technique has decreased the incidence but not prevented it. Recipients with preexisting pulmonary artery hypertension often experience acute right ventricular dysfunction and subsequent chronic dilation, which contributes to the regurgitation. More importantly, repeated EMBs with damage to the valve, chordal apparatus, and papillary muscles account for the majority of severe cases of TR. Generally, even severe TR is well tolerated, but in a small minority of patients with progressive right heart failure due to TR, tricuspid replacement is needed (<3% of all heart transplants). Heart transplant patients with TR are at higher risk of endocarditis than those with no valvular pathology.

Osteoporosis

Osteoporosis remains a common problem in heart transplant recipients, contributing to fracture-associated immobility that may compromise quality of life posttransplantation. The risk factors for osteoporosis may begin well before transplantation. Patients awaiting heart transplantation have a mean average reduction in bone mineral density (BMD) up to 10% compared to age-matched healthy individuals. Contributing factors to bone loss in severe heart failure patients include reduced exercise or immobilization, cardiac cachexia, smoking, alcohol, low calcium intake, renal failure, hypogonadism, heparin, and loop diuretic administration.

Bone loss is most rapid during the first 6 months following transplant, which coincides with the period of aggressive immunosuppression. Lumbar spine and femoral neck BMD declines 3% to 10% and 6% to 11%, respectively, in the first 6 months and stabilizes thereafter. Glucocorticoids are known to cause accelerated bone loss and are associated with a higher-than-normal incidence of vertebral fractures. Glucocorticoids reduce bone density by direct inhibition of osteoblast function and impairment of collagen and new bone formation. Shane et al.[29] showed that at 2 years after cardiac transplant, severe osteoporosis was detected in the lumbar spine in 28% of patients and within the femoral neck in 20% of patients. It is common to perform routine screening of transplant candidates with baseline BMD study prior to transplantation to identify and correct any secondary causes of bone loss. A regimen of elemental calcium, vitamin D supplementation, with or without bisphosphonates, and proper exercise training is indicated pretransplantation, and it is recommended to begin bisphosphonates for all posttransplant patients receiving CSs immediately after transplant and continue at least

through the first year post-transplant. The American College of Rheumatology guidelines recommend calcium and vitamin D supplementation for all patients receiving CSs to prevent osteoporosis.[30] With decreased doses of steroids, recent studies have shown a decrease in bone loss in posttransplant patients when compared to the past.

SURVIVAL

In the current era, the 1-year survival after cardiac transplantation exceeds 85% and approaches 90% at most institutions.[2] The greatest mortality occurs in the first year posttransplantation and the temporal improvement in heart transplant survival over the last decade is due to improvements in outcomes during this time. After year 1, the annual mortality rate is approximately 3.6%, such that the 5- and 10-year survival rates are approximately 70% to 75% and 50% to 60%, respectively.[2] The survival for retransplantation has improved drastically if the patient is undergoing retransplantation at least 12 months after the initial transplant. Currently, the 1-year survival in this group of patients is approximately 84%.[2]

Data from the ISHLT registries have shown that graft failure is the primary cause of death during the first 30 days posttransplantation, accounting for 41% of the deaths, followed by non-CMV infections (14%) and multiorgan failure (13%). After the first month and up until day 365, non-CMV infections account for almost 35% of deaths, followed by graft failure (19%) and acute rejection (12%). After 5 years posttransplantation, CAV and graft failure combined account for 30% of deaths, while malignancies account for 24% and non-CMV infections for 10%.[2]

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QUESTIONS AND ANSWERS

Questions

1. A 28-year-old man underwent heart transplantation 5 years ago for a presumed postviral dilated cardiomyopathy. He is seen at an urgent care clinic with complaints of a nonproductive cough, sore throat, and low-grade fever. He is diagnosed with an upper respiratory tract infection and prescribed clarithromycin, 500 mg twice daily for 10 days. Two weeks later, after completing antibiotics, he returns to the transplant clinic with complaints of generalized fatigue, shortness of breath, and a persistent nonproductive cough. His current immunosuppressive regimen includes prednisone, 10 mg daily; mycophenolate mofetil (MMF), 750 mg twice daily; and tacrolimus, 2 mg twice daily.

Physical examination: Sick-appearing man. Blood pressure is 142/92 mm Hg, heart rate is 98 beats per minute and regular. Oropharynx is clear. Chest with bibasilar crackles. His abdomen shows no organomegaly or ascites. There is 3+ peripheral edema. ECG: Normal sinus rhythm, biatrial enlargement, and incomplete right bundle branch block. Laboratory studies: Hematocrit 36%, white cell count 4,100/μL, BUN 60 mg/dL, creatinine 5.3 mg/dL (baseline 1.3), tacrolimus level 29 ng/mL, and MMF 4.5 ng/mL.

Which of the following is the most likely explanation of the patient's current condition?

a. Humoral rejection with hemodynamic compromise
b. Interaction of tacrolimus with MMF, causing cellular rejection and thus acute renal failure
c. Immunocompromised patient with a viral syndrome
d. Interaction of tacrolimus with clarithromycin, resulting in acute renal failure
e. Noncompliance

2. A 23-year-old woman is seen for routine monthly posttransplant follow-up. She underwent an orthotopic cardiac transplantation 9 months ago for familial dilated cardiomyopathy. She has returned to college and reports that she saw an internist 3 weeks ago and was taken off of diltiazem, 60 mg twice daily, secondary to severe ankle swelling. She reports that her ankle swelling has improved and she is able to walk an hour a day without becoming fatigued or dyspneic. Current medications include prednisone, 10 mg daily; MMF, 500 mg twice daily; cyclosporine, 75 mg twice daily; and bactrim, 1 tablet daily.

Physical examination: Blood pressure 110/78 mm Hg, heart rate 95 beats per minute, and RR 18 per minute. Chest is clear, PMI nondisplaced, normal S_1 and S_2. Extremities: no edema.

ECG: Normal sinus rhythm at 95, with nonspecific ST-T abnormalities.
Laboratory: Hematocrit 37%, white blood cell count 8,400/μL, platelets 220,000/μL, BUN 30 mg/dL, creatinine 1.1 mg/dL, cyclosporine 45 ng/mL, and MMF level 2.2 ng/mL. Right ventricular biopsy shows prominent lymphocytic infiltrate with associated areas of myocyte necrosis with ISHLT Grade 3R (3A) rejection.

Which of the following statements is false?

a. Cyclosporine dose should be increased to achieve adequate trough levels.
b. This rejection episode is most likely secondary to the discontinuation of diltiazem.
c. There is no need to treat this rejection episode; the patient feels great and is hemodynamically stable.
d. Patients should report all changes in medications to the transplant clinic.

3. All of the following are risk factors for posttransplant mortality except:
   a. Diabetes with end-organ damage
   b. Reversible pulmonary hypertension
   c. Active smoking

d. Left ventricular assist device <30 days
e. Active infection

4. What is the most sensitive tool in detecting cardiac allograft vasculopathy (CAV) posttransplantation?
   a. Serial echocardiography
   b. Intracoronary vascular ultrasound
   c. Positron emission scanning
   d. RV endomyocardial biopsy
   e. Coronary angiogram

5. Which of the following is true regarding posttransplant lymphoproliferative disease (PTLD)?
   a. Treatment includes reduction in immunosuppression therapy.
   b. It occurs in approximately 90% of all cardiac transplant patients.
   c. The highest-risk group for developing PTLD is recipients who are Epstein-Barr virus (EBV) seronegative who receive an EBV-seronegative heart.
   d. The lymphomas that arise in PTLD are usually T cell in origin.
   e. The tumor usually arises 1 month after transplantation, with the cervical lymph nodes being the most common site.

Answers

1. Answer D: The patient's clinical picture is most likely secondary to tacrolimus (Tac) toxicity resulting in acute renal failure. Clarithromycin inhibits the cytochrome P450 system, causing increased levels of calcineurin inhibitors (tacrolimus and cyclosporine). The target trough level of tacrolimus >12 months posttransplant is 8 to 10 ng/mL. The patient should discontinue tacrolimus until target trough levels are obtained. This clinical scenario could represent a rejection episode; however, with the given history, tacrolimus toxicity is most likely the culprit. Tacrolimus taken with MMF is a common immunosuppression regimen. There is no increased incidence of renal failure or episodes of cellular rejection with this particular regimen. When taking Tac with MMF, the MMF dose should be decreased to lessen the likelihood of developing MMF toxicity (myelosuppression). The patient is definitely compliant, secondary to elevated trough levels of immunosuppressants.

2. Answer C: The patient's episode of rejection is most likely secondary to discontinuing diltiazem 3 weeks earlier. Diltiazem inhibits the cytochrome P450 system, causing increased levels of cyclosporine and therefore requiring lesser dosages to achieve trough levels. Once diltiazem was discontinued, the dose of cyclosporine should have been increased. Almost all rejection episodes Grade 3R (3A) and higher and all rejection episodes that show hemodynamically instability (regardless of grade) are treated with augmented immunosuppression. It is important for transplant recipients to communicate any changes in medications to the transplant clinic, so these complications can be avoided.

3. Answer B: Risk factors for posttransplant mortality include but are not limited to short-term ventricular assist device use (<30 days), irreversible pulmonary vascular resistance (PVR > 4 Wood units), mechanical ventilation at the time of transplant, active infection, active smoking, diabetes particularly with end-organ damage, and hepatic or renal insufficiency.

4. Answer B: Serial echocardiograms are important for following graft function posttransplant; however, they are not very sensitive for detecting early CAV. Periodic right ventricular biopsy is the standard method of surveillance for cellular rejection, but adds little to the diagnosis of CAV. Positron emission scans are used to detect ischemia, and scarred and hibernating myocardium; however, they suffer from poor sensitivity in detecting CAV. Studies have shown intracoronary ultrasound (IVUS) to be the most sensitive tool in detecting and following the progression of CAV, compared to coronary angiograms.

5. Answer A: PTLD is a unique polyclonal B-cell lymphoma that occurs in approximately 3.4% of all heart transplant recipients. Ninety percent of PTLDs are associated with EBV; with EBV D+/R- being a high-risk group for developing PTLD. These tumors usually arise 12 to 18 months following transplant, after a mononucleosislike illness (fever, sore throat, myalgias, and lymphadenopathy) and commonly are located intra-abdominally. Treatment includes decreasing the level of immunosu- pression, surgical debulking, cytotoxic chemotherapy, and radiation therapy if indicated; however, the response rate of

advanced disease to treatment is poor (<50%).

CHAPTER

Devices for Heart Failure

Sangjin Lee and Maria M. Mountis

Heart failure is a growing health care epidemic. It is estimated that in the United States, there are more than 200,000 people over the age of 45 who have end-stage heart failure for which medical therapy is insufficient.[1] Currently, the gold standard treatment for end-stage heart failure is cardiac transplantation. However, given the limited availability of donor hearts, mechanical circulatory support (MCS) with left ventricular assist devices (LVADs) has become an alternative for patients as a bridge-to-transplantation (BTT) until a suitable donor heart becomes available,[2] a permanent support as destination therapy (DT),[3,4] or in certain situations as a bridge-to-recovery permitting explantation of the device, once there is normalization of cardiac function. The concept of bridge-to-candidacy is occasionally utilized in individuals who have contraindications to transplant at the time of LVAD implant, such as high body mass index (BMI), unacceptable pulmonary hypertension, malignancy, active tobacco or substance use, or untreated or unresolved psychosocial situations, which once resolved may qualify the individual for transplant listing.

There have been significant developments and advances in the design of mechanical assist devices over the past 40 years, such that utilization of these devices has presently become the standard of care in appropriate patients with end-stage heart failure at experienced medical centers worldwide. In this chapter we review the evolution of MCS, including temporary support with the intra-aortic balloon pump (IABP) and extracorporeal membrane oxygenation (ECMO), as well as more permanent available devices for the treatment for advanced heart failure, optimal patient selection, survival outcomes, potential adverse events following MCS implantation and landmark clinical trials. This overview addresses these critical issues and provides a framework for answering expected questions on the General Cardiovascular Board Certification Examination.

IMPORTANT CONSIDERATIONS REGARDING MECHANICAL CIRCULATORY SUPPORT DEVICES

MCS devices were initially developed to bridge patients to recovery versus a bridge, or alternative, to transplantation. Dr. Michael E. DeBakey, in the early 1960s, was the first to report successes with insertion of rudimentary left ventricular assist prototypes. This was the time when open heart surgery was evolving rapidly, but substantial limitations to cardiopulmonary bypass (CPB) were present. In an effort to transiently support patients who were unable to be weaned from CPB after open heart surgery, pneumatically displaced pulsatile devices were used. Slowly, devices evolved with improvements that allowed successful bridging to recovery from postcardiotomy shock and CPB, and in patients with acute myocarditis or in the peri-infarction period, when stunning of potentially viable myocardial tissue had occurred. Use of these devices for patients with advanced heart failure subsequently became more accepted as an option to stabilize a patient before cardiac transplantation. In some patients, though infrequently, recovery of ventricular function occurred and device removal was possible.

Table 18.1 summarizes issues to consider when MCS devices may be possible treatment options. Clinical settings that should prompt consideration of device use commonly include CBP wean failure, acute cardiogenic shock (usually in the setting of an acute coronary syndrome with massive myocardial infarction or fulminant myocarditis), and in the chronic, severely decompensated heart failure patient (American College of Cardiology [ACC]/American Heart Association [AHA] and Heart Failure stage D) as a BTT or as an alternative to transplantation. Rarely, MCS devices are inserted during resuscitative efforts in individuals with the sudden cardiac death syndrome.

TABLE
18.1 MCS Devices: Considerations

Clinical setting
- Failure to wean from CBP
- Acute cardiogenic shock (acute coronary syndrome or fulminant myocarditis setting)
- Chronic severely decompensated heart failure (NYHA Class IV, ACC/AHA stage D)
- Sudden cardiac death syndrome

Circulatory support system role
- Total heart function replacement due to biventricular failure
- Left and/or right ventricular function replacement
- Reduced preload and/or afterload
- Augmentation of systemic blood flow

Clinical goal
- Bridge to clinical improvement
- Bridge to recovery
- Bridge to decision (preimplant contraindications to transplant that have resolved allowing listing for transplant)
- Bridge to transplant
- Destination therapy (as an alternative to transplant)

When making decisions regarding the type of MCS required, consideration of the support system role becomes important. This is related to whether biventricular function assistance is required or individual ventricular assistance is needed. There are times where hybrid device pairings are utilized. For example, once an LVAD is implanted and the patient develops subsequent right ventricle (RV) failure, a temporary right ventricular assist device (RVAD) may be implanted until there is enough RV recovery that allows explant or eventually transplant. If a total artificial heart (TAH) is implanted, the only indication for this is as a bridge to transplant. With a portable driver that is now approved, these patients will be discharged to home to wait for transplant, which was never possible prior to this development.

TYPES OF MECHANICAL SUPPORT DEVICES

The most commonly used MCS device is the IABP. This is a relatively simple device that can be inserted percutaneously through the femoral or axillary artery (on occasion it is inserted intraoperatively and in other configurations) and produces short-term diastolic blood flow augmentation that is particularly beneficial in acute coronary syndromes. The device unloads the heart during systole and augments diastolic retrograde perfusion of the coronary arteries by inflating at precisely timed moments within the diastolic cardiac cycle. Often, placement of the IABP is a bridge to a more sophisticated MCS device. IABPs can be used only for several days before risk of arterial trauma, infection, device failure, or thrombotic complications force their

removal. Flow augmentation is not substantial with these devices, but afterload reduction and increased coronary perfusion frequently is of enough benefit to see patients recover significant ventricular function and survive cardiogenic shock. Advantages of IABPs include their ready availability, ease of insertion, simplistic design, and relatively low cost.

Extracorporeal support devices include continuous-flow (CF) axial or centrifugal pumps that can be inserted percutaneously or during an operative procedure to expose, most commonly, the femoral arteries and veins. A frequently used CF extracorporeal device in an acute situation is the Biomedicus CF device, which is sometimes coupled with an oxygenator to provide CBP. Placing an oxygenator between the device and the arterial input cannula is the configuration referred to as ECMO support. More sophisticated extracorporeal devices are placed at the time of thoracotomy and cardiotomy and generally are pneumatic or electric motor displacement devices with pumping chambers connected paracorporeally to exteriorized cannula. The cannula can be set up in a variety of configurations so that left ventricular, right ventricular, or biventricular bypass can be achieved. The first successful use of a ventricular assist device was by Dr. Michael E. DeBakey in 1966, when an extracorporeal pneumatically displaced pulsatile device was used in a patient who could not be weaned from CPB after valvular heart surgery for rheumatic heart disease with severe heart failure. A cannula was placed in the left atrium for inflow into the device, with the arterial outflow cannula anastomosed to the right axillary artery. The patient survived the operative procedure, was extubated without complications, and native heart recovery occurred. The device was removed in the intensive care unit under local anesthesia, with the cannula being occluded subcutaneously and then allowed to thrombose. The patient survived hospital discharge and led an active life until being mortally injured in an automobile accident.

Intracorporeal devices have been a desirable goal because of the potential for complete component implantation. With a completely implantable system, there are no percutaneous connections and the risk of infection is decreased dramatically. However, there are multiple controlling elements that must be buried within the patient, including the pump itself, cardiac and arterial conduits, a compliance chamber (for pulsatile devices), a pump controller, and a power system with transcutaneous capabilities for energy transfer. Because of the complexity surrounding development of such a device, present intracorporeal devices are for the most part only partially implanted devices. These devices can be implanted intrathoracically or subdiaphragmatically and are either CF or pulsatile units.

COMPONENTS AND CONFIGURATIONS OF MECHANICAL CIRCULATORY ASSIST DEVICES

The first generation of pumps are affixed to inflow and outflow conduits and valves to control blood direction, with the pump chamber itself located between the valves and conduits. The interior of the pump represents the blood component–device interface, where problems such as thrombosis and hemolysis begin. The pump controller is linked to circulatory pressure and an electrocardiographic monitor. Sophisticated electronics regulate a pressure–rhythm pump interface system that usually controls the amount of flow and pressure a device generates. The pump driver or activator is the actual flow-generating system and is either a pneumatically displaced diaphragm or an electric motor moving pusher plates back and forth. The pump requires a power source, and this must come from wall-socket alternating current or some form of a battery pack. Because pneumatic pulsatile devices require displacement of gas-driven volume, an air-displacement management system is necessary, and this can be accomplished with either an external venting line or an implanted compliance chamber. External venting lines also break the skin barrier and are a second externalized access for infection. Implanted compliance chambers have problems with obstruction and breakage of the constantly moving membrane. Because of mechanical wear, the duration of support with the first-generation of pulsatile pumps was approximately 18 to 24 months, at which point the device had to be exchanged if further mechanical support was indicated.

The second generation of mechanical circulatory assist devices utilizes rotary blood pump technology to generate CF and are designed to provide more durable support. There are two types of CF: centrifugal or axial flow. The bearings of the CF rotating impellas are of three designs: blood-immersed, hydrodynamic, and magnetically levitated that generate minimal heat and are near frictionless. These newer pumps are smaller in size and lighter in weight compared to the first generation pulsatile pumps and allow for wider clinical availability (i.e., implantation in women and children). Due to the smaller size of the pump, surgical implantation is technically easier and infection risk is reduced with the smaller percutaneous driveline and the absence of air-displacement systems. The absence of internal valves with only a single internal moving component reduces mechanical wear of the device, with the current longest duration of CF support to date with the HeartMate II device (HM II, Thoratec Corporation, Pleasanton, CA) being over 6 years. These devices are near silent in operation with minimal vibration resulting in improved patient satisfaction. Examples of a pulsatile and a CF pump are depicted in Figure 18.1 and important differences described in Table 18.2.[5] The components of the HM II LVAD are depicted in Figure 18.2.[2] Table 18.3 summarizes the system components.

FIGURE 18.1 A smaller CF LVAD is shown in the lower left. A larger pulsatile LVAD is shown in the upper right

TABLE
18.2 Comparison of Pulsatile- and Continuous-Flow Ventricular Assist Devices

Attribute	Pulsatile-Flow VAD	Continuous-Flow VAD
Size	Large; intracorporeal devices limited to large patients; extracorporeal devices especially suited for smaller patients or for biventricular support	Smaller; accommodates most patients, excluding infants
Blood flow capacity	Up to 10 L/min	Up to 10 L/min
Type of pump	Sac or diaphragm	Centrifugal or axial flow by rotating impeller
Implantation	Extracorporeal or intracorporeal types: subdiaphragmatic intraperitoneal or preperitoneal	Extracorporeal, intracardiac, pericardial, subdiaphragmatic
Main hemodynamic characteristic	Intermittent unloading of ventricle; pulsatile arterial pressure; asynchronous with heart	Continuous unloading of ventricle
Physiologic flow variables	Preload dependent	Preload and afterload dependent

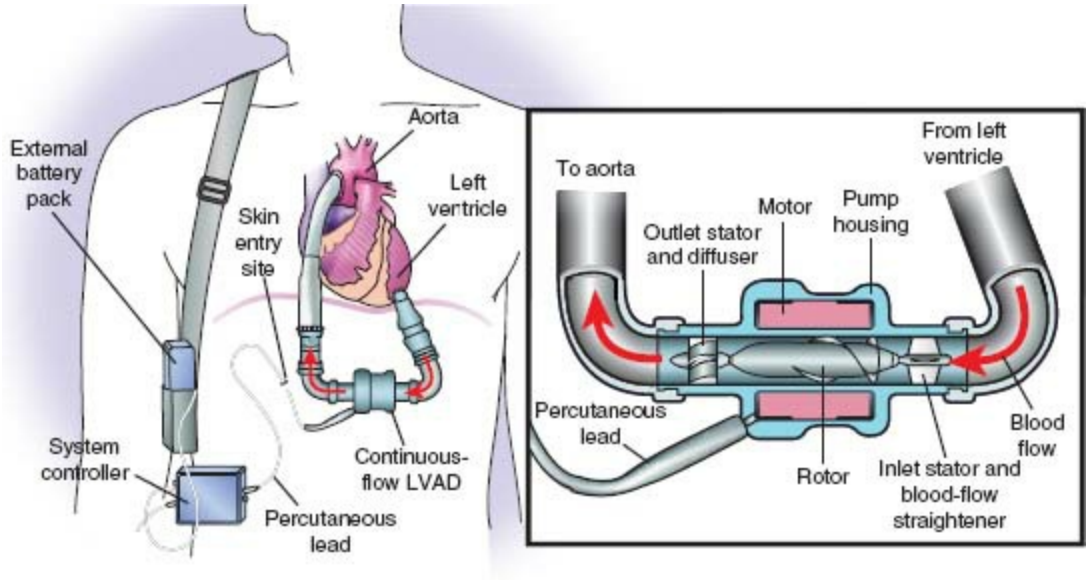

FIGURE 18.2 Components of a CF LVAD.

TABLE
18.3 MCS Devices, Components, and Configurations: System Requirements and Options

Pump (pulsatile or continuous flow)
■ Inflow/outflow conduits
■ Inflow/outflow valves
■ Pump chamber
■ Blood component–device interface
Controller
■ Circulatory pressure/electrocardiographic monitors
■ Pressures–rhythm–pump interface system
Pump driver for pulsatile systems
■ Pneumatic displacement
■ Electric motor pusher plate
■ Impellar motor
■ Centrifugal motor
Driver power source
■ Wall-socket alternating current
■ Battery pack
Air-displacement system for pulsatile systems
■ External venting line
■ Implanted compliance chamber

The SynCardia TAH, as seen in Figure 18.3, is the first FDA-approved TAH as a bridge to transplant, receiving its approval on October 15, 2004, following a 10-year clinical study. There have been more than 900 implants worldwide of the TAH. This device is indicated for eligible patients waiting for heart transplant who require biventricular support. Patient selection is critical and must fulfill the following

conditions: BSA ≥ 1.7 m^2, Echo: LVEDD ≥ 70 mm, chest CT scan: anterior-posterior dimension at T-10 from posterior sternum to anterior spine ≥ 10 cm, and chest x-ray: cardiothoracic ratio ≥ 0.5.

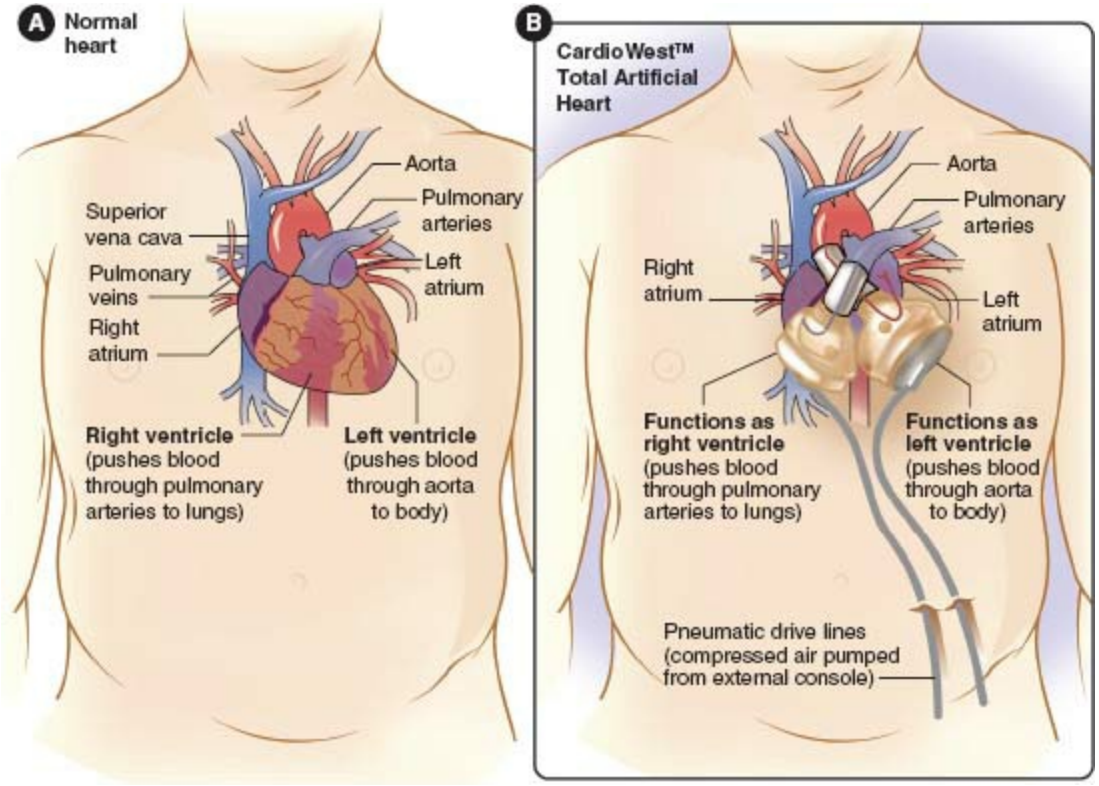

FIGURE 18.3 Components of the SynCardia Total Artificial Heart.

PATIENT SELECTION

Optimal patient selection for MCS in the treatment of advanced heart failure is of utmost clinical importance and is a topic that has repeatedly been tested on previous board examinations. All patients considered for MCS ideally need to undergo a thorough evaluation including assessment of the severity of their heart failure (New York Heart Association [NYHA] Class, ACC/AHA Stage, cardiopulmonary exercise stress testing, invasive hemodynamic studies, and echocardiography). Close evaluation is needed of other comorbidities, end-organ function, anatomic considerations, social support system, and psychological status.

Table 18.4 summarizes end-organ compromise that should raise concerns for MCS candidacy. Mancini et al.[6] described the value of peak oxygen consumption in cardiopulmonary exercise stress testing in the timing of cardiac transplantation in outpatients with severe heart failure. This landmark study has generally been accepted by the ventricular assist device (VAD) community in considering MCS therapy in appropriate patients who have a peak oxygen consumption of <14 mL/kg/min who achieved an adequate anaerobic threshold. Similarly, although no strict hemodynamic or

clinical criteria exist, potential MCS candidates generally have systolic blood pressures <90 mm Hg, pulmonary capillary wedge pressure >20 mm Hg, systemic vascular resistance >2,000 dynes, falling urine outputs despite diuretics (<20 mL/h in an adult), and a cardiac index of <2/L/min/m^2 despite the use of inotropic agents, vasopressors, and occasionally IABP

TABLE
18.4 Challenges that may Compromise Outcomes

- Hepatic cirrhosis
- Liver enzymes > three times upper limit of normal or bilirubin >3.0 mL/dL
- Platelet count <50,000
- PT or PTT > twice control values or INR > 1.8 in patients not anticoagulated
- Hemodynamically significant aortic insufficiency
- Active infection
- Psychosocial issues that might impair compliance
- Irreversible and significant end-organ dysfunction
- Significant "fixed" pulmonary hypertension
- Highly calcified aorta (particularly at proposed site of outflow cannula anastomosis)

Because heart failure is a disease with a wide spectrum of symptoms and presentations, the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile was developed to help classify patients with advanced heart failure.[7] The seven profiles are listed in Table 18.5. Although most (~60%) of patients recently implanted with MCS have been in INTERMACS profiles 1 and 2,[8] emerging evidence suggests that in patients implanted with CF pumps, less acutely advanced heart failure patients have higher short- and long-term survival following LVAD implantation and shorter length of stays compared to patients who are more acutely ill.[9] It is generally accepted that MCS is used to rescue patients with INTERMACS profiles 1 and 2 who are potential BTT candidates. There is now a shift to implant LVADs in inotrope-dependent, advanced heart failure patients with lower INTERMACS profiles. Studies are underway to further investigate their outcomes compared to those on chronic inotropic therapy.

TABLE
18.5 Intermacs Levels

Profile 1	Critical cardiogenic shock
Profile 2	Progressive decline
Profile 3	Stable but inotrope dependent
Profile 4	Resting symptoms
Profile 5	Exertion intolerant
Profile 6	Exertion limited
Profile 7	Advanced NYHA III

The first set of formal recommendations regarding patient selection for mechanical support was described in the consensus statement from the Conference on the Current Applications and Future Trial Design of the Mechanical Cardiac Support in 2000.[10] A set of guidelines still utilized was published by the International Society for Heart and Lung Transplantation (ISHLT) in 2006.[11] Due to the varied experiences in the use of MCS as well as the many types of available devices, a single set of guidelines applicable to all patients is not possible. However, the discussion below highlights the most important general considerations in selecting appropriate candidates for MCS for end-stage heart failure.

Age

Age alone should not be a contraindication to MCS. In general, patients over the age of 60 have more comorbidities than younger patients with an inverse survival relationship, but acceptable outcomes have been reported in multiple studies in select patients ≤70 years of age.[12–14] Although policies vary by institution, if a durable assist device is implanted in a patient >70 years old, they are generally for patients with the intention of DT or for select patients as a bridge-to-transplant.

Body Habitus

Because of the size of the larger, first-generation pulsatile intracorporeal LVADs, it was recommended that these devices should not be implanted in patients with a body surface area of <1.5 m^2 to ensure adequate thoracic and abdominal capacity to accommodate the size of the device. These devices are rarely used in the current era of MCS. The new generation of CF pumps allows a larger group of individuals to benefit from MCS. Individuals whose body surface area is >2.5 m^2 or with an ideal body weight of >150% may pose technical challenges intraoperatively. Currently, a BMI of >35 would not permit a patient to be a transplant candidate, although a device may be placed as a bridge to candidacy pending appropriate weight loss. There is limited experience regarding concurrent weight loss surgery to allow patients to then become transplant eligible, but a topic that we will hear more about in the future.

Renal Function

There have been multiple studies showing improvement of renal function following

implantation of both pulsatile and CF devices in patients without intrinsic kidney disease.[15–18]However, patients with preoperative creatinine ≥3.0 mg/dL have worse outcomes following implantation.[19] Patients with creatinine values in this range may still be considered for MCS if renal injury is acute and is likely to be reversible. Patients with end-stage renal disease on dialysis are not candidates for MCS. There have been cases of patients being supported with VAD therapy that have progressive renal disease and require renal replacement therapy. This poses a much higher risk of morbidity and mortality, primarily due to infection.

Pulmonary Function

Patients with severe underlying lung disease (baseline FEV_1 <1.0) and requiring continuous oxygen supplementation are not appropriate candidates for MCS, as they often have difficulty weaning from postoperative mechanical ventilation, are prone to pulmonary infections, and may continue to be dyspneic once their cardiac status has stabilized. Potential candidates for MCS require formal pulmonary function tests, appropriate imaging studies, and pulmonary evaluation. Patients with mild-moderate lung disease may be considered for MCS.

Hepatic Function

Patients with cirrhosis and liver transaminases ≥ 3x the normal limit are at higher risk for morbidity. If known RV dysfunction is present with associated liver dysfunction, then the need for biventricular support should be considered in patients otherwise being considered for LVAD implantation. Patients with intrinsic cirrhosis or portal hypertension should not be considered candidates for MCS. In certain cases, a liver biopsy and hepatology evaluation may be useful in differentiating primary cirrhosis from secondary congestive hepatopathy. Patients with viral hepatitis are not a contraindication to MCS.

Coagulation Abnormalities

Intra-and perioperative bleeding is a significant risk factor for morbidity and mortality following MCS implantation, and the identification of preoperative coagulation abnormalities is essential. Patients with a spontaneous international normalizing ratio (INR) >2.5 off any anticoagulation are at higher risk and generally not candidates for MCS. In addition, patients with perioperative heparin-induced thrombocytopenia (HIT) are generally not considered candidates, but if MCS is considered, alternative methods of anticoagulation such as direct thrombin inhibitors should be used.

Infectious Concerns

Sepsis is one of the most common causes of morbidity and mortality following MCS implantation. If an infectious etiology is discovered, aggressive anti-infective therapy should be administered and implantation, if possible, be delayed until the infection is

cleared. In fact, a white blood cell count of >10,000/μ,L has been found to be a risk factor of post-implant mortality.[12] Patients considered for MCS therapy are more prone to develop fungal infections that are particularly difficult to eradicate.[20,21] If a device gets implanted while a patient is actively infected, the offending organism can colonize the hardware and will be unable to be eradicated, even with long-term intravenous anti-infective therapy.

Arrhythmias

Unless there is a primary underlying proarrhythmic etiology, such as giant cell myocarditis, ventricular arrhythmias often resolve following LVAD implantation, since wall stress is reduced and the LV is unloaded. LVADs, in the presence of normal pulmonary vascular resistance (PVR), essentially produce a Fontan-like circulation allowing the RV to fill the pump despite even the most malignant dysrhythmias and is tolerated well clinically in MCS-supported patients.[22] At this time, pacemakers and implantable cardioverter defibrillators (ICDs) maintain their usual indications in MCS patients, although little has been studied in this particular field.

Pulmonary Hypertension

Elevated pulmonary pressures are frequently seen in patients with advanced heart failure. This may be due to chronic congestion, severe mitral insufficiency, and elevated pulmonary capillary wedge pressure leading to remodeling of the pulmonary vasculature. Careful consideration must be made to identify whether the patient has pulmonary venous hypertension, pulmonary arterial hypertension, or a combination of both with a transpulmonary gradient >15, PVR > 3 WU, and an elevated pulmonary capillary wedge pressure. In some instances, an LVAD will be placed as DT, since the elevated PVR precludes listing for transplant. With medical therapy and unloading of the ventricle with the LVAD, there may be improvement in PVR and allow listing for transplant.

Right Ventricular Function

The evaluation of RV function deserves special attention in patients being considered for LVAD, especially in patients implanted with a second-generation CF device. RV failure following LVAD implant is an important cause of morbidity and mortality for patients that often require prolonged inotropic therapy or ultimately placement of a RVAD. There have been a number of risk scores devised in an attempt to better predict which patients may develop RV failure after LVAD implantation, to allow for better medical optimization prior to the LVAD implant or for planned simultaneous biventricular support. Fitzpatrick et al. performed a retrospective analysis from 266 patients who underwent LVAD implantation at a single center from 1995 to 2007 and found that the multivariate risk factors predicting the need for biventricular mechanical support were cardiac index ≤2.2 L/min/m^2, RV stroke work index ≤0.25 mm Hg × L/m^2,

severe preoperative RV dysfunction, preoperative creatinine ≥1.9 mg/dL, previous cardiac surgery, and systolic blood pressure <96 mm Hg.[23] Multiple types of LVADs, the majority of which were pulsatile devices, were reviewed in that study. A recent review of patients implanted with a CF LVAD enrolled in the HM II LVAD BTT clinical trial showed that multivariate independent predictors of RV failure following LVAD implant included a central venous pressure/pulmonary capillary wedge pressure ratio >0.63, need for preoperative ventilator support, and blood urea nitrogen level >39 mg/dL.[24] The difficulty in consistently predicting RV failure lies, in part, on the unmasking of native RV dysfunction in the presence of restored cardiac output and increased venous return following LVAD implantation. It is estimated that approximately 20% to 25% of patients undergoing LVAD implant develop RV failure. [25] This continues to be an area of active investigation.

Anatomic Considerations

Perhaps one of the most important anatomic considerations prior to LVAD implantation is the competency of the aortic valve. Following LVAD implantation, the LV is unloaded and pressure rises in the aortic root with output from the device. Pathologic specimens either at time of transplant or autopsy may show commissural fusion of aortic leaflets leading to a central jet of aortic insufficiency. Mild to moderate aortic regurgitation prior to implant may progress to more severe grades of aortic regurgitation and worsening heart failure. This situation is best avoided by preemptively repairing at least moderate grades of aortic insufficiency at the time of LVAD implantation. Other important considerations include repairing severe mitral and tricuspid insufficiency and converting mechanical aortic and mitral valves to bioprosthetic valves at the time of VAD implant. There is increased risk of thrombosis of the mitral valve due to a lower INR goal and in the aortic valve that may remain in the closed position due to VAD speed and lack of native contractility. Interatrial septal abnormalities such as a patent foramen ovale and atrial septal defect are generally closed at the time of surgery. Complex congenital heart anatomy and hypertrophic cardiomyopathy may present surgical challenges that preclude LVAD implantation.

Nutritional Status

Cardiac cachexia (BMI <21 kg/m^2 in males and <19 kg/m^2 in females) is a strong predictor of postoperative morbidity and mortality.[26] Prealbumin and albumin levels should be measured in potential MCS candidates and optimized prior to surgery. Reports of total parenteral nutrition (TPN) to boost nutritional status and improve postoperative outcomes remain anecdotal at this point in time and are not routinely recommended.

Neurologic Function

In patients presenting in acute cardiogenic shock who are supported by mechanical

ventilation at the time of initial evaluation for MCS candidacy, it is often difficult to ascertain the patient's residual neurologic function or to predict full neurologic recovery. This is especially true if any period of anoxic brain injury was sustained as a result of a cardiac arrest. In such cases, a temporary mechanical support device should be employed to allow sufficient time to reassess neurologic function and appropriateness for more durable types of mechanical support. In the advanced heart failure population, low cardiac output states may contribute to confusion or suspected dementia, and then a full neurologic exam, CT scan of the brain, and neuropsychiatric testing are warranted.

Malignancies

Ideally, all age-related, gender-specific, health maintenance exams should be performed prior to consideration of MCS. If any malignancy is discovered, further workup should be pursued. Some patients with potentially curable tumors may undergo MCS implantation, as a means to prolong life to undergo further workup and treatment to become eligible for transplantation, or as DT. Patients with metastatic cancers are not candidates for MCS.

Psychiatric Conditions

Successful MCS therapy requires patient compliance and attention to the maintenance of the pump with changing batteries, keeping the driveline exit site clean, appropriate response to pump alarms, and close follow-up in the clinic setting. The presence of any psychiatric conditions hindering the patient's ability to carry out his/her responsibility caring for the device should raise concerns regarding the patient's candidacy for MCS. Such conditions may include substance abuse/addiction, severe depression, severe anxiety, uncontrolled schizophrenia, and personality disorders that may lead to lack of compliance with care.

Social Evaluation

A thorough evaluation should be undertaken with the assistance of a social worker to ensure that a candidate's support system of family and/or friends as well as the home environment is suitable and conducive to the candidate's success in adjusting back to daily life with MCS. Such a support system is also essential to provide meticulous wound care once the patient is discharged to home and to be present in case emergencies arise, such as pump malfunction. Despite being an optimal candidate from a medical standpoint, the absence of an adequate social network may preclude the use of MCS in certain patients.

ASSESSMENT OF OPERATIVE RISK

Included in a patient's candidacy for MCS involves a detailed assessment of operative

risk. There have been several studies looking at composite risk scores for postoperative mortality in BTT patients.[17,27] The largest study to date is the Destination Therapy Risk Score that estimated 90-day in-hospital, post-LVAD implantation, mortality by Lietz et al.[28] They found that the most important determinants of 90-day, post-LVAD mortality were poor nutritional status, hematologic abnormalities, markers of end-organ dysfunction, right ventricular dysfunction, and lack of inotropic support. In particular, in the order of the most weighted risk factor, a platelet count $\leq 148 \times 10^3/\mu L$, serum albumin $\leq$ 3.3 g/dL, INR > 1.1, use of vasodilator therapy, mean pulmonary artery pressure ≤25 mm Hg, aspartate aminotransferase > 45 U/mL, hematocrit ≥34%, blood urea nitrogen >51 U/dL, and lack of intravenous inotrope use were all multivariate risk factors for 90-day in-hospital mortality following LVAD implantation. It should be noted that these studies evaluated patients implanted with the pulsatile LVADs, although their applicabilities to those patients considered for CF LVAD implantation are likely to be similar and studies are currently under way to investigate this question.

OUTCOMES AFTER CIRCULATORY SUPPORT IMPLANTATION

Infection and bleeding were two of the most common adverse events seen post VAD implant in the 2005 Registry from the International Society for Heart and Lung Transplantation Mechanical Circulatory Support Device (ISHLT-MCSD). [12] Table 18.6 summarizes the postimplantation patient-related events. Infection was seen in approximately one-third of patients with almost 30% having significant bleeding episodes. Neurologic dysfunction was observed in 14% of the registry patients.

TABLE
18.6 ISHLT MCSD 2005 Registry Analysis (N = 655): Postimplantation Patient-Related Events

Event	No. of Patients	Percentage of All Patients
Infection	134	32.5
Bleeding	115	27.8
Arrhythmia	100	24.2
Renal dysfunction	85	20.6
Respiratory dysfunction	66	16.0
Neurologic dysfunction	58	14.0
Right ventricular dysfunction	44	10.7
Hepatic dysfunction	30	7.2
Cardiac tamponade	22	5.3
Thrombotic vascular complication	10	2.4
Hematoma	10	2.2
Pleural effusion	9	2.2
Internal organ compromise	5	1.2
Pacemaker implanted	2	0.5

In 655 patients analyzed in the ISHLT-MCSD Registry (entered between January 2002 and December 2004), 1-month survival was 83% and 12-month survival was 50%, sensoring patients at the time of transplantation. Age played a significant factor in outcomes, with an individual 40 years of age having a predicted 6-month mortality of about 5% versus a 70-year-old patient with a predicted mortality of almost 20% after a LVAD alone was implanted. With the combination of a LVAD and RVAD during the same operation, for a 50-year-old individual, the mortality approaches 20%, compared to a little more 5% for an LVAD alone. In individuals under the age of 30 years receiving MCS as a bridge to transplant, 51% were transplanted at the 6-month mark, with 33% alive and still waiting transplantation and 10% dying before transplant. This should be compared to those individuals >50 years of age who, at the 6-month mark, say only 39% transplanted, with a 33% pretransplant mortality and 27% of patients still waiting for transplant. Interestingly, though recovery sometimes occurs and MCS devices can be explanted, this is a rare event in patients >50 years of age, with only a 0.4% recovery–explantation rate noted over a 12-month period of time, compared to a 6-month explanted–recovery rate observed in patients <30 years of age of 3%. Complications such as bleeding episodes and thromboembolism were most frequent in the first 30 days after implantation, leveling off after this point. This is in contrast to infection episodes, which saw a constant rise throughout the observation period.

Though only 78 patients received a device as DT and were entered into the ISHLT-MCSD analysis, 65% of these patients were alive at the 6-month mark and 34% at 12 months, with a 12-month mortality rate of 55%.

CLINICAL TRIALS OF DEVICE THERAPY

The seminal trial that placed MCS on the map for the treatment of advanced heart

failure was The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH Trial) published by Rose et al.[3] in 2001. This study randomized 129 patients who were not considered transplant candidates to either "best medical therapy" or a HeartMate XVE pulsatile LVAD. All patients had NYHA Class IV symptoms, with advanced heart failure characterized by a mean ejection fraction of 17%, a mean systolic blood pressure of 102 mm Hg, an elevated mean creatinine of 1.8 mg/dL, and dependency on intravenous inotropic support in 70% of patients. The 1- and 2-year survival rates were 52% versus 25% ($p = 0.002$) and 23% versus 8% ($p = 0.09$) for the LVAD versus medical therapy groups, respectively. This translates into a 48% reduction in the risk of death from any cause in the LVAD group compared to the medical therapy group. Indeed, of the 54 deaths in the medical therapy group, 50 were due to heart failure, compared to only one death due to heart failure in 41 deaths noted in the HeartMate group. Minnesota Living with Heart Failure quality-of-life scores were better in the LVAD group.

Despite these results, there were limitations of the first-generation pulsatile LVADs, including the large size of the pump and durability of the device. The newer generation of CF pumps was designed to overcome some of these limitations. The most data on CF pumps to date are with the HM II device (Thoratec Corp, Pleasanton, CA). In 2007, Miller et al. reported the outcomes of 133 patients in a prospective, multicenter study of end-stage heart failure patients awaiting heart transplantation, who were implanted with the HM II device.[2] They showed that the survival rate was 75% at 6 months and 68% at 12 months with significant improvement in functional class and quality of life. This was followed by the results of the HM II DT trial published by Slaughter et al. in 2009.[4] The primary composite endpoint was survival free from disabling stroke and reoperation to repair or replace the device at 2 years. The primary endpoint was achieved in more patients implanted with CF devices versus pulsatile devices (46% vs. 11%; $p < 0.001$). In addition, patients implanted with CF devices had superior survival at 2 years (58% vs. 24%, $p = 0.008$). Both devices significantly improved functional capacity and quality of life.

Initial experience with a third-generation CF magnetically levitated rotary pump; the HVAD (HeartWare Inc, Framingham, MA) that can be implanted intrapericardially was recently published.[29] Twenty-three patients in five centers in Europe and Australia were enrolled with the primary endpoint being survival to heart transplant or survival to 180 days on the device, whichever came first. Actual survival at 6 months was 91% and 86% at 1 year follow-up.

CONCLUSION

MCS devices have matured in robust fashion over four decades with significant advances in both pump design and technology along with improved experience in

patient selection, device implantation, and postoperative management. MCS has now become the standard of care in the treatment of end-stage refractory heart failure in select patients at experienced medical centers. As this technology continues to evolve and experience with the devices improves, it is anticipated that the clinical applicability of MCS will continue to expand in the treatment of advanced heart failure.

HOW TO PREPARE FOR THE BOARDS

Certification and recertification of General Cardiovascular Disease Board questions on the topic of cardiac circulatory support do not require a detailed knowledge of ventricular assist device nuances. The questions are more apt to focus on appropriate selection of patients who might benefit from short-term or long-term device support. Also important is knowledge regarding device complications including infection, bleeding, right ventricular failure, thromboembolism, and renal insufficiency.

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QUESTIONS AND ANSWERS

Questions

1. The patient most likely to benefit from an implantable ventricular assist device as a bridge to cardiac

transplantation is:

a. A patient found to be in full cardiac arrest in the coronary care unit after being admitted with an acute coronary syndrome
b. A New York Heart Association Class II outpatient with ischemic congestive cardiomyopathy and atrial fibrillation, a QRS-complex duration of 130 milliseconds, moderate symptoms, physical findings of congestion, and a blood pressure of 140/80 mm Hg despite treatment with an angiotensin-converting enzyme inhibitor, aldosterone antagonist, and an angiotensin-receptor antagonist
c. A middle-aged-man with idiopathic dilated cardiomyopathy status post-biventricular pace-maker/implantable cardioverter defibrillator (ICD) insertion who is hypotensive in response to oral medication therapies and requires continuous dobutamine infusion to maintain reasonable renal function but who is having intermittent and still problematic episodes of ventricular tachycardia
d. A postoperative coronary artery bypass patient who suffers a sudden ischemic event and, though resuscitated, has steadily increasing inotropic requirements, with blood pressure falling to 50 mm Hg despite polypharmacy with inotropic agents and vasopressors. He has not awakened postsurgery, and his mental status is questionable.
e. A 30-year-old woman who develops pulmonary edema 1 week after a normal delivery and is admitted to the coronary care unit with a blood pressure of 90/50 mm Hg, a heart rate of 110 beats/min, atrial fibrillation, and profound respiratory distress. Hepatic and renal functions are normal.

2. Clinical goals that should be considered when mechanical circulatory support (MCS) devices are inserted include:

a. Bridge to recovery
b. Bridge to clinical improvement
c. Destination therapy (implantation without the goal of heart transplant)
d. Bridge to transplant
e. All of the choices

3. A contraindication to MCS device implantation is:

a. Systolic blood pressure of 80 mm Hg on dobutamine at 10 µg/kg/min
b. A serum creatinine of 2.8 mL/dL
c. A platelet count consistently of 75,000
d. Hepatic cirrhosis on liver biopsy, with normal liver enzymes and bilirubin
e. Presence of insulin-requiring diabetes

4. The most common complication after MCS device implantation is:

a. Neurologic dysfunction
b. Atrial fibrillation
c. Bleeding requiring transfusion
d. Right ventricular dysfunction
e. Systemic infection requiring antibiotics

5. A 56-year-old male with a history of ischemic cardiomyopathy and EF of 10%, blood type O is transferred to your center. He is on milrinone at 0.25 µg/kg/min, furosemide at 10 mg/h, and lisinopril 2.5 mg. On examination, he is tachypneic, BP 88/40 mm Hg, HR 104, lungs with crackles, JVP of 12, audible S_3. Labs noted for Na 133, creatinine of 2.3, AST 56, and albumin 3.9. Social history notable for 1 PPD. The most appropriate therapy at this time is:

a. Initiate carvedilol 6.25 mg BID
b. Add digoxin 250 µg daily
c. Left ventricular assist device (LVAD) implantation as destination therapy (DT)
d. Urgent listing for heart transplant

6. A 47-year-old female presents with nonischemic cardiomyopathy. You decide that she needs a ventricular assist device as a bridge to transplant and are trying to decide regarding the specific

implant. She is 5 ft 2 in and weighs 120 pounds. She has blood type O with a creatinine of 2.6, AST of 105, international normalizing ratio (INR) of 1.8 off Coumadin, RA pressure of 18 and wedge pressure of 10.

a. Pulsatile LVAD
b. Total artificial heart
c. Continuous flow LVAD
d. Paracorporeal BiVAD

7. A 52-year-old man with severe end-stage dilated cardiomyopathy undergoes implantation of a continuous flow (CF) LVAD. It is noted on his intraoperative transesophageal echocardiogram that he has moderate to severe aortic insufficiency. In addition to placement of the LVAD, what operation, if any, should be performed simultaneously?
   a. Replacement of the aortic valve with a mechanical aortic valve
   b. Replacement of the aortic valve with a bioprosthetic aortic valve
   c. No aortic valve surgery

8. All of the following are risk factors for the development of right ventricle (RV) dysfunction post-LVAD implantation except:
   a. Large RV size
   b. RV stroke work index <300 mm Hg × mL/m^2
   c. Severe tricuspid regurgitation
   d. Need for preoperative ventilator support
   e. Central venous pressure < 15 mm Hg

9. A 58-year-old woman is referred to you in your clinic for consideration of advanced heart failure therapy, including possible MCS as a bridge to transplantation (BTT). As part of that workup, you order a cardiopulmonary exercise stress test and she achieves a peak oxygen consumption of 18 mL/kg/min. You identify no other comorbidities except for her heart failure. Would you proceed with your evaluation for possible MCS?
   a. Yes
   b. No

10. Is it possible that implantation of an LVAD can decrease pulmonary artery pressures?
    a. True
    b. False

Answers

1. Answer C: Appropriate selection of patients for ventricular assist device insertion as a BTT is best described for this patient. The gentleman appears to have had aggressive therapies including insertion of a biventricular pacemaker/ICD unit, but he remains compromised with hypotension and is inotropic dependent. Ventricular arrhythmias are compromising his current status. Insertion of a VAD will likely allow withdrawal of the inotrope, restore adequate systemic perfusion, and often in these cases, improve the ventricular arrhythmias as well as other organ function. This would then allow for successful cardiac transplantation. The patient described as in full cardiac arrest is in a very difficult situation, and because of the uncertainties regarding central nervous system integrity after a full cardiac arrest, is not the best candidate for aggressive MCS intervention. Sometimes, in newly presenting patients who are young and otherwise healthy, a temporary percutaneous biomedicus pump or ECMO is used to see if the patient will in fact awaken and improve. The NYHA Class II outpatient appears to be a bit “too well” for heart transplantation, and many things can be done including insertion of a cardiac resynchronization device and intensification of medical therapies to lower his blood pressure and treat the heart failure syndrome more optimally. The postoperative coronary artery bypass patient resembles, in some ways, the patient described as in full cardiac arrest. Using a smaller, less sophisticated temporizing device may be more prudent than implantation of a more permanent device. The 30-year-old woman is likely a peripartum cardiomyopathy patient who, in all likelihood, will have a reasonable

response to medication therapies and correction of her atrial fibrillation. She may require transient intubation, but it is unlikely a device will be required.

2. Answer E: No longer should MCS be considered simply as a bridge to heart transplant. Many options now exist. MCS devices can be used as a bridge to more sophisticated device implantation. They can also be used as a bridge to clinical improvement that perhaps will allow bridging to transplantation, even bridging the patient to recovery, with device removal or use of the device as a permanent alternative to transplantation.

3. Answer D: One of the more feared difficulties after circulatory support device implantation is hepatic failure, which can quickly lead to coagulopathy and systemic organ failure. Even when liver enzymes and bilirubin levels are normal, the finding of hepatic cirrhosis on liver biopsy generally renders a patient at excessive risk for device implantation. This is the sole absolute contraindication included in this question.

4. Answer E: According to the International Society for Heart and Lung Transplantation MCS Device Registry, systemic infection requiring parenteral antibiotic therapy is the most common complication after device insertion and rises in continuous risk fashion over time.

5. Answer C: He currently has a contraindication to listing for transplant with active tobacco use. If he were a transplant candidate, his blood type O would make it difficult to urgently transplant him in many areas of the country. He is decompensated on inotropic therapy with several poor prognostic indicators such as an audible S_3, hyponatremia, hypotension, tachycardia, and end-organ dysfunction. His best option would be to proceed to LVAD implant as DT. Once he ceases tobacco use and verification through nicotine and cotinine levels, then he would be eligible for transplant listing and the indication for VAD would be changed to bridge to transplant.

6. Answer D: She has evidence of right ventricular failure (elevated RA compared to her PCWP, renal and hepatic dysfunction) as well as left ventricular failure and thus she should undergo biventricular mechanical support. She is too small for the implant of TAH; thus, her best option would be implantation of paracorporeal BiVADs.

7. Answer B: The amount of preoperative aortic insufficiency may be underestimated with a high left ventricular end diastolic pressure. Once this pressure is reduced with an LVAD, the amount of aortic insufficiency may increase. Furthermore, it is known that there may be commisural fusion of the aortic valve leaflets with prolonged support with a CF LVAD. Significant development of aortic insufficiency post-LVAD would limit the device's pump performance. Replacement of the aortic valve with a mechanical prosthesis is not advised due to the risk of valve thrombosis during LVAD support. Because of this thrombotic risk, any patient with a preexisting mechanical aortic valve should have it replaced with a bioprosthetic valve at the time of LVAD implantation.

8. Answer E. Central venous pressure < 15 mm Hg is not a risk factor for the development of RV dysfunction post-LVAD implantation.

9. Answer B: It has been shown that patients who achieve a peak oxygen consumption of >14 mL/kg/min do better with their own hearts in the long term rather than with a transplanted heart. Although there are no absolute cutoffs in considering a patient for MCS, it is generally accepted that a patient who achieves a peak oxygen consumption of >14 mL/kg/min should not proceed further for evaluation for MCS as a BTT. It is important to remember, however, that this test should be interpreted in the context of the patient's entire clinical presentation.

10. Answer A: In patients without chronic irreversible primary pulmonary hypertension, implantation of an LVAD can decrease pulmonary artery pressures by unloading the left ventricle. In appropriate patients who otherwise would qualify for heart transplantation except for elevated pulmonary artery pressures, implantation of an LVAD may be considered.

CHAPTER

Myocarditis and Dilated Cardiomyopathy

Andres Schuster and W. H. Wilson Tang

MYOCARDITIS

The concept of myocarditis was first introduced by Corvisart in 1812. The term is broadly defined by an inflammatory infiltration of the myocardium with associated necrosis and/or degeneration.[1] The disease is also known as "myocarditis with cardiac dysfunction" when left ventricular systolic dysfunction is evident. Although there is a tremendously wide spectrum of clinical presentation, it is frequently associated with acute-onset profound cardiac dysfunction leading to rapidly progressive heart failure (HF) and arrhythmia development in an otherwise healthy young person. Myocarditis is also one of the major causes of sudden cardiac death in patients < 20 years old.[2]

Epidemiology and Classification

The exact incidence and prevalence of myocarditis is unclear because the majority of cases of myocarditis may be subclinical in presentation. Nevertheless, myocarditis usually affects younger individuals (median age of 42 years), with a slight predominance of men.[3] The estimated incidence of myocarditis is 1 to 10 per 100,000 persons from military recruits and autopsy studies, and about 1% to 5% of patients with acute viral infections may have some involvement in the myocardium.[4] The incidence of biopsy-proven myocarditis ranges from 9% to 11% in adults and up to 38% in children with acute-onset HF_5. The presence of viral genome in biopsies of patients with idiopathic dilated cardiomyopathy (IDCM) is up to 65% of the individuals, suggesting that viral subclinical myocarditis could be more frequent than suspected and may be the cause of many of the IDCM cases considered "idiopathic."[6]

The classification of myocarditis is confusing but is often defined according to the description of the disease course as "fulminant," "acute," or "chronic" (Table 19.1).[7] With the availability of endomyocardial biopsy techniques in the 1970s, a technical (histologic) definition has been standardized by pathologists:

TABLE
19.1 Clinicopathological Classification of Myocarditis

	Fulminant	Acute	Chronic Active	Chronic Persistent
Prevalence (%)	17	65	11	7
Symptom onset	Distinct	Indistinct	Indistinct	Indistinct
Presentation	Shock	CHF	CHF	Non-CHF
LV function	Severe LVD	LVD	LVD	Normal
Biopsy findings	Multiple foci of active myocarditis	Active or borderline myocarditis	Active or borderline myocarditis	Active or borderline myocarditis
Natural history	Complete recovery or death	Partial recovery or IDCM	IDCM	Non-CHF, normal LV function
Histologic evaluation	Complete resolution	Complete resolution	Ongoing or resolving myocarditis	Ongoing or resolving myocarditis
Immunosuppression	No benefit	Sometimes beneficial	No benefit	No benefit
Long-term survival[a]				Unknown
1-y	93%	85%		
11-y	93%	45%		

[a]Long-term survival data from 147 biopsy-proven myocarditis cases followed at the Johns Hopkins Hospital from 1984 to 1997.

IDCM, idiopathic dilated cardiomyopathy; LVD, LV dysfunction; LV, left ventricular.

Adapted from McCarthy RE III, Boehmer JP, Hruban RH, et al. Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. N Engl J Med. 2000;342:690-695, and Lieberman EB, Hutchins GM, Herskowitz A, et al. Clinicopathologic description of myocarditis. J Am Coll Cardiol. 1991;18:1617-1626.

1. The Dallas criteria (1987)[8] describe the quantity and distribution patterns of lymphocyte infiltrates, and classify into three main types: (a) myocarditis (with or without fibrosis), (b) borderline myocarditis, and (c) no myocarditis. The availability of a second follow-up biopsy may allow further stratification into "ongoing myocarditis," "resolving/healing myocarditis," or "resolved myocarditis."
2. The World Heart Foundation Marburg Criteria (1996)[9] added a quantitative assessment of lymphocyte density (with the cutoff at 14 cells/mm^2) for the stratification of the biopsies. Newer histologic criteria rely on immunohistologic quantification and characterization of immunocompetent infiltrates and cell adhesion molecule expression like anti-CD3, anti-CD4, anti-CD20, and anti-CD28. Criteria based on cellular staining have better sensitivity and could guide immunomodulatory therapy and also have a prognostic value.[10,11]

Etiologies and Pathophysiology

Many infectious and noninfectious agents can cause myocarditis (Table 19.2).[4,12] Viral infection is the most common cause in North America and Europe, with enterovirus (including coxsackievirus) and adenovirus being classically the most frequently

identified viruses.[13,14] Recent data has raised the importance of parvovirus B19 (PVB19) and human herpesvirus-6 as causative agents, not only in biopsies from acute myocarditis patients[15] but also when subjects with IDCM are studied. Pankuweit et al.[16] described the persistence of viral genome of PVB19 in up to 33% of endomyocardial biopsy samples from patients with IDCM, ejection fraction (EF) < 45%, and persistent inflammation in their histology. A recent publication from Stewart et al. showed that PVB19 was the only virus isolated from tissue samples in adult HF patients referred for endomyocardial biopsy but in a lower rate than previously described (12%). Furthermore, they did not support a causative role for PVB19 persistence in the development of HF as there was a lack of correlation between PVB19 genome and HF progression in these patients.[17] Otherwise, two or more viruses have also been described in more than 25% of patients with IDCM,[6] suggesting a simultaneous synergic effect of the different viruses.

TABLE
19.2 Causes of Myocarditis

Infective Causes of Myocarditis

Viral:
- Enteroviruses—coxsackievirus A and B, echovirus, influenza virus, poliovirus
- PVB19
- Herpesviruses—human herpes virus 6
- Adenovirus, mumps, rubella, rubeola
- Cytomegalovirus (CMV)
- Hepatitis B or C viruses
- Human immunodeficiency virus (HIV)

Rickettsial
Fungal: cryptococcosis, aspergillosis, coccidioidomycosis, histoplasmosis
Protozoan: *Trypanosomiasis cruzi* (Chagas disease), *Toxoplasmosis gondii*
Helminthic: trichinosis, schistosomiasis
Bacterial: legionella, clostridium, mycoplasma, streptococci, staphylococci, salmonella/shigella
Spirochetal: *Borrelia burgdorferi* (Lyme disease)

Noninfectious Causes of Myocarditis

Hypersensitive reaction ("eosinophilic myocarditis"):
- Antibiotics (ampicillin, chloramphenicol, tetracycline, sulfisoxazole)
- Diuretics (hydrochlorothiazide, spironolactone)
- Anticonvulsives (phenytoin, carbamazepine)
- Others (lithium, clozapine, indomethacin)
- Tetanus toxoid or smallpox vaccines

Cardiotoxic drugs:
- Catecholamines (especially dobutamine, amphetamines, cocaine)
- Chemotherapeutic drugs (anthracyclines, fluorouracil, streptomycin, cyclophosphamide, IL-2, trastuzumab)

Collagen vascular diseases:
- Systemic lupus erythematosus ("lupus carditis")
- Wegener granulomatosis
- Churg–Strauss syndrome (eosinophilic myocarditis)
- Dermatomyositis/polymyositis
- Scleroderma

Systemic illnesses:
- Sarcoidosis
- Giant-cell myocarditis
- Kawasaki disease
- Large-vessel vasculitis (polyarteritis nodosa, takayasu arteritis)
- Inflammatory bowel diseases (ulcerative colitis, Crohn disease)

Acute rheumatic fever
Bites/stings: scorpion venom, snake venom, wasp venom, black widow spider venom
Chemicals: hydrocarbons, carbon monoxide, thallium, lead, arsenic, cobalt
Physical injury: radiation, heatstroke, hypothermia
Peripartum cardiomyopathy

The precise pathogenic mechanisms of the disease are generally not well understood and may vary according to the causative agent and host factors. The majority of the cases are presumed to be due to a common pathway of host autoimmune-mediated injury. Direct cytotoxic effects of the causative agent plus damage due to myocardial

cytokine expression and direct endothelium injury seem to be the key factors. Clinically, myocardial damage follows the expected course of inflammatory response (Fig. 19.1).[4]

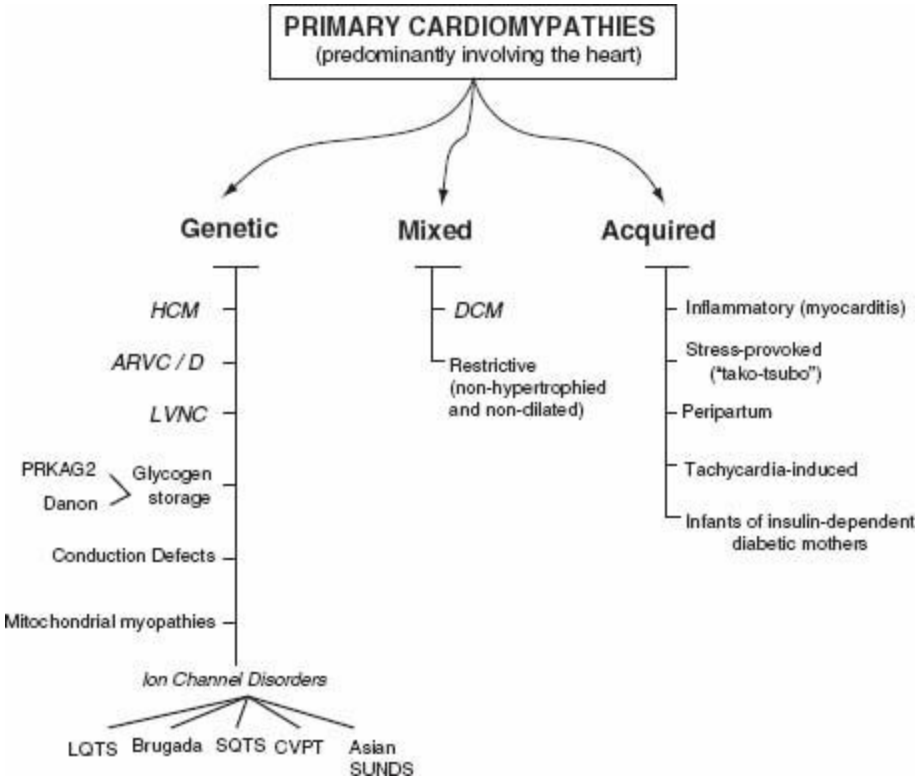

FIGURE 19.1 Classification of primary cardiomyopathies predominantly involving the heart. (From Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation. 2006;113:1807-1816, with permission.)

- Acute phase (0 to 3 days) is characterized by myocyte destruction and cardiac proteins exposure as a direct consequence of the offending agent. There is also cytokine expression and macrophage activation, leading to cell-mediated cytotoxicity and cytokine release that contribute to myocardial damage and dysfunction. In viral myocarditis, viremia is often present, although detection may sometimes be difficult.
- Subacute phase (4 to 14 days): Most patients recover after the acute phase but a subgroup progresses to this second stage that consists of an adaptive immune response. In addition to the continued cytokine production and myocyte destruction by nonspecific autoimmune-mediated injury (through cytotoxic T-and natural killer cells), antibodies are produced against viral proteins (in the subgroup patients with viral myocarditis) and cardiac proteins (including β_1 receptor and cardiac myosin).
- Chronic phase (>14 days) involves a repair process characterized by fibrosis, and downregulation of the immune response. Some patients may have persistence of

autoantibodies and also persistence of viral genome in myocardium. It has been estimated that between 20% and 50% of patients with acute myocarditis can progress to this chronic phase and develop cardiac dilatation and chronic HF.[18] Those cases where inflammation persists on endomyocardial biopsy are considered as "chronic active myocarditis" or "persistent myocarditis." A subclassification of the cardiomyopathy cases with persistent viral genome has been proposed. The patients in which viral clearing fails and have inflammatory disease in the biopsy would be referred as "viral inflammatory cardiomyopathy." Those cases with dilated cardiomyopathy where inflammation is absent would correspond to a "viral cardiomyopathy."[19]

In viral myocarditis, viral isolates differ in tissue tropism and virulence. For example, coxsackie A9 is a self-limiting myocarditis, whereas coxsackie B3 causes severe myocarditis with a high mortality. In addition, the induction of the coxsackie-adenovirus receptor (CAR) and the complement deflecting protein decay accelerating factor (DAF, CD55) may allow efficient internationization of the viral genome.[20] These key molecular determinants for cardiotropic viral infections can be found in up to two-thirds of patients with IDCM. Viral replication may lead to further disruption of metabolism and perturbation of inflammation and its response. More recent evidence of dystrophin disruption by expression of enteroviral protease 2A points to yet another unique pathogenic mechanism.[21] Also, endothelial cells have been recognized as a target for PVB19 infection if they express blood group P antigen, which serves as a cellular receptor for this virus. Therefore, initial parvovirus infection of endothelial cells of small coronary arteries may cause endothelial dysfunction, vasospasm, and ischemia. This may be a cofactor for myocardial damage progression and could also mimic myocardial infarction presentation, what has been called "parvomyocarditis."[22] Interestingly, other investigators have not found histopathologic signs of chronic ischemic disease like subendocardial fibrosis and vacuolization on endomyocardial biopsy of HF patients with a positive tissue PCR for PVB19. These findings contradict the theory of endothelial and ischemic damage related to PVB19.[17]

Clinical Presentation

Myocarditis can be totally asymptomatic or can present with a chest pain syndrome ranging from the mild persistent chest pain of acute myopericarditis (35%) to severe symptoms that resemble myocardial ischemia.[4] About 60% of patients may have history of arthralgias, malaise, fevers, sweats, or chills consistent with viral infections (pharyngitis, tonsillitis, upper respiratory tract infection) usually about 1 to 2 weeks prior to onset. The hallmark symptoms of acute or fulminant myocarditis are those of acute-onset HF in a person without known cardiac dysfunction or with low cardiovascular risks. The diagnosis is usually presumptive, based on patient

demographics and the clinical course (spontaneous recovery following supportive care or death). Patients with an acute HF presentation usually will have tachycardia with a S_3 gallop, jugular venous distension, and peripheral edema. An audible pericardial friction rub may accompany in cases of myopericarditis. In some instances, patients may present with arrhythmia in the form of palpitations caused by supraventricular or ventricular tachyarrhythmia, syncope caused by heart block ("Stokes–Adams attack") or sudden cardiac death.

Additional findings may accompany specific forms of myocarditis. In patients with acute rheumatic fever, associated signs include erythema marginatum, polyarthralgia, chorea, and subcutaneous nodules (Jones criteria for rheumatic fever). In cases of sarcoid myocarditis, lymphadenopathy and arrhythmias are common (up to 70% of affected individuals). Chagas acute infection may present with arrhythmias and cardiac conduction abnormalities. Hypersensitive or eosinophilic myocarditis is often associated with a pruritic maculopapular rash (and history of offending drug use) and eosinophilia in their blood work. The typical presentation of a patient with giant-cell myocarditis involves sustained ventricular tachycardia and rapidly progressive HF leading to cardiogenic shock. These features have low specificities but are often useful and may raise the suspicion of underlying myocarditis.

Evaluation

Inflammation is the hallmark feature of myocarditis. Clinically, an early onset of fever, tachycardia, hypotension, reduced ventricular function, elevated acute phase reactants (erythrocyte sedimentation rate or C-reactive protein), leukocytosis, and increased cardiac enzymes (CK-MB/cardiac troponins) are predictive of myocarditis. However, the prevalence of an increased troponin T in biopsy-proven myocarditis is only 35% to 45%.[23] A lower level of troponin I at admission has been associated with an increased risk for death, heart transplantation, or persistent ventricular dysfunction in patients with fulminant myocarditis.[24] The presence of eosinophilia may suggest hypersensitive (eosinophilic) myocarditis. Novel inflammatory markers that are still under investigation include tumor necrosis factor (TNF)-α, interleukin (IL)-10, serum-soluble Fas, and soluble Fas-ligand levels.[25,26] Elevation of these markers portends a worse prognosis, although they are rarely used in the clinical setting. Serum viral antibody titers are usually increased fourfold or more in the acute phase and gradually fall during convalescence. However, measurement of viral antibody titers is infrequently indicated due to the usual low viral levels at the time of HF presentation and the lack of evidence for antiviral therapy. Because of their low specificity, measurement of anticardiac antibody titers is not indicated (only 62% of myocarditis cases have titers ≥1:40). Screening antinuclear antibodies and rheumatoid factor are often indicated to rule out common rheumatologic problems. Disease-specific testing is indicated if particular conditions such as systematic lupus erythematosus, polymyositis, Wegner

granulomatosus, or scleroderma are suspected.

The electrocardiogram generally reveals sinus tachycardia, although sometimes ST-segment deviation can be found, making it necessary to rule out ischemia especially in patients with cardiovascular risk factors. In some cases, fascicular block, atrioventricular conduction disturbances, or ventricular tachyarrhythmias may be hemodynamically significant. A complete echocardiogram is a standard procedure for patients with suspected myocarditis to (a) exclude alternative causes of HF-like valvular disease, (b) quantify the degree of left ventricular dysfunction to monitor response to therapy, and (c) detect the presence of intracardiac thrombi. Occasionally, focal wall motion abnormalities and presence of pericardial fluid may prompt further workup or intervention. Fulminant myocarditis is often characterized by near normal diastolic dimensions and increased septal wall thickness, whereas acute myocarditis often has increased diastolic dimensions but normal septal wall thickness.[27] Coronary angiography is often performed to rule out coronary disease as cause of new-onset HF in patients with risk factors or with a clinical presentation that mimic myocardial ischemia ("pseudoinfarct pattern"). This is especially relevant in the presence of focal wall motion abnormalities on echocardiography and localizing electrocardiographic changes. Several specialized imaging procedures are available to detect the presence of myocarditis, although they are rarely used clinically. Antimyosin scintigraphy using indium-III monoclonal antimyosin antibody provides identification of myocardial inflammation, with a high sensitivity (91% to 100%) and negative predictive value (93% to 100%) but relatively low specificity (28% to 33%) of detecting myocarditis. Gallium scanning has been utilized to identify severe myocardial cellular infiltration with high specificity (98%) but low sensitivity (36%).[4]

Gadolinium-enhanced cardiac magnetic resonance imaging (MRI) is being used with increasing frequency for noninvasive evaluation of patients with suspected myocarditis. Cardiac MRI can assess different markers of tissue injury, including intracellular and interstitial edema, capillary leakage with hyperemia, and cellular necrosis with fibrosis. The International Group on Cardiovascular Magnetic Resonance in Myocarditis recommended to perform a cardiac MRI when the patient was symptomatic, if the clinical suspicion of myocarditis was high, and if the MRI result will likely impact clinical management. The authors proposed three tissue markers (the “Lake Louise Criteria”) to confirm the diagnosis of myocarditis (Table 19.3). If all sequences can be performed and two or more of the three tissue-based criteria are positive, myocardial inflammation can be predicted with a diagnostic accuracy of 78%; if only late gadolinium enhancement imaging is performed, the diagnostic accuracy falls to 68%.[28]

TABLE
19.3 Cardiac MRI Diagnostic Criteria for Myocarditis

- In the setting of clinically suspected myocarditis, cardiac MRI findings are consistent with myocardial inflammation, if at least two of the following criteria are present:
  1. Regional or global myocardial SI increase in T2-weighted images
  2. Increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images
  3. There is at least one focal lesion with nonischemic regional distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images ("late gadolinium enhancement")
- A cardiac MRI study is consistent with myocyte injury and/or scar caused by myocardial inflammation if late gadolinium enhancement (criterion 3) is present
- A repeat MRI study between 1 and 2 wk after the initial assessment is recommended if:
  1. none of the criteria are present, but the onset of symptoms has been very recent and there is strong clinical evidence for myocardial inflammation.
  2. one of the criteria is present
- The presence of LV dysfunction or pericardial effusion provides additional supportive evidence for myocarditis

Reprinted from Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. J Am Coll Cardiol. 2009;53(17):1475-1487, with permission from Elsevier.

Histology remains the gold standard for the diagnosis of myocarditis, although endomyocardial biopsy is insensitive and not without risks. False negative rates are high[29] (even with multiple biopsy samples) due to the small number of lymphocytes reviewed, difficulties in distinguishing cell types, wide interobserver variability, and the patchy distribution of myocardial inflammation in most patients. Guided biopsy using delay enhancement in contrast MRI was evaluated by Mahrholdt et al., where 21 patients in whom biopsy was obtained from the region of contrast enhancement. In these patients, histopathologic analysis revealed active myocarditis in 19 patients (PVB19, n = 12; human herpes virus type 6, n = 5). In contrast, the remaining 11 patients in whom biopsy could not be taken from the region of contrast enhancement, active myocarditis was found only in one case.[30]

In patients with suspected myocarditis, endomyocardial biopsy is generally reserved for suspected etiology in whom a positive histologic diagnosis will determine a specific treatment, such as giant-cell and sarcoid myocarditis. Giant-cell myocarditis, which can be suspected in subjects presenting with rapidly progressive HF symptoms despite conventional therapy and new-onset frequent ventricular tachyrrhythmia or conduction disturbances, could benefit from immunosuppressive therapy. In most cases,

the histologic criteria only provide confirmation of the diagnosis and perhaps some prognostic information. It is also important to recognize that as the interval from illness onset to the time of the biopsy increases, the yield of the procedure gets lower. A negative endomyocardial biopsy can not convincingly exclude underlying myocarditis or sarcoidosis due to its patchy process and biopsy sampling error and therefore clinical correlation is necessary.

Treatment and Prognosis

There are no hard-and-fast rules for managing myocarditis once the acute events have occurred. In general, patients are treated in the same manner as if they have chronic HF. Clinical follow-up should be close, as persistent chronic inflammation may lead to dilated cardiomyopathy (initially 1 to 3 month intervals for medication and physical activity titration). Serial echocardiographic assessment of ventricular structure and function is often performed, although there is no agreement regarding the frequency of echocardiographic assessment following myocarditis. There is a theoretical increased risk of myocardial inflammation and necrosis, cardiac remodeling, and death with exercise in animal models.[31] Therefore, patients suffering from myocarditis are usually advised to abstain from vigorous exercise for several months in order to limit myocardial demands. Depending on the clinical presentation, standard HF therapy with diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and aldosterone antagonists should be used to delay or reverse disease progression of cardiac dysfunction. Although not proven in human studies, proarrhythmic properties of digoxin have been observed in animal models of myocarditis, and therefore should be avoided. Anticoagulation is usually recommended and indicated to prevent thromboembolic events in patients with apical aneurysm and thrombus (such as in Chagas cardiomyopathy), atrial fibrillation, and prior embolic episodes. Permanent pacemakers should be implanted for persistent heart block or bradyarrhythmia. Implantable cardioverter defibrillators (ICDs) are indicated only after acute phase resolution, in patients with primary and secondary indication of sudden cardiac death prevention. Inotropic therapy often is reserved for those experiencing severe hemodynamic compromise (particularly in fulminant myocarditis). Sometimes, intra-aortic balloon counterpulsation can be used for hemodynamic support and afterload reduction to prevent further deterioration. Mechanical assist devices (left ventricular assist device [LVAD]) and even extracorporeal membrane oxygenation (ECMO) have been used in cases of fulminant myocarditis with the hope for recovery and/or bridge to transplantation. Early consideration for cardiac transplantation should be given especially in severe, progressive, biopsy-proven giant-cell myocarditis and peripartum cardiomyopathy. Registry data have suggested that patients with myocarditis may have increased rejection and reduced survival after heart transplantation as compared to those without, and myocarditis may recur in the allograft in less severe forms.

Table 19.4 summarizes the major clinical trials on immunosuppression therapy for myocarditis and inflammatory cardiomyopathy. Routine immunosuppression therapy (including steroids), antiviral regimen, and nonsteroidal anti-inflammatory agents are not warranted based on current clinical evidence. The findings from the Myocarditis Treatment Trial (with oral prednisone and cyclosporine)[32] and the IMAC study (with intravenous immunoglobulin)[5] indicated that routine immunosuppression therapy may not be effective. The more recently published TIMIC-randomized controlled trial showed positive results with prednisone and azathioprine therapy in 85 patients with virus-negative chronic inflammatory cardiomyopathy, where 88% of them improved their left ventricular ejection fraction (LVEF) and had reverse cardiac remodeling after 6 months of treatment.[33] It seems that the duration of symptoms appears to be a major determinant in the response to immunosuppression. A recent meta-analysis of immunosuppression in patients with IDCM suggested that acute HF (symptoms duration of < 6 months) was associated with a lack of response to immunomodulation and immunosuppression therapy when compared to patients with symptoms for more than 6 months.[34] At present, there is no FDA-approved regimen to treat acute or chronic myocarditis. Immunosuppression or immunomodulation therapy is reserved for the refractory patients with chronic myocarditis and those with biopsy-proven giant-cell myocarditis; in fact, patients with fulminant myocarditis should not be routinely being immunosuppressed but rather supported. Some reports have suggested that eosinophilic or sarcoid myocarditis may respond to highdose steroid therapy. Also, specific therapy for underlying collagen vascular diseases may be used.

TABLE
19.4 Major Clinical Trials of Myocarditis and Inflammatory Cardiomyopathy

	Authors	Year	Drug	Sample	Study Population	Primary Endpoint	Outcomes (Treatment vs. Placebo)
NHLBI Study	Parillo et al.[35]	1989	Prednisone	102	IDCM	Change in LV function at 3 mo	No benefit (4.3% vs. 2.1%)
Myocarditis Treatment Trial	Mason et al.[32]	1995	Prednisone and cyclosporine	111	EMB-proven myocarditis EF <40%	Change in LV function at 7 mo	No benefit (10% vs. 7%)
Multicenter IMAC Trial	McNamara et al.[5]	2001	IVIG	62	Recent onset DCM, EF <40%	Change in LV function at 6 mo	No benefit (14% vs. 14%)
Polish Study	Wojnicz et al.[36]	2001	Prednisone and azathioprine	84	DCM with upregulated HLA	Change in LV function at 24 mo	Benefit (20% vs. 6%)
Italian Cohort	Frustaci et al.[37]	2003	Prednisone and azathioprine	41	EMB-proven myocarditis with CHF	Change in LV function at 12 mo	Benefit (21% vs. 0%)
GCM Treatment Trial	Cooper et al.[44]	2008	Prednisone and cyclosporine	11	EMB-proven GCM	Survival at 1 y	Treatment benefit (72%)
TIMIC Trial	Frustaci et al.[33]	2009	Prednisone and azathioprine	85	EBM-proven inflammatory DCM virus (–)	Change LV function at 6 mo	Treatment benefit (19% vs. –7% EF)

LV, left ventricular; IVIG, intravenous immunoglobulin, HLA, human leukocyte antigen; IDCM, idiopathic dilated cardiomyopathy; EF, ejection fraction; NHLBI, National Heart, Lung & Blood Institute; EMB, endomyocardial biopsy

Recent studies have suggested potential benefits of targeted therapy with

azathioprine and prednisone in patients with recent onset IDCM. An ongoing multicenter European Study on the Epidemiology and Treatment of Cardiac Inflammatory Disease (ESETCID) may provide some further insight.[38] There is likely a category of patients who have an active immune process for whom immunosuppression, immune absorption, or immune regulation will ultimately provide benefit.

Many patients may have full spontaneous clinical recovery, even after weeks of medical and mechanical support (including intra-aortic balloon counterpulsation and mechanical assist devices). In the Myocarditis Treatment Trial, 1-year mortality was 20%, and 4-year mortality was 56%.[30] Interestingly, long-term outcomes do not differ significantly between active and borderline myocarditis by the Dallas criteria. Severe heart block requiring permanent pacemaker placement occurs in approximately 1% of patients. Unfavorable factors for survival include extremes of age (very old or very young), New York Heart Association (NYHA) class at presentation, electrocardiographic abnormalities (QRS alterations, atrial fibrillation, low voltage), syncope, and specific etiologies (peripartum cardiomyopathy, giant-cell myocarditis). Favorable factors for survival include preserved cardiac function, shorter clinical history, or survivors of fulminant presentation at onset. In fact, the prognosis of patients with secondary myocarditis, when compared with patients with idiopathic myocarditis, seems most affected by the primary disease processes.[39] For unclear reasons, survivors of fulminant myocarditis experienced better long-term outcomes than those presenting with acute myocarditis.[40] Adults may present with HF years after the initial index event of myocarditis (up to 12.8% of patients with IDCM had presumed prior myocarditis in one case series). Up to half of patients with myocarditis develop subsequent IDCM over a range of 3 months to 13 years.

Specific Forms of Cardiomyopathy Related to Myocarditis

Chagas Heart Disease

It is estimated that 16 to 18 million persons are infected with Trypanosoma cruzi in South and Central America. While most patients resolve from the acute inflammatory phases of the infection, cardiac involvement usually appears decades after inoculation and is the leading cause of death in persons aged 30 to 50 years in endemic areas. The hallmark of Chagasic cardiomyopathy is arrhythmia that often presents with symptoms of palpitation, syncope, chest pain, and subsequently HF.[41] Frequent complex ectopic beats and ventricular tachyarrhythmias occur in 40% to 90% affected, with sudden cardiac death occurring in 55% to 65% affected. Right bundle-branch block is also frequently seen, sometimes with bradyarrhythmias and high-grade atrioventricular block requiring pacemaker placement. HF is predominantly right-sided, and can be found in 25% to 30% of patients, and sometimes with cerebral or pulmonary thromboembolism.

Apical left ventricular aneurysm, ventricular dilatation, and cardiac fibrosis are commonly found at autopsy. There are several types of serologic tests to confirm the presence of exposure to T. cruzi. Cardiac lesions can be confirmed by in situ polymerase chain reaction in biopsy specimens. Echocardiographic findings may include left ventricular aneurysm with or without thrombi, posterior basal akinesis or hypokinesis with preserved septal contraction, and diastolic dysfunction. Antibiotic therapy in the acute phase with benznidazole or nifurtimox may help to reduce parasitemia and prevent complications.

Giant-Cell Myocarditis

Giant-cell myocarditis (also known as pernicious myocarditis, Fiedler myocarditis, granulomatous myocarditis, or idiopathic interstitial myocarditis) is a rare disorder with unclear etiology. The hallmark feature is the presence of fused, multinucleated (>20 nuclei) epithelioid "giant cells" of histocytic origin within a diffuse, intramyocardial inflammatory infiltrate with lymphocytes. Giant-cell myocarditis often presents with an aggressive clinical course with progression over days to weeks. Rapidly progressive HF transpires in 75% affected, and sustained ventricular tachyarrhythmia is seen in more than 50% affected. Giant-cell myocarditis is often refractory to standard medical therapy, although small observational studies have suggested potential benefits of immunosuppressive therapy.[42,43] Recently, a prospective study with steroids, cyclosporine and OKT3 monoclonal antibody therapy in 11 GCM patients showed a survival free of transplant in 8 of 11 patients at 1 year.[44] Consideration for early cardiac transplantation is appropriate (71% 5-year survival following successful transplantation). Often, mechanical support may be required as a temporary bridge to recovery or transplantation. The prognosis is often dismal without intervention such as cardiac transplant (up to 80% 1-year mortality, with a median survival of 5.5 months from symptom onset). Therefore, early identification of giant-cell myocarditis by means of endomyocardial biopsies may facilitate prompt referral for cardiac transplantation. A 20% to 25% rate of histologic recurrence in surveillance endomyocardial biopsies has been observed following transplantation, but without substantial impact on the clinical course.[45]

Hypersensitive/Eosinophilic Myocarditis

Eosinophilic endomyocardial disease (also known as Loffler endomyocardial fibrosis) occurs as a major complication of idiopathic hypereosinophilic syndrome, as a result of direct toxic damage caused by eosinophil granule proteins within the heart.[46] Drug-induced eosinophilic myocarditis is independent of cumulative dose and duration of therapy. Common inciting agents include catecholamines, chemotherapeutic agents,

ampicillin, and tetanus toxoid (see Table 19.2).[47] The absence of peripheral eosinophilia does not rule out eosinophilic myocarditis. Although observational series suggest potential clinical benefits of corticosteroid therapy, the best strategy is to remove the causative agent once identified.

DILATED CARDIOMYOPATHY

In 1995, the World Health Organization (WHO) defined dilated cardiomyopathy as a myocardial disease characterized by dilatation and impaired contraction of the left ventricle (LV) or both left ventricle and right ventricle (RV) (Table 19.5).[1] It is a common and largely irreversible form of heart muscle disease with an estimated prevalence of 1:2,500. It is the third most common cause of HF and the most frequent of heart transplantation. In the new 2006 classification (see Fig. 19.1), dilated cardiomyopathy has been classified within the group of primary cardiomyopathies of mixed origin (genetic and nongenetic) together with the primary restrictive nonhypertrophied cardiomyopathy.[48]

TABLE
19.5 Major Forms of Cardiomyopathy and their Classification

Clinicopathologic Pattern	Primary Cardiomyopathy	Specific Heart Muscles Disease (Secondary Cardiomyopathy)	Other Cardiovascular Disorders
Dilated cardiomyopathy (systolic dysfunction)	■ Idiopathic ■ Familial	■ Inflammatory myocarditis ■ Alcohol/toxic ■ Peripartum ■ Metabolic	■ Ischemic ■ Valvular ■ Hypertensive ■ Congenital
Hypertrophic cardiomyopathy (diastolic dysfunction)	■ Familial (50%) ■ Idiopathic	■ Amyloidosis	■ Hypertensive ■ Aortic stenosis
Restrictive cardiomyopathy (diastolic dysfunction)	■ Idiopathic ■ Familial	■ Amyloidosis ■ Radiation/endomyocardial fibrosis	■ Pericardial constriction
Arrhythmogenic right ventricular cardiomyopathy	■ Idiopathic ■ Familial		

Adapted from Richardson P, McKenna W, Bristow M, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies. Circulation. 1996;93:841–842.

Often synonymous with "nonischemic cardiomyopathy," dilated cardiomyopathy is a heterogeneous disease, and shares the same common pathophysiologic processes of

myocyte apoptosis and necrosis, fibrosis, and neurohormonal upregulation with specific cardiomyopathies. Clinical presentation of dilated cardiomyopathy ranges from asymptomatic to overt HF, stroke from thromboembolism, arrhythmias, and sudden cardiac death, almost parallel to that of myocarditis. While classification schemes are largely academic and the general diagnostic and therapeutic strategy follows that of all HF etiologies, several specific forms of cardiomyopathy are worth mentioning because they have unique clinical features and specific treatment options that are noteworthy.

Strict diagnostic criteria and epidemiology for IDCM are lacking because many cases go undiagnosed, and many patients who experienced HF do not undergo extensive workup. It has been estimated that the prevalence of IDCM is 0.4 per 1,000 in the general population. However, as more diagnostic techniques become available, specific causes of dilated cardiomyopathy can be identified and fewer cases will be deemed "idiopathic." For example, histologic evidence of myocarditis is seen in 4% to 10% of endomyocardial biopsies of IDCM patients. It is estimated that dilated cardiomyopathy may develop in up to 50% of patients with acute myocarditis[18] and molecular diagnosis of viral involvement have even suggested a viral etiology in up to two-thirds of IDCM cases.[6]

Metabolic cardiomyopathies include amino acid, lipid and mitochondrial disorders, and storage diseases. Certain metabolic deficiencies such as selenium, carnitine, phosphate, calcium, and vitamin B deficiencies can all result in dilated cardiomyopathy, as often seen in patients with anorexia nervosa. Many endocrine disorders (adrenocortical insufficiency, thyroid abnormalities, acromegaly, and pheochromocytoma) also cause secondary cardiomyopathies. However, in cases of metabolic cardiomyopathies such as hemochromatosis, amyloidosis, glycogen storage diseases, and Fabry–Anderson disease, restrictive physiology is the hallmark presentation. Identification of the underlying etiology may aid the appropriate treatment (e.g., phlebotomy and chelation therapy for hemochromatosis, α-galactosidase replacement therapy for Fabry cardiomyopathy).

Several forms of dilated cardiomyopathy may develop early in childhood. Noncompacted myocardium occurs as a result of an arrested endomyocardial morphogenesis, and usually presents in childhood with persisting myocardial sinusoids, prominent trabeculations, and evidence of patchy "spongy" morphology of the embryonic heart. Endocardial fibroelastosis can lead to thickening of LV and left-sided cardiac valves, leading to dilated or restrictive cardiomyopathy.

Inherited Forms of Dilated Cardiomyopathy

Although familial dilated cardiomyopathy accounts for at least 20% to 30% of the cases of dilated cardiomyopathy, genetic screening is rarely performed. Mutations in genes encoding for cytoskeletal proteins (lamin A/C, phospholamban, dystrophin) as well as sarcomeric proteins (myosin heavy chain, cardiac troponin T, actin) have been

described.[49-51] Interestingly, the latter mutations are similar to those found in hypertrophic cardiomyopathy. Furthermore, patients with ion channelopathy (such as long and short QT syndromes, Brugada syndrome, and catecholaminergic polymorphic ventricular tachyarrhythmia) often develop dilated cardiomyopathy. The autosomal form of familial dilated cardiomyopathy is the most prevalent. The clinical expression and penetrance of these inherited gene defects is variable and may encompass skeletal myopathies (including Duchenne, Becker-type, and myotonic dystrophies), neuromuscular disorders (include Friedreich ataxia, Noonan syndrome, and lentiginosis), cardiac conduction system abnormalities, and progression to end-stage HF. The risk of sudden cardiac death is less clearly defined as compared with hypertrophic cardiomyopathy, but appears to be increased, particularly in patients with sarcomeric protein mutations. Family members may be asymptomatic early in the course of disease, but identification of affected individuals with serial echocardiography is important as early treatment may improve prognosis. Patients with familial dilated cardiomyopathy, particularly in those with inherited forms of systolic dysfunction with minimal dilatation (without restrictive physiology), may carry a poor prognosis.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) emerged as a unique entity in the 1995 WHO classification scheme. It is an autosomal dominant disease predominantly affecting the right ventricle by massive or partial replacement of myocardium by fatty or fibro-fatty tissue, and can be detected by MRI or by endomyocardial biopsy (often sparing the trabeculae and the septum).[52] Over 50% of cases are inherited with an autosomal dominant pattern, and mutations in the plakoglobin and desmoplakin genes (recessive form of ARVC known as Naxos disease) have been associated with familial ARVC. Residual islands or strands of myocytes are often electrically unstable, leading to widespread ventricular tachyarrhythmias and sudden death of young individuals. Clinically, they may present in early adulthood with tachyarrhythmias or with right-sided HF (sometimes extending to the LV). Echocardiography may demonstrate a localized RV aneurysm or isolated RV failure, and the electrocardiogram may show slurred ST segments and inverted T waves in anterior leads (epsilon waves) without right bundle branch block. An ICD and treatment with antiarrhythmic drugs are indicated; radiofrequency ablations may be a useful intervention. HF is difficult to manage, and cardiac transplantation can be considered in selective cases.

Mitochondrial cardiomyopathy represents a special form of maternally inherited cardiomyopathy due to mutations in mitochondrial DNA with resultant abnormalities in oxidative phosphorylation. Indeed, the MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, and stroke-like syndrome) can manifest as a cardiomyopathy. Electron microscopy of muscle biopsy specimens may demonstrate giant mitochondria, concentric crystae, and intramitochondrial inclusions. There have also been reports of the association of mutations of the hereditary hemochromatosis

(HFE) gene with IDCM.

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QUESTIONS AND ANSWERS

Questions

1. A 45-year-old female came to see you because of intermittent chest pain and progressive shortness of breath for the last 3 days. She was seen last week by her primary physician because of sinusitis and was placed on azithromycin for 5 days without relief.

Exam: BP 110/80 mm Hg, pulse 110 bpm regular, JVP 10 cm H_2O, bibasilar rales, S_3 gallop, 1 to 2+ pedal edema.

ECG: sinus tachycardia, nonspecific T wave changes.

Echocardiography: left ventricular ejection = 25% 1 to 2+ mitral regurgitation

Which of the following is not an appropriate next course of action?
a. Cardiac catheterization
b. Endomyocardial biopsy to rule out acute lymphocytic myocarditis
c. Start diuretics and angiotensin-converting enzyme (ACE) inhibitors
d. Blood testing for thyroid function tests

2. Her blood work and autoimmune workup were negative. Cardiac catheterization revealed normal coronary arteries. Her clinical course rapidly deteriorated over the course of the next few days, requiring hospital admission for decompensated heart failure (HF). She was found to be in cardiogenic shock, requiring inotropic support for stabilization. An endomyocardial biopsy was performed, and the preliminary results suggested acute lymphocytic myocarditis according to the Dallas criteria. Her cardiac index and hemodynamics were stable other than frequent nonsustained ventricular tachyarrhythmia. Based on this information what is the appropriate therapeutic intervention?
a. Intravenous Solu Medrol
b. Implantable cardioverter defibrillator (ICD)
c. Plasmapheresis
d. No additional therapy at this point

3. What would be her 5-year prognosis if she survives this acute event?
a. 93%
b. 80%

c. 65%
d. 45%

4. Which of the following patients would have a worse prognosis?
   a. A 29-year-old man with giant-cell myocarditis
   b. A 27-year-old woman with fulminant myocarditis
   c. A 35-year-old man with idiopathic restrictive cardiomyopathy
   d. A 25-year-old woman with postpartum cardiomyopathy

Answers

1. Answer B: New-onset HF in a relatively young patient who had a recent bout of upper respiratory tract infection can be a potential clinical presentation of acute myocarditis. That being said, the usual course of action should involve cardiac catheterization to rule out coronary ischemia, blood testing to rule out reversible causes of HF such as hypoor hyperthyroidism, and start therapy with diuretics, ACE inhibitors, and beta-adrenergic blockers. Routine endomyocardial biopsy, even though it may elucidate the definitive diagnosis, does not change the management at this point, and should be reserved only when patients require further evaluation due to decompensation.

2. Answer D: The patient now presents with fulminant myocarditis, requiring inotropic support. She should remain on supportive therapy, and there is no supporting evidence to recommend immunosuppression therapy at this stage. It would also be inappropriate for her to receive an ICD in this acute setting.

3. Answer A: McCarthy and colleagues compared the long-term prognosis between fulminant and acute myocarditis and found a 93% survival for those suffering from fulminant myocarditis at 1-year follow-up, which maintained for the next 10 years.[16]. This is significantly better from those presenting with acute myocarditis (45% at 11 years).

4. Answer A: All the choices possess a poor prognosis except for fulminant myocarditis if supported, but giant-cell myocarditis has the worst prognosis, and cardiac transplantation should be considered.

CHAPTER

Pulmonary Hypertension

Matthias Dupont and W. H. Wilson Tang

The diagnostic workup and treatment of pulmonary hypertension (PH) is part of cardiology as well as pulmonary practices and, due to different etiologies, is also sporadically encountered by rheumatologists, infectious disease specialists (HIV), and pediatricians. In general, PH (in particular, pulmonary arterial hypertension [PAH]) is a devastating disease, not only because it affects relatively young individuals but because the therapeutic options, although evolving, remain somewhat limited. In recent years, substantial progress has been made in unraveling the pathophysiology of PH directly resulting in some new medical therapies. Directions for diagnosis and treatment are formulated as an expert consensus document by ACCF/AHA[1] and as guidelines by the ESC.[2]

DEFINITION AND CLASSIFICATION

PH is defined as mean pulmonary artery pressure (mPAP) >25 mm Hg at rest or >30 mm Hg with exercise. The latter component of this definition is questioned because it is not supported by published data, and healthy individuals can reach much higher values.[3] PH encompasses a heterogeneous group of diseases with a common clinical manifestation. The true scope of the problem is not known, since many people have unrecognized PH. The terms “primary” (idiopathic or familial) and “secondary” PH have been abandoned and were replaced by a classification system adopted during the Second World Symposium on Pulmonary Hypertension in 1998 and most recently modified during the Fourth World Symposium in 2008 (Table 20.1).[4] The aim of this clinical classification system is to group together different manifestations of disease sharing similarities in pathophysiologic mechanisms, clinical presentation, and therapeutic approaches. This makes sense because certain therapies for PAH are not effective in other forms of PH or might even be harmful. In this way, five major

categories are outlined:

TABLE
20.1 Updated Clinical Classification of PH

1 PAH
1.1 Idiopathic PAH
1.2 Heritable
1.2.1 BMPR2
1.2.2 ALK-1, ENG (with or without hereditary hemorrhagic telangiectasia)
1.2.3 Unknown
1.3 Drug- and toxin-induced
1.4 Associated with
1.4.1 Connective tissue diseases
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1.4.6 Chronic hemolytic anemia
1.5 Persistent PH of the newborn
1′ PVOD and/or PCH
2 PH owing to left heart disease
2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
3 PH owing to lung diseases and/or hypoxia
3.1 COPD
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental abnormalities
4 CTEPH
5 PH with unclear multifactorial mechanisms
5.1 Hematologic disorders: myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, and chronic renal failure on dialysis

Reprinted from Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. JACC 2009;54:43-54, with permission from Elsevier.

1. PAH

2. PH owing to left heart disease
3. PH owing to lung diseases and/or hypoxia
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. PH with unclear multifactorial mechanisms

The terms PH, which is a hemodynamic and pathophysiologic condition, and PAH, a clinical condition, are thus not synonymous and one should pay attention to the specific population studied when interpreting trial results.

Pulmonary Arterial Hypertension

Although PAH probably only represents 4.2% of the total PH population, it has been the focus of attention since the first classification in 1973.[5] Most recent data from registries estimate the prevalence around 15 to 50 cases per million adults.[6,7] PAH is characterized by the presence of precapillary PH (pulmonary capillary wedge pressure [PCWP] < 15 mm Hg) in the absence of other causes of precapillary PH such as lung disease, pulmonary embolism, or other rare diseases (see Table 20.1). The nomenclature of the subgroups and the associated conditions has significantly evolved since 1973.

Idiopathic and familial PAHs (previously known as "primary pulmonary hypertension") are rare diseases with a prevalence around six cases per million. Familial cases account for 5% to 10% of all PAH cases. Mutations in the bone morphogenetic protein receptor II (BMPR2) gene have been identified in at least 70% of patients with familial PAH and in 10% to 40% of patients with sporadic, idiopathic PAH.[8,9] Lack of a functional BMPR2 gene appears to affect antiproliferative pathways of vascular cells. Genetic mutations in two other members of the transforming growth factor-β superfamily have also been identified, namely the activin receptor-like kinase 1 (ALK-1) and endoglin (ENG), which are associated with hereditary hemorrhagic teleangi- ectasia.[8] Relatives of patients with familial idiopathic PAH should be advised about the availability of genetic testing and counseling in addition to echocardiographic screening.

PAH has been associated with the use of several drugs and toxins. Already in the 1960s, an association between anorexigens (appetite suppressant drugs that increase serotonin release and block serotonin reuptake) and PAH was observed following the introduction of aminorex fumarate.[10] Subsequently in the 1980s, the same association was noticed after as little as 3 months of exposure to structurally related compounds such as (dex)fenfluramine.[11]

Several patient populations have a higher risk of developing PAH and are worth mentioning. Connective tissue diseases (CTDs), especially the limited cutaneous form of systemic sclerosis (formerly referred to as the CREST syndrome), are infrequently

accompanied by PAH. The prevalence of hemodynamically proven PAH in systemic sclerosis is around 10% and can be the result of an isolated pulmonary arteriopathy as well as associated with interstitial fibrosis.[12] In systemic lupus erythematosus, mixed CTD, rheumatoid arthritis, dermatomyositis, and Sjögren syndrome, PAH is observed to a lesser extent.

The incidence of PAH in patients infected with HIV is approximately 0.5%, which is still 6 to 12 times that of the general population. However, because of this low incidence, routine screening is not recommended.[13] Cirrhosis patients with portal hypertension are another patient population with an increased incidence of PH (5% of patients referred for liver transplantation). This PH can be the result of a high flow state and a proliferative pulmonary arteriopathy with plexiform lesions, the so-called portopulmonary hypertension. The development of PH in this population is poorly understood and may portend poor survival (median 6 months) and high transplant mortality. Medical interventions and liver transplantation may sometimes reverse mild to moderate portopulmonary hypertension.[14]

Congenital heart disease is a well-recognized cause of PAH when the underlying systemic-to-pulmonary shunt is not corrected. It occurs most frequently with conditions where blood flow is high and the pulmonary vasculature is exposed to systemic level pressures (e.g., ventricular septal defect, patent ductus arteriosus). However, high flow only, as in atrial septal defect, can be sufficient. Once pulmonary vascular resistance (PVR) approaches or exceeds systemic vascular resistance, the shunt is reversed leading to desaturation and cyanosis (Eisenmenger syndrome). Although the pulmonary obstructive arteriopathy in this setting is identical to other PAH forms, prognosis is typically better.[15]

Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are two rare disorders that share the histology of PAH but also demonstrate a number of differences and therefore remain somewhat difficult to classify. They are labeled as group 1′, a distinct category but not completely separated from PAH. They exhibit the findings of pulmonary venous hypertension including pulmonary hemosiderosis, interstitial edema, and lymphatic dilatation.

Pulmonary Hypertension Owing to Left Heart Disease

In this category, pathology is situated on the left side of the heart and PH is the result of backward transmission of the pressure elevation (postcapillary passive). In these circumstances, transpulmonary pressure gradient (TPG) and PVR are within normal limits. However, in other circumstances, PAP elevation is greater than PCWP, reflecting an increased TPG and PVR (postcapillary reactive or “out of proportion” PH). The latter can be due to increased vasomotor tone or to fixed structural obstructive remodeling of the pulmonary artery vessels. Some of the newer medical therapies first tested in PAH are now also tested in this “out of proportion” patient population.

Pulmonary Hypertension Owing to Lung Diseases and/or Hypoxia

Group 3 PH encompasses respiratory disease such as chronic obstructive pulmonary disease (COPD), interstitial lung disease, and sleep disordered breathing. These diseases can cause hypoxic vasoconctriction, mechanical stress of hyper- inflated lungs, loss of capillaries, and inflammation.

Chronic Thromboembolic Pulmonary Hypertension

In line with the reasoning behind the present classification, CTEPH forms a different group. Most of the time, it is caused by emboli obstructing pulmonary arteries, but, interestingly, in the nonoccluded areas, a pulmonary arteriopathy indistinguishable from that of PAH can develop.[16] There is accumulating evidence that CTEPH may also develop in the absence of previous pulmonary embolism, being the result of local thrombotic or inflammatory lesions in the pulmonary vasculature.[17]

Pulmonary Hypertension with Unclear Multifactorial Mechanisms

This group comprises a heterogeneous collection of diseases with uncertain pathogenetic mechanisms and pathologic pictures leading to PH.

PATHOPHYSIOLOGY

Applying Ohm's law to the pulmonary circulation results in pressure difference (mPAP − PCWP) = flow (cardiac output [CO]) x resistance (PVR). Formulated like this, elevation of the mPAP must be the consequence of elevation in PCWP, increase in flow, or increase in PVR. However, the capacity of the pulmonary circulation can be increased by both recruitment and distention resulting in lower PVR. This means that flow can increase substantially without an appreciable change in PAPs in physiologic conditions. These low pressure, low resistance, and high compliance characteristics of the pulmonary vascular bed are regulated by a balance of vasodilators/vasoconstrictors and cell proliferation/apoptosis. Various external and host genetic factors may disturb this intricate balance resulting in excessive vasoconstriction, vascular remodeling, and thrombosis leading to pulmonary (arterial) hypertension (Fig. 20.1). Although it is often not clear what exact processes initiate the pathologic changes seen, substantial progress has been made in our understanding of the various biochemical pathways and cell types involved. Like cancer and atherosclerosis, PAH does not have a single cause: a "multihit model" is more likely.[18]

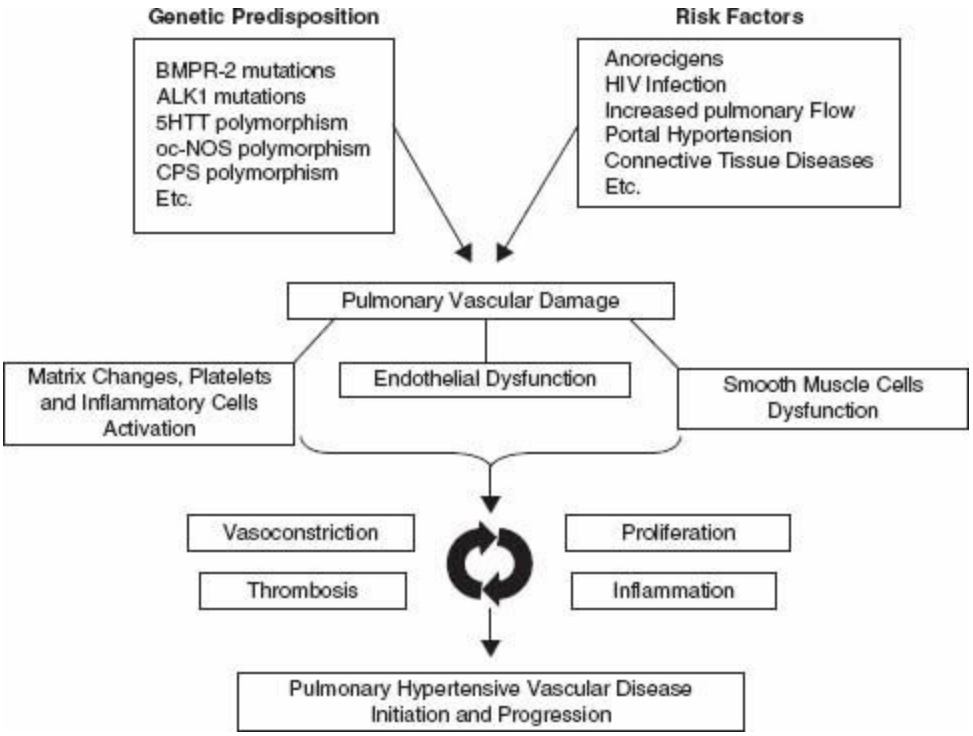

FIGURE 20.1 Pathophysiology of PH. (Galié N, Torbicki A, Barst R, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension: the Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. Eur Heart J. 2004;25:2243–2278, by permission of Oxford University Press.) BMPR-2, bone morphogenetic protein receptor II; ALK-1, activin receptor-like kinase 1; 5HTT, serotonin transporter; ec-NOS, endothelial cell nitric oxide synthase; CPS,carbamyl-phosphate synthase; HIV, human immunodeficiency virus.

Prostacyclin and Thromboxane A_2

Both prostacyclin and thromboxane A_2 are major arachidonic acid metabolites of vascular cells. Prostacyclin is known for its potent vasodilating, antiproliferative, and platelet-inhibiting properties, whereas thromboxane A_2 does the opposite. Typically, in PAH, the balance is shifted toward thromboxane A_2 as assessed by decreased urinary levels of a prostacyclin metabolite, increased urinary thromboxane B_2 levels, and decreased expression of prostacyclin synthase in small- and medium-sized pulmonary arteries.[19,20]

Endothelin-1

Endothelin-1 (ET-1) belongs to a family of vasoconstrictor peptides that plays an important role in vascular control. It is produced by endothelial cells and secreted mainly from the abluminal side toward the adjacent vascular smooth muscle cells. Two types of receptors exist: endothelin receptor A (ET_A), expressed on vascular smooth muscle cells, and endothelin receptor B (ET_B), expressed on both vascular endothelial cells and smooth muscle cells. Stimulation of both receptors on the vascular smooth muscle cells causes vasoconstriction and has a mitogenic effect, whereas stimulation of

the ET_B on the endothelial cells causes vasodilatation via increased production of prostacyclin and nitric oxide (NO). In patients with PH, ET-1 levels are often increased, and ET-A receptors are abundant.[21]

Nitric Oxide

NO is produced in endothelial and epithelial cells in the lung from L-arginine by three isoforms of nitric oxide synthases (NOS). Once formed, the effects of NO are mediated by cyclic guanosine monophosphate (cGMP), which is rapidly inactivated by the phosphodiesterase enzymes, especially type 5 (PDE-5). Decreased endothelial NOS (NOS 3) has been observed in PAH patients. NO is a potent vasodilator, an inhibitor of platelet activation and of vascular smooth muscle cell proliferation. These properties render it an excellent target for therapy (Fig. 20.2).[22]

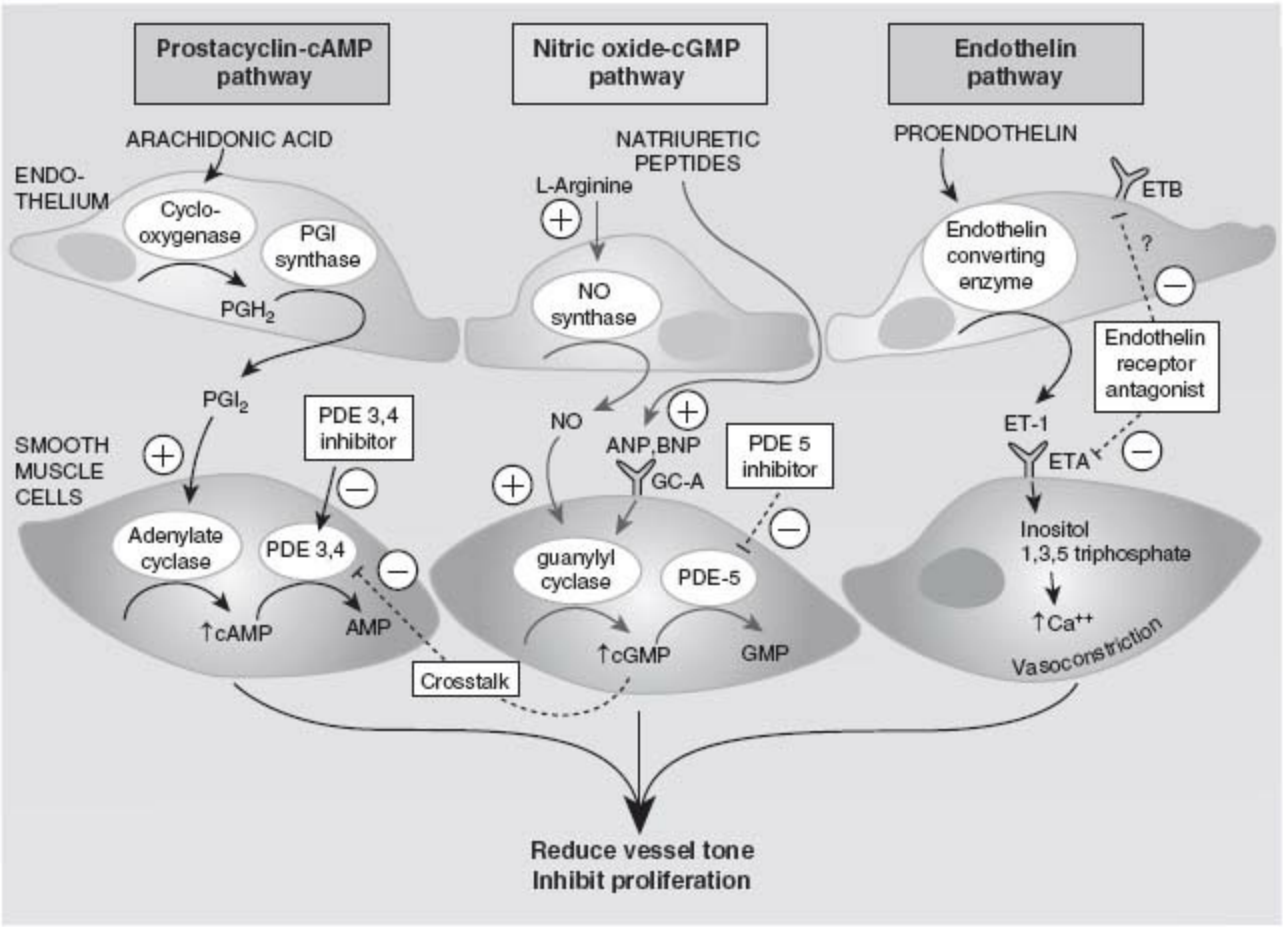

FIGURE 20.2 Targets for current or emerging therapies in PH. (Adapted from Humbert M, Sitbon O, Simonneau G, et al. Treatment of pulmonary hypertension. N Enal J Med. 2004;351:1425–1436.)

Other Vascular Effectors

Serotonin (5-hydroxytryptamine) is also a vasoconstrictor that promotes smooth muscle cell hypertrophy and hyperplasia. Serotonin transporter overexpression has been

associated with PH.[23] Vasoactive intestinal peptide (VIP) has a pharmacologic profile similar to prostacyclins and levels are decreased in PAH patients.[24] Angiopoietin-1, an angiogenic factor essential for vascular lung development, seems to be upregulated in cases of PH, correlating directly with the severity of the disease. In addition, inflammatory cells are ubiquitous in PAH and can further cause pulmonary vascular damage and endothelial dysfunction by cytokine release and cytotoxic effects.

Hemodynamic Consequences

The previously mentioned vasoconstriction, vascular smooth muscle cell proliferation, and thrombosis lead to an elevated PVR and an increase in right ventricular (RV) afterload. This, on its terms, results in RV dilatation and increased free wall tension, leading to hypertrophy. The ability of the right ventricle to compensate and preserve CO is crucial for the further evolution of this disease. Once symptoms of RV failure emerge, manifested as further dilatation, thinning of the wall, and tricuspid regurgitation, prognosis is poor.

DIAGNOSIS AND EVALUATION

Clinical Evaluation

The symptoms of PH are usually gradual in onset and nonspecific explaining why the lag time between symptom onset and diagnosis approaches 2 years in 90% of PAH patients. These symptoms include dyspnea on exertion, fatigue, weakness, chest pain, palpitations, syncope, abdominal distention, and pedal edema. Clinical examination of PH may reveal a left parasternal lift, a loud P_2 at apex, a pan-systolic murmur of tricuspid regurgitation that increases with inspiration, a diastolic murmur of pulmonary insufficiency, and a RV S_3. Jugular vein distension, hepatomegaly with a pulsatile liver, peripheral edema, and ascites are often indicative of advanced stages with frank right-sided heart failure.

At least in certain populations at risk, the careful clinician will suspect the diagnosis whenever the previously mentioned symptoms or signs occur. These populations include:

1. Known BMPR2 mutation
2. First-degree relative of patient with BMPR2 mutation or within pedigree of two or more patients with PAH
3. Systemic sclerosis
4. Sickle cell disease
5. HIV infection
6. Portal hypertension

7. Prior appetite suppressant use
8. Congenital heart disease with shunt
9. Recent acute pulmonary embolism
10. Left heart disease
11. COPD, interstitial lung disease, or sleep apnea

In the first four categories, yearly echocardiographic screening is recommended.[1]

Echocardiography

If PH is suspected based on the history, risk factor assessment, and physical examination, an echocardiogram is the next appropriate study. By using the Doppler technique, peak velocity of the tricuspid regurgitation jet can be measured. From this measured velocity, the pressure difference between right ventricle and right atrium can be estimated on the basis of the simplified Bernoulli equation ($\Delta P = 4v^2$). On the condition that there is no pulmonic valve stenosis, pulmonary artery systolic pressure (PASP) = 4 x (tricuspid regurgitation velocity)[2] + right atrial pressure (RAP). RAP can be estimated on the base of inferior vena cava characteristics.

Other two-dimensional echocardiographic characteristics might raise or reinforce suspicion of PH; for example, right atrial or RV dilatation, flattened interventricular septum with D-shaped left ventricle, increased RV wall thickness, dilatation of the pulmonary artery, and pericardial effusion. These features tend to occur later in the course of the disease. Echocardiography is also helpful in detecting and characterizing left heart disease and congenital cardiac abnormalities.

Although echocardiography is a useful screening tool, Doppler-derived pressure estimation can both underestimate PASP in patients with severe tricuspid regurgitation and overestimate PASP in non-PH patients. Ultimate confirmation should come from right heart catheterization (RHC).

Other (Imaging) Studies

In typical cases of PH, the ECG reflects RA dilatation, RV hypertrophy with strain, and QRS complex frontal plane right axis deviation. In advanced stages of the disease, atrial flutter or atrial fibrillation often occur leading to further clinical deterioration.

Chest x-rays often reveal central pulmonary arterial dilatation with “pruning” (loss) of the peripheral blood vessels, clear lung fields, and a prominent RV border. Chest computed tomography (CT) and ventilation/perfusion (V/Q) scans are indicated to exclude primary parenchymal or thromboembolic diseases as a cause of PH. For excluding thromboembolic disease, V/Q scan is the preferred screening test. A normal or very low probability scan virtually excludes CTEPH, while a high probability scan warrants further evaluation with a pulmonary angiogram. Pulmonary angioscopy is sometimes performed in specialized centers in cases of chronic thromboembolic PH to

determine surgical candidacy.

Hemodynamic Evaluation

RHC is required to confirm the diagnosis of PH, to assess the etiology and severity, to test for vasoreactivity of the pulmonary circulation, and in the follow-up of treatment.[25] When performed at experienced centers, morbidity (1.1%) and mortality (0.055%) rates are low.[26] Consecutively, RAP, right ventricular pressure (RVP), PAP, and PCWP are recorded using a balloon-tipped fluid-filled catheter. CO can be determined by using the thermodilution method and/or the Fick method (measurement of mixed venous saturation SvO_2 needed). The PCWP is supposed to reflect left atrial pressure (LAP) and ultimately, in the absence of mitral stenosis, left ventricular end diastolic pressure (LVEDP). This measurement is very important because it helps differentiating PH associated with left heart disease from other conditions. It is, however, the pressure that is most subject to error in measurement and interpretation. There are several ways to confirm catheter position:

1. Stable fluoroscopic position
2. Presence of highly oxygenated (>95%) blood when a sample is drown from the distal port
3. Stagnation of injected dye in the pulmonary artery

When in doubt, the threshold to perform a left heart catheterization (for direct measurement of LVEDP) should be low.

These pressures can then be used to calculate TPG and PVR.

Hemodynamic Calculations for PH Evaluation:

$$\text{Transpulmonary gradient (TPG)} = \text{mean PAP} - \text{mean PCWP}$$

$$\text{Pulmonary vascular resistance (PVR)} = (\text{TPG} \div \text{cardiac output (in Wood units)}$$

$$= (\text{TPG} \div \text{cardiac output}) \times 80 \text{ (in dynes-s-cm}^{-5}\text{)}$$

Figure 20.3 depicts the evolution of the hemodynamic variables with progression of PAH. Toward the end of the disease spectrum, the RV starts to fail manifested as a decrease in CO. As a result, PAP can decrease again. This decrease does not represent hemodynamic improvement, as indicated by the further increase in PVR. Usually, at this time, RAP and PCWP also start to rise reflecting RV failure and LV diastolic dysfunction, respectively. The latter is the consequence of interventricular septal shift (ventricular interdependence).

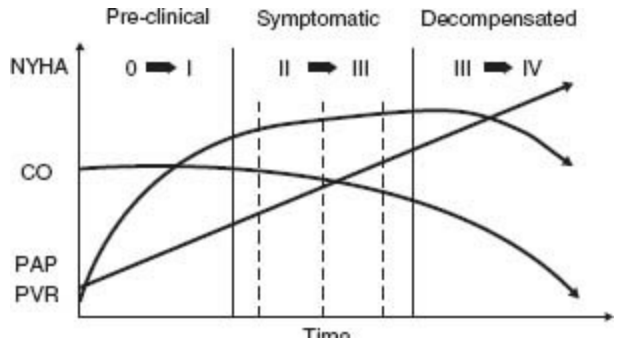

FIGURE 20.3 Evolution of hemodynamic variables in function of disease severity. CO, cardiac output; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance. (Reproduced from Galié N, Manes A, Palazzini M, et al. Pharmacological impact on right ventricular remodelling in pulmonary arterial hypertension. Eur Heart J. 2007;9:H68–H74, by permission of Oxford University Press.)

In PAH, vasoreactivity testing should be performed to identify patients who may benefit from long-term therapy with calcium channel blockers (CCBs). The agent most often used for this is inhaled NO, with (intravenous [IV]) epoprostenol and (IV) adenosine as alternatives. A positive acute response is defined as a >10 mm Hg decrease in mean PAP to reach an absolute value of mean PAP < 40 mm Hg with an increased or unchanged CO. In patients with idiopathic PAH, about 10% to 15% is an acute responder and about half of these will prove to be a long-term responder with a more favorable prognosis.[27,28] This concept is less clear in other forms of PAH, although vasoreactivity testing is still recommended (controversial in congenital heart disease). It is not useful in other forms of PH (group 1′, 2, 3, 4, and 5). In venoocclusive disease and left heart disease, it can even provoke pulmonary edema. However, in patients considered for heart transplantation, pulmonary vasoreactivity testing may be used to assess reversibility and operability.

PROGNOSIS

Evaluating disease severity and predicting survival is important because it may guide clinical management. Best data considering prognosis are available for the idiopathic PAH subset population. The natural history shows survival rates of 68%, 48%, and 34% after 1-, 3-, and 5-year, respectively.[29] There is some evidence that prognosis has improved with pulmonary vasodilator therapies.[30] Recently, an equation has been developed in an attempt to predict survival more exactly.[31] Within the PAH group, prognosis is clearly influenced by underlying etiology, as shown in Figure 20.4.

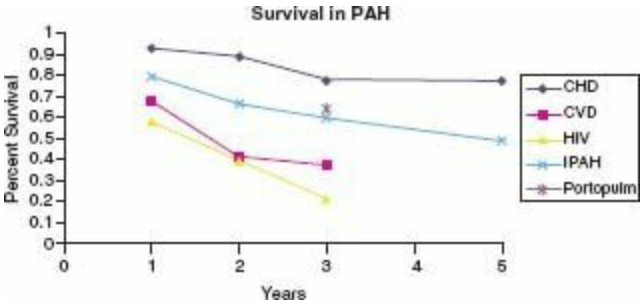

FIGURE 20.4 Mean survival of patients with PAH based on etiology. CHD, congenital heart disease; CVD, collagen vascular disease; HIV, human immunodeficiency virus related; IPAH, idiopathic pulmonary arterial hypertension; Portopulm, portopulmonary hypertension. (Reproduced with permission from the American College of Chest Physicians from McLaughlin VV, Presberg KW, Doyle RL, et al. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines Chest 2004;126:7RS–Q9S)

Table 20.2 outlines clinical, echocardiographic, and hemodynamic features that may predict prognosis in PAH patients. Again, these data are mainly derived from the idiopathic PAH population and it is unknown whether they are transferable to other P(A)H populations.

TABLE
20.2 Prognostic Variables in PH

Lower	Determinants of Risk	Higher
No	Clinical evidence of RV failure	Yes
Gradual	Progression	Rapid
II, III	WHO class	IV
Longer (>400 m)	6 min walk distance	Shorter (<300 m)
Minimally elevated	BNP	Very elevated
Minimal RV dysfunction	Echocardiographic findings	Pericardial effusion significant RV dysfunction
Normal/near normal RAP and CI	Hemodynamics	High RAP, low CI

Reproduced with permission from the American College of Chest Physicians from McLaughlin VV Presberg KW Doyle RL, et al. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. 2004;126:78S–92S.

TREATMENT

General Measures

Generally spoken, treatment of group 2, 3, and 4 PH is concentrated on the underlying condition, while treatment of PAH (group 1) relies on the use of pulmonary vasodilators.

A few general measures apply to all the PH groups:

- Mild physical activity, possibly via exercise rehabilitation, is encouraged, while excessive physical activity should be avoided.

- Influenza and pneumococcal vaccination are recommended.
- Pregnancy carries a 30% to 50% mortality risk and is contraindicated.
- Exposure to high altitude should be avoided and supplemental oxygen is recommended when preflight saturation is <92%.
- Oxygen supplementation is advised to maintain saturation above 90%.
- Diuretic therapy is indicated to manage RV failure with volume overload.
- Digoxin may be considered in the case of atrial tachyarrhythmias.
- Oral anticoagulation is recommended in CTEPH, idiopathic PAH, and advanced disease (e.g., continuous IV therapy).

Pulmonary Vasodilators

Figure 20.5 displays the current treatment algorithm for PAH as suggested by the 2009 ACCF/AHA expert consensus document. The algorithm starts with the division between responders and nonresponders to vasoreactivity testing. For the responders (only 10% to 15% of the idiopathic PAH population), CCBs are the first-line treatment. Careful reassessment for safety and efficacy is mandatory, because only half of these patients will prove to be a long-term responder.[27,28]

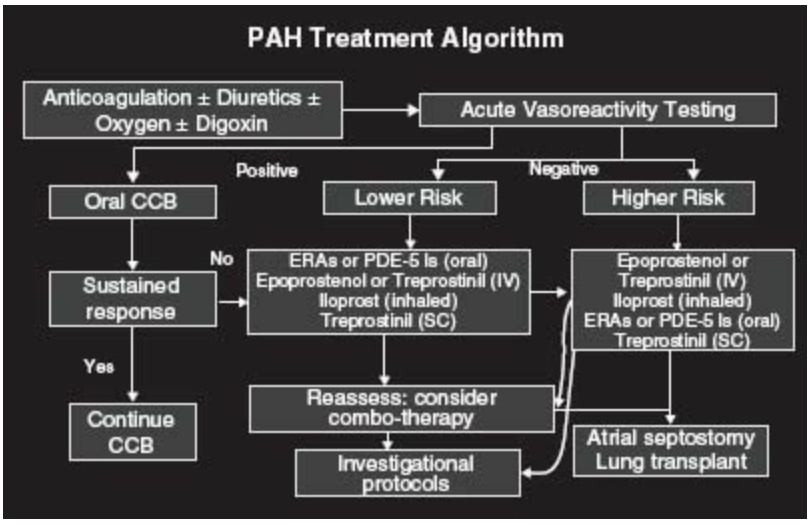

FIGURE 20.5 Treatment algorithm for PAH. CCB, calcium channel blocker; ERA, endothelin receptor antagonist; PDE-5 Is, phosphodiesterase type 5 inhibitors. (Reproduced from McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol. 2009;53(17):1573–1619, with permission from Elsevier.)

Prostacyclin is a potent endogenous vasodilator, inhibitor of platelet aggregation, and also appears to have antiprolifera- tive activity This may explain why epoprostenol (Flolan) can be used to acutely lower PAPs (as used in vasoreactivity testing) as well

as to achieve long-term hemodynamic improvement for PH patients who are vasodilator nonresponders. In randomized controlled trials, epoprostenol has shown to improve functional class, exercise intolerance, hemodynamics, and survival in idiopathic PAH patients[32–34] (Table 20.3). It provokes the same improvement in symptoms in the scleroderma disease spectrum.[35] Efficacy has also been shown in other associated PAH conditions. Epoprostenol has to be administered in a continuous IV infusion, and early titration often results in unbearable side effects of nausea, headache, flushing, jaw and leg pain, and diarrhea. Adverse events related to the delivery system include pump malfunction, local site infection, catheter obstruction, and sepsis. Treprostinil (Remodulin) is another prostacyclin analogue that can be administered by inhalation, orally, or in a continuous subcutaneous way. Improvement in exercise capacity, hemodynamics, and symptoms has been demonstrated in a large randomized controlled trial.[36] Infusion site pain is the most common side effect. Iloprost (Ventavis) is available as an aerosol administration and has a proven beneficial effect in patients with PAH and CTEPH.[37,38]

TABLE
20.3 Randomized Clinical Trials in Patients with PAH

Drug	**Epoprostenol (Flolan)**			**Treprostinil (Remodulin)**	**Iloprost (Ventavis)**	
Major trial *Published*	Rubin. *Ann Intern Med.* (1990)	Barst. *N Engl J Med.* (1996)	Badesh. *Ann Intern Med.* (2000)	Simonneau. *Am J Respir Crit Care Med.* (2002)	Hoeper. *N Engl J Med.* (2000)	Olschewski. *N Engl J Med.* (2002)
Acronym	—	—	—	—	—	AIRS
Route	IV	IV	IV	SC	Inhaled	Inhaled
Patients	"Primary" PAH	"Primary" PAH	IPAH, CTD	IPAH, CTD, CHD	"Primary" PAH	IPAH, CTD, CHD, CTEPH
Sample size	24	81	111	470	24	203
WHO class	3–4	3–4	2–4	2–4	3–4	2–4
Duration	2 mo	3 mo	3 mo	3 mo	12 mo	3 mo
Δ6MWD	?	+47 m	+94 m	+16 m	+85 m	+36 m
Hemodynamic response	—	+	+	+	+	+
Mortality	—	↓	—	—	—	—
Side effects	Jaw pain, flushing, rebound, GI, infusion site pain					

Drug	**Bosentan (Tracleer)**				**Sildenafil (Revatio)**	**Tadalafil (Adcirca)**
Major trial *Published*	Channick. *Lancet* (2001)	Rubin. *N Engl J Med.* (2002)	Galié. *Circulation* (2006)	Jais. *J Am Coll Cardiol.* (2008)	Galié. *Lancet.* (2008)	Galié. *N Engl J Med.* (2005)	Galié. *Circulation.* (2009)
Acronym	—	BREATHE-1	BREATHE-5	BENEFIT	EARLY	SUPER-1	PHIRST
Route	PO	PO	PO	PO	PO	PO	PO
Dosage	62.5–125 mg BID	62.5–250 mg BID	62.5–125 mg BID	62.5–125 mg BID	62.5–125 mg BID	20–80 mg TID	2.5–40 mg QD
Patients	IPAH, CTD	IPAH, CTD	CHD	CTEPH	IPAH, CTD	IPAH, CTD, HIV, CHD	IPAH, CTD, HIV, CHD ± bosentan
Sample size	32	213	54	157	185	278	405
WHO class	3–4	2–4	3	2–4	2	2–3	2–3
Duration	3 mo	4 mo	4 mo	4 mo	6 mo	3 mo	4 mo
Δ6MWD	+76 m	+44 m	+53 m	+2 m	+19 m	+45 m	+44 m
TTCW[a]	—	↑	—	—	↑	→	↑
Side effects	Flushing, ↑ LFTs, edema, teratogenicity				Hypotension, headache, flushing	

[a]Time to clinical worsening (TTCW) = Death, lung transplant, initiation of epoprostenol, hospitalization due to worsening PH, premature withdrawal of study drug (decrease in 6MWD, worsening FC, RV failure, worsening end organ function).

Bosentan (Tracleer) is an oral active dual ET_A/ET_B-receptor antagonist that has been extensively evaluated in PAH patients showing improvement in exercise capacity, functional class, hemodynamics, cardiac performance measured by echocardiography and clinical outcomes[39–43] (see Table 20.3) . Sitaxsentan and Ambrisentan are more selective ET_A-receptor antagonists with similar benefits as bosentan (STRIDE and ARIES trials). Liver injury and teratogenicity are major concerns and require monthly monitoring.

Orally active type 5 phosphodiesterase inhibitors prevent degradation of cGMP causing vasorelaxation. Sildenafil (Viagra or Revatio) has been tested in a randomized controlled trial and confirmed favorable effects on exercise capacity, symptoms, and hemodynamics.[44] Tadalafil (Adcirca) has the same effects, although it also delayed the time to clinical worsening.[45] Headache, flushing, dyspepsia, and epistaxis are possible side effects.

Possible future therapies try to attack the excessive proliferation component of smooth muscle cells in PAH. In this setting, a tyrosine kinase inhibitor (Imatinib) is currently tested.

As outlined by the treatment algorithm, oral therapy with ET-receptor antagonists or PDE-5 inhibitors is first choice in lower risk patients, whereas IV epoprostenol is reserved for the high-risk population. In recent years, combination therapy has emerged as a valid option when treatment goals are not achieved with one compound (the so-called goal-directed therapy). Given the fact that these medications target different pathologic processes, combination therapy is an attractive theoretical option. Table 20.4 points out the results of the most important trials.[45–49]

TABLE
20.4 Combination Therapy Randomized Clinical Trials in Patients with PAH

Drug	Bosentan	Iloprost	Sildenafil	Tadalafil	Treprostinil
Major trial *Published*	Humbert. *Eur Resp J.* (2004)	McLaughlin. *Am J Respir Crit Care Med.* (2006)	Simonneau. *Ann Intern Med.* (2008)	Galié. *Circulation.* (2009)	McLaughlin. *J Am Coll Cardiol.* (2010)
Acronym	BREATHE-2	STEP 1	PACES	PHIRST	TRIUMPH
Route	PO	Inhaled	PO	PO	PO
Dosage	62.5–125 mg BID	5 μg	20–80 mg TID	2.5–40 mg QD	Up to 54 μg
Patients	IPAH, CTD	IPAH, APAH	IPAH, APAH, CHD	IPAH, CTD, HIV, CHD	IPAH, APAH
Background therapy	Epoprostinil	Bosentan	Epoprostenol	Bosentan	Bosentan or Sildenaphil
Sample size	33	67	267	212	235
WHO class	3–4	3	1–4	2–3	3–4
Duration	4 mo	3 mo	3 mo	4 mo	3 mo
Δ6MWD	Not significant	+26 m	+29 m	+23 m	+14 m
TTCW	—	↑	↑	↑	→

The pulmonary vasodilators have also undergone evaluation and are increasingly used in other (non-PAH) PH groups.[50] Scientific proof for this, however, is limited. The current evidence is summarized as follows:

- Pulmonary vasodilators are not recommended in chronic lung disease.
- Prostanoids and ERAs were associated with an increased event rate in patients with LV dysfunction and are contraindicated.
- There is some evidence of improvement in quality of life and exercise performance by sildenafil in patients with left heart disease and in patients bridged to transplantation with a left ventricular assist device.[51,52]
- In the setting of CTEPH, prostanoids, ERAs, or PDE-5 inhibitors may be used to improve hemodynamics before surgery and in patients with predominantly peripheral disease or persistent PH after surgery.

Surgical Therapies

In patients with CTEPH, surgery (pulmonary endarteretomy) is a potentially curative option, only in patients with accessible (proximal) disease. The evaluation and procedure should be performed in high-volume centers. The role of balloon atrial septostomy in the treatment of PAH patients is uncertain. It is rarely performed unless for palliation for advanced PAH patients with recurrent syncope and/or right heart failure despite all available medical treatments. RV assist devices have emerged as a therapy in postoperative RV failure in the presence of PH. Finally, (heart)–lung transplantation should be considered in a subset of eligible patients who remain in NYHA functional Class III or IV, or in those who cannot achieve a significant exercise and hemodynamic improvement after 3 months of epoprostenol therapy.

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QUESTIONS AND ANSWERS

Questions

1. A 45-year-old woman with a history of hypertension presented with dyspnea upon exertion. You obtained an echocardiogram showing normal left ventricular systolic and diastolic function, normal right ventricular (RV) size and function, normal valvular function, but an estimated right ventricular systolic pressure (RVSP) of 56 mm Hg with 1 to 2+ tricuspid regurgitation. Your next step should be:
   a. To perform a pulmonary angiogram
   b. To perform to right heart catheterization (RHC)
   c. To start oral bosentan therapy and follow-up in 6 weeks
   d. To repeat an echocardiogram in 6 months
2. Prognosis is variable between the different subgroups of pulmonary arterial hypertension (PAH). Which of the following subgroups has traditionally the best prognosis?
   a. Idiopathic PAH
   b. PAH associated with connective tissue disease
   c. PAH associated with congenital heart disease
   d. PAH associated with portal hypertension
3. The following observation is not a typical characteristic of PAH:
   a. Decreased urinary levels of thromboxane B_2
   b. Decreased levels of urinary prostacyclin metabolites
   c. Increased levels of endothelin-1 (ET-1)
   d. Decreased endothelial nitric oxide synthetase
4. To exclude chronic thromboembolic pulmonary hypertension (CTEPH) as a cause of unexplained pulmonary hypertension (PH), the recommended investigation is:
   a. D-dimer level
   b. Multirow CT angiography
   c. V/Q scan
   d. Multirow computed tomography (CT) angiography and ventilation/perfusion (V/Q) scan
5. Routine diagnostic workup for PAH in a patient with CREST syndrome and presenting with dyspnea upon exertion should include all of the following except:
   a. Transthoracic echocardiography
   a. RHC
   a. Pulmonary function testing with diffusion capacity (DLCO)
   a. Genetic testing for BNPR2 mutation
6. A positive acute response to vasoreactivity testing is defined as:
   a. A decrease of 10% in pulmonary artery pressure (PAP) mean to a value <40 mm Hg with preserved or increased cardiac output (CO)
   b. A decrease of 10 mm Hg in PAP mean to a value <40 mm Hg with preserved or increased CO
   c. A decrease of 10% in PAP mean to a value <40 mm Hg with a 10% increase in CO
   d. A decrease of 10 mm Hg in PAP mean to a value < 40 mm Hg with a 10% increase in CO
7. The only pulmonary vasodilator that showed a survival benefit in a RCT is:
   a. Epoprostenol

b. Iloprost
c. Bosentan
d. Sildenafil

8. RHC was performed on a patient suspected to have PH on the basis of an echocardiogram. The following values were obtained: RA 8, RV 68/8,PA 68/32/43, pulmonary capillary wedge pressure (PCWP) 25, CO 3 L per minute, CI 1.5 L/min/m^2. The pulmonary vascular resistance (PVR) expressed in Wood units (WU) is:
   a. 18 WU
   b. 4,66 WU
   c. 1 2 WU
   d. 6 WU

9. The previous example is a typical example of:
   a. PAH
   b. PH due to left heart disease
   c. PH due to left heart disease with “out-of-proportion” PH
   d. CTEPH

10. In the latest (Dana point) classification of PH, schistosomiasis, one of the world’s most commonest causes of PH, is classified as:
   a. Group 1.4: PAH associated with certain conditions
   b. Group 3: PH owing to lung disease and/or hypoxia
   c. Group 4: similar as CTEPH
   d. Group 5: PH with unclear, multifactorial mechanisms

Answers

1. Answer B: Echocardiographic estimations of RVSPs may potentially overestimate the true PAPs, and should be confirmed by RHC in the setting of a clinical suspicion for PH.

2. Answer C: PAH associated with congenital heart disease (see Fig. 20.4).

3. Answer A: Increased urinary levels of thromboxane B_2 are more typical.

4. Answer C: A normal V/Q scan rules out CTEPH.

5. Answer D: CREST syndrome patients have a higher probability of developing PH, and should be screened, particularly with symptom onset. Echocardiography and RHC are reasonable tools to detect PH, and pulmonary function testing may reveal lung parenchymal abnormalities. Genetic screening is indicated only in familial cases of PH, and the incidence of BMPR2 gene mutation in patients with CREST syndrome and PH is actually low.

6. Answer B.

7. Answer A: Epoprostenol.[33]

8. Answer D: PVR (WU) = mean PAP – PCWP/CO = 43 – 25/3 = 6 WU.

9. Answer C: PCWP >15 mm Hg pointing to left heart disease (although elevation of PCWP at the end of the disease spectrum in PAH is also possible), PVR >3 WU points to “out-of-proportion” PH.

10. Answer A: Schistosomiasis is currently classified in group 1 PAH because it shares the specific clinic and pathologic characteristics with other forms of PAH.

CHAPTER

Heart Failure with Normal Ejection Fraction

Andrew O. Zurick, III and Allan L. Klein

Diastolic dysfunction refers to a functional abnormality of myocardial relaxation, distensibility, or filling in the diastolic phase of the cardiac cycle. Heart failure with normal ejection fraction (HFNEF), previously referred to as diastolic heart failure, has increased in prevalence and now accounts for up to 50% of all cases of heart failure. To make the diagnosis of HFNEF, three conditions must be fulfilled: (a) the presence of symptoms or signs of heart failure, (b) the presence of normal or mildly abnormal systolic function, (c) evidence of diastolic left ventricular (LV) dysfunction. HFNEF is increasingly common and can be associated with significant morbidity and mortality, with comparable prognostic outlook among patients with heart failure with reduced ejection fraction (HFREF). Several pathophysiologic definitions of HFNEF have been proposed:

1. Impaired ventricular filling capacity without a compensatory increase in left atrial (LA) pressure
2. Abnormal ventricular filling resulting in inadequate cardiac output with a mean pulmonary venous pressure of <12 mm Hg
3. Resistance to filling of either or both ventricles with an inappropriate shift of the pressure–volume loop.

These definitions all have an abnormal resistance to filling, causing elevated left-sided filling pressures and congestion. Diastolic dysfunction impairs filling of the ventricle by impairing relaxation (early diastole), reducing compliance (early to late diastole), or by external constraint from the pericardium. Numerous pathologic processes and disease states may produce the clinical constellation of diastolic dysfunction. Ultimately, HFNEF is distinguished from HFREF, at the macroscopic level, by concentric LV remodeling, rather than eccentric.

PHYSIOLOGY OF DIASTOLE

Effective diastolic filling depends on the relationship between transmitral LA and LV pressures. Several factors influence this relationship: (a) active myocardial relaxation, (b) intrinsic passive LV compliance, and (c) extrinsic passive properties, including pericardial restraint and ventricular interaction.

PHASES OF DIASTOLE

Diastole is the period from the closure of the aortic valve to the termination of mitral inflow. It is divided into two periods: (a) an isovolumic relaxation period and (b) an auxotonic period that includes rapid filling, diastasis (slow filling), and atrial systole.

Isovolumic Relaxation Phase

The isovolumic relaxation time period occurs from the time of aortic valve closure to mitral valve opening during which there is active relaxation of the contracted myocardium generating a fall in LV pressure without a change in volume. There is active, energy-dependent myocyte relaxation until mid-diastole. Isovolumic relaxation ends when the LV pressure falls below the LA pressure, resulting in mitral valve opening, at which point the rapid filling phase commences.

Rapid Filling Phase

The auxotonic period occurs from mitral valve opening until mitral valve closure. When the LV pressure falls below LA pressure, the mitral valve opens, initiating the rapid filling phase. The elastic recoil and "untwisting" of the ventricle generated by myocardial relaxation creates a suction effect that augments the LA–LV pressure gradient, resulting in rapid filling of the ventricle. Blood acceleration occurs as a result of the development of an LA-to-LV pressure gradient. Blood rapidly enters the left ventricle from the left atrium during the early filling period. In normal hearts, approximately 70% to 80% of LV filling occurs during this phase of diastole. Rapid filling ends as atrial and ventricular pressures equalize.

Diastasis (Slow Filling) Phase

As rapid ventricular filling progresses, LV pressure gradually increases and briefly exceeds LA pressure, resulting in deceleration of mitral inflow and onset of diastasis. Diastasis typically accounts for <5% of filling.

Atrial Filling (Contraction) Phase

The onset of atrial contraction (atrial filling) in late diastole results in a brief increase in the transmitral gradient, forcing blood across the mitral valve and a small amount of

regurgitation into the pulmonary veins. In normal hearts, this accounts for 20% to 25% of ventricular end-diastolic volume, with only a small rise in mean pulmonary venous pressure. Diastole ends and systole begins with the onset of ventricular contraction, resulting in a rapid increase in LV pressure that closes the mitral valve.

DETERMINANTS OF DIASTOLIC FUNCTION

Diastolic function depends on four major factors:

1. Active myocardial relaxation. This is mediated by intracellular ATP and calcium. Relaxation results from calcium sequestration into the sarcoplasmic reticulum by the calcium-ATPase pump after contraction. Abnormal relaxation may result from either elevated cytosolic levels of calcium in diastole or inadequate intracellular ATP levels. Factors that may affect isovolumic relaxation include internal loading forces, external loading states, and reduced or inhibited myocardial contractility.
2. Passive pressure–volume relationships (i.e., LV compliance). This is determined by the viscoelastic nature of the myocardium; chamber size, shape, and wall thickness; right and LV pressure–volume interaction; intrathoracic pressure; and pericardial restraint. As LV volume increases during diastole, an increase in LV pressure ensues. The slope of the pressure–volume curve during diastole (dP/dV) represents the chamber stiffness; and the inverse of this relation (dV/dP) is the chamber compliance (Fig. 21.1).
3. Left atrium (including atrial function), pulmonary vein, and mitral valve characteristics. In young, healthy, normal individuals, the atrial contribution is <20% of the total volume, whereas in older normal subjects, this atrial “kick” contributes a greater proportion of total LV filling.
4. Heart rate. As the heart rate increases, the diastolic filling period preferentially decreases with respect to the systolic ejection period.

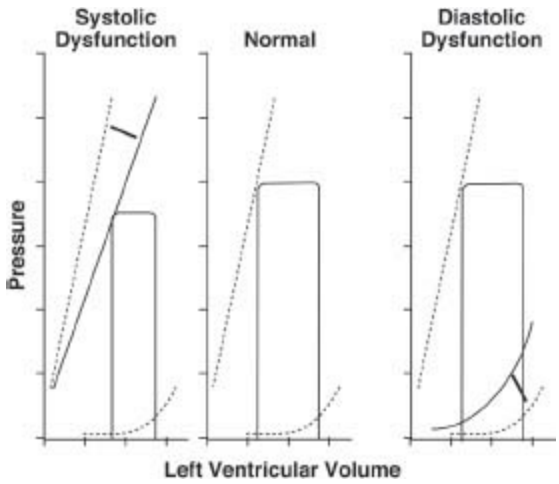


FIGURE 21.1 Schematic representation of ventricular pressure–volume loops. The center panel demonstrates the normal situation. Note the exponential nature of the curve through late diastole. In systolic dysfunction **(left),** the end-systolic pressure line is displayed downward and is manifest by a decreased ability of the left ventricle to generate high pressures for a given volume. Diastolic dysfunction involves an upward and leftward shift of the exponential curve, a result of elevated filling pressures for a given volume. (Adapted from Katz AM. Influence of altered inotropy and lusitropy on ventricular pressure-volume loops. J Am Coll Cardiol. 1988;11:438–445.)

CLINICAL PRESENTATION

Recent consensus documents have now reported that nearly 50% of patients with heart failure have HFNEF. The clinical presentation of heart failure may include flash pulmonary edema and hypertensive heart disease, advanced ischemic heart disease, or hypertensive hypertrophic cardiomyopathy. Patients who often do not respond to heart failure treatment include patients with aortic stenosis, hypertrophic cardiomyopathy, infiltrative cardiomyopathy, and constrictive pericarditis. Typically, elderly patients with hypertension are at highest risk for developing the clinical syndrome of HFNEF. Signs and symptoms of HFNEF include the following:

1. Dyspnea on exertion and reduced exercise tolerance
2. With disease progression, patients may have dyspnea at rest, paroxysmal nocturnal dyspnea, and orthopnea.
3. Right-sided diastolic dysfunction can cause peripheral edema, bloating, and ascites.

PHYSICAL EXAMINATION

Physical examination cannot effectively separate patients with diastolic heart failure from those with systolic heart failure. Most patients with diastolic heart failure have hypertension or coronary artery disease. On auscultation, an audible S4 (stage I diastolic dysfunction by Doppler echocardiography, indicative of abnormal relaxation) or S3 (stage III diastolic dysfunction by Doppler echocardiography, indicative of reduced compliance) can be heard. There may be pulmonary rales, jugular venous distension, and edema.

LABORATORY EXAMINATION

ECG

The most common abnormality is an LV hypertrophy pattern. LA abnormality may also be seen.

Radiography

There are no specific findings on a chest x-ray. Pulmonary congestion with a normal cardiac silhouette suggests the presence of diastolic dysfunction.

Echocardiography

Echocardiography is the modality of choice to assess for diastolic dysfunction. Findings on an echocardiogram may include the following:

1. Normal LV systolic function and isolated diastolic dysfunction. Patients with abnormal systolic function have secondary diastolic function.
2. LV hypertrophy
3. LA enlargement. LA volume reflects the cumulative effects of filling pressures over time. Accurate measurements of LA volume are obtained using the apical 4-chamber and 2-chamber views, and this assessment is clinically important as there is a significant relationship between LA remodeling and echocardiographic indices of diastolic function. Previous observational studies have shown that LA volume index $\geq$ 34 m L/m^2 is an independent predictor of heart failure, atrial fibrillation, ischemic stroke, and death.
4. Evidence of impaired ventricular filling. This has four stages (Fig. 21.2):

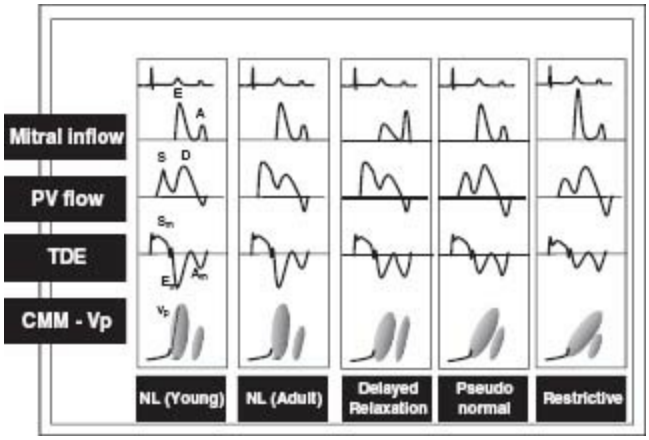


FIGURE 21.2 Stage I or impaired relaxation pattern, stage II or pseudonormal pattern, stage III or restrictive filling pattern, and stage IV or irreversible restrictive pattern. (Adapted from Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. J Am Coll Cardiol. 1998;32:865–875.)

- Stage I or impaired relaxation pattern. The time from the peak early (E) wave to the baseline (the deceleration time; DT) is prolonged to >220 milliseconds. The early/atrial (E/A ratio) is <1 and the isovolumic relaxation time is >100 milliseconds. Color M-mode flow propagation slope is <40 cm/s. Tissue Doppler annulus early velocity is <8 cm/s. In addition, the LA volume index should be increased, ≥34 cm/m^2.
- Stage II or pseudonormal pattern. This is associated with a normal appearance of

the transmitral inflow pattern with an E/A ratio between 1 and 2, a DT between 150 and 220 milliseconds, and an isovolumic relaxation time between 60 and 100 milliseconds. To distinguish this from normal, the pulmonary venous pattern is analyzed and shows a prolonged and increased atrial reversal time >35 cm/s and the pulmonary venous systolic-to-diastolic flow is normal or <1. Color M-mode reveals a flow propagation slope <40 cm/s. Tissue Doppler annulus early velocity is <8 cm/s.

- Stage III or restrictive filling pattern. There is reduced LV compliance. Elevated peak E-wave velocity and rapid deceleration are due to increased LV stiffness. The E/A ratio is >2, DT <150 milliseconds, and isovolumic relaxation time is <60 milliseconds. Color M-mode reveals flow propagation slope <40 cm/s, and tissue Doppler annulus early velocity is usually <8 cm/s.
- Stage IV or irreversible restrictive pattern. This stage is similar to the findings of stage III, with no change in the Doppler pattern with preload-reducing maneuvers, and is associated with a substantially increased risk of death.

The modern assessment of diastolic function with echocardiography includes assessment of several Doppler parameters: (a) transmitral inflow velocities, (b) pulmonary venous flow velocities, (c) tissue Doppler mitral annulus velocities, (d) mitral inflow propagation velocities, and (e) Doppler estimation of pulmonary arterial pressures from tricuspid regurgitant flow velocities. Other echocardiographic parameters that sometimes contribute useful information regarding diastolic function include Tei index, B bump on mitral valve M-mode echocardiography, pulmonary valve regurgitant flow velocity, estimated pulmonary artery pressure from tricuspid regurgitant flow velocity, and size and respiratory change of the inferior vena cava. Doppler flow patterns can also be used to estimate LA and LV filling pressures. An increased E/A ratio, a shortened deceleration and isovolumic relaxation time, a decreased atrial filling fraction, a decreased pulmonary venous systolic fraction, an elevated and prolonged atrial reversal flow velocity, and increased LA volume may suggest an elevated mean LA pressure. By combining the mitral E wave, a variable that correlates modestly with LA pressure, and one that is associated with ventricular relaxation and is relatively preload independent (color M-mode propagation velocity or tissue Doppler echocardiography early filling velocity), closer approximations of LA pressure can be obtained. Algorithms for assessment of LV filling pressure and for grading diastolic dysfunction have been proposed in recent American Society of Echocardiography guidelines published in 2009 (Fig. 21.3). Additionally, now through the use of diastology stress testing, a grade 1 filling pattern can be changed to a grade 2 filling pattern with exercise or preload augmentation (Fig. 21.4).

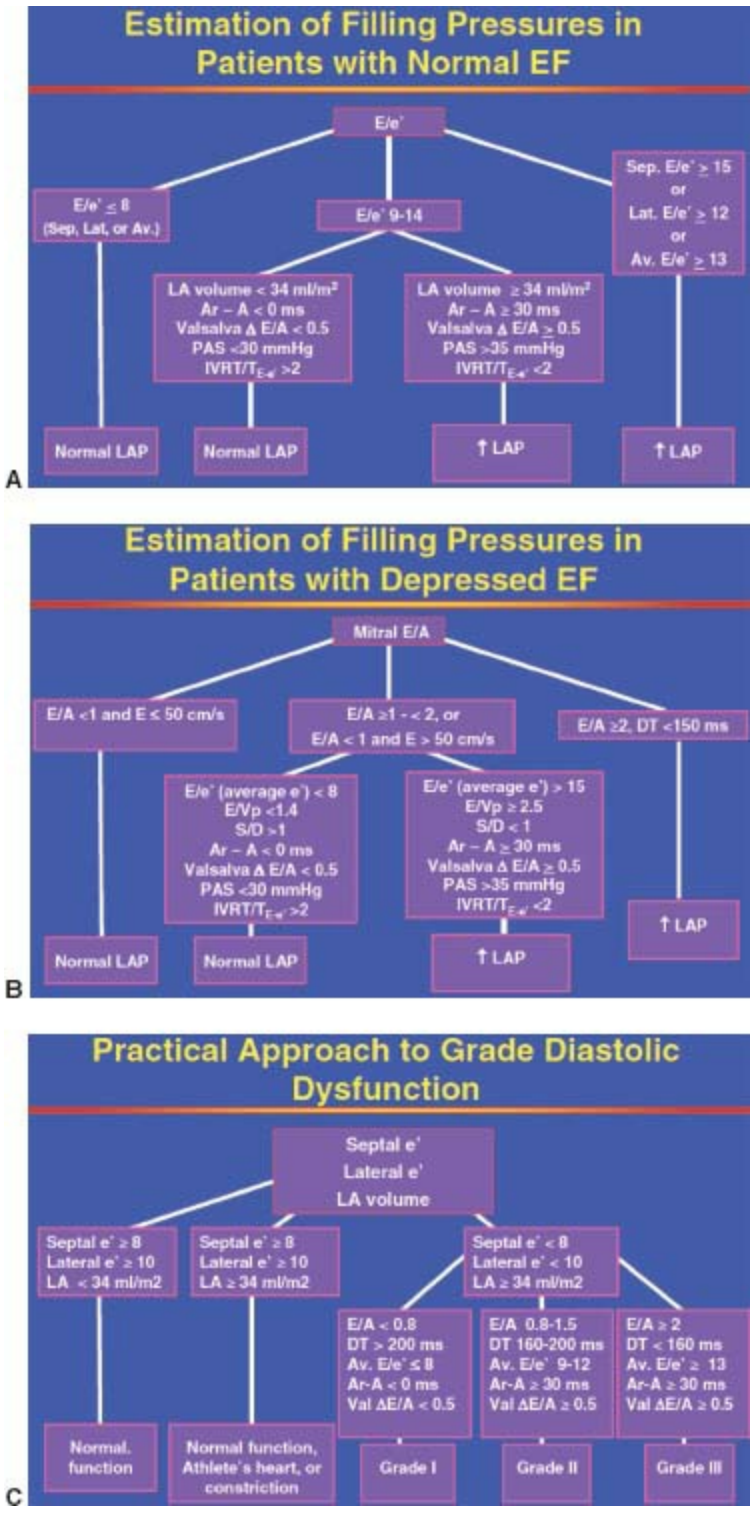


FIGURE 21.3 A:An algorithm for assessment of LV filling pressure in patients with normal ejection fraction (EF). **B:** An algorithm for assessment of LV filling pressure in patients with depressed EF. **C:** Algorithm for grading diastolic dysfunction. Ar-A, difference in duration of the atrial reversal wave (pulmonary vein) and of the atrial wave of mitral inflow; LA, left atrial; Av, Average; LAP, normal left atrial pressure; ↑LAP, increased left atrial pressure; PAS, pulmonary arterial systolic pressure; IVRT, isovolumic relaxation time; DT, mitral inflow E wave deceleration time; Val, Valsalva; mitral inflow E velocity (E). e′, early diastolic velocity at the mitral annulus; Vp, flow propagation velocity; S/D, pulmonary venous systolic (S) and diastolic (D) flow wave ratio. (From Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography. JASE. 2009;22:107–133, with permission from Elsevier.)

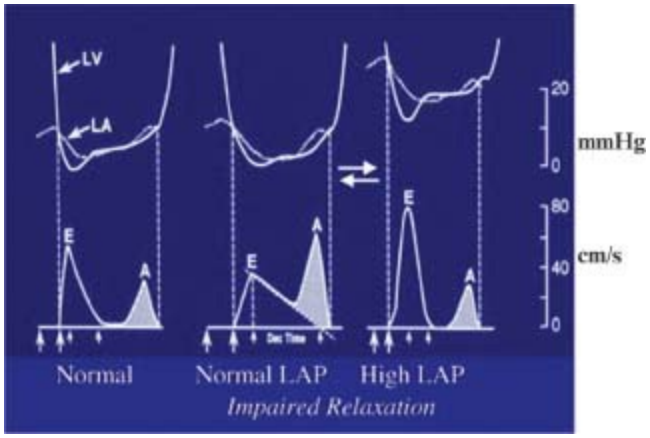
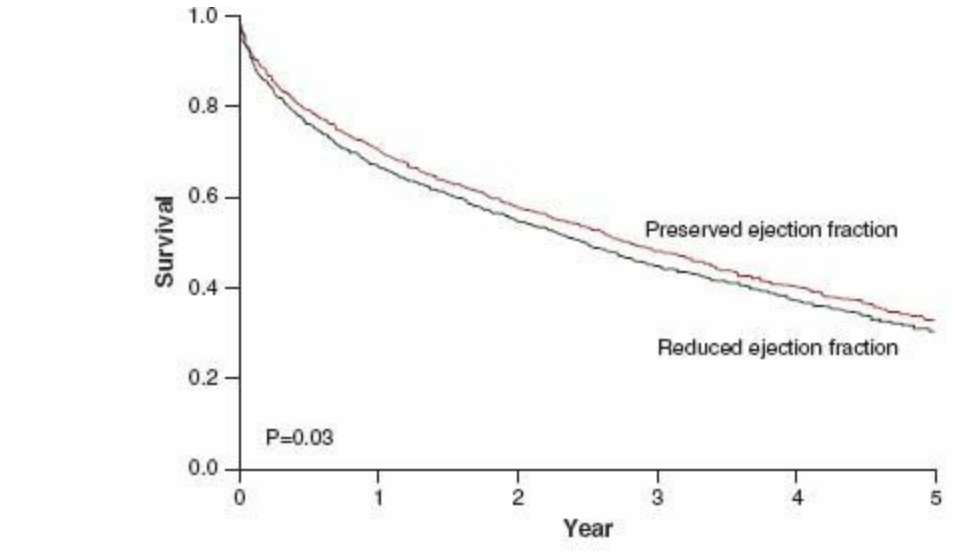


FIGURE 21.4 Diastolic stress echocardiography reflecting changes in exercise-induced diastolic filling pressures. Nagueh et al. showed that e′ remained unchanged with increased transmitral gradient in patients with diastolic dysfunction. (From Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography. JASE 2009;22:107–133, with permission from Elsevier.)

PROGNOSIS

Despite earlier studies that suggested better outcomes among HFNEF patients compared with HFREF patients, more recent data suggest similar prognosis with both entities. Additionally, diastolic dysfunction, particularly of a moderate or severe degree, has now been shown to be a powerful predictor of increased morbidity and mortality (Fig. 21.5). It has been observed that 22% to 29% of patients with HFNEF die within 1 year of hospital discharge and 65% die within 5 years.



No. at Risk						
Reduced ejection fraction	2424	1637	1350	1049	813	604
Preserved ejection fraction	2166	1539	1270	1001	758	574

FIGURE 21.5 Kaplan-Meier survival curves for patients with heart failure and preserved or reduced ejection fraction. (Reprinted from Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure

with preserved ejection fraction. N Engl J Med. 2006;355:251–259, with permission from the Massachusetts Medical Society.)

TREATMENT OF DIASTOLIC HEART FAILURE

Treatment consists of reducing elevated filling pressures, maintaining atrial contraction, decreasing heart rate, preventing ischemia, improving relaxation, and implementing strategies to regress LV hypertrophy. Treatment is generally geared toward the management of the underlying pathologic condition in addition to the following:

1. Diuresis as needed to decrease central venous pressure
2. Beta-blockers to improve ventricular relaxation and enhance filling
3. Angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, calcium channel blockers, and other antihypertensives to decrease blood pressure and for afterload reduction
4. Restoration of normal sinus rhythm (NSR) in patients with atrial fibrillation and atrial flutter

The multicenter CHARM study has shown that treatment with Candesartan resulted in fewer readmissions for congestive heart failure with no difference in cardiovascular death or the combined endpoint of cardiovascular death or hospitalizations (Fig. 21.6). Additionally, data from the ancillary digitalis investigation group trial have shown that digoxin had no effect on mortality or all-cause of cardiovascular hospitalizations among patients with HFNEF already receiving ACEI and diuretics. The more recent, randomized, double-blind, placebo-controlled I-PRESERVE trial (Fig. 21.7) sought to determine if treatment with the angiotensin receptor blocker, irbesartan, reduced morbidity and mortality among 4,128 patients with HFNEF. Irbesartan did not reduce the composite primary endpoint of mortality or cardiovascular hospitalization.

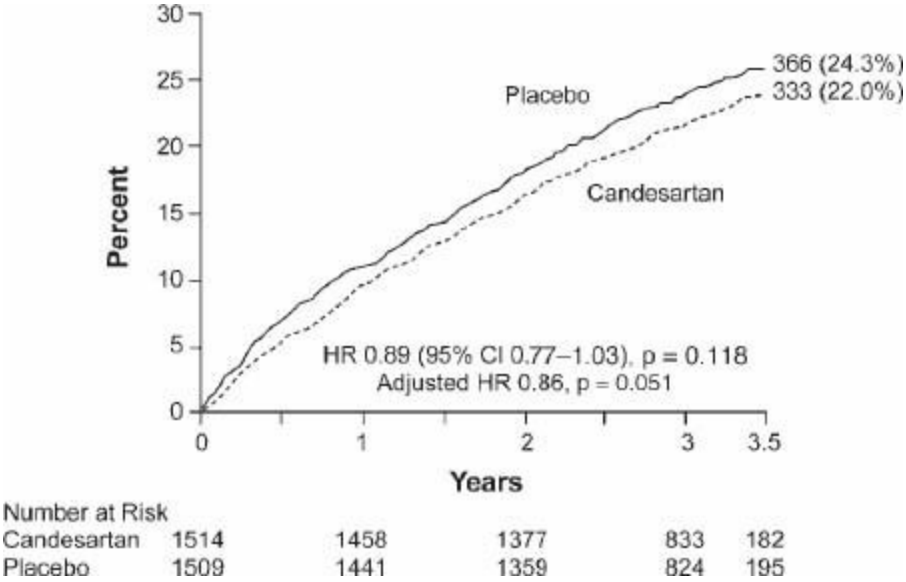


FIGURE 21.6 Time to cardiovascular death or hospital admission for congestive heart failure in the CHARM study. (Reprinted from Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003;362:777–781, with permission from Elsevier.)

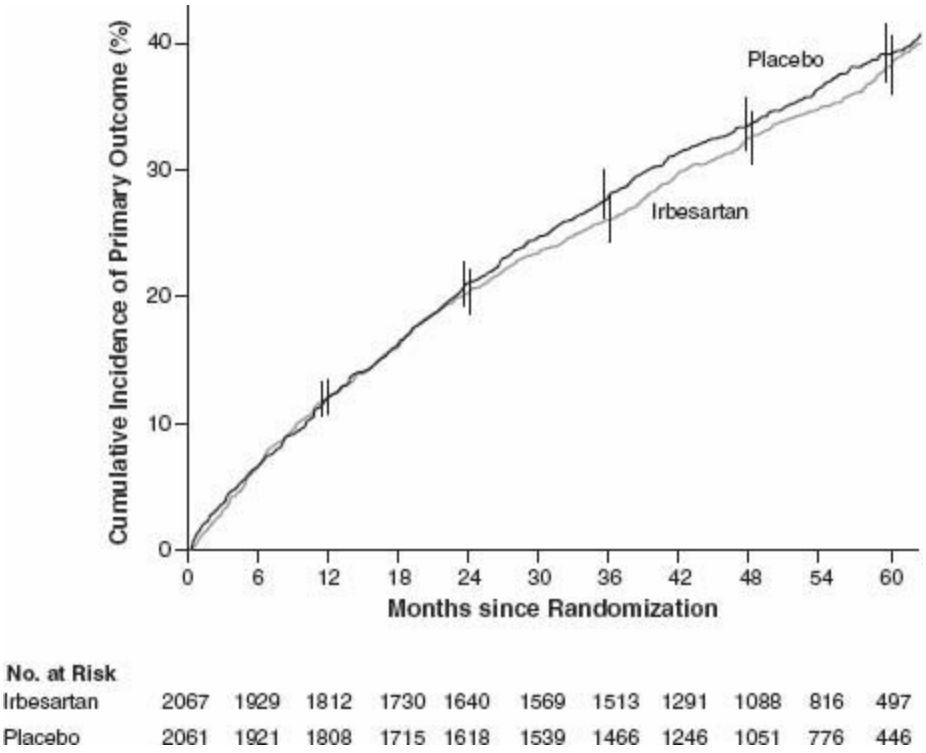


FIGURE 21.7 Time to death from any cause or hospitalization for prespecified cardiovascular causes (worsening heart failure, myocardial infarction, stroke, atrial or ventricular arrhythmia, and myocardial infarction or stroke occurring during hospitalization for any cause) shown for patients receiving irbesartan and those receiving placebo in the i-PRESERVE trial. (Reprinted from Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008;359:2456–2467, with permission from the Massachusetts Medical Society.)

RESTRICTIVE CARDIOMYOPATHIES

Restrictive cardiomyopathy is defined as a disease of the myocardium, which is characterized by "restrictive filling and reduced diastolic volume of either or both ventricles with normal or near-normal systolic function." Systolic function may be normal in the early stage of the disease, whereas wall thickness may be normal or increased depending on the etiology. The disease may be "idiopathic" or associated with other disease, such as amyloidosis.

Restrictive cardiomyopathies are recognized as primary and secondary, in which the secondary forms include the specific heart muscle diseases in which the heart is affected as part of a multisystem disorder—for example, infiltrative, storage, and noninfiltrative diseases. A "working classification" of restrictive cardiomyopathy is shown in Figure 21.8. Infiltrative cardiomyopathies can be further divided into interstitial and storage disorders. In interstitial diseases, the infiltrates localize to the interstitium (between myocardial cells), as with cardiac amyloidosis and sarcoidosis. In storage disorders, the deposits are within cells, as with hemochromatosis and glycogen storage diseases. These secondary forms of restrictive cardiomyopathies are probably more common than the primary form and display the classic restrictive hemodynamics only in their advanced form. The prototypical secondary restrictive cardiomyopathy is cardiac amyloidosis.

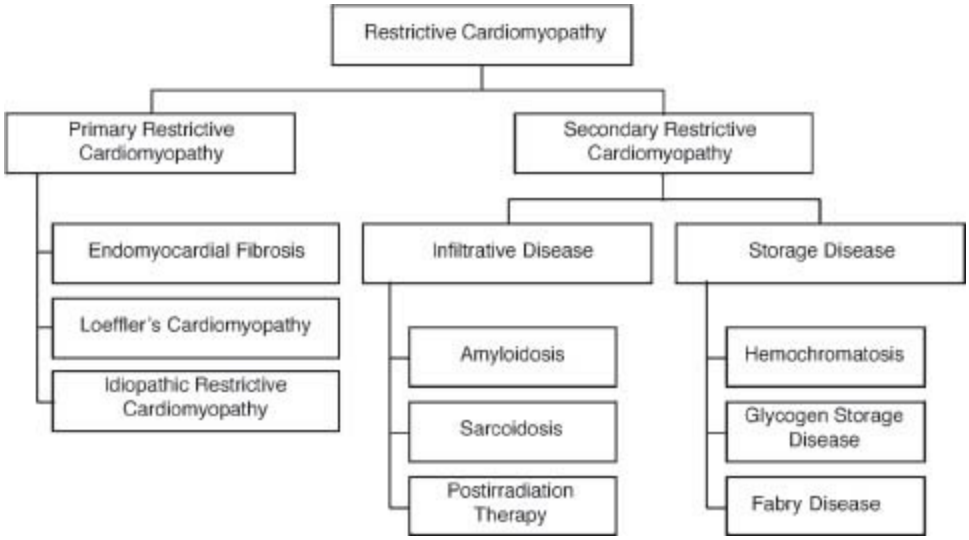


FIGURE 21.8 Working classification of restrictive cardiomyopathy. (From Leung DY, Klein AL. Restrictive cardiomyopathy; diagnosis and prognostic implications. In: Otto CM, ed. Practice of Clinical Echocardiography. Philadelphia: WB Saunders; 1997:474–493, with permission from Elsevier.)

Primary Restrictive Cardiomyopathies

Idiopathic restrictive cardiomyopathy is associated with familial transmission and skeletal myopathies. There is no specific pathology on endomyocardial biopsies. The atria are disproportionately large, with normal LV function. Histologic examination

shows nonspecific degenerative changes seen in other cardiomyopathies, including interstitial fibrosis that may also occur in the sinoatrial and the atrioventricular nodes, causing possible heart block. Most small series show a protracted clinical course in adults, with a mean survival of 4 to 14 years (mean: 9 years).

Loffler endocarditis is associated with idiopathic hypereosinophilia. There is endocardial thickening, obliteration of the LV apex, and a high incidence of thromboembolism. Steroids and hydroxyurea may be helpful in management.

Endomyocardial fibrosis is endemic to tropical Africa. It occurs in the left and the right ventricular apices with obliteration and involvement of the subvalvular apparatus. Thromboembolism is common. Treatment is mainly palliative, although surgical debulking has been attempted, with increased surgical mortality.

Secondary Restrictive Cardiomyopathies

Amyloidosis is caused by deposition of insoluble proteins in the heart consistent with the "stiff heart" syndrome. Amyloidosis can be classified by the type of protein deposited. The primary type (AL type) is the most common (85% of the population). It is caused by fibrils composed of **k**- or **λ**-immunoglobulin light chains, often associated with multiple myeloma. Cardiac amyloidosis is mostly caused by primary amyloidosis (AL type). Secondary amyloidosis (AA type) is rare, with the fibrils consisting of protein A, a nonimmunoglobulin. Familial amyloidosis results from the production of a mutant prealbumin protein (transthyretin [TTR]). There are six different identified types that present with a cardiomyopathy, neuropathy, or nephropathy. In familial amyloidosis, cardiac involvement occurs in 28% of patients at the time of diagnosis; however, it usually presents late in the course of the disease.

Patients with cardiac amyloidosis present with HFNEF resulting from amyloid protein infiltration. Patients may present with various degrees of progressive biventricular heart failure, depending on the stage of disease, as shown by two-dimensional and Doppler echocardiography (Fig. 21.9). The prognosis can often be determined using Doppler echocardiography (Fig. 21.10). Treatment consists of chemotherapy and diuresis. Dose-intensive melphalan with autologous stem cell transplantation is currently being evaluated. Cardiac transplantation is generally not performed for patients with cardiac amyloidosis because this is a systemic illness with progressive extracardiac amyloid deposition.

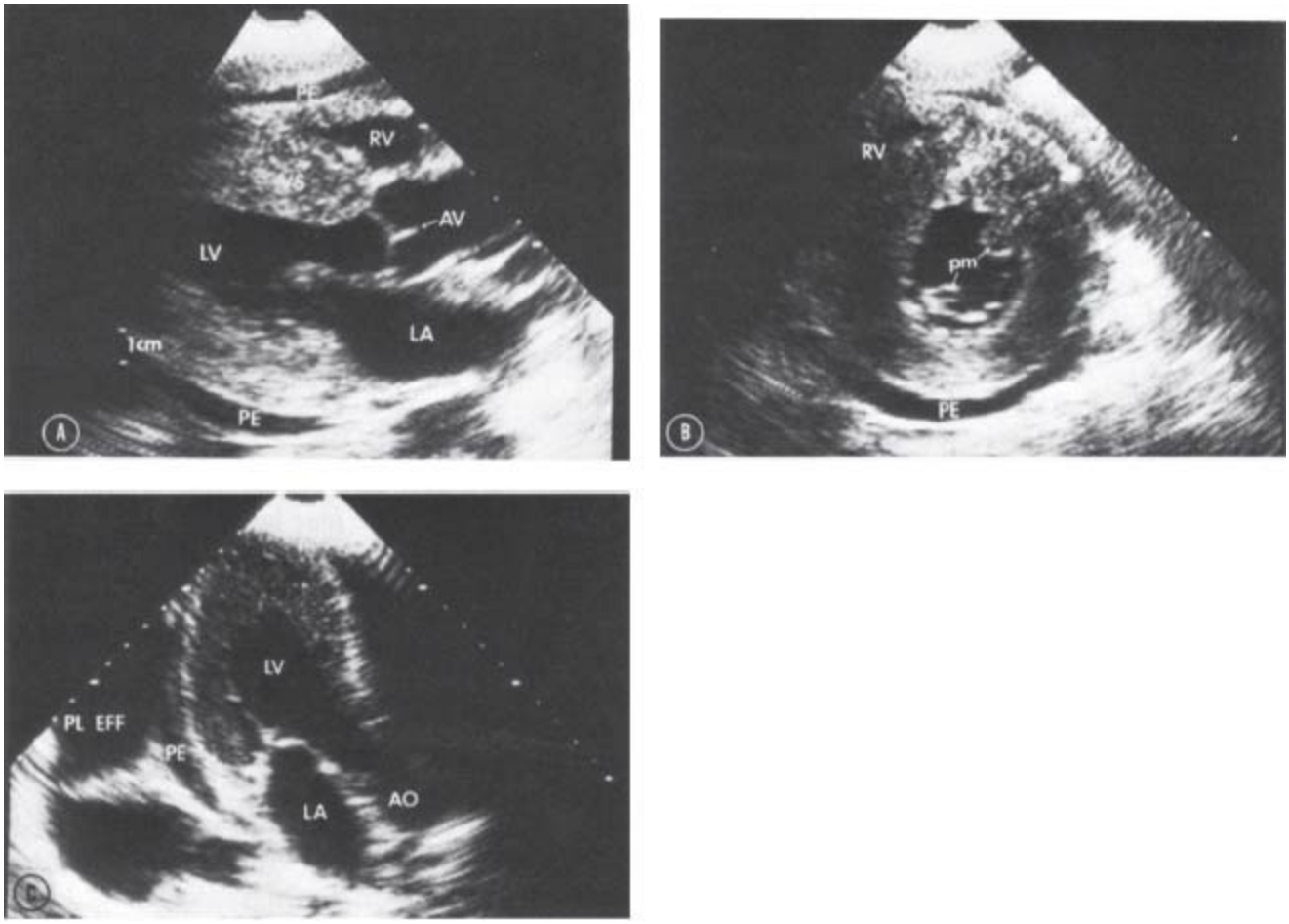


FIGURE 21.9 Parasternal long **(A)** and short-axis **(B)** and apical long-axis **(C)** views show typical echocardiographic features of advanced cardiac amyloidosis. Note that LV size is normal with markedly thickened ventricular walls (ventricular septum = 22 mm, posterior wall = 18 mm, and right ventricular free wall = 15 mm) and its characteristic granular sparkling appearance. Small pericardial effusion (PE) and left pleural effusion (PLEFF) are also present. AO, aorta; AV, aortic valve; LA, left atrium; LV, left ventricle; PM, papillary muscle; RA, right atrium; RV, right ventricle; VS, ventricular septum. (From Klein AL, Oh JK, Miller FA, et al. Two-dimensional and Doppler echocardiographic assessment of infiltrative cardiomyopathy. J Am Soc Echocardiogr. 1988;1:48–59, with permission.)

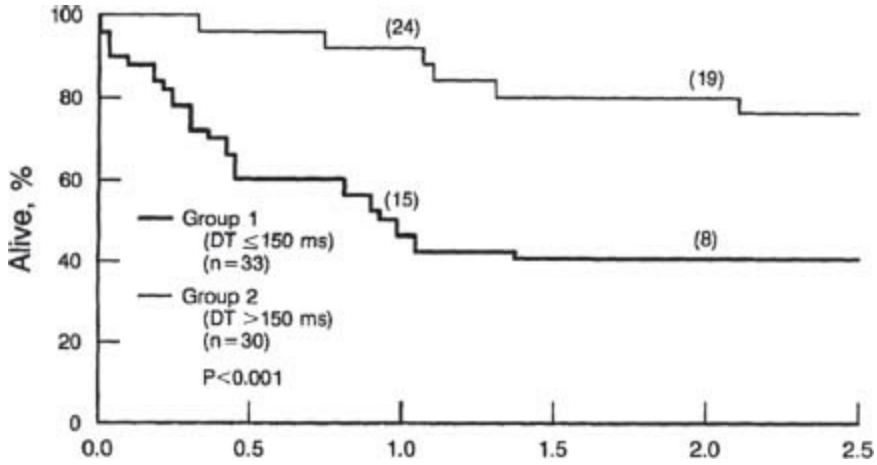


FIGURE 21.10 Survival in 63 patients with cardiac amyloidosis subdivided on the basis of the deceleration time of 150 milliseconds. Patients with a shortened deceleration time of <150 milliseconds (bold line) had a significantly reduced survival compared with patient subgroup having deceleration time >150 milliseconds. (From Klein AL, Hatle

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Hemochromatosis can be primary, representing a recessive genetic disease, or secondary, due to iron overload (e.g., from blood transfusions). Phlebotomy may improve cardiac symptoms.

Storage disorders may be caused by a number of enzymatic defects that lead to accumulation of lipids or polysaccharides in the myocardium.

Sarcoidosis is a multisystem disease characterized histologically by the formation of granulomas in many tissues. Among patients dying with sarcoidosis, in whom autopsy is performed, noncaseating granulomas involving the myocardium are found in up to 25% of patients. Most patients are asymptomatic, but rhythm and conduction disorders may predominate. VT is the most common arrhythmia. Sudden death can occur in up to 17% of patients with extensive myocardial involvement. Steroid treatment is used for patients with conduction block or arrhythmias.

ACKNOWLEDGMENT

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QUESTIONS AND ANSWERS

Questions

1. A 63-year-old male engineer undergoes echocardiography 2 months following a large posterolateral myocardial infarction due to acute stent thrombosis in his proximal left circumflex coronary artery. Which of the following is associated with a better prognosis?
   a. Ejection fraction (EF) of 29%
   b. E/e′ of 23
   c. Presence of moderate-to-severe mitral regurgitation (MR) with ERO = 0.3 cm^2
   d. Lateral wall e′ of 6 cm/s
   e. Deceleration time of 133 milliseconds
2. The best two-dimensional (2-D) and Doppler echocardiographic finding to differentiate restrictive cardiomyopathy from constrictive pericarditis would be to evaluate:
   a. Pulmonary venous flow pattern
   b. Atrial size
   c. Early diastolic mitral annular velocity
   d. Mitral inflow pattern
   e. Inferior vena cava dilatation
3. Which parameters are relatively preload independent?
   a. Mitral inflow E wave
   b. Tissue Doppler echo annular E′ wave
   c. Color M-mode flow propagation velocity
   d. Tissue Doppler echo annular E′ wave and color M-mode flow propagation velocity
4. Which of the following is the most common symptom associated with diastolic heart failure?
   a. Chest pain
   b. Paroxysmal nocturnal dyspnea
   c. Exertional dyspnea
   d. Dyspnea at rest
5. A 67-year-old obese woman is experiencing increasing dyspnea, fatigue, leg swelling and peripheral neuropathy that have developed over the past 9 months. Physical exam reveals a mildly distressed patient with visible dyspnea and 3+ bilateral leg edema. Auscultation is difficult and only distant heart sounds can be discerned. Electrocardiogram shows low voltage and a pseudoinfarct pattern. At this time, which is the best diagnostic study?
   a. Echocardiogram with respirometry
   b. Angiography
   c. Cardiac CT scan
   d. Cardiac MRI

Answers

1. Answer D: Regional ischemic injury will decrease the longitudinal systolic and diastolic excursion of

the affected wall. Therefore, a lower value of e′ in the lateral wall of this patient is not an entirely unexpected finding (lateral e′ should normally be ≥10 cm/s). It is now recommended to acquire and measure tissue Doppler signals at least at the septal and lateral sides of the mitral annulus and calculate their average to measure E/e′. The other possible answers each have been shown to carry important prognostic information in patients with a history (recent or not) of myocardial infarction.

2. Answer C: Differentiating restrictive from constrictive pericarditis by echocardiography can be particularly challenging. Mitral inflow, pulmonary venous flow, or tricuspid inflow does not always exhibit the typical respiratory changes displayed in textbooks. The inferior vena cava (IVC) is commonly dilated in patients with constriction; however, this can also be seen in patients with advanced restrictive cardiomyopathy. Atrial size will usually be increased in patients with restrictive cardiomyopathy, but constrictive pericarditis will also eventually result in (particularly right-sided) atrial enlargement. In patients with restrictive cardiomyopathy, myocardial relaxation (e′) will be severely impaired; whereas in patients with constriction, annular vertical excursion will usually be preserved. A septal e′ velocity ≥7 cm/s has been shown to be highly accurate in differentiating patients with constrictive pericarditis from those with restrictive cardiomyopathy.

3. Answer D: Both tissue Doppler echocardiography annular E′ wave and color m-mode flow propagation are measures of relaxation and are relatively preload independent. Mitral inflow E wave is dependent on preload.

4. Answer C: Exertional dyspnea. With exertion, diastolic filling worsens and left ventricular (LV) filling pressure increases, resulting in dyspnea.

5. Answer A: Echocardiogram with respirometry. Echocardiography is the modality of choice for the initial assessment of cardiac amyloidosis.

CHAPTER

Hypertrophic Cardiomyopathy

Anthony J. Hart and Harry M. Lever

PREVALENCE AND DEFINITION

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular disease.[1] The prevalence in the general adult population for people with phenotypic evidence of HCM is estimated at 1 per 500.[2] It is the most common etiology for sudden cardiac death (SCD) in young adults.[3,4]

HCM has traditionally been defined as myocardial hypertrophy of ≥1.5 cm without an identifiable cause (Figs. 22.1 and 22.2). Other etiologies of hypertrophy must be excluded before diagnosing HCM (Table 22.1). While there are multiple synonyms for HCM, including muscular subaortic stenosis (MSS), hypertrophic obstructive cardiomyopathy (HOCM), and idiopathic hypertrophic subaortic stenosis (IHSS), the World Health Organization (WHO) recommends that HCM be used as the term for the disease.

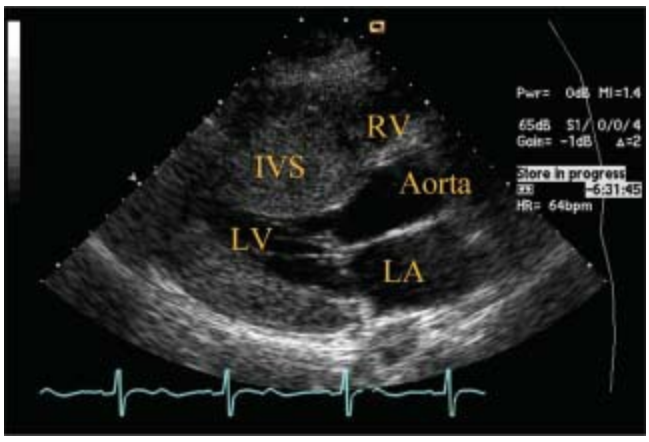

FIGURE 22.1 Transthoracic echocardiogram of HCM in the young—diffuse hypertrophy. Parasternal long-axis view depicts a markedly thickened interventricular septum. The thickening is diffuse, extending from base to beyond the midventricle. LV, left ventricle; RV, right ventricle; LA, left atrium; IVS, interventricular septum.

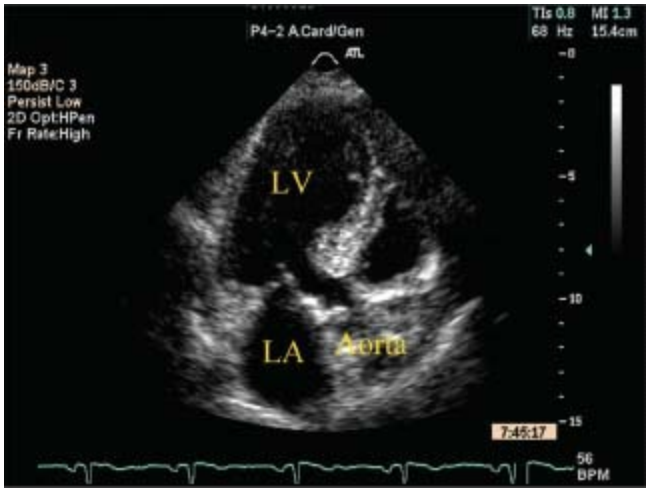

FIGURE 22.2 Transthoracic echocardiogram of HCM in the elderly—proximal septal hypertrophy. Apical three-chamber view depicts focal thickening of the interventricular septum at its base. The midventricle appears to be uninvolved. LV, left ventricle; LA, left atrium.

TABLE
22.1 Alternative Causes of LV Wall Thickening

■ Long-standing hypertension
■ Aortic stenosis
■ Amyloidosis
■ Fabry disease
■ Friedreich Ataxia
■ Danon disease
■ Noonan syndrome
■ Pompe disease

CLASSIFICATION

HCM can be classified as obstructive or nonobstructive, depending on the presence of a left ventricular outflow tract (LVOT) gradient, either at rest or with provocative maneuvers. Seventy percent of subjects with HCM have LVOT gradients ≥30 mm Hg at rest or with exercise.[5] Obstruction is caused by systolic anterior motion (SAM) of the mitral valve leaflet.

Anatomic variants of HCM exist, and these can be categorized based on the location of the hypertrophy (e.g., proximal septal, apical, or diffuse). Apical hypertrophy is also known as Yamaguchi disease (Fig. 22.3). Additionally, distinct forms of HCM appear to exist, depending on age. Younger patients tend to have hypertrophy of the entire septum (see Fig. 22.1), whereas older patients generally have basal septal hypertrophy, known as a sigmoid septum (see Fig. 22.2).[6] It is believed that these are two different disease processes. The majority of elderly HCM (diagnosed at >50 years of age) were

negative for mutations for HCM, especially when a sigmoid septum was present, whereas younger subjects with HCM were more likely to have mutations for HCM.[7]

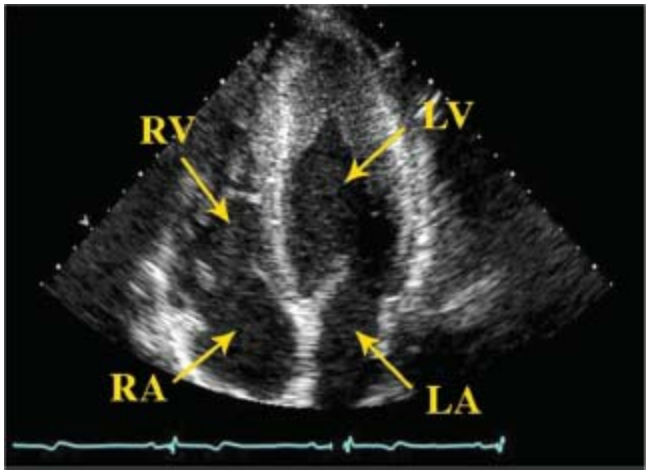

FIGURE 22.3 Transthoracic echocardiogram of apical variant of HCM (Yamaguchi). Apical four-chamber view depicts ventricular thickening of the apex. LV, left ventricle; LA, left atrium; RV, right ventricle; RA, right atrium.

PATHOPHYSIOLOGY AND HISTOLOGY

LVOT obstruction is the pathophysiologic change in obstructive HCM (Figs. 22.4 and 22.5). When SAM occurs, the mitral valve leaflets are pulled or dragged anteriorly toward the ventricular septum, producing LVOT obstruction.[8] The left ventricle (LV) thus must generate higher pressures to overcome the obstruction and to pump blood systemically. Premature closure of the aortic valve frequently occurs, caused by the decline in pressure distal to the LVOT obstruction.

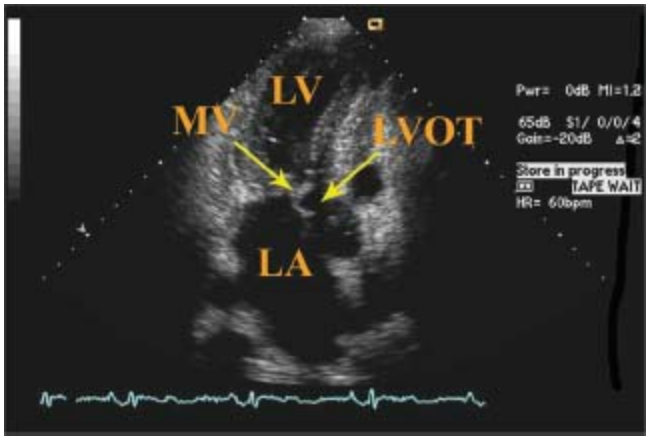

FIGURE 22.4 Transthoracic echocardiogram of SAM of mitral valve. Apical three-chamber view illustrates SAM of the mitral valve, resulting in obstruction of the LVOT. LV, left ventricle; LA, left atrium; MV, mitral valve; LVOT, left ventricular outflow tract.

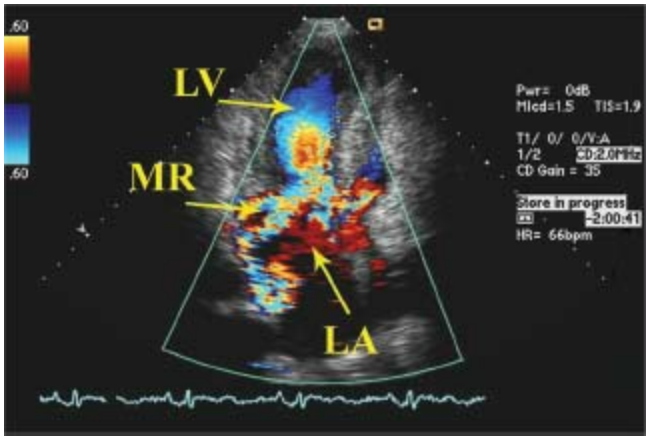

FIGURE 22.5 Transthoracic echocardiogram of mitral regurgitation in HCM. Apical three-chamber view illustrates the classic posterolaterally directed mitral regurgitation jet in HCM. The jet direction occurs secondary to SAM of the mitral valve. LV, left ventricle; LA, left atrium; MR, mitral regurgitation jet.

Dynamic obstruction occurs with HCM, whereas fixed obstruction occurs with aortic stenosis and subvalvular aortic membranes. In dynamic obstruction, the degree of obstruction depends to a larger extent on cardiac contractility and loading conditions. This is contrasted in fixed obstruction, where cardiac contractility and preload have little effect on the degree of obstruction. An underfilled LV results in greater obstruction because there is less separation between the interventricular septum and the mitral valve. As the LV cavity gets smaller and the flow stream is directed against the mitral valve, the SAM of the mitral valve occurs. Augmenting cardiac contractility also increases LVOT obstruction, because a more vigorous contraction is more likely to cause the obstructing components to come into contact. As the mitral leaflet comes closer against the septum, the outflow tract is decreased in size, which further increases the pressure difference. This feedback loop is represented on continuous-wave Doppler imaging as the concave contour (Fig. 22.10).

Histologically, HCM manifests as hypertrophied, disorganized cardiac myocytes present throughout the myocardium. The abnormal cells may take on bizarre shapes, and the connections among cells are often in disarray. Myocardial scarring and growth of the collagen matrix also occur.[1] The mechanism of scarring continues to be elucidated but appears to reflect small intramural coronary arteriole dysplasia.[9]

SYMPTOMS AND CLINICAL COURSE

While the most common symptom of HCM is dyspnea on exertion, the majority of patients with HCM are asymptomatic.[10] Importantly, symptoms are not always concordant with severity of LV outflow tract obstruction and may be more closely related to diastolic dysfunction.[4]

With diastolic dysfunction, the increased chamber thickness in HCM results in

increased left ventricular (LV) stiffness, impaired filling, and relaxation. These diastolic abnormalities result in elevated left atrial, LV end-diastolic, and pulmonary pressures. Symptoms may also be caused by mitral regurgitation from SAM of the mitral valve, LVOT obstruction, arrhythmias such as atrial fibrillation, and myocardial ischemia. Patients may also complain of chest pain with exertion, syncope or near syncope, or palpitations. Eating may make symptoms worse because of splanchnic vasodilation and the resulting decrease in systemic vascular resistance.[11]

The clinical course of HCM is variable. In one community cohort, 23% of subjects with HCM had normal life expectancy.[12] Other patients may have premature death. Annual mortality rate from HCM is approximately 1%.[1] Congestive heart failure and atrial fibrillation may be part of the natural history of HCM. SCD is a frequent and catastrophic initial presentation.[13] SCD tends to occur in younger patients and may occur during heavy exertion, light exertion, or even at rest. In an unselected, community-based population with HCM, the estimated incidence of SCD is approximately 0.1% to 0.7% per year.[14],[15]

PHYSICAL EXAMINATION

The physical examination may provide several clues that suggest obstructive HCM. With LVOT obstruction, a harsh systolic murmur exists at the upper sternal border. It is important that this murmur be differentiated from that of mitral regurgitation, which can also be present in HCM secondary to SAM of the mitral valve. Palpation of the carotid pulse aids in distinguishing HCM from aortic stenosis or the presence of a subvalvular aortic membrane. With HCM, little difficulty exists during early systole in ejecting the blood through the LVOT into the aorta; therefore, the carotid upstroke is brisk. As systole progresses, LVOT obstruction occurs, resulting in a collapse in the pulse and then a secondary rise as LV pressure increases to overcome the obstruction. This sign is known as a bisferiens, or spike-and-dome, pulse. In contrast, because the fixed obstruction of aortic stenosis or a subvalvular aortic membrane is present during the entire cardiac cycle, the carotid upstroke in these entities is the classic parvusettardus pulse, a carotid pulse with delayed amplitude and upstroke. Therefore, if any patient carrying a diagnosis of HCM has decreased carotid pulses, this should prompt thoughts of a mistaken diagnosis and further investigation into a fixed obstruction of the LVOT.

Unless congestive heart failure has developed, the lungs are clear and the jugular venous pressure is normal. The point of maximal impulse is often forceful and sustained, and a palpable S4 gallop may be present. Occasionally, a bifid apical impulse may be palpated; the first impulse represents forceful atrial contraction and the second impulse represents sustained ventricular contraction.

The classic auscultatory finding for HCM is a crescendo–decrescendo systolic

murmur along the left sternal border that increases with the Valsalva maneuver. The Valsalva maneuver decreases preload, which results in decreased filling of the LV. An underfilled LV results in increased obstruction. The response in HCM to various physiologic and pharmacologic maneuvers is illustrated in Table 22.2.

TABLE
22.2 The Response in HCM to Various Physiologic and Pharmacologic Maneuvers

	Ventricular Volume	LVOT Gradient	Murmur Intensity
Valsalva	Decrease	Increase	Increase
Amyl nitrite	Decrease	Increase	Increase
Isoproterenol	Decrease	Increase	Increase
Hand grip	Increase	Decrease	Decrease
Phenylephrine	Increase	Decrease	Decrease
Beta-blocker	Increase	Decrease	Decrease

LVOT, left ventricular outflow tract.

During the cardiac examination, it is also imperative to listen carefully for a mitral regurgitation murmur as SAM of the mitral valve frequently causes mitral regurgitation. The remainder of the physical examination is generally unremarkable in HCM.

DIAGNOSTIC TESTING

Labs, Chest X-Ray, and Electrocardiogram

Blood work generally is unremarkable, with the exception of an elevated plasma B-type natriuretic peptide (BNP).[16] The chest x-ray is often normal. The electrocardiogram (ECG) may show LV hypertrophy. Occasionally, a pseudoinfarct pattern (with Q waves in the anterolateral leads) may be present on ECG. Figure 22.6 illustrates this pseudoinfarct pattern in a patient with HCM, normal LV systolic function, and no known coronary artery disease. In the apical variant of HCM, the ECG may have deep T-wave inversions in the anteroapical leads (Fig. 22.7). Left atrial abnormality may be present if the patient has had long-standing mitral regurgitation from SAM of the mitral valve. Atrial fibrillation may also be present.

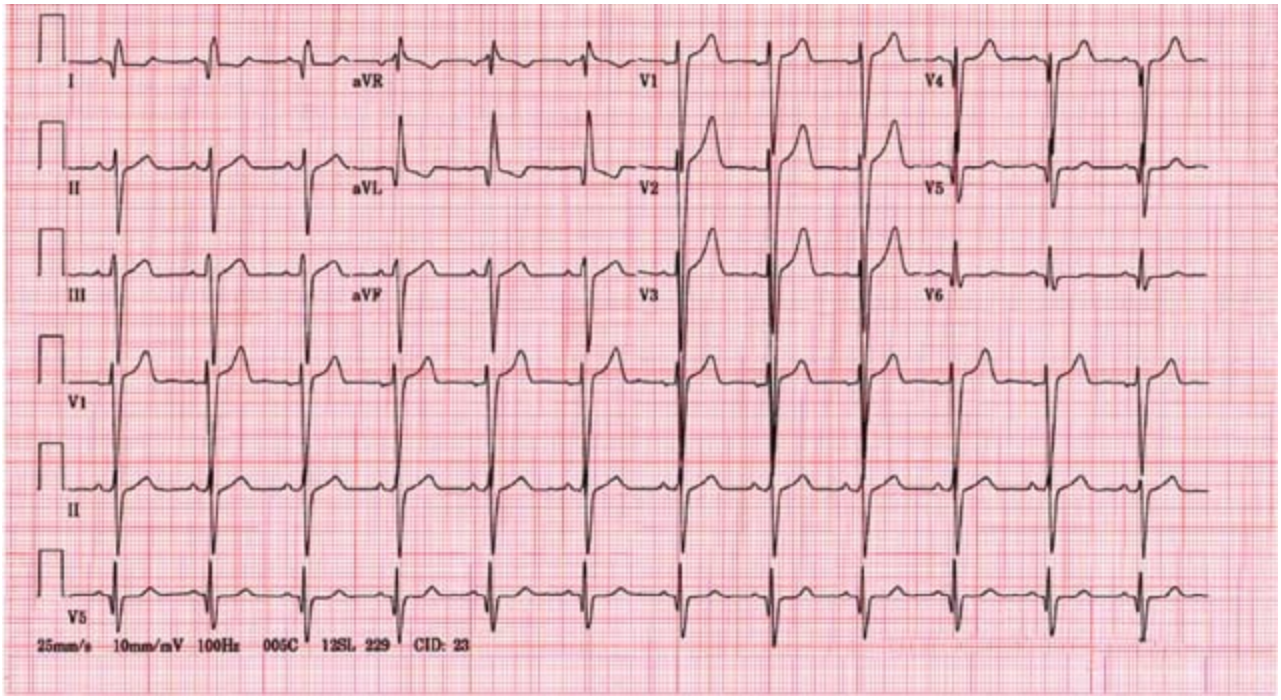

FIGURE 22.6 Pseudoinfarct pattern on ECG in HCM. In HCM, a pseudoinfarct pattern (Q waves in lateral leads) may sometimes be noted. This patient had normal LV systolic function and normal coronary arteries.

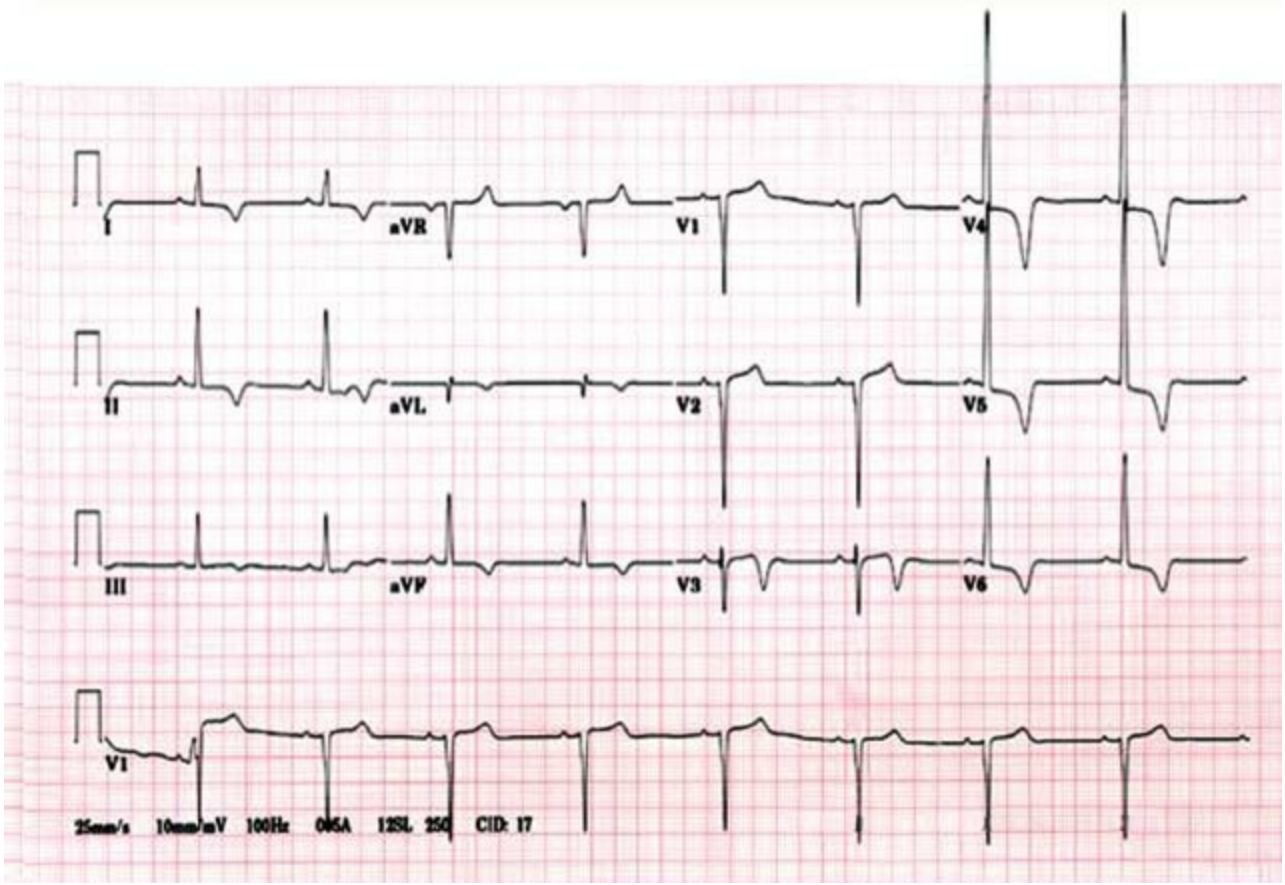

FIGURE 22.7 ECG in apical HCM (Yamaguchi). The classic ECG for apical HCM has deep anteroapical T-wave inversions.

Echocardiography

Transthoracic echocardiography (TTE) is currently the primary clinical modality for diagnosing HCM. The septum should be visualized and measured in the parasternal long-axis, apical long-axis, apical four-chamber, and parasternal short-axis views. The major diagnostic criterion for HCM is LV wall thickness of ≥15 mm in the absence of other causes for increased ventricular thickness.[4] The LV is nondilated and hyperdynamic. Figures 22.1 and 22.2 are TTE images from HCM patients with marked hypertrophy of the inter-ventricular septum. Figure 22.4 illustrates SAM of the mitral valve and resulting LVOT obstruction. During TTE, particular attention should be paid to the septal thickness; location and pattern of hypertrophy; site and magnitude of LVOT obstruction; presence of SAM of the mitral valve; and presence of premature closure of the aortic valve.

Given the frequency of no obstruction at rest, subjects with suspected HCM should undergo provocative testing during TTE with amyl nitrite, Valsalva, or exercise (treadmill or bicycle) to determine whether latent obstruction exists. Amyl nitrite is a vasodilator that decreases preload to the LV, followed by a compensatory increase in heart rate. Exercise results in an increase in contractility and heart rate. The physiologic effects of amyl nitrite and exercise thus result in an increase in LVOT gradient. In our experience, supervised exercise stress tests in patients with HCM are safe, with a major complication rate of 0.04%.[17] Dobutamine is generally not recommended for the purposes of provoking LVOT gradients, for gradients provoked by dobutamine are of questionable clinical significance.[4]

Pulse-wave Doppler should be performed to record LV and left atrial inflows to assess diastolic function. Diastolic abnormalities, which are common in HCM secondary to the thickness and stiffness of the LV, are unfortunately not specific for the diagnosis of HCM.

The mitral valve should be interrogated in multiple views to assess for the presence of mitral regurgitation, which is commonly present when SAM of the mitral valve leaflet is present (see Fig. 22.4). SAM of the mitral valve has a classic appearance in M mode, where the mitral valve leaflets can be seen to approach and often contact the interventricular septum (Fig. 22.8). In HCM, the mitral valve leaflets may be elongated and anterior displacement of the papillary muscles of the mitral valve may also occur.[18] With SAM, the mitral regurgitation may range from mild to severe and is posteriorly and laterally directed in the left atrium because of incomplete leaflet apposition (see Fig. 22.5). If the direction of the color jet of mitral regurgitation is central or anterior, then suspicion should be raised for intrinsic abnormalities of the mitral valve.

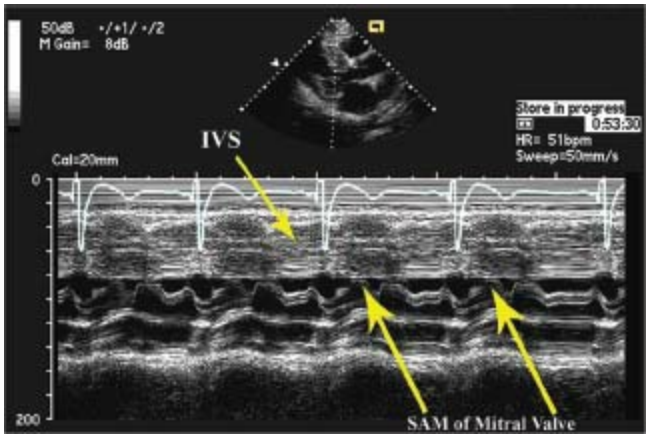

FIGURE 22.8 M-mode of SAM of mitral valve in HCM. With SAM of the mitral valve, the mitral leaflet contacts the interventricular septum during systole in a patient with HCM, as illustrated in this transthoracic M-mode echocardiograph. Normally, the mitral leaflets should be well away from the septum during ventricular systole. IVS, interventricular septum; SAM, systolic anterior motion.

Fixed obstructions such as aortic stenosis, subvalvular aortic membrane, and supravalvular aortic membrane can result in secondary hypertrophy of the interventricular septum, as distinct from the primary hypertrophy of the septum in HCM. In aortic stenosis, the aortic valve is calcified and has restricted mobility, whereas in HCM, the obstruction occurs below the aortic valve, and the aortic valve structure and function are preserved. Subvalvular aortic membranes (Fig. 22.9) and supravalvular aortic membranes may be difficult to visualize on TTE, in which case transesophageal echocardiography may need to be performed to assess for the presence of these structures.

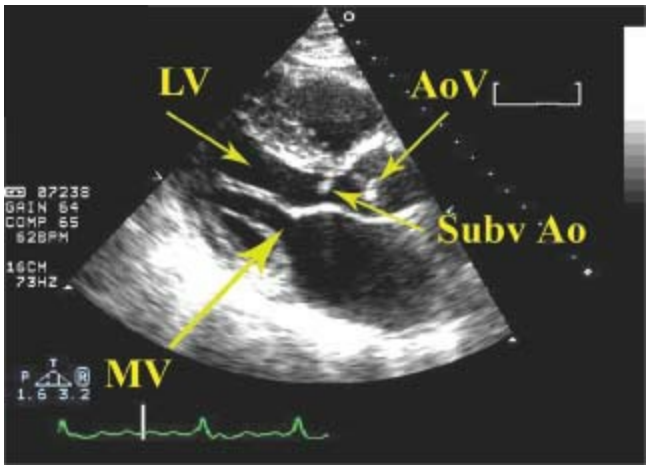

FIGURE 22.9 Subvalvular aortic membrane. Subvalvular aortic membranes must be distinguished from HCM, for both can result in a thickened septum and an LVOT gradient. Although subvalvular aortic membranes may sometimes be difficult to visualize by TTE, in this example a membrane below the aortic valve is clearly seen. LV, left ventricle; MV, mitral valve; AoV, aortic valve; SubvAo, subvalvular aortic membrane.

Continuous-wave Doppler imaging aids in the differentiation of HCM from fixed

obstructions. The modified Bernoulli equation [pressure = 4 x (velocity)^2] is used with the continuous-wave Doppler tracing through the LVOT to calculate the LVOT gradient. Figure 22.10 illustrates the difference between continuous-wave Doppler signals from HCM and from fixed obstructions. During early systole, blood still flows through the LVOT in HCM; however, with continued contraction of the LV, exacerbated by SAM of the mitral valve, an outflow tract gradient develops. Thus, with HCM, the continuous Doppler signal classically is described as having a late systolic dagger shape, because the obstruction is late peaking as a result of its dynamic nature. In contrast, a fixed obstruction is present during all of systole. Thus, the continuous-wave Doppler signal for fixed obstructions is a smoother contour that peaks earlier.

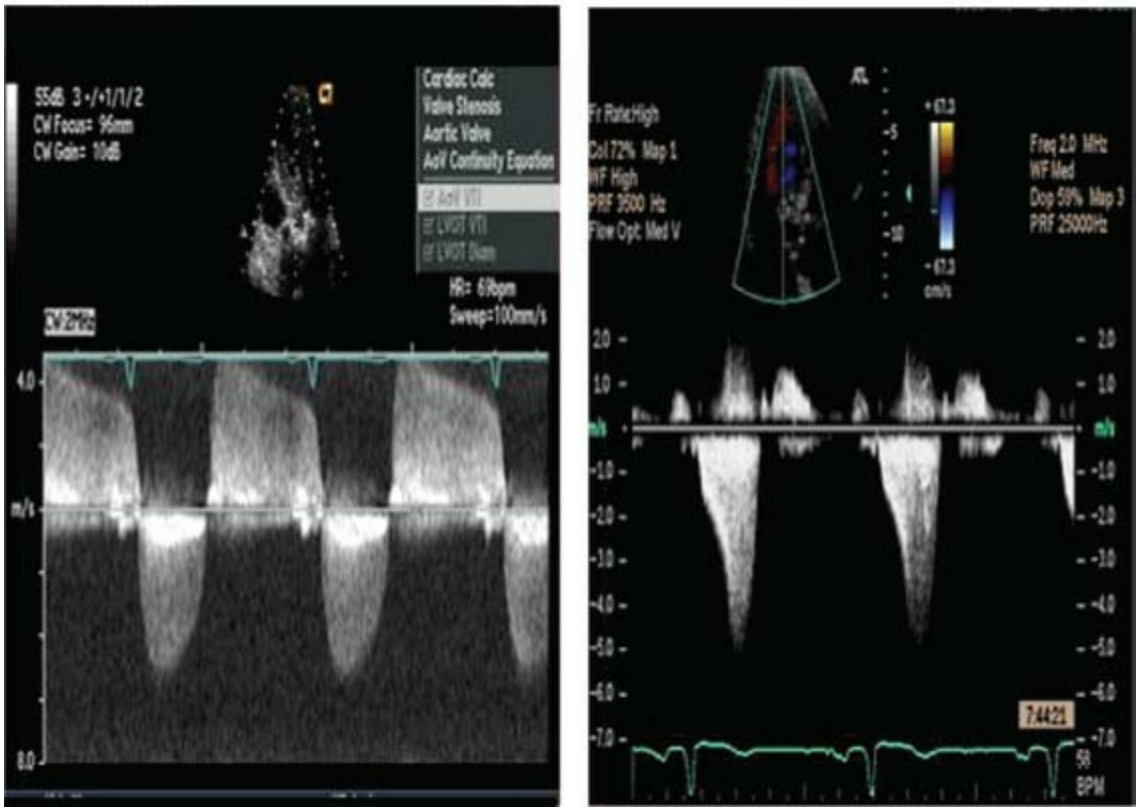

FIGURE 22.10 Continuous-wave Doppler profile comparison of aortic stenosis and HCM. Continuous-wave Doppler profiles from TTE for aortic stenosis **(left)** and HCM **(right)** are illustrated. The Doppler profile in aortic stenosis has a smooth, symmetric contour because the obstruction is fixed, whereas the Doppler profile in HCM has a late-peaking, dagger-shaped appearance as a result of the dynamic nature of the obstruction, with its peak in mid-late systole.

The continuous-wave Doppler profile of HCM also must be differentiated from that of mitral regurgitation. The mitral regurgitation jet is generally higher velocity (~6 m/s), whereas the LVOT obstruction jet is often in the 4- to 5-m/s range. The mitral regurgitation velocity tracing also has a smoother, symmetric contour, unlike the dagger-shaped profile of HCM. The mitral regurgitation jet may be late peaking because mitral regurgitation may not occur until SAM has occurred, which occurs partway through

systole. However, the mitral regurgitation tracing should extend beyond aortic valve closure, up to the point at which mitral forward flow occurs with diastole. In contrast, the LVOT obstruction signal ends at aortic valve closure.

One promising modality is tissue Doppler, which is sensitive for identifying reduced shortening velocities and may help differentiate between HCM and athlete's heart, as well as between nonobstructive HCM and hypertensive heart disease with LV hypertrophy.[19–21] A transmitral E/septal Ea ratio ≥ 15 has been demonstrated to be a predictive indicator for SCD. Another emerging imaging technique is strain imaging using speckle tracking. Strain imaging continues to evolve while offering complementary information on segmental LV function and its relationship with hypertrophy and fibrosis.[22,23]

Transthoracic Echocardiogram—Distinguishing HCM from Athlete's Heart

Because preathletic screening is one means by which the diagnosis of HCM is raised, it is imperative to distinguish HCM from athlete's heart. Several findings on echocardiography help distinguish HCM from athlete's heart. In HCM, the septal thickness is usually >15 mm, whereas in an athlete's heart, septal thickness is <15 mm. Left atrial enlargement often occurs with HCM secondary to long-standing mitral regurgitation from SAM of the mitral valve and/or diastolic dysfunction, whereas in an athlete's heart, the left atrial size should be normal. The LV should not be dilated in end diastole in HCM, whereas in athletes, it is common for LV end diastolic diameter to be >45 mm. Finally, diastolic dysfunction often exists in HCM as a result of the increased ventricular thickness and stiffness, whereas diastolic function should be normal in athletes. If it is still not certain whether a patient has HCM or athlete's heart, the athlete should stop training; after 3 to 6 months, ventricular hypertrophy will persist with HCM, whereas with athlete's heart, hypertrophy should regress.

Cardiac Magnetic Resonance

Cardiac magnetic resonance (CMR) has emerged as a highly useful tool in the diagnosis of HCM. It provides a comprehensive evaluation of myocardial anatomy, including those patients with atypical forms of HCM and those with papillary muscle abnormalities.[18,24–26] CMR can also assist with identification of alternative diagnoses such as of Fabry disease and cardiac amyloidosis.

CMR can also provide an accurate assessment of LV function.[25,27–29] Additionally, the use of gadolinium-based contrast agents can identify the presence and distribution of myocardial fibrosis.[30,31] Several recent studies have examined the relationship between scar burden as assessed in CMR and the incidence of SCD, and it remains an evolving

area of interest.[32,33]

Cardiac Catheterization

While the use of cardiac catheterization has become less relevant in the era of echocardiography and CMR, it is still useful as an adjunctive test in cases where there are discordant data from Doppler echocardiography and the physical exam. Cardiac catheterization may reveal concomitant coronary disease prior to septal myectomy and can also delineate the size and extent of the septal perforators prior to alcohol ablation.

Patients with HCM often have no obstructive coronary artery disease. However, they may have thickened vessels and small-vessel disease from increased collagen deposition in the intima and media.[1] The mismatch between myocardial oxygen supply and demand, driven primarily by the increased myocardial mass, may then cause myocardial ischemia. Microvascular dysfunction is present in HCM patients and is associated with worse clinical outcomes.[34]

The left ventriculogram demonstrates cavity obliteration and a hyperdynamic LV. LVOT gradients can be assessed by positioning a JR4 or multipurpose diagnostic catheter near the LV apex and recording ventricular pressures during slow catheter pullback. A pigtail catheter may not give accurate gradient measurements because there are multiple side holes extending along the distal portion of the catheter, in contrast to the JR4 and multipurpose catheters, which provide true end-hole measurements.

HCM physiology is demonstrated after a premature ventricular contraction (PVC) by the Brockenbrough response (Fig. 22.11). In the beat following a PVC, there is increased filling of the LV from the compensatory pause. The augmented preload results in augmented contractility. In patients with HCM, the increased contractility results in subsequent worsening of the LVOT obstruction. Thus, during the beat after the PVC, there is an increase in LV systolic pressure, a decrease in aortic systolic pressure, and thus an increase in the gradient between LV and aorta. In contrast, in normal subjects, the increased contractility associated with the post-PVC beat results in an increase in both LV systolic and aortic systolic pressure, and there is no gradient between the LV and aorta.

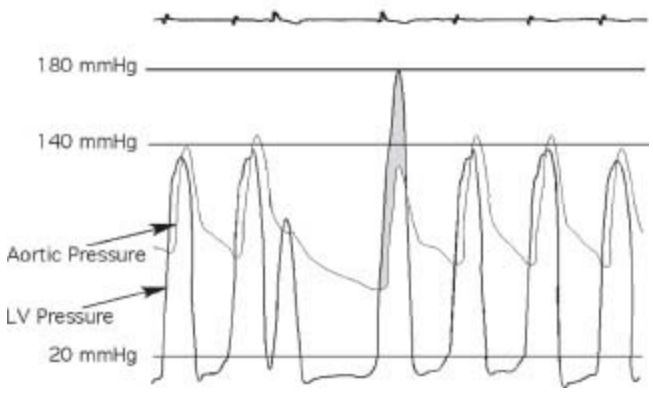

FIGURE 22.11 The Brockenbrough response to a PVC. In normal subjects, a PVC results in a compensatory pause, increased ventricular filling, and subsequent increased cardiac contractility. There is no LV–aortic gradient, either at rest or in the beat post-PVC. The aortic pulse pressure in the beat post-PVC usually increases because of the increased contractility. In contrast, as illustrated in the figure, the Brockenbrough response in the post-PVC beat (fourth beat) suggests HCM. In HCM, the increased contractility occurring with the post-PVC beat results in increased LVOT obstruction and a subsequent increase in the LV-aorta gradient (shaded) as well as decreased aortic pulse pressure during the post-PVC beat.

GENETICS OF HCM

Several hundred mutations involving at least 27 HCM susceptibility genes have thus far been identified.[35] The mutations associated with HCM are inherited in an autosomal dominant pattern and primarily involve the myosin, actin, or troponin components of the cardiac sarcomere. The most common mutations that cause HCM involve the β-myosin heavy chain (chromosome 14), myosin-binding protein C (chromosome 11), and cardiac troponin-T (chromosome 1). However, having the HCM genotype does not necessarily imply that subjects will have the phenotypic traits of HCM. Variable penetrance exists, and environmental factors as well as modifier genes affect whether a particular subject will manifest HCM phenotypically.

DNA analysis is the most definitive method for diagnosing HCM.[4] With time, genetic testing has become less expensive and readily available.

SCREENING OF FAMILY MEMBERS

Traditionally, it has been recommended that first-degree relatives of HCM patients be screened on a 12- to 18-month basis, beginning at age 12 years, with a 12-lead ECG and TTE. The recommended screening interval reflects the fact that latent HCM may be unmasked by growth spurts and subsequent worsening hypertrophy during adolescence. Evidence of late-onset ventricular hypertrophy occurring well into adulthood has spurred a push toward continuing serial echocardiograms past adolescence and into middle age for HCM relatives.[36] It is now recommended that adult relatives of HCM patients undergo screening transthoracic echocardiograms at a minimum of every 5 years.

Genetic testing has also been incorporated into the screening process.[35] If the patient has a HCM-causing mutation identified, then first-degree relatives can be screened for the presence of that mutation as well. If a relative is mutation positive, then surveillance should be done in a close manner with an annual clinical and echocardiographic exam. If a relative is mutation negative, then casual or no further routine surveillance can be elected provided the TTE is negative and the relative is asymptomatic.

THERAPY

Treatment options for HCM include pharmacologic therapy, septal myectomy, percutaneous alcohol septal ablation, and heart transplantation. Additionally, pacemaker implantation has been performed, but randomized trials have indicated a substantial placebo effect.

Medical Therapy

Treatment with beta-blockers is considered first-line therapy as they improve symptoms and exercise intolerance.[37] By decreasing contractile force, beta-blockers decrease the outflow gradient during exercise and decrease oxygen demand. Beta-blockers also lengthen diastolic filling by slowing the heart rate, thus improving any component of myocardial ischemia. We generally start patients on metoprolol, 50 mg twice a day, or extended-release metoprolol, 50 mg daily. If the patient continues to be symptomatic, the dose of metoprolol/extended-release metoprolol can be increased further by 25-mg increments every few weeks. Alternative beta-blocker choices include propranolol, nadolol, or atenolol.

Second-line therapy includes the calcium channel blocker verapamil and the Class IA antiarrhythmic agent disopyramide. Both nondihydropyridine calcium channel blockers and disopyramide exert a negative inotropic effect and improve ventricular relaxation. The extended-release formulation of verapamil can be started at 240 mg daily and increased by 60 mg every few weeks up to 480 mg daily. Calcium channel blockers have been shown to decrease symptoms in comparison to placebo.[37] Verapamil should not be used in patients with severe pulmonary hypertension, because this subgroup may develop excessive vasodilation that worsens LVOT obstruction and cardiac output, resulting in pulmonary edema or even death.[38] Diltiazem has been used in HCM patients, but there are few data on its effectiveness.

The extended-release formulation of disopyramide may be started at 150 mg twice a day. Disopyramide improves diastolic function and lowers the LVOT gradient.[39] Anticho-linergic side effects may occur with disopyramide. Concomitant therapy with beta-blockers is recommended because disopyramide may cause accelerated A–V nodal conduction, which may be deleterious, especially during episodes of atrial fibrillation.

Certain pharmacologic agents should be avoided or used with caution in HCM. Nondihydropyridine calcium channel blockers, such as nifedipine and amlodipine, should be avoided because they cause peripheral vasodilation, which may result in decreased LV filling and worsening of outflow tract obstruction. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, which also cause peripheral vasodilation, should be avoided. Diuretics, if deemed necessary, should be used cautiously, because subjects with HCM often have stiff ventricles that require high filling pressures. Digoxin is not favored in HCM because its positive inotropic effect may worsen LVOT obstruction. Finally, drugs such as dopamine, dobutamine, and

norepinephrine can have deleterious effects in the treatment of acute hypotension due to the positive inotropic effects and should not be used. For cases of refractory hypotension that do not respond to IV fluid administration, phenylephrine, a pure alpha agonist that causes vasoconstriction, can be used.

Septal Myectomy

Septal myectomy is considered the most definitive treatment for patients with medically refractory, symptomatic, obstructive (resting or latent gradient of 50 mm Hg or more) HCM.[4] In contrast, subjects with gradients >50 mm Hg but no or only mild symptoms are generally treated medically until more severe symptoms manifest. Young patients with marked LVOT obstruction (gradient ≥ 75 mm Hg) should be considered for septal myectomy despite the lack of significant symptoms. In assessing risk and benefit of septal myectomy, the young age of this subgroup decreases the operative risk. Septal myectomy is not indicated in midcavity obstruction. However, in one study, patients with apical hypertrophy complicated by progressive, drug-refractory diastolic heart failure with severely limiting symptoms experienced improved functional status following apical myectomy.[40]

Septal myectomy involves resecting part of the proximal septum through an aortotomy so that the outflow tract obstruction is lessened (Fig. 22.12). Sometimes myectomy may be combined with other cardiac surgery such as coronary artery bypass surgery, mitral valve repair, or mitral valve replacement.

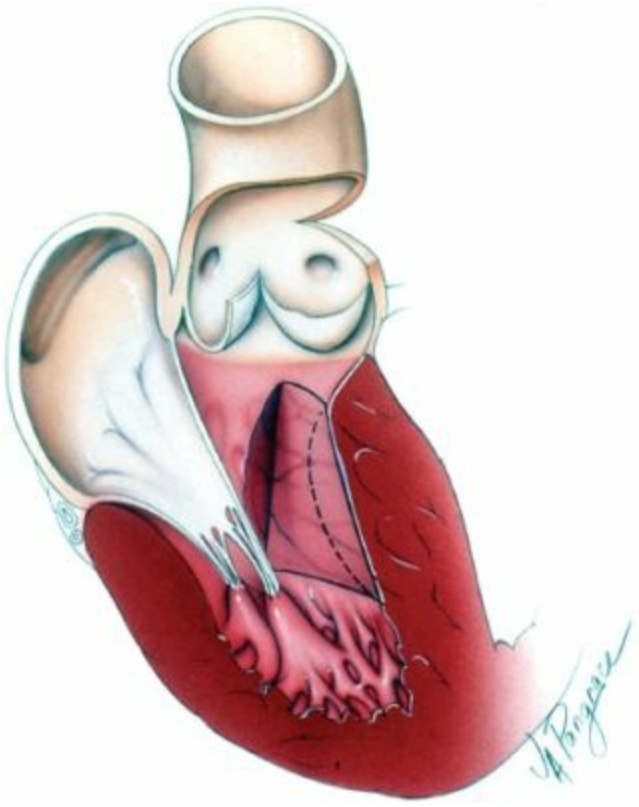

FIGURE 22.12 Septal myectomy. Septal myectomy involves resecting a portion of the proximal septum.

Operative mortality for isolated myectomy is low, at approximately 0% to 4%.[41–45] Increasing age and concomitant cardiac procedures may increase the surgical risk. Septal myectomy is associated with high success rates in decreasing LVOT gradients[46–48] and in improving symptoms[46,48–50] and exercise capacity.[47] Symptom improvement occurs from decreasing the LVOT gradient as well as decreasing the severity of any associated mitral regurgitation. Results postmyectomy are durable. Rarely is reoperation needed secondary to recurrence of LVOT obstruction.[4]

Long-term survival in HCM patients undergoing isolated myectomy is 93% to 96% at 5 years and 83% to 87% at 10 years.[44,51] Multivariate predictors of overall mortality include age ≥50 years at time of surgery, concomitant coronary artery bypass graft surgery, female gender, history of preoperative atrial fibrillation, and left atrial diameter of ≥46 mm.[45] For patients undergoing a myectomy combined with other cardiac surgery, primarily coronary artery bypass graft surgery or valve surgery, 5-year survival was 80% and 10-year survival was also 80%.[51]

Retrospective, nonrandomized data suggest that long-term survival for HCM subjects undergoing myectomy does not differ significantly when compared to the age- and sex-matched general population.[44] Furthermore, myectomy patients had higher survival rates than obstructive HCM patients who did not undergo surgery.[44] Thus, myectomy patients appear to fare no worse than the general population. Although randomized comparisons are needed, nonrandomized data suggest that survival may actually be improved in HCM patients who undergo myectomy.[44]

Preexisting conduction abnormalities influence the likelihood of needing permanent pacemakers postmyectomy. Left bundle branch block is common after surgical myectomy, occurring in 93% of subjects.[52] Thus, subjects with preexisting right bundle branch block are at high risk for requiring a permanent pacemaker postmyectomy. In subjects with normal conduction systems on ECG, there was a 2% rate of permanent pacemaker implantation postmyectomy, whereas for patients with preexisting conduction abnormalities, there was a 10% incidence of permanent pacemaker implantation.[52]

Percutaneous Alcohol Septal Ablation

For patients with medically refractory HCM and resting or provocative gradients ≥50 mm Hg who are poor surgical candidates or for those who choose not to undergo open heart surgery, alcohol septal ablation is another option (Fig. 22.13). In the late 1990s, unbridled enthusiasm for alcohol ablation resulted in the fact that by 2000, >3,000 alcohol ablations had been performed for HCM, more than the number of myectomies

performed since the introduction of myectomies approximately 40 years ago.[53] This optimism has been tempered and presently, alcohol ablation is considered second-line therapy behind myectomy for medically refractory, obstructive HCM.[54]

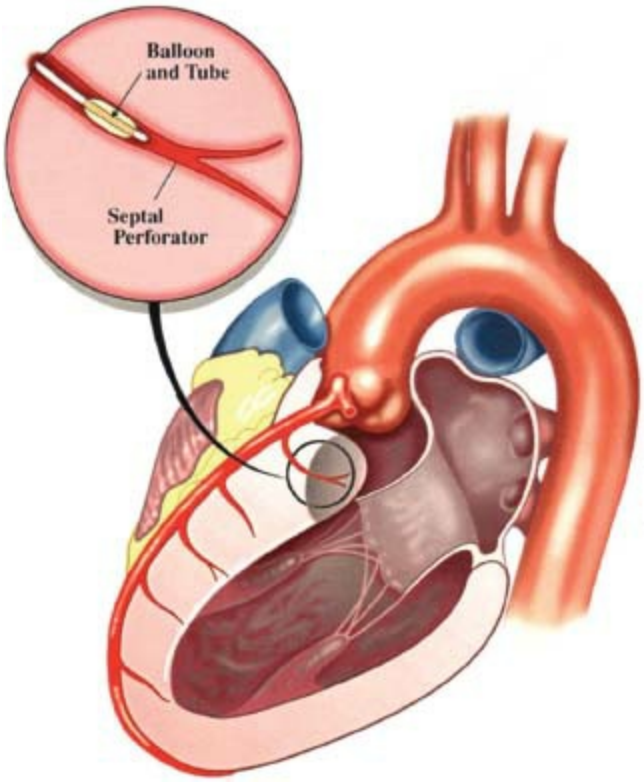

FIGURE 22.13 Alcohol septal ablation. In alcohol septal ablation, a balloon is inflated in the proximal septal perforator and alcohol is injected into the septal artery through the distal port of the balloon. The goal is to create a controlled myocardial infarction of the proximal septum, resulting in shrinkage of the septum and lessening of the LVOT obstruction.

Review of the patient's cardiac anatomy is critical in selecting subjects for alcohol ablation. In order for alcohol ablation to succeed, LVOT obstruction needs to be secondary to contact of the mitral valve with the proximal septum. If the LVOT obstruction actually occurs in the mid-distal LV cavity, then alcohol ablation will not be of benefit.

Because of the lack of randomized controlled trials and a suitable control population, alcohol ablation has not been shown to improve survival. Alcohol ablation does result in decreased LVOT gradients and an improvement in symptoms,[21,55,56] with persistence of benefit at 2 to 3 years.[57] Effectiveness of alcohol ablation extends to include the elderly population.[58] There is also a decrease in LV filling pressures[59] and a decrease in septal thickness.[56,60] In 3-month follow-up data, we reported a decrease in LVOT gradient from 64 to 28 mm Hg and an improvement in New York Heart Association (NYHA) class from 3.5 to 1.9 after alcohol ablation.[56] Predictors of

unsatisfactory outcomes after alcohol septal ablation include a residual LVOT gradient after ablation of >25 mm Hg in the cardiac catheterization lab as well as a peak creatinine kinase (CK) of <1,300 U/L.[61]

At the Cleveland Clinic, most alcohol ablations have been performed on elderly, suboptimal surgical candidates. We generally prefer that the septum be between 1.8 and 2.5 cm, to provide a safety margin; if the septum is too thick, favorable ablation results may be difficult to attain, whereas if it is too thin, the patient is at higher risk for development of a ventricular septal defect. A septum <1.8 cm thick in a patient with the clinical picture of HCM often indicates that mitral valve abnormalities, such as long leaflets, abnormal insertion of the papillary muscles, or anterior displacement of the mitral valve apparatus may be the primary etiology for the LVOT obstruction. Such mitral valve abnormalities contraindicate alcohol septal ablation.

Complications of alcohol ablation include right bundle branch block,[52,62,63] complete heart block (requiring a permanent pacemaker), a large anterior wall myocardial infarction, ventricular tachycardia or fibrillation, and pericarditis. The risks of alcohol ablation include a 2% to 4% procedural mortality rate and a 9% to 27% incidence of patients requiring permanent pacemakers.[52,57,59,60,63,64]

Alcohol ablation, unlike septal myectomy, results in myocardial scar. Thus, a theoretical risk exists that alcohol ablation may increase the risk of SCD, especially in light of the fact that an arrhythmogenic substrate is already present with HCM. One study of 123 HCM patients who already had implantable cardioverter-defibrillators (ICDs) for primary prevention of SCD and were undergoing alcohol ablation found that alcohol ablation was not proarrhythmic.[65] This is in contrast to other published studies that have shown that ICD therapy was fourfold more common after alcohol ablation than following the more established surgical myectomy.[4] However, SCD has been reported several months after successful alcohol ablation.[66]

Comparison of Septal Myectomy and Alcohol Ablation

Overall, comparisons between myectomy and alcohol ablation indicate that both are effective in reducing LVOT gradient and improving symptoms, but the procedural complication rate exceeds that of myectomy[67] (Table 22.3). A comparison of the two modalities at the Cleveland Clinic suggested slight superiority of myectomy on the basis of larger and more consistent reductions in LVOT gradient.[56]This nonrandomized study of 51 HCM patients who underwent either myectomy or alcohol ablation found that of the 26 patients who underwent septal myectomy, LVOT gradient was significantly reduced, from 62 mm Hg premyectomy to 7 mm Hg postmyectomy. In the 25 alcohol ablation subjects, LVOT gradient was significantly reduced from 64 mm Hg preablation to 28 mm Hg. New York Heart Association class improved significantly, from 3.3 to 1.5 in the myectomy group and from 3.5 to 1.9 in the alcohol ablation group.[56] In this

study, five patients underwent myectomy secondary to persistent provocable gradients from alcohol ablation.

TABLE
22.3 Comparison of Septal Myectomy and Percutaneous Alcohol Septal Ablation

	Surgical Myectomy	Percutaneous Alcohol Septal Ablation
Invasiveness	Invasive	Less invasive
Onset of reduction in LVOT gradient	Instantaneous	Some effect instantly, but more often 6–12 mo for full effect
Procedural mortality[4,77]	1%–2%	1%–2%
Effect on LVOT gradient[4,77]	Decreases to <10 mm Hg	Decreases to <25 mm Hg
Conduction abnormality postprocedure[54]	Left bundle branch block	Right bundle branch block
Recovery time	1 wk	A few days
Need for permanent pacemaker—all patients[54,60]	3%–10%	12%–27%
Need for permanent pacemaker if no preexisting conduction abnormalities[54]	2%	13%
Length of follow-up	30–40 y	6–8 y
Success rate	>95%	>85%

A recent meta-analysis of septal myectomy versus alcohol ablation concluded that there is a similar mortality rate and functional status between the two procedures, but with increased conduction abnormalities and a higher postintervention LVOT gradient.[68]

Another nonrandomized cohort study of 44 patients found similar improvements in LVOT gradients and NYHA classification after either myectomy or ablation.[69] However, in this study, myectomy was noted to have superior results with respect to exercise parameters, including peak oxygen consumption and peak work rate achieved.

A nonrandomized study compared 41 alcohol ablation patients from Baylor to an age- and gradient-matched cohort of myectomy patients performed at the Mayo Clinic.[64] The functional and hemodynamic changes after 1 year were similar in the two groups, although the alcohol ablation group did have a significantly higher incidence of permanent pacing.[64]

Associated severe coronary artery disease or valvular abnormalities that warrant surgical intervention are factors that further tip the balance toward myectomy over alcohol ablation, for concomitant cardiac surgery can be performed at the time of myectomy. It is crucial to completely assess the degree and etiology of any mitral regurgitation that exists. A subject with HCM and severe mitral regurgitation secondary to SAM could potentially be a candidate for either septal myectomy or alcohol ablation if the primary abnormality is the septal thickness, and it is believed that reducing the septal thickness will alleviate the SAM. In contrast, a subject with HCM and severe mitral regurgitation secondary to intrinsic valvular abnormalities would not be a good

candidate for alcohol ablation because in this instance, decreasing the septal thickness would not positively impact the mitral regurgitation.

Permanent Pacemaker Implantation

Pacemaker implantation has been used historically to alleviate the symptoms of HCM, but this procedure has fallen out of favor. It was hypothesized that initiating ventricular contraction at the right ventricular apex and distal septum would alter the sequence of ventricular contraction such that the outflow gradient would be decreased and symptoms improved. However, this was not borne out in double-blind, randomized crossover trials.[70,71] Furthermore, in a nonrandomized, concurrent cohort study of 39 patients who underwent either surgical myectomy or received permanent pacemakers, surgical patients demonstrated larger decreases in LVOT gradient (76 to 9 mm Hg versus 77 to 55 mm Hg) and larger improvements in symptoms and exercise duration.[72]

INFECTIVE ENDOCARDITIS PROPHYLAXIS

While the latest American College of Cardiology (ACC)/American Heart Association (AHA) guidelines reversed the long-standing recommendation of routine antimicrobial prophylaxis for infective endocarditis in patients with HCM, it is notable that this change was not done in response to any new data.[73] Given that infective endocarditis is a well-documented and profound complication in patients with HCM, routine antimicrobial prophylaxis for infective endocarditis should be strongly considered.[74]

SUDDEN CARDIAC DEATH

The most serious complication of HCM is SCD, with an incidence of 0.1% to 0.7% per year.[14,15] The first presentation of HCM may be SCD, generally from ventricular arrhythmias. Among subjects with HCM, SCD is more common in adolescents and young adults,[75] but it can occur at any age.

Holter monitors have been recommended as a means of risk stratification for primary prevention of SCD. Ventricular arrhythmias are very common, with 88% of HCM patients having PVCs and 31% of HCM patients having nonsustained ventricular tachycardia on 24-hour Holter monitoring.[76] Nonsustained ventricular tachycardia had a 95% negative predictive value and 9% positive predictive value for SCD.[76]Thus, the absence of nonsustained ventricular tachycardia on 24-hour Holter is reassuring, but is nonspecific if present. Electrophysiologic testing has not been shown to be predictive of SCD in HCM, and presently has little role in risk stratification in HCM.[4]

While survivors of SCD warrant an ICD, primary prevention of SCD in HCM patients is less well defined. An ICD firing rate of 11% per year has been reported in

ICDs implanted for secondary prevention and 5% per year when implanted for primary prevention of SCD.[77] ACC/AHA/North American Society of Pacing and Electrophysiology 2002 guidelines designate ICD implantation for secondary prevention to be a Class I indication, whereas ICD implantation for primary prevention in HCM is a Class IIb indication.[78] Antiarrhythmic therapy for primary prevention generally is not recommended in asymptomatic patients.

Major risk factors for SCD in HCM are shown in Table 22.4 and include LV wall thickness >30 mm[10], prolonged or repetitive episodes of nonsustained ventricular tachycardia on Holter monitor[79], family history of SCD, no change or a decrease in blood pressure with exercise[80], and syncope or near syncope.[13,81] An LVOT gradient of ≥30 mm Hg is considered a minor risk factor for SCD.[82]

TABLE
22.4 Risk Factors for SCD

- LV wall thickness >30 mm
- Prolonged or repetitive episodes of nonsustained ventricular tachycardia on Holter monitor
- Family history of SCD
- No change or a decrease in blood pressure with exercise
- Syncope or near syncope

In a multicenter registry study of ICDs implanted between 1986 and 2003 in 506 unrelated patients with HCM, there was a 3.6% rate per year of appropriate ICD therapy for primary prevention of SCD.[83] Of the patients that had an ICD placed for primary prevention and experienced appropriate therapy for ventricular tachycardia, 35% had only one risk factor. This suggests that a single risk factor for SCD may be enough to warrant implantation of an ICD in select patients with HCM.

HCM AND ATHLETICS

Patients with HCM should be restricted from competitive athletics or strenuous athletic activity because of the risk for SCD.[84,85] Low-level exercise and participation in informal recreational activities, such as bowling and golf, are generally acceptable but should be considered on an individual basis.

ATRIAL FIBRILLATION AND HCM

Atrial fibrillation, which occurs in 28% of HCM subjects, is the most prevalent

sustained arrhythmia in HCM.[14] HCM subjects with atrial fibrillation have lower long-term survival rates compared to those in sinus rhythm.[14,86] One study attributed the lower survival to an excess of heart failure-related deaths as opposed to SCD.[86]

Atrial fibrillation is a significant cause of morbidity in HCM. Strokes occur in 6% of subjects with HCM, nearly all of whom have atrial fibrillation.[87] Medical treatment of persistent atrial fibrillation in HCM includes anticoagulation with warfarin and rate control, preferably with beta-blockers.

HCM patients who develop atrial fibrillation may present with acute clinical deterioration. The hypertrophied ventricle is stiff and may require atrial contraction for optimal filling. Losing the atrial contribution to ventricular filling may result in decreased cardiac output and potentially pulmonary edema. The substantial morbidity and increased mortality associated with atrial fibrillation in the setting of HCM justifies an aggressive approach to attempting to maintain sinus rhythm.

Given that HCM patients often tolerate atrial fibrillation poorly, expeditious TEE followed by electrical cardioversion is generally preferred. Amiodarone or sotalol is the preferred therapy for pharmacologic conversion to sinus rhythm or maintenance of sinus rhythm in HCM patients. Digoxin should be avoided in HCM patients, particularly in those with resting or latent obstruction, because of its positive inotropic effect. Atrial fibrillation ablation or the maze procedure may be considered for those with refractory, highly symptomatic atrial fibrillation. In a small number of patients with severe HCM and atrial fibrillation, we have performed combined maze-myectomy procedures.[88]

HCM AND PREGNANCY

Although pregnant women with HCM are at slightly higher risk for maternal or fetal complications than the average pregnant woman, the absolute morbidity and mortality rate for asymptomatic pregnant women with HCM is low.[89,90] However, patients with resting or provocable LVOT obstruction should be referred to a high-risk obstetrician for care in collaboration with a cardiologist. Generally, such women do not need to undergo cesarean section and can deliver vaginally. Adequate fluid intake during pregnancy should be emphasized in pregnant women with HCM to ensure that the LV does not become underfilled. Certain beta-blocking drugs, such as extended-release metoprolol, can be continued during pregnancy but require increased monitoring for fetal bradycardia. While there is a lack of evidence, there is a theoretical concern for sympathetic blockade and loss of venous return from the lower extremities with spinal anesthesia. However, there are case reports of successful use of both regional and general anesthesia in patients with HCM.[91]

NONOBSTRUCTIVE HCM

Nonobstructive HCM is diagnosed when there is ventricular thickness of >15 mm in the absence of other etiologies, and when no significant LVOT obstruction exists (i.e., LVOT gradient <30 mm Hg with provocation). Approximately 30% of HCM patients do not have LVOT obstruction. Provocative maneuvers used to exclude latent obstruction include Valsalva, amyl nitrite, and exercise. Because some patients have difficulty performing a Valsalva, we generally challenge patients with amyl nitrite when we are trying to exclude latent obstruction.

The treatment of patients with nonobstructive HCM is difficult and less effective than in those with obstructive disease. Pharmacologic therapy is the primary modality of treatment. Beta-blockers may be used to control heart rate and decrease contractility, and calcium channel blockers may improve diastolic function. Alcohol ablation and septal myectomy are not performed in subjects who do not have LVOT obstruction. Over time, HCM may become "burned out" and evolve into a picture similar to a dilated cardiomyopathy, with decreased LV systolic function and a dilated LV. Such a subset comprises approximately 5% of all HCM subjects.[4] In patients with symptoms and signs of congestive heart failure, standard heart failure therapy such as beta-blockers, diuretics, ACE inhibitors, and digoxin may be necessary. Heart transplantation is an option for end-stage nonobstructive HCM.

CONCLUSIONS

HCM is the most common genetic cardiovascular disorder and the most common cause of SCD in young adults. A harsh systolic murmur along the left sternal border that increases with Valsalva in conjunction with brisk carotid upstrokes strongly suggests HCM. TTE is presently the preferred modality for diagnosing HCM, although in the near future, HCM may be diagnosed by genetic testing. Beta-blockers are first-line medical therapy for HCM, with verapamil and disopyramide as alternatives. Septal myectomy is first-line therapy for obstructive HCM (generally, LVOT gradient >50 mm Hg) that is refractory to medical therapy, with alcohol septal ablation only in patients deemed poor operative candidates The available therapeutic options for HCM are associated with high success rates in improving symptoms and decreasing LVOT gradients in combination with low mortality rates.

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QUESTIONS AND ANSWERS

Questions

1. All of the following increase the gradient in hypertrophic cardiomyopathy (HCM) except:
   a. Valsalva maneuver
   b. Squatting
   c. Amyl nitrite
   d. Isoproterenol

2. Which of the following is an appropriate screening protocol for family members of patients with HCM?
   a. Serial ECG and echocardiogram every 5 years for a 14-year-old child of an HCM patient.
   b. Serial ECG and echocardiogram on a first-degree adult relative every 10 years of an HCM patient.
   c. Serial ECG and echocardiogram on a gene-negative first-degree relative of a patient who is gene positive for a β-myosin heavy-chain mutation every 5 years.
   d. Cessation of screening for a myosin-binding protein C mutation positive first-degree relative of a patient with a myosin-binding protein C mutation positive patient.
   e. Serial ECG and echocardiogram every 18 months for a 17-year-old child of an HCM patient.

3. All of the following are true of the Brockenbrough response except:
   a. There is increased filling of the left ventricle (LV) with the compensatory pause.
   b. The premature beat causes a decrease in contractility in HCM but not in normal individuals.
   c. There is an increase in ventricular pressure in both normal individuals and in patients with HCM.
   d. There is a decrease in aortic pressure in HCM.
   e. There is an increase in aortic pressure in normal individuals.

4. Echocardiography is the primary clinical modality for diagnosing HCM. Which of the following findings is (are) commonly seen in HCM?
   a. A septum >15 mm
   b. Preclosure of the aortic valve
   c. Anterior displacement of the papillary muscles
   d. Elongated mitral leaflets
   e. All of the choices

5. All of the following drugs are useful in the treatment of HCM except:
   a. Metoprolol
   b. Disopyramide
   c. Enalapril
   d. Diltiazem
   e. Phenylephrine

6. Which of the following is a risk factor for sudden death in HCM?
   a. Septal thickness >30 mm
   b. Prolonged or repetitive episodes of nonsustained ventricular tachycardia
   c. Family history of sudden death
   d. Syncope or near syncope
   e. No change or a decrease in blood pressure with exercise
   f. All of the choices

7. All of the following are appropriate medications to treat patients with HCM and atrial fibrillation except:
   a. Sotalol

b. Metoprolol
c. Amiodarone
d. Digoxin
e. Verapamil

Answers

1. Answer B: The Valsalva maneuver decreases venous return and thus decreases ventricular volume, thus accentuating the systolic anterior motion (SAM) and thus increasing the gradient. Amyl nitrite causes peripheral vasodilation and tachycardia. Both of these factors cause the LV to decrease in size and thus increase the gradient. Isoproterenol increases the contractility and thus decreases ventricular volume, which increases the gradient. Standing decreases venous return and decreases ventricular volume. Squatting increases the vascular resistance and venous return, thus increasing ventricular volume and reducing the SAM, which reduces the gradient.

2. Answer E: First-degree relatives of a mutation-positive HCM patient who are mutation negative do not need routine screening. If a mutation is identified in the index case and the first-degree relative is also gene positive, then they should have routine screening ECG and echocardiogram. If no gene mutation is identified in the index patient, then all first-degree relatives should be screened. Screening should occur every 12 to 18 months while in adolescence. This frequent cycle should be followed into early adulthood at which point screening can be scaled back to a minimum of every 5 years. Exceptions to the rule include relatives who do not have the gene mutation that has been identified in the index HCM patient in which case screening can be stopped.

3. Answer B: The Brockenbrough maneuver causes the contractility to increase in both normal individuals and in patients with HCM. All of the other statements are true.

4. Answer E: The definition for the diagnosis of HCM is that the septum must be 15 mm or greater in the absence of any disease known to cause hypertrophy. Preclosure of the aortic valve is commonly seen on M-mode echo of the aortic valve in the presence of left ventricular outflow tract (LVOT) obstruction. Anterior displacement of the papillary muscles is frequently seen in HCM and contributes to the development of outflow tract obstruction. Elongated mitral leaflets have been recognized for some time in HCM but are now more easily seen with better instrumentation.

5. Answer C: Enalapril is an angiotensin-converting enzyme inhibitor, and it can worsen obstruction by decreasing both preload and afterload. Metoprolol is a beta-blocker and thus, by slowing the heart rate, may allow for prolonging diastolic filling and lessen the provocable outflow tract gradient. It is also a negative inotrope. It is somewhat less helpful if there is resting obstruction. Disopyramide has a negative inotropic effect on the LV and thus frequently diminishes LVOT obstruction. Diltiazem is a calcium channel blocker that has some negative inotropic effect and may lessen LVOT obstruction. In addition, it improves diastolic filling. Phenylephrine may be life saving in the treatment of hypotension-associated severe LVOT obstruction. It is a pure vascular constrictor and does not increase the contractility of the heart.

6. Answer F: Although all of these factors have been shown to have a high negative predictive accuracy, the positive predictive accuracy is low.

7 Answer D: Digoxin should be avoided as it increases contractility, which in turn can increase obstruction. All other medications are reasonable as part of a rhythm- or a rate-controlling strategy.

CHAPTER

Congenital Heart Disease in the Adult

Richard A. Krasuski and David S.Majdalany

Adults with congenital heart disease (CHD) are a rapidly growing population of patients owing to advances in the diagnosis and treatment of children with CHD. Most children with CHD are now expected to survive to adulthood either with or without the aid of surgical correction or palliation. According to recent estimates, there are now nearly a million adults with CHD, and these numbers should continue to rise with further advancements in diagnosis and treatment. Although ideally served by cardiologists with advanced training in adult CHD, most of these patients receive the majority of their care from primary care physicians and general cardiologists, even though few cardiology training programs have a formalized adult CHD curriculum. Being aware of the often unique clinical presentations, and having a general understanding of the anatomy and the pathophysiologic consequences of congenital disease is vital to facilitating the timing of percutaneous, electrophysiologic, and surgical interventions.

GENERAL CONCEPTS

An organized approach to diagnosis and management is especially important in patients with CHD, and the critical first step is gathering historical data. Reviewing the pediatric and operative records, if available, is essential in understanding the complexities of the cardiac and vascular anatomy and to define the outcomes of previous diagnostic studies and surgeries. Surgical procedures have changed considerably over the last several decades, and anatomic presumptions based on current practice may not apply.

Certain signs and symptoms should prompt an extensive evaluation of adults with CHD, particularly syncope and progressive exertional dyspnea. Arrhythmias are not uncommon in adults with CHD and often originate near the myocardial scars of previous

surgeries. The most common of tachycardia seen is macroreentry within the atrial muscle. Supraventricular arrhythmias, such as atrial flutter or fibrillation, are often poorly tolerated due to a dependence on atrial mechanical function. Ventricular arrhythmias, typically microreentrant ventricular tachycardia, which can result in sudden death, may develop in adult patients with CHD as a late complication of prior ventriculotomy and patching of a ventricular septal defect (VSD). The incidence of ventricular arrhythmias in adults with corrected tetralogy of Fallot (TOF) is estimated between 0.5% and 6%, with independent risk variables that include a widened QRS interval (>180 milliseconds) on a surface electrocardiogram (ECG), significant right ventricular dilation, and older age at time of surgical repair.

Hemodynamic derangements can be quite subtle, such as pulmonic regurgitation following a patch outflow repair of TOF. Since pulmonary regurgitation has a low-pressure gradient, it can be missed during auscultation and routine echocardiography and can eventually result in right ventricle (RV) enlargement and increased risk of sudden death.

Diagnostic imaging is a critical adjunct, and less invasive modalities such as echocardiography are an important first step (see Chapter 24). Limitations of echocardiography include difficult windows due to excessive scar tissue from previous surgeries, concomitant lung disease, and obesity. Subsequent computerized tomography (CT) scanning or magnetic resonance imaging (MRI) may add substantially to the anatomic description, especially in patients with unclear great vessel or pulmonary vascular anatomy. The use of MRI has expanded with more widely available scanners and simplified scanning protocols. It is important to remember, however, that CT scanning is complicated by the need for intravenous contrast and exposure to radiation, and MRI is generally not compatible with current implantable cardiac devices.

Diagnostic cardiac catheterization, though generally performed later in the diagnostic workup of CHD patients than in the past, remains the gold standard for pressure measurement, cardiac output calculation, and vascular resistance determination. The relative size of shunts lesions can be assessed using oximetry, and the hemodynamic consequences of additional blood flow can be assessed. Most importantly, cardiac catheterization affords the opportunity to intervene and palliate or repair anatomic defects or to clarify the suitability of further surgical intervention.

Anatomic shunting can be quantified in the catheterization laboratory by examining the blood oxygen saturations in the respective chambers. The mixed venous (MV) saturation is the saturation of blood returning to the right atrium (RA) with contributions from the inferior vena cava (IVC), superior vena cava (SVC), and coronary sinus (CS). IVC saturation is normally higher than the SVC due to high renal blood flow and less oxygen extraction by the kidney. The CS saturation is very low, but its volume of contribution is negligible and usually ignored. To normalize the MV saturation, three times the SVC saturation is added to the IVC saturation and the sum divided by 4.

Because so much mixing of blood with differing saturations occurs in the RA, an 11% increase in oxygen step-up (saturation increase from a chamber to its successive chamber) is required to diagnose a shunt lesion between the SVC and the RA. A 7% increase is necessary to detect a shunt between the RA and the RV and a 5% increase to detect a shunt between the RV and the pulmonary artery (PA). A quick and simple measure of the overall size of a left-to-right shunt ratio can be obtained by using the formula: (aortic saturation-MV saturation)/(PV saturation-PA saturation). The PV saturation can be assumed to be 97% if not directly measured.

In general, a "significant shunt" is present when the shunt ratio is ≥1.5:1.0. This simplified definition may not apply to older adults, however. As pulmonary hypertension develops and RV compliance falls, a left-to-right shunt that was 3:1 for 30 years may become <1.5:1 due to the gradual reversing of the shunt. In fact, the left-to-right shunt may totally reverse at some point and result in arterial desaturation, the so-called Eisenmenger syndrome. The significance of a shunt in the adult must, therefore, be examined in the context of the other hemodynamics, chamber sizes, and the history of the defect over time.

Pulmonary hypertension is a frequent complication of certain CHDs. It can be secondary to pulmonary venous hypertension from elevated left-sided filling pressures, or the result of systemic-to-PA shunting. For unclear reasons, shunts proximal to the tricuspid valve (atrial septal defects [ASDs] or partial anomalous pulmonary venous return) infrequently result in pulmonary hypertension (~15% of cases) despite high pulmonary blood flow. The development of pulmonary hypertension from shunts distal to the tricuspid valve, however, is very dependent on pulmonary blood flow. For example, a large unrestricted VSD may not result in pulmonary hypertension if the pulmonary circuit is protected by concomitant pulmonary valvular or subvalvular obstruction.

To help differentiate the cause of pulmonary hypertension, the pulmonary vascular resistance should be determined: (mean PA pressure-mean pulmonary capillary wedge pressure [mm Hg])/(pulmonary blood flow [liters per minute]). Higher resistances (>7 Wood units or a ratio of the pulmonary-to-systemic vascular resistance of >0.5) have been associated with considerably higher perioperative mortality. In addition, assessment of pulmonary vascular reactivity with endothelium-dependent vasodilators, such as inhaled nitric oxide or intravenous adenosine, may provide additional prognostic information in these patients by confirming whether any of the observed pulmonary hypertension has a vasoconstrictor component. In patients with shunt lesions and pulmonary arterial hypertension (mean PA pressure ≥25 mm and mean pulmonary capillary wedge pressure ≤15 mm Hg), growing evidence supports the use of selective pulmonary vasodilator therapy (such as endothelin blockers and phosphodiesterase-5 inhibitors) to improve exercise capacity and reduce symptoms. No patients with CHD should be started on these medications, however, without first undergoing thorough

hemodynamic assessment in the catheterization laboratory.

TYPES OF CONGENITAL LESIONS

Congenital heart lesions can be divided into three general categories (by descending incidence): simple shunt lesions, obstructive lesions, and complex lesions—acyanotic and cyanotic. The most frequently encountered abnormalities in these categories are mentioned below.

Shunt Lesions

Intracardiac shunts are the most common form of congenital heart lesion and are frequently diagnosed in otherwise healthy adults. They are associated with increased pulmonary blood flow, which can lead to right heart chamber enlargement and arrhythmias, as well as pulmonary hypertension. The surgical correction of many of these lesions has been determined to be safe and efficacious. Recently, percutaneous device closures have been increasingly utilized in order to avoid the morbidity and mortality of surgery. There are three main types of shunt lesions to be aware of: ASD, VSD, and patent ductus arteriosus (PDA). All these lesions demonstrate left-to-right shunting under normal physiologic conditions.

Atrial Septal Defect

The ASD is the most common congenital heart defect encountered in adults (excluding mitral valve prolapse and bicuspid aortic valve), accounting for up to 15% of all adult CHD. It results from the failure of proper embryologic development of the atrial septum. Almost a third of patients with ASD will have associated additional malformations such as pulmonary stenosis, VSD, mitral valve prolapse, subaortic stenosis, aortic coarctation, and anomalous pulmonary venous drainage.

There are many different types of ASD (see Chapter 24), the most common of which (75% of the cases) is the secundum ASD, in which the defect lies in the middle of the atrial septum. The secundum ASD is often mistaken for other abnormalities or overlooked because the symptoms associated with it, typically fatigue, palpitations, and breathlessness, can be subtle and nonspecific. Other less common variations of ASD include the sinus venosus ASD in which there is abnormal fusion of the vena cava (superior or inferior) to the left atrium. This defect is almost always associated with partial anomalous return of the pulmonary veins (right superior or both right pulmonary veins draining into the SVC or RV). Because of its location, this defect can be missed on transthoracic echocardiography and usually requires either transesophageal echo or advanced radiographic imaging to make the diagnosis. The primum ASD involves the lower portion of the atrial septum and typically affects the ventricular septum as well (the so-called AV canal defect). Both AV valves are structurally abnormal and the

mitral valve is typically cleft. This defect is commonly seen in patients with trisomy 21 (Down syndrome). The least common ASD, the CS septal defect, involves unroofing of the CS, which results in shunting from the left to the RA. Commonly, a persistent left SVC or an abnormal pulmonary venous drainage accompanies CS ASD. Important differences in the clinical findings among the various types of ASD are listed in Table 23.1.

TABLE
23.1 Unique Features of the ASDs

	Secundum ASD	Primum ASD	Sinus Venosus ASD
Unique anatomical features	Partial anomalous pulmonary venous return (only ~10%)	1. Mitral valve involvement 2. ±VSD	Partial anomalous pulmonary venous return
Physical exam findings	1. Fixed split S_2 2. Pulmonic outflow murmur	1. Same as Secundum ASD 2. Murmurs of MR ± VSD	Same as secundum ASD
ECG	1. RSR' pattern 2. Incomplete RBBB 3. ± Right axis	1. RBBB 2. Left axis 3. ±1 degree AV block	1. Same as secundum 2. ± Leftward shifted P-wave axis (inverted P in lead III)

ASD should be suspected whenever right heart enlargement is present without an alternative explanation. Physical examination findings, such as a fixed split second heart sound (due to loss of differential effects on right- and left- sided filling pressures from a drop in intrathoracic pressure that normally occurs during inspiration) and a pulmonic outflow murmur (the result of increased pulmonary blood volume from shunting), can also be overlooked. The flow of blood across the defect (shunt) is determined by the size of the defect and the compliance of the atria. Occasionally, patients can present late in life with ASD-related symptoms when the left atrial pressure rises because of a stiff left ventricle and diastolic dysfunction (usually the result of long-standing hypertension or coronary artery disease). On electrocardiography, an incomplete right bundle branch block, right-axis deviation, abnormal P-wave axis, and right atrial enlargement are commonly seen. Due to anatomic position of the conduction bundles, a superior left axis is usually noted in primum ASD. On chest x-ray prominent pulmonary arteries, right atrial and ventricular enlargement and pulmonary plethora can be seen.

The larger the left-to-right shunt in patients with ASD, the greater is the risk for long-term complications such as atrial fibrillation (typically occurring in the fifth decade) and pulmonary hypertension. The latter condition affects up to 5% to 10% of adults with ASD, and if left uncorrected can result in Eisenmenger syndrome. In Eisenmenger syndrome, the pulmonary vascular resistance increases to the point that shunting is reversed (becoming right to left) and systemic oxygenation decreases. Patients with this complication will not improve their oxygen saturation when oxygen is administered to them (the telltale sign of a right-to-left shunt). Multiple complications

eventually ensue, and until recently, this condition was considered irreversible. Another condition associated with ASD is stroke, which presumably results from paradoxical embolization (blood clots forming in the extremities and reaching the cerebral circulation by passing through the ASD).

The guideline-based indication to repair an ASD is right heart enlargement from volume overload resulting from the ASD, regardless of whether the patient is symptomatic or asymptomatic. At this time, only the secundum ASD has been successfully occluded through percutaneous methods. All other types of ASD require surgical closure.

Repair of an ASD may also be reasonable in the context of paradoxical embolism or documented platypneaorthodeoxia and should be considered in the presence of a hemodynamically significant net left-to-right shunt and PA pressure or pulmonary vascular resistance <2/3 systemic levels or if the pulmonary hypertension is vasoreactive. The timing of closure of an ASD appears important. Closure after the age of 40 is associated with an increased incidence of arrhythmias (i.e., atrial fibrillation) compared with closure before age 40. Epidemiologic evidence also suggests that long-term survival is worse with unrepaired defects, but the difference is lost as the patient is older at the time of repair and outcomes may be worsened with repair after pulmonary hypertension has become well established.

Ventricular Septal Defect

VSD is the most common congenital heart defect seen in children. Defects can occur at various locations in the septum but most commonly occur in either the membranous or the muscular portions (see Chapter 24). Perimembranous VSD is the most common (80% of the cases), occurring in the membranous septum and adjacent to the septal tricuspid valve leaflet. Small defects, typically muscular VSDs, often close spontaneously during childhood. One type of defect, the so-called outflow (or supracristal VSD), can be occluded by one of the aortic leaflets prolapsing into it. This can result in the development of rather significant and progressive aortic regurgitation. VSDs are often isolated lesions but are also common defects in complex abnormalities such as TOF and congenitally corrected transposition of the great vessels.

Small VSDs produce a very loud systolic murmur and frequently a palpable thrill at the left sternal border. Patients with small defects are asymptomatic and require regular follow-up without a need for intervention. Larger defects have less conspicuous murmurs.

Clinical presentation in adulthood depends on the defect size and the pulmonary vascular resistance. Left-to-right shunting across the defect can lead to left ventricular volume overload and pulmonary hypertension. Large defects are more likely to present in childhood with symptoms of heart failure. VSD is also the most frequent cause of Eisenmenger syndrome, with shunt reversal to right to left. The unrepaired adult may

present with symptoms of heart failure, exercise intolerance, infective endocarditis (IE), pulmonary hypertension, and cyanosis or arrhythmias.

On electrocardiography, patients with large VSD and significant pulmonary hypertension will have isolated right ventricular or biventricular hypertrophy. The chest x-ray typically is normal in patients with small VSD; however, in those with large left-to-right shunt, left atrial and left ventricular enlargement as well as increased pulmonary vascular markings may be noted.

Cardiac catheterization is helpful in assessing the operability of an adult patient with VSD and pulmonary hypertension, including quantification of shunting and assessment of pulmonary pressures, pulmonary vascular resistance, and pulmonary vasoreactivity.

VSD closure is indicated with evidence of left ventricular volume overload, large pulmonary-to-systemic flow (Q_p/Q_s >2), or in patients with history of IE. Closure of a VSD may also be reasonable in the setting of a Q_p/Q_s >1.5 with left ventricular systolic or diastolic dysfunction or with PA pressure and pulmonary vascular resistance <2/3 systemic levels. VSD closure is usually accomplished surgically, although some muscular VSD may be amenable to catheter device closure.

Patent Ductus Arteriosus

PDA, the second most common congenital heart defect seen in adults (~10% to 15% of all CHD in adults), is a persistent communication between the descending aorta and the left PA at the level of the left subclavian artery. It has been associated with maternal rubella. PDA is present as an isolated lesion in most adults, unlike in children where it is frequently seen with more complex heart defects. Patients with PDA have a continuous murmur (systole and diastole) that is often described as a "machinery murmur," heard best under the left clavicle and accompanied by a widened pulse pressure. Like in VSD, patients with a large, uncorrected PDA can present with dyspnea and easy fatigability as well as Eisenmenger physiology with differential cyanosis and clubbing.

The ECG of adults with PDA may be normal or show left atrial enlargement, left ventricular enlargement, or right ventricular hypertrophy (in setting of pulmonary hypertension). The chest x-ray may show cardiomegaly and increased pulmonary venous markings depending on the size of the shunt. The need for closure of a PDA in adults is uncommon. Defects can be ligated surgically or closed percutaneously (device closure or coils) depending on size.

Stenotic Lesions

Pulmonary Stenosis

Pulmonic stenosis (PS) is the most common congenital valve lesion to necessitate therapy in adults. It is occasionally associated with Noonan syndrome, in which the valve is usually dysplastic. Gradients across the pulmonary outflow tract can involve the valvular level, but may also involve the infundibulum (right ventricular outflow tract) and/or the peripheral pulmonary arteries. Careful tracking of the gradient is critical for decision making.

Patients may present with an asymptomatic systolic murmur or with exercise intolerance. Findings on cardiac examination depend on the severity of the PS, pathology of the valve, and any associated lesions. Patients may have elevated jugular venous pressure with a prominent "A" wave, a right ventricular heave, a systolic ejection murmur, an ejection click that decreases with inspiration, a wide splitting of S_2, and/or a reduced or an absent P_2.

On electrocardiography of PS, right atrial enlargement, right-axis deviation, and right ventricular hypertrophy may be noted. Chest radiography demonstrates right atrial enlargement, dilation of the PA, and occasionally vascular fullness in the left base greater than the right base (Chen sign) due to preferential blood flow to the left lung.

Generally, the diagnosis of PS is accomplished with echocardiography. An intervention is felt warranted when the peak instantaneous transvalvular gradient exceeds 60 mm Hg in an asymptomatic patient (mean Doppler gradient >40 mm Hg) or in a symptomatic patient with a peak gradient >50 mm Hg (mean Doppler gradient >30 mm Hg), though patients with lesser gradients may benefit if it can be clearly shown that exertional symptoms (typically exertional dyspnea) accompany elevated gradients during provocation. Interventions on PS can include percutaneous balloon valvuloplasty, surgical pulmonary valvotomy, or valve replacement with the balloon procedure generally favored.

Coarctation of the Aorta

Aortic coarctation (CoA) is a common congenital heart defect, accounting for approximately 8% of all congenital defects. It likely results from extraneous ductal tissue that contracts following birth. It is associated with Turner syndrome. Anatomically it can occur before, at the level of or after the ductus arteriosus, though adults with previously undiagnosed CoA will almost always have postductal lesions. The most common presentation in adults is the fortuitous discovery during secondary workup for systemic hypertension. Lower extremity and renal hypoperfusion leads to a hyperrenin state that may not abate even after coarctation repair. In most patients, there is upper-extremity hypertension and the development of collateral vessels around the coarctation to the lower extremity. These collateral channels result in a continuous murmur heard over the back, and involvement of the intercostal arteries leads to the familiar rib notching noted on chest x-rays. Extensive collateral vessels may mask the

severity of the obstruction by reducing the gradient across the coarctation. Associated cardiac defects include bicuspid aortic valve (present in up to 85% of cases), subaortic stenosis, VSD, mitral valve abnormalities, aortic aneurysms as well as cerebral aneurysms in the circle of Willis (seen in up to 10% of patients and which can lead to CNS bleeding).

Adults with CoA may present with hypertension and discrepant upper- and lower-extremity pulses. They may complain of claudication, leg fatigue, or exertional headaches. Accelerated coronary artery disease, stroke, aortic dissection, and congestive heart failure are common complications in the unoperated patient or those intervened on in childhood. On examination, hypertension is present in the right arm relative to the lower extremity. A radial-femoral pulse delay may be noted. There may be an ejection click with a systolic murmur in the setting of a bicuspid aortic valve. Continuous murmur in the parasternal areas and around the left scapula may be heard due to the flow through collateral vessels.

Electrocardiographic findings in aortic coarctation may include left ventricular hypertrophy with associated repolarization abnormalities. On chest x-ray, rib notching due to collateral vessels may be noted as well as dilation of the proximal aorta and a "3 sign" due to indentation at the coarctation site.

Echocardiography with a focus on the descending aorta is an excellent noninvasive test to make the clinical diagnosis in patients with suspicious clinical findings. Cardiac MRI and CT scanning can identify the precise location and anatomy of the coarctation and assess the entire aorta and the collateral vessels. Cardiac catheterization is indicated to assess for concomitant coronary artery disease when surgery is planned as well as when catheter-based interventions are contemplated.

Repair of coarctation of the aorta may be accomplished via percutaneous catheter intervention or surgically. The main indication for intervention of CoA is a peak-to-peak coarctation gradient >20 mm Hg. Intervention may also be sought with lower gradients in the setting of significant aortic narrowing on anatomic imaging with radiologic evidence of extensive collateral flow.

Surgery was previously the mainstay in the approach to native CoA, with available options including resection and end-to-end anastomosis, subclavian flap, prosthetic patch aortoplasty, and interposition (tube bypass) grafting. Angioplasty and stenting is now considered the procedure of choice in patients with recoarctation following surgery and is experiencing a greatly expanding role in treatment of primary CoA.

Complex Lesions (Acyanotic)

Transposition of the Great Arteries

Transposition of the great arteries (TGA) refers to an abnormality in the embryologic separation of the great vessels, which results in the aorta emanating from the RV and the

PA coming off the left ventricle. There are two varieties that are most commonly seen in adults: D-TGA and L-TGA.

In D-TGA, the great arteries arise from the wrong ventricle; as such surgical intervention is required during childhood. The surgery may include an atrial baffle (a Senning or Mustard procedure) where blood is baffled from the vena cavae to the left atrium and from the pulmonary veins to the RA. The primary long-term concern in these patients is that the RV is ill-prepared to serve as a systemic ventricle. It can weaken and fail over time (usually when the patient enters their 30s and 40s), and these patients typically also develop significant systemic atrioventricular valve (SAVV) (tricuspid valve in the mitral position) regurgitation. Other common complications include baffle obstruction, baffle leak, pulmonary venous obstruction, and conduction disturbances and arrhythmias.

Patients with D-TGA can also be surgically corrected during childhood with an arterial switch (Jatene procedure), where the ascending aorta and the main PA are transected and reattached to the opposite root with transplantation of the coronary arteries into the "neoaorta." Long-term concerns after this operation include coronary insufficiency with myocardial ischemia, stenosis at the anastomotic sites, ventricular dysfunction and arrhythmias, and aortic and pulmonary regurgitation.

The ECG may be normal in D-TGA (post arterial switch) or may reveal right-axis deviation and right ventricular hypertrophy (postatrial baffle). On chest radiography, because of the parallel relationship of the great vessels, a narrow mediastinal shadow is common. Ventricular size and pulmonary markings vary depending on the patient's clinical status.

L-TGA is the so-called congenitally repaired lesion and consists of atrioventricular and ventricular-arterial discordance. This variation results in a circulation where the circulation goes from vena cavae to RA to left ventricle to PA to pulmonary veins to left atrium to RV to aorta. Associated anomalies are common in L-TGA and include VSD, PS, abnormalities of the SAVV, and conduction abnormalities, with complete heart block occurring at a rate of approximately 2% per year. Many patients with L-TGA may be asymptomatic and escape diagnosis until adulthood. They may present with heart failure due to significant SAVV regurgitation or systemic ventricular dysfunction, arrhythmias, or complete heart block.

On electrocardiography, PR prolongation may be noted and there may be complete heart block. Because of the inversion of the left and right bundle branches, a pattern of inferior infarction may be seen. On chest radiography, the vascular pedicle may be abnormal or narrow and the ventricular silhouette has a "humped" appearance. Cardiomegaly may be noted as well as dextrocardia, which also occurs with D-TGA.

Again, in L-TGA, the problem remains a RV pumping into the systemic circulation. Surgical repair for important SAVV regurgitation should be undertaken before the systemic ventricular function deteriorates (ejection fraction <45%). Patients with

systemic ventricular dysfunction may benefit from therapy with beta-blockers and afterload reducers such as ACE inhibitors or angiotensin II receptor blockers. Cardiac transplantation is often considered in the patients with severe systemic ventricular dysfunction refractory to medical therapy.

Complex Lesions (Cyanotic)

Tetralogy of Fallot

TOF, a so-called conotruncal abnormality, is the constellation of four findings: an aorta that overrides the right ventricular outflow tract, right ventricular outflow obstruction, a large subaortic VSD, and hypertrophy of the RV The frequent coexistence of an ASD can make for a "pentalogy." Other associations with TOF include a right aortic arch in a fourth of the patients as well as anomalous left anterior descending coronary artery arising from the right coronary artery, passing anterior to the right ventricular outflow tract. Occasionally, unrepaired patients with TOF can present in adulthood owing to a remarkable balance between the pulmonic obstruction and the VSD, which limits cyanosis.

Early palliation with a systemic to arterial shunt (i.e., Blalock–Taussig, which connects the subclavian artery and the PA) facilitates growth of the pulmonary arteries and is a precursor to definitive surgical repair in the young child. Definitive repair comprises closure of the VSD, as well as relief of the right ventricular outflow tract obstruction, which may include simple resection of infundibular stenosis, patch augmentation of the right ventricular outflow tract that may disrupt the pulmonary valve or pulmonary valvotomy resulting in significant pulmonic regurgitation. Though tolerated for several years, the RV eventually succumbs to volume overload and progressively increases in size. Surgical repair of this condition involves implanting a pulmonary homograft or a pulmonary valve bioprosthesis, the latter of which may now be able to be implanted percutaneously.

Findings on clinical examination of the unoperated patient may include cyanosis, clubbing, a right ventricular lift, a thrill at the left sternal border due to severe pulmonary obstruction, or a loud continuous murmur over the thorax as a result of aortopulmonary collaterals in the setting of severe right ventricular outflow tract obstruction. After surgical repair, a diminished or an absent radial pulse (post Blalock–Taussig shunt), a soft ejection murmur across the right ventricular outflow tract, a low-pitched diastolic murmur from pulmonary regurgitation, or an absent P_2 may be noted.

On the ECG of a patient with repaired TOF, a complete right bundle branch block is typically present. Chest radiography may be normal post-TOF repair; however, cardiomegaly may be seen in the setting of significant pulmonic and/or tricuspid valve regurgitation. A right aortic arch is often seen.

After repair of TOF, cardiomegaly as well as development of atrial or ventricular

arrhythmia should prompt search for an underlying hemodynamic abnormality, commonly pulmonary regurgitation. Intervention on the pulmonary valve, whether surgically or percutaneously, is indicated in the setting of severe pulmonary regurgitation and associated symptoms, moderate-to-severe right ventricular dysfunction or enlargement, moderate-to-severe tricuspid regurgitation, or the development of symptomatic or sustained atrial or ventricular arrhythmias. Other indications for surgical intervention on patients with repaired TOF include residual right ventricular outflow tract obstruction, residual VSD ($Q_p/Q_s > 1.5$) and severe, symptomatic aortic regurgitation. As the RV may be suboptimally assessed by echocardiography, cardiac MRI can be useful to quantitatively evaluate the RV and aid in determining the ideal timing of intervention. It is also best at quantifying pulmonary regurgitation.

Ebstein Anomaly

Ebstein anomaly is the result of inferior displacement of the tricuspid valve into the RV, which results in "atrialization" of the RV As a result, the RV is very small and not infrequently hypocontractile. The posterior and septal leaflets of the tricuspid valve are often small and inadequate, while the anterior leaflet is very large and redundant, resembling a "sail." The latter feature results in the characteristic "sail sound," which occurs during closure of the tricuspid valve, followed by the tricuspid regurgitation murmur (if present). Over 50% of patients have either an ASD or a patent foramen ovale (PFO) present and right-to-left shunting through these defects results in cyanosis. About 25% of the patients have an accessory conduction pathway (Wolf–Parkinson–White syndrome). The age at presentation depends on the degree of anatomic and hemodynamic derangements. In adulthood, patients commonly present with exercise intolerance, dyspnea, fatigue, symptomatic arrhythmias, and right-sided heart failure.

The ECG of Ebstein patients shows very tall (Himalayan) P waves, which are a characteristic finding. Preexcitation may be noted as well as QRS prolongation with a "splintered" right bundle branch block pattern. Chest radiography may reveal marked cardiomegaly with clear lung fields. The cardiac contour tends to be "globular" due to right atrial enlargement. The diagnosis is typically confirmed using echocardiography. There is also an increasing role for cardiac MRI for clearer delineation of cardiac structure and function.

Surgery involves complex repair or replacement of the tricuspid valve in addition to closure of the atrial communication, and should be limited to centers with extensive experience in this area. Indications for surgery include significant symptoms or worsening exercise capacity, cyanosis (oxygen saturation <90%), progressive cardiomegaly on chest x-ray (often defined as a cardiothoracic ratio >60%), paradoxical embolism, and severe tricuspid regurgitation with progressive right ventricular dilation or dysfunction.

Eisenmenger Syndrome

As mentioned above, Eisenmenger physiology refers to the condition where an intracardiac shunt has resulted in extensive pulmonary vascular disease and pulmonary hypertension that is so severe that the shunt has reversed. The physical exam of these patients is notable for cyanosis (which often worsens during exercise) and clubbing. If differential clubbing is seen (usually clubbing of the feet and the left arm and not the right arm), then the clinical diagnosis is Eisenmenger physiology in the context of PDA. On physical exam, the jugular venous pressure is elevated; there may also be a right ventricular heave, a palpable P_2 that is loud on auscultation, a systolic ejection click, and a diastolic murmur due to pulmonary regurgitation. Because pulmonary and systemic pressures only slightly differ, a systolic murmur across the lesion is generally not heard.

In general, patients with Eisenmenger syndrome have better long-term survival than comparable patients with idiopathic (primary) pulmonary hypertension, but their functional limitation is considerable. They may present with dyspnea on exertion, palpitations, progressive cyanosis, hemoptysis, syncope, or volume overload. Rapid deterioration can be seen during atrial or ventricular arrhythmias or with complications such pulmonary embolism or infection, or generally any condition that results in even transient hypotension.

There are a number of complications that result from long-standing hypoxia, including significant erythrocytosis (elevated red blood cell count). Symptoms of hyperviscosity (changes in mental status, fatigue, and headache) are quite rare, and phlebotomy should only be performsed to relieve these symptoms (typically in the presence of a hematocrit >65%) in the absence of dehydration. If phlebotomy is attempted, it should be accompanied by at least equal fluid replacement. Repeated phlebotomy can result in iron deficiency and actually increases the risk of hyperviscosity. Iron should be repleted in these patients if deficiency is present. Patients with Eisenmenger syndrome often develop proteinuria and a decreased glomerular filtration rate (GFR). Because of the low GFR and the high turnover of red blood cells, elevated uric acid levels are frequently seen and can result in acute renal failure, particular after administration of contrast dye if the patient is not adequately hydrated. Patients with Eisenmenger physiology are at risk of both thrombosis and hemorrhage, hemoptysis that may be life threatening, cerebral abscesses, stroke, scoliosis, and arthropathy as well as pigment gallstones. They may present with cardiac ischemia in the setting of coronary artery compression by a dilated PA, right ventricular ischemia, or atherosclerosis.

Patients with Eisenmenger physiology should avoid dehydration, moderate-to-severe strenuous exercise, exposure to excessive heat, chronic high altitude, and pregnancy. If catheterization or noncardiac surgery is required, they should be

hospitalized in centers with adult CHD expertise and experienced cardiac anesthesia. All intravenous lines should be filtered to exclude air bubbles. Improved quality of life has been noted with the use of pulmonary vasodilators in patients with Eisenmenger physiology and survival may be positively impacted. Transplantation has also offered limited survival benefits albeit with significant quality of life improvement for this patient population.

GENERAL MANAGEMENT STRATEGIES

Although adult patients with CHD can be intimidating at first presentation, sticking to basic concepts can be helpful in choosing appropriate management strategies.

Patients with intracardiac shunts should be counseled to avoid high-risk activities such as scuba diving and have filtering devices placed on all intravenous lines whenever hospitalized to prevent the risk of paradoxical embolization. Noncardiac surgery should be considered on a patient- per-patient basis only after the risks and benefits have been carefully considered, particularly in the patient with Eisenmenger syndrome. Most adults with CHD will require lifelong follow-up and should be referred to tertiary care centers with expertise in their care.

Some patients with CHD are at increased risk of developing IE and should be educated on the recommendations for prophylaxis that were revised in 2007. According to the new guidelines, antibiotic prophylaxis before dental procedures is recommended to the "high-risk" group of patients with CHD including (1) those with prior IE; (2) those with prosthetic heart valves; (3) those with palliated or unrepaired cyanotic CHD, including surgically constructed palliative conduits and shunts; (4) those with repaired CHD with prosthetic material or device, whether placed percutaneously or surgically, during the first 6 months postprocedure; and (5) those with repaired CHD with residual defects at the site or adjacent to the site of a prosthetic device or patch that prevents endothelialization.

Approximately 18% of congenital heart defects are associated with a congenital syndrome, including coexisting cognitive and neurologic deficits or chromosomal abnormalities (Down syndrome with trisomy 21 and TOF with 22q11.2 deletion). These patients should be appropriately screened for coexisting noncardiac conditions affecting them including sleep apnea, endocrinopathies, renal disease, and psychiatric issues with appropriate referrals provided. Patients should also be counseled on important topics such as pregnancy, genetic counseling, and contraception. For illustrative cases of CHD lesions, please refer to Chapter 24.

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QUESTIONS AND ANSWERS

Questions

1. You are seeing a 27-year-old female postal employee in outpatient clinic. She has a history of asthma treated with inhalers, though her pulmonary function tests and methacholine challenge were recently normal. She has noted progressive fatigue over the past months and finds that getting up large hills on her mail route gets her out of breath. On examination, she has a fixed split second heart sound and soft systolic ejection murmur over the left upper sternal border. Her lungs are clear and all her extremity pulses are equal and of normal intensity. All the following would be expected to be present on her diagnostic studies except:
   a. Unexplained right heart enlargement on echocardiography
   b. An RSR' (incomplete bundle branch block) pattern on electrocardiogram (ECG)
   c. Unexplained mild pulmonary hypertension
   d. Right-to-left shunt by bubble study on echocardiography
   e. Decreased pulmonary vascularity on chest x-ray

2. You are evaluating a 35-year-old female librarian with a history of complex congenital heart disease (CHD). She tells you that she has a "hole in the heart" but was told about 10 years ago that it was "too late to operate." Her health has recently been stable and she denies worsening dyspnea, headaches, chest pain, or other symptoms. She is currently able to walk from her home to her mail box (~300 ft) before she has to stop and rest. On exam, she appears cyanotic but is breathing comfortably. She has a loud pulmonic closure sound and a II/VI holosystolic murmur at the right lower sternal border. There are no surgical scars over her back or chest and her pulses are equal in all four extremities. Her bloodwork demonstrates:
   White blood cell count = 8,000
   Hemoglobin = 22.4
   Platelets = 295,000
   Urea nitrogen = 1
   Creatinine = 0.9
   Reasonable therapeutic considerations in this patient include all of the following except:
   a. Endocarditis prophylaxis with dental procedures
   b. Supplemental oxygen to wear at night or with exertion
   c. Phlebotomy of 2 units with equal volume repletion

d. Invasive assessment of cardiac hemodynamics followed by initiation of bosentan
e. Avoiding studies that administer intravenous contrast dye

3. Which of the following statements about atrial septal aneurysm (ASA) is true?
   a. The term ASA is used to describe a very floppy interatrial septum.
   b. An ASA occurs when there is overabundant tissue in the septum primum.
   c. The most widely accepted definition of an ASA is >15-mm excursion from left-to-right atrium on echocardiography.
   d. The presence of an ASA in patients with patent foramen ovale (PFO) and presumed embolic stroke appears to increase the risk of subsequent stroke.
   e. All of the choices

4. Which of the following statements about PFO is the most accurate?
   a. PFO is uncommon in the general population, less common in patients with cryptogenic stroke; and its optimal management is well defined and evidence based.
   b. PFO is common in the general population, more common in patients with cryptogenic stroke; and its optimal management in most cases remains to be defined.
   c. PFO is uncommon in the general population, more common in patients with cryptogenic stroke; and its optimal management in most cases remains to be defined.
   d. PFO is common in the general population, less common in patients with cryptogenic stroke; and its optimal management in most cases remains to be defined.
   e. PFO is common in the general population, more common in patients with cryptogenic stroke; and its optimal management is well defined and evidence based.

5. All of the following statements about anomalous pulmonary venous return are correct except:
   a. Anomalous pulmonary venous return can lead to right heart enlargement and elevations in pulmonary arterial pressures.
   b. Sinus venosus atrial septal defects [ASDs] are often associated with anomalous pulmonary veins.
   c. Cardiac computed tomography, magnetic resonance imaging (MRI), and transesophageal echocardiography are all reasonable modalities to assess for anomalous pulmonary veins.
   d. A bubble study during transthoracic echocardiography can help detect an anomalous pulmonary vein.

6. You are seeing a 35-year-old flight attendant with a history of coarctation of the aorta. At age 10, the patient underwent a coarctation resection and end-to-end anastomosis. She has noted no limitations since that time but notes that in general she has had slightly “less stamina” that her friends and colleagues over the past several years. On exam, she has equal blood pressures in all four extremities and a soft systolic ejection murmur. All of the following statements are true concerning this patient except:
   a. It is likely that the patient has a bicuspid aortic valve.
   b. There is a 10% chance that the patient has a berry aneurysm in the brain.
   c. The type of surgery that the patient underwent makes the possibility of aneurysmal dilatation at the surgical site very likely.
   d. The patient is at a higher risk of developing hypertension than the general population.
   e. All of the choices are true.

7. The lesions that constitute tetralogy of Fallot (TOF) include all of the following except:
   a. A ventricular septal defect (VSD)
   b. An overriding aorta
   c. An ASD
   d. Right ventricular outflow obstruction
   e. Right ventricular hypertrophy

8. A 21-year-old college student presents for a routine medical checkup. He has never seen an adult cardiologist and last saw a pediatric cardiologist while in high school. He has been told he has

congenitally corrected transposition with an intact ventricular septum and no known valvular dysfunction. All of the following concerns about this young man are valid except:
   a. His systemic right ventricle (RV) is at risk for dilatation and failure.
   b. He has a 10% lifetime risk of develop Eisenmenger syndrome.
   c. His systemic tricuspid valve is at risk for developing significant regurgitation.
   d. He has a 32% lifetime probability of developing complete heart block.
   e. All of the choices are correct.

9. All of the following syndromes and cardiac anomalies are associated except:
   a. Trisomy 21 and atrioventricular canal defects
   b. Noonan syndrome and pulmonic stenosis (PS)
   c. Holt-Oram syndrome and ASDs
   d. Marfan syndrome and mitral valve prolapse
   e. Williams syndrome and VSDs

10. Which of the following statements regarding Ebstein anomaly is not correct?
   a. An ASD or a PFO is present in up to 80% of patients.
   b. The cardinal feature is an apically displaced tricuspid valve resulting in atrialization of ventricular tissue.
   c. Wolf-Parkinson-White syndrome is common in these patients and multiple tracts can exist.
   d. A bicuspid aortic valve is commonly present.
   e. A “sail sound” is a common finding on physical examination.

11. You are seeing a 34-year-old gentleman in clinic. He has a history of TOF and underwent a palliative Blalock-Taussig at 10 months followed by a complete repair at age 3. He has been reasonably active for several years but recently has been “slowing down” a little bit. His physical examination demonstrates scars over his left scapulae and midsternum. He has a III out of VI systolic ejection murmur and a II out of IV diastolic murmur over the left upper sternum. He has clear lungs and equal pulses in all four extremities and no peripheral edema. An echocardiogram is somewhat limited in quality due to the fact he is a rather large individual, but you are able to see evidence that the right heart appears enlarged and there is some pulmonic regurgitation present. The ECG shows some widening of the QRS complex with right bundle branch block morphology. The most reasonable next step in the diagnostic evaluation of this patient would be:
   a. A repeat echocardiogram with a saline microcavitation (bubble) study
   b. An electrophysiologic study to look for ventricular arrhythmias
   c. A cardiac catheterization to formally examine the hemodynamics
   d. A cardiac MRI study
   e. The initiation of diuretics and digitalis

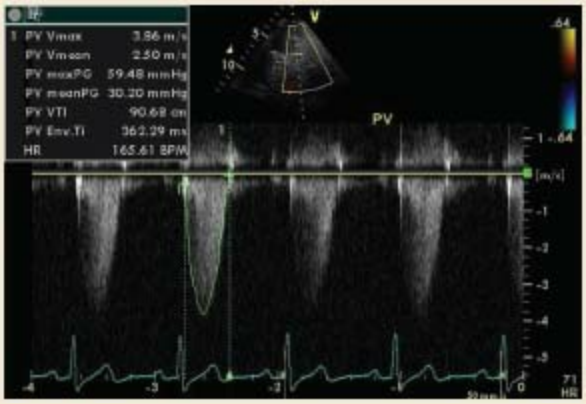
12. You have been asked to see a 45-year-old woman with a VSD. She has been in excellent health for many years and voices no particular complaints. She had been taking antibiotic prophylaxis with dental procedures but discontinued this as a result of the recent guideline changes. On examination, she has a III/VI pansystolic murmur and normal intensity first and second heart sounds. Her lungs are clear and she has no jugular venous distention. All of the following characteristic would argue for a benign clinical course in this patient except:
   a. A loud murmur
   b. Normal intensity heart sounds
   c. A supracristal (or subaortic) morphology
   d. The absence of right or left heart enlargement
   e. All of the choices are benign characteristics.

13. A 28-year-old woman is referred to you for evaluation of a heart murmur. She states she is a longdistance runner and has not noted any significant symptoms. On examination, you note very brisk pulses and her blood pressure is 100/40 mm Hg. Her murmur extends from systole into diastole, and there is a near “machinery”-type quality to it. The remainder of her physical examination is essentially

unremarkable, as is her bloodwork. The most likely cardiac anomaly in this case is:

a. An ASD
b. Coarctation of the aorta
c. A patent ductus arteriosus (PDA)
d. Congenitally corrected transposition with a VSD and pulmonic valve stenosis
e. VSD

14. A 40-year-old man is referred to you for evaluation of a heart murmur. He had been active until about 3 years ago when he experience severe pain in his right knee that was eventually diagnosed as a ligamental tear. He underwent open operative repair and has been limited since that time. As a result, he has gained approximately 30 pounds since that time and states he now gets out of breath with anything more than moderate activity. On examination, he has a systolic ejection murmur heard best over the left upper sternal border. There is no radiation to the carotid arteries. An echocardiogram is performed and demonstrates a doming pulmonic valve with trace regurgitation. The Doppler tracing shown is obtained across the pulmonic valve.



The most appropriate next step would be:

a. Continued observation with yearly visits and echocardiography
b. Referral for pulmonic valvuloplasty
c. Referral for surgery after diagnostic angiography
d. Stress echocardiography
e. MRI

15. A 19-year-old basketball player is brought to the emergency department after he collapsed on the court. He received bystander cardiopulmonary resuscitation and was apparently defibrillated using an automatic external defibrillator (AED). All of the following abnormalities should be part of the differential diagnosis for this young man with the exception of:

a. Anomalous origin of the coronary arteries (from opposite cusps).
b. Hypertrophic cardiomyopathy
c. Congenitally prolonged QT syndrome
d. ASD
e. Arrhythmogenic right ventricular dysplasia

Answers

1. Answer E: The lung x-ray in this case would be expected to demonstrate increased lung vascularity. The patient describe in this case has an ASD. The telltale physical examination findings are the pulmonic outflow murmur resulting from increased pulmonary blood flow due to left-to-right shunting and the fixed split second heart sound. ASDs, if sufficiently large, lead to right heart enlargement and an incomplete right bundle branch block pattern on electrocardiography. Pulmonary hypertension can result from increased blood flow and up to 10% may develop Eisenmenger physiology if uncorrected. As with any atrial flow communication a bubble study on echocardiography would be expected to be positive providing the right atrial pressure can be made to exceed the left atrial pressure (such as following a

Valsalva maneuver).

2. Answer C: Phlebotomy should not be performed in patients with Eisenmenger physiology unless they demonstrate evidence suggesting active sludging due to polycythemia. Suggestive symptoms include headaches and visual changes. Unnecessary phlebotomy can provoke iron deficiency, which can further increase the risk of sludging and its consequences. If phlebotomy is necessary, equal volume replacement with saline is essential. Iron levels should be checked in these patients and repleted as necessary. As with all cyanotic heart disease, endocarditis prophylaxis for dental procedures is recommended. The use of oxygen has not been well studied in this population but is reasonable if it affords the patient symptomatic improvement. An oral endothelin blockade, bosentan, has been demonstrated in a randomized, placebo-controlled study to improve functional capacity and reduce symptoms compared to placebo for patients with Class III symptoms. Since our patient seems fairly limited, this may be a very reasonable therapeutic option for her. Any procedures requiring the use of anesthesia or contrast dye should be approached very carefully in patients with Eisenmenger syndrome due to the risk for adverse consequences.

3. Answer E: An ASA is a floppy interatrial septum resulting from overabundant tissue in the septum primum. A total septal excursion of >15 mm has been most widely accepted as the definition for this entity. If the septal excursion is less, it is generally referred to as a "redundant atrial septum." In patients with cryptogenic stroke and a PFO, a concurrent ASA appears to significantly increase the risk of future stroke.

4. Answer B: The foramen ovale is the interface between the septum primum and the septum secundum and in utero provides an important route that blood can take to bypass the fetal lungs (which are collapsed until birth). In about 25% of humans, the flap of tissue making up the foramen ovale does not fuse after birth and results in a PFO. Several studies have demonstrated an increased incidence of PFO in patients with cryptogenic (otherwise unexplained) stroke. Though several management strategies exist for patients with cryptogenic stroke and PFO including anticoagulation, antiplatelet therapy, and percutaneous and surgical closure, no clear consensus regarding therapy exists and studies are ongoing to try to answer this very important question.

5. Answer D: A bubble study would not be expected to be abnormal in the presence of an anomalous pulmonary vein unless a concurrent ASD was present. Normally, all four pulmonary veins drain back to the left atrium. Rarely one or multiple pulmonary veins can drain back to the RA and result in a left-to-right shunt. This can result in right heart enlargement and even pulmonary hypertension. Anomalous pulmonary veins are present in most sinus venosus ASDs and in up to 10% of secundum ASDs. Though transthoracic echocardiography is generally unable to image an anomalous pulmonary vein, CT, MRI, and transesophageal echocardiography are all helpful in its detection.

6. Answer C: End-to-end resection of an aortic coarctation is most likely to be complicated by eventual recoarctation, which can often be approached percutaneously. Another procedure that was previously popularized for coarctation repair, the so-called patch aortoplasty, can lead to aneurysmal dilatation, and these patients require very close monitoring. Coarctation of the aorta is believed to result from the migration of ductus arteriosus tissue into the aorta proper. As a result, constriction of the aorta occurs and leads to upper-extremity hypertension and lower-extremity hypoperfusion. In the adult, this lesion is most commonly diagnosed during evaluation for secondary causes of hypertension. A bicuspid aortic valve is present in 50% to 85% of patients and ascending aortic enlargement can also be seen. There is also a 10% chance of having a concurrent berry aneurysm. Despite surgical or percutaneous repair, patients are at increased risk of developing hypertension, even in the absence of an appreciable residual gradient.

7. Answer C: The lesions of TOF include a VSD, an overriding aorta, the presence of right ventricular outflow obstruction (valvular or subvalvular), and right ventricular hypertrophy. The concurrence of an ASD has been referred to a "pentalogy," but is not part of the primary lesion complex.

8. Answer B: In the absence of any significant shunt lesions, there is no risk to this patient of developing Eisenmenger syndrome. Congenitally corrected transposition of the great vessels implies that the patient has both atrioventricular and ventriculoarterial discordances. In other words, his venous draining enters the RA, which is connected to a left ventricle and then is taken to the lungs via the pulmonary artery (PA). Pulmonary venous return then enters the left atrium and enters the RV, which then pumps

blood to the body through the aorta. Although this reproduces a near-normal circulation, the RV has not been adequately designed to withstand the workload of being a systemic ventricle. As a result, it begins to fail. Also, the tricuspid valve (the systemic AV valve—valves always follow their respective ventricles) begins to leak. Patients with congenitally corrected transposition have conduction issues and are prone to developing heart block.

9. Answer E: The characteristic cardiovascular lesion of Williams syndrome is supravalvular aortic stenosis, though coarctation of the aorta and peripheral PA stenosis has also been described. The characteristic lesion of trisomy 21 (Down syndrome) is an atrioventricular canal defect (also known as a primum ASD/VSD), though ASD, VSD, and PDA are also common. Noonan syndrome has most classically been associated with dysplastic or stenotic pulmonic valves. Holt-Oram syndrome is an autosomal dominant disorder in which ASDs and VSDs are most common. Marfan syndrome's most worrisome cardiovascular involvement is of the aorta, which can lead to dissection and even death. Many of these patients have concurrent mitral valve prolapse, though it is less likely a cause of morbidity or mortality.

10. Answer D: A bicuspid aortic valve does not appear to be a common finding in most patients with Ebstein anomaly. Ebstein anomaly is characterized by apical displacement of the septal and the posterior tricuspid valve leaflets, leading to atrialization of the RV. An atrial flow communication (ASD or PFO) exists in up to 80% of patients. The ECG often demonstrates very large or "Himalayan" P waves. Wolf-Parkinson-White syndrome is present in up to 30% of patients with half of these having multiple accessory tracts. The loud snapping sound of the ballooning leaflets has been compared to that of a sail flapping in the wind and can be a very characteristic examination finding.

11. Answer D: Primary repair of TOF entails not only closing the VSD but also resecting the right ventricular outflow obstruction and often placing a patch over the resected tissue. Because the valve is often dysplastic, significant regurgitation of the pulmonic valve results. This patient demonstrates the typical examination of patient with prior repair complicated by significant pulmonic valve regurgitation. These patients do remarkably well for many years but then develop progressive right heart dilatation, heart failure, and arrhythmias. Widening of the QRS complex has been well described as a precursor to adverse clinical outcomes. The timing of reoperation to implant a pulmonic valve is very challenging, and the status of the RV appears to be the most important determining factor. A bubble study would only clarify whether an atrial level or a pulmonary shunt was present, which is unlikely to be a pathophysiologic contributor to this case. Though arrhythmias are a complication of right heart dilatation, the role of electrophysiologic testing in this population of patients is far from clear, and in this patient without a history of syncope would not be indicated. It is also unlikely that invasive hemodynamics would provide crucial diagnostic information. Finally, without evidence for significant volume overload, the initiation of diuretics and digoxin would not be recommended at this time.

12. Answer C: Of the various types of VSDs, supracristal (subaortic) defects should be monitored closely because of their predilection for spontaneous closure by aortic leaflet tissue resulting in significant aortic regurgitation. The patient in this case has a small, restrictive, and asymptomatic VSD. Flow in such cases is determined by the size of the shunt and the compliance of the ventricles. Smaller lesions in general will have increased turbulence and thus louder murmurs. Thus, a louder murmur isolated to systole is reassuring in this case as is the presence of normal intensity heart sounds. In the presence of pulmonary hypertension, the pulmonic component of the second heart sound is often accentuated. Cardiac chamber enlargement results from volume overload and its absence in this case again suggests a more benign lesion.

13. Answer C: PDA is the persistence of an in utero communication between the aorta and the left PA, which is again designed to bypass blood away from the collapse lungs. It is the third most common congenital heart defect found in adults and is generally found in isolation in the adult. Most adult patients with patent ductus are asymptomatic, though this depends on the size of the left-to-right shunt and the size of the ductus. Frequently, this lesion is discovered by the unusual quality of a continuous murmur at the left upper sternal border that can often sound like an innocent venous hum. Because a patent ductus is an aortopulmonary runoff, however, the pulse pressure frequently is widened, and the pulses are brisk to bounding. Because of the risk of endocarditis, some advocate repair, even if the shunt is not significant. Fortunately, most ductus lesions can be now be closed in the catheterization laboratory

without the need for surgery.

14. Answer B: This patient has PS with peak gradient of 60 mm Hg. Class I guideline indications for valvuloplasty are a peak echo gradient ≥60 mm Hg in the asymptomatic adult and ≥50 mm Hg if symptomatic. Stress echocardiography would be of little utility as the rest gradient is already sufficient to recommend an intervention; in patients with less gradient and symptoms, a stress test may demonstrate a provokable gradient that correlates with symptoms and would imply a benefit from intervention. Magnetic resonance is useful to establish the location of narrowing (valvular, subvalvular, or supravalvular) in difficult to image cases, but in this patient the echo images have established that the narrowing is valvular. Though surgery can be performed in these patients if multiple lesions coexist, percutaneous balloon valvotomy is now the preferred therapy in the majority of patients with isolated valvular PS.

15. Answer D: Though an ASD does increase the risk of developing atrial fibrillation later in life and unrepaired may shorten lifespan, there has been no link between ASD and sudden death. The most common lesions to exclude in a young person who suffers a sudden death include hypertrophic cardiomyopathy, an autosomal dominant disorder that results in abnormal myocardial architecture and increases arrhythmogenic risk. Abnormal coronary artery origins appear to be a risk for sudden death as well, though the mechanism remains poorly understood and controversial. It may be due to compression between the great vessels or an abnormal slit-like orifice at the take-off of the vessel from the aortic cusp. Congenital QT-prolongation can result in sudden death and can occasionally be diagnosed from an ECG. Arrhythmogenic RV dysplasia and Brugada syndrome are other abnormalities that disturb the normal electrophysiologic milieu and increase the risk for sudden death.

CHAPTER

Essential Echocardiographic Images in Adult Congenital Heart Disease

Ellen Mayer Sabik

Congenital heart disease is by definition an abnormality in cardiac structure that is present at birth, even if it is not diagnosed until later in life. These defects are usually the result of altered embryonic development of a normal structure or failure of development. Four categories of etiologic agents may be responsible for this abnormal development, and these are the same influences that may cause cancers. They include hereditary and chromosomal defects (Table 24.1), viruses (rubella with patent ductus arteriosus [PDA]), chemicals (thalidomide with truncus arteriosus or tetralogy of Fallot), and radiation (x-irradiation with ventricular septal defects [VSDs]). Although these agents cause certain known defects, most defects have no specific cause and the etiology may in fact be multifactorial. The incidence of congenital heart disease (excluding bicuspid aortic valve and myxomatous mitral valve (MV) disease with mitral valve prolapse [MVP]) is approximately 0.5% to 0.8% of live births. Congenital cardiac malformations are much more common in stillbirths than in live births. Some congenital lesions have a high rate of survival without surgery and may be seen in the unoperated adult with different relative frequencies (Table 24.2). Other lesions, with worse prognosis, are usually not seen in adults. However, as both diagnosis and treatment (both medical and surgical) improve, more of these patients are surviving into adulthood and are more likely to be seen in a cardiology office as adults. Thus, all cardiologists should be familiar with the lesions discussed in this chapter.

TABLE
24.1 Chromosomal Anomalies and Their Congenital Syndromes Associated with Heart Defects

	Common Associated Lesions		
Anomaly	**1**	**2**	**3**
Trisomy 13	VSD	PDA	Dextrocardia
Trisomy 18	VSD	PDA	PS
Trisomy 21	VSD	AV canal	ASD
Turner syndrome (45, X)	Coarctation	AS	ASD
Noonan syndrome	PS	ASD	

VSD, ventricular septal defect; PDA, patent ductus arteriosus; PS, pulmonic stenosis; AV atrioventricular; AS, aortic stenosis; ASD, atrial septal defect.

TABLE
24.2 Congenital Heart Defects in the Unoperated Adult

Most Common	Less Common	Rare
■ Bicuspid aortic valve ■ PS ■ Coarctation of aorta ■ ASD	■ VSD ■ Discrete subaortic stenosis ■ PDA ■ Ebstein anomaly ■ Tetralogy of Fallot ■ Coronary arteriovenous fistula ■ Sinus of Valsalva aneurysm ■ Corrected transposition of great arteries	■ Complete transposition ■ Double-outlet right ventricle ■ Truncus arteriosus ■ Tricuspid atresia ■ Univentricular heart

ATRIAL SEPTAL DEFECTS

Atrial septal defect (ASD) accounts for 22% of adult congenital defects. Excluding bicuspid aortic valves and MVP, ASDs are the most common form of adult congenital heart disease. They make up 10% of all congenital heart defects and demonstrate a female-to-male preponderance of 3:2. Diagnosis of ASD is aided by the following features:

- On auscultation, a wide fixed split S_2 with a pulmonary flow murmur is heard.
- On electrocardiogram (ECG), ostium primum (OP) ASD shows marked left-axis or right bundle branch block (RBBB) with signs of right ventricular (RV) enlargement. There may be first-degree atrioventricular (AV) block. Ostium secundum (OS) ASD is marked by RSR or rSR in V_1, QRS <0.11 seconds, right axis deviation, right ventricular hypertrophy (RVH), and possibly first-degree AV block and right atrial enlargement (RAE).
- Shunt can be visualized by echocardiography with color Doppler and agitated saline

contrast.

- Shunt at the atrial level is a potential source of paradoxical embolus.

The locations of types of ASD are shown in Figure 24.1. The four types of ASD are:

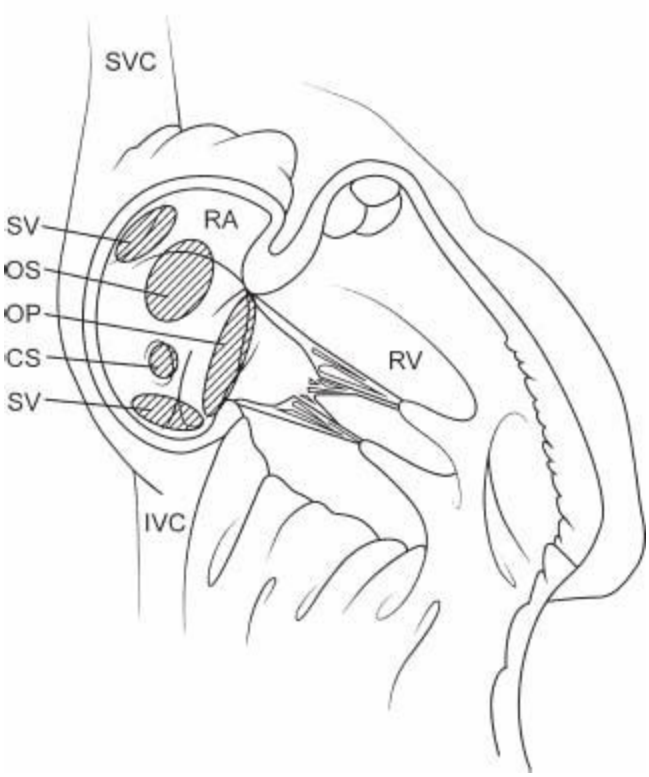


FIGURE 24.1 Location of types of ASD. SV, sinus venosus ASD; OP, ostium primum ASD; OS, ostium secundum ASD; CS, coronary sinus ASD.

- Primum ASD
- Secundum ASD
- Sinus venosus (SV)
- Unroofed coronary sinus (CS)

Primum Atrial Septal Defect

Primum ASD accounts for 20% of cases of ASD (Fig. 24.2A–C) and is part of an AV canal defect in which embryonic endocardial cushions fail to meet normally and partition the heart (Figs. 24.3 and 24.4).

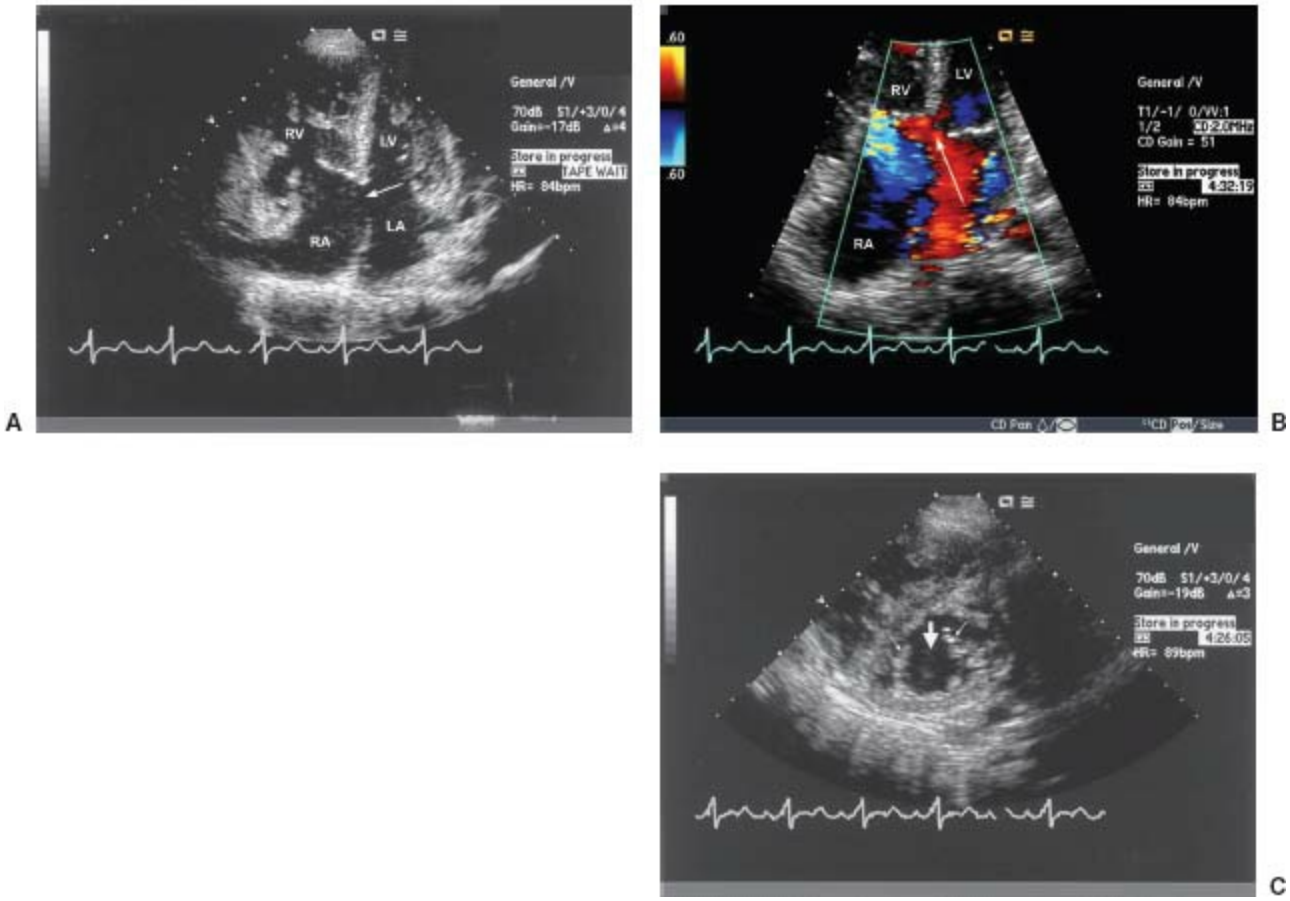


FIGURE 24.2 A: Apical four-chamber view of a patient with AV canal defect. Note the primum ASD (arrow) and the dilated right side. **B:** Magnified apical four-chamber view with color Doppler demonstrating the left-to-right flow (arrow) across the primum ASD. **C:** Parasternal short axis-view demonstrating the cleft anterior mitral leaflet with a gap (arrow) representing the cleft in the anterior mitral leaflet (AML).

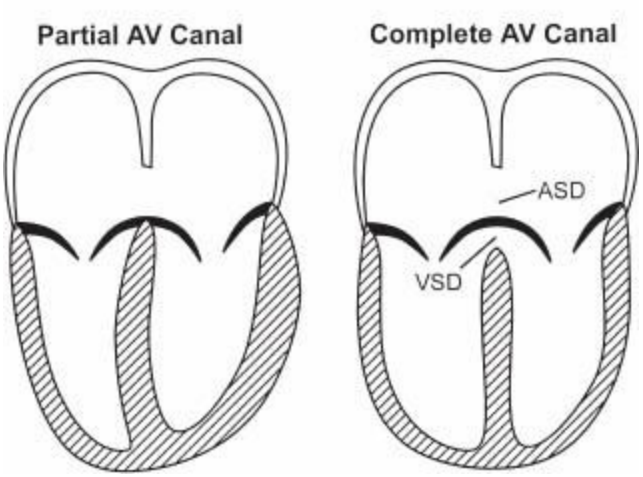


FIGURE 24.3 Apical four-chamber view of partial AV canal defect **(left)** and complete AV canal defect **(right)**. The partial AV canal defect has a primum ASD, cleft MV, and widened anteroseptal tricuspid commissure. The complete AV canal defect has all of these and a VSD.

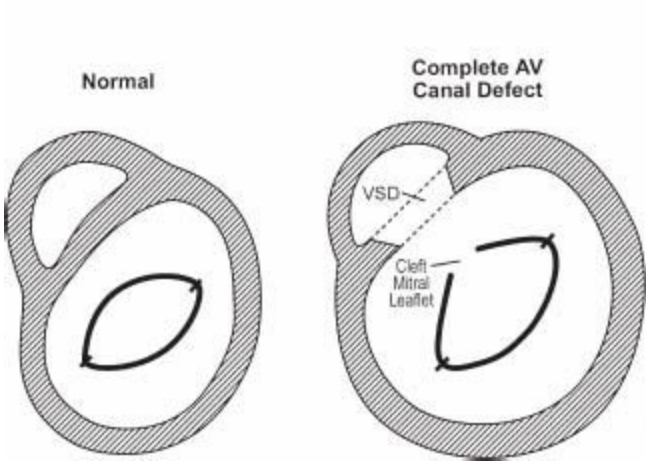


FIGURE 24.4 Parasternal short-axis view showing complete AV canal defect **(right)** compared to a normal heart **(left).** Note the cleft anterior mitral leaflet and VSD in the complete AV canal defect.

A complete AV canal defect consists of four components:

- Inlet VSD
- Primum ASD
- Cleft MV
- Widened anteroseptal tricuspid commissure

A partial AV canal defect is as above without the VSD.

Secundum Atrial Septal Defect

Secundum ASD is an ASD at the fossa ovalis (Fig. 24.5A–D). It is the most common form of ASD (75% of cases). The following features distinguish a secundum ASD:

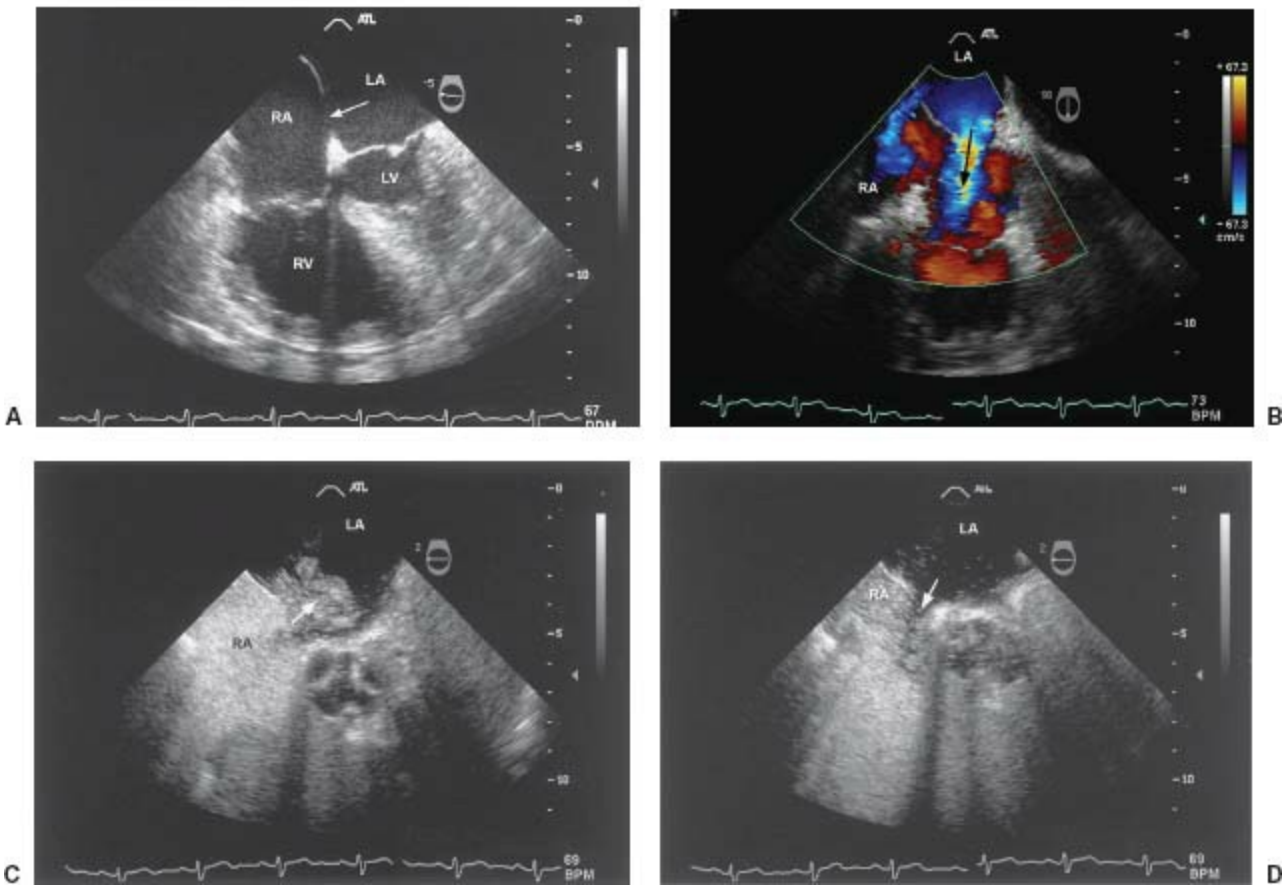


FIGURE 24.5 A: Four-chamber midesophageal view of a TEE demonstrating a secundum ASD (arrow). **B:** TEE with color Doppler demonstrating the left-to-right flow across the secundum ASD. Note that although there is one larger shunt, there are multiple defects with shunting through the atrial septum. **C:** TEE with agitated saline contrast demonstrating the intermittent right-to-left shunting across the secundum ASD. **D:** TEE with agitated saline contrast demonstrating the intermittent left-to-right shunting across the secundum ASD and the unopacified blood from the left side of the heart (specifically the leftatrium [LA]) displacing the contrastwithin the RA. The combination of this image and the prior image demonstrates the bidirectional shunting across this ASD.

- Left-to-right shunt, because the right ventricle (RV) is thin walled and fills more easily than the left ventricle and pulmonary vascular resistance is lower than systemic
- Pulmonary blood flow is often two to four times normal.
- Dilated right side due to right atrial (RA) and RV volume overload
- The pulmonary artery (PA) is often dilated.

Sinus Venosus Atrial Septal Defect

Sinus venosus ASD accounts for 5% of ASD (Fig. 24.6). The following are typical features:

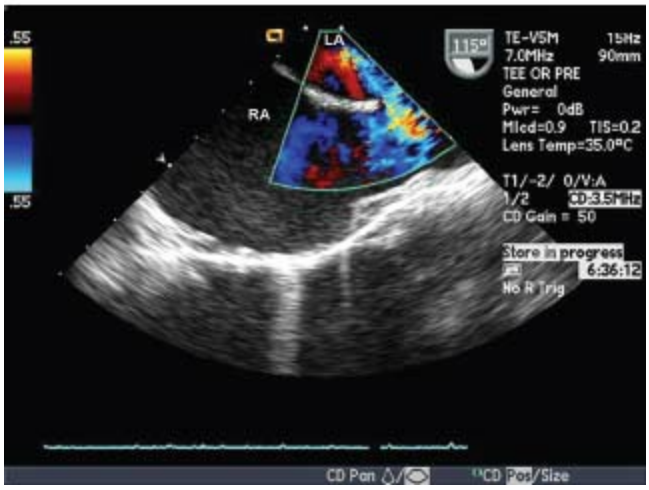


FIGURE 24.6 Bicaval TEE view with color Doppler demonstrating a sinus venosus ASD with left-to-right shunting. This ASD is located near the connection between the SVC and the RA.

- Defect near the junction of the superior vena cava (SVC) or the inferior vena cava (IVC) with the RA (posterior to fossa ovalis)
- Often difficult to detect (typically requires transesophageal echocardiography [TEE])
- If unexplained right-sided dilatation is seen on the echocardiogram, echocardiography should be performed with agitated saline contrast to look for a shunt, with follow-up TEE if needed.
- Superior sinus venosus ASD is almost always associated with partial anomalous pulmonary venous (PV) return: right PV to either SVC or high RA.

Coronary Sinus Atrial Septal Defect

Coronary sinus ASD is very rare. A distinguishing feature is that the roof of the CS is absent.

VENTRICULAR SEPTAL DEFECT

VSD is the most common form of congenital abnormality at birth but accounts for only 10% cases of congenital heart disease in adults (Fig. 24.7). Distinguishing features include the following:

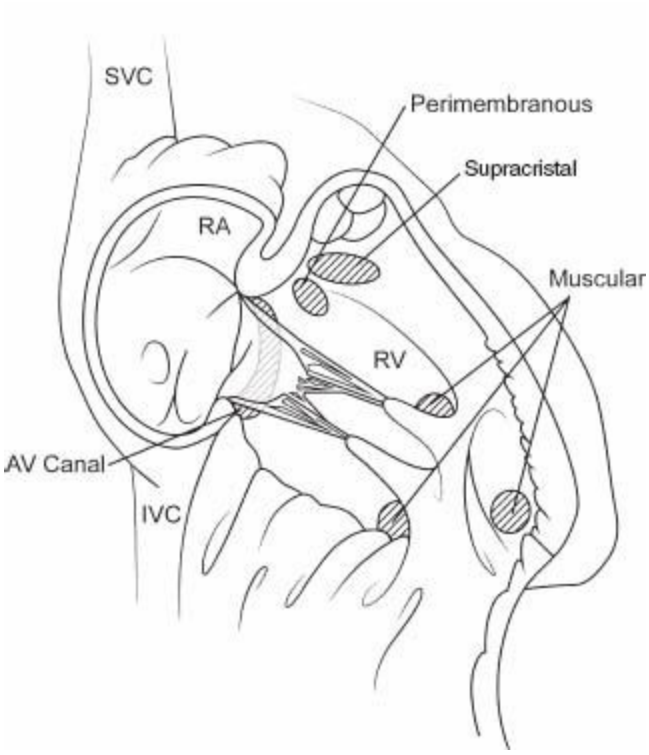


FIGURE 24.7 Locations of types of VSD: membranous, muscular (may be multiple), supracristal, or "subpulmonic" AV canal defects.

- At least 50% to 80% of VSDs close spontaneously.
- Perimembranous VSD is the most common form of VSD.
- VSD carries a risk of endocarditis.
- Perimembranous VSD is often associated with a ventricular septal aneurysm formed by septal leaflet of tricuspid valve (TV) closing defect (the defect may be larger than appears).
- Restrictive VSDs have high-velocity jets with a large pressure difference between the right and left ventricles (larger defects are associated with a low-velocity jet). Recall the modified Bernoulli equation: $\Delta P = 4V^2$.

Types of VSDs include the following:

- Membranous VSD: accounts for 80% of cases of congenital VSD, has the highest rate of spontaneous closure (Fig. 24.8A,B)
- Muscular VSD: accounts for 10% of VSD and may be multiple (Fig. 24.9)
- Supracristal VSD: accounts for 5% of VSD (Fig. 24.10A,B), involves left ventricular outflow track (LVOT)/right ventricular outflow track (RVOT), and carries a high incidence of aortic insufficiency (AI) due to prolapse of right coronary cusp (RCC) or left coronary cusp (LCC) into the VSD
- AV canal defect: discussed in relation to ASD

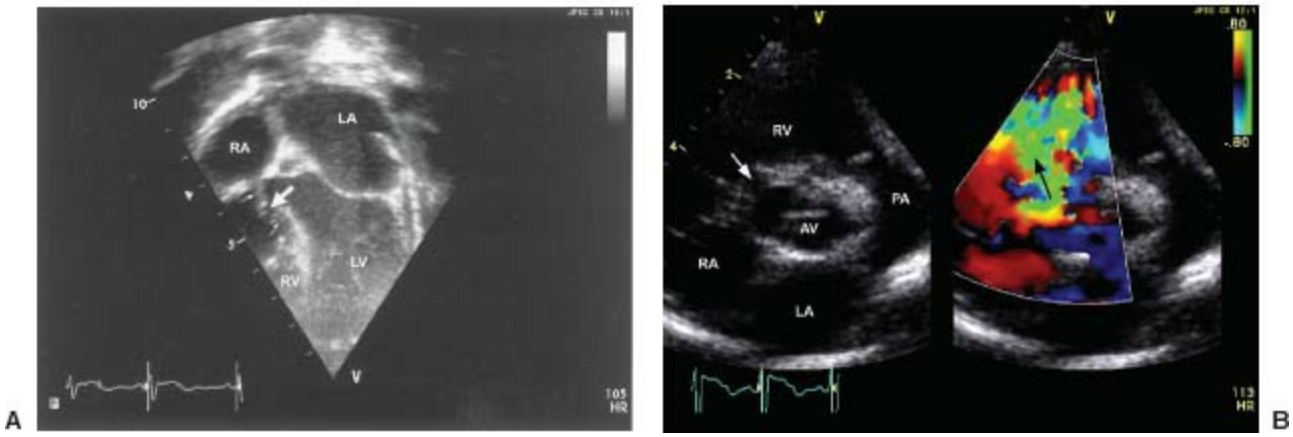


FIGURE 24.8 A Inverted apical four-chamber view (pediatric convention) demonstrating a perimembranous VSD with a ventricular septal aneurysm formed as the septal leaflet of the TV attempts to close the defect. The big arrow denotes the VSD and the region enclosed by the smaller arrows demonstrates the extent of the ventricular septal aneurysm. **B:** Parasternal short-axis views (two-dimensional (2-D) images on the left and color Doppler images on the right) demonstrate a perimembranous VSD with a 2-D defect noted near the RV inflow region near the TV, with left-to-right shunting seen in that location.

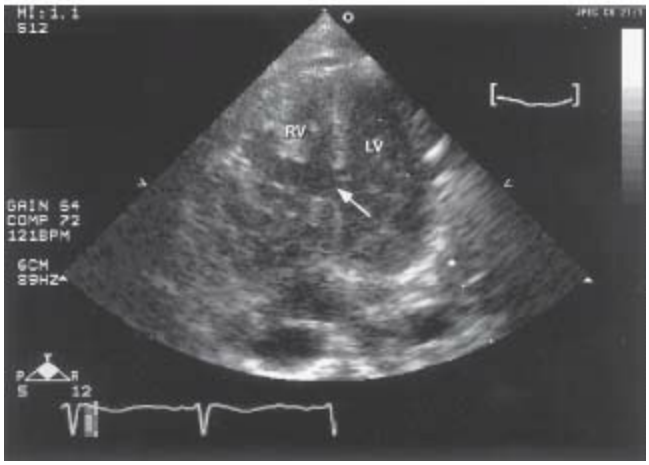


FIGURE 24.9 Apical four-chamber view demonstrating a large muscular VSD in the midseptum. Note the dilated right side as a result of long-term left-to-right shunting and right-sided volume overload.

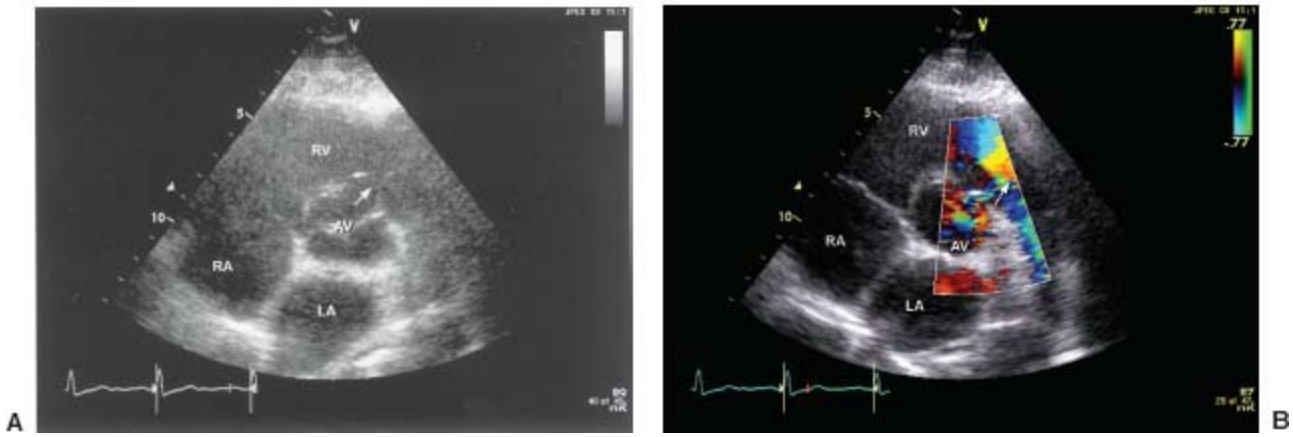
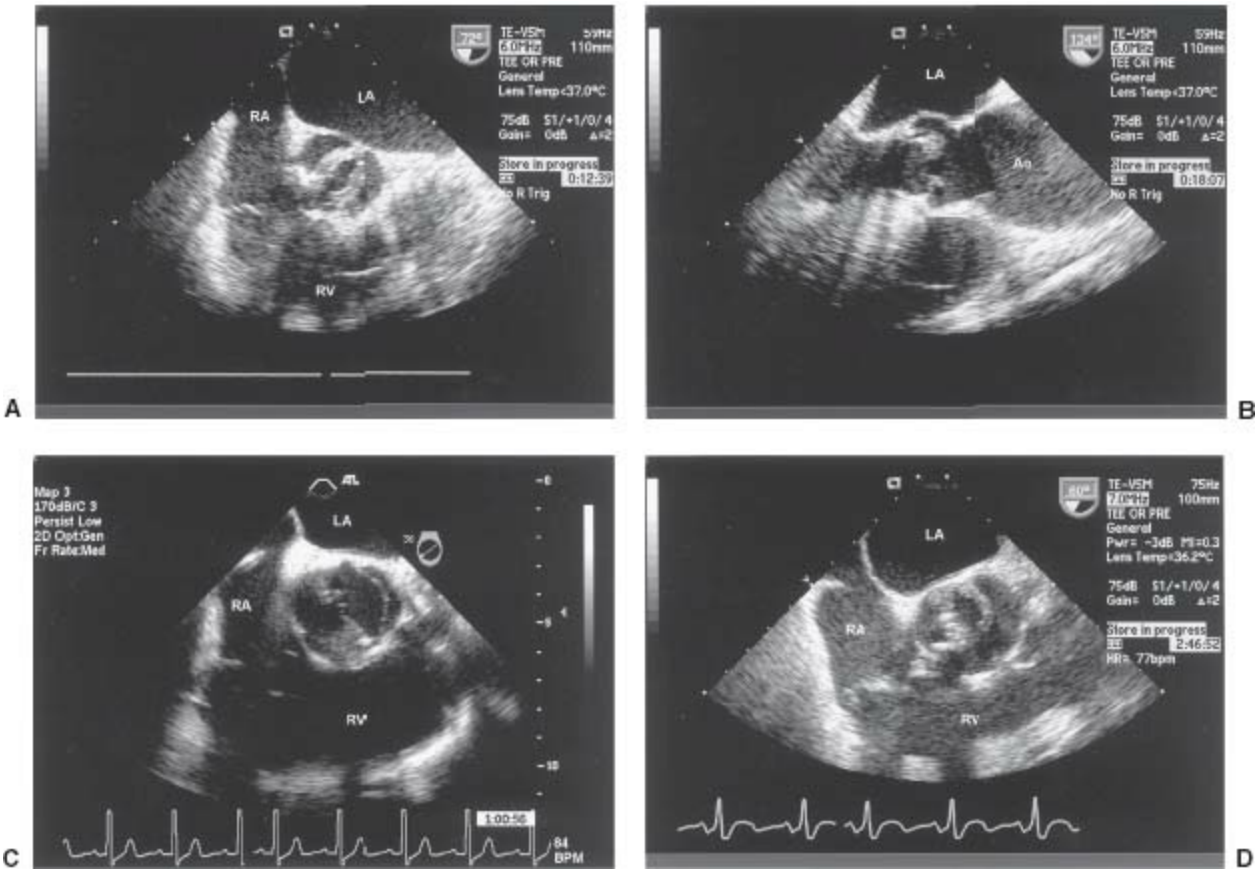


FIGURE 24.10 A: Parasternal short-axis view demonstrating the 2-D defect of a supracristal VSD located near the RVOT. **B:** Parasternal short-axis view with color Doppler demonstrating a fine jet of left-to-right flow through the

supracristal VSD.

BICUSPID AORTIC VALVE

Bicuspid aortic valve occurs in 1% to 2% of the general population. The most common form is a fusion of the RCC and the LCC. Congenital abnormalities of aortic cusp anatomy are shown in Figure 24.11A–G. Characteristics of bicuspid aortic valve include the following:



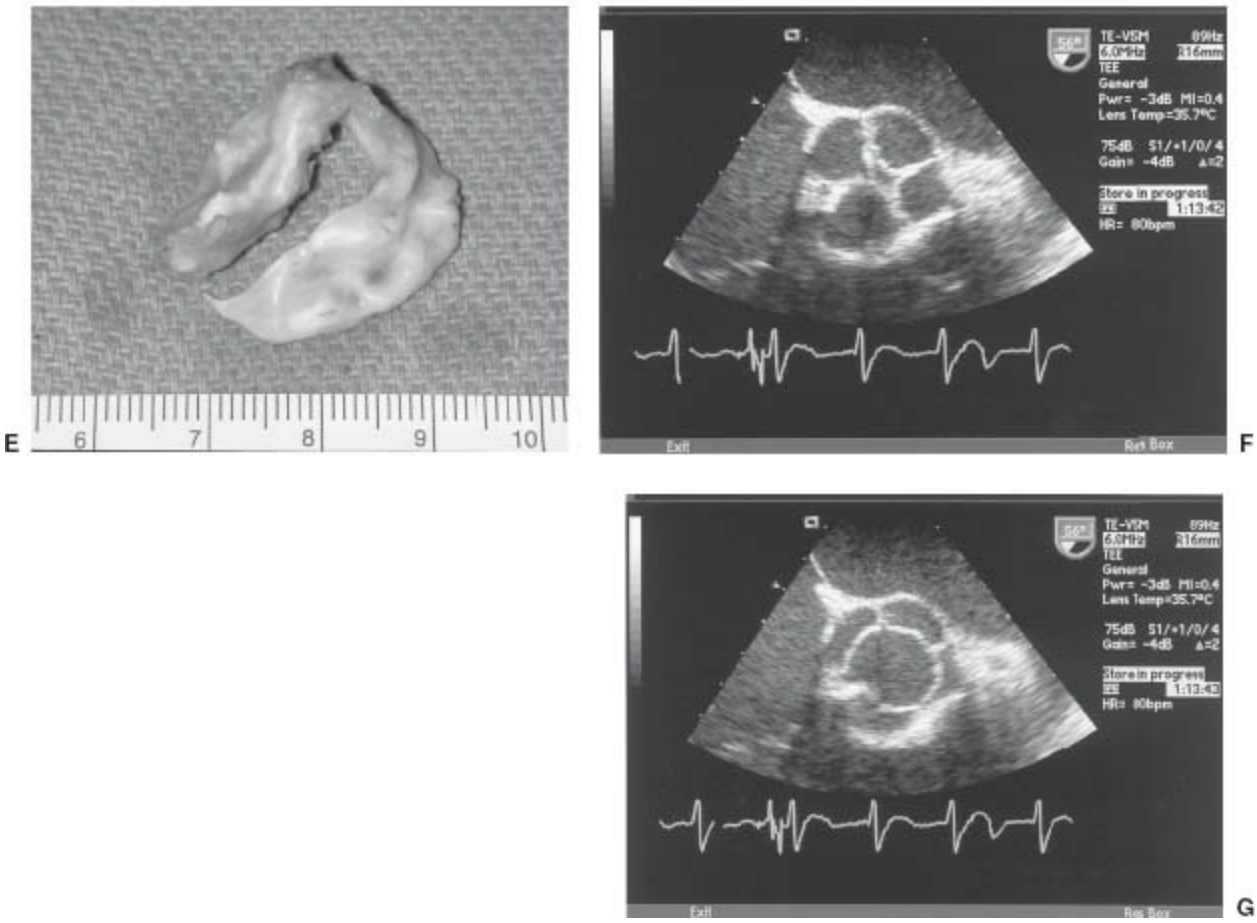


FIGURE 24.11 A: Midesophageal short-axis view of the aortic valve demonstrating a bicuspid aortic valve with fusion of the right coronary cusp (RCC) and the left coronary cusp (LCC). The leaflets are somewhat thickened and there is a combination of aortic regurgitation as well as a component of stenosis. **B:** Long-axis midesophageal view demonstrating doming of a bicuspid aortic valve. Because of the significant leaflet doming, it is very important to obtain an on-axis, short-axis view. Off-axis images may cause overestimation of a planimetered aortic valve area (therefore underestimating the degree of AS). **C:** Midesophageal short-axis view of the aortic valve demonstrating a bicuspid aortic valve with non-coronary cusp (NCC) and right coronary cusp (RCC) fusion. **D:** Midesophageal short-axis view of the aortic valve demonstrating a unicuspid aortic valve. Note the eccentric opening with a single commissure at the 11:00 position. **E:** Gross pathologic specimen of a unicuspid aortic valve. **F:** Magnified midesophageal short-axis view of the aortic valve demonstrating a quadricuspid valve in diastole. **G:** Magnified midesophageal short-axis view of the aortic valve demonstrating a quadricuspid valve in systole. Note the presence of four separate cusps.

- The mechanism of AI is prolapse of the conjoined cusp.
- The long-axis view shows asymmetric closure of the AV with doming leaflets.
- It may be associated with coarctation of the aorta. At least 50% of patients with coarctation have bicuspid AV; fewer with bicuspid valves have coarctation.
- Early (typically ages 30s to 40s), affected individuals have problems with AI. RCC and LCC fusion produces a posteriorly directed jet.
- Later (typically, ages 50s to 60s), they have problems with aortic stenosis (AS).
- AI may be amenable to valve repair.
- Patients with bicuspid aortic valves have an aortopathy which may cause aortic

dilatation with increased risk of dissection. Typically indications for aortic surgery based on size of the aorta are the same as those used for Marfan patients

Helpful hint: To identify and name cusps, look for the interatrial septum. The leaflet closest to the interatrial septum is the noncoronary cusp (NCC). The LCC is always at the right of the screen.

SUBAORTIC AORTIC STENOSIS

Subaortic aortic stenoses, or subaortic membrane, is shown in Figure 24.12A,B and involves the following features:

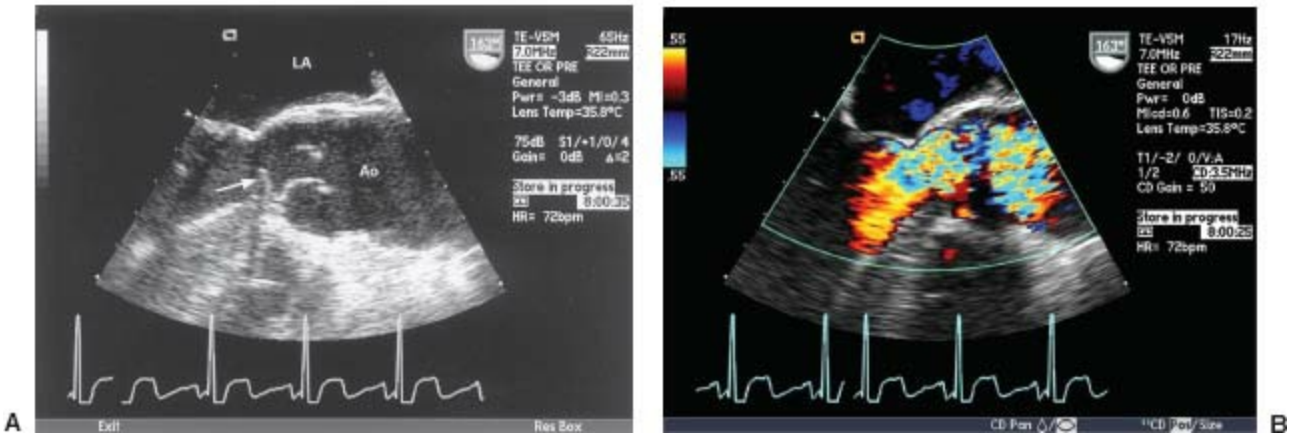


FIGURE 24.12 A: Magnified midesophageal long-axis view of the aortic valve and LVOT demonstrating a subaortic membrane 1 mm beneath the aortic valve. **B:** Magnified long-axis view of the aortic valve and LVOT with color Doppler demonstrating a subaortic membrane with the color disturbance/acceleration occurring in the LVOT at the site of the membrane. It is important to note that the color acceleration occurs before the aortic valve, which should alert the cardiologist to the presence of a membrane (by transthoracic echocardiography [TTE] or transeophageal echocardiography (TEE), even if the membrane is not seen by 2-D imaging alone).

- The membrane is usually 1 to a few millimeters below the AV.
- It may be associated with perimembranous VSD, coarctation of the aorta, or valvular AS.
- Eccentric turbulent flow through the AV often traumatizes and causes scarring, leading to development of AI.
- Patients are at risk for endocarditis; however, antibiotic prophylaxis is no longer recommended.
- Patients can develop left ventricular hypertrophy (LVH) in response to high gradients.
- A small percentage of membranes grow back postresection.
- Surgical excision is appropriate for patients with symptoms, LVH with strain, or significant outflow gradients. It may or may not be appropriate for patients who are

asymptomatic with low gradient. Resection may prevent trauma to the AV and help prevent the development of AI.

PATENT DUCTUS ARTERIOSUS

In the fetus, the ductus diverts blood flow from the non-functioning pulmonary circuit into the aorta and back to the placenta. It normally closes within 24 to 48 hours of birth. PDA is found in 2% of adults with congenital heart disease (Figs. 24.13A,B and 24.14A,B). It is distinguished by the following:

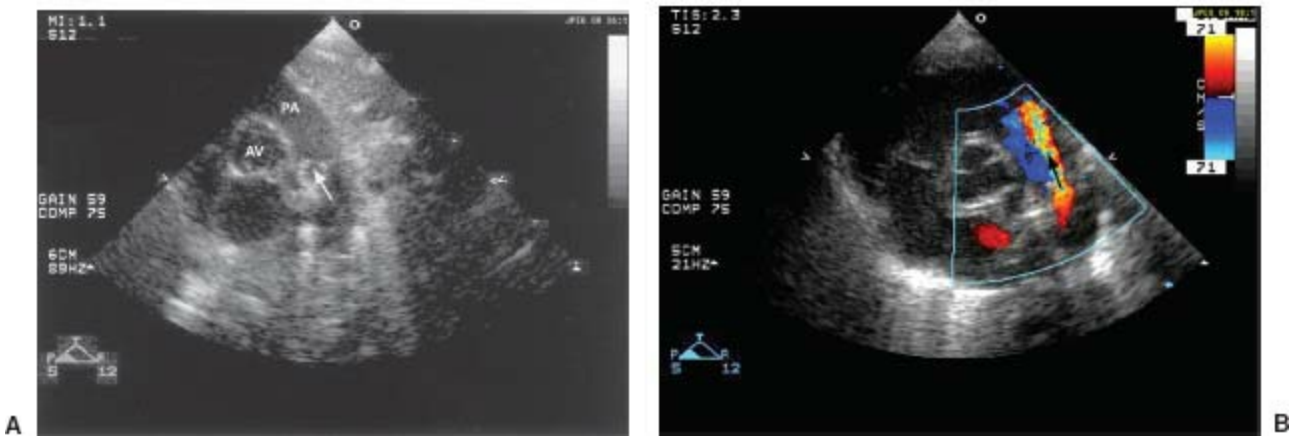


FIGURE 24.13 A: Parasternal short-axis view demonstrating the opening of a PDA into the PA (arrow). **B:** Parasternal short-axis view with color Doppler demonstrating flow from the descending aorta into the PA (arrow).

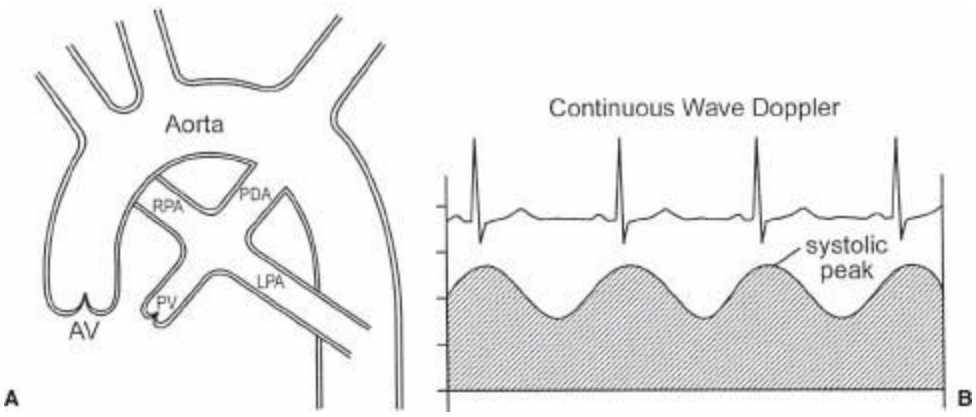


FIGURE 24.14 A: Diagram of PDA. Aortic arch view with great vessels arising superiorly off the aorta, with the patent ductus arising from the aorta across from the origin of the subclavian artery, with flow into the PA. **B:** Continuous-wave Doppler pattern of flow in PDA.

- It is usually isolated, but it can occur with complex lesions, coarctations, or VSD.
- When the ductus remains patent after birth, there is left-to-right shunting through the ductus arteriosis. Therefore, there is an abnormal persistent fetal connection between the left PA and the descending aorta.
- Auscultation reveals a machinery-type murmur.

- Applying a modified Bernoulli equation, one can use the peak systolic velocity of the PDA jet to determine the systolic gradient between the aorta and the PA.
- If PDA is left untreated, patients may develop congestive heart failure (CHF) from chronic left heart volume overload. Rarely, they can develop endocarditis and therefore need antibiotic prophylaxis. Typically, antibiotic prophylaxis is continued for 6 months after surgical or percutaneous closure.

COARCTATION OF THE AORTA

Coarctation of the aorta in adults involves a discrete ridge or focal narrowing of the descending aorta opposite the ligamentum arteriosus of the ductus arteriosus (Fig. 24.15A). Characteristics of this condition include the following:

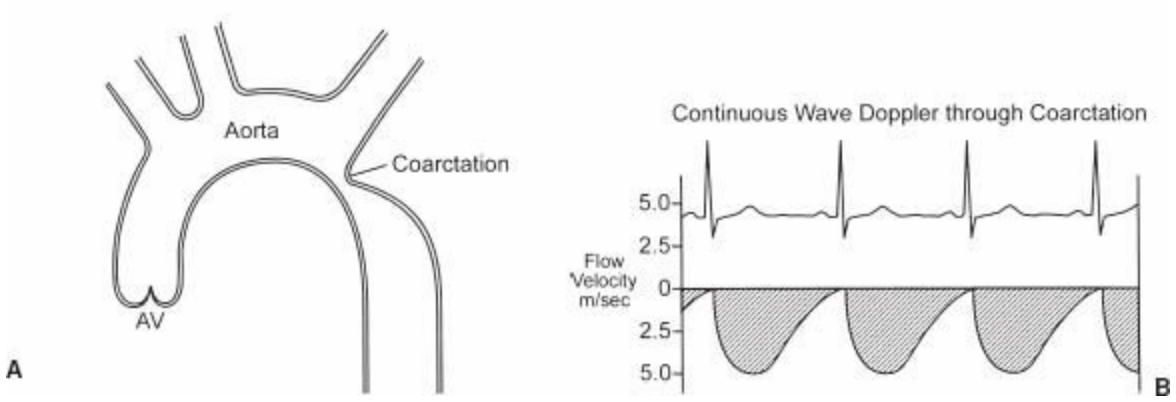


FIGURE 24.15 A: Diagram of coarctation of the aorta. Aortic arch view showing narrowing immediately distal to the takeoff of the subclavian artery. **B:** Continuous-wave Doppler in the proximal descending aorta across the coarctation, with classic "sawtooth" flow pattern.

- Clinical presentation includes hypertension, a decrease in femoral pulses, and LVH.
- Fifty percent of adults with coarctation have bicuspid aortic valves.
- Continuous-wave Doppler through the proximal descending aorta displays high peak velocity in systole and a gradient that persists into diastole (Fig. 24.15B).
- Alternative imaging modalities may be needed to define the anatomy of coarctation exactly.
- Chest radiography shows rib notching due to development of collaterals (intercostal arteries) (Fig. 24.16).

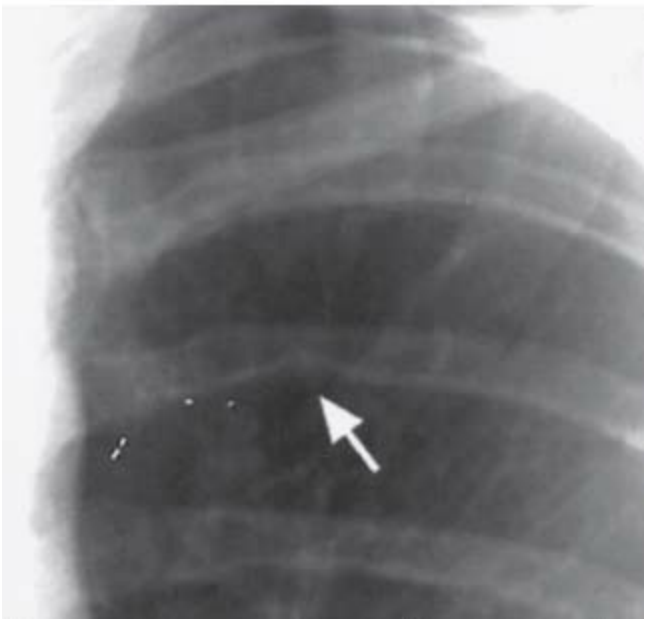


FIGURE 24.16 Chest radiograph demonstrating rib notching (arrow) that is characteristic of coarctation of the aorta, resulting from the markedly increased blood flow through the intercostal arteries.

Coarctation of the aorta is further illustrated in Figure 24.17A–D.

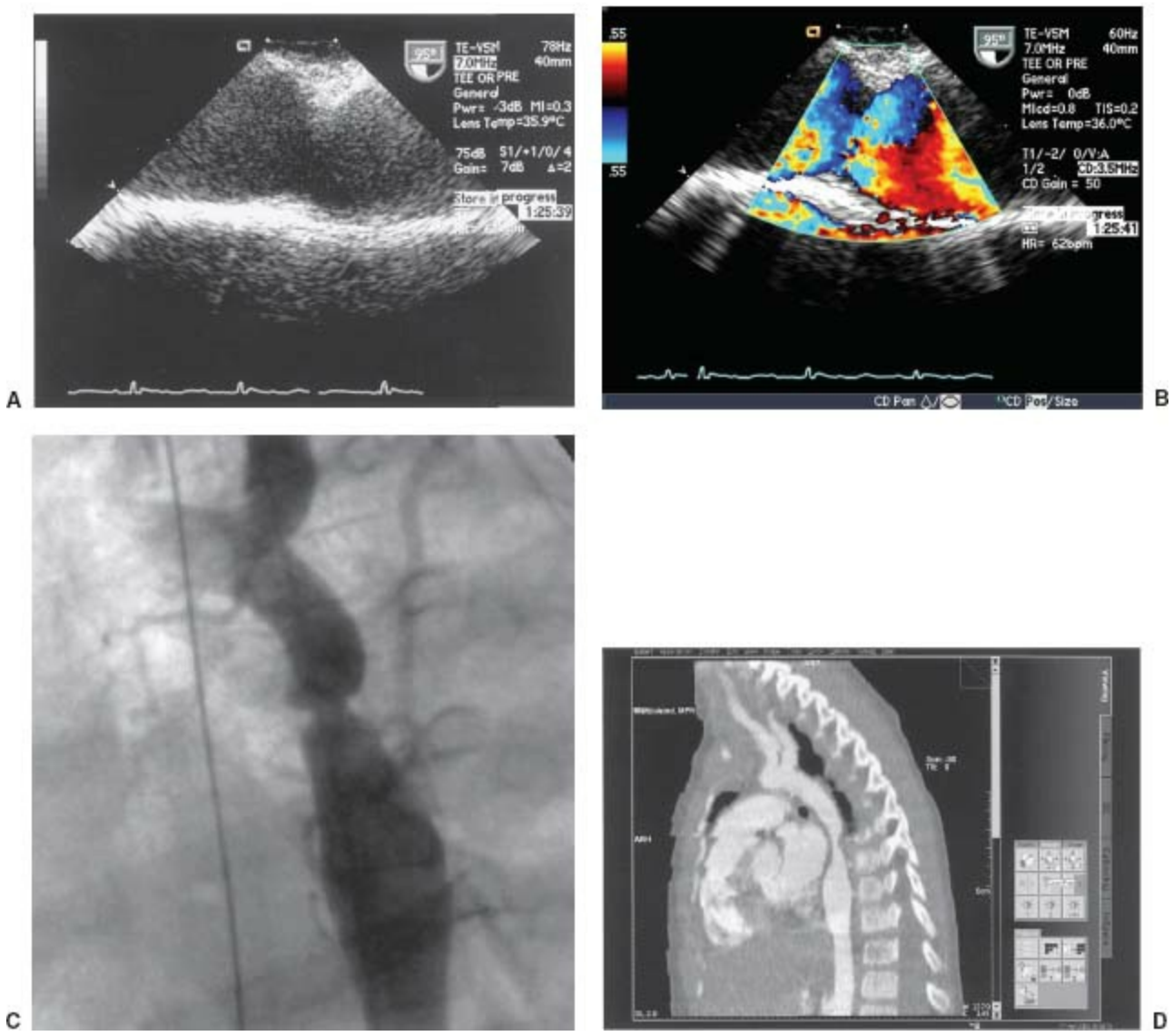


FIGURE 24.17 A: TEE long-axis view of the proximal descending aorta demonstrating the coarctation narrowing. **B:** TEE long-axis view of the proximal descending aorta with color Doppler demonstrating flow acceleration across the coarctation narrowing. **C:** Aortography demonstrating aortic coarctation narrowing in the descending aorta. **D:** MRI sagittal view of the thoracic aorta demonstrating coarctation narrowing.

PULMONIC STENOSIS

Pulmonic stenosis (PS) can be valvular, subvalvular (infundibular), or supravalvular (Fig. 24.18A–C). The following features distinguish PS:

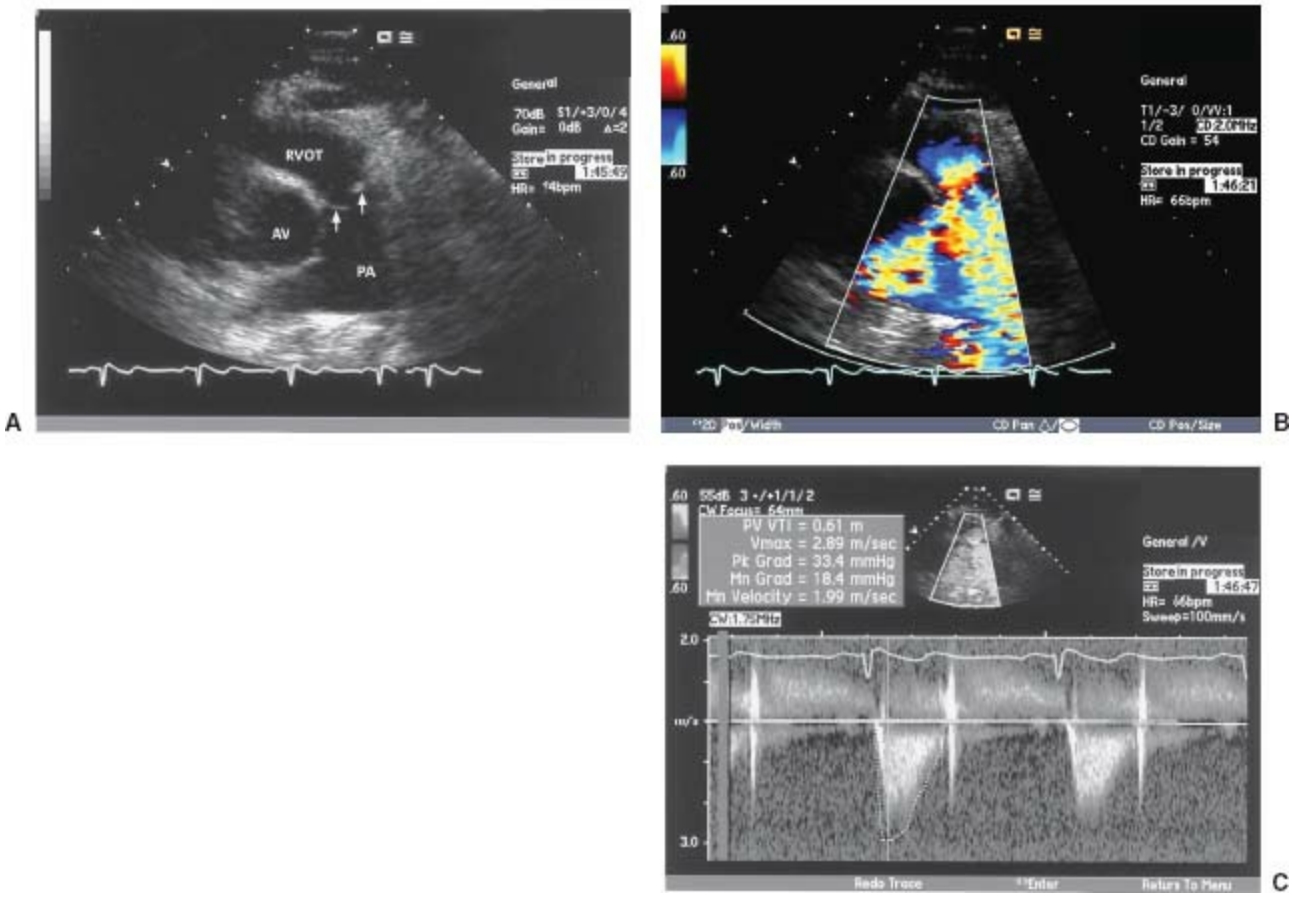


FIGURE 24.18 A: Parasternal short-axis view demonstrating doming of the stenotic pulmonic valve. **B:** Parasternal short-axis view with color Doppler demonstrating flow acceleration across the stenotic pulmonic valve. There is a relatively large proximal flow convergence zone proximal to the pulmonic valve, due to the high transvalvular gradient. **C:** Continuous-wave Doppler across the pulmonic valve with traced peak and mean pressure gradients. (Peak/mean gradients are 33/18 mm Hg.)

- ECG findings may be normal in mild cases.
- Right-axis deviation and RVH are seen on ECG in moderate cases.
- The degree of RVH correlates with the severity of the PS.
- On chest radiograph, the heart size is usually normal, but the main PA is prominent.
- Pulmonary vascular marking are usually normal but may be decreased in severe cases.
- Balloon valvuloplasty is often the procedure of choice for treatment (with RV pressure ≥50 mm Hg). Surgery is often reserved for cases of failed percutaneous intervention.
- Although patients are at increased risk for endocarditis, subacute bacterial endocarditis (SBE) prophylaxis is no longer recommended.

TETRALOGY OF FALLOT

The four elements of tetralogy of Fallot are:

1. VSD (large and nonrestrictive)
2. Overriding aorta
3. Infundibular PS
4. RVH

Defects in this condition result from abnormal conotruncal septation (anterior deviation of the infundibular septum). About 15% of patients also have ASD, making the condition "pentalogy" of Fallot. Other associated defects may include valvular PS (50% to 60%), right aortic arch (25%), muscular VSD (2%), and coronary anomalies (5%).

Early in life, mild PS may be present with no significant shunting, known as "pink tetralogy." As subvalvular PS increases with time, pulmonary blood flow decreases and patients develop significant right-to-left shunting, causing cyanosis, or "blue tetralogy."

Tetralogy of Fallot is illustrated in Figure 24.19A–D.

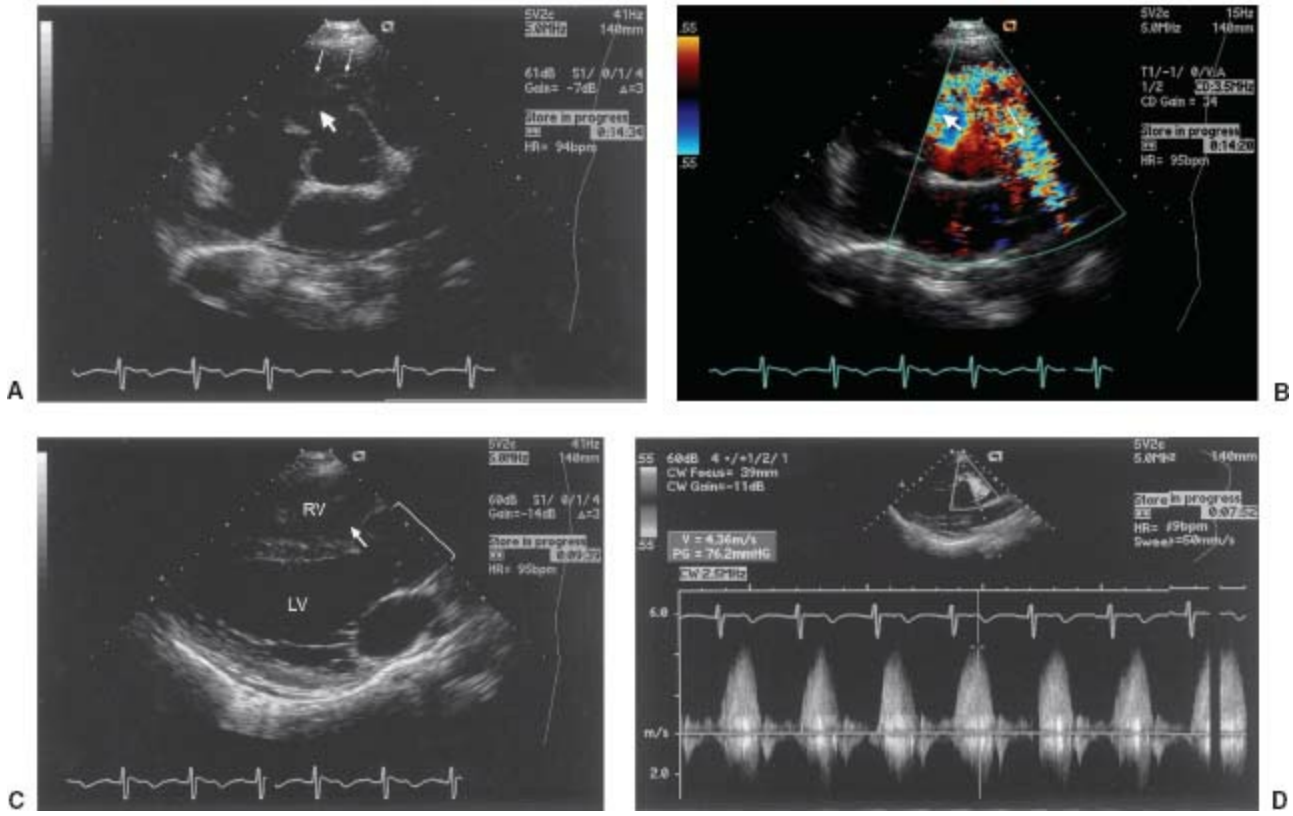


FIGURE 24.19 A: Parasternal short-axis view demonstrating a large, nonrestrictive VSD (thickarrow) and infundibular PS (thin arrows) with hypertrophy of the RVOT. **B:** Parasternal short-axis view with color Doppler showing a large VSD with significant left-to-right shunting (thickarrow) and the color acceleration/high-velocity flow associated with subpulmonic PS (long thin arrow) . **C:** Parasternal long-axis view demonstrating a large perimembranous VSD and an overriding aorta. **D:** Continuous- wave Doppler through the RVOT/pulmonic valve demonstrating the high pressure gradients of the infundibular PS. The peak gradient across the stenosis is 76 mm Hg.

EBSTEIN ANOMALY OF THE TRICUSPID VALVE

Ebstein's anomaly of the TV is characterized by apical displacement of the TV into the RV (Fig. 24.20). The following features distinguish this condition:

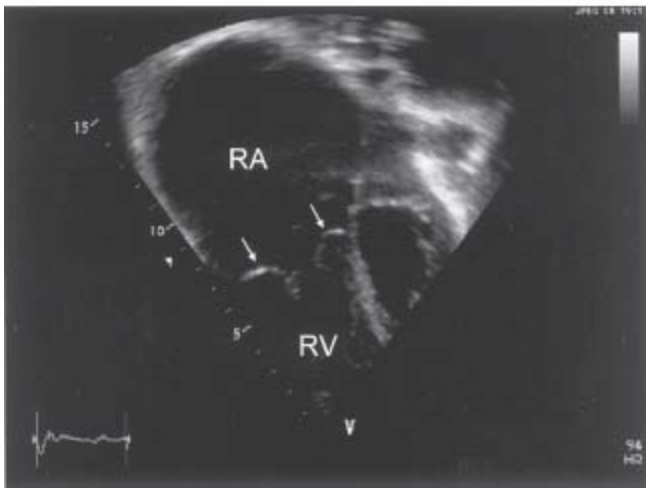


FIGURE 24.20 Apical four-chamber view (pediatric view) demonstrating apical displacement of the TV with apical tethering of the leaflets causing severe tricuspid regurgitation (TR). Note the severe RA dilatation.

- TV tissue is dysplastic, with portions of the septal and inferior cusps adherent to RV away from the AV junction.
- Clinical manifestations are variable, depending on associated manifestations.
- Patent foramen ovale (PFO) or secundum ASD is present in >50% cases.
- A common important associated defect is PS or atresia.
- Other associations include primum ASD and VSD or congenitally corrected transposition.
- Wolf–Parkinson–White syndrome (WPW) is found in 10% to 15% of patients with Ebstein anomaly.
- ECG commonly shows RBBB or WPW. Most common is giant P waves and prolonged P–R interval with variable degrees of RBBB.
- The presence of WPW increases the risk of paroxysmal supraventricular tachycardia.
- Chest radiography shows a large RA and small RV with decreased pulmonary vascularity if a large right-to-left shunt is present.

TRANSPOSITION OF THE GREAT ARTERIES

Transposition of the great arteries (D-TGA) is defined as "ventriculoarterial discordance," with the aorta connected to the RV and the PA connected to the left ventricle (Fig. 24.21A,B). It is caused by abnormal conotruncal septation in development, with "D-transposition" denoting that the direction of septal rotation is in a dextro, or rightward, direction (Fig. 24.22).

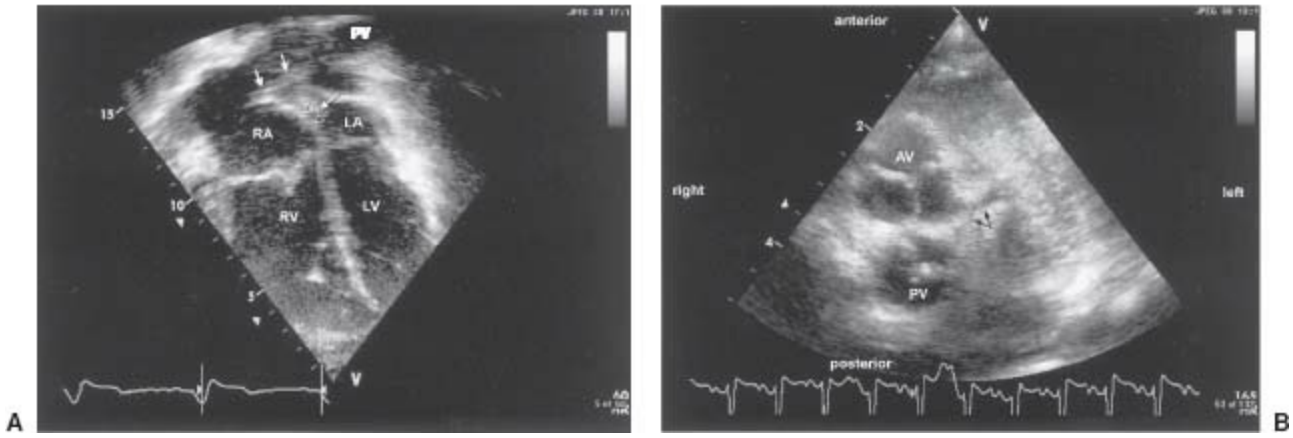


FIGURE 24.21 A: Apical four-chamber view with baffles (arrows) at the atrial level directing blood from the pulmonary veins to the RA and caval flow directed to the LA. Note that the pacemaker wire is within the LA (a clue to the presence of D transposition). **B:** Parasternal short-axis view of both the aortic and pulmonic valves showing the parallel course of the great vessels in D-TGA. In D transposition, the aorta (with the left coronary artery marked by arrows) is located anterior and to the right of the PA.

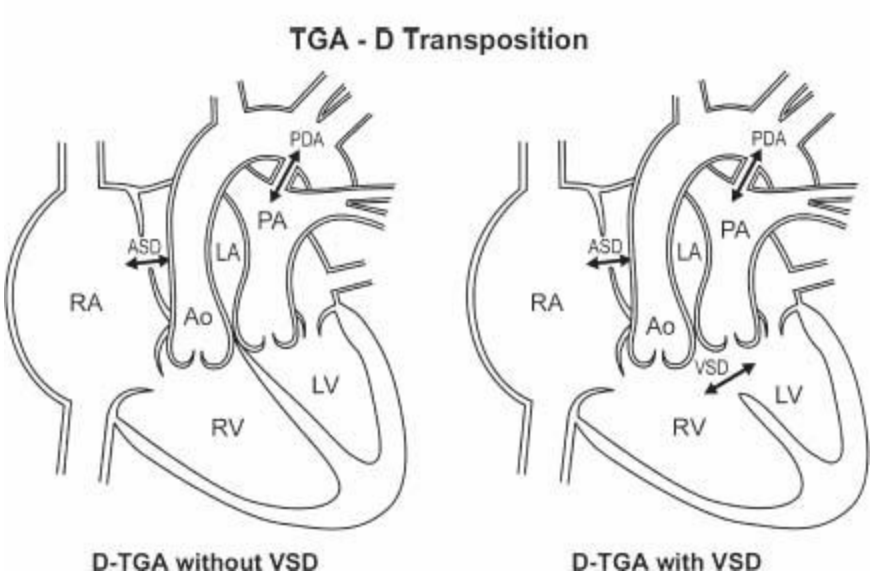


FIGURE 24.22 Diagram of d transposition both with and without VSD.

TGA may or may not have associated lesions. There must be mixing of venous and systemic blood at some level for survival (ASD, VSD, or PDA). Otherwise, the pulmonic circulation and the systemic circulation would be two separate and parallel circuits, which is not compatible with life. Common associated defects include ASD, perimembranous VSD, coarctation of the aorta, PS, and PDA. Further features of this condition include the following:

- The aorta is anterior and to the right of the PA, because the aorta arises from the RV. The two great arteries run parallel (Fig. 24.23).
- There is fibrous continuity between the anterior mitral leaflet and the pulmonic valve

compared to the normal relationship with continuity between the anterior mitral leaflet and the aortic valve.

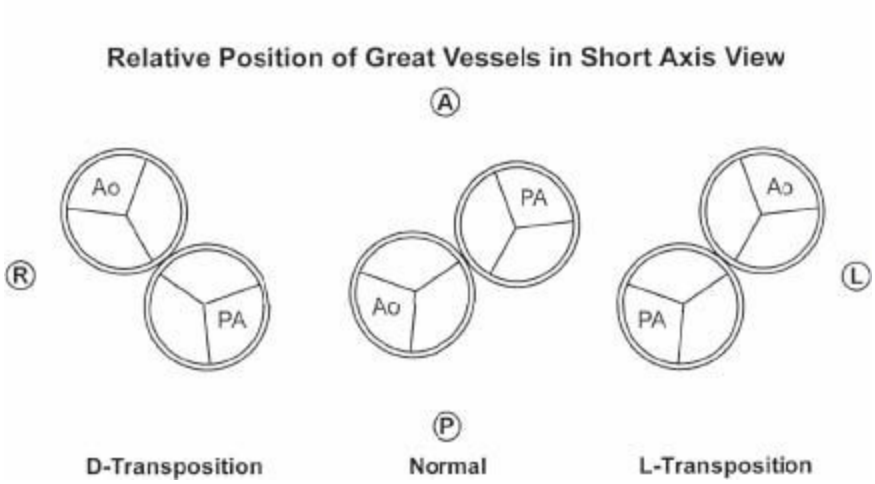


FIGURE 24.23 Relative position of great arteries in TGA. Normal position of great arteries **(center):** the PA wraps anteriorly around the aorta. d transposition **(left):** great arteries run parallel, with the aorta anterior and to the right of the PA. l transposition **(right):** great arteries run parallel with the aorta anterior and to the left of the PA.

CONGENITALLY CORRECTED TRANSPOSITION OF THE GREAT ARTERIES

Congenitally corrected D-TGA is defined as levotransposition, or L-transposition, in which the great arteries are transposed and the ventricles are inverted as well (Fig. 24.24A,B).

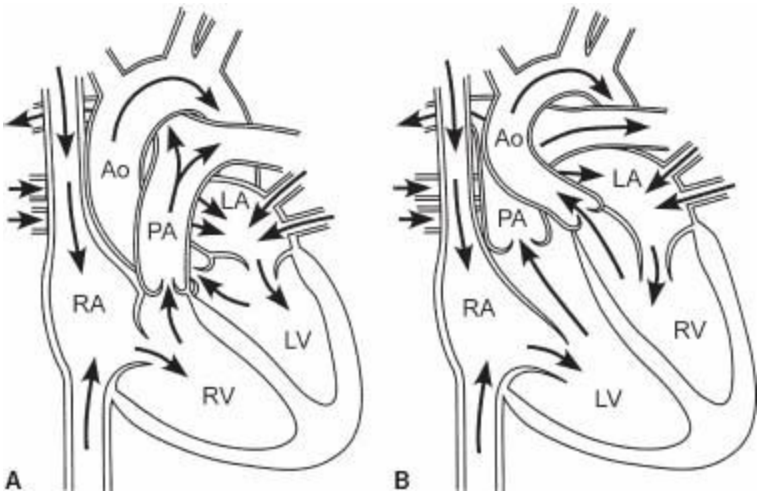


FIGURE 24.24 Normal blood flow versus blood flow and anatomy in congenitally corrected transposition. In congenitally corrected transposition **(right),** systemic venous return → RA → LV → PA → lungs. Pulmonary venous return → LA → RV → Aorta → body.

There is a "double switch" that allows a physiologically appropriate flow of blood. Atria are in normal position and are connected to the "opposite ventricle." Systemic

venous return is pumped to the lungs by the morphologic left ventricle and PV return is pumped to the aorta by the morphologic RV. Echocardiographic features include the following (Fig. 24.25A–C):

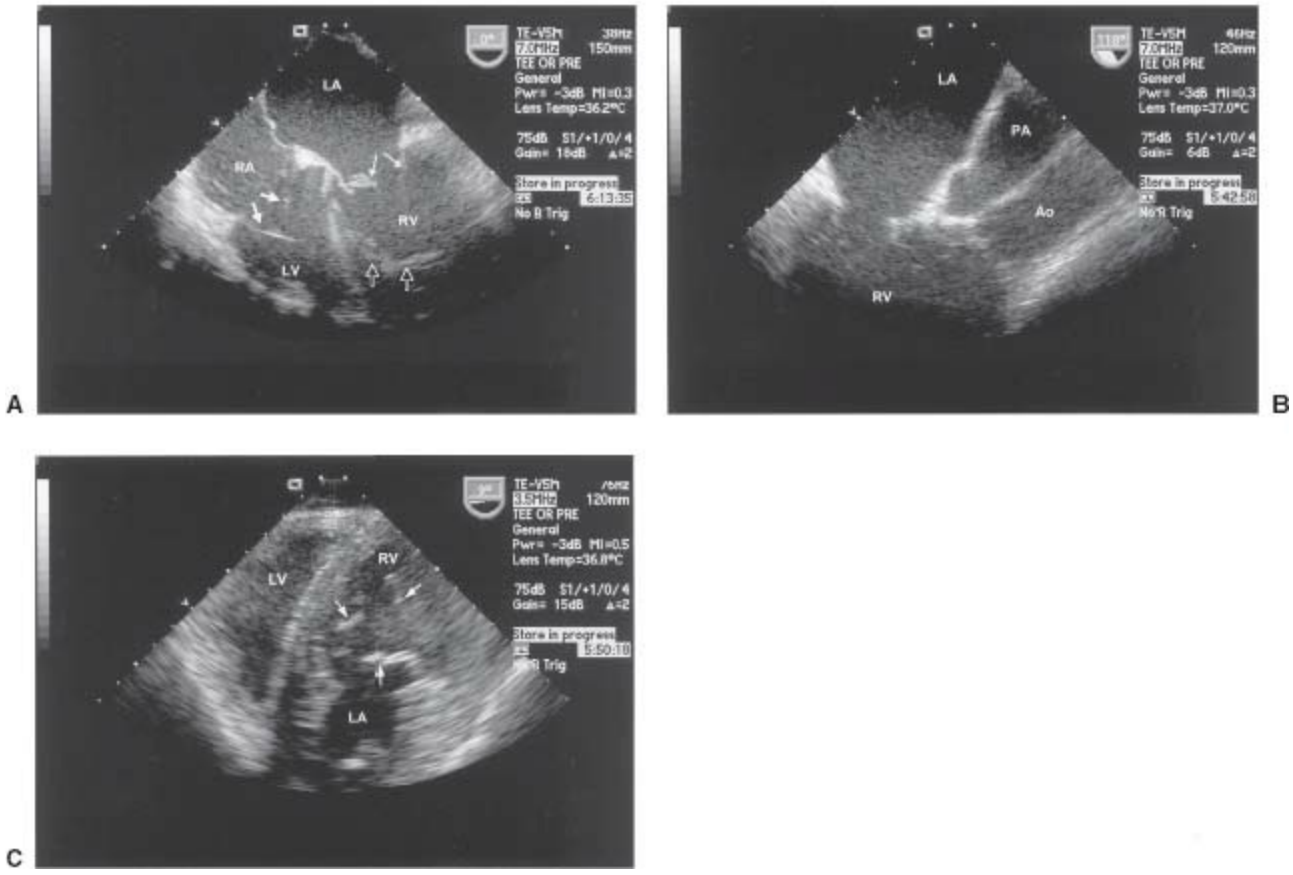


FIGURE 24.25 A: Apical four-chamber view of a patient with congenitally corrected D-TGA with an apically placed TV on the left side of the heart with the systemic RV. Note the location of the moderator band within the systemic ventricle. The LV pumps blood to the lungs. **B:** TEE demonstrating the parallel course of the great arteries with the anterior mitral leaflet contiguous with the pulmonic valve with a separation between the atrial mitral leaflet and the aortic valve. **C:** Deep transgastric view demonstrating the systemic RV with the left-sided TV (arrows).

- The TV is the apically displaced AV valve with respect to the MV.
- The morphologic RV is identified by the presence of a moderator band and the presence of trabeculations. Recall that AV valves always feed the appropriate ventricle (i.e., TV always feeds the RV).
- The left ventricular (LV) is identified by its smooth walls, absence of moderator band, and continuity between the AV and semilunar valves.
- There is discontinuity between the left-sided AV valve and the semilunar valve (aortic).
- The PA and aorta run parallel (as opposed to normal orthogonal position). The aorta lies anterior to the PA.

Several associated lesions can be found in patients with congenitally corrected D-TGA.

Abnormalities of left-sided TV occur in 90% of patients. Ebstein-type abnormality is the most common of these, with apical displacement of the valve and the septal leaflet typically being most deformed. VSD occurs in 70% of patients, most commonly perimembranous. Pulmonic outflow obstruction (i.e., LVOT obstruction) occurs in 40% of patients, sometimes in conjunction with VSD. Patients have an increased risk of acquired complete heart block due to the abnormally placed AV node.

On chest radiograph, because the aorta is anterior and to the left, the left heart border is straightened. The left PA is not well defined. If there is PS, there may be decreased lung markings; and if there is a VSD, there may be increased lung markings.

On ECG, typically one can see left-axis deviation. A variety of AV node conduction abnormalities may be seen and over time progress to complete heart block.

OPERATIONS FOR CONGENITAL HEART DISEASE

Surgical techniques to treat congenital heart disease have evolved over the last 50 years. Early techniques were predominantly palliative, providing temporary relief of symptoms or of a clinical condition. Over time, with improvement in diagnostic as well as surgical capabilities, corrective techniques were developed. Corrective operations can achieve “normal anatomy,” “normal hemodynamics,” and/or normal physiology. Some surgical approaches may require staged procedures. The trend has been toward performing corrective procedures earlier, with fewer palliative procedures being performed. Many acronyms are used to describe the various surgical techniques (Table 24.3). As more of these surgical techniques are performed, more of these patients will survive into adulthood and will transition to the care of specialists in adult cardiology. Having a basic knowledge of simple congenital heart disease as well as of classic postoperative conditions will be useful for all cardiologists.

TABLE
24.3 Palliative and Corrective Operations for Congenital Heart Lesions

Name of Operation	Palliative versus Corrective	Anatomy/Description	Goal/Outcome
Blalock–Taussig shunt (classic) (1944)	P	Shunt from subclavian artery to PA	↑ pulmonary blood flow
Modified Blalock–Taussig shunt	P	Gortex interposition graft from subclavian artery to PA	↑ pulmonary blood flow
Potts shunt (1946)	P	Anastomosis of descending aorta and left PA	↑ pulmonary blood flow
Waterston shunt (1960)	P	Anastomosis of ascending aorta to right PA	↑ pulmonary blood flow
Central shunt	P	Gortex graft from ascending aorta to PA	↑ pulmonary blood flow
Glenn shunt (1954)	P	Shunt from SVC to right PA	Provides low-pressure flow to PA
PA band	P	Band around main PA	↓ pulmonary blood flow
Fontan operation	C	Separate systemic and pulmonary circulations by creating cavopulmonary connection	■ Directs systemic venous blood to lungs ■ Allows ventricle(s) to pump PV blood to body ■ ↓ Volume load from single ventricle
Jatene (1975)	C	Arterial switch for transposition	
Mustard (1964)	C	Pericardial baffle to redirect PV return toward TV and systemic return toward MV	Atrial-level correction for transposition
Sennig (1959)	C		Atrial-level connection/inversion for D transposition
Rastelli (1969)	C	Connecting LV with aorta and RV with PA	Providing corrected circulation—LV pumping to systemic circulation and RV-to-pulmonary circulation

LV left ventricle; RV, right ventricle; PA, pulmonary artery; SVC, superior vena cava; MV, mitral valve.

SUGGESTED READINGS

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King ME. Echocardiographic evaluation of the adult with un-operated congenital heart disease. In: Otto CM, ed. The Practice of Clinical Echo. Philadelphia: WB Saunders; 1997:697–728.

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QUESTIONS AND ANSWERS

Questions

1. A cleft mitral valve (MV) is associated with which of the following conditions?
   a. Secundum atrial septal defect (ASD)

b. Primum ASD
c. Coarctation of the aorta
d. Sinus venosus (SV) ASD
e. Tetralogy of Fallot

2. All of the following regarding bicuspid aortic valves are true except:
   a. May be associated with coarctation of the aorta
   b. Often associated with posteriorly directed jets of aortic insufficiency (AI)
   c. Commonly seen with congenitally corrected transposition of the great vessels
   d. May be amenable to aortic valve repair
   e. Most common type involves fusion of the right coronary cusp (RCC) and left coronary cusp (LCC)

3. A sinus venosus ASD is most often associated with which of the following?
   a. Coarctation of the aorta
   b. Marfan syndrome
   c. Partial anomalous pulmonary venous (PV) drainage
   d. Tetralogy of Fallot

4. All of the following regarding Ebstein's anomaly are true except:
   a. A portion of the right ventricular (RV) is atrialized.
   b. Tricuspid valve (TV) leaflets are dysplastic and adherent to the RV.
   c. Common important associated defects include pulmonic stenosis (PS) or atresia.
   d. A patent foramen ovale (PFO) or secundum ASD is associated in >50% of cases.
   e. A common associated defect is coarctation of the aorta.

5. Complications associated with a subaortic membrane include all of the following except:
   a. AI
   b. Left ventricular hypertrophy (LVH)
   c. Atrial arrhythmias
   d. May recur postresection

6. Which of the following lesions are associated with an aortopathy which may increase a patient's risk for developing an aortic dissection?
   a. Hypertrophic obstructive cardiomyopathy (HOCM)
   b. Bicuspid Aortic Valve
   c. PS
   d. Sinus Venosus ASD
   e. Mitral valve prolapse (MVP)

7. The most common form of ASD seen in adults is:
   a. Secundum ASD
   b. Primum ASD
   c. Unroofed coronary sinus (CS)
   d. Sinus venosus ASD
   e. Supracristal ASD

8. All of the following are features of Tetralogy of Fallot except:
   a. Right ventricular hypertrophy (RVH)
   b. Ventricular septal defect (VSD)
   c. ASD (primum)
   d. Infundibular PS
   e. Overriding aorta

9. Which statement is true regarding patients with coarctation of the aorta?
   a. Fifty percent of patients with bicuspid aortic valves have coarctation of the aorta.

b. Patients typically have asymmetric septal hypertrophy.
c. PW Doppler in the descending aorta demonstrates pan diastolic flow reversal..
d. CW Doppler through the proximal descending aorta displays a high peak velocity in systole and a gradient that persists into diastole.

10. All of the following may be true for a patient with PS except:
a. Balloon valvuloplasty is often the procedure of choice for treatment (for RV pressures >50mm Hg).
b. EKG may show right axis deviation and RVH.
c. Pulmonary Artery may be dilated on chest X-ray (CXR).
d. Pulmonary vascular markings may be increased in severe cases.
e. The degree of RVH correlates with the severity of PS.

Answers

1. Answer B: A cleft MV is part of an atrioventricular (AV) canal defect, which is due to failure of the embryonic endocardial cushions to meet and partition the heart normally. A complete endocardial cushion defect has four components: primum ASD, cleft MV, inlet VSD, and a widened anteroseptal tricuspid commissure. A partial AV canal defect does not have the VSD.

2. Answer C: The most common form is fusion of the RCC and LCC, and the mechanism of AI in those patients is prolapse of the conjoined cusp. The conjoined cusp in the case of RCC and LCC fusion is anterior, and thus the AI is directed posteriorly. At least 50% of patients with coarctation of the aorta have a bicuspid valve. A bicuspid aortic valve with severe AI can often be surgically repaired, depending on the expertise of the surgical center.

3. Answer C: A sinus venosus ASD is a defect located near the junction of the inferior vena cava (IVC) or superior vena cava (SVC) and the right atrial (RA). It is typically difficult to see by surface echocardiogram, often requiring a transesophageal echocardiography (TEE) for diagnosis. It is usually associated with drainage of the right pulmonary veins to the RA.

4. Answer E: Ebstein's anomaly of the TV is characterized by apical displacement of the TV into the RV. As a result, a portion of the RV becomes atrialized. TV tissue is dysplastic, with portions of the septal and inferior leaflets becoming adherent to the RV. Clinical manifestations depend on associated conditions. An important associated defect is PS or atresia. Other associations include primum ASD and VSD, and congenitally corrected transposition of the great vessels.

5. Answer C: The turbulent, high-velocity jets produced by the membrane damage the aortic valve over time, and patients often develop AI that requires surgery. The subaortic membrane is a fixed obstruction, which requires the left ventricle to develop high intracavitary pressures for ejection. As the left ventricular (LV) pumps against the fixed obstruction, LVH develops (similar to what is seen with valvular AS). Subaortic membranes are known to recur occasionally postresection, although the frequency with which this occurs is unknown.

6. Answer B: Patients with a bicuspid aortic valve have an aortopathy involving cystic medial necrosis and decreased expression of fibrillin-1 with a tendency toward aneurysm formation and an increased risk for aortic dissection. The guidelines used for timing of aortic surgery for a dilated aorta in a patient with a bicuspid aortic valve are the same as those used in Marfan's patients.

7. Answer A: Secundum ASDs are the most common form of ASD at 75% with primum ASD representing 20%, sinus venosus ASDs in 5% and unroofed coronary sinus ASDs being rare. Supracristal is a type of VSD, not ASD.

8. Answer C: A primum ASD is part of either a partial or complete AV canal defect. The other features of a complete AV canal defect include inlet VSD, cleft MV, and Widened anteroseptal tricuspid commissure. The features of Tetralogy of Fallot include VSD, RVH, Infundibular PS, and overriding aorta.

9. Answer D: Fifty percent of patients with coarctation of the aorta have a bicuspid AV; however, the percentage of patients with bicuspid AVs who have a coarct is much smaller. CW Doppler through the proximal descending aorta in a patient with a coarctation of the aorta does show a high peak gradient as

well as a gradient that persists into diastole. Pan diastolic flow reversal in the descending aorta by PW Doppler is characteristic of severe AI, not a coarctation of the aorta.

10. Answer D: All of the above are true in a patient with PS except answer d. In fact pulmonary vascular markings may be decreased in patients with severe PS due to decreased flow to the lungs due to the severe obstruction to flow at the level of the pulmonic valve. There is not an increase in lung markings in these patients.

SECTION V ■ CARDIAC ELECTROPHYSIOLOGY

CHAPTER

Twelve-Lead Electrocardiography

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The electrocardiogram (ECG) is an essential diagnostic test. In many ways, it is an ideal diagnostic modality because it is noninvasive, is readily performed without discomfort or potential patient injury, is inexpensive, and its results are immediately available. Most important, it provides a diagnostic window of cardiovascular surveillance for a multitude of cardiac pathophysiologic problems, including valvular, myocardial, pericardial, and ischemic heart disease. The ECG's diagnostic utility is critically dependent on its accurate interpretation. This chapter addresses the diagnostic possibilities encountered in routine ECG interpretation, including a broad collection of clinical examples. A clinical history, detailed interpretation, and diagnostic summary are included for each tracing. A detailed review of this chapter will provide comprehensive preparation for the Cardiovascular Medicine Subspecialty Board Examination.

BOARD PREPARATION

To receive a passing score on the Cardiovascular Medicine Subspecialty Board Examination, the examinee must also receive a passing score on the ECG subsection. To best prepare for the ECG section, familiarization with the scoring sheet is essential. The scoring sheet is sent to each examinee before the test date, with diagnoses grouped systematically for easy reference. In preparation, understanding and being able to recognize each diagnosis is a "foolproof" preemptive approach.

A RECOMMENDED APPROACH TO ELECTROCARDIOGRAM INTERPRETATION

To ensure accurate and consistent ECG interpretation, a systematic approach is

required. ECG interpretation is not an exercise in pattern recognition. To the contrary, employing a methodical strategy based on a thorough knowledge of the cardiac conduction sequence, cardiac anatomy, cardiac physiology, and cardiac pathophysiology can be applied to all ECGs, regardless of the findings.

One systematic approach to each ECG is to ascertain the following in this recommended order:

1. Assess the standardization and identify the recorded leads accurately.
2. Determine the atrial and ventricular rates and rhythms.
3. Determine the P-wave and QRS-complex axes.
4. Measure all cardiac intervals.
5. Determine if cardiac chamber enlargement or hypertrophy is present.
6. Assess the P-wave, QRS-complex, and T-wave morphologies.
7. Draw conclusions and correlate clinically.

Cardiac pathology is manifest differently on the surface ECG, depending on which lead is interrogated. Each lead provides an "electrical window of opportunity" and, by this virtue, offers a unique electrical perspective. The experienced electrocardiographer amalgamates these different windows into a mental three-dimensional electrical assessment, drawing accurate conclusions pertaining to conduction system and structural heart disease. For example, precordial lead V_1 predominantly overlies the right ventricle, explaining why right ventricular cardiac electrical events are best observed in this lead. Likewise, precordial lead V_6 overlies the left ventricle. This lead optimally represents left ventricular cardiac electrical events.

Assess the Standardization and Identify the Recorded Leads Accurately

Standard ECG graph paper consists of 1-mm × 1-mm boxes divided by narrow lines, which are separated by bold lines into larger, 5-mm × 5-mm boxes. At standard speed (25 mm/s), each small box in the horizontal axis represents 0.040 second (40 milliseconds) of time and each large box represents 0.200 second (200 milliseconds). At standard calibration (1 mV/10 mm), each vertical small box represents 0.1 mV and each vertical large box represents 0.5 mV. One must be very careful to inspect the standardization square wave (1 mV in amplitude) at the left of each ECG to determine the calibration of the ECG. ECGs with particularly high or low voltages are often recorded at half standard or twice standard, respectively. In these cases, the 1-mV square wave possesses an amplitude of either 5 or 20 mm. This distinction is important because it will affect the interpretation of all other voltage criteria. All further references to amplitude in this chapter are under the assumption of the default or preset standardization (1 mV/10 mm).

Determine the Atrial and Ventricular Rates and Rhythms

The first step in determining the rate and rhythm is to identify atrial activity. If P waves are present, it is important to measure the P wave to P wave interval (P–P interval). This determines the rate of atrial depolarization. To estimate quickly either an atrial or ventricular rate on a standard 12-lead ECG, one can count the number of 5-mm boxes in an interval and divide 300 by that number. For example, if there are four boxes between P waves, the rate is 300 divided by 4, or 75 complexes per minute.

Once the atrial activity and rate are identified, the P-wave frontal plane axis should be ascertained. A normal P-wave axis (i.e., -0 to 75 degrees) typically reflects a sinus node P-wave origin. A simple way of determining a normal P-wave axis is to confirm a positive P-wave vector in leads I, II, III, and aVF. An abnormal P-wave axis supports an ectopic or non–sinus node P-wave origin.

Several possible atrial and junctional rhythms are listed below. They are grouped by cardiac rhythm origin and subsequently subcategorized by atrial rate. Distinguishing features are italicized for emphasis.

Rhythms of Sinus Nodal and Atrial Origin

Normal Sinus Rhythm A normal sinus rhythm (NSR) is defined as a regular atrial depolarization rate between 60 and 100 per minute of sinus node origin, as demonstrated by a positive P-wave vector in leads I, II, III, and aVF.

Sinus Bradycardia Sinus bradycardia is characterized by a regular atrial depolarization rate <60 per minute of sinus node origin, as demonstrated by a positive P-wave vector in leads I, II, III, and aVF. (This is similar to NSR, except the rate is slower.)

Sinus Tachycardia Sinus tachycardia is characterized by a regular atrial depolarization rate ≥100 per minute of sinus node origin, as demonstrated by a positive P-wave vector in leads I, II, III, and aVF. (This is similar to NSR, except the rate is faster.)

Sinus Arrhythmia Sinus arrhythmia is characterized by an irregular atrial depolarization rate between 60 and 100 per minute of sinus node origin, as demonstrated by a positive P-wave vector in leads I, II, III, and aVF. (This is similar to NSR, except there is irregularity in the P–P interval >160 milliseconds.)

Sinus Arrest or Pause Sinus arrest or pause is characterized by a pause of >2.0 seconds without identifiable atrial activity. This may be caused by frank sinus arrest or may be simply a sinus pause secondary to:

- Nonconducted premature atrial contraction (PAC), in which case, a P wave can be seen deforming the preceding T wave

- Sinoatrial block (SA block), which, like atrioventricular (AV) nodal block, has several forms

First-degree SA block involves a fixed delay between the depolarizing SA node and the depolarization exiting the node and propagating as a P wave. Because the delay is fixed, this delay cannot be detected on the surface ECG.

Second-degree SA block has two varieties. In Type I (Wenckebach) SA block, there is a progressive delay between SA nodal depolarization and exit of the impulse to the atrium. This is manifest as a progressive shortening of the P–P interval until there is a pause, reflecting an SA node impulse that was blocked from exiting the node. In Type II SA block, there is a constant P–P interval with intermittent pauses. These pauses also represent an SA node impulse that was blocked from exiting the node. However, in this case, the duration of the pause is a multiple of the basic P–P interval.

Third-degree SA block demonstrates no P-wave activity, as no impulses exit the sinus node. On the surface ECG, this is indistinguishable from sinus arrest, in which there is no sinus node activity.

Sinus Node Reentrant Rhythm Sinus node reentrant rhythm is characterized by a reentrant circuit involving the sinus node and perisinus nodal tissues. Given the sinus origin, the P-wave morphology and axis are normal and indistinguishable from a normal sinus P wave. The rate is regular at a rate of 60 to 100 per minute. (This is very similar to NSR, except characterized by abrupt onset and termination.)

Sinus Node Reentrant Tachycardia Sinus node reentrant tachycardia is characterized by a reentrant circuit involving the sinus node and perisinus nodal tissues. Given the sinus origin, the P-wave morphology and axis are normal and indistinguishable from a normal sinus P wave. The rate is regular at a rate of ≥100 per minute. (This is very similar to sinus tachycardia, except characterized by abrupt onset and termination.)

Ectopic Atrial Rhythm Ectopic atrial rhythm is characterized by a regular atrial depolarization at a rate of 60 to 100 per minute from a single nonsinus origin, as reflected by an abnormal P-wave axis. The PR interval may be shortened, particularly in the presence of a low ectopic atrial origin, closer to the AV node with a reduced intra-atrial conduction time. In the presence of slowed atrial conduction, the PR interval may be normal or even prolonged.

Ectopic Atrial Bradycardia Ectopic atrial bradycardia is characterized by a regular atrial depolarization at a rate of ≤60 per minute from a single nonsinus origin, as reflected by an abnormal P-wave axis. (This is similar to an ectopic atrial rhythm, except slower.)

Atrial Tachycardia Atrial tachycardia is characterized by a regular, automatic tachycardia

from a single, ectopic atrial focus typically with an atrial rate of 180 to 240 per minute. The ventricular rate may be regular or irregular, depending on the AV conduction ratio. The P-wave axis is abnormal, given the ectopic atrial focus. (This is similar to an ectopic atrial rhythm, except faster.)

Wandering Atrial Pacemaker A wandering atrial pacemaker (WAP) has a rate of 60 to 100 per minute from multiple ectopic atrial foci, as evidenced by at least three different P-wave morphologies on the 12-lead ECG, possessing variable P–P, PR, and R–R intervals. Be careful not to confuse this dysrhythmia with atrial fibrillation (AF). Unlike AF, discrete P waves are identifiable.

Multifocal Atrial Tachycardia Multifocal atrial tachycardia (MAT) is characterized by a rate of >100 per minute with a P wave preceding each QRS complex from multiple atrial ectopic foci, as evidenced by at least three different P-wave morphologies on the 12-lead ECG possessing variable P–P, PR, and R–R intervals. The ventricular response is irregularly irregular, given the unpredictable timing of the atrial depolarization and variable AV conduction. Nonconducted atrial complexes during the ventricular absolute refractory period are also often present. Be careful not to confuse this dysrhythmia with AF. Unlike AF, discrete P waves are identifiable. (This is similar to WAP, but the atrial rate is faster.)

Atrial Fibrillation AF is characterized by a rapid, irregular, and disorganized atrial depolarization rate of 400 to 600 per minute devoid of identifiable discrete P waves, instead characterized by fibrillatory waves.

In the absence of fixed AV block, the ventricular response to AF is irregularly irregular. Be careful not to confuse this dysrhythmia with WAP or MAT. The key is the lack of identifiable P waves.

Atrial Flutter Atrial flutter (AFL) is characterized by a rapid, regular atrial depolarization rate of 250 to 350 per minute, representing an intra-atrial reentrant circuit. The atrial waves are termed “flutter waves” and often demonstrate a “saw-toothed” appearance, best seen in leads V_1, II, III, and aVF.

Although the atrial rate is regular, the ventricular response rate may be either regular or irregular, depending on the presence of fixed versus variable AV conduction. Common AV conduction ratios are 2:1 and 4:1.

Rhythms of Atrioventricular Nodal and Junctional Origin

Atrioventricular Nodal Reentrant Tachycardia Atrioventricular nodal reentrant tachycardia (AVNRT) is a micro-reentrant dysrhythmia that depends on the presence of two

separate AV nodal pathways. Slowed conduction is present in one pathway and unidirectional conduction block is present in the second pathway. This is a regular rhythm with a typical ventricular rate of 140 to 200 per minute, with abrupt onset and termination. Its onset is often initiated by premature atrial complexes (PACs). Atrial activity typically consists of inverted or retrograde P waves occurring before, during, or after the QRS complex, best identified in lead V_1. The QRS complex may be conducted normally or aberrantly.

Atrioventricular Reentrant Tachycardia Atrioventricular reentrant tachycardia (AVRT) is a macro-reentrant circuit that consists of an AV nodal pathway and an accessory pathway. This dysrhythmia may conduct antegrade down the AV nodal pathway with retrograde conduction through the accessory pathway (orthodromic AVRT), or antegrade down the accessory pathway with retrograde conduction up the AV nodal pathway (antidromic AVRT). As opposed to AVNRT, the P wave is always present after the QRS complex. With antidromic AVRT, the QRS complex, by definition, is aberrantly conducted (wide).

Junctional Premature Complexes Junctional premature complexes are premature QRS complexes of AV nodal origin that may have resultant retrograde P waves (a negative P-wave vector in leads II, III, and aVF) occurring immediately before (with a short PR interval), during, or after the QRS complex.

AV Junctional Bradycardia AV junctional bradycardia is characterized by QRS complexes of AV nodal origin that occur at a regular rate of <60 per minute. These represent a subsidiary pacemaker and may have resultant retrograde P waves (negative P-wave vector in leads II, III, and aVF) that occur immediately before (with a short PR interval), during, or after the QRS complex.

Accelerated AV Junctional Rhythm Accelerated AV junctional rhythm is characterized by QRS complexes of AV nodal origin that occur at a regular rate of 60 to 100 per minute. These represent a subsidiary pacemaker and may have resultant retrograde P waves (negative P-wave vector in leads II, III, and aVF) that occur immediately before (with a short PR interval), during, or after the QRS complex. (This dysrhythmia is similar to AV junctional bradycardia, except faster.)

AV Junctional Tachycardia AV junctional tachycardia is characterized by QRS complexes of AV nodal origin that occur at a regular rate of typically 100 to 200 per minute. This dysrhythmia emanates from the AV junction and serves as a dominant cardiac pacemaker with an inappropriately rapid rate. Retrograde P waves may be identified (negative P-wave vector in leads II, III, and aVF) that occur immediately before (with a

short PR interval), during, or after the QRS complex. (This dysrhythmia is similar to AV junctional rhythm, except faster.)

Rhythms of Ventricular Origin

Idioventricular Rhythm Idioventricular rhythm is a regular escape rhythm of ventricular origin that possesses a typically widened QRS complex (>100 milliseconds) at a rate of <60 per minute. This is often seen in cases of high-degree AV block, in which the ventricle serves as a subsidiary pacemaker.

Ventricular Parasystole Ventricular parasystole is an independent, automatic ventricular rhythm that emanates from a single ventricular focus characterized by a widened QRS complex with regular discharge and ventricular depolarization. Because the rhythm is independent and not suppressible, ventricular parasystole is characterized by varying coupling intervals and unchanged interectopic R—R intervals. Fusion complexes can be observed when the parasystolic focus discharges simultaneously with native ventricular depolarization. When the ventricle is absolutely refractory, the parasystolic focus is not recorded on the surface ECG, but its discharge remains unabated.

Accelerated Idioventricular Rhythm Accelerated idioventricular rhythm (AIVR) is a regular rhythm of ventricular origin that typically has a widened QRS complex at a rate of 60 to 100 per minute. It is often seen in cases of high-degree AV block, in which the ventricle serves as a subsidiary pacemaker plus in cases of coronary artery reperfusion. (AIVR is similar to idioventricular rhythm, except faster.)

Ventricular Tachycardia Ventricular tachycardia (VT) is a sustained cardiac rhythm of ventricular origin that occurs at a typical rate of 140 to 240 per minute. In differentiating this from supraventricular tachycardia with aberrant conduction, the following features suggest VT:

- AV dissociation
- Fusion or capture complexes
- Wide QRS (≥140 milliseconds if right bundle branch block [RBBB] morphology; ≥160 milliseconds if left bundle branch block [LBBB] morphology)
- Left-axis QRS complex deviation
- Concordance of the precordial-lead QRS complexes
- QRS morphologies similar to those of PVCs on the current or previous ECG
- Tachyarrhythmia initiated by a PVC
- If RBBB morphology, possessing an RSr′ pattern (as opposed to an rSr′ pattern)

Polymorphic Ventricular Tachycardia Polymorphic VT is a paroxysmal form of VT with a nonconstant R—R interval, a ventricular rate of 200 to 300 per minute, QRS complexes of alternating polarity, and a changing QRS amplitude that often resembles a sine-wave pattern (torsades de pointes). It is often associated with a prolonged QT interval at arrhythmia initiation.

Ventricular Fibrillation Ventricular fibrillation (VF) is a terminal cardiac rhythm with chaotic ventricular activity that lacks organized ventricular depolarization.

Determine the P-Wave and QRS-Complex Axes

A normal P-wave axis varies from 0 to 75 degrees but is usually between 45 and 60 degrees. P waves with a normal axis are upright in leads I, II, III, and aVF and inverted in lead aVR. An abnormal P-wave axis should prompt the interpreter to consider non-sinus nodal rhythms, dextrocardia, or limb lead reversal, among other causes.

To ascertain th frontal-plane axis of the QRS complex, the QRS-complex vector is assessed in each of the limb leads. A recommended approach is to search for the limb lead in which the QRS complex is isoelectric (i.e., the area of positivity under the R wave is equal to the area of negativity above the Q and S waves). The QRS-complex frontal-plane axis will be perpendicular to the isoelectric lead, thus narrowing down the axis to one of two possibilities (90 degrees clockwise or 90 degrees counterclockwise of the isoelectric lead's axis). Next, one examines a limb lead whose vector is close to one of the two possible axes. Based on whether the QRS is grossly positive or negative in that lead, one can deduce which of the two possible axes is correct.

An alternative approach is as follows:

1. Assess the QRS complex vector in leads I and aVF. If both are positive, the QRS complex is between 0 and +90 degrees and is therefore normal.
2. If the QRS-complex vector is positive in lead I and negative in aVF, assess the QRS-complex vector in lead II. If it is positive in lead II, the QRS-complex axis is between -30 and 0 degrees and is leftward but still not pathologically deviated. If the QRS complex is negative in lead II, then the QRS-complex axis is between -90 and -30 degrees, and therefore abnormal left-axis QRS-complex deviation is present.
3. If the QRS-complex vector is negative in lead I and positive in lead aVF, abnormal right-axis QRS-complex deviation is present.
4. If the QRS-complex vector is negative in both leads I and aVF, the QRS-complex axis is profoundly deviated to between -90 and -180 degrees.

Measure All Cardiac Intervals

PR Interval

A normal PR interval is between 120 and 200 milliseconds. This represents the interval between P-wave onset and QRS-complex onset. The PR interval represents intra-atrial and AV nodal conduction time. A short PR interval (<120 milliseconds) is suggestive of facile intra-atrial or AV conduction and may represent ventricular preexcitation. A prolonged PR interval (>200 milliseconds) reflects delayed intra-atrial or AV conduction. In the setting of a varying PR interval, conduction block or AV dissociation may be present.

R–R Interval

The R–R interval is inversely proportional to the rate of ventricular depolarization. If AV conduction is normal, the ventricular rate should equal the atrial rate.

Atrioventricular Block

First-Degree AV Block First-degree AV block occurs when the PR interval is prolonged (>200 milliseconds), and each P wave is followed by a QRS complex. Typically the PR interval is constant.

Second-Degree AV Block, Mobitz Type I (Wenckebach) Second-degree AV block, Mobitz Type I (Wenckebach) is characterized by progressive prolongation of the PR interval, terminating with a P wave followed by a nonconducted QRS complex. Normal antegrade conduction resumes with a repetitive progressive prolongation of the PR interval with each cardiac depolarization, resuming the cycle. This results in a "grouped beating" pattern. In its most common form, the R-R interval shortens from beat to beat (not including the interval in which a P wave is not conducted). This typically represents conduction block within the AV node, superior to the bundle of His.

Second-Degree AV Block, Mobitz Type II Second-degree AV block, Mobitz Type II is characterized by regular P waves followed by intermittent nonconducted QRS complexes in the absence of atrial premature complexes. The resulting R-R interval spanning the nonconducted complex is exactly double the conducted R-R intervals. This typically represents AV conduction block below the bundle of His and has a high propensity to progress to more advanced forms of AV block.

Note that when there is AV block with a ratio of 2:1, one cannot definitively distinguish between Mobitz Type I and Type II. Longer rhythm strips, maneuvers, and intracardiac recordings may be necessary. A widened QRS complex supports Mobitz Type II but lacks certainty.

Third-Degree AV Block (Complete Heart Block) Third-degree AV block (complete heart

block) is characterized by independent atrial and ventricular activity with an atrial rate that is faster than the ventricular rate. PR intervals vary with dissociation of the P waves from the QRS complexes. Typically the ventricular rhythm is either a junctional (narrow complex) or ventricular (wide complex) rhythm. (Note this should be distinguished from AV dissociation, which is also characterized by independent atrial and ventricular activity, but the ventricular rate is faster than the atrial rate.)

QRS Complex Interval

The QRS complex interval is best measured in the limb leads from the onset of the R wave (or Q wave if present) to the offset of the S wave. A normal QRS duration is <100 milliseconds.

If the QRS duration is between 100 and < 120 milliseconds, the morphology should be further inspected for features of one or more of the following:

1. Incomplete RBBB: QRS complex duration 100 to 120 milliseconds, with a RBBB morphology with an R′-wave duration of ≥30 milliseconds (rsR′ in V_1; terminal S-wave slowing in leads I, aVL, and V_6).
2. Left anterior fascicular block (LAFB):
   - QRS duration <120 milliseconds
   - Significant left-axis deviation (-45 to -90 degrees)
   - Positive QRS-complex vector in lead I, negative QRS-complex vectors in the inferior leads (II, III, aVF)
   - Absence of other causes of left-axis deviation, such as an inferior myocardial infarction or ostium primum atrial septal defect (ASD)
3. Left posterior fascicular block (LPFB): Early activation along the anterior fascicles produces a small r wave in leads I and aVL, and small q waves inferiorly. Mid and late forces in the direction of the posterior fascicles produce tall R waves inferiorly, deep S waves in I and aVL, and QRS-complex right-axis deviation.
   - QRS duration <120 milliseconds
   - Right axis (>120 degrees)
   - Absence of other clinical causes of right-axis QRS-complex deviation, such as pulmonary hypertension or right ventricular hypertrophy (RVH)
   - rS QRS-complex pattern in leads I and aVL
   - qR QRS-complex pattern in the inferior leads

If the QRS complex duration is >120 milliseconds, the morphology should be further inspected for the following features:

1. Right bundle branch block: The early depolarization vectors in RBBB are similar to

normal depolarization reflecting left ventricular electrical events, producing early septal q waves in leads I, aVL, V_5, and V_6, plus an early RS pattern in leads V_1 and V_2. Given the right bundle branch conduction block, an unopposed QRS-complex vector representing delayed and slowed right ventricular depolarization is identified. These unopposed delayed left-to-right depolarization forces produce the characteristic broad second R′ wave in leads V_1 and V_2, plus the deep broad S waves in leads I, aVL, V_5, and V_6.

- QRS duration ≥120 milliseconds
- rsr′, rsR′, or rSR′ in lead V_1 ± lead V_2
- Broad (>40 milliseconds) S wave in leads I and V_6
- T-wave inversion and down-sloping ST depression often seen in leads V_1 and V_2

2. Left bundle branch block: LBBB represents an altered left ventricular depolarization sequence. The right ventricle is depolarized in a timely manner via the right bundle branch. The left ventricle is depolarized after right ventricular depolarization via slowed right-to-left interventricular septal conduction. Because left ventricular depolarization initially transpires via the terminal branches of the left-sided conduction system, left ventricular depolarization occurs via an altered sequence with a prolonged QRS-complex duration.
   - QRS-complex duration ≥120 milliseconds
   - Broad and notched and/or slurred R wave in leads aVL, V_5, and V_6
   - Absent septal Q waves in leads I, avl, V_5, and V_6
3. Intraventricular conduction delay:
   - QRS complex duration >100 milliseconds
   - Indeterminate morphology not satisfying the criteria for either RBBB or LBBB

QT Interval

The QT interval demonstrates heart rate interdependence. The QT interval is directly proportional to the R-R interval. The QT interval shortens as heart rate increases. To account for this variability with heart rate, the corrected QT interval (QT_c) is calculated, in which the QT interval is divided by the square root of the R-R interval. Normative tables for heart rate and gender are available. A normal QT_c is typically <440 milliseconds. A less cumbersome approximation involves measuring the QT interval directly (typically in lead II). If this is >50% of the R-R interval, this supports QT-interval prolongation. In this circumstance, calculating a QT_c interval is appropriate.

Differential diagnosis of a prolonged QT interval includes the following:

- Congenital (idiopathic, Jervell-Lange-Nielsen syndrome, Romano-Ward syndrome)
- Medications (psychotropics, antiarrhythmics, antimicrobials, etc.)
- Metabolic disorders (hypocalcemia, hypokalemia, hypothyroidism, hypomagnesemia, etc.)
- The morphology of QT-interval prolongation in hypocalcemia deserves special mention. Typically, hypocalcemia produces prolongation and straightening of the QT interval as a result of prolongation of the ST segment, without frank widening of the T wave.
- Neurogenic, such as an intracranial hemorrhage
- Ischemia

Determine If Cardiac Chamber Enlargement or Hypertrophy Is Present

If a patient is in sinus rhythm, the atria can be evaluated by analyzing the P-wave morphology in leads II, V_1, and V_2. Given the superior right atrial location of the sinus node, right atrial depolarization precedes left atrial depolarization. Therefore, right atrial depolarization is best represented in the first half of the surface ECG P wave. In lead II, if a bimodal P wave is present, the first peak represents right atrial depolarization and the second peak represents left atrial depolarization. In leads V_1 and V_2, the P wave is typically biphasic. The early portion is upright, representing right atrial depolarization toward leads V_1 and V_2, with the negative latter half representing left atrial depolarization, away from these leads.

Right Atrial Abnormality

Delayed activation of the right atrium due to hypertrophy, dilation, or intrinsically slowed conduction can result in the summation of right and left atrial depolarization. This typically produces a tall peaked P wave (≥2.5 to 3 mm) in lead II.

Left Atrial Abnormality

Delayed activation of the left atrium due to hypertrophy, dilation, or intrinsically slowed conduction can result in a broadening (>110 milliseconds) and notching of the P wave in lead II, or a deeper inverted phase of the P wave in leads V_1 and V_2:

- Negative terminal phase of P wave in lead V_1 or V_2 ≥ 40 milliseconds in duration and ≥1 mm in amplitude, or
- Biphasic P wave in lead II with peak-to-peak interval of ≥40 milliseconds (This is not very sensitive, but is quite specific.)

Right Ventricular Hypertrophy

In RVH, there is a dominance of the right ventricular forces, which produce prominent R waves in the right precordial leads and deeper S waves in the left precordial leads. RVH is suggested by one or more of the following:

- Right-axis QRS-complex deviation (>+90 degrees)
- R:S ratio in lead $V_1 > 1$
- R wave in $V_1 \geq 7$ mm
- R:S ratio in $V_6 < 1$
- ST-T-wave "strain" pattern in right precordial leads supported by asymmetric T-wave inversion
- Right atrial abnormality in the absence of:
  - Posterior-wall myocardial infarction
  - Wolff-Parkinson-White (WPW) syndrome
  - Counterclockwise rotation
  - Dextrocardia
  - RBBB

Left Ventricular Hypertrophy

Several criteria have been described and validated for the diagnosis of left ventricular hypertrophy (LVH) by electrocardiography.

1. Sokolow and Lyon: Amplitude of the S wave in lead V_1 + amplitude of the R wave in V_5 or V_6 (whichever is the tallest) ≥35 mm
2. Cornell: Amplitude of the R wave in aVL + amplitude of the S wave in V_3 >28 mm for men, or >20 mm for women
3. Romhilt-Estes: This is a scoring system in which a total score of 4 indicates "likely LVH," and a score of ≥5 indicates "definite LVH."
   - Voltage criteria = 3 points:
     Amplitude of limb lead R wave or S wave ≥20 mm or
     Amplitude of S wave in V_1 or $V_2 \geq 30$ mm or
     Amplitude of R wave in V_5 or $V_6 \geq 30$ mm
     ST-T-wave changes typical of strain (in which the ST segment and T-wave vector is shifted in a direction opposite to that of the QRS complex vector) = 3 points (only 1 point if the patient is taking digitalis)
   - Left atrial abnormality = 3 points:
     Terminal portion of P wave in $V_1 \geq 40$ milliseconds in duration and ≥1 mm in amplitude

- Left-axis deviation = 2 points:
  Axis ≥ -30 degrees
- QRS duration = 1 point:
  Duration ≥90 milliseconds
- Intrinsicoid deflection = 1 point:
  Duration of interval from the beginning of the QRS complex to the peak of the R wave in V_5 or V_6 ≥ 50 milliseconds

Combined or Biventricular Hypertrophy

Combined ventricular hypertrophy is suggested by any of the following:

- ECG meets criteria for isolated RVH and LVH. This is the most reliable criterion.
- Precordial leads demonstrate LVH by voltage, but there is right-axis deviation (>+90 degrees) in the frontal plane.
- Precordial leads demonstrate LVH, with limb leads demonstrating right atrial abnormality.

Assess the P-Wave, QRS-Complex, and T-Wave Morphologies

Once the cardiac rate, rhythm, axes, intervals, and chambers have been assessed, one should proceed with the identification of various morphologies that suggest pathologic states. There have been virtually innumerable descriptions of various morphologic criteria for a broad spectrum of pathologic states, but here we discuss those that are most common and/or most important.

ECG Abnormalities and Corresponding Differential Diagnoses

Incorrect Lead Placement or Lead Fracture Incorrect lead placement or lead fracture is most commonly identified in the limb leads, with a negative P-wave vector in leads I and aVL and normal precordial R-wave progression.

Low Voltage Low voltage in limb leads is defined as a QRS-complex amplitude of <5 mm in each of the standard limb leads (I, II, and III). Low voltage of all leads is defined as low voltage in the limb leads plus a QRS-complex amplitude of <10 mm in each of the precordial leads.

Low voltage on the ECG may be of primary myocardial origin or secondary to high-impedance tissue conduction. Differential diagnosis possibilities include the following:

- Cardiomyopathy (infiltrative or restrictive)
- Pericardial effusion
- Pleural effusion

- Anasarca
- Obesity
- Myxedema
- Chronic obstructive pulmonary disease

Q Waves Q waves represent an initial negative QRS-complex vector. Pathologic Q waves are present if they are ≥1 mm (0.1 mV) in depth and ≥40 milliseconds in duration.

Q waves are most commonly associated with a myocardial infarction. To diagnose a myocardial infarction, Q waves must be identified in two contiguous leads:

- Inferior leads—II, III, and aVF
- Anteroseptal leads—V_2 and V_3
- Anterior leads—V_2, V_3, and V_4
- Lateral leads—V_5 and V_6
- High lateral leads—I and aVL
- Posterior leads V_1 and V_2 (R-wave amplitude greater than S-wave amplitude)

Contiguous regions on an ECG include the following:

- Inferior, posterior, and lateral
- Anteroseptal, anterior, and lateral
- Lateral and high lateral

Other etiologies of Q waves include:

- "Septal" Q waves (small Q waves as a result of the septal left-to-right depolarization vector)—leads I, aVL, V_5, and V_6
- Hypertrophic cardiomyopathy—any lead
- LAFB—leads I and aVL
- WPW syndrome—any lead

ST-Segment Elevation ST-segment elevation refers to elevation of the segment between the terminal aspect of the QRS complex and the T-wave onset. This elevation is relative to the isoelectric comparative TP segment located between the end of the T wave and the start of the P wave.

Causes of ST-segment elevation include the following:

- Acute myocardial injury: convex upward ST-segment elevation in at least two

contiguous ECG leads

- Coronary spasm (Prinzmetal angina): similar morphology to acute myocardial injury, with the distinction that the ST-segment elevation is typically transient
- Pericarditis: diffuse concave upward ST-segment elevation not confined to contiguous ECG leads
- Left ventricular aneurysm: most often seen in the right precordial leads, with convex upward ST-segment elevation overlying an infarct zone, with ST-segment elevation persisting for months to years after the initial myocardial infarction
- LBBB: typically discordant from the QRS-complex vector
- Early repolarization: manifest as J-point elevation with normal ST segments, best seen in the lateral precordial leads
- Brugada syndrome: ST-segment elevation in the right precordial leads with a pattern of right ventricular conduction delay
- Hypothermia: Osborne waves

ST-Segment Depression The most common causes of ST-segment depression are the following:

- Myocardial ischemia or non-ST-segment elevation myocardial infarction (NSTEMI): Horizontal or down-sloping ST-segment depression demonstrates the greatest specificity for myocardial ischemia. Positive cardiac biomarkers distinguish ischemia versus infarction.
- Ventricular hypertrophy: Down-sloping asymmetric ST-segment depression and T-wave inversion is often present in both LVH and RVH.

Peaked T Waves The most common causes of peaked, positive T waves are the following:

- Hyperkalemia
- Hyperacute phase of myocardial infarction
- Acute transient ischemia (Prinzmetal angina)

U Waves U waves are seen immediately following the T wave. They are best observed in leads V_2, V_3, and V_4 and are typically up to one quarter the amplitude of the T wave. Prominent U waves are ≥1.5 mm (≥0.15 mV) in amplitude.

Prominent U waves are commonly observed in the presence of:

- Hypokalemia
- Bradyarrhythmias
- Drugs

Pathologic States and Corresponding ECG Abnormalities

Myocardial Injury and Infarction

- Acute myocardial infarction: Q waves and ST-segment elevation. Reciprocal ST-segment depression is often observed but is not necessary.
- Recent myocardial infarction: Q waves with ischemic T-wave changes, often inverted; the ST segments are typically no longer elevated.
- Age-indeterminate myocardial infarction: persistent Q waves devoid of ST-segment elevation or ischemic T-wave changes
- Acute myocardial injury: regional ST-segment elevation without Q waves

Acute Pericarditis Acute pericarditis is characterized by diffuse ST-segment elevation and/or PR-segment depression. Lead aVR classically demonstrates PR-segment elevation and is highly specific.

- Diffuse ST-segment elevation
- Diffuse PR-segment depression with PR-segment elevation in lead aVR
- T-wave inversions typically do not appear until ST-segment elevations have resolved.

Pericardial Effusion The ECG manifestations of pericardial effusions are a result of the increased impedance of the electrical signal through the pericardial fluid collection coupled with translational cardiac motion within the pericardium. These include:

- Electrical alternans
- voltage QRS complexes

Digitalis Effect

- Most commonly manifests as ST-segment and T-wave changes
- Concave depression/sagging of the ST segment (usually without frank J-point depression) seen best in leads V_5 and V_6
- PR-interval prolongation
- T-wave flattening with QT-interval shortening

Digitalis Toxicity Digitalis toxicity exerts its effects via a combination of an increase in myocardial automaticity plus suppression of sinus nodal and AV nodal pacemaker function. This manifests as a combination of conduction defects and arrhythmias including but not limited to:

- Atrial tachycardia
- Accelerated junctional rhythm

- First-, second-, or third-degree AV block
- Bidirectional ventricular tachycardia (VT with alternating right and LBBB morphology)
- VF

Hyperkalemia

- Tall, peaked, narrow-based T waves
- PR-interval prolongation
- Advanced conduction block
- Atrial standstill or arrest
- Widening of the QRS complex, which can progress to a "sine wave" pattern
- VT or fibrillation

Hypokalemia

- Prominent U waves, especially in leads V_2, V_3, and V_4
- ST-segment depression
- Decreased T-wave amplitude
- Increase in P-wave amplitude and duration

Hypercalcemia

- Shortened QT_c, predominantly via decreased ST-segment duration

Hypocalcemia

- Prolonged QT_c, predominantly via increased ST-segment duration and straightening without a significant increase in the T-wave duration

Sick Sinus Syndrome Sick sinus syndrome is characterized by combinations of the following:

- Marked sinus bradycardia
- Sinus arrest
- Prolonged recovery time of the sinus node following PACs or atrial tachyarrhythmias
- Alternating bradycardia and tachycardia

Acute Cor Pulmonale The following suggest acute cor pulmonale:

- Sinus tachycardia

- Anterior precordial T-wave inversion (leads V_1 to V_3)
- Right atrial abnormality
- Right-axis QRS-complex deviation
- An S1, Q3, T3 QRS complex limb lead pattern
- RBBB (may be transient)

Atrial Septal Defect, Secundum The following ECG findings are suggestive of a secundum ASD:

- Right-axis QRS-complex deviation
- Incomplete RBBB
- RVH
- Right atrial abnormality
- PR-interval prolongation

Atrial Septal Defect, Primum The following ECG findings are suggestive of a primum ASD:

- Left-axis QRS-complex deviation
- PR-interval prolongation
- Incomplete RBBB

Dextrocardia The following ECG findings suggest dextrocardia:

- Precordial R-wave regression (R-wave amplitude decreases from V_1 to V_6)
- Negative P-wave vector in leads I and aVL

WPW syndrome is suggested by the following ECG findings:

- Shortened PR interval (<120 milliseconds)
- Delta wave representing ventricular preexcitation (slurring of the initial portion of the QRS complex)
- QRS complex may be wide, representing altered ventricular depolarization.

Hypertrophic Cardiomyopathy The following ECG criteria are suggestive of hypertrophic cardiomyopathy:

- High-voltage QRS complex
- Deep Q waves not ascribable to a specific coronary artery territory
- ST-T-wave changes including deep T-wave inversions

Hypothermia The following ECG criteria are suggestive of hypothermia:

- Osborne waves (elevated J point that is proportional to the degree of hypothermia)
- Bradycardia
- PR-interval, QRS-complex interval, and QT-interval prolongation

Myxedema The following ECG criteria are suggestive of myxedema:

- Sinus bradycardia
- PR-interval prolongation
- Low-voltage QRS complexes

SUGGESTED READINGS

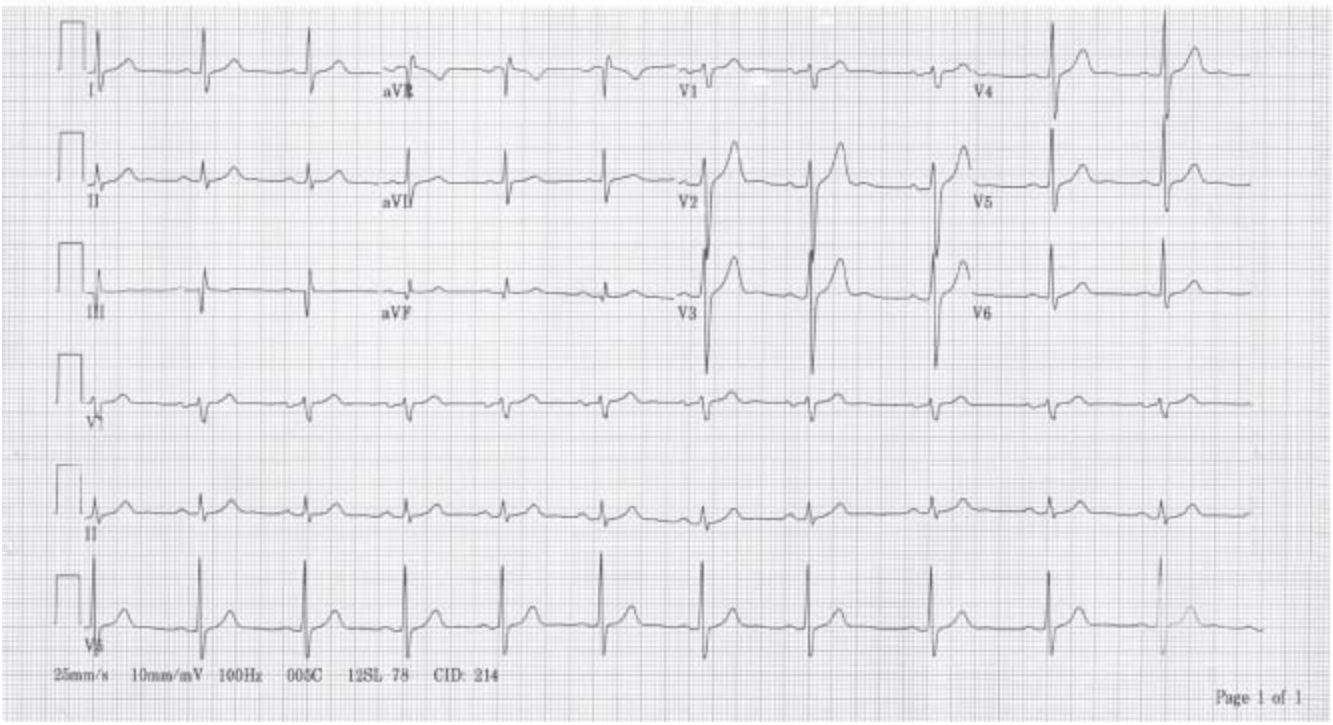
Rimmerman CM, Jain AK. Interactive electrocardiography. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.

Surawicz B, Knilans TK, Chou T-C. Chou's Electrocardiography in Clinical Practice: Adult and Pediatric. 5th ed. Philadelphia, PA: WB Saunders; 2001.

Topol EJ, Califf RM. Textbook of Cardiovascular Medicine. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002.

ELECTROCARDIOGRAM CASE HISTORIES

ELECTROCARDIOGRAM #1



Clinical History

A 52-year-old man presents for a routine physical examination in the Preventive Medicine Department. His past medical history includes elevated triglycerides and a low HDL cholesterol value. He is otherwise in good health.

Electrocardiogram Interpretation

The cardiac rhythm is normal sinus rhythm with evidence of sinus arrhythmia best seen in the lead V_1 rhythm strip. No pathologic Q waves are present, the ST segments are normal, and all cardiac intervals are normal. This represents a normal ECG and an example of sinus arrhythmia.

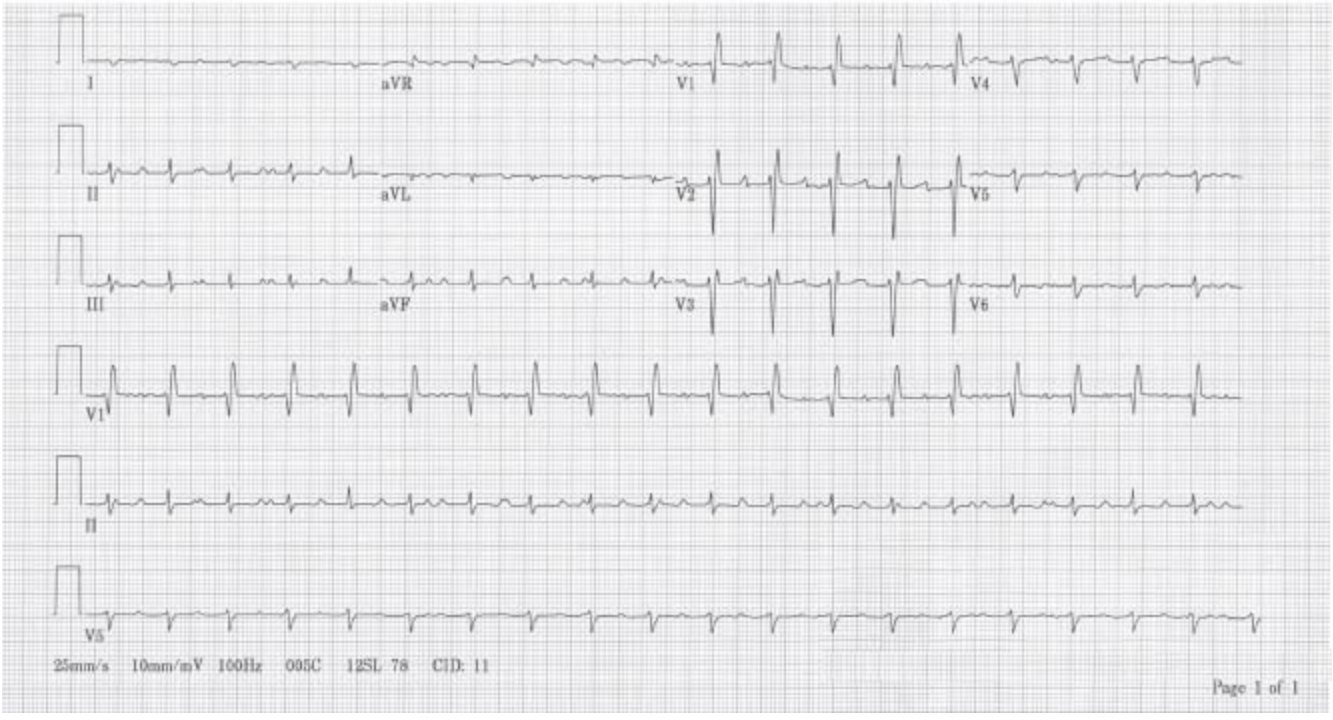
Commentary

Sinus arrhythmia is a common and normal finding as depicted on this ECG. The sinus rate increases with inspiration and decreases with expiration.

Keyword Diagnoses

NSR
Sinus arrhythmia
Normal ECG

ELECTROCARDIOGRAM #2



Clinical History

The patient is a 56-year-old man who underwent a cardiac transplant procedure 6 weeks prior to this ECG, secondary to an idiopathic nonischemic dilated cardiomyopathy and recurrent VT. His medications at the time of this ECG included digoxin, furosemide, lisinopril, potassium, and aspirin.

Electrocardiogram Interpretation

The cardiac rhythm is sinus tachycardia, in that the P waves demonstrate a normal axis with a constant P-P interval preceding each QRS complex at a regular rate >100 per minute. A second set of P waves is noted as a constant P-P interval at a slightly longer P-P interval compared to the conducted P waves. This represents the native atrium in this cardiac transplant patient, which is still depolarizing via the native sinus node. The donor P wave that immediately precedes each QRS complex demonstrates first-degree AV block. Diffuse nonspecific ST-T changes are present. QRS-complex frontal-plane right-axis deviation is present in that the QRS-complex vector is negative in lead I and positive in leads II, III, and aVF. Low-voltage QRS complexes are seen in the limb leads, in that each complex is <5 mm in amplitude. An rsR′ QRS-complex morphology is present in lead V_1 with an overall normal QRS-complex duration supporting incomplete RBBB.

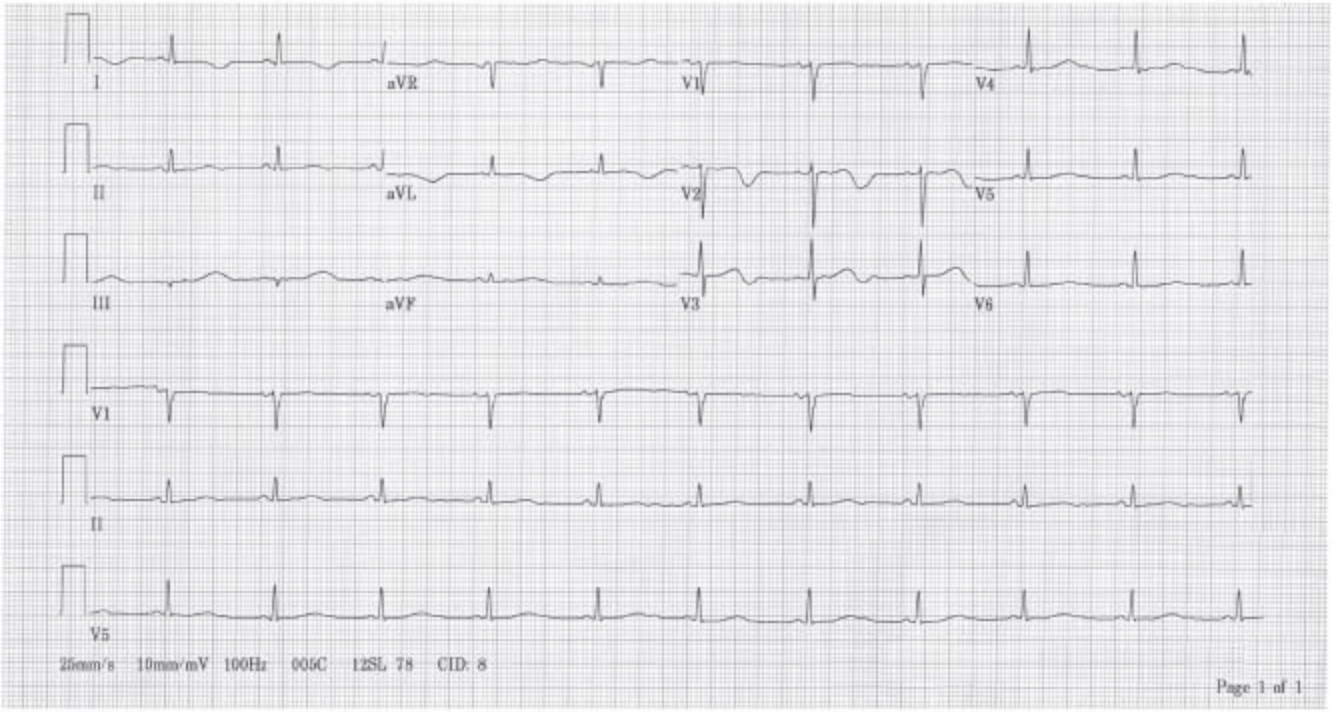
Commentary

The presence of dual functioning atria in a recent cardiac transplant patient is a common finding. The native atria gradually extinguish themselves and the donor atria become the dominant atrial pacemaker. The presence of incomplete RBBB in a post-cardiac transplant patient is also a common finding.

Keyword Diagnoses

Sinus tachycardia
First-degree AV block
Right-axis deviation
Incomplete RBBB
Nonspecific ST-T changes
Low-voltage QRS
Cardiac transplant

ELECTROCARDIOGRAM #3



Clinical History

The patient is a 41-year-old man with myelodysplastic syndrome and insulin-requiring diabetes mellitus, who has been admitted for bone marrow transplantation. His serum potassium at the time of this ECG was 3.4 mEq/L.

Electrocardiogram Interpretation

This ECG emphasizes the necessary methodical approach to interpretation. The ECG demonstrates NSR. In assessing the intervals, it is most notable for a prolonged QT interval.

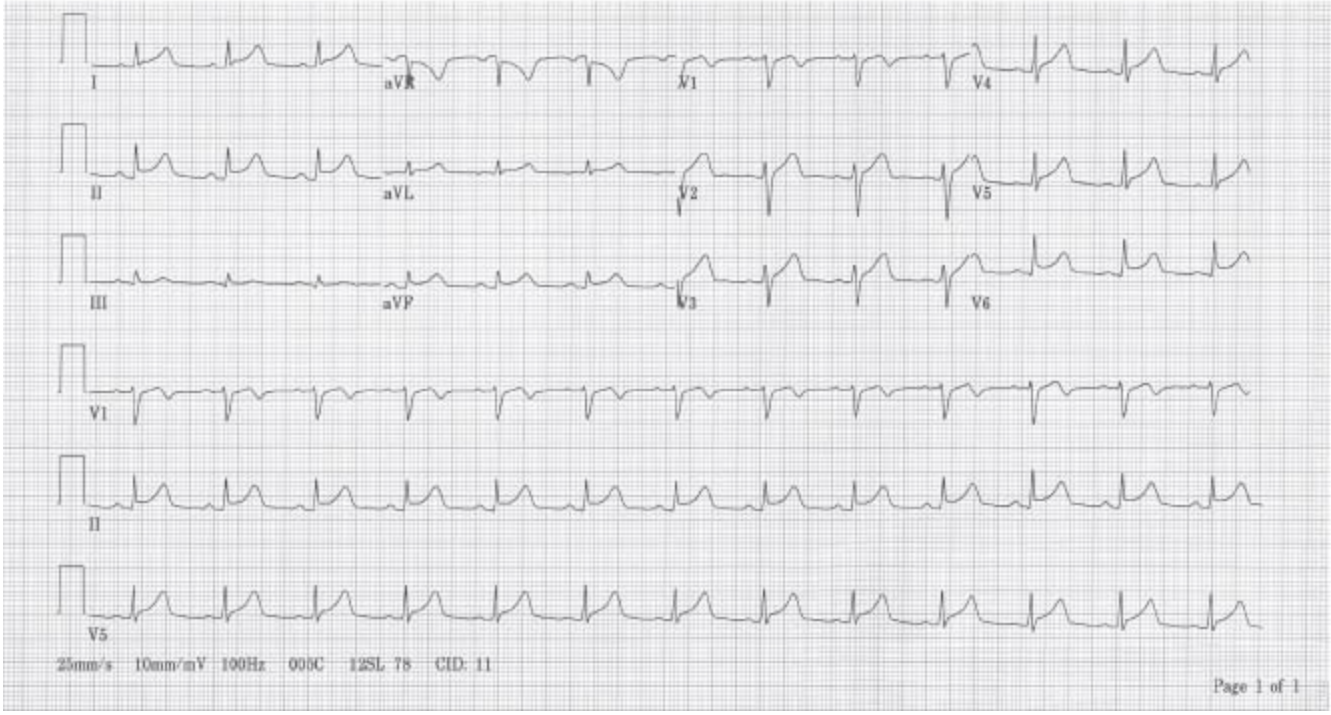
Commentary

This ECG demonstrates the common findings seen in hypokalemia. There is a prolongation of the QT interval, prominent U waves, and T-wave flattening.

Keyword Diagnoses

NSR
Prolonged QT interval
Nonspecific ST-T changes
U waves
Hypokalemia

ELECTROCARDIOGRAM #4



Clinical History

A 39-year-old woman, an unrestrained passenger in a motor vehicle accident, suffered an aortic transection distal to the left subclavian artery. This ECG was taken postoperatively, shortly after thoracic aorta repair.

Electrocardiogram Interpretation

The heart rate and cardiac rhythm are both normal. This represents NSR. This ECG is most notable for diffuse ST-segment elevation not confined to a particular coronary artery territory, which is most consistent with acute pericarditis. Lead aVR is helpful because there is elevation of the atrial repolarization segment. This segment is termed the PR segment and is located between the terminal aspect of the P wave and QRS-complex onset.

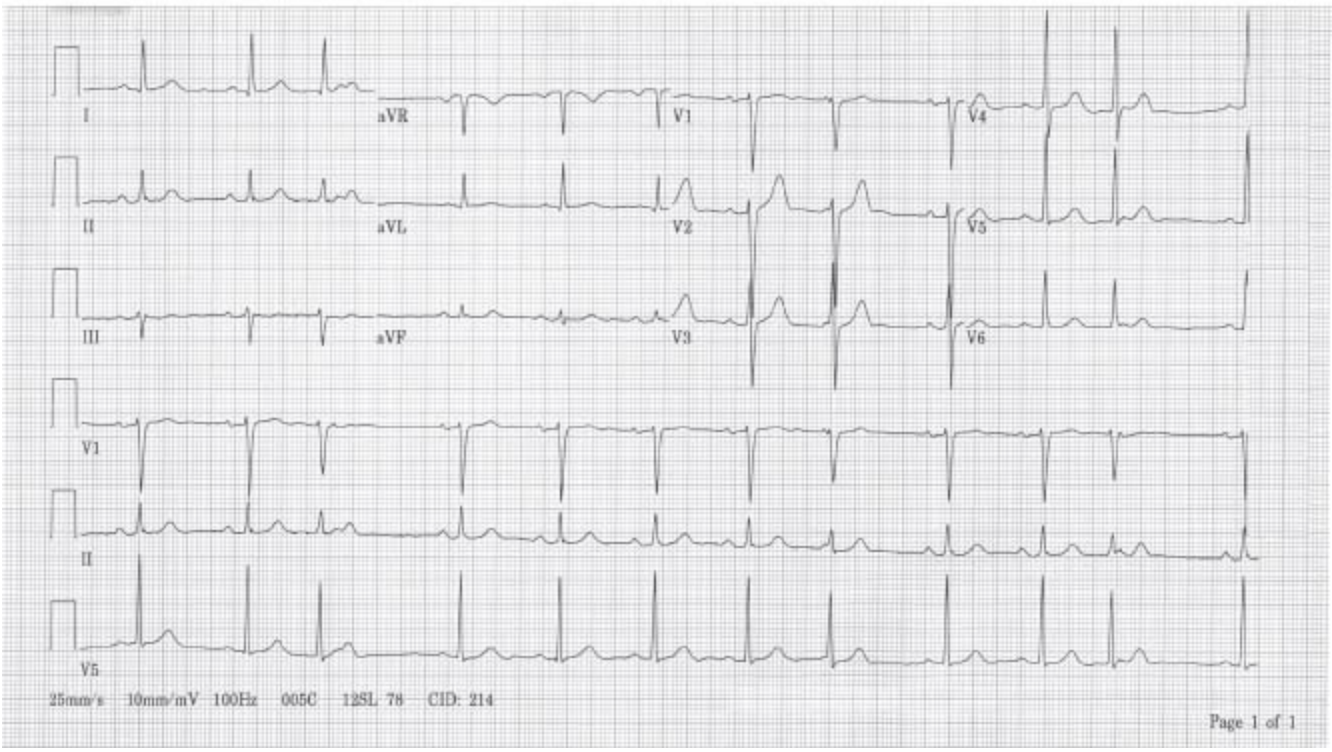
Commentary

When the PR segment is elevated in lead aVR, this serves as a specific sign for pericarditis. This may be the only ECG finding supporting pericarditis and remains an important marker to identify.

Keyword Diagnoses

NSR
Pericarditis

ELECTROCARDIOGRAM #5



Clinical History

A 62-year-old man is undergoing preoperative anesthesia clearance prior to planned rotator cuff repair. His past medical history is notable for hypertension but no known cardiac disease. His medications include verapamil.

Electrocardiogram Interpretation

NSR is present. The 3rd, 8th, and 11th QRS complexes are premature junctional complexes. A P wave does not precede the 3rd and 11th QRS complexes and demonstrates a similar QRS-complex morphology to the native QRS complex. This is otherwise a normal ECG.

Commentary

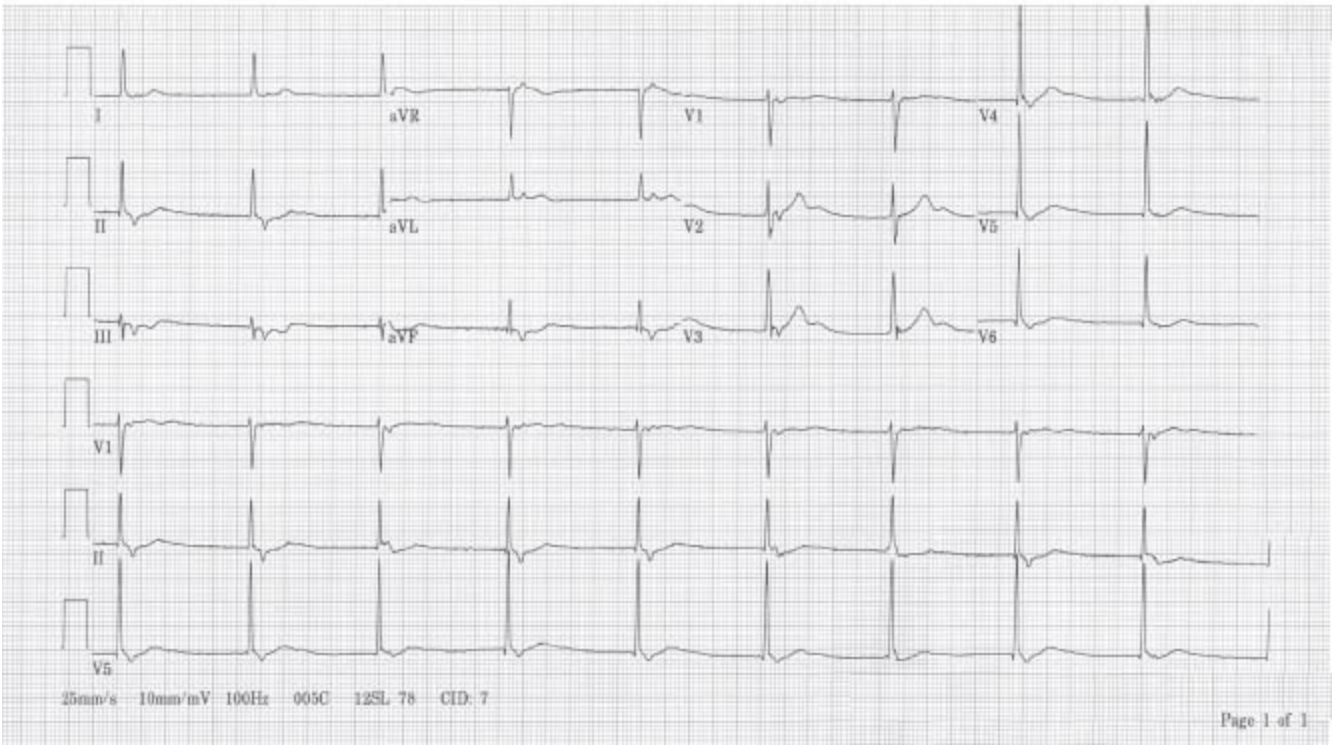
Premature junctional complexes are an otherwise normal finding. Frequently, retrograde P waves are seen in the presence of premature junctional complexes. An example of retrograde P waves is seen within the ST segment following the 3rd and 11th QRS complexes.

Keyword Diagnoses

NSR
Premature junctional complex

Normal ECG
Retrograde P waves

ELECTROCARDIOGRAM #6



Clinical History

A 59-year-old man with coronary artery disease status post remote percutaneous transluminal coronary angioplasty of the right coronary artery re-presents with chest discomfort. A myocardial infarction was excluded by cardiac enzymes and a subsequent stress test was normal. The patient was thought to be suffering from noncardiac musculoskeletal chest discomfort.

Electrocardiogram Interpretation

The cardiac rhythm demonstrates a regular bradycardia with retrograde P waves after each QRS complex. The P waves possess a negative vector in the inferior leads, as the atrial wave of depolarization is traveling superiorly, opposite the normal direction of conduction. The QRS complex is of normal duration. This represents a junctional bradycardia. The causes of this could be many, including sinus node disease, medication administration, increased vagal tone, atrial conduction system disease, myocardial ischemia, or valvular heart disease. Prominent positive U waves are present in leads V_2 to V_4.

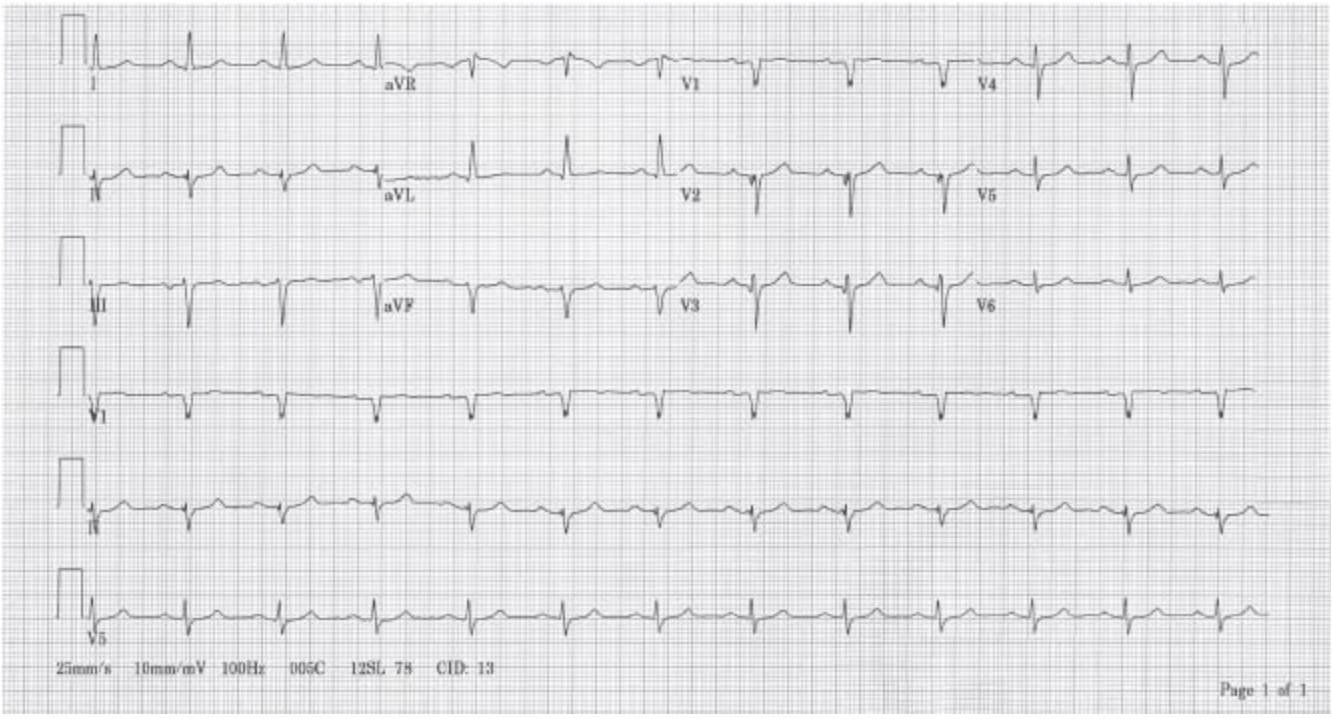
Commentary

In this case, the R-R interval is constant with absent atrial activity prior to each QRS complex. Depending on the relative retrograde versus antegrade conduction rates, a retrograde P wave may occur before, within, or after the QRS complex. In this example, antegrade conduction from the AV junction to the ventricle is faster than retrograde conduction from the AV junction to the atrium and therefore explains the P wave occupying the proximal ST segment after the QRS complex.

Keyword Diagnoses

Junctional bradycardia
Retrograde P waves
U waves

ELECTROCARDIOGRAM #7



Clinical History

A 62-year-old man with severe three-vessel coronary artery disease has been referred for coronary artery bypass graft surgery. A recent cardiac catheterization demonstrated normal left ventricular systolic function without evidence of a prior myocardial infarction. Mediations at the time of this ECG included atenolol, gemfibrozil, and folic acid.

Electrocardiogram Interpretation

The cardiac rhythm is NSR with a positive QRS-complex vector in lead I and negative QRS-complex vectors in leads II, III, and aVF, consistent with left anterior hemiblock. Q waves are present in leads V_2 to V_3, suggesting an anteroseptal myocardial infarction of indeterminate age. This is a difficult diagnosis in the setting of left anterior hemiblock, as the QRS-complex vector is now displaced inferiorly and posteriorly away from leads V_2 and V_3. This in fact may represent a Q wave based on axis deviation instead of a true myocardial infarction.

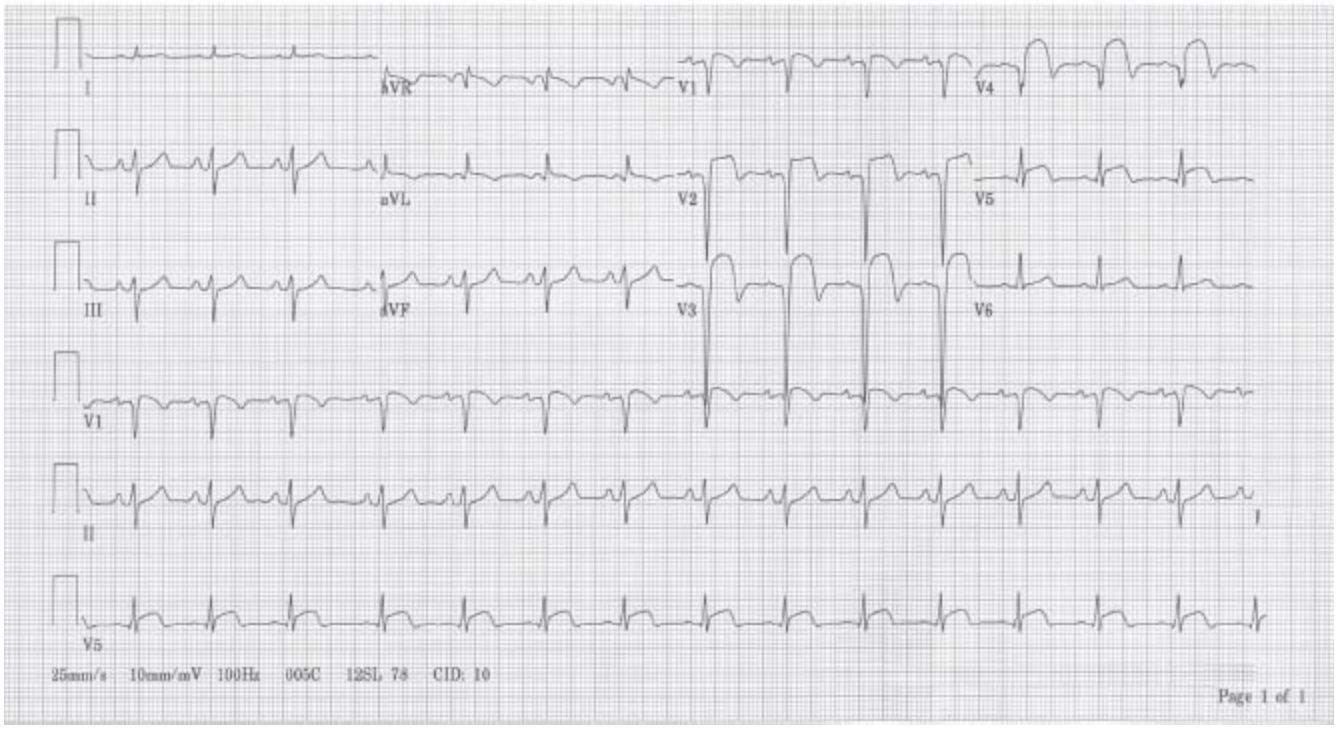
Commentary

Placing leads V_2 and V_3 one interspace lower and repeating the ECG may be helpful, as the new presence of an R wave would negate the possibility of a prior anteroseptal myocardial infarction. In this setting, an echocardiogram may be helpful to evaluate anteroseptal and septal wall motion. Thus, the correct interpretation of this ECG is NSR with left anterior hemiblock but cannot exclude a septal myocardial infarction of indeterminate age.

Keyword Diagnoses

NSR
Left anterior hemiblock

ELECTROCARDIOGRAM #8



Clinical History

A 46-year-old man who had a myocardial infarction 2 years before this ECG presented to the emergency room with a 6-hour history of acute severe substernal chest discomfort. The patient underwent emergency cardiac catheterization and percutaneous transluminal coronary angioplasty of a severe proximal left anterior descending coronary artery stenosis.

Electrocardiogram Interpretation

The cardiac rhythm is regular, with a normal P-wave axis denoting NSR. A leftward QRS-complex frontal-plane axis is present in the setting of a normal QRS-complex duration, fulfilling the criteria for left anterior hemiblock. Most striking on this ECG is the maximal 7-mm ST-segment elevation noted in leads V_2 to V_5, I, and aVL with Q-wave formation indicating an extensive acute anterolateral myocardial infarction. There is an ongoing acute myocardial injury pattern with terminal T-wave inversion representing an evolving acute infarction.

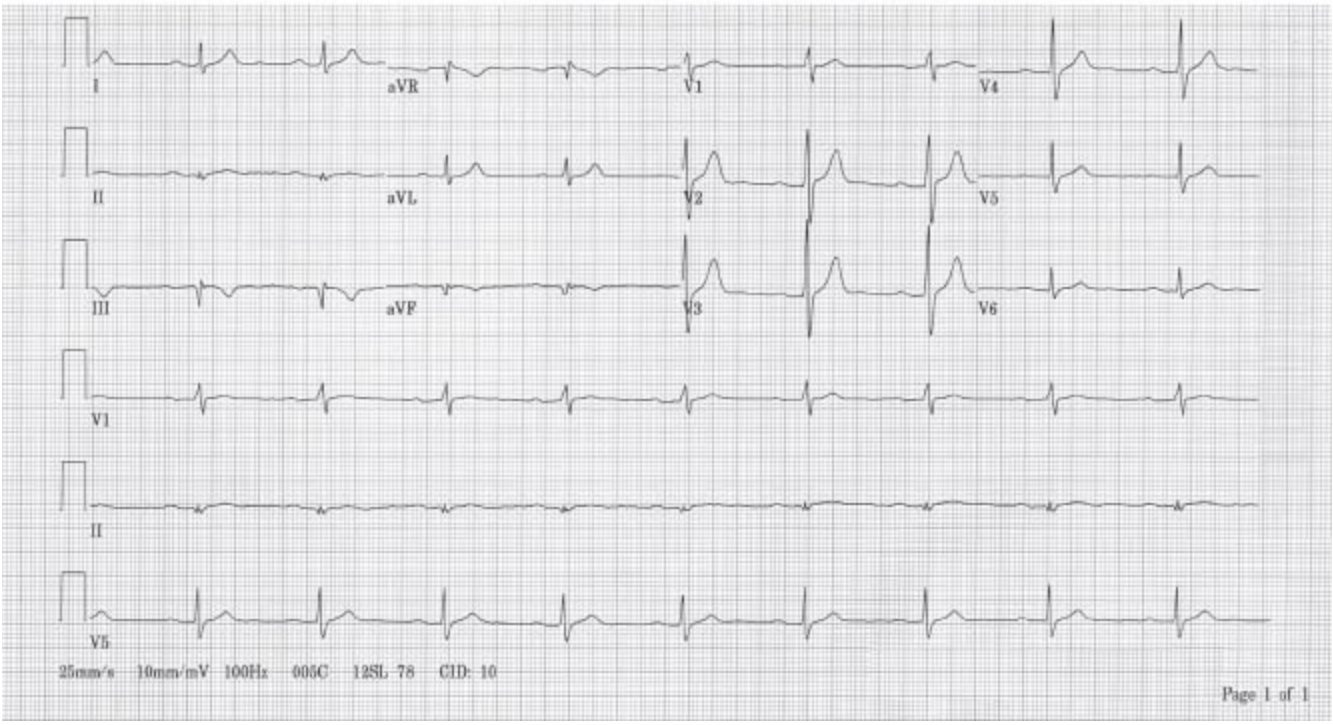
Commentary

This ECG is an example of an evolving extensive acute anterolateral myocardial infarction. There is concomitant injury and infarction occurring, as prominent Q waves are present with ST-segment elevation. Presumably the left anterior descending obstruction is proximal to the first septal perforator branch, as ST-segment elevation is present in lead V_1.

Keyword Diagnoses

NSR
Left anterior hemiblock
Anterolateral myocardial infarction, acute
Acute myocardial injury

ELECTROCARDIOGRAM #9



Clinical History

A 47-year-old man presented to an outside medical facility with an ECG consistent with an acute inferior myocardial infarction. He received urgent thrombolytic therapy and was accepted in hospital transfer for cardiac catheterization. Comorbid conditions included long-term tobacco use and hypercholesterolemia. A cardiac catheterization demonstrated severe right coronary artery disease, which was treated with percutaneous coronary intervention.

Electrocardiogram Interpretation

Important findings on this ECG include sinus bradycardia with a prolonged PR interval, supporting first-degree AV block. Pathologic Q waves are present in leads III and aVF, with coved nonelevated ST segments and terminally negative T waves. This supports an inferior myocardial infarction, possibly recent. A tall R wave is noted in leads V_1 and V_2, and in the setting of an inferior myocardial infarction raises the high likelihood of a concomitant posterior myocardial infarction. This ECG is best characterized as sinus bradycardia, first-degree AV block, and a recent inferoposterior myocardial infarction.

Commentary

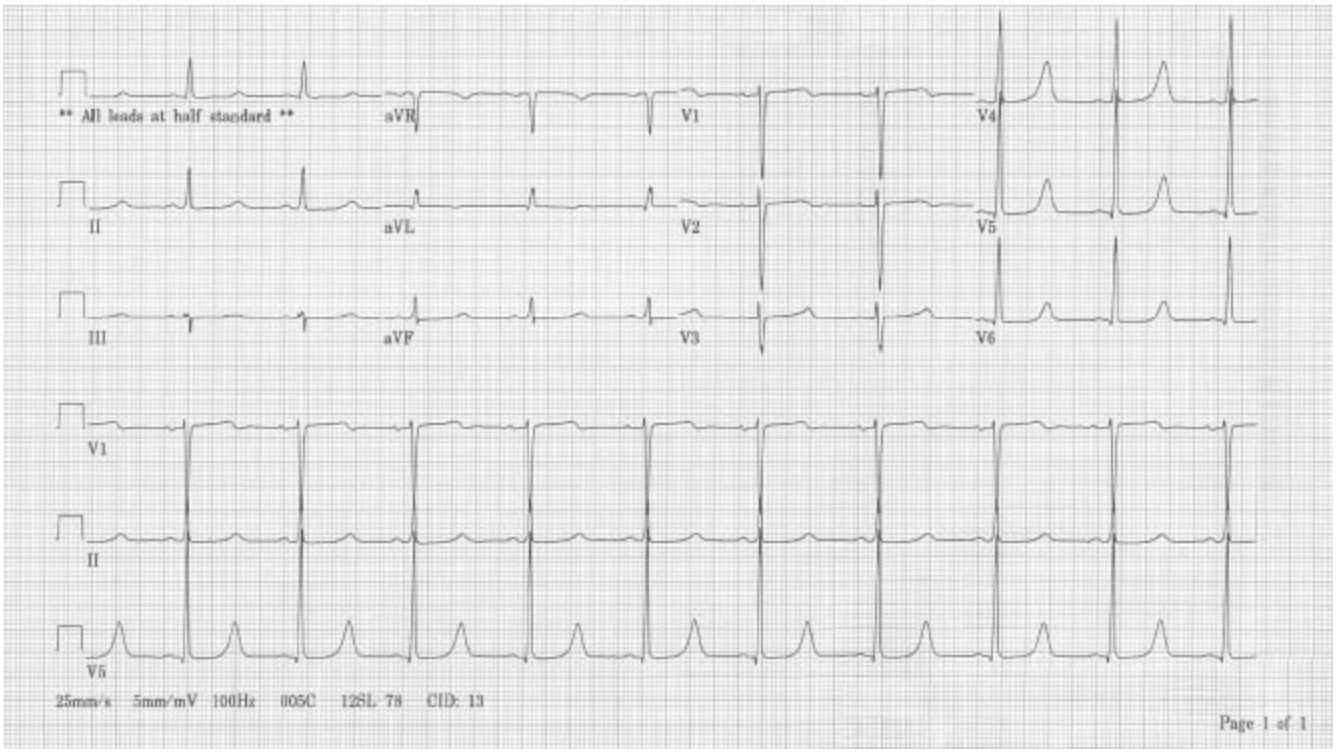
In the presence of an inferoposterior myocardial infarction, it is important to assess the lateral leads for Q-wave formation. On this ECG, the lateral leads are normal. Given the patient's history of a right coronary artery myocardial infarction, by inference, it is likely that leads V_5 and V_6 are represented electrocardiographically by a left circumflex

coronary artery.

Keyword Diagnoses

Sinus bradycardia
First-degree AV block
Inferoposterior myocardial infarction, recent

ELECTROCARDIOGRAM #10



Clinical History

A 47-year-old woman with dialysis-requiring renal failure secondary to long-standing hypertension has presented to the hospital with recent-onset shortness of breath. At the time of this ECG, her serum calcium level was 7.2 mg/dL and her serum potassium level was 6.4 mEq/L.

Electrocardiogram Interpretation

This ECG was obtained at half standardization. Therefore each complex is one half the voltage of a standard ECG. The atrial rate is 60 per minute, regular and of normal axis. This represents NSR. The QRS complexes are normal. A prolonged QT interval is present, and the ST segment is straightened as seen in patients with hypocalcemia. Peaked T waves, particularly notable in leads V_4 to V_6, are narrow based and symmetric, denoting hyperkalemia.

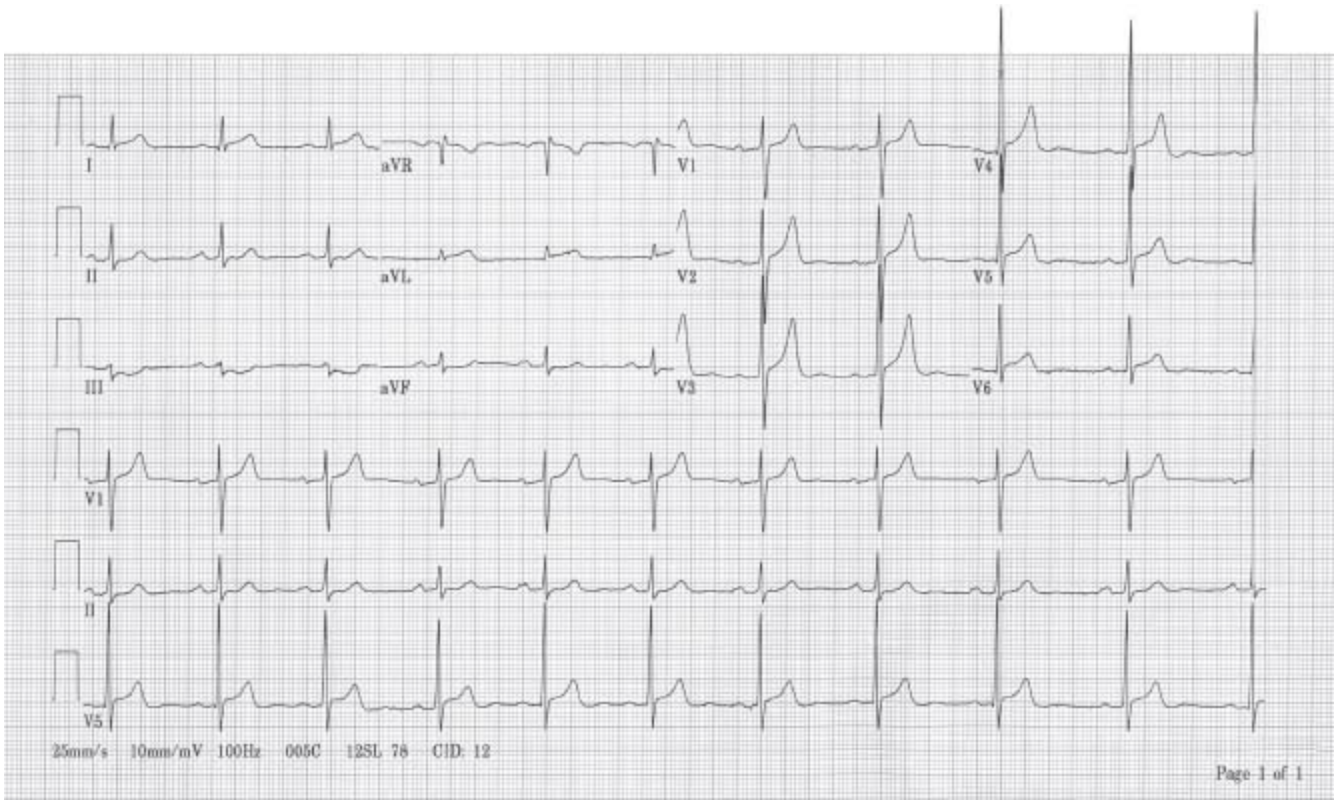
Commentary

This combination of findings is commonly seen in a chronic renal failure patient and reflects both hypocalcemia and hyperkalemia. The ECG may serve as the initial clinical clue to the presence of these electrolyte abnormalities. The patient also demonstrates increased QRS-complex voltage consistent with LVH. This is not diagnosed from this ECG, given the absence of secondary ST-T changes. Diagnosing LVH solely on the basis of increased QRS-complex voltage suffers from reduced specificity.

Keyword Diagnoses

Half standardization
NSR
Prolonged QT interval
Peaked T waves
Hypocalcemia
Hyperkalemia

ELECTROCARDIOGRAM #11



Clinical History

A 58-year-old man presented to the hospital with an acute chest pain syndrome. He underwent a diagnostic cardiac catheterization that demonstrated an acute occlusion of the left circumflex coronary artery.

Electrocardiogram Interpretation

NSR with sinus arrhythmia at a rate slightly >60 per minute is present. ST-segment depression is seen in lead III and less so in lead aVF. In this case, a search for an ECG explanation is important. ST-segment elevation is seen in leads I and aVL. This represents high lateral acute myocardial injury as seen in an early left circumflex territory acute high lateral myocardial infarction. The initial clue on this tracing is the pronounced reciprocal ST-segment depression best seen in lead III.

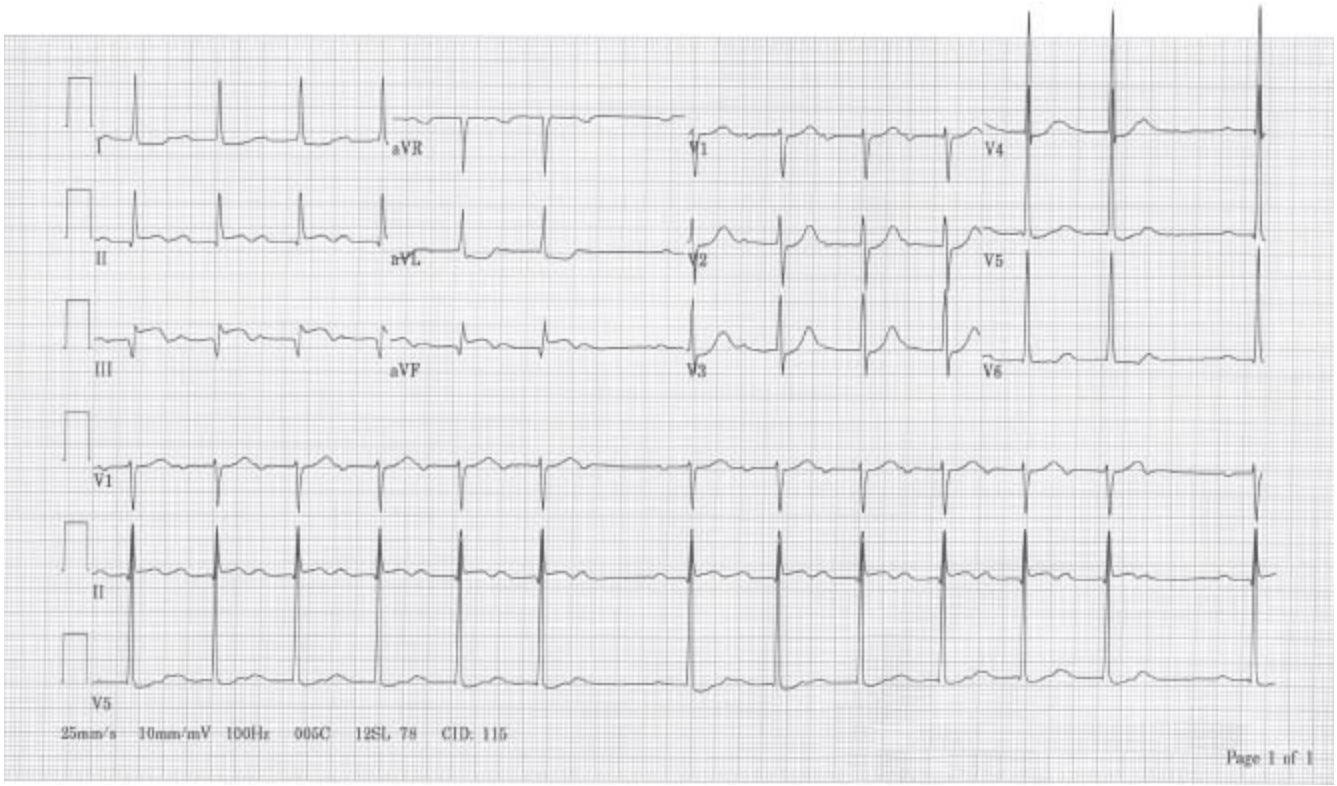
Commentary

Acute myocardial injury patterns can be subtle on an ECG. Oftentimes reciprocal changes are the first clue, as demonstrated here in lead III. The left circumflex coronary artery territory tends to be the most electrocardiographically silent. A careful search for subtle ST-segment elevation often localizes the abnormality to the high lateral leads.

Keyword Diagnoses

NSR
Sinus arrhythmia
High lateral myocardial infarction, acute
Acute myocardial injury

ELECTROCARDIOGRAM #12



Clinical History

A 74-year-old man presented to the hospital with suddenonset anterior chest discomfort and the accompanying ECG was obtained. An urgent cardiac catheterization was followed by a percutaneous transluminal coronary angioplasty to the right coronary artery, as acute thrombus was present. Medications at the time of this ECG included intravenous heparin, intravenous nitroglycerin, aspirin, and metoprolol.

Electrocardiogram Interpretation

NSR is present. Progressive PR-interval prolongation ensues, with an eventual nonconducted QRS complex. This represents a 7:6 second-degree Mobitz Type I (Wenckebach) AV block cycle. A 1.5-mm ST-segment elevation with Q waves is seen in the inferior leads, consistent with an acute inferior myocardial infarction. This explains the Wenckebach AV block, secondary to AV nodal ischemia during a period of acute myocardial injury. Lead V_1 does not demonstrate evidence of ST-segment elevation that would suggest concomitant right ventricular myocardial injury. Reciprocal ST-segment depression is present in leads I and aVL.

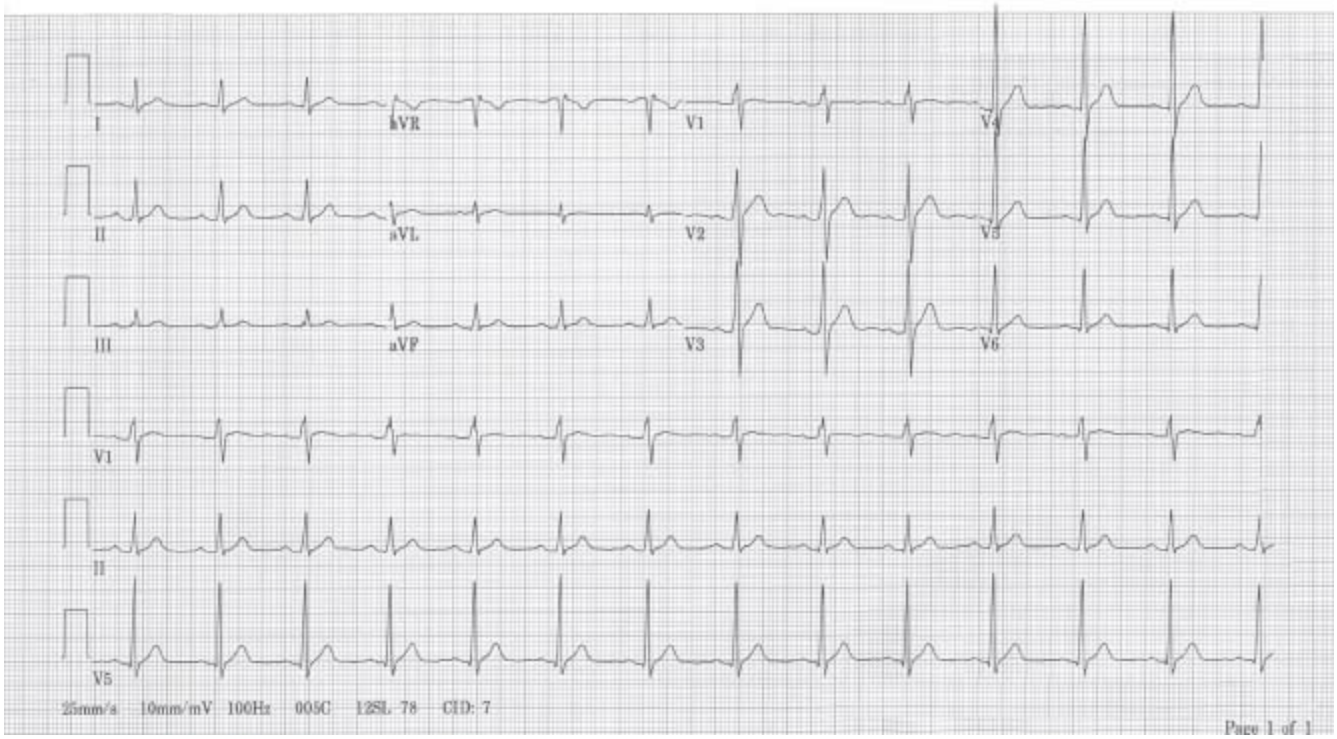
Commentary

Second-degree Mobitz Type I Wenckebach AV block occurring in the setting of acute myocardial injury does not require temporary pacemaker placement. Close observation of the patient's cardiac rhythm is warranted, as this patient subgroup can progress to more advanced forms of heart block.

Keyword Diagnoses

NSR
Second-degree Mobitz Type I Wenckebach AV block
Inferior myocardial infarction, acute
Acute myocardial injury

ELECTROCARDIOGRAM #13



Clinical History

The patient is a 50-year-old man with recently diagnosed multiple myeloma and a serum calcium level of 13.1 mg/dL.

Electrocardiogram Interpretation

This ECG demonstrates NSR. The QRS complexes are normal in both duration and morphology. The only identifiable abnormality is a short QT interval with a truncated ST segment. This is abnormal and represents an ECG marker of hypercalcemia.

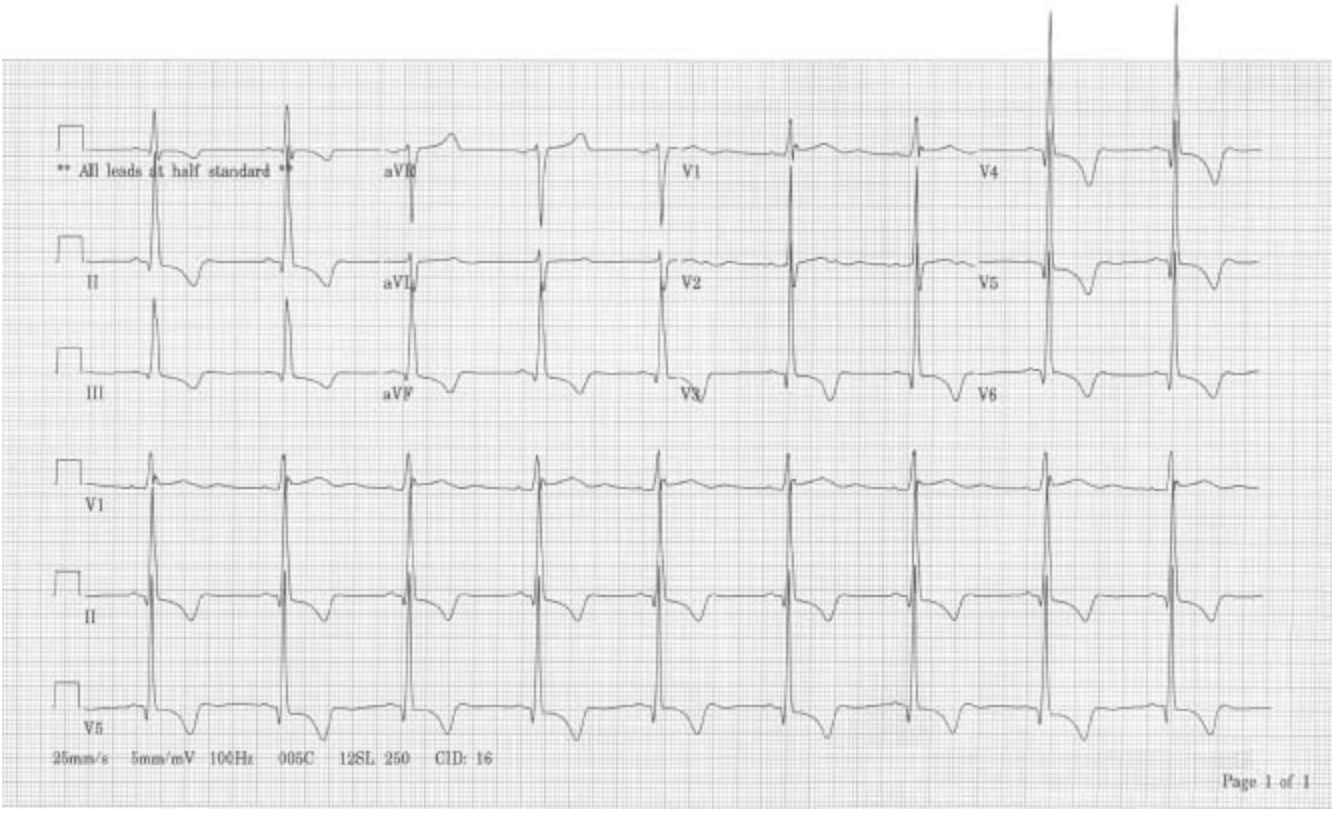
Commentary

This ECG emphasizes the need to carefully assess the ECG intervals on each tracing. The routine ECG may be the only clinical marker of underlying serum electrolyte disturbances. It is important to identify these abnormalities, as prompt clinical treatment is frequently warranted.

Keyword Diagnoses

NSR
Short QT interval
Hypercalcemia

ELECTROCARDIOGRAM #14



Clinical History

A 74-year-old man with hypertrophic cardiomyopathy is being seen in follow-up in the Psychiatry Department for chronic depression. His cardiac medications include verapamil and atenolol.

Electrocardiogram Interpretation

The atrial rhythm is regular, at a rate <60 per minute with a normal P-wave axis. This satisfies the ECG criteria for sinus bradycardia. This ECG is obtained at half standardization. Despite this, prominent QRS-complex voltage is seen in the precordial leads and inferiorly. A tall R wave is present in leads V_1 and V_2. This suggests the presence of both LVH with secondary ST-T changes and RVH. This is an example of biventricular hypertrophy with secondary ST-T changes. Prominent Q waves are seen in this patient with hypertrophic cardiomyopathy reflecting septal depolarization.

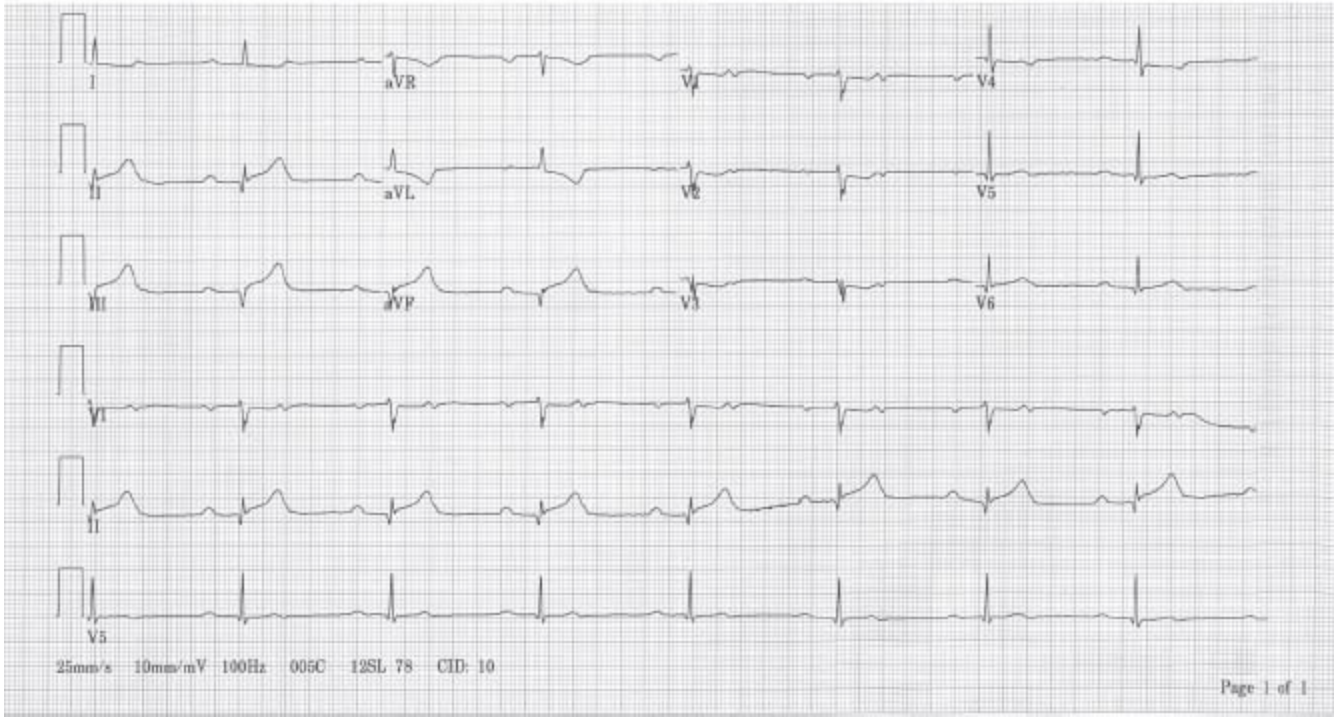
Commentary

In this diagnostic setting, prominent septal Q waves are frequently present as seen on this ECG. It is important to distinguish Q waves secondary to septal depolarization from the possibility of an underlying age-indeterminate myocardial infarction. Oftentimes this is not possible and requires further adjunctive testing.

Keyword Diagnoses

Half standardization
Sinus bradycardia
Biventricular hypertrophy with secondary ST-T changes
Hypertrophic cardiomyopathy

ELECTROCARDIOGRAM #15



Clinical History

A 64-year-old man presented to an outside Emergency Room with an acute-onset chest discomfort syndrome and was accepted in urgent hospital transfer for cardiac catheterization. The patient received immediate thrombolytic therapy. A cardiac catheterization demonstrated a 100% distal occlusion of a saphenous vein graft to the right coronary artery, which was successfully angioplastied.

Electrocardiogram Interpretation

On this tracing, the atrial rhythm is best assessed in the lead V_1 rhythm strip. Regular P waves occur at a rate of approximately 100 per minute, with a P wave preceding each QRS complex and a P wave following each QRS complex within the terminal aspect of the T wave. This represents NSR with 2:1 AV block. Inferior Q waves are present with J-point elevation, ST-segment elevation, and ST-segment straightening consistent with an acute inferior myocardial infarction and acute myocardial injury. Reciprocal ST-segment depression is seen in leads I, aVL, and V_2 to V_4. This conduction abnormality is a result of ischemia of the AV node due to the acute right coronary artery myocardial

infarction. Small Q waves approximately 30 milliseconds in duration are present in leads V_4 to V_6. Associated ST-T changes are present. This suggests the possibility of an age-indeterminate anterolateral myocardial infarction. Clinical correlation with the patient's history is necessary.

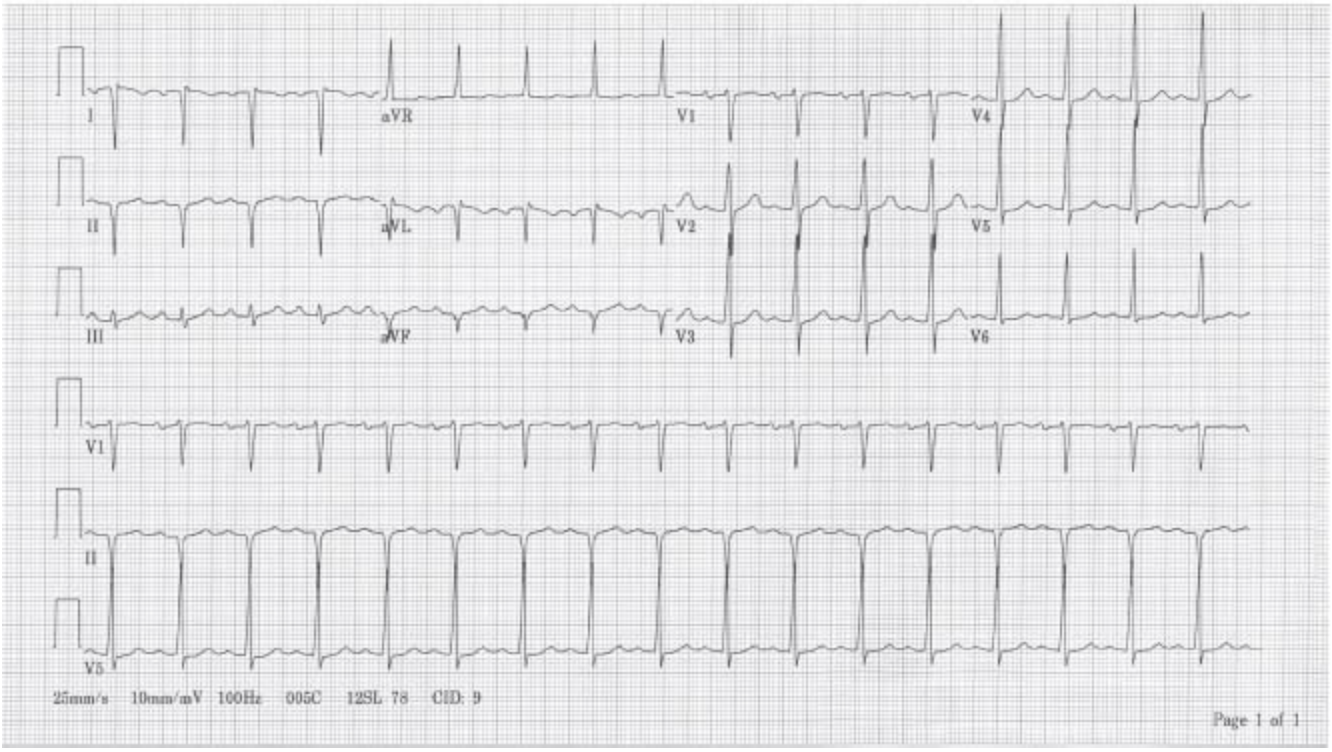
Commentary

It is not clear whether this cardiac rhythm is second-degree Mobitz Type I Wenckebach AV block or second-degree Mobitz Type II AV block. A longer recording with rhythm strip analysis would be helpful to evaluate for periods of Wenckebach AV block with varying conduction ratios. In the setting of 2:1 AV block and acute myocardial injury, temporary pacemaker placement is indicated, as this patient subgroup can proceed to complete heart block and hemodynamic deterioration.

Keyword Diagnoses

NSR
2:1 AV block
Inferior myocardial infarction, acute
Acute myocardial injury

ELECTROCARDIOGRAM #16



Clinical History

A 44-year-old man with severe peripheral vascular disease has been admitted for lower extremity revascularization surgery. He has known coronary artery disease and is status post myocardial infarction in the remote past, location unknown. His medications included insulin, carbamazepine, amitriptyline, and warfarin.

Electrocardiogram Interpretation

This ECG demonstrates a regular atrial rhythm supporting sinus tachycardia at a rate slightly >100 per minute. The P-wave vector is negative in both leads I and aVL. When the P wave demonstrates a dominant negativity in both leads I and aVL, the differential diagnosis includes misplaced limb leads and dextrocardia. Normal R-wave progression is seen in leads V_2 to V_6, which does not support a diagnosis of dextrocardia. Therefore this is an example of misplaced limb leads. The right arm and left arm leads have been reversed. Lead I is inverted. Leads AVR and AVL are reversed, as are leads II and III. Lead AVF is relatively unaffected. Despite this technical error, a dominant Q wave is seen in both leads II and aVF (representing leads III and aVF), possibly suggesting an age-indeterminate inferior myocardial infarction. This does not represent a high lateral myocardial infarction despite the presence of Q waves in leads I and aVL, as these are secondary to the misplaced limb leads.

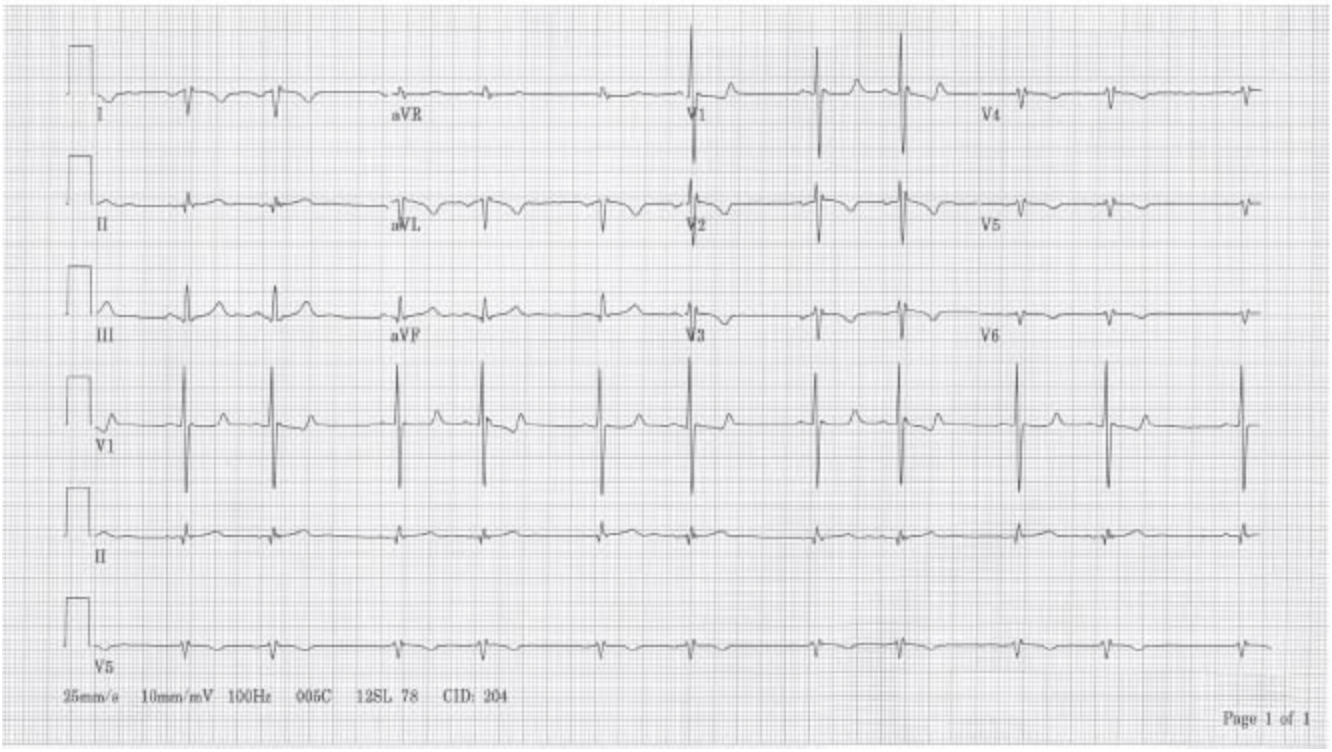
Commentary

It is appropriate to repeat this tracing, checking limb lead placement more carefully, to document this patient's ECG with normally placed leads.

Keyword Diagnoses

Sinus tachycardia
Misplaced limb leads

ELECTROCARDIOGRAM #17



Clinical History

A 22-year-old woman presents for evaluation of dysplastic nevi. She has known dextrocardia but is on no current medications.

Electrocardiogram Interpretation

This tracing demonstrates an abnormal P-wave axis with a negative P-wave vector in leads I and aVL. The differential diagnoses for this finding are misplaced limb leads versus dextrocardia. A prominent R wave is seen in lead V_1, with R-wave regression as one proceeds from leads V_2 to V_6. A premature atrial complex is present.

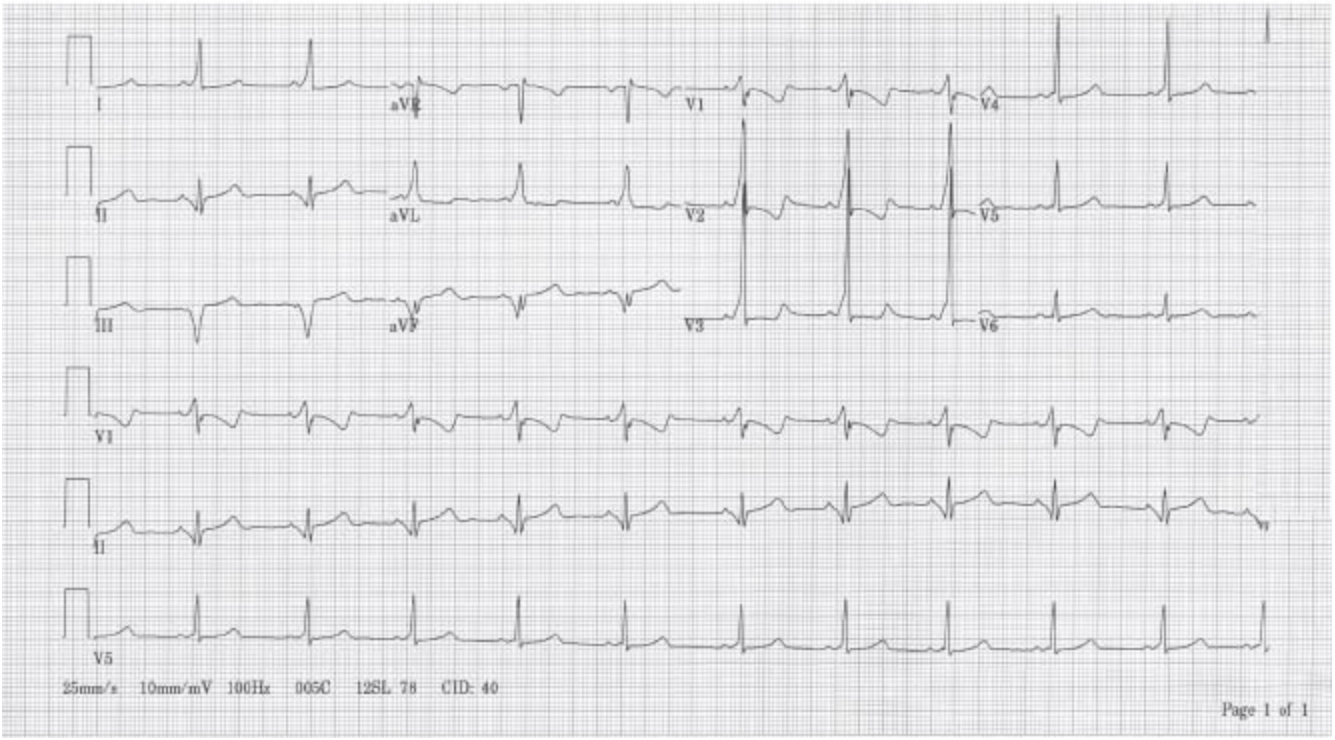
Commentary

Recognizing the presence of dextrocardia is important, because normal ECGs can be interpreted as significantly abnormal. Upon first glance, the frontal-plane QRS-complex axis appears deviated extremely rightward, possibly even suggesting a high lateral myocardial infarction. The important diagnostic clue present on this ECG is the negative P-wave vector in leads I and aVL. This finding, together with R-wave regression seen in leads V_2 to V_6, confirms the presence of dextrocardia.

Keyword Diagnoses

NSR
Premature atrial complex
Dextrocardia

ELECTROCARDIOGRAM #18



Clinical History

A 37-year-old woman with WPW syndrome returned for a repeat evaluation in the setting of medication-induced fatigue and persistent palpitations. Her medications include propranolol. The patient subsequently underwent successful radiofrequency ablation of a right ventricular posteroseptal accessory pathway.

Electrocardiogram Interpretation

NSR is present. The PR interval is short, with a slurred upstroke to the QRS complex best seen in leads V_1 to V_3, I, and aVL, all supporting ventricular preexcitation and WPW syndrome. Inferior Q waves are present, denoting accessory pathway conduction and a pseudoinfarction pattern. This is not indicative of an inferior myocardial infarction.

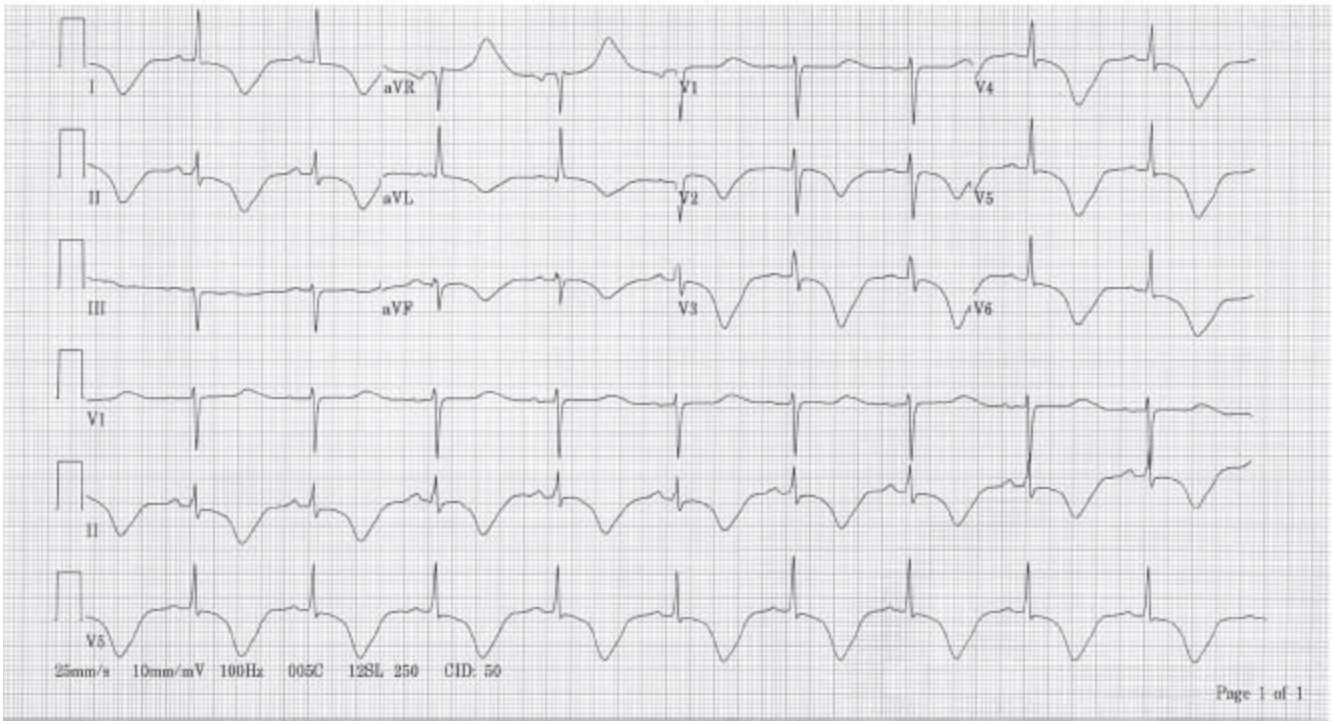
Commentary

WPW syndrome is a common cause of a pseudoinfarction pattern. When the accessory pathway vector is directed opposite an ECG lead, this generates a negative deflection. The inferior Q waves on this ECG have a slurred downstroke with a shortened PR interval representing a delta wave.

Keyword Diagnoses

NSR
WPW syndrome
Pseudoinfarction pattern

ELECTROCARDIOGRAM #19



Clinical History

A 59-year-old woman presented with a chest discomfort syndrome and the above ECG. She subsequently underwent cardiac catheterization that demonstrated normal coronary arteries and global mild left ventricular systolic dysfunction. Neurology was consulted about the possibility of a subarachnoid hemorrhage, and this was excluded. Her past medical history includes hypertension.

Electrocardiogram Interpretation

The atrial rate is regular and slightly <60 per minute. The P-wave axis and morphology appear normal, supporting sinus bradycardia. Nonspecific ST-T changes in the form of diffuse T-wave inversion and a prolonged QT interval are present. This is seen in both profound myocardial ischemia and also central nervous system events such as a subarachnoid hemorrhage. Clinical correlation is important. If in fact this represents a myocardial origin, these ECG findings are most often found in severe subendocardial ischemia or infarction. This is also known as “eggshell” infarct, as a large portion of the subendocardium is infarcted, conferring a worse prognosis on this patient group.

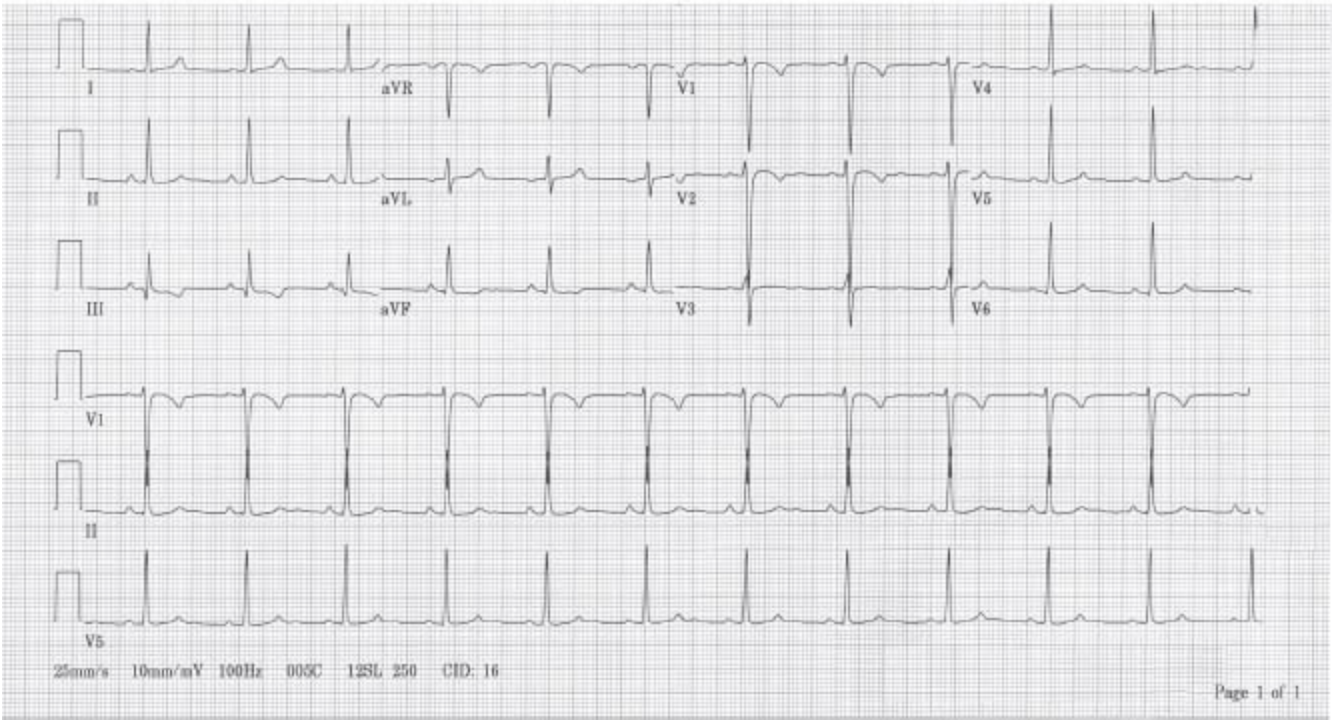
Commentary

The findings on this ECG are most consistent with diffuse subendocardial myocardial ischemia or infarction versus a central nervous system event. Both possibilities were excluded in this patient. Given the mild global left ventricular systolic dysfunction, these findings may represent myocarditis or an early form of a cardiomyopathy in which the ECG demonstrates more pronounced findings. Serial cardiac imaging studies such as echocardiography would be important to evaluate for occult progression of her left ventricular systolic dysfunction.

Keyword Diagnoses

Sinus bradycardia
Nonspecific ST-T changes
Prolonged QT interval
Ischemia
Central nervous system event

ELECTROCARDIOGRAM #20



Clinical History

A 22-year-old woman has been admitted to the hospital for evaluation and treatment of schizophrenia. She is on no current medications.

Electrocardiogram Interpretation

This is a normal ECG. The cardiac rhythm is NSR, as the P wave axis in leads I, II, and III is normal and the atrial rate is approximately 70 per minute. T-wave inversion is present in leads V_1 and V_2. In a young patient, this is a normal finding and demonstrates a persistent juvenile T-wave pattern.

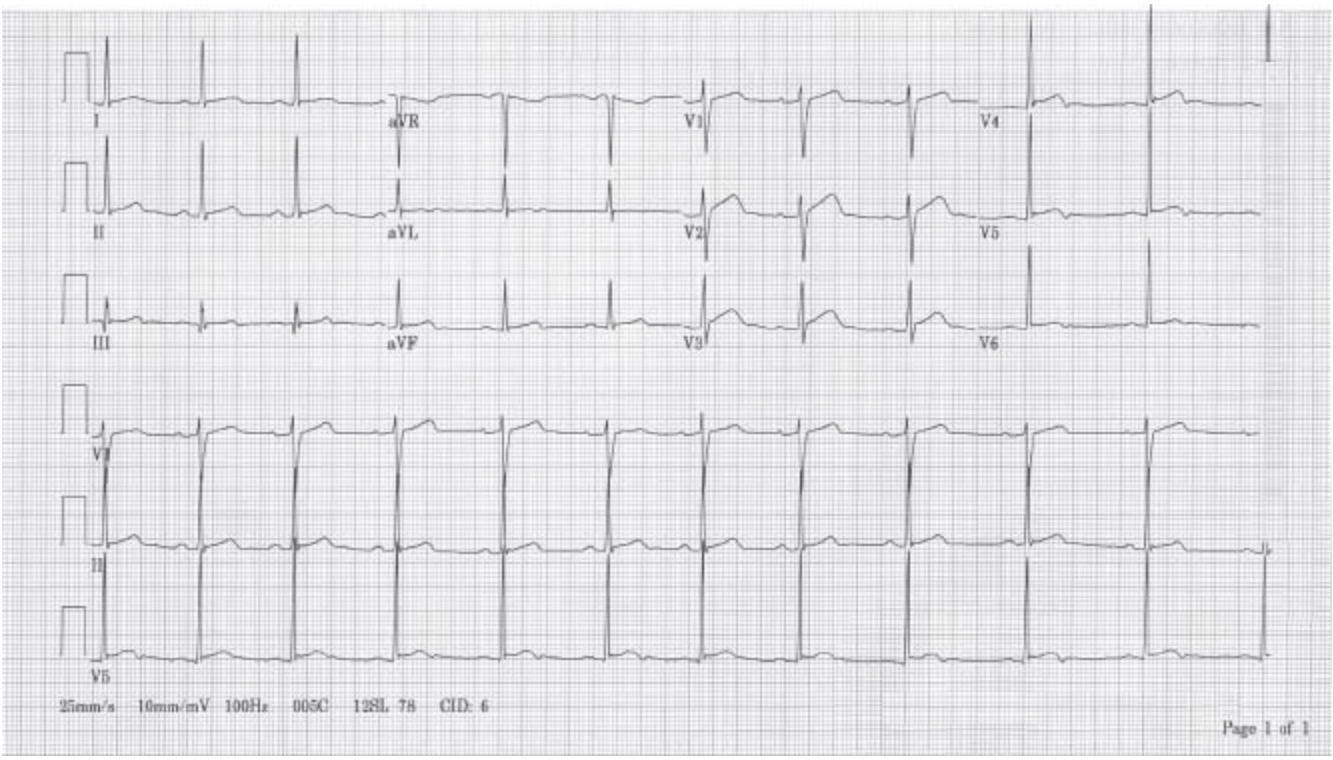
Commentary

It is important to recognize normal variants when interpreting ECGs. The persistent juvenile T-wave pattern is a normal variant and should not be confused with underlying cardiac pathology such as myocardial ischemia or a cardiomyopathy.

Keyword Diagnoses

NSR
Juvenile T-wave pattern
Normal ECG

ELECTROCARDIOGRAM #21



Clinical History

A 30-year-old African American man is being evaluated in the presurgical department prior to inguinal hernia repair. He has no known prior cardiac history. An echocardiogram was normal, without evidence of structural heart disease.

Electrocardiogram Interpretation

Regular P waves with a normal axis at a slightly varying rate of approximately 60 to 75 per minute indicate NSR and sinus arrhythmia. Nonspecific ST-T changes are present throughout the ECG. J-point elevation and ST-segment elevation are seen in leads V_2 to V_6, I, II, and aVF. This indicates the possibility of an acute myocardial injury pattern but does not support an individual coronary artery territory. The atrial repolarization segment in lead aVR is normal, without evidence to support pericarditis. This represents early repolarization.

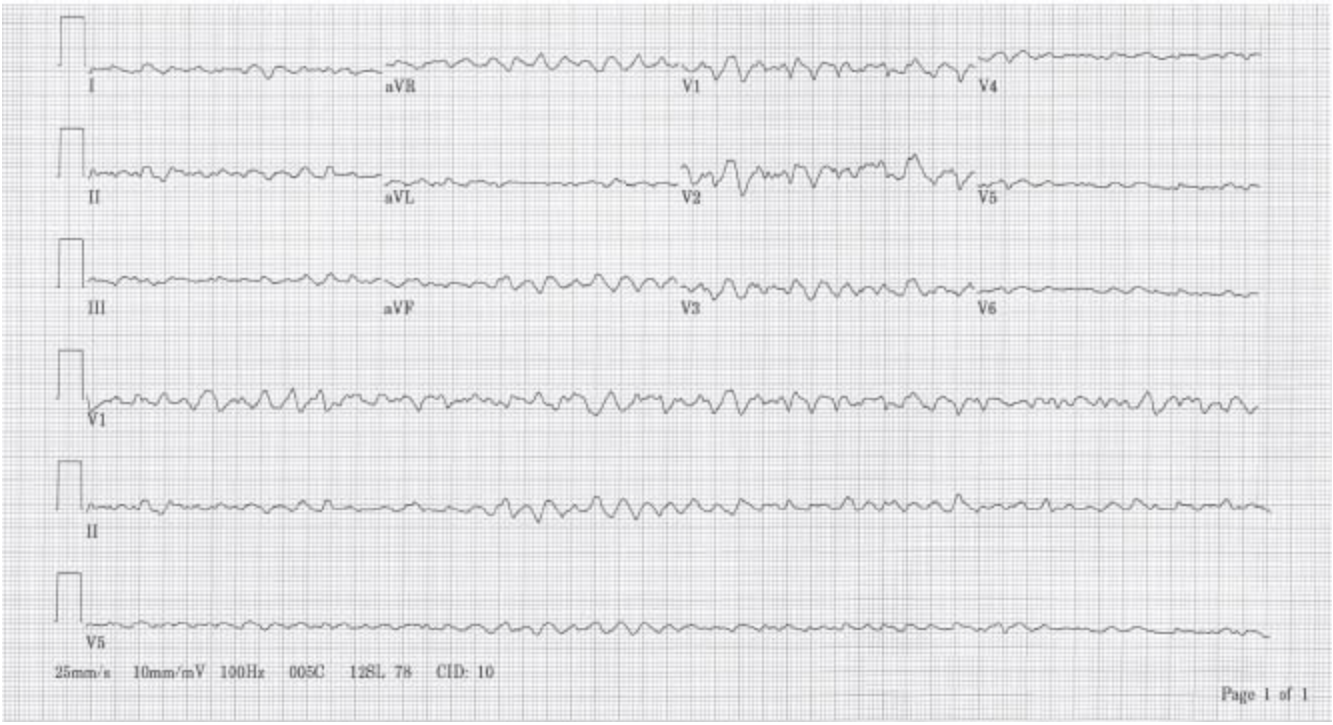
Commentary

The ST-T changes on this ECG are not normal. However, in younger African American patients, nonspecific ST-T changes with this morphology can represent a normal variant. This was confirmed by the normal resting echocardiogram.

Keyword Diagnoses

NSR
Sinus arrhythmia
Normal ECG
Early repolarization

ELECTROCARDIOGRAM #22



Clinical History

A 65-year-old man with advanced coronary artery disease and resulting severe left ventricular systolic dysfunction is awaiting cardiac transplantation. This ECG was obtained while the patient was fully conscious and dependent on a left ventricular assist device. The patient underwent successful cardiac transplantation surgery.

Electrocardiogram Interpretation

The ECG baseline is chaotic, without discernible organized atrial or ventricular activity. This represents VF and is a terminal heart rhythm.

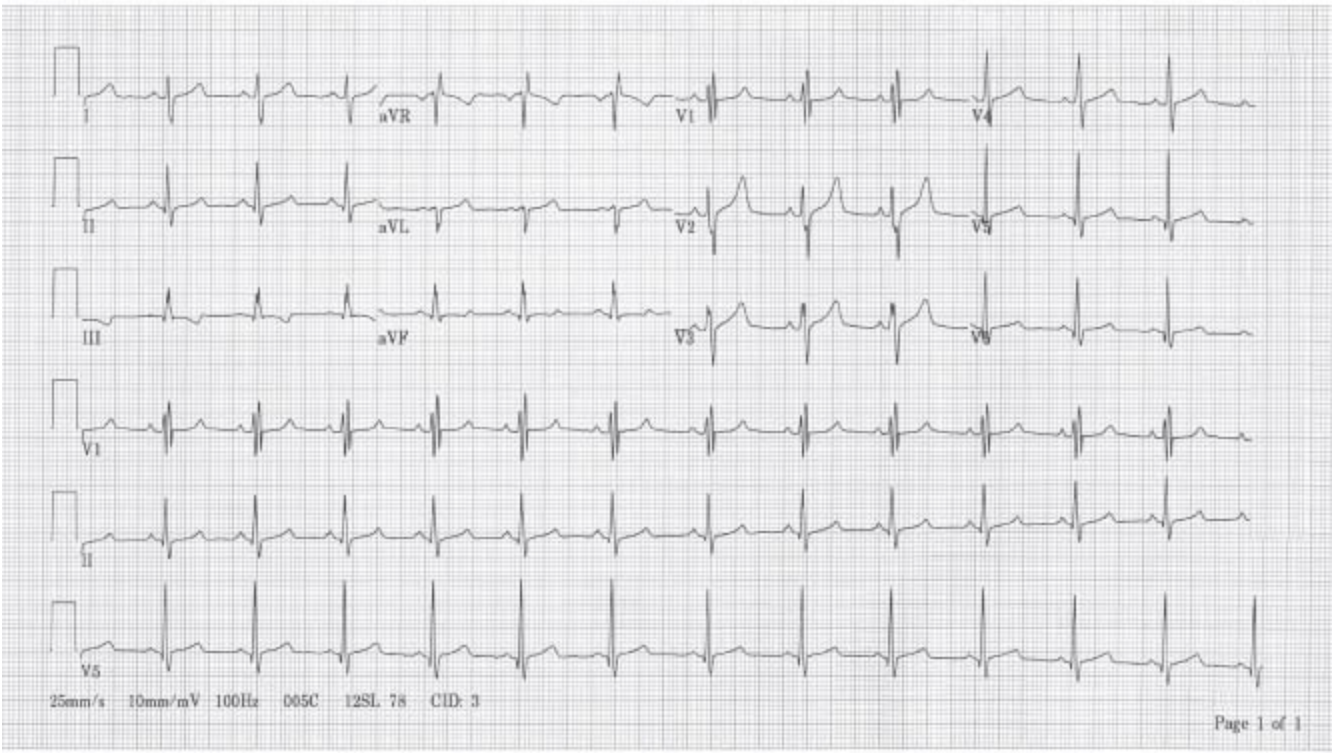
Commentary

This is a rare opportunity to obtain a recording of VF on a 12-lead ECG. There is a complete absence of organized cardiac electrical activity.

Keyword Diagnosis

VF

ELECTROCARDIOGRAM #23



Clinical History

A 19-year-old man was seen preoperatively, prior to intended ostium secundum ASD repair. A recent echocardiogram demonstrated a moderate-sized ostium secundum ASD

with left-to-right shunt flow, a dilated right ventricle with normal right ventricular systolic function, and moderate pulmonary hypertension.

Electrocardiogram Interpretation

The cardiac rhythm is NSR, as a P wave of normal axis precedes each QRS complex. The QRS-complex frontal-plane axis demonstrates right-axis deviation, as the QRS-complex vector is negative in lead I and positive in leads II, III, and aVF. An rsR′ QRS-complex morphology is noted in lead V_1. This represents an unusual pattern for right ventricular conduction delay, and in the setting of QRS-complex right-axis deviation raises the possibility of an ASD.

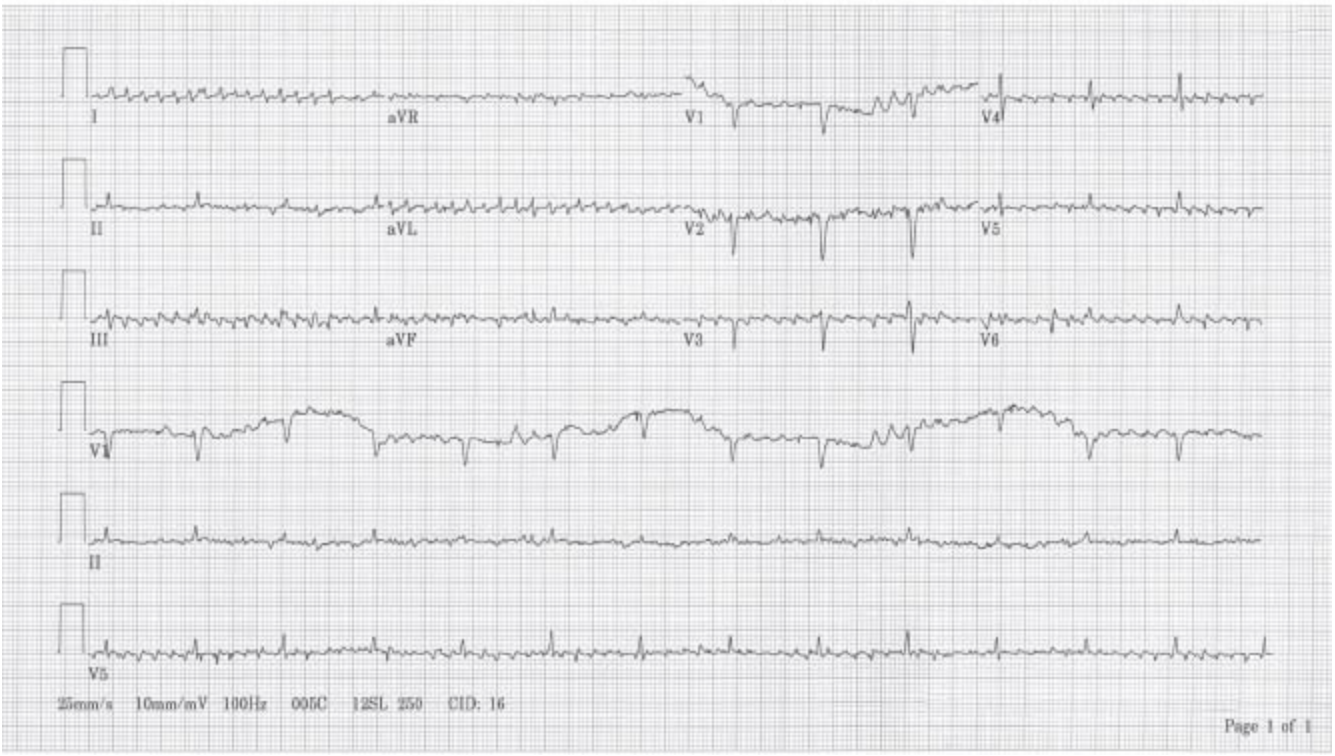
Commentary

The right ventricular conduction delay as seen in lead V_1 is characteristic of an ASD. Unlike an ostium primum ASD, in which the QRS-complex frontal-plane axis is deviated leftward, in the setting of an ostium secundum ASD, the QRS-complex vector is normal or deviated rightward. In this circumstance, given the left-to-right interatrial shunt, the rightward deviation of the QRS-complex vector is secondary to the volume overload of the right ventricle.

Keyword Diagnoses

NSR
Right-axis deviation
Ostium secundum ASD

ELECTROCARDIOGRAM #24



Clinical History

A 62-year-old woman with fevers and chills of 2 days' duration was admitted with suspected sepsis. Comorbid conditions include rheumatoid arthritis and chronic obstructive pulmonary disease.

Electrocardiogram Interpretation

A prominent baseline artifact consistent with electrical interference is present. This significantly compromises the ECG interpretation. Despite this technical difficulty, QRS complexes occur at regular intervals. Low-voltage QRS complexes are present in the limb leads, as no complex is >5 mm in amplitude. Given the baseline artifact, no identifiable atrial activity is present. The constant QRS-complex cycle length suggests NSR. ST-T-segment and T-wave flattening is suspected, consistent with nonspecific ST-T changes.

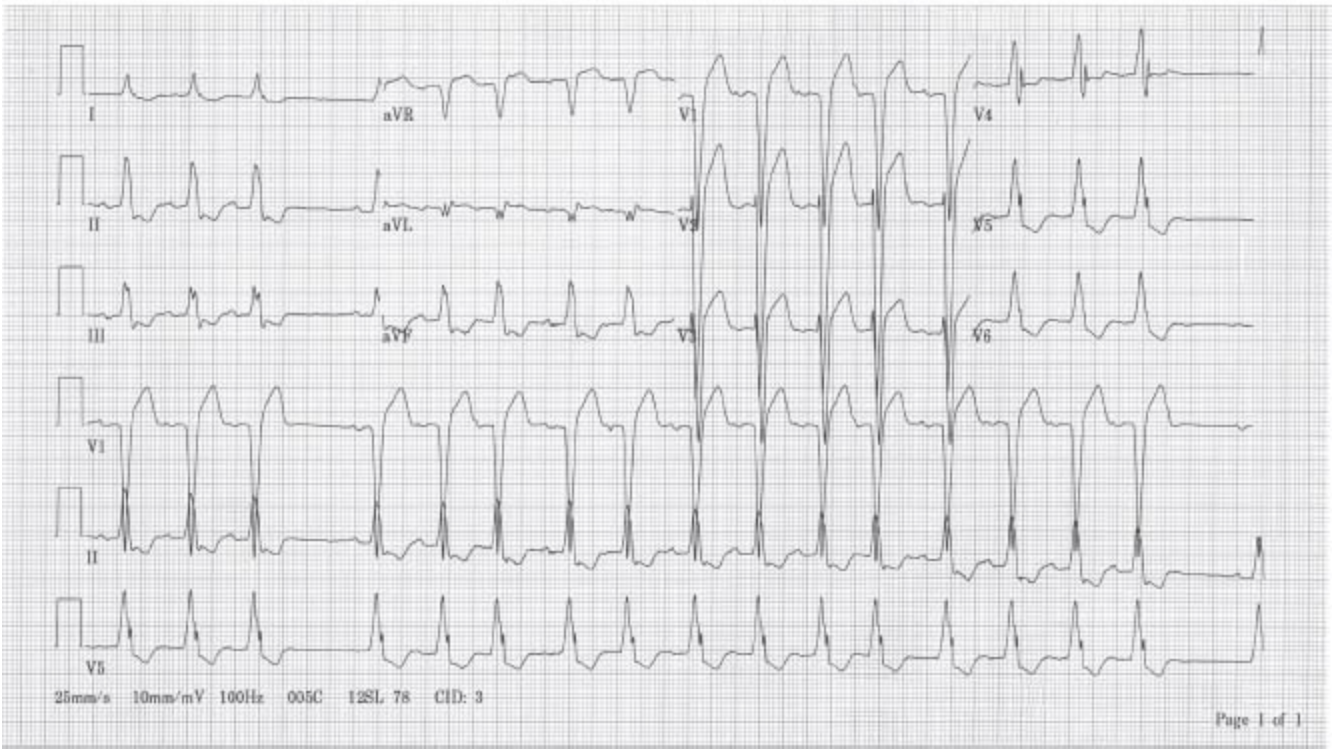
Commentary

The prominent baseline artifact merits a repeat examination, as this artifact interferes significantly with ECG interpretation.

Keyword Diagnoses

Baseline artifact
NSR
Low-voltage QRS—limb leads
Nonspecific ST-T changes

ELECTROCARDIOGRAM #25



Clinical History

A 76-year-old man with two prior coronary artery bypass graft surgeries and moderate left ventricular systolic dysfunction has returned for outpatient cardiology follow-up. The patient is being seen preoperatively prior to a planned carotid endarterectomy. His comorbid conditions include severe chronic obstructive pulmonary disease, paroxysmal AF, and chronic renal insufficiency. His medications included prednisone, digoxin, enalapril, furosemide, and warfarin.

Electrocardiogram Interpretation

A P wave precedes each QRS complex at a rate >100 per minute, supporting sinus tachycardia. The 6th, 8th, and 12th P waves are premature, reflecting PACs. The QRS complex is widened, with a complete LBBB morphology. An apparent pause occurs between the third and fourth QRS complexes. No P wave is identified, but the P-P interval is twice that of the intrinsic P-P interval. The sinus node discharges on time, but the depolarization wave is blocked from exiting the sinus node and depolarizing the atrium. This is known as sinus exit block. No identifiable atrial activity in the form of a P wave is seen. The next P wave occurs when expected, as the sinus node discharges without exit block transpiring.

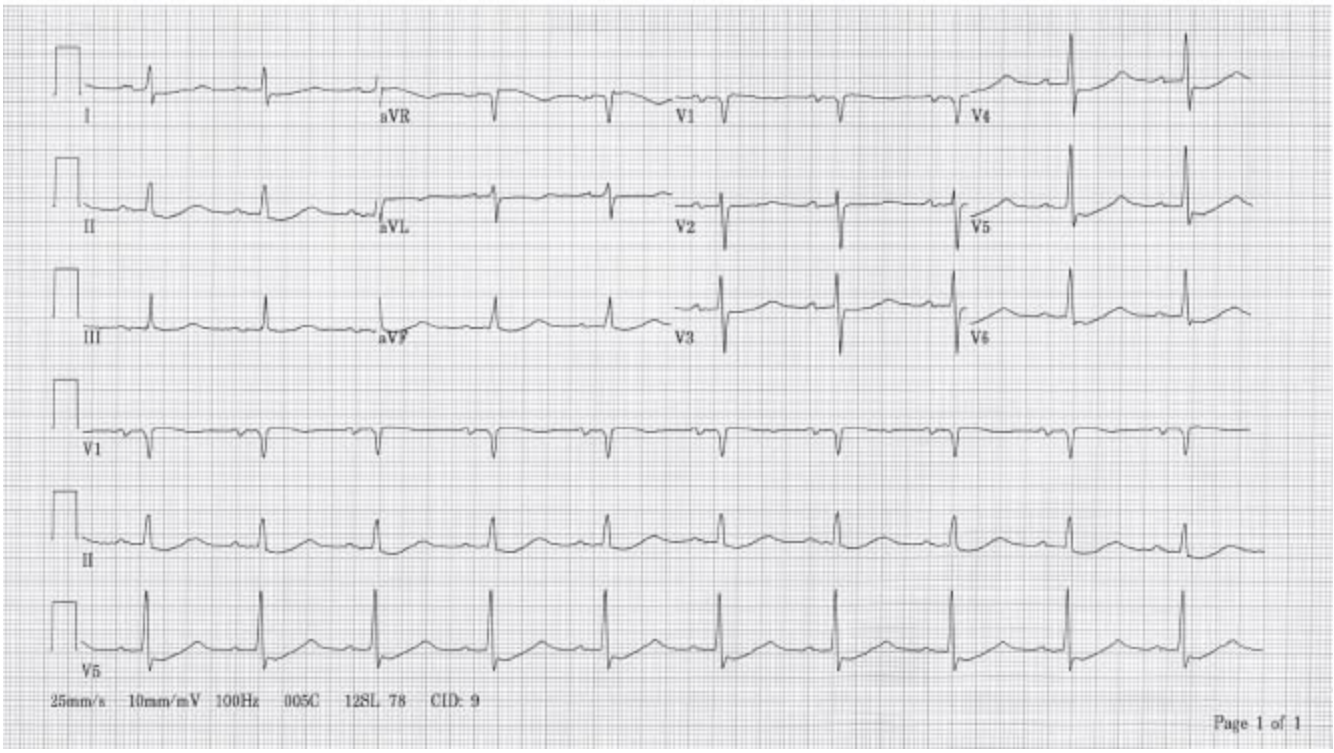
Commentary

To diagnose the presence of sinus exit block, the R-R interval encompassing the sinus exit block should be twice the baseline R-R interval. This ECG also demonstrates significant conduction system disease, given the presence of complete LBBB. This is most likely secondary to the patient's advanced ischemic heart disease.

Keyword Diagnoses

Sinus tachycardia
Premature atrial complex
Sinus exit block
Complete LBBB

ELECTROCARDIOGRAM #26



Clinical History

A 72-year-old man with advanced peripheral vascular disease has been admitted to the hospital for a semielective below-the-knee amputation. His past medical history includes chronic obstructive pulmonary disease, a remote myocardial infarction, and prior pacemaker placement. His medications include quinidine and digoxin.

Electrocardiogram Interpretation

The cardiac rhythm is NSR, as the P waves occur at regular intervals with a normal axis

slightly >60 per minute. The PR interval is prolonged to 220 milliseconds, representing first-degree AV block. Left atrial abnormality is seen, as the P-wave morphology is terminally negative in lead V_1 and bifid in lead II. Diffuse nonspecific ST-T changes are present. Most important, each lead demonstrates a prominent prolonged QT interval. Both the QT-interval prolongation and ST-segment scooping are secondary to the concomitant quinidine effect and digitalis effect.

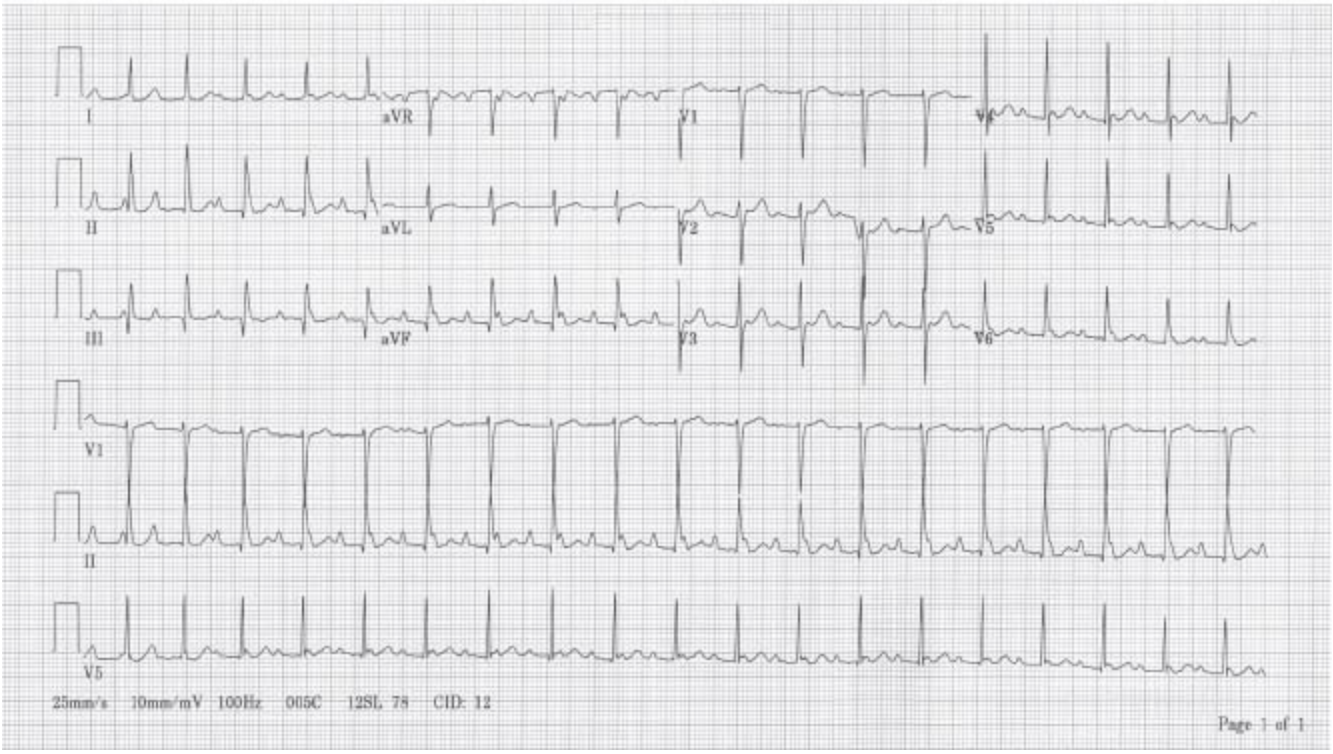
Commentary

QT-interval prolongation in the setting of quinidine administration may represent quinidine toxicity and near-future proarrhythmia. Comparison with prior ECGs is important to confirm whether this is a new or preexisting finding.

Keyword Diagnoses

NSR
First-degree AV block
Left atrial abnormality
Prolonged QT interval
Nonspecific ST-T changes
Digitalis effect
Quinidine effect

ELECTROCARDIOGRAM #27



Clinical History

A 77-year-old woman status post an acute left middle cerebral artery occlusion and urokinase administration is now experiencing recurrent atrial arrhythmias. Medications at the time of this ECG included diltiazem, topical nitroglycerin, and isosorbide mononitrate. An echocardiogram performed during this hospitalization demonstrated moderate left atrial enlargement and normal left ventricular systolic function without evidence of a prior myocardial infarction.

Electrocardiogram Interpretation

This ECG demonstrates two P waves for each QRS complex, best seen in lead aVF. The second P wave occurs on the downslope of the S wave at the beginning of the ST segment. This represents ectopic atrial tachycardia with 2:1 AV conduction. There are small narrow inferior Q waves that are not of diagnostic significance.

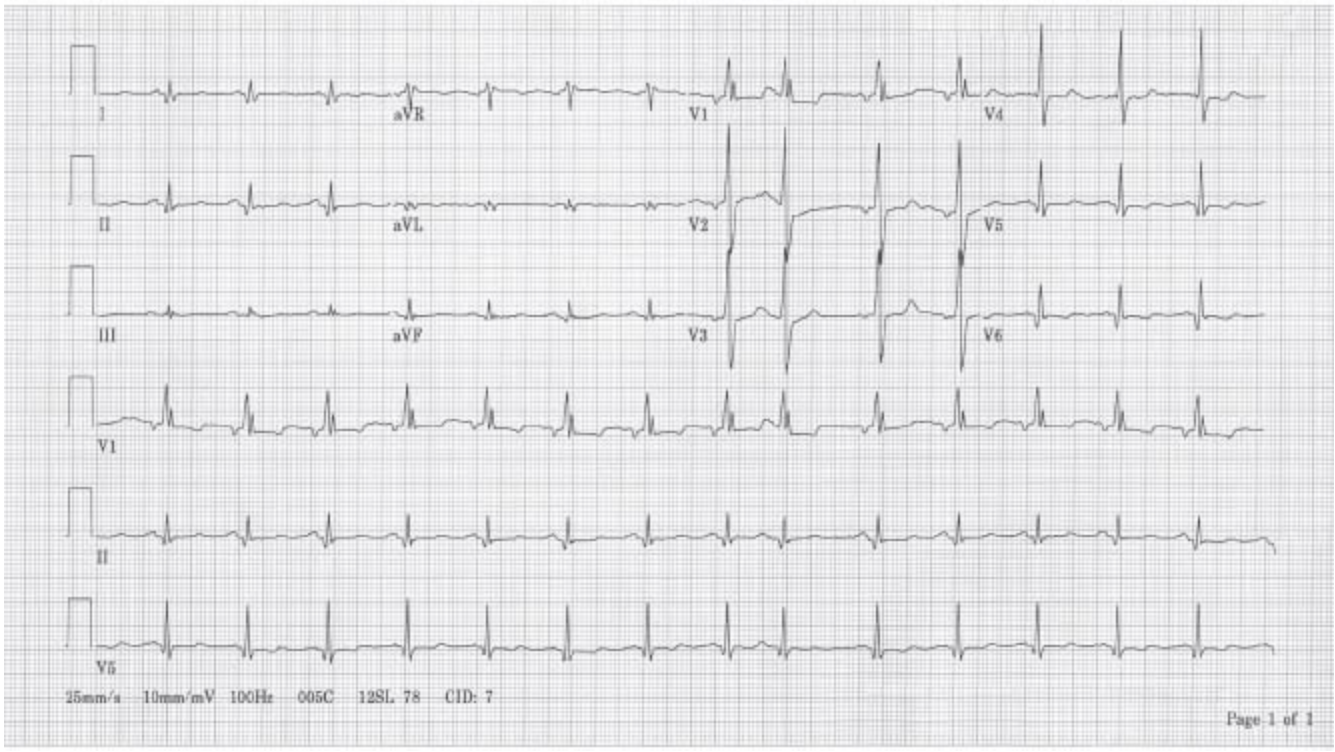
Commentary

When interpreting ECGs that show arrhythmias, it is important to survey each lead, which may yield a subtle and different clue. For this tracing, regular atrial activity is seen best in the inferior leads. Other leads such as lead V_1 demonstrate nearly isoelectric atrial activity and suggest a junctional tachycardia. When a tachycardia is present, it is important to ascertain the shortest P-P interval and compare it to the R-R interval. Without this approach, 2:1 AV conduction may be overlooked.

Keyword Diagnoses

Ectopic atrial tachycardia
2:1 AV conduction

ELECTROCARDIOGRAM #28



Clinical History

A 66-year-old man status post recent coronary artery bypass graft surgery, paroxysmal AF, and a cerebrovascular accident has returned for a follow-up evaluation after his bypass surgery. Other comorbidities include hypertension, non-insulin-requiring diabetes mellitus, and hyperlipidemia.

Electrocardiogram Interpretation

NSR is present. The 9th P wave is premature, reflecting a premature atrial complex with a similar QRS-complex morphology. The QRS-complex duration is prolonged but <120 milliseconds. Lead V_1 demonstrates an Rsr′ QRS-complex pattern indicating an incomplete RBBB. Q waves of diagnostic duration are present in the inferior, lateral, and high lateral leads, indicating an inferolateral myocardial infarction of indeterminate age. R waves are prominent in leads V_1 and V_2, suggesting an age-indeterminate posterior myocardial infarction. This is likely one event and is best characterized collectively as an age-indeterminate inferoposterolateral myocardial infarction. Left atrial abnormality is seen in lead V_1, as the terminal P-wave vector is negative.

Commentary

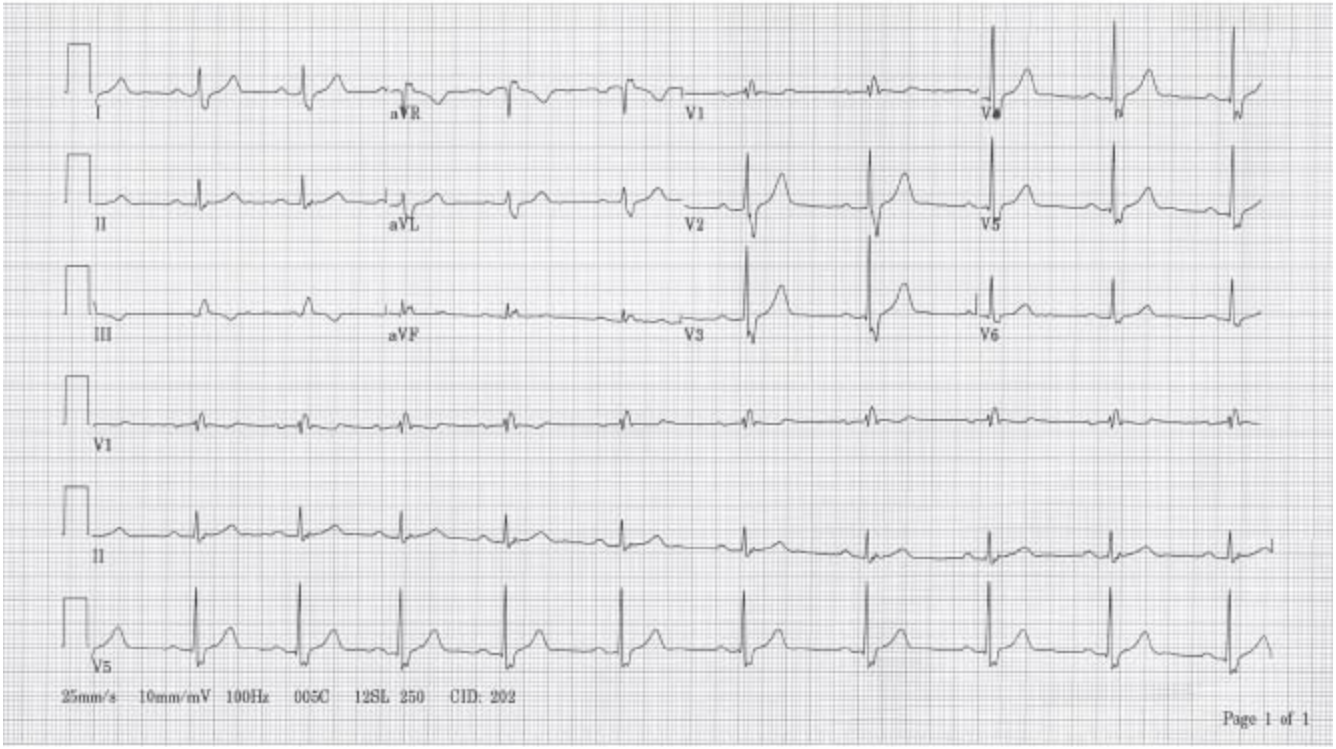
The most important findings on this ECG are the diagnostically wide Q waves present in leads I, aVL, and V_5 and V_6, consistent with an age-indeterminate lateral myocardial infarction. In the presence of a lateral myocardial infarction, it is important to identify

other potential areas of infarction. Typically, lateral infarctions may extend both posteriorly and inferiorly. The inferior Q waves are of diminutive depth and of only 30 milliseconds duration. In the setting of prominent R waves in leads V_1 and V_2 and prominent lateral Q waves, these findings together suggest an associated inferoposterior myocardial infarction.

Keyword Diagnoses

NSR
Premature atrial complex
Left atrial abnormality
Incomplete RBBB
Inferoposterolateral myocardial infarction, age-indeterminate

ELECTROCARDIOGRAM #29



Clinical History

A 40-year-old man with a history of "an enlarged heart" since a young age is seeking a cardiac evaluation. A prior echocardiogram demonstrated evidence of Ebstein anomaly.

Electrocardiogram Interpretation

The cardiac rhythm is NSR. This PR interval is borderline prolonged. Right ventricular conduction delay is evidenced by complete RBBB. This is best seen in lead V_1, with an

rsr′ QRS complex, and also in leads I, aVL, and V_6, with a widened QRS complex and terminal S wave indicative of right ventricular conduction delay. Leads V_2 and V_3 demonstrate primary T-wave changes, as depolarization and repolarization demonstrate similar polarity.

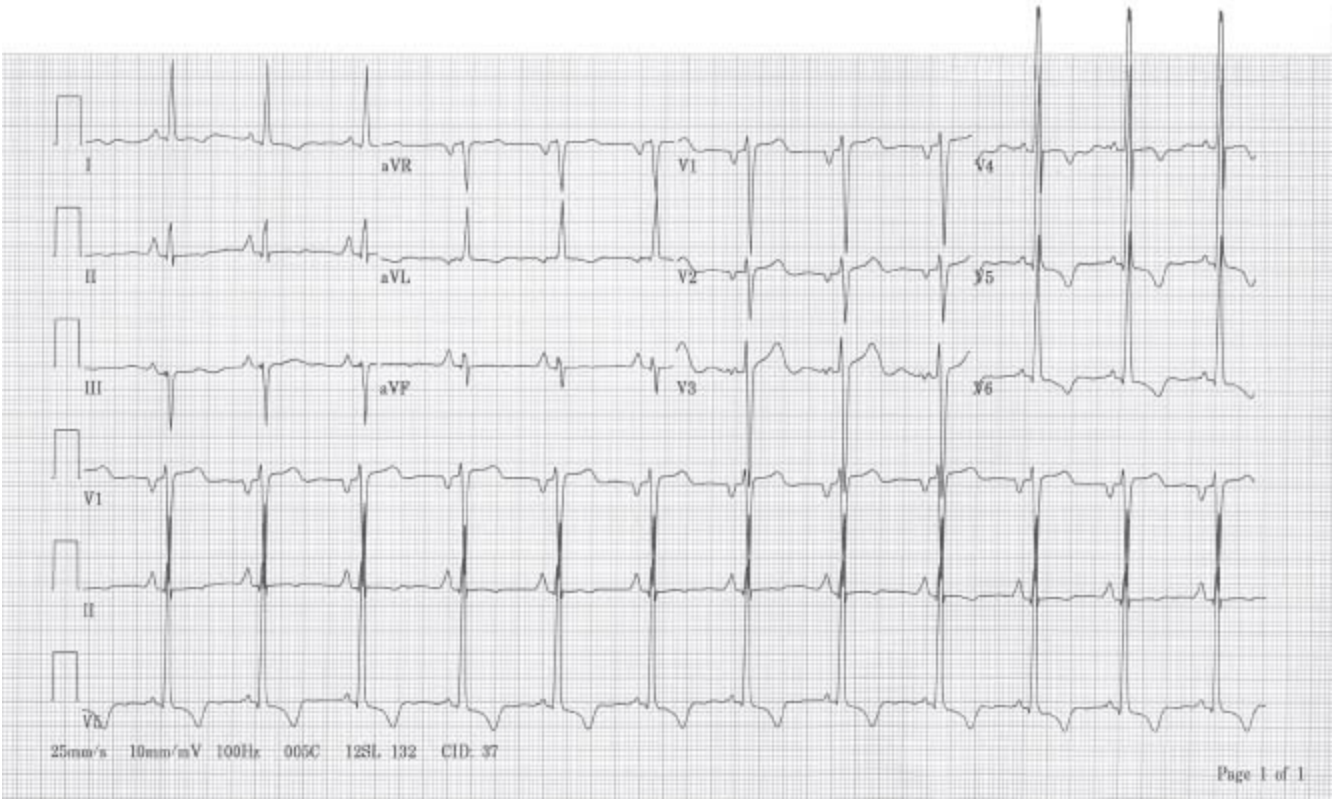
Commentary

Ebstein anomaly is characterized by apical right ventricular displacement of the tricuspid valve septal and/or posterior leaflets, resulting in "atrialization" of the right ventricle. Frequently, these patients suffer from tricuspid insufficiency, right ventricular systolic dysfunction, and resulting slowed right ventricular conduction as evidenced by complete RBBB and 1-degree AV block. These patients also frequently have one or more accessory pathways.

Keyword Diagnoses

NSR
Complete RBBB
Primary T-wave changes
Ebstein anomaly

ELECTROCARDIOGRAM #30



Clinical History

A 63-year-old man with an approximately 25-year history of hypertension presents to the hypertension clinic for further evaluation. He has noticed recent dyspnea upon exertion. Medications at the time of this tracing included lisinopril.

Electrocardiogram Interpretation

NSR is present, as each QRS complex is preceded by a P wave of normal axis. The P-wave morphology is abnormal, with a terminal negativity in lead V_1 consistent with left atrial abnormality. In lead II, the P-wave amplitude is >3 mm, consistent with right atrial abnormality. Prominent precordial QRS-complex voltage is present, with asymmetric ST-T changes indicative of LVH with secondary ST-T changes. Negative U waves are seen in the lateral precordial leads, supporting the presence of LVH.

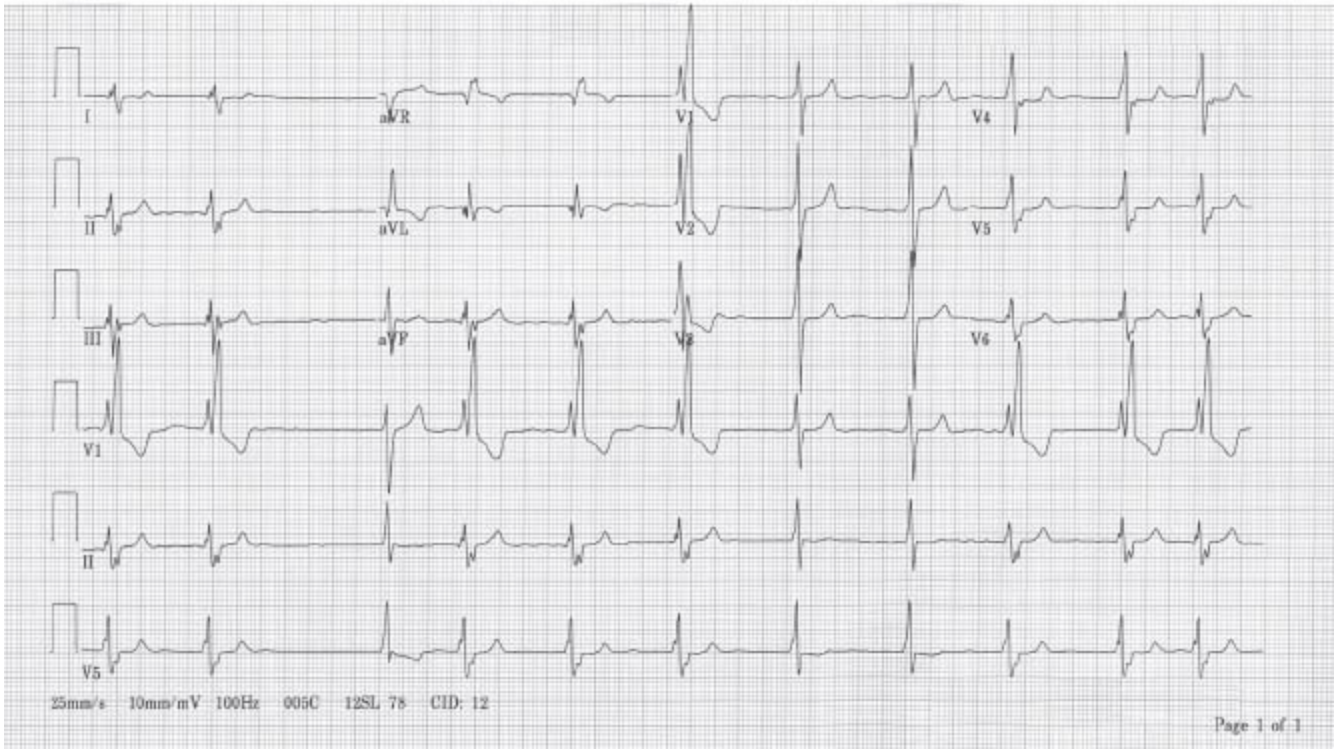
Commentary

This ECG satisfies many criteria for LVH. In addition to the prominent QRS-complex voltage and asymmetric T-wave inversion indicative of a strain pattern, a slightly prolonged QRS complex and prominent left atrial abnormality are also present. Negative U waves are readily seen. The differential diagnosis of negative U waves includes coronary artery disease and LVH. With the associated ECG findings, the negative U waves are secondary to LVH.

Keyword Diagnoses

NSR
Left atrial abnormality
Right atrial abnormality
LVH with secondary ST-T changes
Negative U waves

ELECTROCARDIOGRAM #31



Clinical History

A 47-year-old man with a history of aortic stenosis status post prior aortic valve replacement re-presents with perivalvular moderately severe aortic insufficiency and congestive heart failure. Comorbid conditions include insulin-requiring diabetes mellitus and a recently repaired rectal fistula. His medications included insulin, potassium, metolazone, metoprolol, captopril, and digoxin.

Electrocardiogram Interpretation

The ECG baseline demonstrates an absence of organized atrial activity. The ventricular response is irregularly irregular, representing AF. An intermittent complete RBBB pattern is seen at shorter R-R intervals. Note that the initiation of the complete RBBB occurs at a shorter R-R interval than does sustaining the complete RBBB. This is a typical finding in acceleration-dependent complete RBBB. With QRS-cycle length slowing, the complete RBBB transiently disappears. There is no evidence of a prior myocardial infarction. High lateral nonspecific ST-T changes are present.

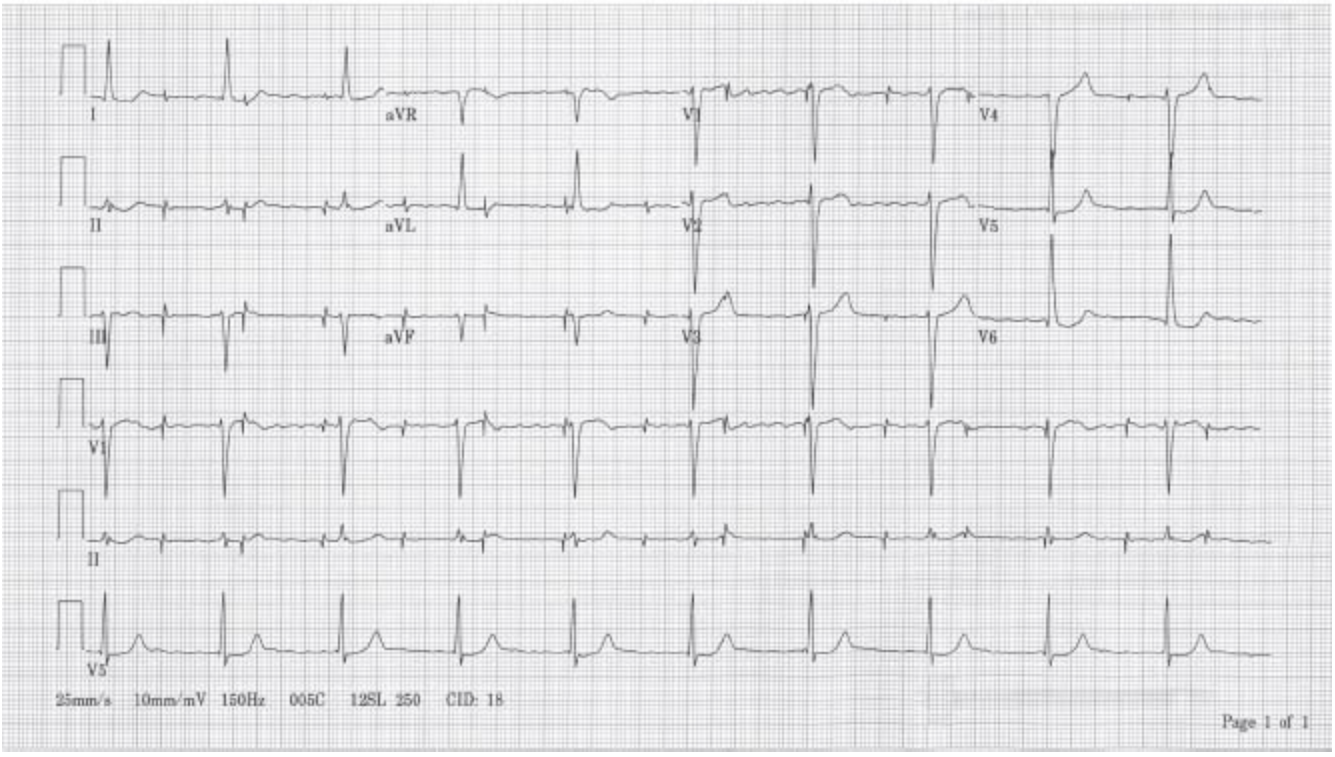
Commentary

Acceleration-dependent complete RBBB is a common ECG finding. The right bundle branch has a longer refractory period than the left bundle branch, and therefore ratedependent right bundle branch conduction delay is a more common entity. This may precede permanent complete RBBB.

Keyword Diagnoses

AF
Acceleration-dependent complete RBBB
Nonspecific ST-T changes

ELECTROCARDIOGRAM #32



Clinical History

A 72-year-old woman with advanced AV block necessitating prior permanent pacemaker placement returns for pacemaker follow-up. Comorbid conditions include coronary artery disease, hypertension, and hyperlipidemia. Medications at the time of this ECG included metoprolol, aspirin, digoxin, and simvastatin.

Electrocardiogram Interpretation

The ECG baseline is devoid of discrete atrial activity. This represents AF. The QRS complexes occur at regular R-R intervals at a ventricular rate slightly >60 per minute. This is an unexpected finding in the presence of AF. This represents an accelerated junctional rhythm and AV dissociation. Presumed ventricular pacemaker deflections occur at regular intervals throughout the ECG with no relationship to the QRS complexes. This represents both pacemaker sensing failure and pacemaker capture failure. Lateral and high lateral nonspecific ST-T changes are demonstrated. The scooping of the ST segments supports the presence of digitalis effect.

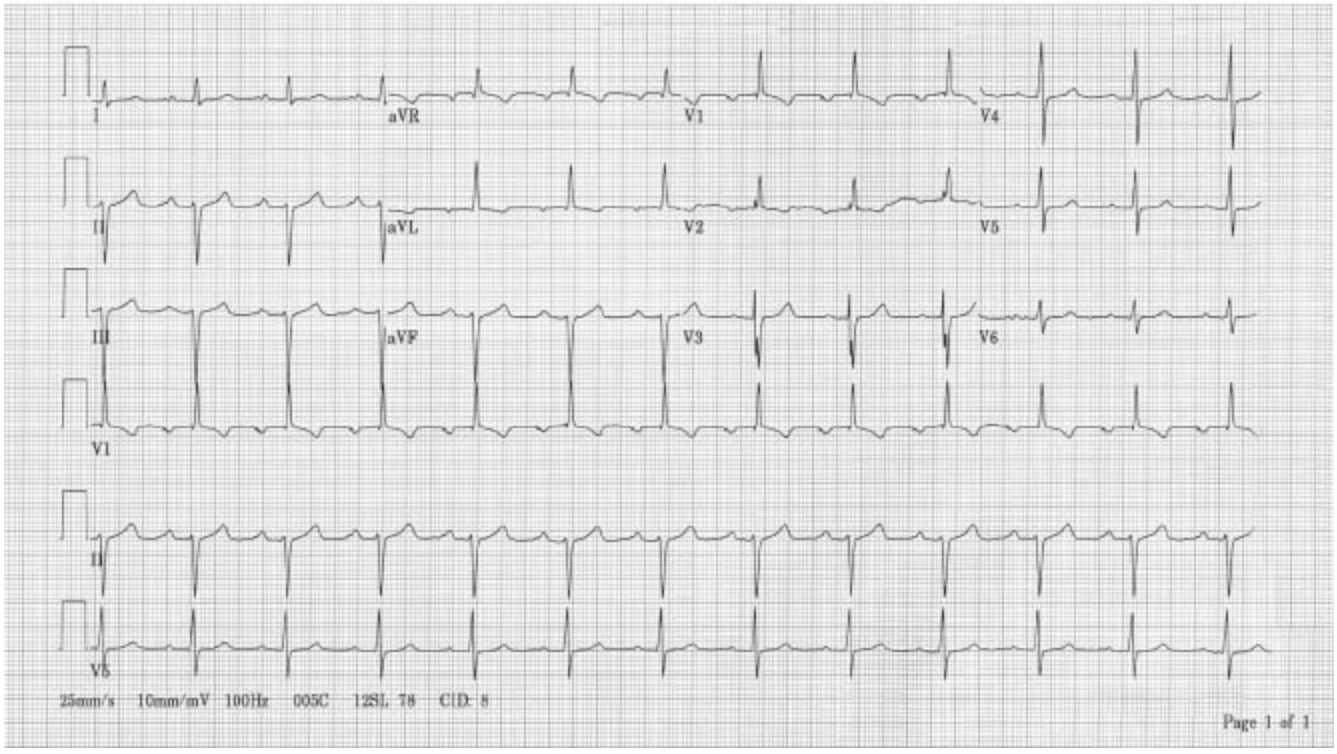
Commentary

This ECG demonstrates abnormal pacemaker function, necessitating further evaluation. This may represent pacemaker lead dislodgement. In the presence of AF, it is important to evaluate the ECG for a second independent cardiac rhythm. The important clue on this tracing is the constant R-R interval. AV dissociation and an accelerated junctional rhythm both support the possible presence of digitalis toxicity, warranting further clinical investigation.

Keyword Diagnoses

AF
Accelerated junctional rhythm
AV dissociation
Ventricular pacemaker
Pacemaker sensing failure
Pacemaker capture failure
Nonspecific ST-T changes
Digitalis effect

ELECTROCARDIOGRAM #33



Clinical History

A 34-year-old woman with a history of an AV canal and ostium primum ASD status post surgical repair is readmitted for a cardiac evaluation. She is experiencing

paroxysmal atria dysrhythmias and is on no current medications.

Electrocardiogram Interpretation

This patient is known to have ostium primum ASD. This ECG demonstrates a group of findings consistent with this diagnosis. The atrial rhythm is NSR. The PR interval is prolonged at 240 milliseconds, representing first-degree AV block. The P wave is terminally negative in lead V_1 and broadened in lead II, suggesting left atrial abnormality. The QRS-complex axis is deviated leftward, satisfying the criteria for left-axis deviation, as the QRS-complex frontal-plane vector is positive in lead I and deeply negative in leads II, III, and aVF. An rsR′ QRS complex is seen in lead V_1 with a normal QRS-complex duration, supporting incomplete RBBB.

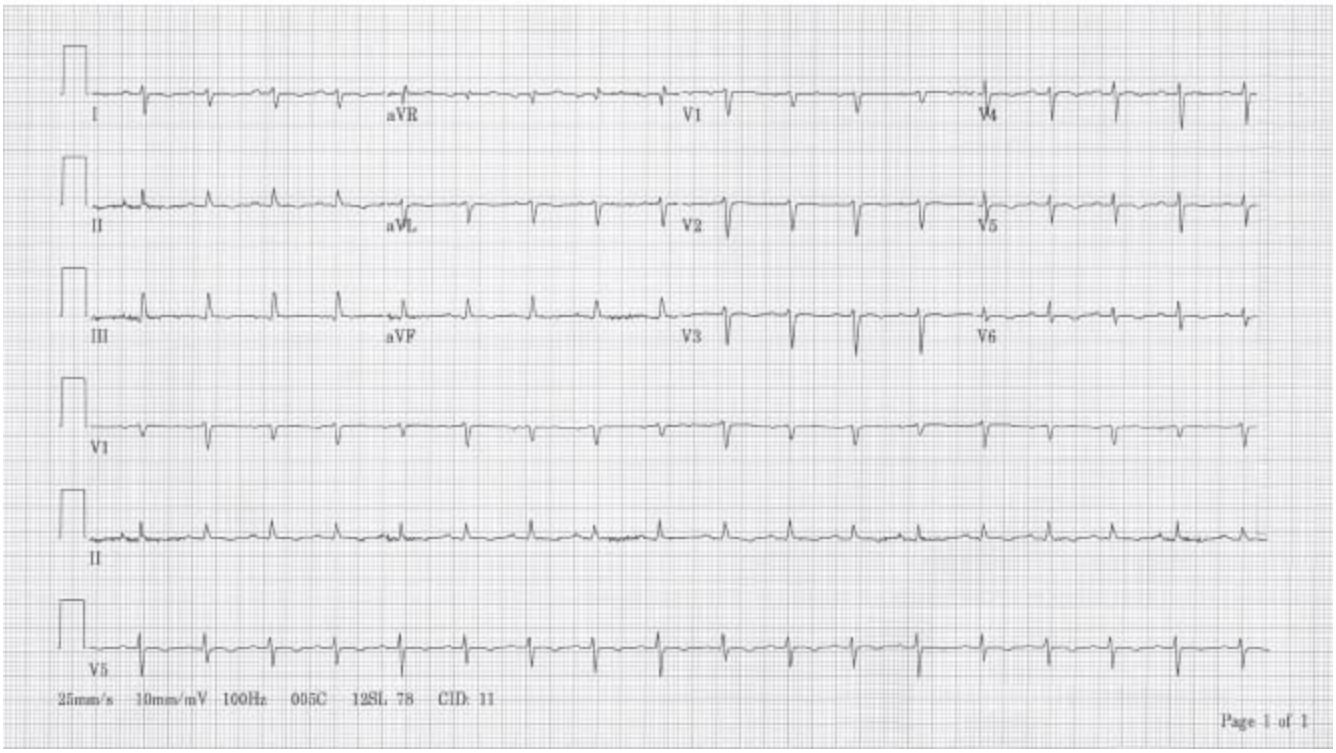
Commentary

A narrow rsR′ QRS complex morphology in the presence of left-axis deviation and left atrial abnormality are a group of findings consistent with the diagnosis of an ostium primum ASD.

Keyword Diagnoses

NSR
First-degree AV block
Incomplete RBBB
Left atrial abnormality
Left-axis deviation
Ostium primum ASD

ELECTROCARDIOGRAM #34



Clinical History

A 38-year-old man presented with severe dyspnea of 1 week's duration. An echocardiogram demonstrated a large pericardial effusion with evidence supporting cardiac tamponade. The patient underwent urgent surgical pericardial drainage.

Electrocardiogram Interpretation

The cardiac rhythm is sinus tachycardia, as the P waves are of normal axis and precede each QRS complex at an atrial rate slightly >100 per minute. The frontal-plane QRS-complex axis demonstrates right-axis deviation, as the QRS-complex vector is negative in lead I and positive in leads II, III, and aVF. There are diffuse low-voltage QRS complexes. Nonspecific ST-T changes are also seen. Alternation of the QRS-complex voltage, best seen in rhythm strip lead V_1, is apparent. This alternation occurs with every other QRS complex and is termed electrical alternans. Electrical alternans is an ECG marker of a large pericardial effusion.

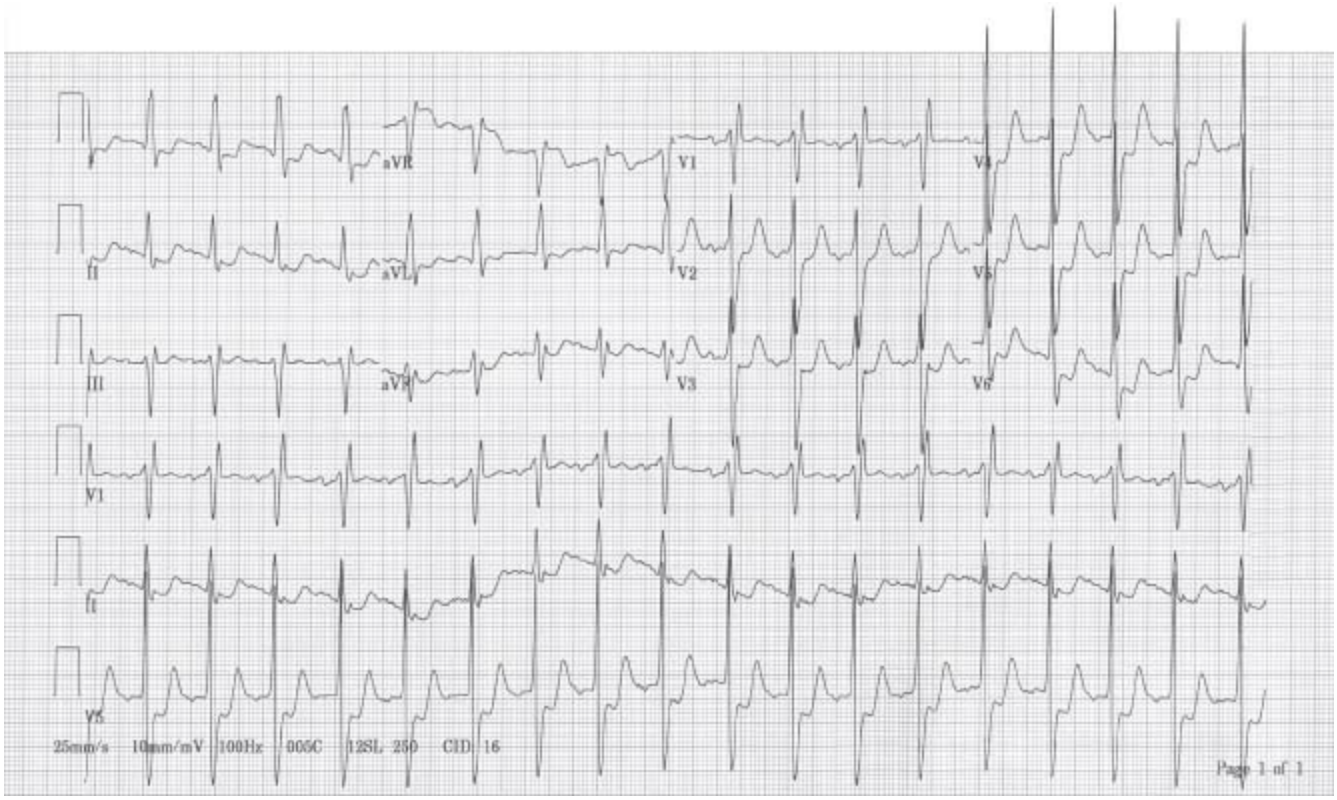
Commentary

The ECG findings of diffuse low-voltage QRS complexes and electrical alternans suggest the presence of a significant pericardial effusion and cardiac tamponade. The electrical alternans is secondary to the beat-to-beat variability of cardiac position. This is sometimes referred to as a "swinging heart."

Keyword Diagnoses

Sinus tachycardia
Right-axis deviation
Nonspecific ST-T changes
Low-voltage QRS
Electrical alternans
Pericardial effusion
Cardiac tamponade

ELECTROCARDIOGRAM #35



Clinical History

A 69-year-old woman with a history of severe subaortic stenosis presented to the hospital with a several-day history of dyspnea consistent with congestive heart failure. A cardiac catheterization demonstrated a 100-mm Hg pressure gradient between the left ventricular outflow tract and the left ventricle. Her medications at the time of this ECG included diltiazem, furosemide, and doxazosin.

Electrocardiogram Interpretation

A P wave of normal axis precedes each QRS complex at a regular rate of approximately 110 per minute, reflecting sinus tachycardia. An rSR′ QRS complex is present in lead V_1 with a QRS-complex duration of 140 milliseconds, consistent with complete RBBB. The P wave in lead V_1 demonstrates a terminal negativity and is bifid in lead II,

supporting left atrial abnormality. Down-sloping 3- to 4-mm ST-segment depression is present in leads V_4 to V_6, I, and II, consistent with myocardial ischemia and possibly an NSTEMI.

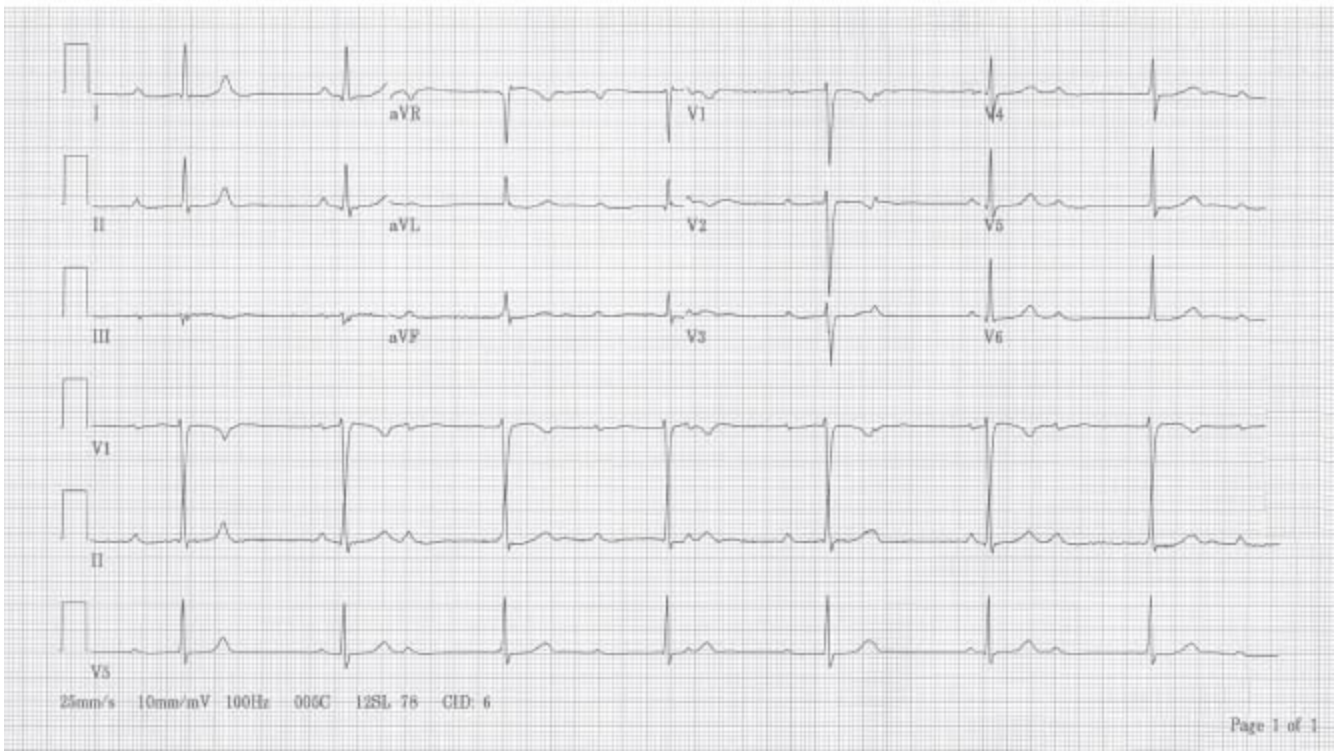
Commentary

Most often, myocardial ischemia is a bedside diagnosis and requires clinical correlation. In this case, the down-sloping ST-segment depression in the setting of a congestive heart failure exacerbation and subaortic stenosis most likely does represent myocardial ischemia. To confirm this suspicion, a follow-up tracing should be obtained after treatment, to demonstrate interval improvement and ST-T-change resolution.

Keyword Diagnoses

Sinus tachycardia
Complete RBBB
Left atrial abnormality
Myocardial ischemia

ELECTROCARDIOGRAM #36



Clinical History

A 29-year-old woman who was 37 weeks pregnant was admitted to the hospital for close observation of pregnancy-induced hypertension. She has known complete heart

block without cardiovascular symptoms requiring no specific treatment or evaluation other than periodic Holter monitoring.

Electrocardiogram Interpretation

On this tracing, the cardiac rhythm is best discerned in rhythm strip lead V_1. P waves occur at regular intervals at an atrial rate of approximately 85 per minute. The P-wave axis as ascertained in leads I, II, and aVF is upright and normal. This suggests NSR. The PR interval varies and suggests a lack of association between the P waves and the QRS complexes. The QRS complexes are of normal duration and occur regularly at a rate of approximately 45 per minute. These findings collectively support NSR, junctional bradycardia, and complete heart block.

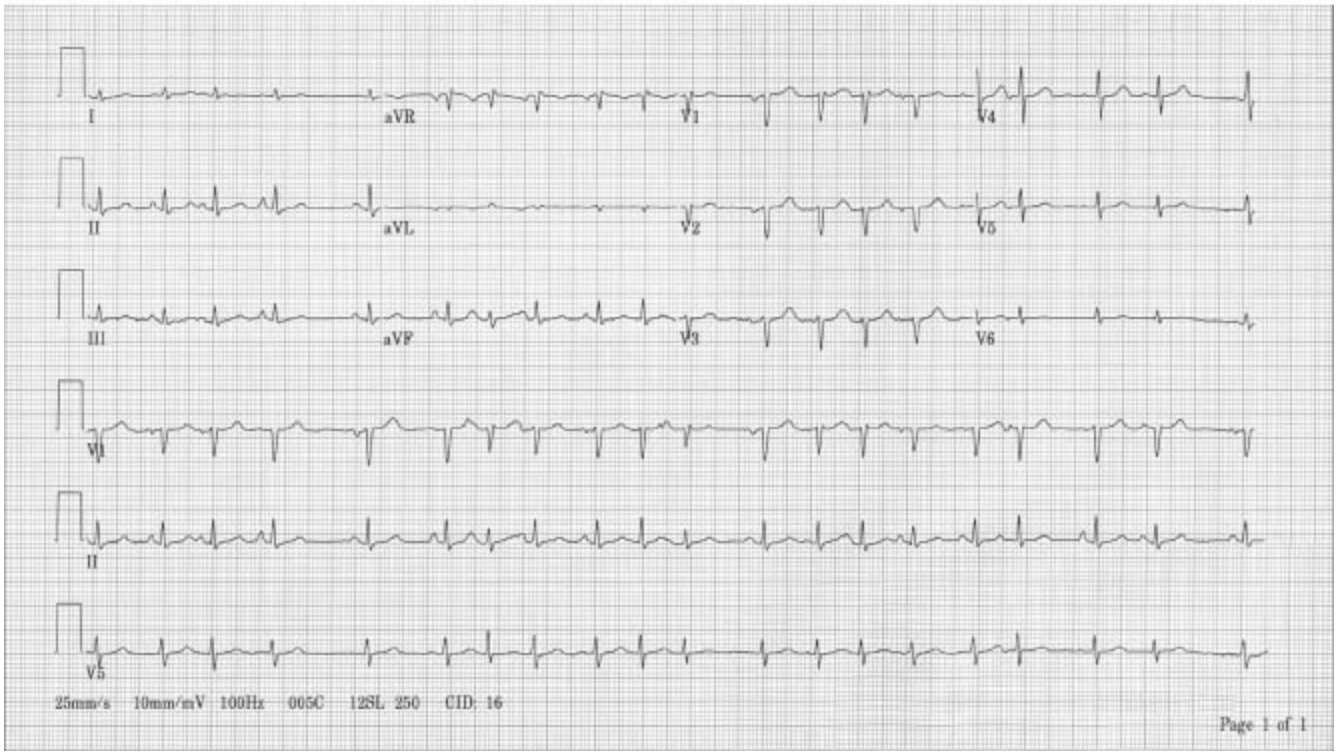
Commentary

The ECG criteria for complete heart block include two independent cardiac rhythms, lack of AV association, and a non-competing ventricular rhythm that is slower than the atrial rhythm.

Keyword Diagnoses

NSR
Junctional bradycardia
Complete heart block

ELECTROCARDIOGRAM #37



Clinical History

A 72-year-old man was admitted to the hospital for further evaluation of an erythematous and bullous eruptive rash. His past medical history includes hypertension and chronic obstructive pulmonary disease, for which he takes prednisone and numerous inhalers.

Electrocardiogram Interpretation

The ventricular rate is rapid, irregular, and >100 per minute, representing a tachycardia. Each QRS complex is preceded by a P wave of differing morphology and PR-interval duration. This represents MAT. Nonspecific ST-T changes are present in the lateral leads.

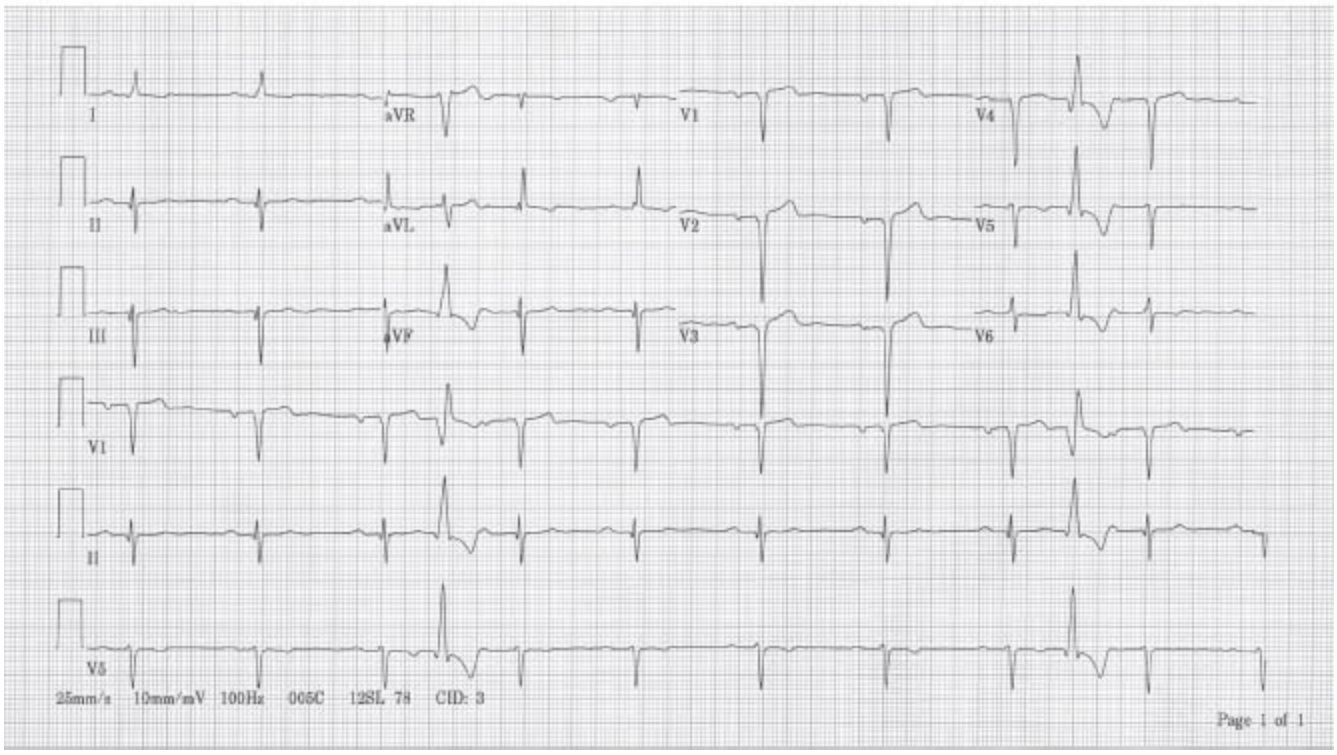
Commentary

MAT is a common dysrhythmia in patients with advanced chronic obstructive pulmonary disease. This dysrhythmia commonly demonstrates resistance to pharmacologic therapy and is best addressed by treating the underlying condition, in this case the chronic obstructive pulmonary disease.

Keyword Diagnoses

MAT
Nonspecific ST-T changes

ELECTROCARDIOGRAM #38



Clinical History

A 53-year-old man with diffuse coronary artery disease status post inferior and anterior myocardial infarctions 15 years prior to this ECG returns for routine cardiology follow-up. Subsequent to the myocardial infarctions, the patient underwent ventricular aneurysmectomy. He continued with symptoms of stable angina pectoris in the setting of mild mitral insufficiency and moderate left ventricular systolic dysfunction. His medications include digoxin, furosemide, and captopril.

Electrocardiogram Interpretation

On this tracing, with many findings, a systematic approach is necessary. Sinus bradycardia is present. The PR interval is prolonged, indicating first-degree AV block. The QRS-complex axis is deviated leftward secondary to diagnostic Q-wave formation in leads II, III, and aVF, supporting an age-indeterminate inferior myocardial infarction. Additional Q waves are noted in leads V_2 to V_4, representing an age-indeterminate anterior myocardial infarction. Premature complexes differing from the native QRS-complex morphology are seen without a preceding P wave. These are premature ventricular complexes (PVCs). The PR interval immediately following each PVC is prolonged and reflects retrograde concealed conduction of the PVC into the conduction system slowing antegrade conduction to the ventricle. Unlike most PVCs, there is no compensatory pause and therefore these are classified as interpolated PVCs.

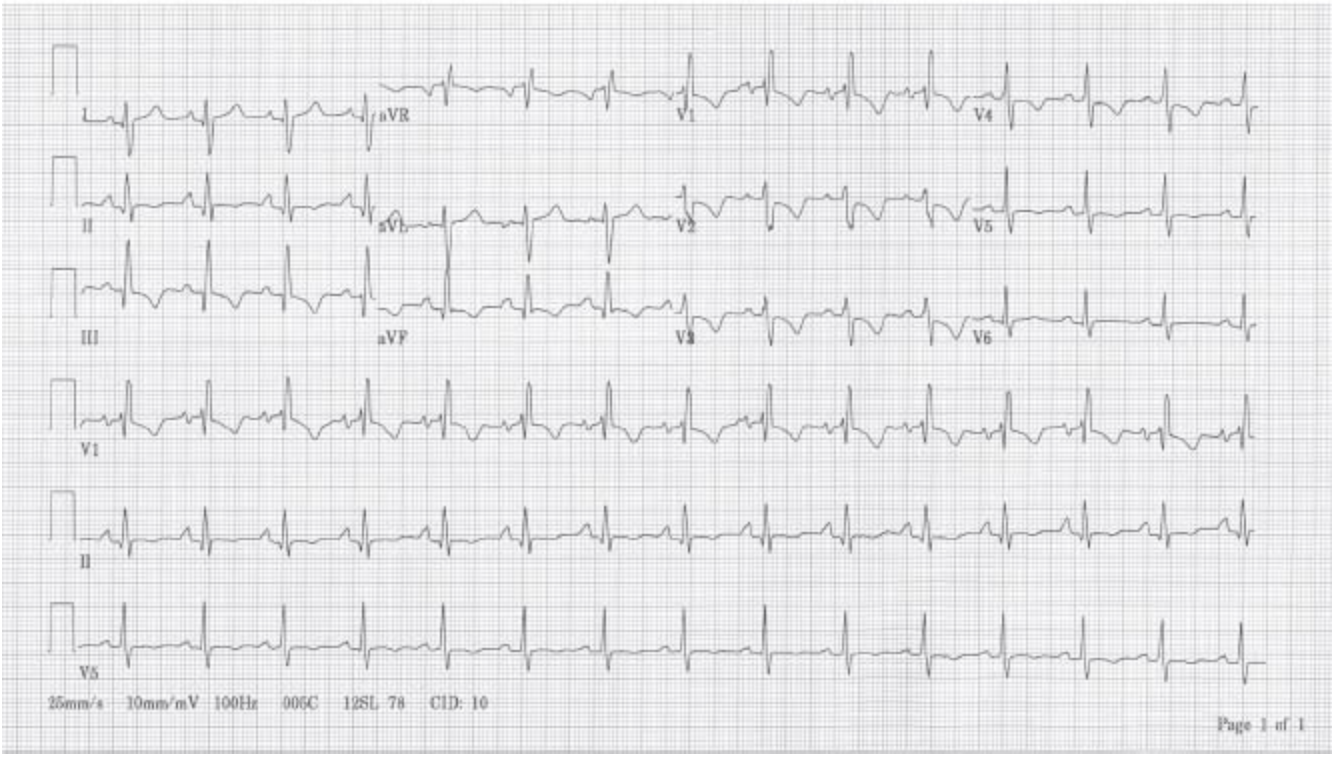
Commentary

Frequently, ECGs demonstrate a myocardial infarction in two separate myocardial territories, as demonstrated on this tracing. The PVCs are of complete RBBB morphology and therefore are left ventricular in origin. They demonstrate prominent inferior and anterolateral Q waves, supporting the presence of both prior myocardial infarctions.

Keyword Diagnoses

Sinus bradycardia
First-degree AV block
Inferior myocardial infarction, age indeterminate
Anterior myocardial infarction, age indeterminate
Interpolated PVC Concealed conduction

ELECTROCARDIOGRAM #39



Clinical History

A 57-year-old woman with a history of adenocarcinoma of the rectum and a pulmonary embolism presented to the hospital urgently, secondary to severe shortness of breath and respiratory failure. Pulmonary angiography demonstrated evidence of both acute and subacute pulmonary emboli and severe pulmonary hypertension. The patient expired shortly after this ECG.

Electrocardiogram Interpretation

NSR is present. Frontal-plane QRS-complex right-axis deviation is noted, given the positive QRS-complex vector in leads II, III, and aVF and a negative QRS-complex vector in lead I. Incomplete RBBB is best seen in lead V_1 with an rsR′ QRS-complex pattern. Also notable in lead V_1 is a terminally negative P-wave vector suggesting left atrial abnormality. In lead II, the P wave is peaked and 3 mm in amplitude, supporting right atrial abnormality. Nonspecific ST-T changes are noted throughout the tracing. Given the incomplete RBBB, right atrial abnormality, and right-axis deviation, RVH with secondary ST-T changes merits consideration.

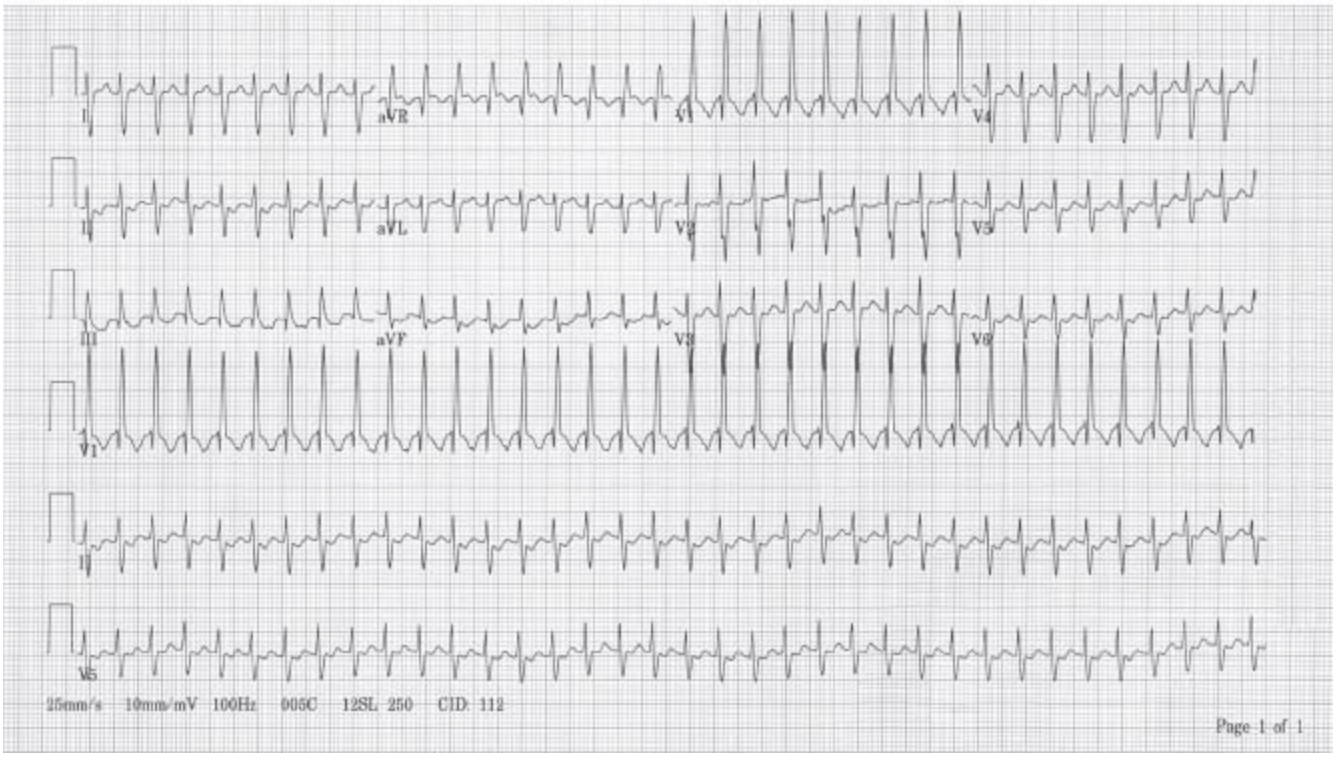
Commentary

This ECG is consistent with an acute pulmonary embolism. It demonstrates a dominant S wave in lead I and a Q wave with T-wave inversion in lead III. This is the so-called S1, Q3, T3 QRS-complex pattern described in the setting of an acute pulmonary embolism.

Keyword Diagnoses

NSR
Right-axis deviation
Incomplete RBBB
Left atrial abnormality
Right atrial abnormality
Nonspecific ST-T changes
Pulmonary embolism

ELECTROCARDIOGRAM #40



Clinical History

A 41-year-old man with a history of intravenous substance use, endocarditis, and prior mitral and tricuspid valve replacement re-presents with symptoms and signs of congestive heart failure. He has also noted recent-onset palpitations.

Electrocardiogram Interpretation

This ECG demonstrates a regular narrow QRS-complex tachycardia. P waves are possibly seen within the nadir of the ST segment in lead III. Determination of the exact cardiac rhythm is difficult and would require further testing in the form of an electrophysiology study. Therefore, this is best categorized as a supraventricular tachycardia. The QRS-complex frontal-plane axis demonstrates right-axis deviation, as the QRS-complex vector is negative in lead I, isoelectric in lead II, and positive in leads III and aVF A prominent rsR′ QRS complex of normal duration is seen in lead V_1. In the presence of QRS-complex frontal-plane right-axis deviation, this represents RVH. Diffuse nonspecific ST-T changes are also present.

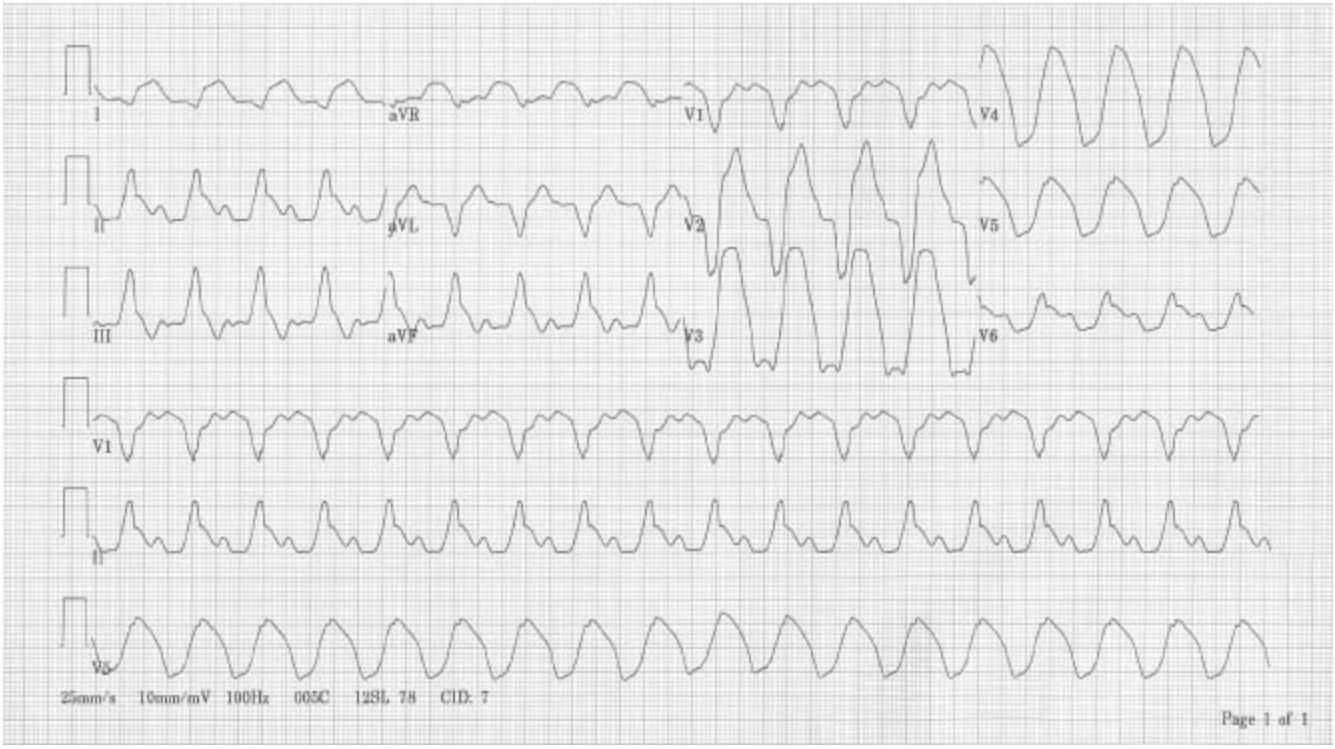
Commentary

This patient was known to have advanced tricuspid valvular heart disease, prosthetic valve mitral stenosis, pulmonary hypertension, and RVH. The atrial arrhythmias may be secondary to the cardiac valvular abnormality.

Keyword Diagnoses

Supraventricular tachycardia
Right-axis deviation
RVH
Nonspecific ST-T changes

ELECTROCARDIOGRAM #41



Clinical History

A 67-year-old woman with dialysis-requiring renal failure is recently postoperative after an exploratory laparotomy for an ischemic bowel. This patient became septic, hypotensive, and hyperkalemic. This ECG represents her terminal heart rhythm prior to expiring.

Electrocardiogram Interpretation

Sinus tachycardia is present. The PR interval is prolonged, representing first-degree AV block. The QRS complex is markedly prolonged, demonstrated by a nonspecific intraventricular conduction delay.

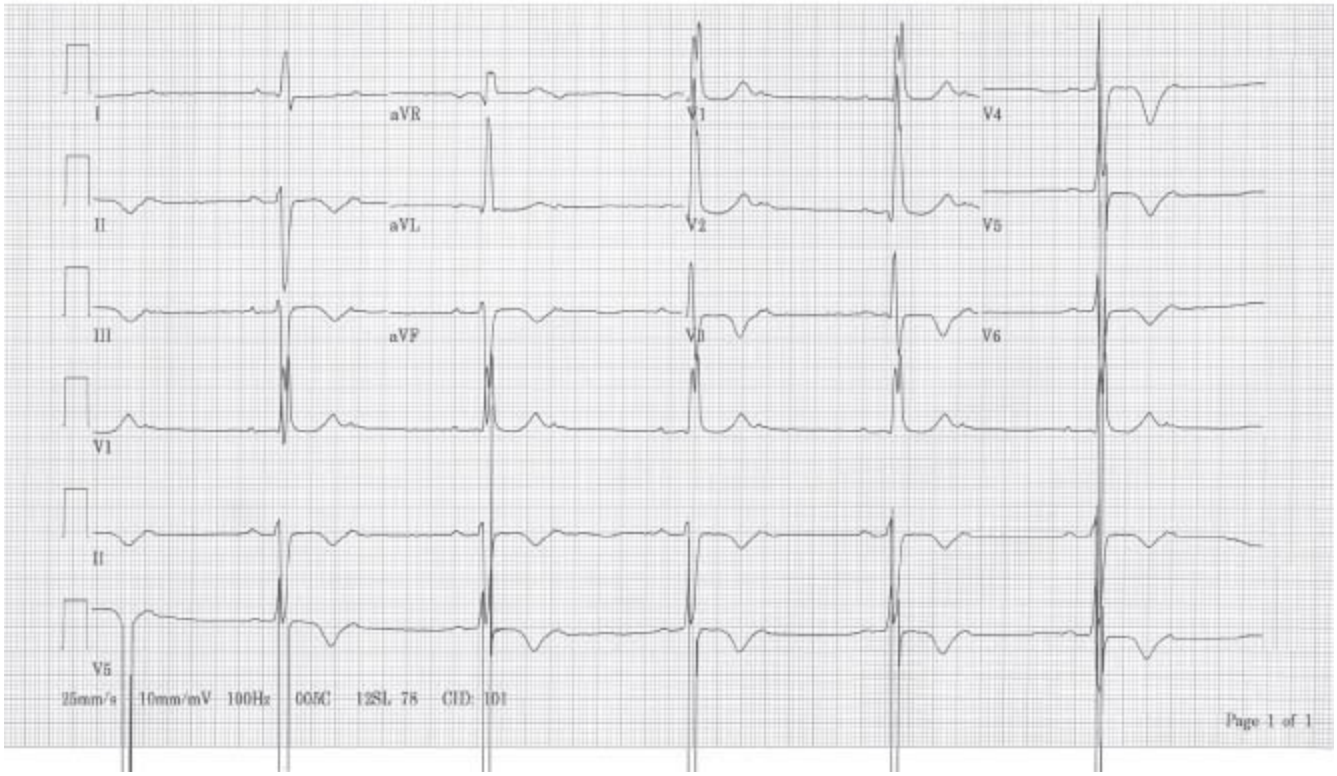
Commentary

In extreme forms of hyperkalemia, ventricular arrhythmias are common, as is profound widening and prolongation of all ECG intervals. The ST-segment elevation in leads V_2 and V_3 has been termed a dialyzable current of injury.

Keyword Diagnoses

Sinus tachycardia
First-degree AV block
Nonspecific intraventricular conduction delay
Hyperkalemia

ELECTROCARDIOGRAM #42



Clinical History

A 94-year-old woman was admitted to the hospital with acute-onset diarrhea and dehydration. She was noted to have lower-extremity swelling, and venous Doppler studies demonstrated an acute deep venous thrombosis. A subsequent ventilation perfusion scan was interpreted as high probability for an acute pulmonary embolism.

Electrocardiogram Interpretation

In the lead V_1 rhythm strip, a P wave is seen preceding each QRS complex. A P wave is also noted immediately following each T wave. This demonstrates a regular P-P interval at an atrial rate of approximately 70 per minute, denoting NSR. The QRS complex is broadened, with an RSR′ QRS-complex pattern in lead V_1, suggesting complete RBBB. The T wave is upright in lead V_1, supporting primary T-wave changes. The QRS-complex frontal-plane axis is deviated leftward, with a positive QRS-

complex vector in lead I and negative QRS-complex vectors in leads II, III, and aVF, consistent with left anterior hemiblock. Given the bifascicular block, the 2:1 AV block most likely represents second-degree Mobitz Type II AV block. Diffuse nonspecific ST-T wave changes are seen. Sinus arrhythmia is also documented. The P-P interval encompassing the QRS complexes is shorter than the P-P interval between the QRS complexes. This is more precisely termed ventriculophasic sinus arrhythmia. This has no known clinical significance.

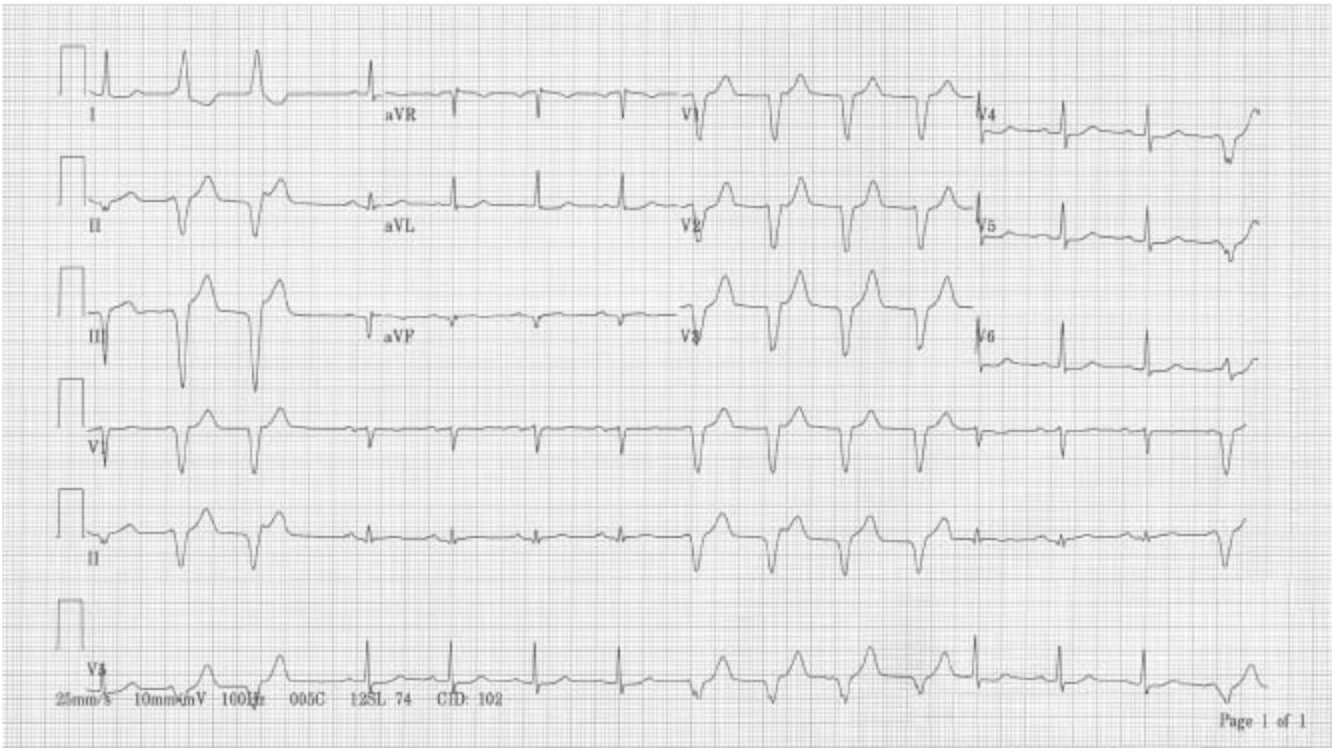
Commentary

Given the bifascicular block and 2:1 AV block, this patient has advanced conduction system disease. It is not known if these findings were new in the setting of her suspected acute pulmonary embolism.

Keyword Diagnoses

NSR
2:1 AV block
Complete RBBB
Left anterior hemiblock
Nonspecific ST-T changes
Sinus arrhythmia

ELECTROCARDIOGRAM #43



Clinical History

A 61-year-old man was seen in cardiology outpatient follow-up after an acute inferior myocardial infarction 3 years prior to this ECG. This was followed by urgent right coronary artery percutaneous transluminal coronary angioplasty. He feels well, with infrequent episodes of angina pectoris. His medications include metoprolol, aspirin, nicotinic acid, simvastatin, and vitamins.

Electrocardiogram Interpretation

The atrial rhythm is most easily identified in the lead V_1 rhythm strip and lead aVF. In these leads, P waves are seen to precede each QRS complex at a rate of approximately 85 per minute, representing NSR. The 2nd, 3rd, 8th, 9th, 10th, and 11th QRS complexes are wide, with a complete left bundle branch configuration. This represents an AIVR. The native QRS complex is abnormal, with a wide Q wave present in leads III and aVF indicating an age-indeterminate inferior myocardial infarction. The first QRS complex is intermediate between the native QRS complex and the AIVR complex and represents a ventricular fusion complex. P-wave activity is seen during the AIVR as a downward deflection within the proximal ST segment of the third QRS complex noted best in leads II, III, and V_1. This supports simultaneous atrial activity and AV dissociation.

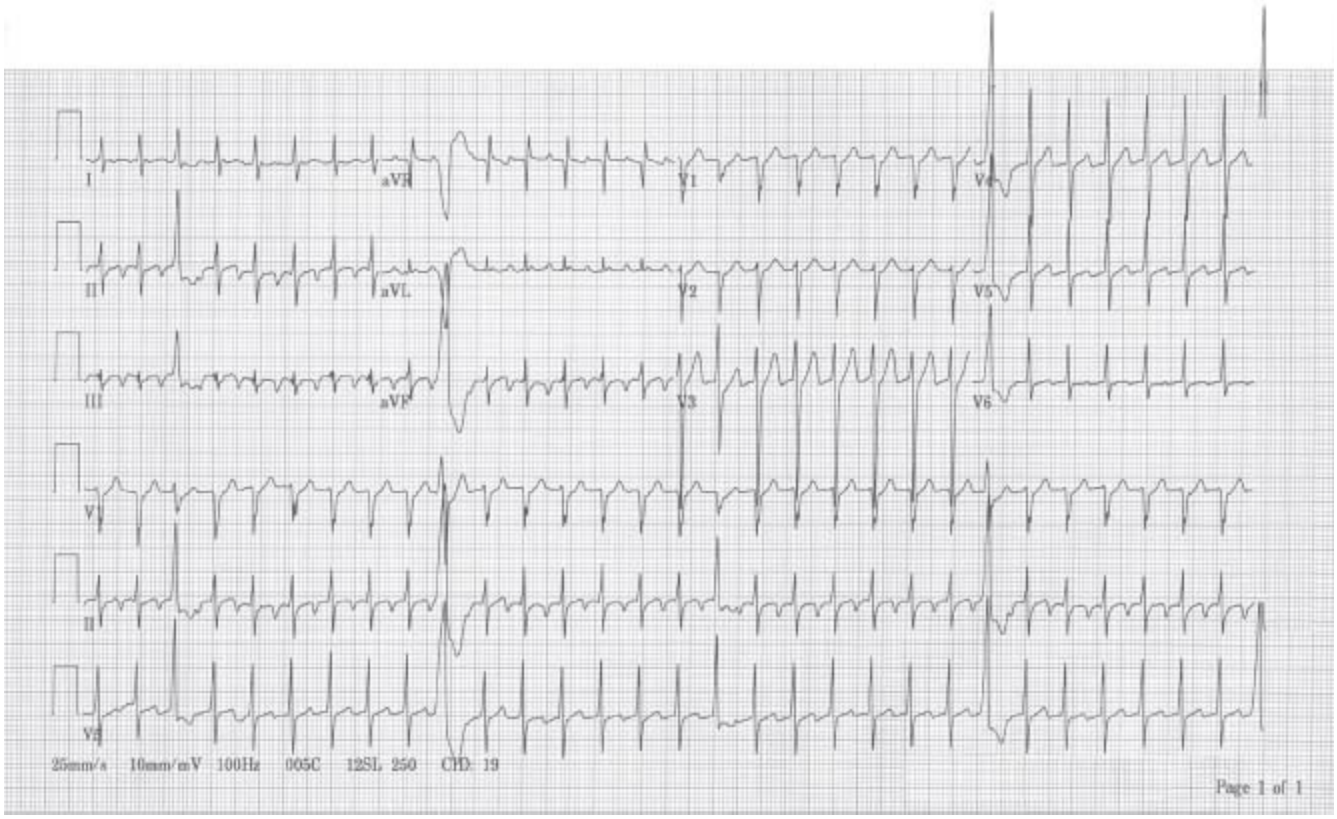
Commentary

This patient also had a history of syncope following his myocardial infarction. An electrophysiology study demonstrated readily inducible sustained monomorphic VT, and he underwent subsequent defibrillator placement.

Keyword Diagnoses

NSR
AIVR
Fusion complex
Inferior myocardial infarction, age indeterminate
AV dissociation

ELECTROCARDIOGRAM #44



Clinical History

A 72-year-old man with recently diagnosed myasthenia gravis was admitted for rehabilitation. His past medical history includes diabetes mellitus, chronic obstructive pulmonary disease, recurrent AF, and coronary artery disease.

Electrocardiogram Interpretation

On this ECG, the atrial rhythm is best discerned in lead aVL. This demonstrates a P wave preceding and immediately following a diminutive QRS complex. This represents AFL with 2:1 AV conduction. Another possibility is a rapid ectopic atrial tachycardia. Diffuse nonspecific ST-T changes are present, as are frequent PVCs. The frequent PVCs occur at a constant interectopic interval with a differing coupling interval to the immediately preceding QRS complex. There is evidence of ventricular fusion complexes between the native QRS complex and a PVC. These features together confirm the presence of ventricular parasystole.

Commentary

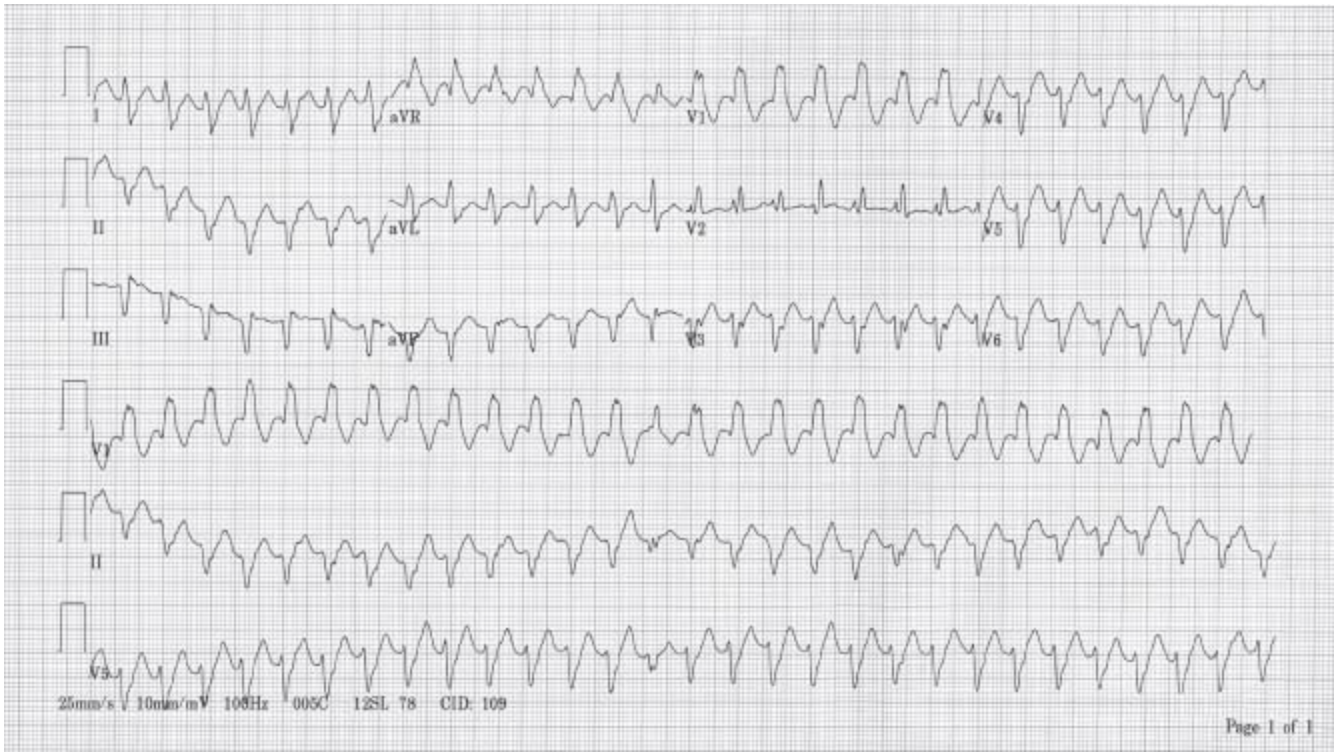
This is an unusual tracing, as the atrial rhythm is best discerned in lead aVL. This underscores the importance of a systematic evaluation of each ECG lead, particularly in the setting of an atrial dysrhythmia. The P wave immediately following the QRS complex is best seen in lead aVL and allows for the accurate diagnosis of this atrial

dysrhythmia. When frequent PVCs are present, it is also important to evaluate for the presence of ventricular parasystole. Ventricular parasystole is an independent automatic dysrhythmia that discharges at a constant rate from the same ventricular focus.

Keyword Diagnoses

AFL
2:1 AV conduction
PVC
Nonspecific ST-T changes
Ventricular parasystole
Fusion complex

ELECTROCARDIOGRAM #45



Clinical History

A 49-year-old man with recurrent idiopathic left VT was referred for radiofrequency ablation. A recent echocardiogram demonstrated normal left ventricular systolic function without evidence of a prior myocardial infarction. His medications include verapamil, sotalol, simvastatin, and aspirin.

Electrocardiogram Interpretation

This ECG demonstrates a regular wide QRS-complex tachycardia at a rate of approximately 175 per minute. This tachycardia demonstrates a complete RBBB

morphology with a qR QRS-complex pattern in lead V_1 and terminal S-wave slowing in leads V_1 and V_6. The QRS-complex frontal-plane axis is deviated far leftward, is prolonged, and has a qR QRS-complex pattern in lead V_1, suggestive of VT. In the center of the tracing, best seen in leads V_1 and aVF, a more narrow QRS complex occurs. This is a sinus capture complex and lends greater support to the diagnosis of VT. In lead aVF, within the sinus capture QRS complex, a prominent Q wave is seen with ST-segment elevation, suggestive of an acute inferior myocardial infarction. Periodic P waves are seen throughout the tracing, suggesting an independent atrial rhythm and AV dissociation. The precise atrial rhythm diagnosis is not discernible on this tracing. Wandering baseline artifact is also seen.

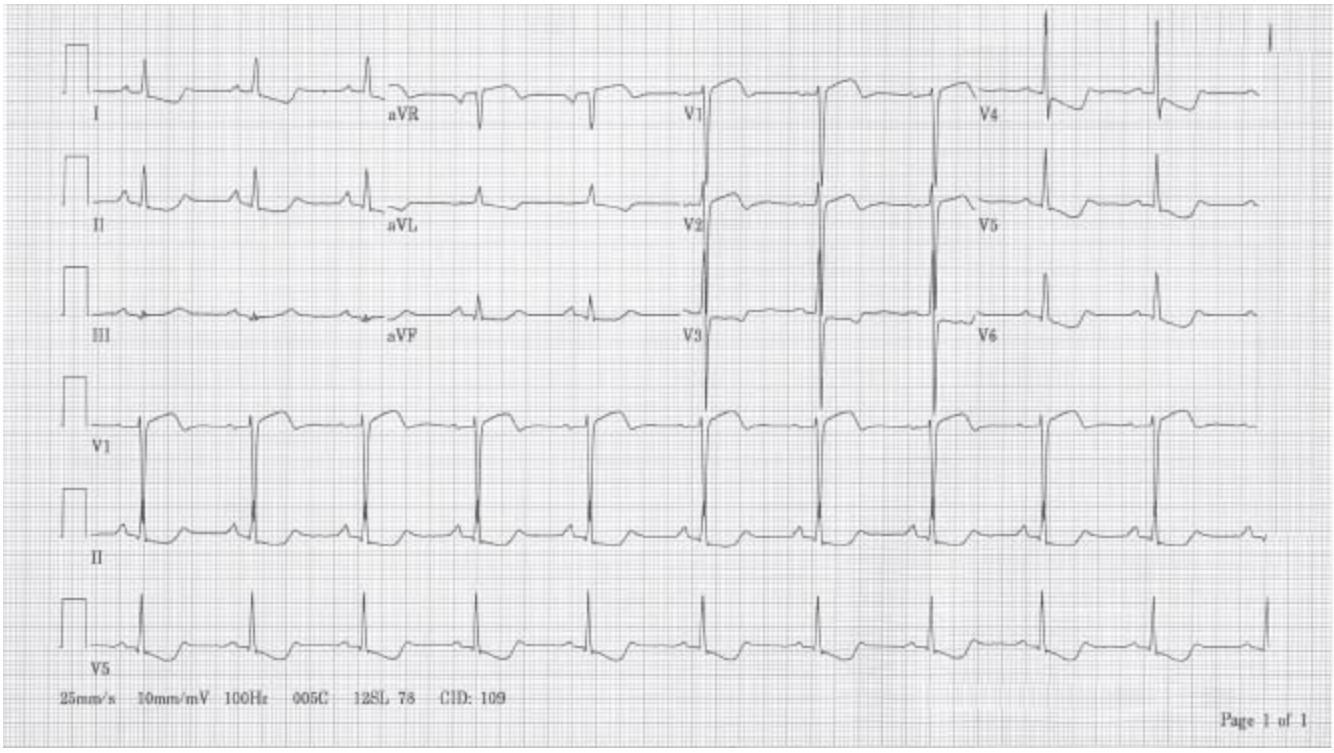
Commentary

This ECG contains important features supporting the presence of VT. When assessing a wide complex tachycardia, each of these features should be specifically sought. They include AV dissociation in the presence of an independent atrial rhythm and sinus capture complexes. Not seen on this ECG but often present in the setting of VT are ventricular fusion complexes. The apparent Q wave occurring in lead aVF remains unexplained, given the patient's normal heart function and normal regional wall motion on echocardiography.

Keyword Diagnoses

VT
Sinus capture complex
AV dissociation
Inferior myocardial infarction, acute
Baseline artifact

ELECTROCARDIOGRAM #46



Clinical History

A 48-year-old woman presented with severe hypertrophic cardiomyopathy and pronounced symptoms of exertional dyspnea and presyncope immediately status post-percutaneous alcohol ablation of her first septal perforator branch of the left anterior descending coronary artery. The patient was resting comfortably in the intensive care unit.

Electrocardiogram Interpretation

The cardiac rhythm is NSR, as the P-wave vector is upright in leads I, II, III, and aVF. The atrial rate is regular and slightly >60 per minute. Approximately 2 mm of ST-segment elevation is seen in lead V_1, and 1 mm of ST-segment elevation is present in lead V_2. Reciprocal ST-segment depression is seen inferiorly and laterally. This represents an acute septal myocardial infarction and acute myocardial injury.

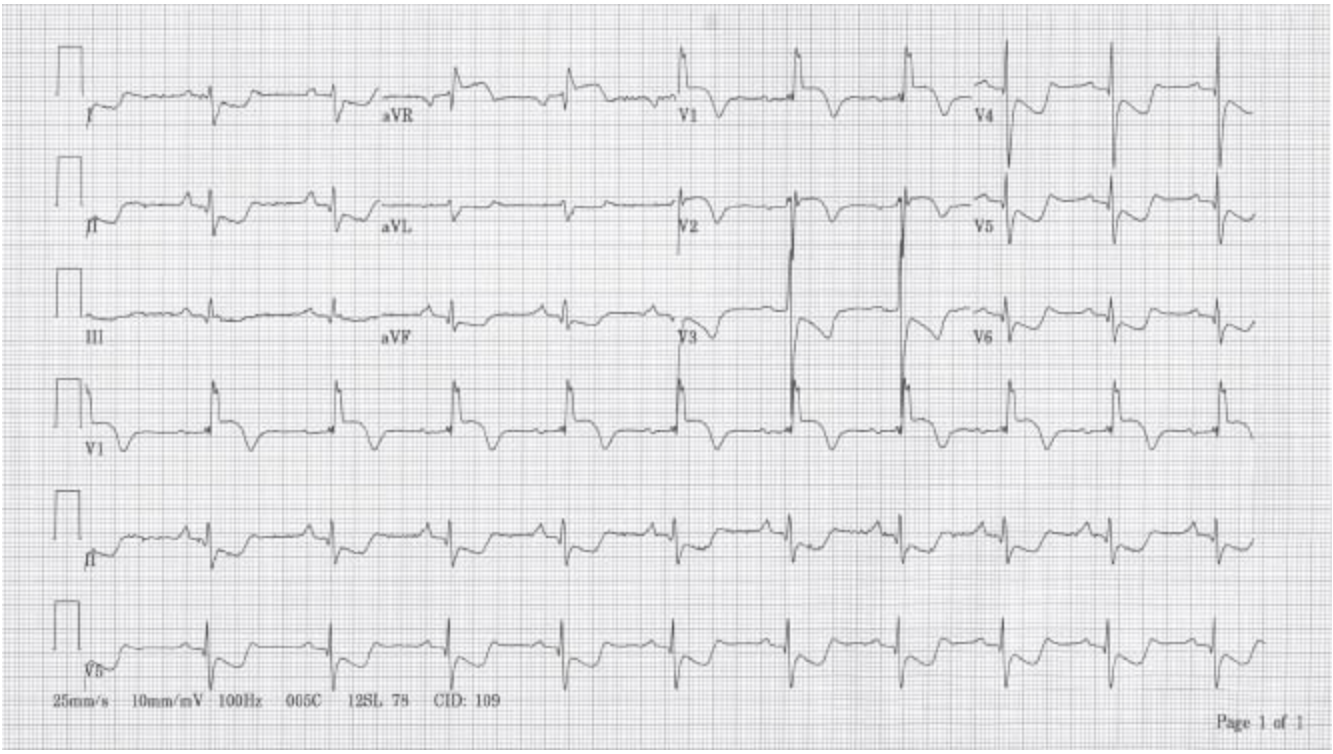
Commentary

The ST-segment elevation in leads V_1 and V_2 reflects the proximal septal iatrogenic myocardial infarction created by the alcohol injection. This is a pure proximal septal myocardial injury pattern reflected electrocardiographically. The purpose of this procedure is to infarct the proximal interventricular septum and therefore reduce the degree of left ventricular outflow tract obstruction, avoiding otherwise necessary cardiac surgery.

Keyword Diagnoses

NSR
Septal myocardial infarction, acute
Acute myocardial injury

ELECTROCARDIOGRAM #47



Clinical History

A 48-year-old woman presented with severe hypertrophic cardiomyopathy and pronounced symptoms of exertional dyspnea and presyncope immediately status postpercutaneous alcohol ablation of her first septal perforator branch of the left anterior descending coronary artery. The patient was resting comfortably in the intensive care unit.

Electrocardiogram Interpretation

The cardiac rhythm is sinus bradycardia with a normal P-wave axis slightly <60 minute. An RsR′ QRS complex is seen in lead V_1 with terminal S-wave slowing in leads I, aVL, and V_5 and V_6, consistent with complete RBBB. The QRS-complex frontal-plane axis is deviated far rightward, as the QRS-complex vector is negative in lead I and positive in leads III and aVF. Prominent ST-segment elevation of at least 2 mm is seen in leads V_1 and V_2, consistent with an acute septal myocardial infarction and an acute myocardial

injury pattern. Diffuse reciprocal ST-segment depression is present.

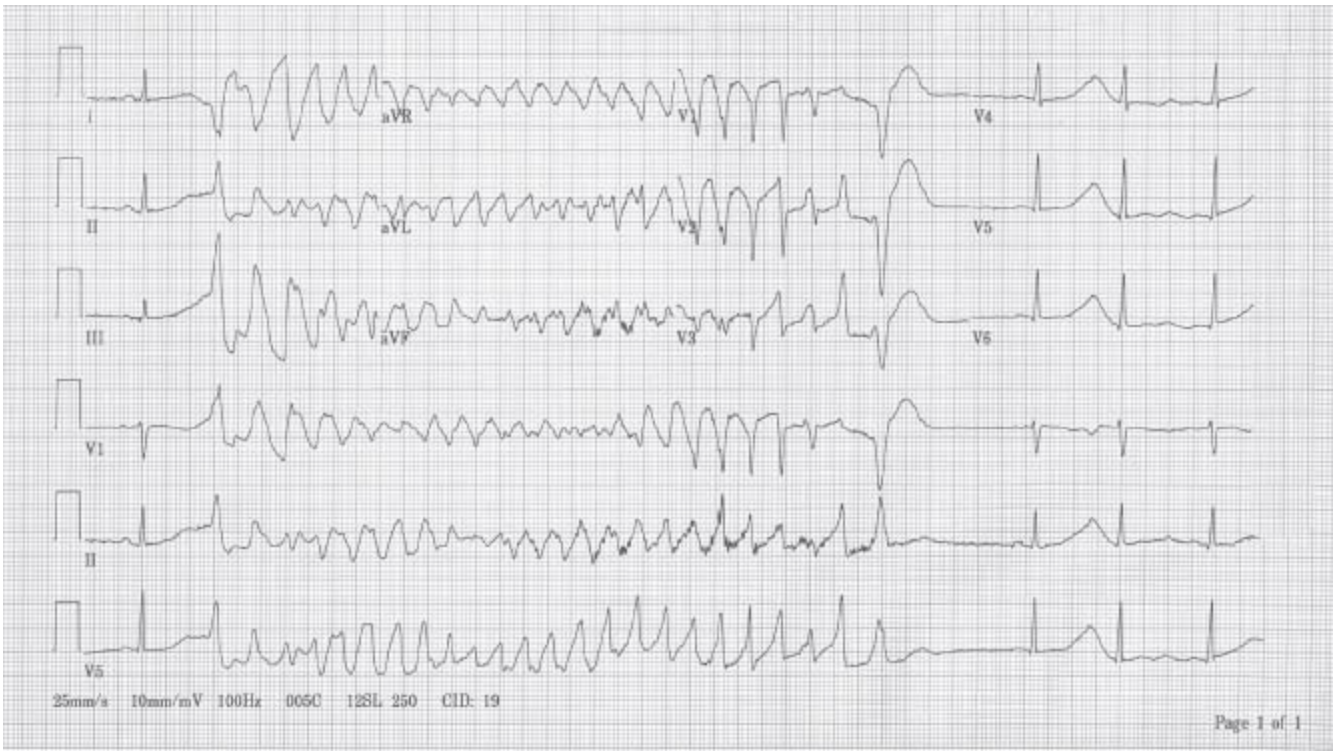
Commentary

This ECG was obtained several hours after ECG #46 and reflects the same patient. This demonstrates similar findings as tracing #46, with the exception of a newly developed complete RBBB and extreme QRS-complex frontal-plane right-axis deviation. The finding of new extreme right-axis QRS-complex deviation reflects left posterior hemiblock. This is an example of a bifascicular block. Inferior Q waves are more prominent on this tracing compared to tracing #46 and reflect the left posterior hemiblock and not the interval development of an inferior myocardial infarction.

Keyword Diagnoses

Sinus bradycardia
Septal myocardial infarction, acute
Complete RBBB
Left posterior hemiblock
Acute myocardial injury

ELECTROCARDIOGRAM #48



Clinical History

A 51-year-old woman with metastatic breast carcinoma is undergoing bone marrow transplantation. Her serum potassium level at the time of this ECG was 2.9 mEq/L.

Electrocardiogram Interpretation

The extreme left-hand portion of this ECG demonstrates upright P waves in leads I, II, and III, suggesting NSR. A prolonged QT interval is present, with nonspecific ST-T changes. The first QRS complex is reflective of NSR and a native QRS complex. This is followed by a PVC, and a disorganized wide QRS-complex tachycardia ensues. The wide QRS-complex tachycardia has a changing or rotating axis consistent with torsades de pointes. A fine baseline artifact is present.

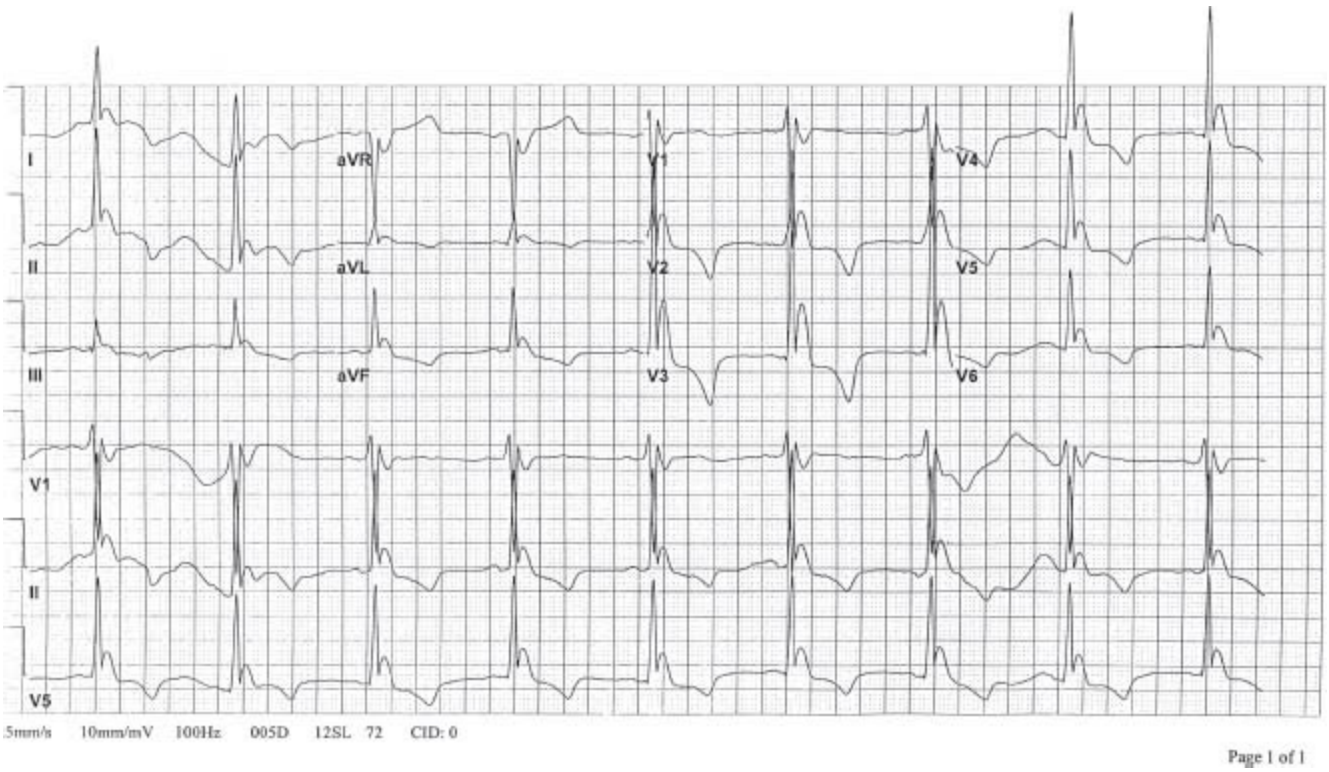
Commentary

Torsades de pointes is a potentially fatal ventricular arrhythmia, in this instance triggered by extreme hypokalemia. It is also seen in the presence of antiarrhythmic therapy initiation. It is characterized as a wide QRS-complex VT with a varying QRS-complex axis as depicted on this ECG. Prompt correction of any underlying metabolic disturbance and withdrawal of potentially contributing medications is essential.

Keyword Diagnoses

NSR
Prolonged QT interval
Torsades de pointes
Baseline artifact
Nonspecific ST-T changes
Hypokalemia

ELECTROCARDIOGRAM #49



Clinical History

A 42-year-old man was found unconscious under a bridge and brought to the Emergency Department by ambulance.

Electrocardiogram Interpretation

Sinus bradycardia is present, as the atrial rate is regular at approximately 50 beats per minute. Baseline artifact, especially in leads I and II, is noted. The QRS complex is significantly widened, with a terminal QRS-complex delay, evident in all leads. Diffuse nonspecific ST-T changes denoting abnormal repolarization are also seen. This is an example of profound hypothermia and Osborne waves. The Osborne or "J" waves represent the terminal QRS-complex conduction delay.

Commentary

Hypothermia is a medical emergency. This ECG is a classic example. The etiology of the Osborne wave is not completely clear but is related to slow cardiac conduction. Atrial arrhythmias and PR-interval prolongation are often identified. Osborne waves are named for the person who first identified them and their relationship to hypothermia.

Keyword Diagnoses

Sinus bradycardia
Baseline artifact
Osborne wave

Hypothermia

CHAPTER

Electrophysiologic Testing, including His Bundle and Other Intracardiac Electrograms

Edwin T. Zishiri and Mina K. Chung

This chapter aims to summarize the components of a comprehensive electrophysiology (EP) study. However, the components of a diagnostic EP study are usually selected based upon the indications for the study. Readers who are primarily aiming for a board certification exam should primarily direct their attention to components listed in the Summary to this chapter and to the Review questions.

INDICATIONS FOR ELECTROPHYSIOLOGIC TESTING

Indications for performance of an EP study have evolved somewhat in recent years with the indications for implantable cardioverter–defibrillators (ICDs) expanding to defined populations without the need for a "positive" EP study. Thus, the use of EP studies for risk stratification of patients at possible high risk for sudden cardiac death has become more limited. Based on recent multicenter trials, ICDs are being indicated for primary prevention of sudden cardiac death in patients with:

- Prior myocardial infarction (MI), at least 40 days before and left ventricular ejection fraction (LVEF) ≤35% with New York Heart Association (NYHA) functional class II or III; or LVEF <30% with NYHA functional class I
- Nonischemic cardiomyopathy, LVEF ≤35%, and NYHA functional class II or III

These patients do not require EP studies to qualify for ICD implantation. However, ICD implantation is also indicated in patients who have LVEF <40%, prior MI, nonsustained ventricular tachycardia (NSVT), and inducible sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) at EP study. Thus, EP studies can be indicated for risk stratification in patients who do not yet have indications for an ICD. These patients include patients with coronary artery disease (CAD), prior MI, LVEF ≤40%, and

NSVT. Clinical guidelines regarding the use of EP studies in the risk stratification of patients prior to device implantation may be obtained from the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) 2008 guidelines for device implantation.[1]

An EP study is also helpful in the diagnosis of patients presenting with syncope of undetermined etiology and in the diagnosis of wide complex tachycardia. EP studies may also be used to assess for bradyarrhythmias, including sinus node or atrioventricular (AV) conduction system disease, particularly in patients with possible infra-Hisian conduction system disease.

The most common application for EP studies, however, is for the diagnosis and mapping of tachyarrhythmias as part of a catheter mapping and ablation procedure. The diagnosis of supraventricular tachycardia (SVT) type and localization of ablatable supraventricular and ventricular substrates are integral parts of ablation procedures (see ACC/AHA/ESC guidelines for management of patients with supraventricular arrhythmias[2]).

Clinical competency guidelines are reported in the ACC/AHA clinical competence statement on invasive EP studies, catheter ablation, and cardioversion.[3]

THE BASICS OF ELECTROPHYSIOLOGY STUDIES

During an EP study, multipolar catheters are positioned, typically in the right ventricular apex (RVA) and/or right ventricular outflow tract, the His bundle, the coronary sinus (CS), and/or the right atrium (RA) (Fig. 26.1). Programmed electrical stimulation (PES) is performed via bipolar electrodes by pacing at various rates and by introduction of premature extrastimuli. Typical baseline recordings include the surface electrocardiograms (ECGs), particularly leads I, AVF, V_1, and V_6, as well as intracardiac electrograms (EGMs) from the high right atrium (HRA), His bundle (His, or HBE), RVA, and CS. The electrodes are by convention numbered consecutively with the most distal electrode being number 1.

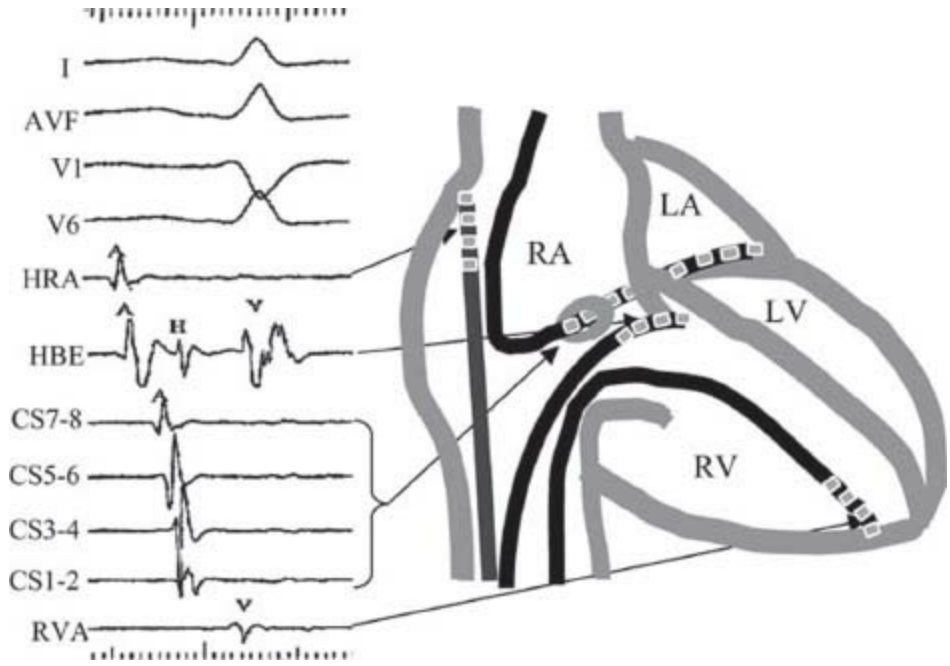


FIGURE 26.1 Typical catheter positions and recordings during EP studies. RA, right atrium; LA, left atrium; LV, left ventricle, RV, right ventricle.

Intracardiac Electrograms

When approaching the interpretation of intracardiac EGMs, it is useful to understand the differences between the surface ECG and intracardiac EGMs. The surface ECG is recorded on the body surface and reflects the electrical activity of the whole heart. The intracardiac EGM is recorded within the heart and is usually filtered differently from surface ECGs to remove high-frequency noise and low-frequency interference (e.g., from respiration). The intracardiac EGM reflects local electrical activity in the heart near the recording electrodes. The display or paper speed is generally faster than the conventional 25 mm/s surface 12-lead ECG speed. Time markers are generally present at the top or bottom of EGM tracings.

When interpreting intracardiac EGMs, the reader should orient himself/herself to the tracings, using the labels, which are usually displayed along the left margin. The atrial and ventricular activity can be identified by correlation with the surface ECG recordings. EGMs reflect local depolarization. EGMs from atrial or ventricular catheters show local atrial or ventricular depolarization, respectively. EGMs recorded at either the mitral or tricuspid annulus show both atrial and ventricular depolarization. Thus, EGMs from the CS show both atrial and ventricular EGMs. In the CS, the atrial EGMs are typically large in amplitude and the ventricular EGMs smaller, unless the catheter is advanced into a ventricular branch. His bundle EGMs are recorded at the tricuspid annulus and will typically display atrial, His, and ventricular EGMs with the size of the atrial or ventricular component dependent on whether the recording electrodes are situated more proximally in the atrium or distally in the ventricle.

Cycle Lengths versus Rates

During an EP study, intervals are more commonly measured than rates. The "cycle length" of pacing drives or rhythms is measured. The conversion between cycle length and rates are as follows: Cycle length (milliseconds) = 60,000 per rate (bpm). Conversely, rate (bpm) = 60,000 per cycle length (milliseconds). Thus, a rate of 60 bpm corresponds to a cycle length of 1,000 milliseconds, 100 bpm corresponds to 600 milliseconds, 120 bpm corresponds to 500 milliseconds, 150 bpm to 400 milliseconds, and 200 bpm to 300 milliseconds.

Baseline Intervals

Typical baseline intervals reported in EP studies include the sinus cycle length (SCL), defined as the interval between sinus atrial EGMs (A-A interval or P-P interval), the surface PR, QRS, and QT intervals. The AH and HV intervals are the most commonly measured intervals (Fig. 26.2). The AH interval is measured on the His bundle catheter (HBE) as the time interval from the first major deflection at its baseline crossing to the onset of the His bundle EGM. The AH interval estimates conduction time across the AV node (AVN). The AH interval is highly variable and dependent upon vagal tone, medications, and preceding atrial rates, but typically ranges from 50 to 130 milliseconds. The HV interval is also measured on the HBE. The HV interval is the interval from the onset of the His deflection to the earliest onset of ventricular activation on any surface lead or intracardiac EGM. The normal HV interval ranges from 35 to 55 milliseconds. Other baseline intervals are less commonly measured unless markedly abnormal. These include the PA interval, defined as the earliest onset of surface P wave to the earliest intra-cardiac atrial EGM (normal 20 to 60 milliseconds). The His width from the beginning to end of the His deflection generally ranges from 10 to 25 milliseconds. The RB-V interval measures the interval from the onset of the right bundle potential to the earliest ventricular activation on any surface lead or intracardiac EGM.

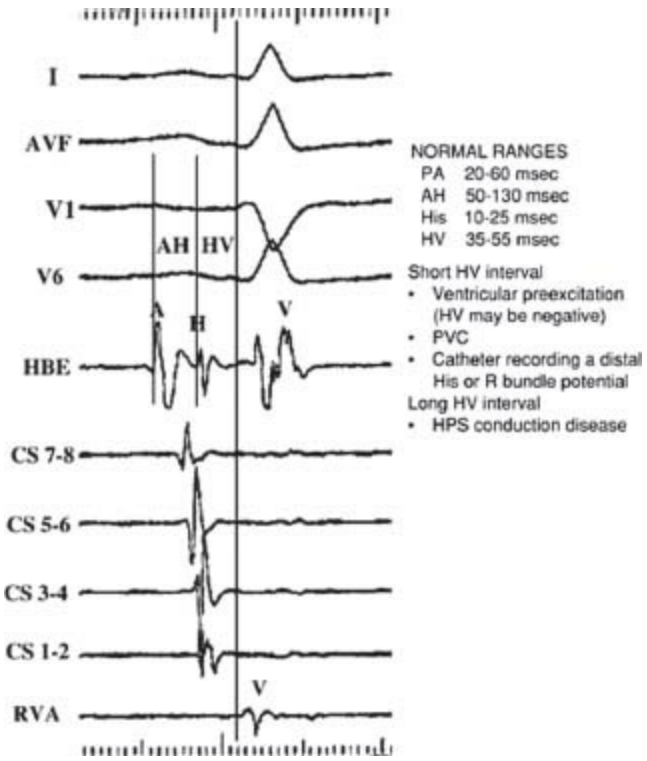


FIGURE 26.2 AH and HV intervals.

Normal Activation Sequences

Anterograde Atrial and Ventricular Activation Sequence. Normal atrial activation during sinus rhythm is from the HRA to low RA and then concentrically from proximally to distally along the CS. Normal ventricular activation is from the RV apex and concentrically from proximal to distal along the CS (Fig. 26.3 left panel).

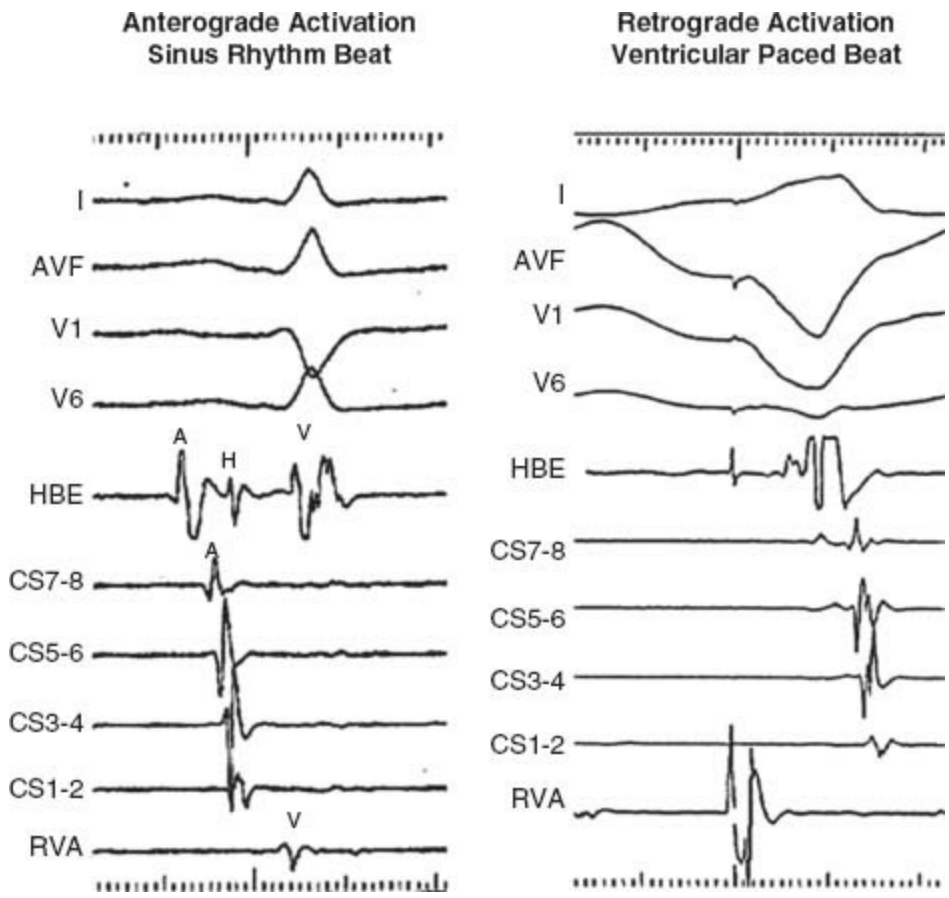


FIGURE 26.3 Normal activation patterns: anterograde and retrograde activation.

Retrograde Atrial Activation Sequence. The sequence of atrial activation during ventricular pacing is from the septum proximally to distally along the CS and from low RA in the midline to high RA (Fig. 26.3 right panel).

PES. During an EP study, pacing at various cycle lengths (or rates) or various intracardiac sites is performed. The length of this pacing train can be programmed. Common paced cycle lengths (PCLs) are at 600 milliseconds (100 bpm), 500 milliseconds (120 bpm), and 400 milliseconds (150 bpm). The stimuli during the fixed drive train are termed S_1. Premature extrastimuli may be introduced in intrinsic rhythm or after a fixed paced drive train (Fig. 26.4). The first extrastimulus is termed S_2. The second extrastimulus, when introducing double extrastimuli, is termed S_3. The third extrastimulus, when introducing triple extrastimuli, is termed S_4, and so on. The common terminology of the paced stimuli, their subsequent intracardiac EGMs and intervals, is summarized below:

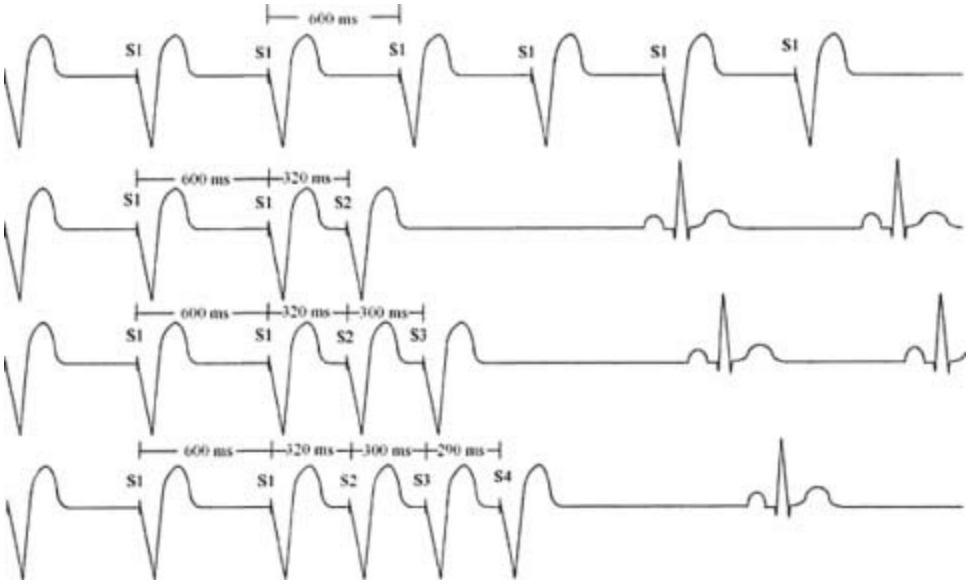


FIGURE 26.4 Programmed ventricular stimulation.

Pacing Drive Trains and Extrastimuli

S_1 = drive train pacing stimulus

- Continuous overdrive burst, or
- During programmed extrastimuli, typically eight pacing stimuli at a fixed PCL

PCL = paced cycle length (e.g., PCL 600 milliseconds = S_1S_1 interval, pacing rate 100 bpm)

S_2 = first extrastimulus (S_1-S_2 = coupling interval between S_2 and S_1)

S_3 = second extrastimulus (S_2-S_3 = coupling interval between S_2 and S_3)

S_4 = third extrastimulus (S_3-S_4 = coupling interval between S_3 and S_4)

A_1 = atrial EGM associated with S_1 drive or spontaneous atrial rhythm

A_2 = atrial EGM associated with S_2 or the first spontaneous atrial EGM after A_1

A_3 = atrial EGM associated with S_3 or the second spontaneous atrial EGM after A_1

H_1 = His bundle EGM associated with S_1 drive or spontaneous rhythm

H_2 = His bundle EGM associated with S_2 or after second spontaneous depolarization

V_1 = ventricular EGM associated with S_1 drive or spontaneous ventricular rhythm

V_2 = ventricular EGM associated with S_2 or the first spontaneous ventricular EGM after A_1

V_3 = ventricular EGM associated with S_3 or the second spontaneous ventricular EGM after A

Refractory Periods

The effective refractory period (ERP) is defined as the longest interval after onset of depolarization that fails to propagate. The ERP is usually determined during PES with

the delivery of single extrastimuli after paced drive trains. With each successive drive train, the coupling interval is progressively shortened, until the extrastimulus fails to capture the stimulated tissue. This coupling interval identifies the ERP (Fig. 26.5). This interval represents the longest coupling interval that fails to capture the conduction system or myocardium distal to the stimulus (e.g., in the ventricle, S_1-S_2 interval that produces a V_1 but no V_2) The relative refractory period (RRP) is the longest S_1-S_2 interval resulting in conduction delay distal to the stimulus, for example, when the output interval (V_1-V_2) is longer than the S_1-S_2 interval (e.g., when "latency" of ventricular activation is observed). The functional refractory period (FRP) is the minimum interval between two consecutively conducted impulses, that is, the shortest output possible (e.g., the shortest V_1-V_2 interval). A summary and the normal ranges of ERPs are as follows:

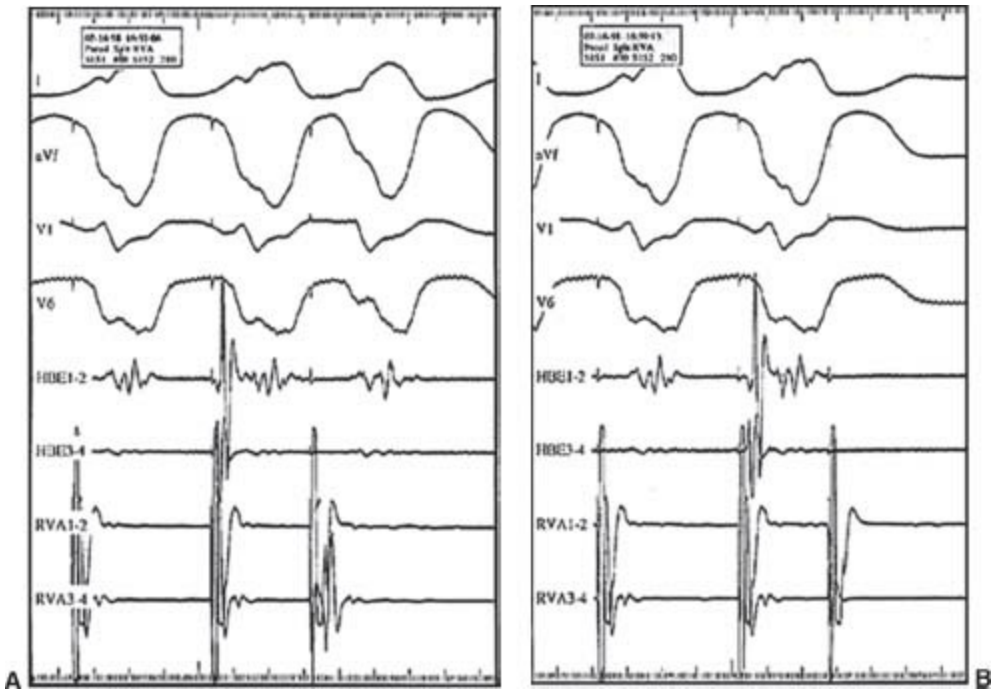


FIGURE 26.5 VERP. **A:** PCL 400 milliseconds, CI 280 milliseconds. **B:** PCL 400 milliseconds, CI 260 milliseconds (VERP).

- ERP—longest interval (e.g., S_1-S_2 interval) that fails to propagate.

$$S_1\text{-}S_2 = V_1\text{—no } V_2 \text{ (input measurement)}$$

- RRP—Longest S_1-S_2 interval resulting in conduction delay

$$S_1\text{-}S_2 \neq V_1\text{-}V_2 \text{ (input} \neq \text{output)}$$

- FRP—minimum interval between two consecutively conducted impulses. Shortest V_1-V_2 (shortest output possible)

Normal Effective Refractory Periods

Atrial ERP	170–300 ms
AVN ERP	230–430 ms
His ERP	330–450 ms
Ventricular ERP	170–290 ms

BRADYARRHYTHMIA EVALUATION BY EPS

EP study to assess bradyarrhythmias is not indicated if symptomatic bradycardia has already been documented or if patients already have a clear indication for a permanent pacemaker. However, EP study may be helpful in patients with sinus node or AV conduction disease and symptoms but for whom noninvasive monitoring has failed to document correlation of the bradyarrhythmia with symptoms; patients in whom symptoms might also be due to another arrhythmia (e.g., atrial, supraventricular, VT); or patients with a permanent pacemaker who continue to have symptoms.

SINUS NODE FUNCTION

The sinus cycle length (SCL) is defined as the A-A interval during sinus rhythm. Assessment of sinus node function may include assessment of the sinus node recovery times (SNRTs) and/or the sinoatrial conduction time (SACT).

SNRT. Atrial overdrive pacing is performed at a rate faster than the sinus rate for approximately 30 seconds, usually at multiple PCLs (e.g., PCL 700, 600, 500, 400 milliseconds). The SNRT is the interval from the last paced atrial EGM to the return sinus atrial EGM (Fig. 26.6). SNRT usually lengthens as PCL shortens until retrograde sinus node entrance block occurs at which point the sinus node is no longer being overdriven as quickly. Then, as PCL shortens further, SNRT typically shortens. Maximal SNRT is the longest SNRT measured after pacing at different PCLs and is reported with the PCL that produces the longest SNRT.

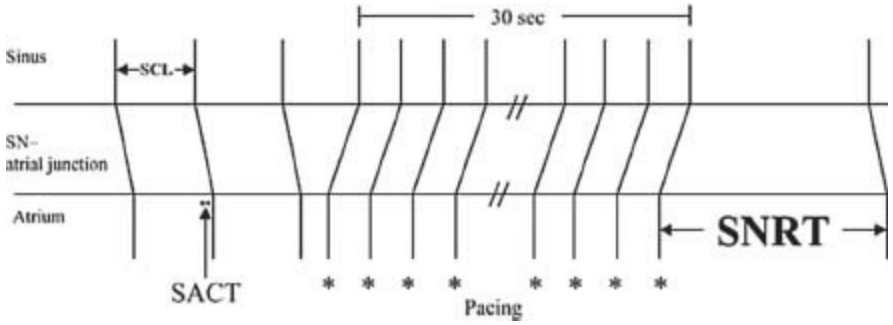


FIGURE 26.6 Determination of SNRT.

Corrected Sinus Node Recovery Time (CSNRT). The CSNRT is the difference between

the maximal SNRT and the SCL. Normal CSNRT is <550 milliseconds. The CSNRT corrects for the variation of SNRT with baseline SCL.

Total Sinus Node Recovery Time. After overdrive atrial pacing, the time from the last paced atrial EGM until the SCL returns to prepaced rate represents the total SNRT. Normal is <5 seconds.

Secondary Pauses. The presence of secondary pauses should be noted after testing for SNRT. A secondary pause represents an interval longer than the initial SNRT interval occurring after the initial sinus recovery beat after overdrive atrial pacing.

SACT. The SACT is a measure of conduction time from sinus activation to local atrial activation in the region surrounding the sinus node. SACT can be estimated by pacing and recording close to the sinus node and measuring the time to the first spontaneous atrial beat after a single premature beat or slow overdrive train of atrial pacing. (Normal 50 to 125 milliseconds.)

Indirect SACT—Narula Method (Fig. 26.7).From a catheter placed in the HRA in the region of the sinus node, a drive train (commonly eight beats) of atrial overdrive pacing is delivered at a PCL approximately 50 milliseconds (50 to 150 milliseconds) faster than the sinus rate. This rate is assumed to be fast enough such that the last beat will capture the sinus node but slow enough to avoid significant prolongation of SNRT. The interval from the last paced stimulus to the first return sinus activation recorded by the atrial EGM on the pacing catheter is measured. The estimated SACT = (Escape interval – SCL)/2. This assumes that the conduction times into and out of the sinus node are equal.

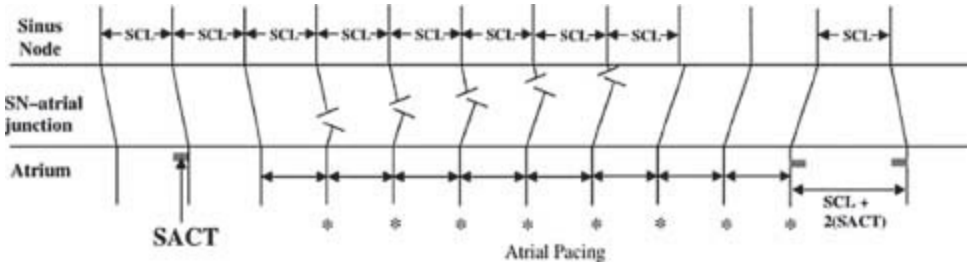


FIGURE 26.7 Estimation of SACT, Narula method.

Indirect SACT—Strauss Method (Fig. 26.8). During sinus rhythm (A_1), single premature atrial beats (A_2) are delivered, starting with a long coupling interval and decrementing by 10 milliseconds. The atrial EGM of the sinus return beat (A_3) is recorded. The sinus return intervals after the premature beats (A_2-A_3) are plotted against A_1-A_2 intervals (Fig. 26. 8E). Four zones can be described:

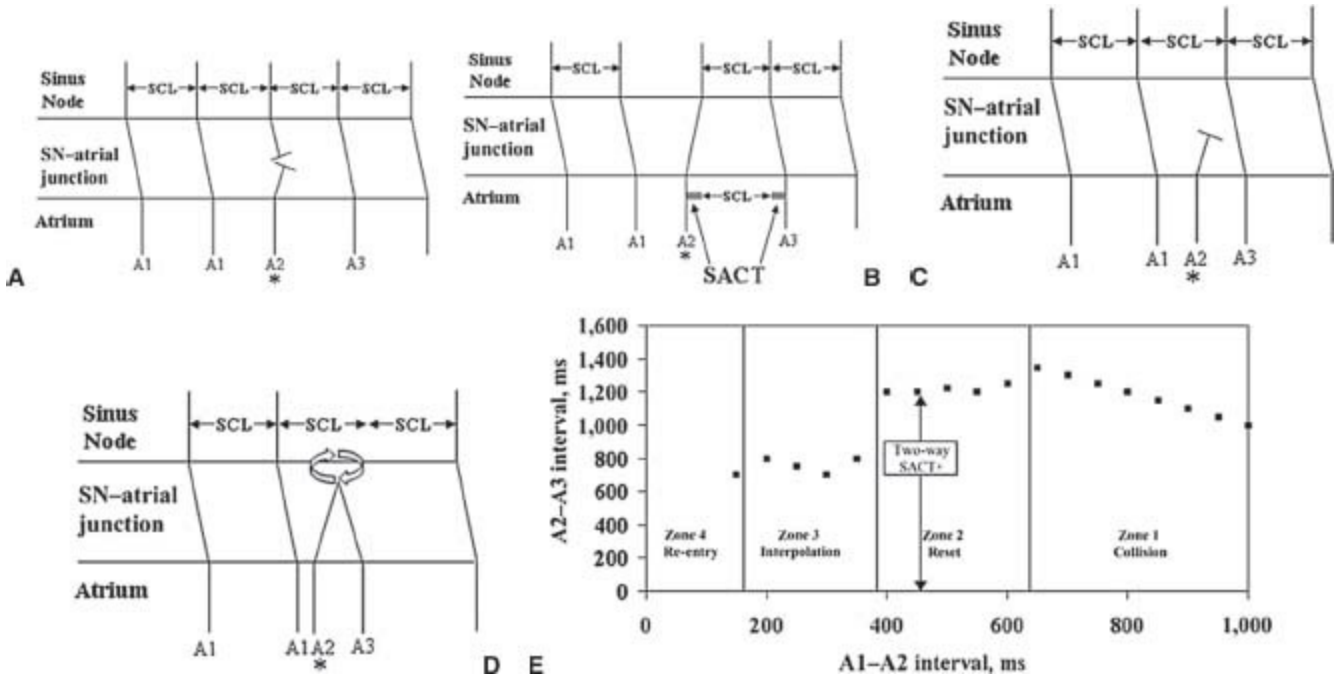


FIGURE 26.8 Estimation of SACT, Strauss method. **A:** Zone 1,zone of collision. **B:** Zone 2, zone of reset. **C:** Zone 3, zone of interpolation. **D:** Zone 4, zone of re-entry. **E:** A_1–A_2 versus A_2–A_3.

one of Collision or Nonreset (Zone 1, Fig. 26. 8A). Very late-coupled premature atrial beats (A_2) collide with the preceding sinus node outgoing activation (A_t) and do not penetrate into the sinus node. Thus, the sinus node is unaffected, and the next sinus activation (A_3) occurs on time (i.e., the sinus node timing is not reset). In this A_1-A_2 zone of collision, as A_1-A_2 coupling interval shortens, A_2-A_3 prolongs by the same amount. Thus, (A_1-A_2) + (A_2-A_3) = 2 × (A_1-A_1).

one of Reset (Zone 2, Fig. 26. 8B): In this zone, the premature atrial extrastimuli (A_2) penetrate the sinus node and reset the timing of the sinus node, resulting in an advancement in the time of the next sinus activation (A_3). During this zone, A_2-A_3 interval stays relatively constant, representing a plateau in the A_1-A_2 versus A_2-A_3 plot. This A_2-A_3 interval consists of the escape interval of the sinus node and the two-way SACT (A_2-A_3 = A_1-A_1 + 2-way SACT). The two-way SACT is estimated as the difference between the plateau A_2-A_3 and the SCL (A_1-A_1). Thus, two-way SACT = A_2A_3-A_1-A_1

one of Interpolation (Zone 3, Fig. 26. 8C): As the premature atrial extrastimulus (A_2) coupling interval (A_1-A_2) shortens further, entrance block may occur in the tissue surrounding the sinus node. In this zone, the premature atrial impulse may not penetrate the sinus node. The escape or return sinus interval (A_2-A_3) shortens, because A_2 does not reset the node. The A_1-A_3 interval may be the same as the A_1-A_1 interval (SCL). In other words, (A_1-A_2) + (A_2-S_3) = (A_1-A_1). However, if A_2 conducts to the perinodal tissue, causing the return or escape sinus beat to conduct slower on its way out of the sinus node, A_2-A_3 may be slightly prolonged, so the sum of (A_1-A_2) + (A_2-S_3) may be slightly longer than A_1-A_1 during some parts of this zone.

one of Reentry (Zone 4, Fig. 26. 8D): In some patients, a reentrant beat is induced by a short-coupled atrial extrastimulus. In this zone, A_1-A_3 is shorter than the SCL A_1-A_1.

The SACT by Strauss method may be estimated in a shorter protocol by introducing atrial premature beats (A_2) at approximately 40% to 60% of the SCL and measuring A_2-

A_3 at several A_1-A_2 coupling intervals. If the A_2-A_3 intervals are relatively constant (variation <50 milliseconds), then it is assumed these have been delivered during the plateau phase (Zone 2) and the SACT can be calculated. However, if a stable A_2-A_3 is not achieved, then the Strauss SACT should not be reported.

Sinus Node Effective Refractory Period (SNERP): Sinus node depolarization may be recorded directly, but is technically difficult. Recording may not be successful even with use of high gains and filtering to allow low-frequency signals. SNERP may be indirectly estimated as the A-A_2 interval at which Zone 3 interpolation begins in the Strauss SACT method. At this A-A_2 interval, neither sinus node reset nor activation occurs.

Intrinsic Heart Rate (IHR): The intrinsic sinus rate is inferred as the sinus rate after application of autonomic blockade, using both atropine and propranolol to block vagal and sympathetic inputs, respectively IHR varies with age and can be estimated by the formula: IHR = 118.1 – 0.57 (age)

The sensitivity for sinus node dysfunction causing symptoms is approximately 54% for CSNRT, approximately 51% for SACT, approximately 64% for combined CSNRT + SACT with specificity approximately 88%. The low sensitivity and specificity of EP study for detection of sinus node dysfunction limits its value in prediction of future events in asymptomatic patients.

Response to Carotid Sinus Massage: Right and left carotid sinus massage may be performed in patients with syncope of undetermined etiology and no evidence of carotid vascular disease. A sinus pause or AV block >3 seconds with reproduction of clinical symptoms is considered a positive response to carotid sinus massage. A cardioinhibitory response occurs in >70% of patients with a positive response, a vasodepressor response (BP drop <50 mm Hg) in approximately 15%, and both in others.

ASSESSMENT OF AV CONDUCTION

The AVN and His-Purkinje system (HPS) function are tested using atrial pacing, atrial extrastimuli, and pharmacologic challenge techniques. The AH interval estimates conduction time through the AVN. The HV interval assesses infra-Hisian conduction and estimates conduction time from the His bundle to the first onset of ventricular activation. Retrograde conduction is tested by ventricular pacing and ventricular extrastimuli.

Baseline AV Conduction

AH Interval. The AH interval (Fig. 26.2), an estimation of the conduction time through the AVN, is measured on the HBE from the first major deflection as it crosses baseline to the onset of the His bundle EGM. Normal range is greatly variable based on

autonomic tone and medications. The input to the AVN is estimated by the atrial EGM and the output of the AVN by the His deflection on the HBE tracing.

HV Interval. The HV interval (Fig. 26.2) is measured on the HBE from the onset of the His deflection to the earliest onset of ventricular activation seen on any surface lead or intracardiac EGM. The normal range for HV intervals is 35 to 55 milliseconds. A short HV interval may be seen in ventricular preexcitation syndromes, where HV may be negative when ventricular activation is preexcited by anterograde conduction through an accessory pathway that beats out ventricular activation by the AVN to HPS. A short HV may also be measured if a premature ventricular depolarization occurs prior to ventricular activation, and also if the HBE is placed distally and is recording a distal His or right bundle potential. A long HV interval suggests HPS conduction disease.

RB-V Interval. This interval measures the onset of the right bundle potential to the earliest ventricular activation on any surface lead or intracardiac EGM.

Incremental Atrial Pacing

Anterograde AV conduction can be studied during incremental atrial pacing, which refers to atrial pacing at shorter and shorter PCLs. The presence of decremental AV conduction, typical of AVN conduction, and the pattern of ventricular activation are determined to help distinguish whether anterograde conduction occurs via the AVN or via an accessory pathway.

AH Decrement. The AH interval normally prolongs as atrial pacing rate increases (as PCL is shortened). This is termed "decremental conduction," which is a property of AV nodal tissue. Failure to decrement AV conduction (AH may decrement but AV interval may stay constant with shortening of the HV interval) suggests the presence of an accessory pathway. Conduction through a typical accessory pathway is usually nondecremental.

Pattern of Ventricular Activation. Conduction through the AVN and HPS inscribes a narrow QRS in the absence of aberrancy, or block in a component of the HPS. Conduction through a typical accessory pathway usually does not decrement. However, as atrial PCL shortens (at faster paced rates), conduction through the AVN will decrement. In the presence of an accessory pathway, slower conduction through the AVN may allow a larger contribution of ventricular activation to occur via the accessory pathway. This may be manifest as a wider QRS with more and more preexcitation becoming evident at faster PCLs.

PCL of AV Block. The longest atrial PCL associated with a failure of AV conduction is considered the PCL of AV block. This PCL is sometimes termed the "Wenckebach PCL" when conduction block occurs in a second-degree AV block Mobitz I pattern, which is the normal response of the AVN to atrial pacing at shorter PCLs. A typical accessory pathway generally blocks in a 2:1 fashion rather than in a Wenckebach pattern.

PCL of HV Block. This interval is the longest atrial PCL at which block occurs below the His bundle (His deflection without following ventricular activation). This represents an abnormal finding if infra-Hisian block or HV prolongation occurs at atrial PCLs longer than 400 milliseconds.

AV BLOCK: AV NODE VERSUS INFRA-HISIAN BLOCK

EP studies can be useful in determining the level of AV block. Block in the AVN is usually associated with a narrow QRS. On intracardiac EGMs recorded at the HBE, an atrial EGM that blocks with no His deflection indicates block occurred in the AVN (Fig. 26.9 left panel). Infra-Hisian block is usually associated with a wider QRS. At the HBE, an atrial EGM and His deflection is inscribed, but with no succeeding ventricular activation. Thus, activation proceeded from the atrium, through the AVN, to the His bundle, with subsequent block occurring below the His bundle (Fig. 26.9 right panel).

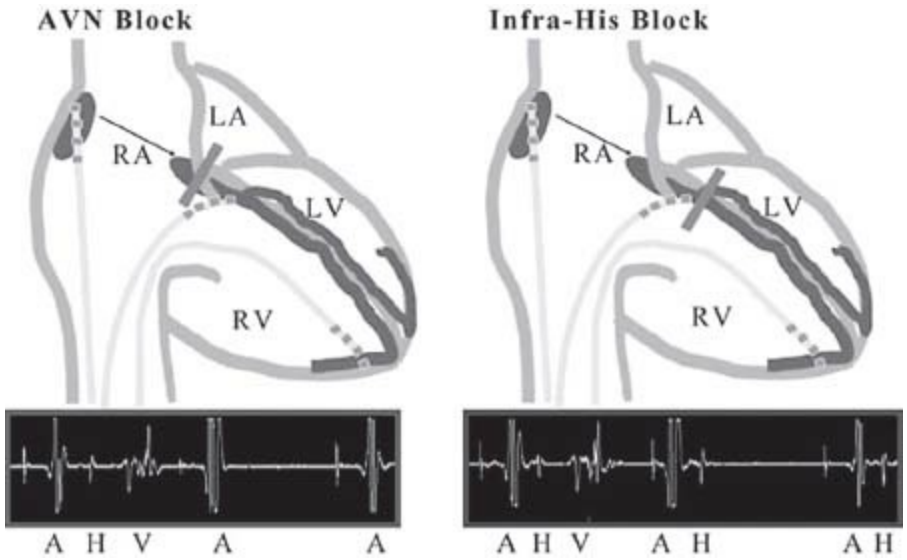


FIGURE 26.9 Level of AV block.

AV block occurs when the atrial impulse either is not conducted to the ventricle or is conducted with delay at a time when the AV junction is not refractory. It is classified on the basis of severity into three types.

First-Degree AV Block. In first-degree AV block, conduction is prolonged (PR interval >200 milliseconds), but all impulses are conducted. The conduction delay may be due to conduction slowing in the AVN, the HPS, or both. If the QRS complex is narrow and normal, the AV delay usually occurs in the AVN. This may be determined on baseline His bundle recordings, where AH or HV interval prolongation indicates the level of delayed conduction (Fig. 26.10).

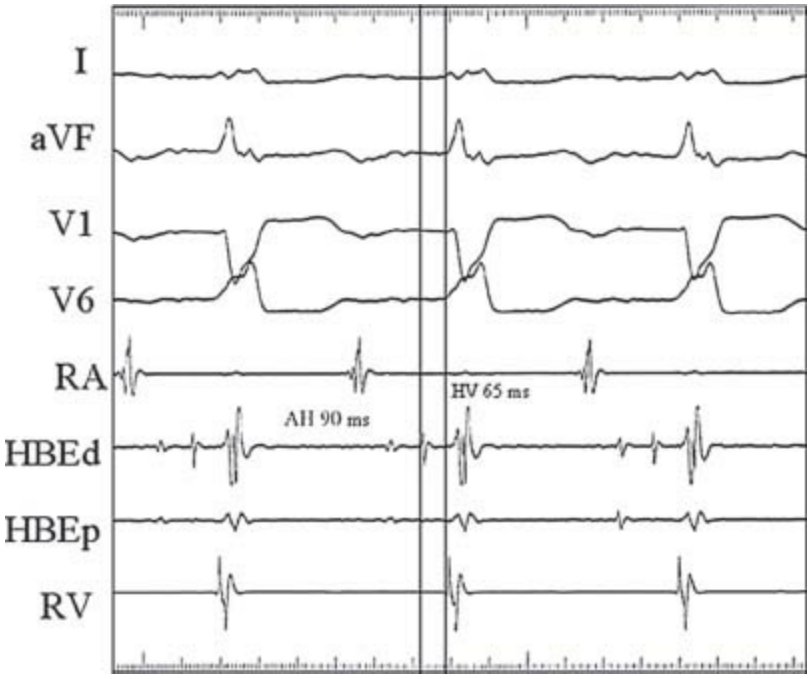


FIGURE 26.10 First-degree AV block. In this example, the PR interval is 255 milliseconds. The AH interval is 90 milliseconds and the HV interval is 65 milliseconds. At least part of the prolonged conduction is due to delay in the HPS.

Second-Degree AV Block. In second-degree AV block, intermittent block in conduction occurs. In Mobitz type I (Wencksebach) second-degree AV block, progressive prolongation of the PR interval occurs before the block in conduction. In the usual Wenckebach periodicity (Fig. 26.11), the PR interval gradually increases, but with a decreasing increment, thus leading to a gradual shortening of the RR intervals. The longest PR interval usually precedes the block, and the shortest PR interval usually occurs after the block, thereby resulting in the long RR interval of the blocked impulse being shorter than twice the basic PP interval.

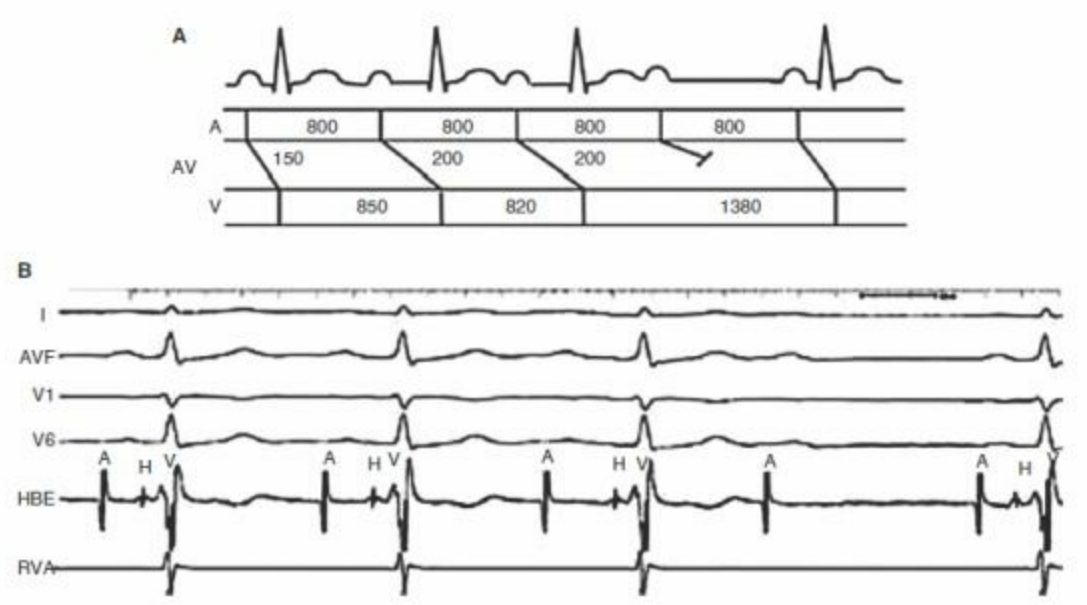


FIGURE 26.11 Second-degree AV block, Mobitz type I (Wenckebach) periodicity. **A:** Ladder diagram of Wenckebach periodicity. The AV interval gradually prolongs prior to the blocked beat. **B:** Intracardiac EGMs of second-degree AV block with Wenckebach block. The AH gradually prolongs prior to the blocked atrial impulse. The block occurs in the AVN.

Variants of this pattern are not uncommon. In Mobitz type II second-degree AV block, PR intervals before the block are constant, and there are sudden blocks in P-wave conduction. Advanced or high-degree AV block refers to a block of two or more consecutive impulses. In Mobitz type I block, the level of the block is almost always at the AVN, particularly with a narrow QRS complex. Rarely, type I Wenckebach periodicity in the HPS may be seen in patients with a wide QRS or bundle branch block. In contrast, Mobitz type II block is almost always at the level of the HPS and has a higher risk of progressing to complete AV block. In 2:1 AV block, conduction block may occur in either the AVN or HPS. Again, a narrow QRS suggests the level of block is at the AVN and a wide QRS suggests block is infra-Hisian; however, there are exceptions, as can be confirmed by His bundle recordings (Figs. 26.12 and 26.13). It should also be noted that block can occur in both the AVN and infra-Hisian levels.

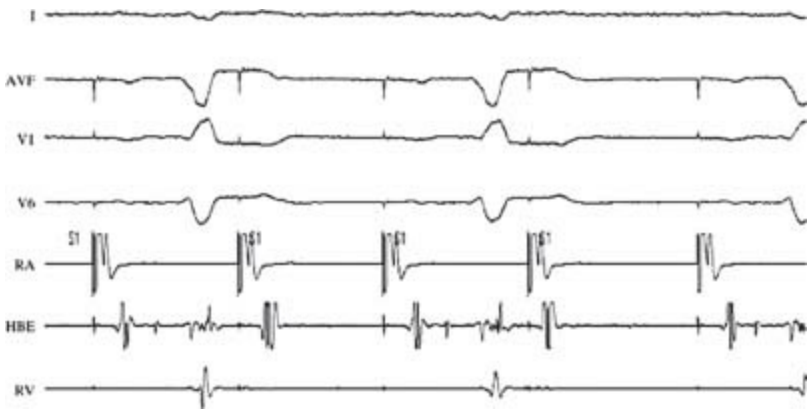


FIGURE 26.12 2:1 AV block in the AVN during atrial pacing.

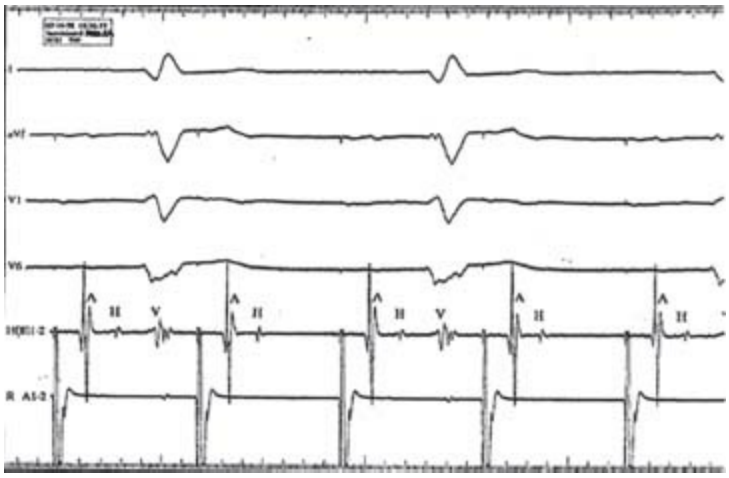


FIGURE 26.13 2:1 AV block due to infra-Hisian block during atrial pacing.

Third-Degree AV Block. In third-degree (complete) AV block, no impulses are conducted from the atria to the ventricles. The level of the block can occur at the AVN (usually congenital), His bundle, or in the HPS (usually acquired). Escape beats that are junctional (often with narrow QRS) at rates of 40 to 60 bpm generally occur with congenital complete AV block. Escape beats that are ventricular in origin (with wide QRS) often are slow, ranging from 30 to 40 bpm. The level of block can again be confirmed by His bundle recordings.

Atrioventricular Dissociation. It should be noted that AV dissociation, which refers to independent depolarization of the atria and ventricles, is not always due to complete AV block. It may be caused by:

1. Physiologic interference resulting from slowing of the dominant pacemaker (e.g., sinus node) and escape of a subsidiary or latent pacemaker (e.g., junctional or ventricular escape),
2. Physiologic interference resulting from acceleration of a latent pacemaker that usurps control of the ventricle (e.g., accelerated junctional tachycardia or VT), and
3. AV block preventing propagation of the atrial impulse from reaching the ventricles, thus allowing a subsidiary pacemaker (e.g., junctional or ventricular escape) to control the ventricles.

Patients with complete AV block have AV dissociation and, generally, a ventricular rate that is slower than the atrial rate. Patients with AV dissociation, however, may have complete AV block or dissociation resulting from physiologic interference, with the latter typically having a ventricular rate that is faster than the atrial rate.

ASSESSMENT OF AV NODE PHYSIOLOGY

Besides incremental atrial pacing to assess the AVN conduction, including the point at which block occurs (Wenckebach cycle length), AVN physiology can be more carefully dissected and studied using atrial extrastimulus testing.

Atrial Extrastimulus Testing. AV nodal physiology assessment is generally performed at several atrial PCLs (e.g., PCL 600, 500, 400 milliseconds) with eight-beat trains of atrial overdrive pacing (A_1), followed by delivery of a premature atrial extrastimulus (A_2). The coupling interval of the extrastimulus (A_1-A_2) is shortened by 10 to 20 milliseconds with each succeeding drive train.

Dual AVN Pathway Physiology. AV nodal conduction curves (Fig. 26.14) can be plotted (A_1-A_2 vs. A_2H_2 or A_1-A_2 vs. H_1H_2). A discontinuous AV nodal conduction curve (AH interval jump of >50 milliseconds after a decrease in A_1-A_2 coupling interval of 10 milliseconds) suggests the presence of two conduction pathways (typically a fast-conducting AV nodal pathway with a longer refractory period than a

slow-conducting AV nodal pathway which has a shorter refractory period) (Fig. 26.15). Dual AVN physiology is confirmed by the occurrence of an AV nodal echo beat, in which antero-grade conduction down the slow AVN pathway is followed by retrograde conduction to the atria via the slow pathway (Fig. 26.15). This typical echo beat occurs with atrial activation occurring within 70 milliseconds of the onset of ventricular activation; on intracardiac EGMs, atrial and ventricular activation occurs near simultaneously.

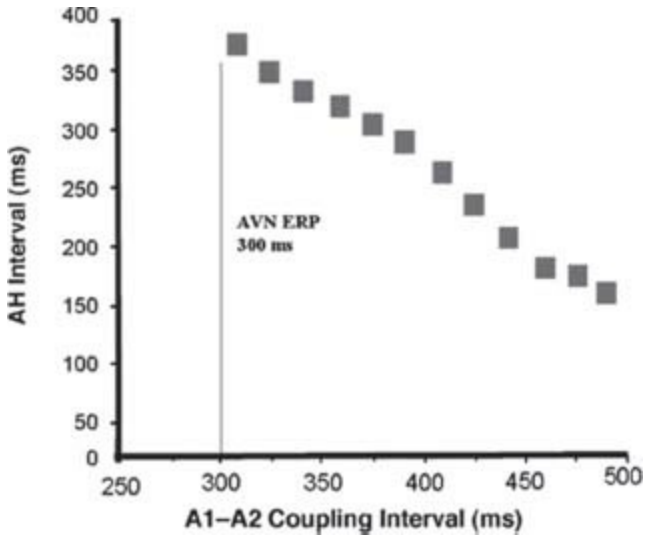


FIGURE 26.14 Normal AVN conduction curve.

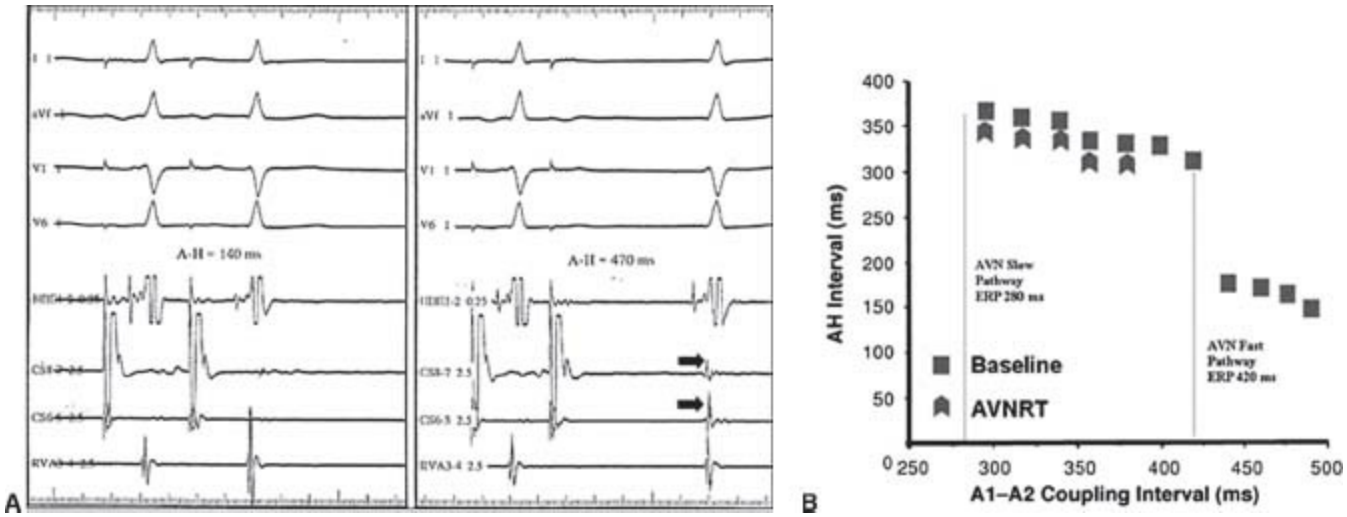


FIGURE 26.15 AH jump and AVN echo beat. **A:** Single atrial premature extrastimuli are delivered after eight-beat paced drive cycles. The AH interval is 140 milliseconds with a coupling interval of 290 milliseconds. After a coupling interval of 280 milliseconds, the AH interval "jumps" to 470 milliseconds, indicating the presence of dual AVN pathway physiology. The atrial EGMs evident in the CS leads (arrows) indicate the AVN echo beat with retrograde conduction to the atria. **B:** AVN conduction curve demonstrating an AH jump at the fast pathway ERP of 420 milliseconds and induction of echo beats and AVNRT.

AV Nodal Refractory Periods. The AV Nodal Effective Refractory Period (AVN ERP) is the longest A_1-A_2 interval that fails to conduct through the AVN (Fig. 26.16).

Prolongation may occur with high vagal tone or concomitant medications. Other refractory periods that can be measured include the AV Nodal Relative Refractory Period (AVN RRP), which represents the longest A_1-A_2 which results in an $H_1H_2 > A_1$-A_2 during atrial extrastimulus testing. The AV Nodal Functional Refractory Period (AVN FRP) is the shortest H_1H_2 interval (AVN output) observed during extrastimulus testing.

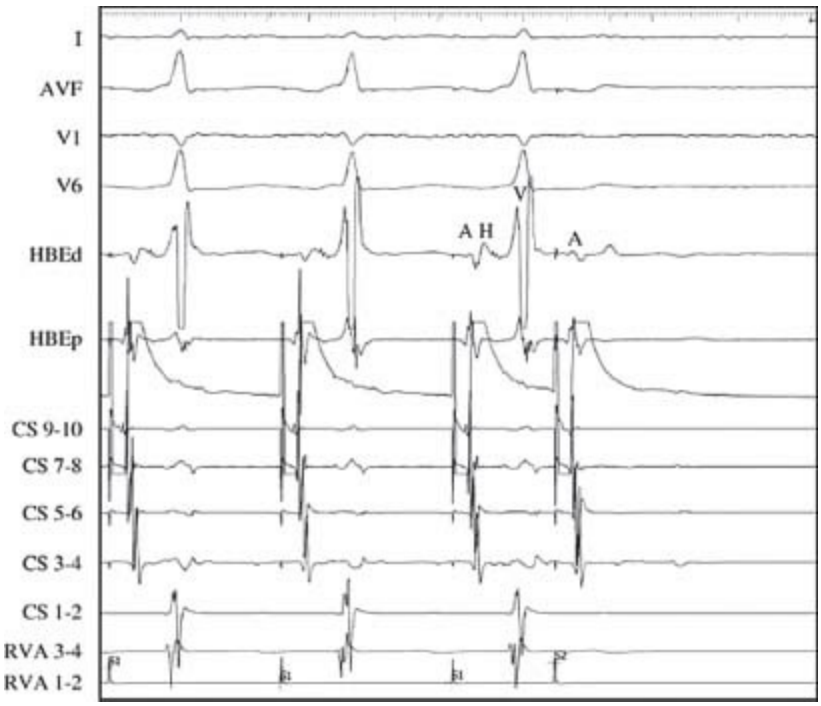


FIGURE 26.16 AV node effective refractory period (AVN ERP).

Incremental Ventricular Pacing

While not a component of EP testing that directly assesses anterograde AV conduction, incremental ventricular pacing (pacing in the ventricle at faster and faster cycle lengths) can help determine whether retrograde conduction occurs via the AVN (Fig. 26.17) or an accessory pathway (Fig. 26.18). Atrial activation occurring with a midline activation pattern that decrements with more rapid pacing rates or a shorter premature extrastimulus coupling interval suggests conduction via the His-Purkinje–AVN system. In this pattern, concentric activation is seen in the CS leads with earliest atrial activation occurring at the AVN, septal region, and later activation occurring at more lateral atrial sites (Fig. 26.17).

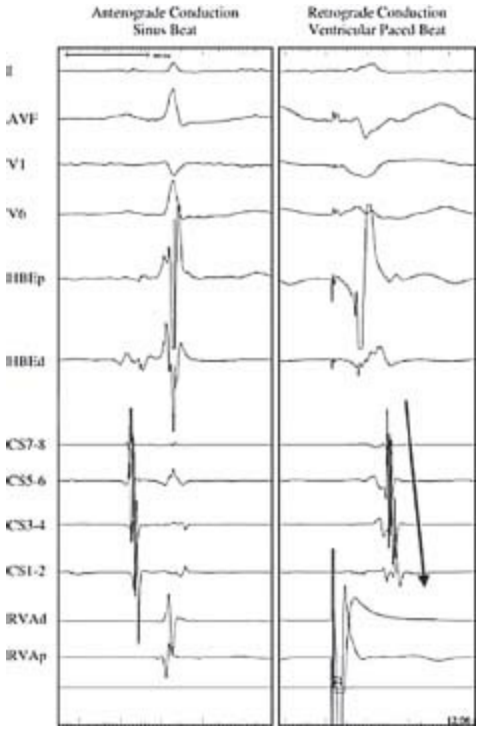


FIGURE 26.17 Normal anterograde and retrograde activation.

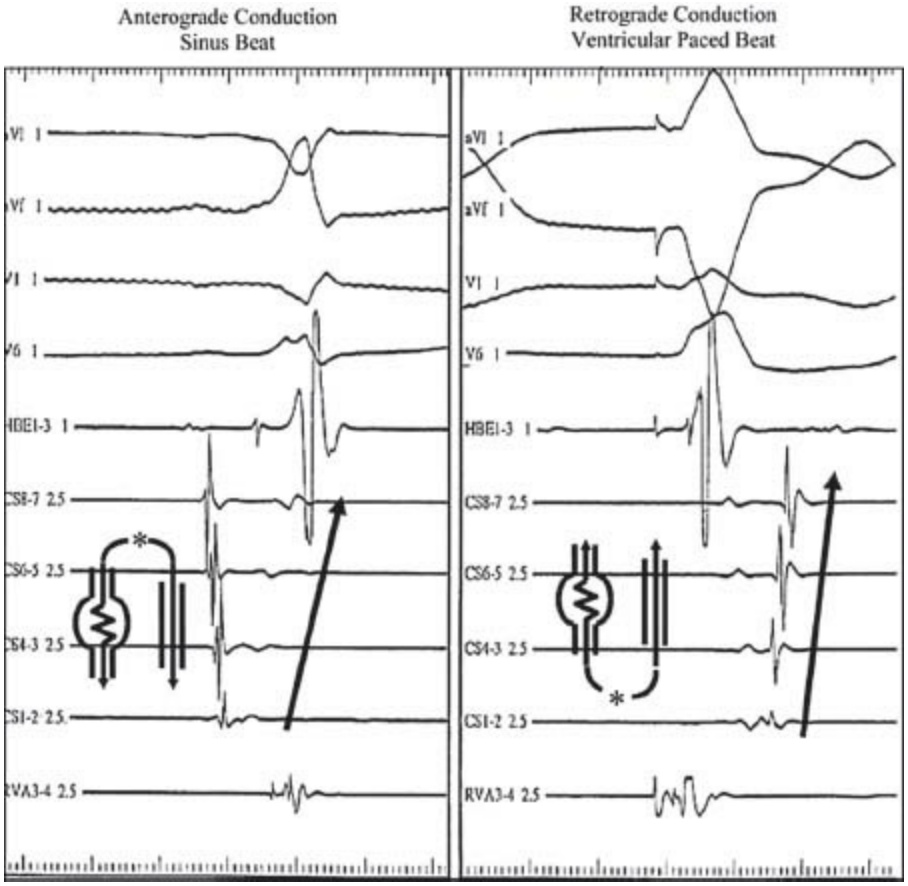


FIGURE 26.18 Abnormal anterograde and retrograde activation: left-sided accessory pathway.

In contrast, retrograde conduction via a left lateral free wall accessory pathway (Fig.

26.18) would cause an eccentric activation pattern with earliest ventricular activation occurring near the accessory pathway in the lateral CS leads and earliest retrograde atrial activation in the distal CS as well.

PCL of VA Block. The longest ventricular PCL associated with failure of retrograde VA conduction is determined by decremental ventricular pacing. Pacing is performed at shorter and shorter cycle lengths. During retrograde AV nodal conduction, VA intervals gradually increase as pacing cycle length shortens. PCL is shortened until VA block occurs (e.g., retrograde Wenckebach or 2:1 VA block). In the presence of a typical accessory pathway, a constant VA interval is usually observed, and VA block occurs when the accessory pathway refractory period is reached. This usually occurs with a 2:1 VA block pattern, rather than in a retrograde Wenckebach pattern.

Ventricular Extrastimulus Testing. Analogous to atrial extrastimulus testing, single premature ventricular extrastimuli (V_2) are delivered after eight-beat trains of ventricular pacing (V_1) at several ventricular PCLs (e.g., PCL 600, 500, 400 milliseconds). The coupling interval of the extrastimulus (V_1V_2) is shortened by 10 to 20 milliseconds with each succeeding drive train. In this manner, retrograde VA conduction can be assessed. Decremental retrograde conduction suggests conduction is occurring via the His-Purknje – AVN system. Retrograde conduction via a typical accessory pathway is generally nondecremental, unless the accessory pathway is an atypical, decremental pathway. In addition, retrograde atrial activation patterns are examined to determine if atrial activation occurs with a typical AV nodal midline activation pattern (Fig. 26.17).

TACHYARRHYTHMIA EVALUATION BY EPS

Ventricular Tachycardia

Most patients undergoing EP study for assessment of ventricular arrhythmias have coronary artery disease or dilated cardiomyopathy, and reduced left ventricular function.

In selected patients, EP study may be useful for assessment of risk and need for ICD implantation, drug testing, assessment of device/antitachycardia pacing function, or mapping for ablation. EP testing has limited sensitivity and specificity in the prediction of arrhythmic events in nonischemic disease. EP studies have been more useful in risk stratification of patients with CAD after MI. Based on data from Multicenter Unsustained Tachycardia Trial (MUSTT)[4] and Multicenter Automatic Defibrillator Implantation Trial (MADIT),[5] survival is improved with ICD implantation in patients with CAD, prior MI, nonsustained VT, and LVEF ≤40%, and inducible sustained VT or reproducibly inducible VF with double ventricular extrastimuli that is not suppressible with an antiarrhythmic drug (MADIT).[5] These studies provide a rationale for

performing EP studies for risk stratification in these patient groups. MADIT II[6] demonstrated the value of prophylactic ICD implantation without EP testing in patients with CAD and LVEF ≤30%. DEFINITE[7] and SCDHeFT[8] studied the value of prophylactic ICD implantation and included patients with nonischemic cardiomyopathy. SCD-HeFT demonstrated survival benefits for ICD implantation in ischemic or nonischemic cardiomyopathy patients with heart failure and LVEF ≤35% without the need for EP testing. EP testing is generally not necessary in patients who have criteria that already meet approved ICD indications.

Patients with normal LV function and VT usually have special types of ventricular arrhythmias that may be studied by EP testing, particularly in conjunction with mapping and ablation.

Ventricular Programmed Stimulation Protocols

Several stimulation protocols have been of utility in stratifying risk for sustained ventricular arrhythmias. Some of the most common are summarized below:

Pacing sites:	RVA, RVOT
Drive cycle lengths:	PCL 600 and 400 milliseconds (S_1); eight-beat drive trains
Number of Extrastimuli:	1 to 3 extrastimuli (S_2 to S_4)
	Decrementing extrastimuli by 10 milliseconds starting with last until S_2 is refractory
Pacing sites:	RVA, RVOT
Drive cycle lengths:	PCL 350, 400, 600 milliseconds (S_1); eight-beat drive trains
Number of Extrastimuli:	Four extrastimuli (S_2-S_5) beginning at 290, 280, 270, 260 milliseconds
	decrementing 10 milliseconds with each drive until S_2 is refractory

Short-long-short protocol:

Pacing sites:	RVA, RVOT
Drive cycle lengths:	PCL 400; six- or eight-beat drive trains (S_1)
Number of Extrastimuli:	S_2 at 600 milliseconds; S_3 shorter and decrementing until S_3 refractory

Ventricular overdrive burst pacing.

Ventricular Effective Refractory Period (VERP). Single ventricular premature extrastimuli are delivered with shortening coupling intervals until the stimulus fails to capture the ventricle (Fig. 26.19). The VERP is the longest ventricular extrastimulus V_1V_2 that fails to capture the ventricle during ventricular extrastimulus testing. It is measured from pacing stimulus to pacing stimulus and is recorded at different sites (e.g., right ventricular apical [RVA], right ventricular outflow tract [RVOT]) and PCLs (e.g., 600, 400 until S_2 is refractory).

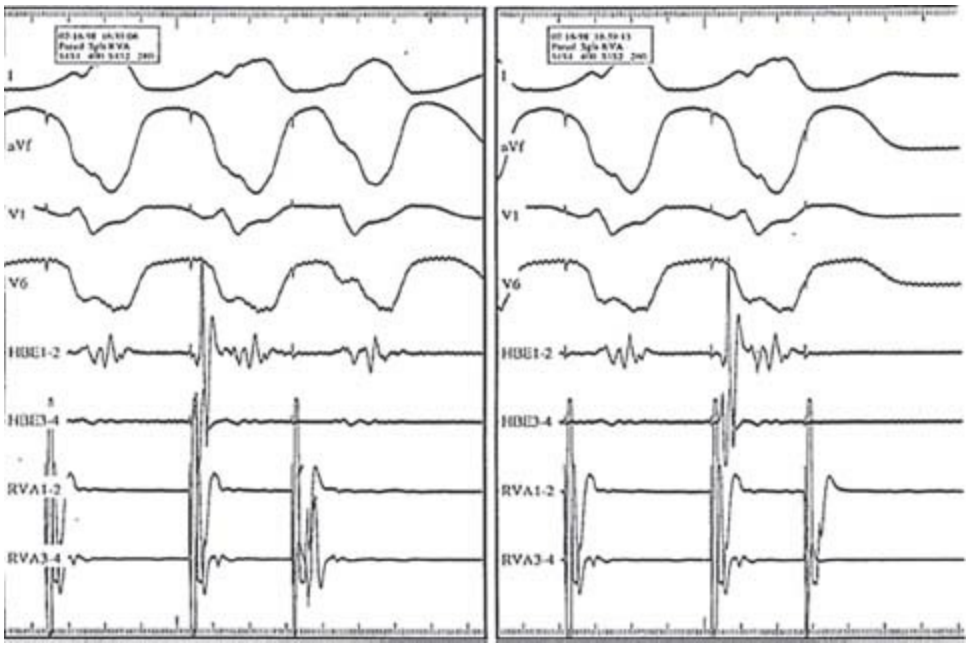


FIGURE 26.19 Determination of VERP by ventricular extrastimulus delivery. Single ventricular premature extrastimuli are introduced with shortening coupling intervals until the stimulus fails to capture the ventricle. In this example, at PCL 400 milliseconds, a ventricular premature extrastimulus captures the ventricle at a coupling interval of 280 milliseconds, but fails to capture the ventricle at 260 milliseconds. The VERP is 260 milliseconds at PCL 400 milliseconds.

Ventricular Functional Refractory Period (VFRP). The VFRP is the shortest ventricular coupling interval produced with premature ventricular stimulation. The VFRP is measured from EGM to EGM and recorded at different sites (e.g., RVA, RVOT) and PCLs (e.g., 600, 400 until S_2 is refractory).

Induced Arrhythmias. Definitions of ventricular arrhythmias that can be induced with programmed ventricular stimulation include the following:

- Repetitive ventricular responses—1 to 3 PVCs
- NSVT—three or more ventricular complexes lasting <30 seconds
- Sustained VT—VT lasting >30 seconds or requiring earlier termination due to hemodynamic compromise
- Sustained monomorphic VT—sustained VT of uniform morphology
- Sustained polymorphic VT—sustained VT of multiform morphology
- Pleiomorphic VT—multiple morphologies of monomorphic VT
- Ventricular flutter—rapid VT<220 or 240 milliseconds CL with no isoelectric baseline and a sine wave appearance
- VF—disorganized chaotic ventricular complexes with loss of organized ventricular contraction.

Morphology. Morphology of VT can be described by bundle branch block morphology and axis using surface ECG leads I, aVF, and V_1:

Lead V_1:	Positive ⇒ right bundle branch block (RBBB) morphology	Negative⇒ left bundle branch block (LBBB) morphology
Lead I:	Positive ⇒ left axis	Negative⇒ right axis
Lead aVF:	Positive ⇒ inferior axis	Negative⇒ superior axis

VA Relationship During VT. VA dissociation can be readily recognized using intracardiac atrial and ventricular EGMs (Fig. 26.20), helping to confirm the diagnosis of VT.

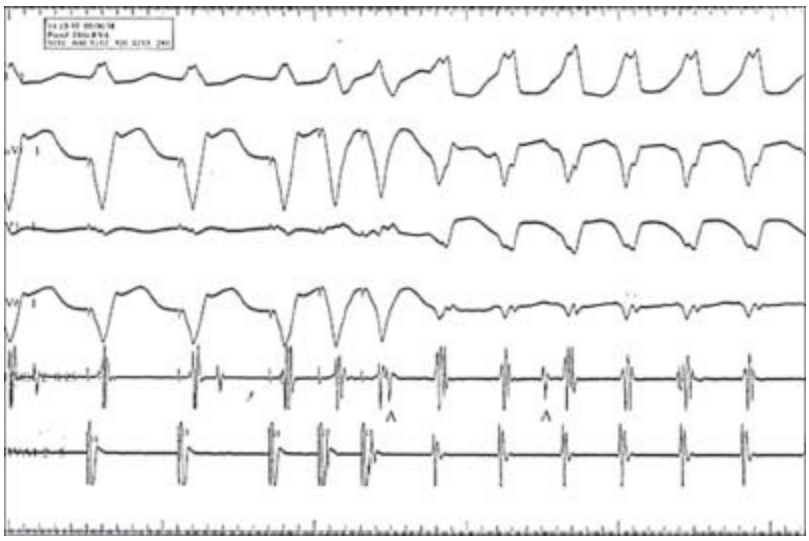


FIGURE 26.20 Ventricular stimulation and induction of sustained monomorphic VT with VA dissociation, LB/LSA morphology. VA dissociation is evident during the induction pacing sequence as well as during VT. A, atrial activation.

Supraventricular Tachycardia

During EP studies performed for the diagnosis and mapping of SVT, multipolar catheters are generally placed in the HRA or CS, at the His bundle (HBE), and in the right ventricle (RVA or RVOT). SVT mechanisms include atrial arrhythmias (including ectopic atrial tachycardia, macroreentrant atrial tachycardia, atrial flutter, and atrial fibrillation), AV node reentrant tachycardia (AVNRT), and atrioventricular reciprocating tachycardia (AVRT) mediated by an accessory pathway.

Stimulation Protocols. Programmed atrial and ventricular stimulation protocols are used in the determination of SVT mechanism and are summarized as follows:

Ventricular Pacing.Incremental ventricular pacing at constant rates, but delivered at progressively faster PCLs, is used for assessment of VA conduction. In particular, retrograde atrial activation pattern (via AVN vs. accessory pathway) is examined to determine the earliest atrial activation site from atrial EGMs recorded on catheters at various atrial sites (Figs. 26.17 and 26.18). The shortest cycle length at which 1:1 VA conduction occurs is recorded and the pattern of VA block at shorter cycle lengths examined. A decremental VA conduction pattern (longer VA times with faster pacing rates) that is concentric (earliest atrial activation in septal leads and later activation in lateral free wall electrodes) suggests retrograde conduction is occurring via the AVN. Retrograde conduction using an accessory pathway may cause an eccentric atrial activation pattern in the CS (earliest atrial activation in the posterior or lateral CS in left-sided accessory pathways, Fig. 26.18) or early activation away from the septum in the RA. In addition, typical accessory pathways do not display significant decremental conduction, so VA conduction times generally are constant. Exceptions occur for septal accessory pathways in which earliest activation will be at septal leads, and also for decremental accessory pathways in which VA conduction times may be longer at faster pacing rates.

Programmed Ventricular Stimulation. Premature ventricular extrastimuli. Single premature ventricular beats are delivered at one or more drive cycle lengths (e.g., 600, 400 milliseconds) to assess retrograde refractory periods, pattern and change in retrograde atrial activation patterns, site of retrograde VA block, and the presence of dual retrograde AVN pathway physiology.

Atrial Pacing. Assessment of anterograde conduction is performed with atrial pacing and programmed atrial stimulation. Baseline AH and HV intervals are assessed and evidence for decremental AVN conduction is sought. Anter-ograde conduction via the AVN is characterized by increasing AH intervals with faster atrial pacing rates. The shortest PCL at which 1:1 AV conduction occurs and the pattern of anterograde activation and block at PCL shorter than this are noted. A Wenckebach AV block pattern and a narrow QRS supports conduction occurring anterogradely through the AVN. Anterograde ventricular preexcitation by an accessory pathway may become more manifest by atrial pacing, as faster pacing rates will cause decremental, or slower, conduction through the AVN. Thus, at faster atrial pacing rates, the AVN will conduct slower, leading to later ventricular activation from the AVN–HPS. Since conduction through a typical accessory pathway does not significantly decrement with more rapid pacing rates and ventricular activation times via the accessory pathway will remain relatively constant, there is less contribution of ventricular activation that occurs via the AVN and more via the accessory pathway (Fig. 26.21). Another potential important function of burst atrial pacing is the induction of SVT for mapping and ablation.

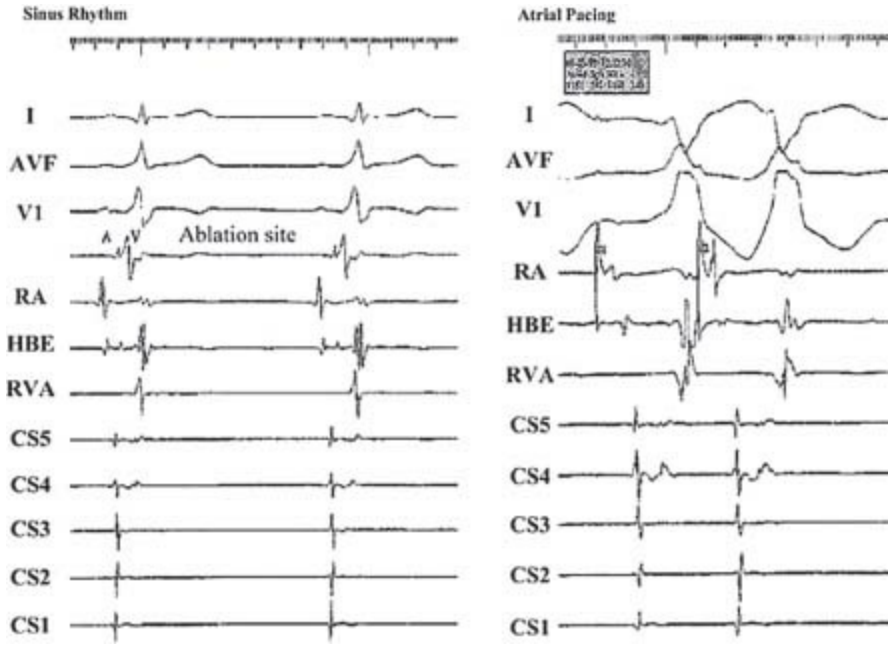


FIGURE 26.21 Left free wall accessory pathway. In sinus rhythm **(left panel),** there is fusion of ventricular activation occurring via the atrial node and accessory pathway. During atrial pacing and introduction of premature atrial extrastimuli **(right panel),** preexcitation becomes more manifest as activation via the AVN decrements and becomes later, leaving a larger component of ventricular activation to occur via the accessory pathway.

Programmed Atrial Stimulation. Delivery of single or double atrial extrastimuli may serve to study AVN physiology, determine the presence of an accessory pathway and its refractory period, and to induce SVT. Single premature beats are delivered after fixed drive cycles (e.g., typically after eight-beat 600, 500, and/or 400 milliseconds PCL atrial drive trains). Normal AVN physiology is characterized by decremental conduction: the faster the stimulation (shorter A_1A_2 coupling intervals or faster PCLs), the slower the AVN conducts and the longer the AH interval becomes (Fig. 26.22 APD_1 and APD_2). The following are typical SVT substrates that may be demonstrated:

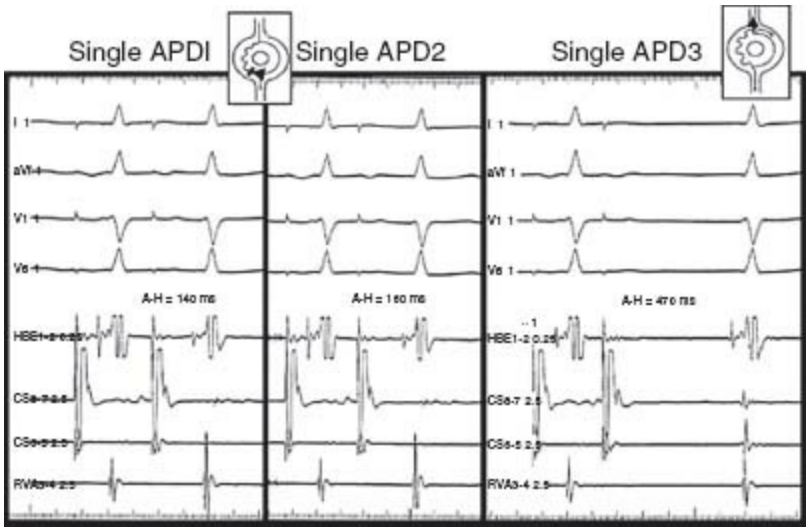


FIGURE 26.22 Single atrial extrastimuli. Dual AVN physiology and induction of single typical AVN echo beat. Single APD, and single APD_2: decremental AVN conduction with longer AH interval after shorter A,-A $_2$ coupling interval. Decremental AVN conduction is demonstrated with AH 140 and 160 milliseconds with shortening of APD coupling interval (APD, to APD_2). Single APD_3: AH jump (>50-millisecond increase in AH interval for a 10-millisecond decrease in A,-A_2 coupling interval) with single typical AV nodal echo (note atrial activation seen in the CS with a short VA interval). APD, atrial premature depolarization.

- AH (jump >50 milliseconds over a decrement of 10 milliseconds in A_1S_2) ⇒ dual AVN physiology (Fig. 26.22 APD_2 and APD_3).
- Induction of AV nodal echo beats or AVNRT by occurrence of block typically in the fast pathway and conduction delay in the slow pathway allowing recovery for retrograde fast pathway conduction and activation of retrograde atrial depolarization (Figs. 26.22 APD_3 and 26.23)
- Induction of orthodromic AVRT by causing antegrade block in the AP so it is excitable when the impulse returns to conduct retrograde to the atrium.

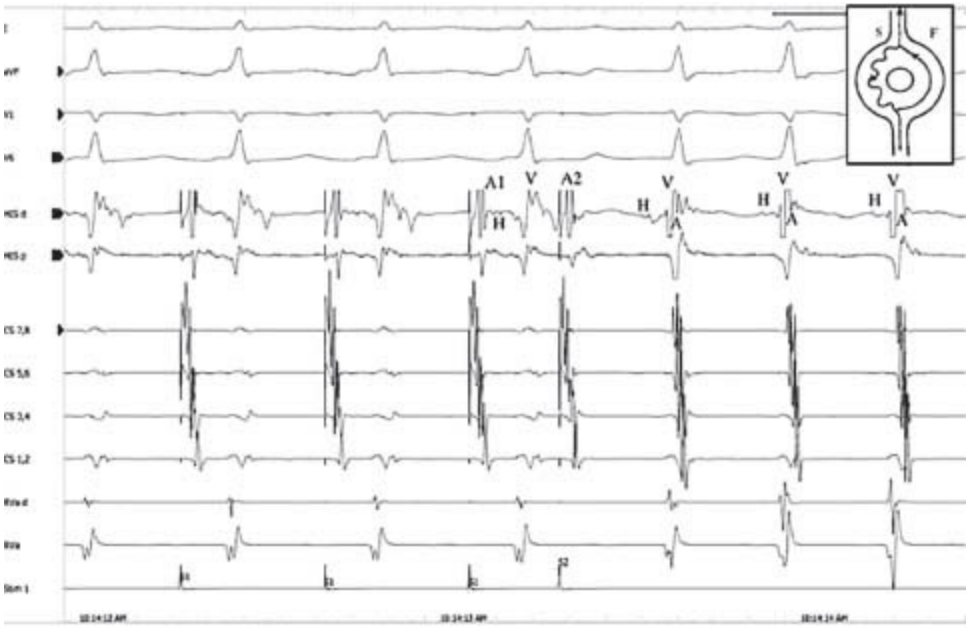


FIGURE 26.23 Initiation of AVNRT single APDs CS 400/250 AH jump, initiation of AVNRT.

Refractory Periods. As in the ventricle, refractory periods of the components of the anterograde conduction system can be determined and are defined as follows:

Atrial Effective Refractory Period = longest atrial coupling interval (A_1A_2) that fails to capture the atrium, measured from pacing stimulus to pacing stimulus.

Atrial Functional Refractory Period (AFRP) = shortest atrial coupling interval during premature atrial stimulation (A_1A_2), measured from EGM to EGM.

Fast AVN Pathway ERP = longest atrial coupling interval that produces an AH jump to conduction via the slow pathway, measured from EGM to EGM during atrial extrastimulus testing.

Slow AVN Pathway ERP = longest atrial coupling interval that produces a block in slow pathway conduction (if only two pathways are present and the fast pathway has already blocked, slow AVN pathway ERP = AVN ERP), measured from EGM to EGM during atrial extrastimulus testing.

Accessory Pathway Anterograde ERP = longest atrial coupling interval that produces a block in accessory pathway conduction, measured from EGM to EGM during atrial extrastimulus testing.

Accessory Pathway Retrograde ERP = longest ventricular coupling interval that produces a block in retrograde accessory pathway conduction, measured from EGM to EGM during ventricular extrastimulus testing.

Minimum Preexcited R-R during Atrial Fibrillation.Short R-R intervals suggest a short AP ERP and potential increased risk.

Activation Patterns. As discussed above, the pattern of atrial and ventricular activation is examined. The anterograde ventricular activation sequence is the sequence of ventricular activation during sinus rhythm, atrial pacing, atrial extrastimuli, or SVT.

Eccentric activation of the CS suggests a left-sided accessory pathway (Fig. 26.18 left panel). The atrial activation sequence is the sequence of atrial activation during ventricular pacing, ventricular extrastimuli, or SVT. Eccentric retrograde activation of the CS suggests a left-sided accessory pathway (Figs. 26.18 right panel and 26.24).

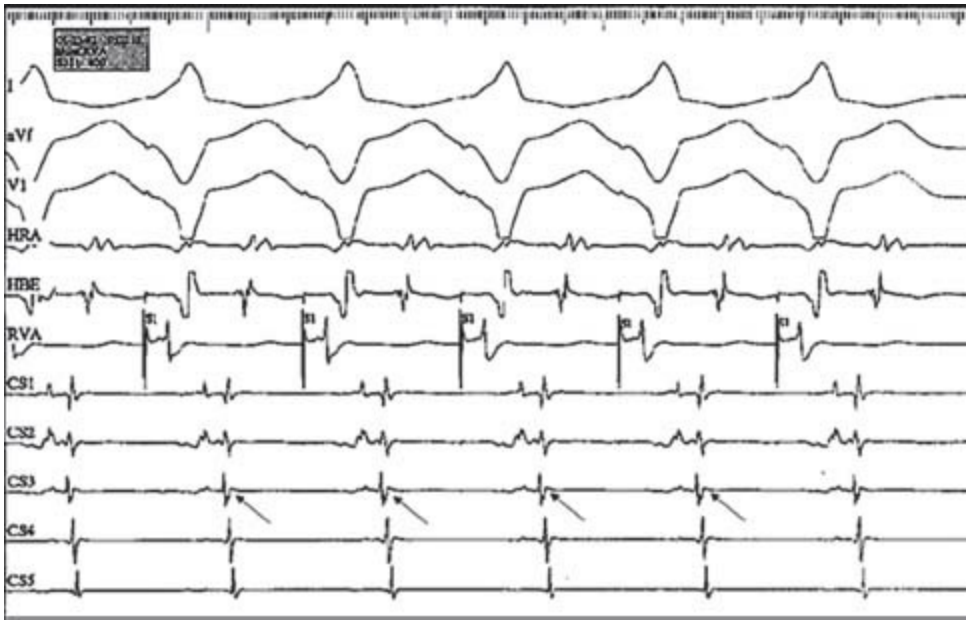


FIGURE 26.24 Left-sided accessory pathway. Retrograde atrial activation during ventricular pacing—earliest retrograde atrial activation at CS 3 (arrows).

Inducible Supraventricular Tachyarrhythmias. Types of SVTs that may be induced include the following:

AV node reentrant tachycardia—AVNRT is usually associated with dual AV nodal pathway physiology (discontinuous AVN conduction curves; an AH "jump") (Figs. 26.15 and 26.22). In typical AVNRT, antegrade conduction occurs via the slow AVN pathway (long AH) and retrograde conduction via the fast AVN pathway with near simultaneous atrial and ventricular activation (Figs. 26.22 and 26.23). In atypical AVNRT, antegrade conduction occurs via the fast AVN pathway (with a short PR) and retrograde conduction via the slow AVN pathway (long R-P interval).

Atrioventricular reentrant tachycardia—AVRT refers to accessory pathway-mediated reentrant tachycardia. In AVRT, there is 1:1 AV association, as the atria and the ventricles are integral components of the reentrant circuit. In orthodromic AVRT, antegrade conduction occurs via the AVN (with a narrow QRS in the absence of bundle branch block/aberration) and retrograde conduction occurs via the accessory pathway (Figs. 26.25 and 26.26). In antidromic AVRT, antegrade conduction occurs via the accessory pathway (with wide QRS) and retrograde conduction via the AVN or another accessory pathway.

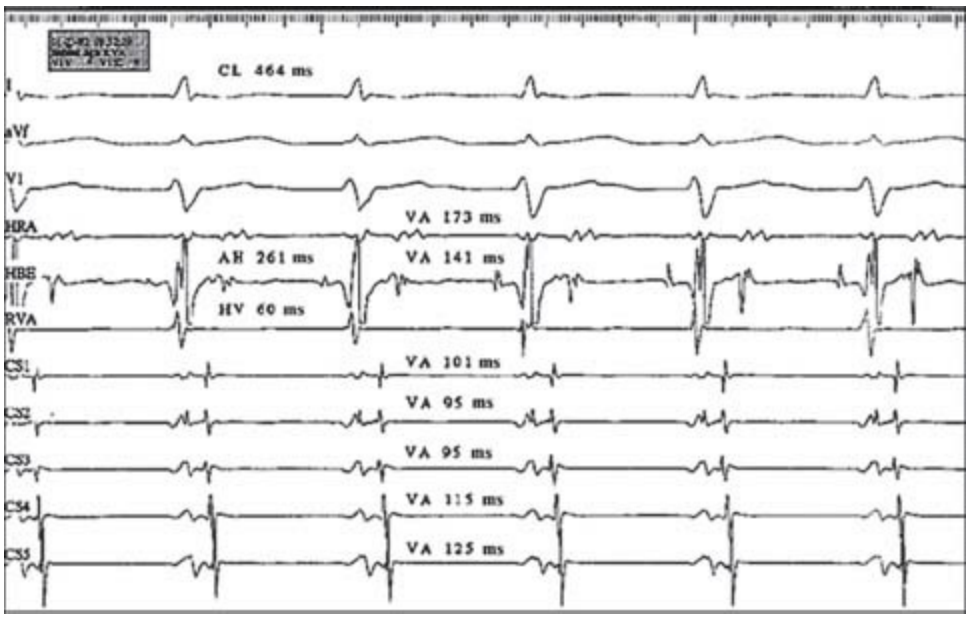


FIGURE 26.25 Left-sided accessory pathway mediating orthodromic AVRT—earliest retrograde atrial activation occurs via an accessory pathway at CS 2-3 (VA interval 95 milliseconds).

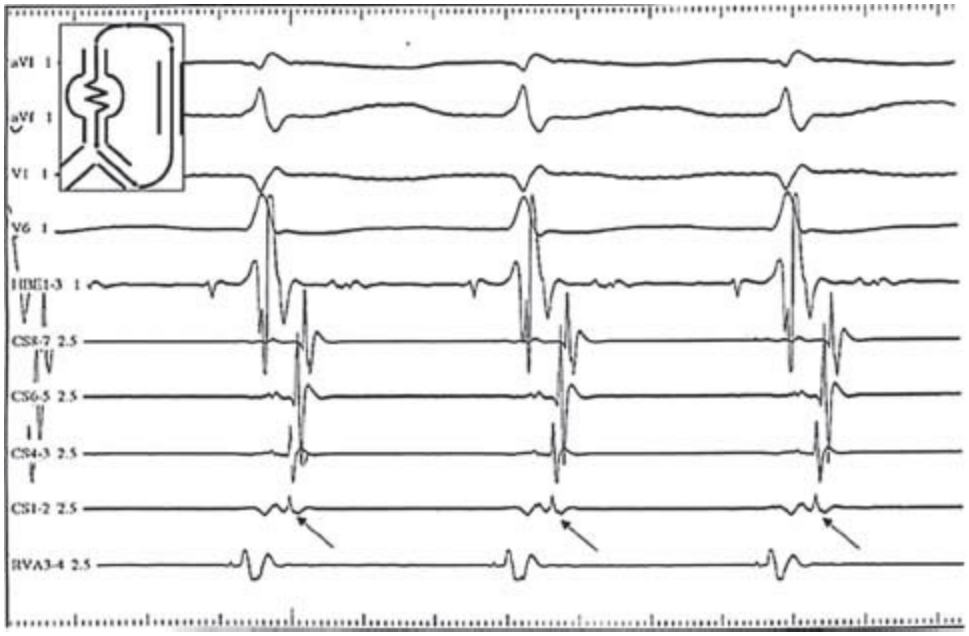


FIGURE 26.26 Left free wall accessory pathway mediating orthodromic AVRT—earliest atrial activation occurs in the distal CS at CS 1-2 (arrows).

Atrial flutter—In type I (typical) atrial flutter, right atrial activation proceeds in a counterclockwise activation pattern through the posterior isthmus between the inferior vena cava and tricuspid annulus. There may also be clockwise activation utilizing the isthmus. Type II (atypical) atrial flutter refers to atrial flutter using non–isthmus-dependent flutter circuits.

Atrial tachycardia—Atrial tachycardias may be macroreentrant in mechanism, including most incisional or scar-related atrial tachycardias, or due to ectopic (to the sinus node) foci and/or automatic mechanisms.

Atrial fibrillation—This most common sustained clinical arrhythmia typically initiates from pulmonary vein ostial or other focal triggering sites or microreentrant circuits. It may sustain with multiple wandering reentrant circuits.
Sinus node reentrant tachycardia—This tachycardia is characterized by a similar P wave morphology to sinus rhythm and may be induced and terminated with premature extrastmuli.
Inappropriate sinus tachycardia—Inappropriate sinus tachycardia (IST) is characterized by an inappropriately high resting sinus rate and enhanced sensitivity to adrenergic stimulation.
Evaluation during tachycardia. Once a tachycardia is induced, various observations and maneuvers can be performed to help determine the SVT mechanism. These include:

- Morphology: Narrow complex, RBBB or LBBB aberrant conduction, or preexcited
- Atrial activation sequence
- Ventricular activation sequence
- HA or VA interval—short HA interval (<100 milliseconds) suggests AVNRT, longer HA intervals (>100 milliseconds) suggests orthodromic AVRT mediated by an accessory pathway.
- Single ventricular premature extrastimuli during SVT (Fig. 26.27)—If single ventricular premature extrastimuli delivered during His refractoriness advances retrograde atrial activation, then a retrogradely conducting or concealed accessory pathway is present. However, this only demonstrates the presence of an accessory pathway. It does not prove that the pathway is an integral part of the circuit, as it could be a bystander pathway.
- Bundle branch block aberration in SVT (Figs. 26.28 to 26.30)—VA interval prolongation during aberration in SVT indicates a retrogradely conducting accessory pathway ipsilateral to the bundle branch block. On a surface ECG recording, this may be manifest by a longer cycle length (slower rate) during the wide complex tachycardia/aberration than during narrow complex conduction (Fig. 26.28). The prolongation of the cycle length occurs due to a prolongation of VA conduction times. Bundle branch block aberration ipsilateral to the accessory pathway results in longer retrograde (VA) activation times due to additional time required for transseptal myocardial conduction (Figs. 26.28 to 26.30). Demonstration of such a change in VA time with aberration demonstrates the presence of the accessory pathway ipsilateral to the bundle branch blocked and also indicates that the accessory pathway is a component of the reentrant circuit.

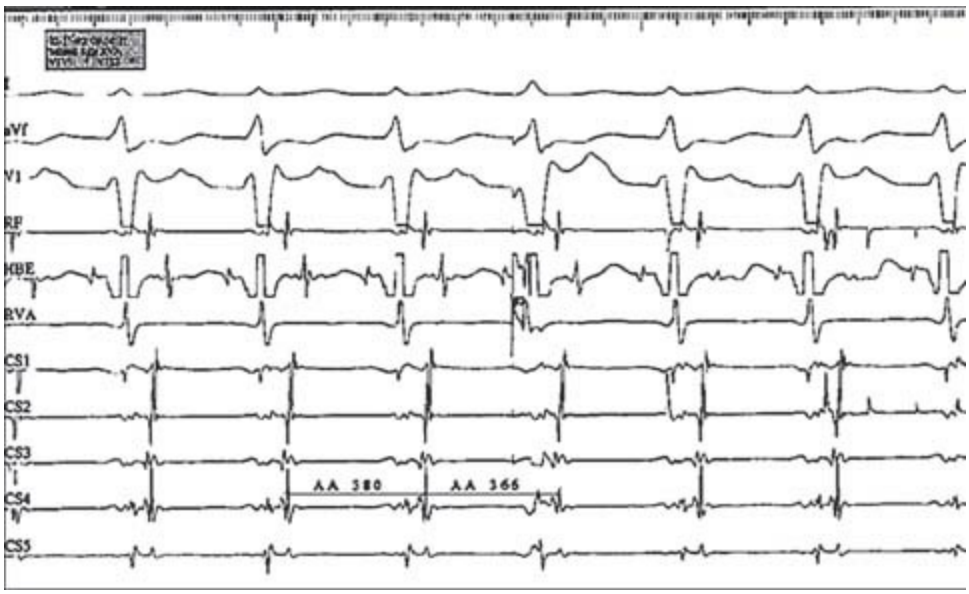


FIGURE 26.27 Orthodromic AVRT with single VPD introduced during His refractoriness. The single ventricular extrastimulus delivered during His bundle refractoriness advances retrograde atrial activation, suggesting the presence of a ret-rogradely conducting accessory pathway, in this case located in the right posteroseptal region.

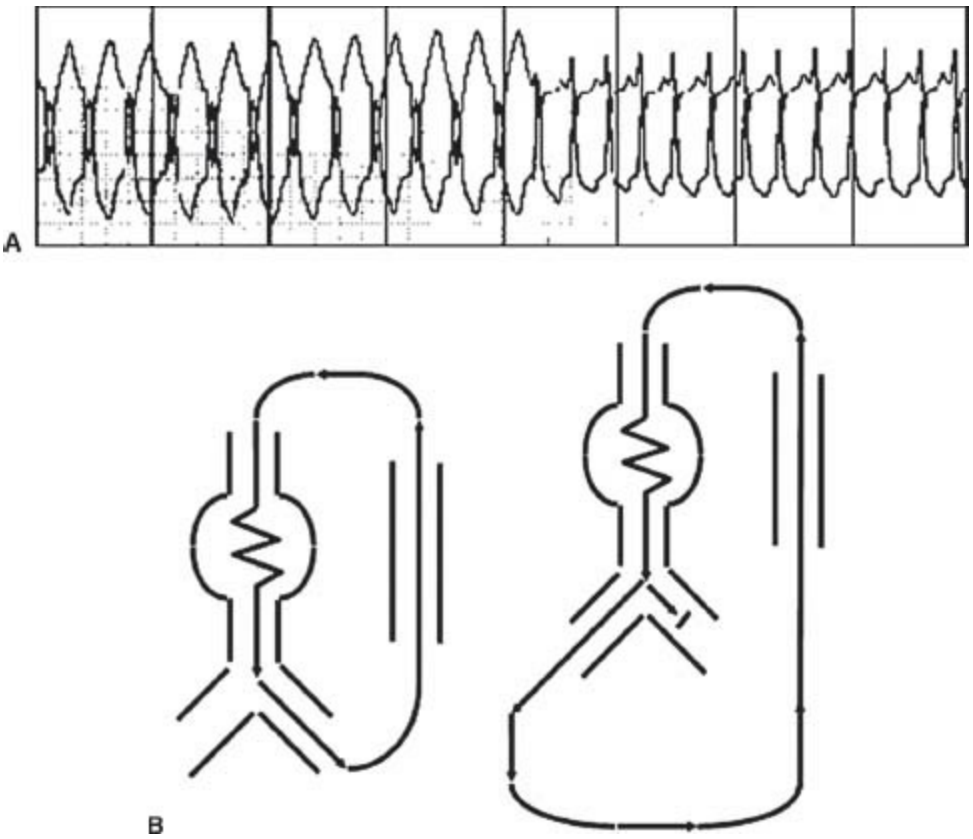


FIGURE 26.28 A: Conversion of wide complex to narrow complex tachycardia with longer RR interval during wide complex tachycardia. This is diagnostic for AVRT with an accessory pathway ipsilateral to the bundle branch block. **B:** Orthodromic AVRT with ipsilateral BBB. BBB aberration ipsilateral to the accessory pathway results in longer retrograde (VA) activation times as a result of additional time required for transseptal myocardial conduction.

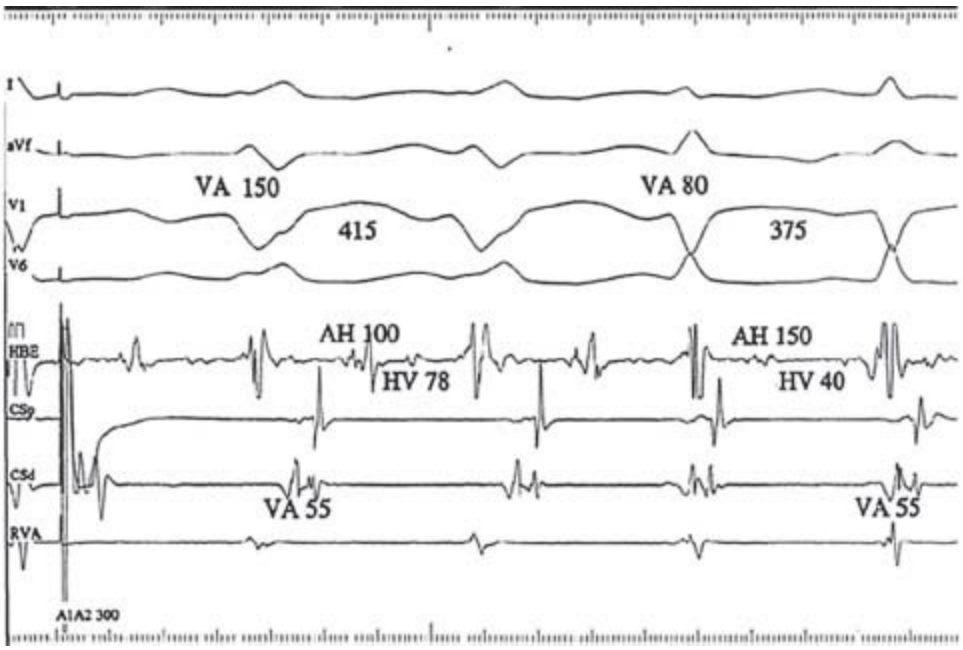


FIGURE 26.29 Initiation of orthodromic AVRT with initial LBBB aberration. Retrograde VA activation times are longer during LBBB aberration, indicating participation of a left-sided accessory pathway. Local VA time measured nearest the accessory pathway (CS distal 55 milliseconds) is similar, but earliest ventricular to atrial activation is longer with LBBB aberration.

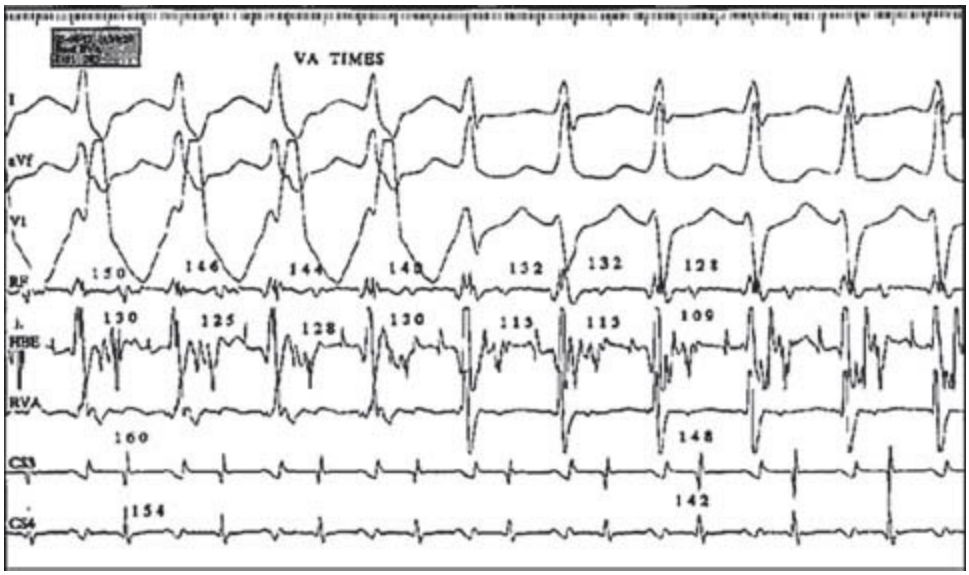


FIGURE 26.30 RBBB aberration during AVRT utilizing a right posteroseptal accessory pathway. Retrograde VA activation times are longer during RBBB aberration, confirming the presence of a right-sided accessory pathway.

Mapping During Ablation

A diagnostic EP study is critical to confirmation and definition of arrhythmia substrate prior to ablation of most SVTs and VTs. Currently, various mapping techniques based on determination of earliest activation sites include the utilization of electrophysiologic recordings and various electroanatomic, contact catheter and noncontact mapping systems that can graphically tag and record activation times in three-dimensional space

with computer generation of a display of activation or voltage maps. Although ablation of some arrhythmias is based on anatomic locations (e.g., slow pathway region for AVNRT or pulmonary vein antral isolation for atrial fibrillation ablation), successful ablation of other tachycardias often requires determination of the earliest site of activation, which helps to determine the location of the targeted arrhythmia substrate. An example is shown Figure 26.31, which demonstrates the fusion of atrial and ventricular EGMs on the ablation catheter at the site of an accessory pathway. Ablation here using radiofrequency energy resulted in prompt ablation of the pathway, loss of ventricular preexcitation, and restoration of normal AV conduction.

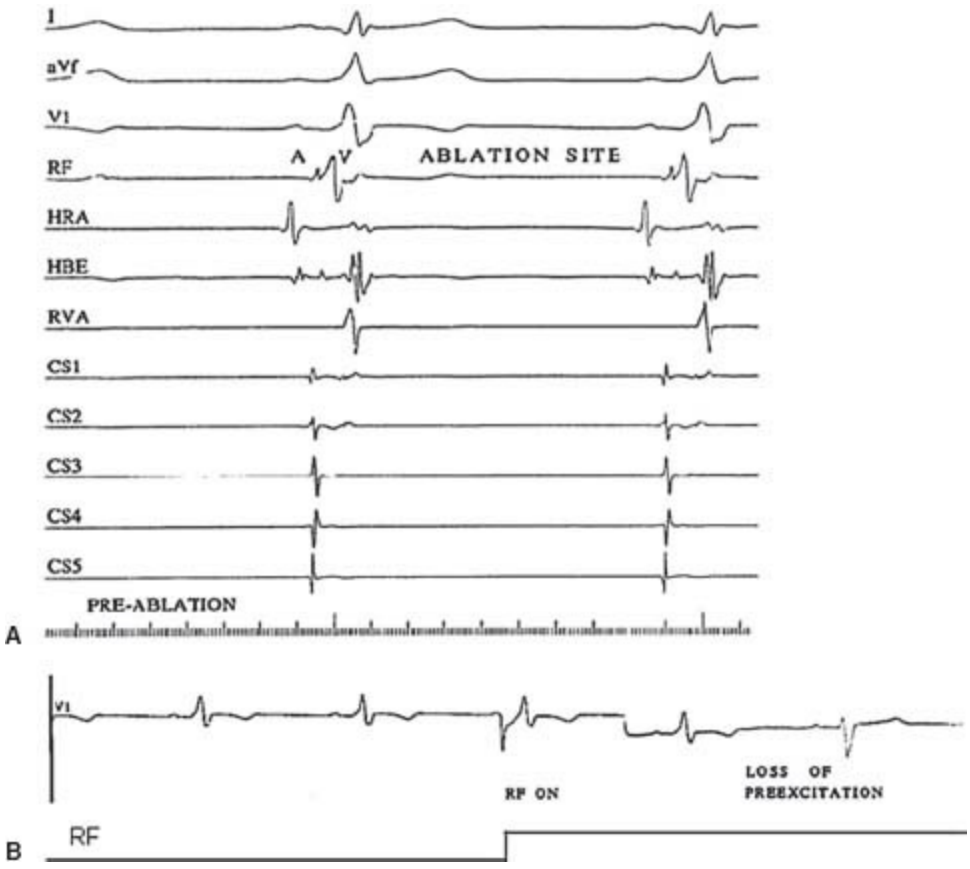


FIGURE 26.31 Left-sided accessory pathway. **A:** Successful ablation site. **B:** Radiofrequency ablation.

SUMMARY

This chapter aims to summarize the components of a comprehensive diagnostic EP study. For users of this book aiming for cardiovascular board exam review, I would suggest focusing upon:

- Recognition of the His bundle EGM and determination of the sites of AV block (AV nodal vs. infra-Hisian block);
- Recognition of VA dissociation during wide complex tachycardia using intracardiac EGMs, indicating the rhythm is most likely VT;

- Recognition of the initiation of AVNRT with demonstration of an “AH jump” and induction of an SVT with near simultaneous atrial and ventricular activation;
- Recognition of a left free wall accessory pathway with abnormal, eccentric early activation via a more distal CS location (e.g., rather than the normal earliest activation at the septum and later activation in the lateral CS/left atrial or ventricular free wall);
- Recognition that bundle branch block that manifests during SVT with a longer cycle length or longer VA time indicates the presence of an accessory pathway ipsilateral to the bundle branch block.

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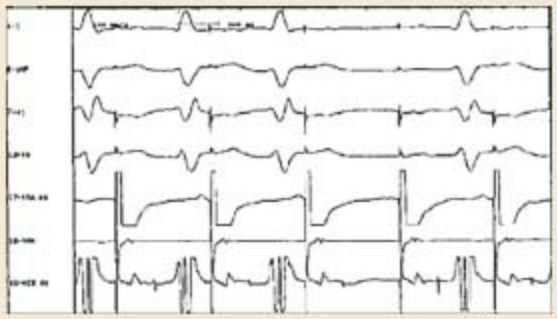
QUESTIONS AND ANSWERS

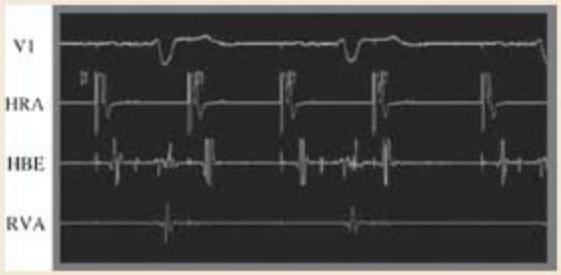
Questions

1. Where is the site of block?



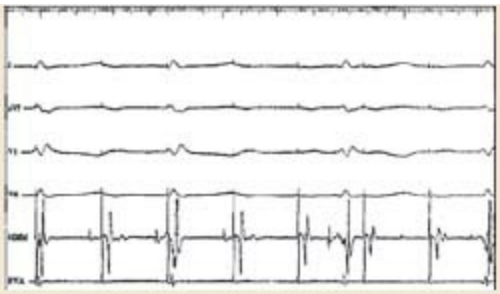
   a. AVN node (AVN)
   b. Infra-His
   c. Intra-His
   d. AVN and Infra-His

2. Where is the site of block?



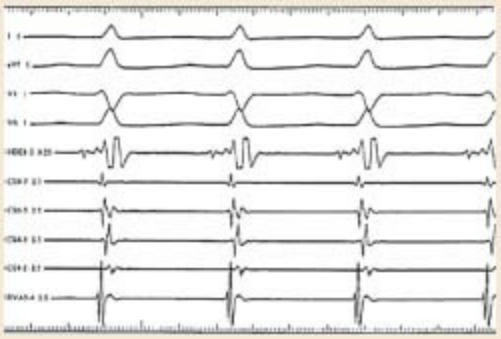
   a. AV node (AVN)
   b. Infra-His
   c. Intra-His
   d. AVN and Infra-His

3. Where is the site of block?



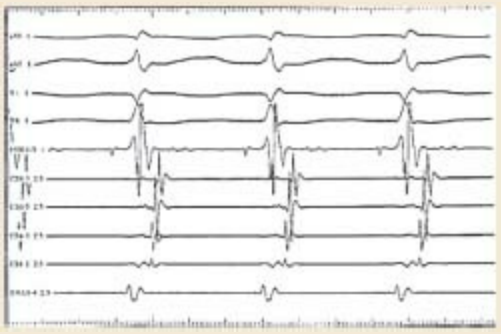
a. AVN
b. Infra-His
c. Intra-His
d. AVN and Infra-His

4. What is the diagnosis?



a. Orthodromic AVRT
b. Left-sided accessory pathway
c. Atrial tachycardia
d. AVN reentrant tachycardia

5. What is the diagnosis?



a. Left-sided accessory pathway
b. Right-sided accessory pathway
c. AVN reentrant tachycardia
d. Sinus tachycardia

Answers

1. Answer B: The tracing shows atrial pacing with right bundle branch block (RBBB) and second-degree AV block without prolongation of the PR or AH intervals prior to the blocked beat (third paced beat). On this third paced beat, the His electrode shows an atrial EGM followed by a His deflection, but no following ventricular EGM or QRS. Thus, the block occurs below the bundle of His (infra-Hisian block).

2. Answer A: The tracing shows atrial pacing (S, drive) with 2:1 AV block. Inspection of the His bundle EGM tracings demonstrate S, atrial pacing stimuli followed by atrial EGMs. After the first paced beat, there is a His bundle EGM followed by a ventricular EGM and QRS on the surface electrocardiogram (ECG). After the second paced beat, no His bundle EGM follows the atrial EGM. The next paced beats repeat this pattern. The block is at the level of the AVN, because conduction is blocked prior to arrival to the His bundle.

3. Answer D: This tracing shows second-degree AV block during atrial pacing. The His bundle EGM demonstrates the atrial pacing stimuli followed by atrial EGMs. After the first atrial paced beat, there is a long AH interval followed by a His EGM, but no ventricular EGM or QRS. This beat blocks below the His bundle. After the second paced beat there is a slightly longer AH interval followed by a ventricular EGM on the RVA tracing and a corresponding surface QRS. After the third paced beat, the AH is longer still, but there is no conduction after the His EGM to the ventricles. This beat again shows infra-Hisian block. After the fourth paced beat, there is no His electrogram. This beat blocks in the AVN and the series shows AVN Wenckebach occurring (gradually prolonging AH interval followed by block in the AVN). The fifth paced beat shows conduction after the block with a shorter AH interval followed by conduction to the ventricles. The sixth paced beat shows a small His deflection with slightly longer AH, but infra-Hisian block (no ventricular activation). The seventh paced beat shows a slightly longer AH interval with conduction to the ventricles. Thus, the tracing demonstrates two levels of block—in the AVN (Mobitz I Wenckebach pattern) and infra-Hisian block.

4. Answer D: The tracing shows a narrow QRS complex tachycardia with a cycle length of 350 milliseconds. The coronary sinus (CS) atrial EGMs show a concentric atrial activation pattern (earliest at CS 7 to 8 at the septum and later at more distal CS electrodes) with near simultaneous activation of the atrium and ventricle. The earliest atrial activation is likely the small deflection at the onset of the QRS on the HBE tracing, which actually slightly precedes the ventricular activation. This pattern is consistent with AVN reentrant tachycardia.

5. Answer A: This tracing shows a narrow complex tachycardia with cycle length of 370 milliseconds. The anterograde activation occurs via the AVN and HPS (AH seen in HBE 1 to 3 with narrow QRS). The earliest atrial activation occurs in the distal CS at CS 1 to 2. This eccentric activation pattern indicates retrograde activation via a left lateral accessory pathway. The tachycardia is consistent with orthodromic AVRT using a retrogradely conducting left-sided accessory pathway.

CHAPTER

Sudden Cardiac Death and Ventricular Tachycardia

Daniel J. Cantillon and Oussama Wazni

DEFINITION OF SUDDEN CARDIAC DEATH

Sudden cardiac death (SCD) is defined by 2006 American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines as the abrupt cessation of cardiac activity so that the victim becomes unresponsive, without normal breathing or circulation, which progresses to death in the absence of any corrective measures. The definition excludes noncardiac conditions such as pulmonary embolus, intracranial hemorrhage, or airway obstruction. However, it does not exclude nonarrhythmic deaths, as the terminal rhythm is often unknown.

EPIDEMIOLOGY OF SUDDEN CARDIAC DEATH

The incidence of SCD is estimated to be 300,000 to 400,000 per year in the United States. The mortality rate is high, with only 2% to 15% of patients reaching the hospital alive. Fifty percent of these hospitalized patients die before discharge. There is a high recurrence rate of 35% to 50%. More than 75% to 85% of SCDs are associated with ventricular arrhythmias. The most common arrhythmias are ventricular tachycardia (VT) (62%), torsades de pointes (TdP) (13%), primary ventricular fibrillation (VF) (8%), followed by bradycardia (7%). SCD is the first presentation of cardiac disease in 25% of patients. The incidence increases with age at an absolute incidence of 0.1% to 0.2% per year. Men are more commonly affected (3:1). SCD in patients < 35 years of age is most commonly associated with hypertrophic cardiomyopathy (HCM). In patients >35 years old, SCD is most commonly associated with coronary artery disease. Determinants of survival are rapid external defibrillation and bystander cardiopulmonary resuscitation. Hospital-based cooling protocols are being increasingly adopted to improve the neurologic prognosis for sudden death survivors.

RISK FACTORS AND PATHOPHYSIOLOGY

Risk factors include the following:

- Prior cardiac arrest: high recurrence rate, up to 35% to 50% at 2 years
- Syncope in the presence of coexisting cardiac diseases
- Reduced left ventricular (LV) function and congestive heart failure (CHF)
- Ventricular premature contractions and nonsustained ventricular tachycardia (NSVT) post-myocardial infarction
- Myocardial ischemia and/or documented scar
- Conduction system disease

The pathophysiology is determined by trigger factors and an underlying substrate conducive to arrhythmia. The mechanism of SCD can be related to any of the following pathophysiologic mechanisms:

- Anatomical reentry around scarred myocardium
- Functional reentry using a diseased His–Purkinje system, or areas of nonhomogeneous (anisotropic) conduction
- Ischemia, electrolyte imbalance, ion channel abnormalities, surges in neurosympathetic tone, antiarrhythmic drugs
- Rapid and irregular ventricular activation (i.e., atrial fibrillation [AF] with rapid ventricular response in Wolff–Parkinson–White [WPW]).
- Bradycardic SCD is overall uncommon; however, it remains important in specialized situations like cardiac transplant recipients.

SUDDEN CARDIAC DEATH AND CORONARY ARTERY DISEASE

Coronary artery disease is present in 80% of those with SCD. Approximately 75% have a history of prior myocardial infarction (MI). Sudden death can be the first clinical manifestation in up to 25% of patients with coronary artery disease. Approximately 65% have three-vessel obstructive coronary disease. Risk factors include depressed LV systolic function and frequent ventricular premature depolarizations (VPDs). However, the Cardiac Arrhythmia Suppression Trial (CAST) study demonstrated that suppression of VPDs with class IC medications resulted in higher mortality. Data from large clinical trials have identified groups of patients with coronary artery disease, depressed LV systolic function, and nonsustained ventricular arrhythmias at increased risk for SCD, as discussed later in this chapter.

NONISCHEMIC CARDIOMYOPATHY

Patients with impaired LV systolic function in the absence of coronary artery disease are at increased risk for ventricular tachyarrhythmias and SCD, particularly those with symptomatic heart failure. In the heart failure population, total mortality is approximately 25% at 2.5 years, with SCD accounting for 25% to 50% of these cases. Mortality due to SCD is much higher in New York Heart Association (NYHA) classes II and III than in class IV patients, who have excess mortality due to pump failure.

Dilated Cardiomyopathy

Fifty percent of deaths in this patient subgroup are arrhythmic. Left ventricular ejection fraction (LVEF) is predictive of sudden death, due to either circulatory failure or fatal arrhythmia. Ventricular ectopy is very common and does not appear to be as predictive of SCD as it is in patients with coronary artery disease. Up to 80% of patients may have NSVT on Holter monitoring. Inducibility for ventricular tachyarrhythmias at the time of electrophysiologic (EP) study is also less predictive when compared to patients with coronary disease and has almost no role in risk stratification. While some modalities such as abnormal microvolt T-wave alternans and heart rate variability have been associated with increased risk in this population, only LVEF $\leq$35% and the presence of symptomatic heart failure are recommended by practice guidelines for the purposes of risk stratification, particularly regarding selecting candidates for implantable cardioverter-defibrillator (ICD) implantation.

Hypertrophic Cardiomyopathy

HCM is an autosomal dominant disease with incomplete penetrance associated with ever-increasingly discovered genetic mutations. The overall incidence of SCD is 2% to 4% in adults and up to 6% in children. It is the most common cause of SCD in young athletes. Maron et al. have identified factors associated with increased risk such as the presence of NSVT, hypotension with exercise, unexplained syncope, septal thickness >3 cm, and a family history of sudden death in a first-degree relative younger than 50 years old. Among patients with HCM and primary prevention ICDs, appropriate therapy was uncommon among patients with none of these risk factors and occurred in 14% of patients with one risk factor, 11% in patients with two risk factors, and 17% in patients with three or more risk factors. In addition, cardiac magnetic resonance imaging (MRI) has been increasingly utilized for risk stratification in HCM patients as the presence of basal septal scar is associated with VT as well as histopathologic changes. The role of genetic testing for risk stratification has not been established despite the identification of certain high-risk mutations, such as the LAMP2 gene.

Arrhythmogenic Right Ventricular Cardiomyopathy

Progressive fibrofatty right ventricular tissue replacement is the pathologic hallmark of this disease. There is a strongly familial pattern; its prevalence may be up to 20% worldwide for SCD in young patients (U.S. 3%). MRI is the most useful imaging modality to make the diagnosis. Characteristic epsilon waves may be present on the electrocardiogram (ECG), as shown in Figure 27.1. The frequency and the severity of ventricular arrhythmias in this disease are progressive, thus making these patients candidates for ICD implantation.

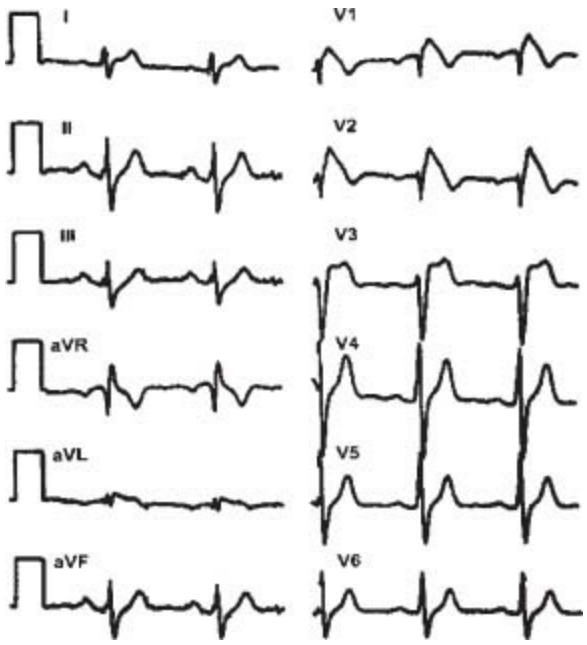


FIGURE 27.1 ECG reading in ARVD.

INHERITTED AND ACQUIRED CHANNELOPATHIES

Long-QT Syndrome

Long-QT syndrome consists of the inherited abnormalities that prolong cardiac repolarization as measured by the corrected QT (QTc) interval on surface ECG, which confer an increased risk of SCD by polymorphic ventricular tachycardia (PMVT) or TdP. There are numerous identified mutations involving mostly sodium and potassium ion channels (Table 27.1). Abnormal QTc cutoff values are commonly selected as >440 milliseconds in men and >460 milliseconds in women, although actual cardiac events occur on a skewed curve and are highest among patients with QTc > 500 milliseconds. The most common symptoms associated with long QT syndrome are palpitations and syncope, although associations also exist with seizure disorders. Characteristic clinical triggers for arrhythmia events have been described by genotype including exercise or swimming (LQT1), auditory stimuli, or during the postpartum period (LQT2) and during sleep (LQT3). Features associated with higher risk for SCD include the Jervel and Lange-Nielsen syndrome (congenital deafness), syncope or ventricular arrhythmias

while on beta-blocker therapy, QTc > 500 milliseconds with an LQT1 or LQT2 genotype, female gender, and family history of SCD. Standard treatment includes beta-blocker therapy, but this remains somewhat controversial in the case of LQT3, where the clinical response rate is lowest. According to 2008 ACC/AHA/HRS device therapy guidelines, patients with syncope or ventricular arrhythmias while on beta-blocker therapy can be considered for primary prevention ICD implantation. The 5-year sudden-death risk in patients on beta-blocker therapy (Long QT Registry) is <1% in asymptomatic patients, 3% in the syncope group, and 13% in the SCD group. Mexiletine, a sodium channel blocker, may be helpful in reducing the burden of ventricular arrhythmias among patients with LQT3, due to the attributable gain-of-function mutation in SCN5A resulting in voltage-gated sodium channels remaining open longer than normal.

TABLE
27.1 Familial Long-QT Syndromes

Syndrome	Chromosome	Channel
LQT1	11p15.5	I_{Ks} alpha (KVLQT1)
LQT2	7q35–36	I_{Kr} (HERG)
LQT3	3p21–24	I_{Na} (SCN5A)
LQT4	4q25–27	unknown
LQT5	21q22.1–22.2	I_{Ks} beta (KCNE1)
LQT6	21q22.1–22.2	I_{Kr} (KCNE2)
LQT7	17q23	$K_{Ir2.1}$ (KCNJ2)

A prolonged QT interval can also be acquired and secondary to other causes:

- Electrolyte derangements
  - Acute hypokalemia
  - Chronic hypocalcemia
  - Chronic hypokalemia
  - Chronic hypomagnesemia
- Medical conditions
  - Bradyarrhythmias (complete heart block, sick sinus syndrome, bradycardia)
  - Cardiac (myocarditis, tumors)
  - Endocrine: hyperparathyroidism, hypothyroidism, pheochromocytoma
  - Neurologic (cerebrovascular accident, encephalitis, head trauma, subarachnoid hemorrhage)
  - Nutritional (alcoholism, anorexia nervosa, liquid-protein diet, starvation)
- Drugs

- Antiarrhythmics: class IA (disopyramide, procainamide), class III (sotalol, dofetilide)
- Tricyclic antidepressants (amitriptyline, desipramine)
- Antifungals (itraconazole, ketoconazole)
- Antihistamines (astemizole, terfenadine)
- Antimicrobials (Bactrim, E-mycin, pentamidine)
- Neuroleptics (phenothiazines, thioridazine)
- Organophosphate insecticides
- Promotility agents (cisapride)
- Oral hypoglycemics (Glibenclamide)

Brugada Syndrome

The hallmark of this condition is ST-segment elevation in the right precordial leads (Fig. 27.2) attributable to sodium channel defects, including the SCN5A mutation. However, specific genetic mutations are identified in less than half of tested patients. Brugada syndrome is most common in Southeast Asia, affecting mostly men (4:1). The usual mode of inheritance is autosomal dominant. The ST segment may normalize and may be unmasked by drugs (procainamide, flecainide, ajmaline), which may uncover the characteristic ST elevation. Patients with Brugada syndrome are at increased risk of SCD, particularly those with prior torsades/PMVT and unexplained syncope. The role of EP testing in risk stratification remains controversial, although there are some data to support its use in identifying patients more likely to benefit from an ICD. Quinidine, due to blockade of I_{to}, may have a role in decreasing the burden of ventricular arrhythmias.

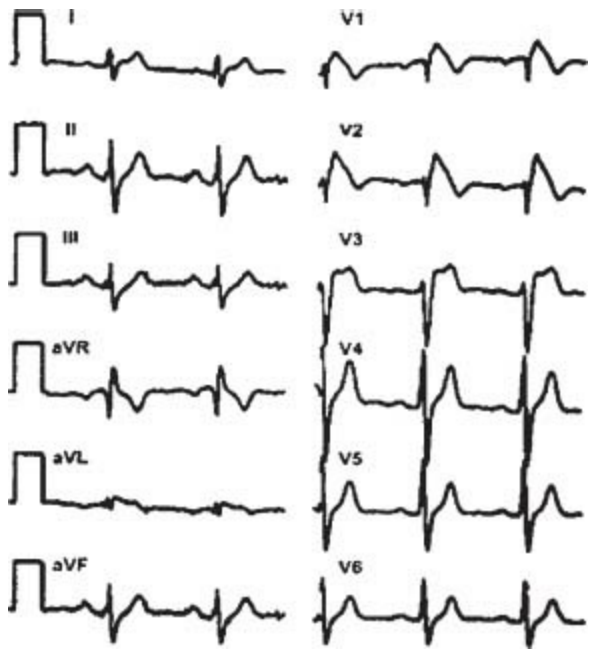


FIGURE 27.2 ECG reading in Brugada syndrome.

Short-QT Syndrome

The short-QT syndrome is characterized by QTc intervals <300 milliseconds and associated with SCD by VT and VF. Gain-of-function mutations in the gene for outward potassium currents have been shown to be responsible for this congenital syndrome. HERG (or KCNH2) and KCQN1 gene mutations have been identified in some families. Management consists of implantation of an ICD and possibly quinidine, which can prolong the QT interval and prevent VT.

Idiopathic Ventricular Fibrillation

Primary (idiopathic) VF, by definition, occurs in the absence of the recognized channelopathies and structural heart disease. For decades, this condition has remained poorly understood until work by Haïssaguerre et al. described a high prevalence of an early repolarization pattern detected on the surface ECG among patients with idiopathic VF when compared to a control group (31% vs. 5%). Early repolarization was defined as elevation of the QRS-ST junction (the J point) by >0.1 mV above the baseline in at least two leads, or notching of the terminal QRS in the inferior limb leads, lateral limb leads, or lateral precordial leads. Subsequent experimental data have linked defective modulation of cardiac repolarization to increased risk for ventricular arrhythmias in such patients. These data challenge the long-held notion that early repolarization, commonly present among African American males and athletes, is always a benign finding.

OTHER CARDIAC CONDITIONS ASSOCIATED WITH SUDDEN DEATH

Wolff–Parkinson–White Syndrome

WPW syndrome is caused by accessory atrioventricular connections. There is a 0.1% incidence of SCD per year, with risk related to the conduction properties of the bypass tract. SCD is related to AF conducting rapidly antegrade over the bypass tract into the ventricles, which can then degenerate into VF. The risk is elevated when the shortest R-R interval in AF is <250 milliseconds (240 beats/min), which indicates a pathway capable of rapid antegrade conduction. WPW is now curable with catheter ablation in >95% cases. Asymptomatic patients with WPW in low-risk occupations or with loss of pre-excitation during exercise testing do not require ablation.

Valvular Heart Disease

Any primary valvular pathology associated with depressed LV systolic function confers increased risk for ventricular arrhythmias. Specific valvulopathies such as aortic stenosis, when severe or critical, confer increased risk even when LV systolic function

is preserved. Mitral valve prolapse, in rare cases, has been associated with ventricular arrhythmias and SCD also in the setting of preserved LV systolic function. However, literature in this field is limited to case reports and small series data. It remains unclear to what extent valvular correction modifies this risk, and the 2006 ACC/AHA/HRS sudden death guidelines defer treatment recommendations according to the established criteria for mitral valve correction.

Other SCD causes without primary arrhythmia etiology:

- Acute aortic dissection, particularly with retrograde extension causing hemopericardium
- Mechanical complications following MI such as rupture, tamponade
- Congenital heart disease, including coronary anomalies (between aorta and pulmonary artery)
- Cyanotic heart disease, right-to-left intracardiac shunts
- Commotio cordis (VF associated with chest trauma)
- Acute myocarditis
- Infiltrative cardiomyopathies such as cardiac amyloid or sarcoid
- Chagas disease: multifocal myocarditis, CHF
- Muscular dystrophies: myocardial scarring, conduction system disease

EVALUATION AND MANAGEMENT

Sudden Cardiac Death Survivors

A complete history and physical examination focusing on risk factors, medications, illicit substances, and family history should be obtained. Laboratory evaluation should identify any related electrolyte abnormalities, particularly among patients with renal dysfunction. A complete cardiac evaluation includes a 12-lead ECG, ambulatory Holter or inpatient telemetry monitoring, a surface echocardiogram, an ischemia workup (stress testing or coronary angiography), and possibly MRI in selected scenarios such as to evaluate the possibility of arrhythmogenic right ventricular dysplasia (ARVD) or infiltrative cardiomyopathies. Other imaging modalities, such as cardiac positron emission tomography (PET) scans, are selectively utilized to identify proinflammatory conditions such as cardiac sarcoid. In general, ACC/AHA/HRS practice guidelines recommend identification and treatment of reversible causes among sudden death survivors. Among SCD survivors, diagnostic EP studies have limited prognostic value and are not routinely performed except in selected cases such as investigating the etiology of an unknown widecomplex tachycardia. In the majority of SCD survivors, an ICD is indicated in the absence of a transient arrhythmia due to identifiable, reversible causes (i.e., VF within 24 to 48 hours of acute ST-segment elevation MI). In the AVID

trial, SCD survivors who received an ICD demonstrated an improved 3-year survival rate of 75.4% when compared to 64.1% with antiarrhythmic drug therapy.

VENTRICULAR TACHYCARDIA

Coronary Artery Disease

Sustained monomorphic VT is most commonly related to scar created by prior MI that can be initiated by spontaneous ventricular ectopy. An acute ischemic event, in contrast, is more commonly associated with PMVT or VF such as in acute ST-segment elevation MI. This distinction becomes blurred when transient ischemia causes an increase in spontaneous ventricular ectopy capable of initiating monomorphic VT in a patient with underlying scar, or PMVT/VF when critically timed VPDs occur during cardiac repolarization.

For secondary prevention, ICD therapy is recommended for hemodynamically intolerant sustained ventricular tachyarrhythmias >30 seconds in duration or requiring abortive therapy (i.e., shocks). This includes patients with acute MI with events occurring beyond 48 hours and not related to immediately reversible causes (i.e., overinjection of contrast dye during angiography of the right coronary artery). For primary prevention, ICD therapy is recommended in patients beyond 40 days post-MI with LVEF $\leq$ 35% on optimal medical therapy and with life expectancy >1 year. Key trials in formulating these primary prevention indications include the MADIT-2 trial (ICD benefit for patients post-MI with LVEF < 30% and NYHA class I symptoms) and SCD-HeFT (ICD benefit for LVEF $\leq$35% and NYHA class II symptoms). In addition, patients may be considered for a primary prevention ICD with prior MI, LVEF <40%, NSVT detected by ambulatory Holter or telemetry and inducible VT with programmed stimulation at the time of EP study, largely on the basis of the MADIT-1 trial (LVEF $\leq$ 35% with NSVT) and MUSST registry (LVEF $\leq$ 40% with NSVT).

Current ICD therapy can terminate up to 80% of all spontaneous VT with antitachycardia pacing (ATP). However, up to one-third of patients will still require antiarrhythmic medications to suppress VT and to minimize shocks and ATP. Catheter ablation of reentrant circuits is indicated for patients with VT that is refractory to medications and requiring multiple ICD shocks.

Dilated Cardiomyopathy

More than a quarter of patients with dilated cardiomyopathy (DCM) have NSVT on Holter monitoring during a 24-hour period. ICD implantation is recommended for secondary prevention in patients with DCM and prior sustained VT/VF, and also as primary prevention for patients with LVEF $\leq$ 35% with NYHA class II symptoms based on the SCD-HeFT trial. The 2008 device therapy guidelines also allow a primary prevention ICD to be offered to patients with DCM, LVEF $\geq$ 35%, and NYHA class I

symptoms, although this is based on weaker evidence. In addition to scar-related VT, patients with DCM are particularly susceptible to bundle-branch reentry VT. This is a VT most commonly occurring with left bundle branch bundle (LBBB) morphology. Electrophysiologic testing reveals abnormal conduction in the His–Purkinje system as measured by a prolonged HV interval in sinus rhythm. Most frequently, the right bundle is used as the antegrade limb and the left bundle as the retrograde limb of the tachycardia, and the right bundle is typically targeted for catheter ablation.

Ventricular Tachycardia and the Structurally Normal Heart

Outflow-Tract Ventricular Tachycardia

VT occurring in patients without structural heart disease most commonly originates from discrete foci in the right and the left ventricular outflow tracts (LVOTs). The right ventricular outflow tract (RVOT) is more common than the LVOT by a ratio of 9:1. However, data by Iwai et al. suggest these tachycardias share identical electrophysiologic mechanisms and clinical behavior due to embryologic origin in the maturation of the outflow tract. Outflow-tract tachycardias can occur as sustained monomorphic VT, frequent salvos of NSVT, or frequent symptomatic VPDs. Reported mechanisms include triggered activity due to delayed-after-depolarization (during phase 4). This mechanism is unique when compared with VT caused by reentry or enhanced automaticity. Unlike catecholaminergic polymorphic ventricular tachycardia (CPMVT), outflow-tract VTs are always monomorphic and most commonly elicited by either the warm-up or the cooldown phases of exercise that can be mimicked in the EP lab during the "wash-out" phase of an isoproterenol infusion.

The classic ECG pattern for RVOT VT is a LBBB with precordial R-wave transition in V_2–V_3, and an inferior limb lead axis, with tall R waves in II, III, and aVF. LVOT VT can occur either with a RBBB morphology, inferior axis, or a LBBB morphology, inferior axis with earlier precordial R-wave transition by V_2 (Fig. 27.3). In the EP lab, outflow-tract tachycardia may be induced with programmed stimulation and has a characteristic pharmacologic response of adenosine sensitivity in most cases. Mapping and ablation of the site of earliest origin is highly successful. Left-sided foci are also commonly ablated from left and right coronary cusps above the aortic valve. Outflow-tract VTs are not associated with SCD, and catheter ablation is curative. Therefore, ICD therapy is not indicated (class III recommendation by 2008 guidelines).

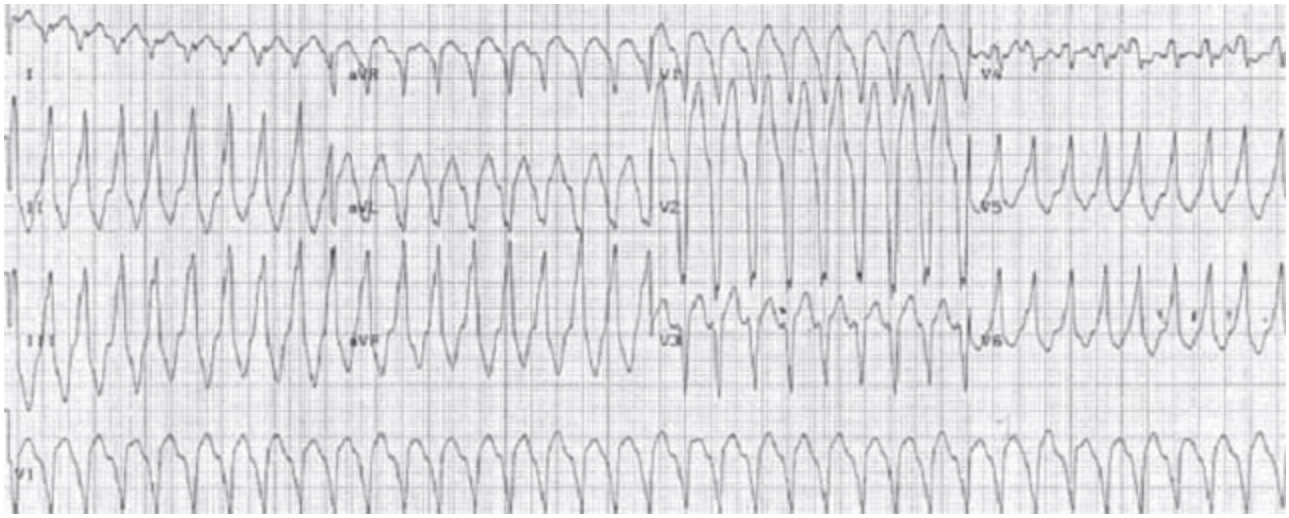


FIGURE 27.3 ECG reading in RVOT VT.

Idiopathic Left Ventricular Tachycardia

This is a paroxysmal VT that occurs predominantly in men, most commonly involving the LV anterior and posterior fascicles. It is characterized by the following triad: (a) inducibility by atrial pacing or premature complexes, (b) RBBB morphology most commonly with left anterior hemiblock pattern, and (c) absence of structural heart disease. This type of VT is highly sensitive to calcium channel blockers like verapamil. Ventricular activation at the earliest site is usually preceded by highfrequency potentials termed Purkinje potentials. Ablation at these sites is highly successful in terminating this arrhythmia. In the absence of concomitant structural heart disease, true fascicular VT is not associated with SCD and thus not recommended for ICD implantation according to the 2008 guidelines.

ACKNOWLEDGMENTS

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QUESTIONS AND ANSWERS

Questions

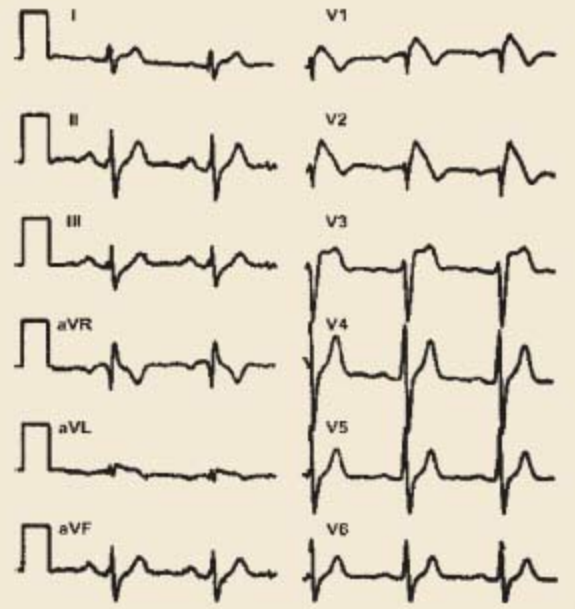
1. Clinical features associated with increased risk for sudden cardiac death (SCD) among patients with hypertrophic cardiomyopathy (HCM) include all of the following except:
   a. Septal thickness >3 cm
   b. Syncope or hypotension associated with exercise
   c. Dynamic left ventricular outflow-tract (LVOT) gradient >100 mm Hg by Doppler echocardiography
   d. Nonsustained ventricular tachycardia (NSVT)

2. A primary prevention implantable cardioverter- defibrillator (ICD) is most strongly indicated in which of following patients?
   a. Male patient with syncope, QTc 440 milliseconds, and LQT1 genotype not previously treated with beta-blockers
   b. Young patient with syncope, NSVT, and diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy (ARVC), including cardiac magnetic resonance imaging (MRI)
   c. Asymptomatic patient with newly diagnosed nonischemic dilated cardiomyopathy (DCM), left ventricular ejection fraction (LVEF) 35%
   d. Young patient without structural heart disease and monomorphic ventricular tachycardia (VT) (left bundle branch bundle [LBBB] morphology, right inferior axis, precordial R-wave transition in V_3)

3. A diagnostic EP study is least useful in which of the following clinical scenarios?
   a. Risk stratification in a patient with coronary artery disease, LVEF 38% with NSVT
   b. Risk stratification in a patient with DCM, LVEF 20%, and heart failure symptoms
   c. Risk stratification and evaluation for arrhythmia mechanism in a patient with a Brugada pattern electrocardiogram (ECG) and unexplained syncope
   d. Evaluation of arrhythmia mechanism and possible ablative therapy for a patient with symptomatic wide-complex tachycardia of unknown etiology

4. Bundle branch reentry VT is most commonly associated with:
   a. Enhanced automaticity in the right bundle
   b. Enhanced automaticity in the left bundle
   c. Supranormal conduction in the His bundle
   d. Abnormally slow conduction in the His-Purkinje system

5. The ECG shown is consistent with:



a. Acute anteroseptal MI
b. Abnormal SCN5A channel
c. Abnormal KCQN1 channel
d. Old anteroseptal MI with an aneurysm

Answers

1. Answer C: Clinical features associated with SCD among patients with HCM include NSVT, hypotension associated with exercise, unexplained syncope, septal thickness >3 cm, and a family history of sudden death in a first-degree relative younger than 50 years old. Dynamic LVOT gradients by Doppler echocardiography, even when elevated, are not a commonly applied as a guidelines-based risk stratification tool for SCD.

2. Answer B: ARVC is a progressive disease involving fibrofatty infiltration, and patients with VT are highly likely to have recurrences despite medical therapy. Among patients with symptomatic long QT syndrome, response to beta-blocker therapy is highest among patients with the LQT1 genotype. The SCD risk is very low among male patients treated with beta-blockers, LQT1 genotype, and a QT interval in this range. Among patients with DCM, the 2008 guidelines do not specify a treatment duration requirement, unlike CMS reimbursement criteria. However, ICD implantation is recommended for patients with LVEF ≤ 35% and symptomatic heart failure (class I recommendation for NYHA functional class II or greater, and class II recommendation for NYHA functional class I). In choice d, all of these features are associated with VT originating from the right ventricular outflow tract (RVOT), which is curable by catheter ablation and not associated with SCD. ICD implantation is a class III recommendation among such patients.

3.Answer B: A diagnostic EP study is least predictive for future ventricular tachyarrhythmia events among patients with nonischemic cardiomyopathy, and would not alter management in the patient described in choice b, who is recommended for a primary prevention ICD. The patient in choice a, however, meets guidelinesbased criteria for further risk stratification using EP study to evaluate candidacy for a primary prevention ICD. EP testing for risk stratification among patients with the Brugada syndrome remains controversial. However, EP testing is not completely unreasonable to evaluate a possible arrhythmia mechanism for any patient with unexplained syncope. It is certainly not the weakest indication among the choices listed. In keeping with this concept, choice d actually highlights the strength of an EP study, which is to define the precise arrhythmia mechanism in a patient with a poorly tolerated, wide complex tachycardia that cannot be definitively diagnosed by other clinical criteria (i.e., distinguishing VT from supraventricular tachycardia (SVT) with aberrant conduction or pre-excited tachycardia). This is particularly true where catheter ablation can be curative.

4. Answer D: Abnormally slow conduction in the His-Purkinje system sets up the conditions of reentry required to sustain this kind of tachycardia.

5. Answer B: The ECG is consistent with abnormal SCN5A channel, which causes the Brugada syndrome.

CHAPTER

Atrial Fibrillation and Flutter

John Rickard and Mohamed Kanj

Atrial fibrillation (AF) is the most common sustained arrhythmia seen in clinical practice. There are estimated to be more than 2 million patients with AF in the United States. The prevalence and incidence of AF increase with advancing age. The mainstay of therapy includes pharmacologic rate control and antiarrhythmic therapy, cardioversion, and antithromboembolic management. Non-pharmacologic therapies, including ablation, device, and surgical approaches, are also becoming increasingly utilized.

EPIDEMIOLOGY

Prevalence

- 0.4% general population
- 0.2% in population 25 to 34 years old
- 2% to 5% in population >60 years old
- 18% in population >85 years old
- 8% to 14% in hospitalized patients

Incidence

- The incidence of AF increases from <0.1% per year (>160,000 new US cases year) in those under 40 years of age to 1.5% per year in females and 2% per year in males over the age of 80 (Kannel et al. 1983).
- 20% to 40% after cardiac surgery

FACTORS PREDISPOSING TO ATRIAL FIBRILLATION

The most common cardiovascular (CV) diseases associated with AF are hypertension and ischemic heart disease. Other predisposing conditions include:

- Advancing age
- Rheumatic heart disease (especially mitral valve disease)
- Nonrheumatic valvular disease
- Cardiomyopathies
- Congestive heart failure (CHF)
- Congenital heart disease
- Sick sinus syndrome/degenerative conduction system disease
- Wolff–Parkinson–White syndrome
- Pericarditis
- Pulmonary embolism
- Thyrotoxicosis
- Chronic lung disease
- Neoplastic disease
- Postoperative states
- Diabetes
- Normal hearts affected by high adrenergic states, alcohol, stress, drugs (especially sympathomimetics), excessive caffeine, hypoxia, hypokalemia, hypoglycemia, or systemic infection

MORBIDITY AND MORTALITY

Survival

The presence of AF leads to a 1.5- to 2-fold increase in total and CV mortality (Emelia et al., 1998). Factors that may increase mortality include:

- Age
- Mitral stenosis
- Aortic valve disease
- Coronary artery disease (CAD)
- Hypertension
- CHF

Patients with myocardial infarction (MI) or CHF have higher mortality if AF is present.

Stroke/Thromboembolism

AF predisposes to stroke and thromboembolism.

- Five- to sixfold increased risk of stroke (17-fold with rheumatic heart disease [RHD])
- 3% to 5% per year rate of stroke in nonvalvular AF
- Single major cause (50%) of cardiogenic stroke
- 75,000 strokes per year
- Silent cerebral infarction risk
- Risk increases with age, concomitant CV disease, and stroke risk factors

Tachycardia-Induced Cardiomyopathy

Persistent rapid ventricular rates can lead to tachycardia-mediated cardiomyopathy and left ventricular (LV) systolic dysfunction. These are, however, reversible with ventricular rate control and regularization. Control can be achieved with medical rate control, atrioventricular (AV) node ablation, or achievement of sinus rhythm (SR). An atrial cardiomyopathy may develop leading to structural remodeling with an increase in atrial size.

Symptoms and Hemodynamics

- Rapid ventricular rates
- Irregularity of ventricular rhythm
- Loss of AV synchrony
- Symptoms: limitation in functional capacity, palpitations, fatigue, dyspnea, angina, CHF

PATHOGENESIS

While the pathophysiology of AF remains incompletely understood, it has been shown that AF requires a trigger and a substrate to sustain reentry. The triggering mechanism in most patients comes from ectopic firing within the pulmonary veins into which sleeves of atrial myocardium extend. Once AF has been sustained for a period of time, electrical and structural changes take place within the atria that can convert transient AF to persistent AF. Electrical changes, such as shortening of the atrial refractory period, occur shortly after AF onset and are reversible with conversion back to SR. Structural changes may take longer to develop, however, and are less amenable to reversal. In patients with CHF, the pathophysiology of AF is somewhat different. In this patient population, areas of interstitial fibrosis are found within the atria that lead to heterogeneous electrical conduction. These areas of slowed electrical conduction

predispose to the development of AF.

- Electrical activation: rapid, multiple waves of depolarization with continuously changing, wandering pathways
- Intracardiac electrograms: irregular, rapid depolarizations, often >300 to 400 beats/min (bpm)
- Mechanical effects:
  - Loss of coordinated atrial contraction
  - Irregular electrical inputs to the AV node and His–Purkinje system leading to irregular ventricular contraction
- Surface electrocardiogram:
  - No discrete P waves
  - Irregular fibrillatory waves
  - Irregularly, irregular ventricular response

Atrial Flutter Reentrant Mechanism

Cavotricuspid Isthmus-Dependent Atrial Flutter

- Cavotricuspid isthmus (CTI)-dependent flutters refers to circuits, which involve the isthmus of tissue in the right atrium between the tricuspid annulus and inferior vena cava (IVC) (Fig. 28.1).
- The circuit can propagate around the isthmus in a clockwise or counterclockwise direction.
- Counterclockwise atrial flutter is characterized by dominant negative flutter waves in the inferior leads and positive flutter deflection in lead V_1.
- Clockwise atrial flutter is characterized by positive flutter waves in inferior leads and negative flutter waves in lead V_1.
- In contrast to coarse AF, the flutter waves on an ECG will usually have the same morphology, amplitude, and cycle length.
- Ablation of the CTI is curative.

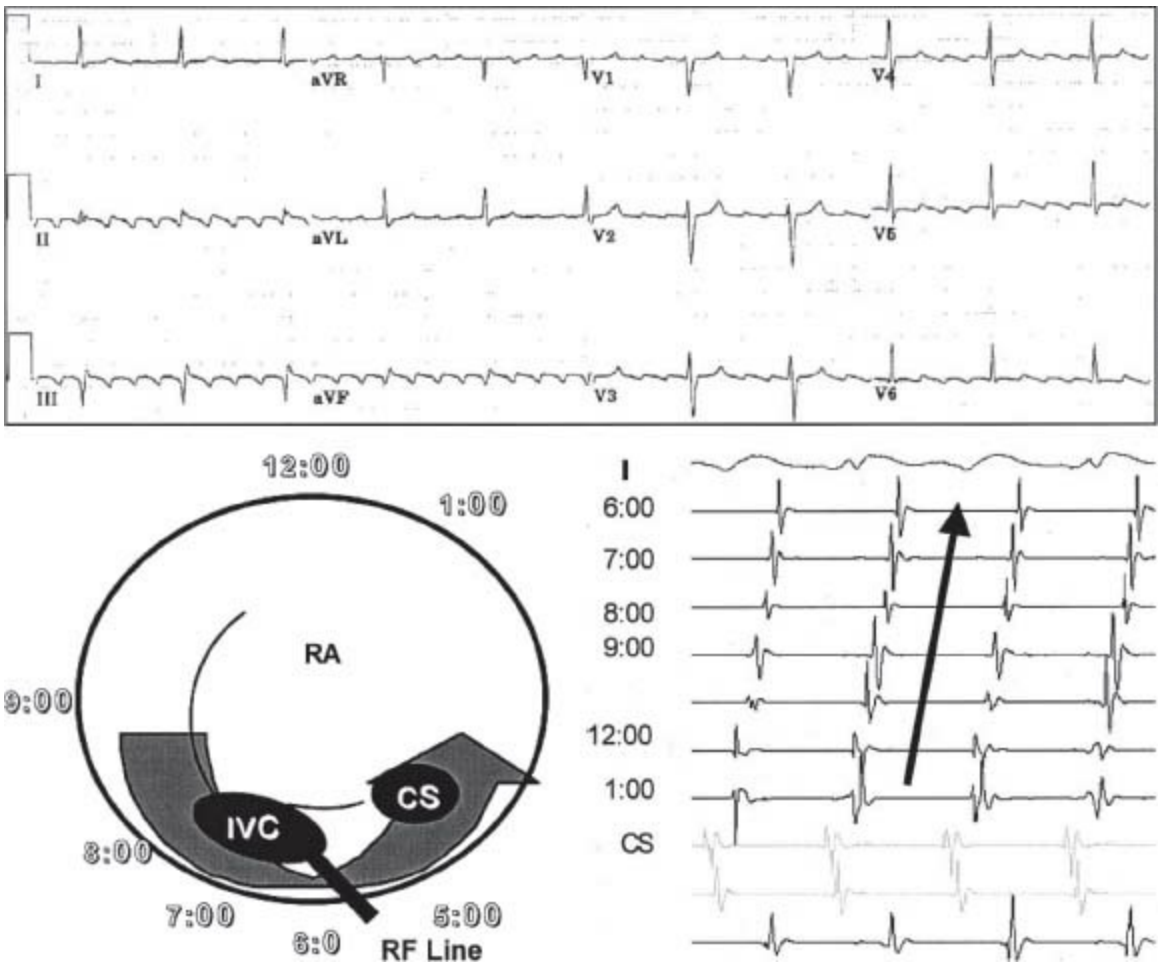


FIGURE 28.1 Type I counterclockwise right atrial flutter.

Noncavotricuspid Isthmus-Dependent Atrial Flutter

- Noncavotricuspid isthmus (NCTI)-dependent flutters do not use the CTI. NCTI flutters are often related to atrial scar which creates a conduction block and a central obstacle that allows for reentry.
- NCTI can be found in patients with prior cardiac surgery involving the atrium, such as repair of congenital heart disease, mitral valve surgery, or maze procedure as well as in patients post pulmonary vein isolation procedures.
- NCTI-dependent flutters are less common than CTI flutters.

Treatment

- Atrial flutter may be difficult to treat medically (it is notoriously difficult to rate control) and may develop with organization of AF reentrant flutter circuits during treatment with antiarrhythmic therapy.
- Successful ablation is dependent on identifying a critical portion of the reentry circuit where it can be interrupted with catheter ablation.

ATRIAL FIBRILLATION DEFINITIONS

- Lone: Patients under the age of 60 years with absence of cardiopulmonary or other conditions predisposing to AF
- New Onset: First episode of AF
- Recurrent: Has two or more paroxysmal or persistent episodes
- Paroxysmal: Self-terminating within 7 days, generally lasting 24 hours
- Persistent: Is not self-terminating within 7 days or is terminated with treatment
- Permanent: Persistent despite cardioversion

EVALUATION

History

- Precipitating factors and conditions
- Alcohol, caffeine, sympathomimetics, herbal supplements, or other drug use
- Duration and frequency of episodes
- Degree of associated symptoms
- Manner of AF initiation
- Prior therapies for AF (past antiarrhythmic drugs that may have failed or past ablation attempts)

Documentation of Atrial Fibrillation and Initiation

- ECGs, rhythm strips
- Transtelephonic (remote) event monitoring
- Evaluation for precipitating bradycardia, paroxysmal supraventricular tachycardia (PSVT), atrial flutter, atrial ectopy, atrial tachycardia

Diagnostic Testing

- Lab studies—thyroid function, renal, and hepatic tests
- Echocardiogram—evaluate LV function, valves, atrial size
- Functional stress testing or cardiac catheterization—evaluate for CAD in patients with risk factors and evaluate candidacy for 1C agents

MANAGEMENT OF ATRIAL FIBRILLATION

Treatment Strategies

- Ventricular rate control
  - AV nodal–blocking drugs
  - Atrioventricular node (AVN) modification/ablation and pacing
- Achievement and maintenance of SR
  - Antiarrhythmic drugs
  - Cardioversions
  - Nonpharmacologic therapies
    - – Ablation
    - – Surgery—Maze procedure
- Anticoagulation

Atrial Fibrillation Follow-Up Investigation of Rhythm Management

The Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study (Wyse et al., 2002) was a multicenter trial of rate versus rhythm control strategies (Table 28.1). It tested the hypothesis that in patients with AF, total mortality with primary therapy intended to maintain SR is equal to that with primary therapy intended to control heart rate. The study randomized 4,060 patients (>65 years old or with risk factors for stroke), with a primary endpoint of total mortality. No significant difference in total mortality was found among strategies, although there was a strong trend toward better survival in the rate-control arm. The study also showed that continued anticoagulation is important even in the rhythm-control arm, so this may be the best strategy in relatively asymptomatic older patients with good rate control.

TABLE
28.1 Rate Control versus Rhythm Control

	Potential Benefits	Potential Risks
Maintenance of SR	Better control of symptoms Reduced risk from anticoagulation Avoidance of electrical and structural remodeling	Increased risk of adverse effects (including death) Higher cost
Control of heart rate alone	Lower risk of adverse effects (including death) Possibly lower cost	Poorer relief of symptoms Increased risk from anticoagulation

Control of Ventricular Rate

Rapid ventricular rates can cause symptoms and/or ventricular dysfunction. The goal of treatment, a heart rate of 70 to 100 bpm at rest, can be achieved pharmacologically with

agents that slow AV nodal conduction, such as digoxin, beta-adrenergic blockers, and calcium channel blockers (Table 28.2). These agents, however, should not be used in patients with ventricular preexcitiation due to the risk of very rapid antidromic conduction during AF over the pathway. In patients who are hemodynamically stable with evidence of pre-excited AF, amiodarone, ibutilide, procainamide, or disopyramide are acceptable choices.

TABLE
28.2 Pharmacologic Rate Control for Atrial Arrhythmias

Agent	Loading Dose	Maintenance Dose	Side Effects Toxicity	Comments
Digoxin	0.25–0.5 mg IV or PO, then 0.25 mg every 4–6 h to 1 mg in first 24 h	0.125–0.25 mg PO or IV per day	Anorexia, nausea; AV block; ventricular arrhythmias; accumulates in renal failure	Used in CHF; vagotonic effects on the AV node; delayed onset of action; narrow therapeutic window; less effective in postop, paroxysmal AF with high adrenergic states
Beta-blockers				
Propranolol	1 mg IV every 2–5 min to 0.1–0.2 mg/kg	10–80 mg PO t.i.d–q.i.d.	Bronchospasm; CHF; ↓ BP	Effective in heart rate control; rapid onset of action; esmolol is short acting
Metoprolol	5 mg IV every 5 min to 15 mg	25–100 mg PO b.i.d–t.i.d.		
Esmolol	500 μg/kg IV over 1 min	50 μg/kg IV for 4 min; repeat load PRN and ↑ maintenance 20–50 μg/kg/min every 5–10 min		
Calcium channel blockers				
Verapamil	2.5–10 mg IV over 2 min	5–10 mg IV every 30–60 min or 40–160 mg PO t.i.d or 120–480 mg/d, sustained release	↓ BP, CHF ↑ digoxin levels	Rapid onset, can be used safely in COPD and DM
Diltiazem	0.25 mg/kg over 2 min; repeat PRN every 15 min at 0.35 mg/kg	5–15 mg/h IV or 30–90 mg PO q.i.d or 120–360 mg sustained release per day		Often well tolerated with low-LVEF patients

The RACE II trial compared strict rate control (resting heart rate <80 bpm) to lenient rate control (resting heart rate<110 bpm) in patients with permanent AF. Lenient rate control was comparable to strict rate control in terms of reaching the components of the primary endpoint. In addition, lenient rate control was much easier to achieve compared to strict rate control.

Digoxin

Digoxin has direct and indirect effects on the AV node, with a primary vagotonic effect. Advantages include:

- It is inexpensive.

- It can be given intravenously
- It can be used safely in patients with heart failure.
- It is effective in controlling resting ventricular rates in chronic, persistent AF.

Disadvantages are that:

- Peak onset of heart rate-lowering effect is delayed by 1 to 4 hours.
- The therapeutic window is narrow.
- It is less effective in rate control of paroxysmal AF and should never be used as the sole agent for rate control in these patients.
- It is less effective for rapid rates during hyperadrenergic states, when vagal tone is low, for example, during exercise or in acute MI and ICU settings, because of increased sympathetic tone.

Digoxin should be used with caution in elderly patients and in patients with decreased renal function.

Beta-Adrenergic Blockers

Advantages of beta-adrenergic blockers are that they:

- Are very effective for heart rate control, even with exercise
- Can be given intravenously
- Have rapid onset of action
- Have long-term benefits in patients with LV dysfunction

Disadvantages of beta-adrenergic blockers are that they:

- May provoke bronchospasm
- Are negatively inotropic and may exacerbate CHF
- May reduce exercise tolerance as a result of their negative inotropy and chronotropy

Calcium Channel Blockers

The advantages of calcium channel blockers such as verapamil and diltiazem include:

- Intravenous availability
- Rapid onset of action
- Can be used safely in chronic obstructive pulmonary disease (COPD) and diabetes mellitus

Disadvantages include:

- Negative inotropic effects
- Can cause hypotension
- Long-term safety questioned

Class I or III Antiarrhythmic Drugs

Sotalol, dronedarone, amiodarone, propafenone, and flecainide can contribute to ventricular rate control.

NONPHARMACOLOGIC RATE CONTROL

Complete AV Junction Ablation

Radiofrequency catheter ablation of the AV node is usually technically easy to accomplish. It is best used in cases of atrial arrhythmias refractory to standard therapies in highly symptomatic patients.

- Advantages
  - Effectively controls rapid ventricular rates
  - Significant symptomatic relief and improvement in quality of life demonstrated
  - Can reverse tachycardia-mediated cardiomyopathy
- Disadvantages
  - Requires a permanent, rate-responsive pacemaker
  - The patient is pacemaker dependent.
  - Pacing RV alone may significantly worsen ventricular function. Biventricular pacing may be considered in patients with impaired LV systolic function.

RESTORATION OF SINUS RHYTHM

Electrical Cardioversion

Electrical cardioversion is the most effective method of restoring SR. In this technique, a shock is synchronized to the R wave. The optimal patch positioning is anterior–posterior (e.g., right parasternal to left paraspinal). For standard monophasic external cardioversion, usual initial energies are 200 J for AF and 50 to 100 J for atrial flutter. Energies can be increased up to 300 J if initial efforts are unsuccessful. Biphasic external conversion, however, requires less energy as a rule. All electrical cardioversion requires sedation with a short-acting anesthetic such as etomidate or methohexital, which is one limitation, compared to pharmacologic cardioversion.

Cardioversion is urgently indicated for patients with clinical instability (e.g., hypotension, ischemia, CHF). It is electively indicated for patients who remain in

symptomatic AF after a trial of pharmacologic therapy. Electrical cardioversion is contraindicated in patients with AF and digoxin toxicity or hypokalemia.

Pharmacologic Conversion

A small, randomized, controlled study showed no effect of digoxin on conversion rate. However, quinidine, procainamide, flecainide, propafenone, sotalol, amiodarone, dofetilide, and ibutilide have shown success rates of 31% to 90%. Procainamide, ibutilide, and amiodarone are available for intravenous administration.

Procainamide is usually administered at a dose of 10 to 15 mg/kg IV at ≤50 mg/min, then at 1 to 2 mg/min. It is necessary to monitor blood pressure, as hypotension may require slowing the infusion rate; hemodynamic effects may limit dosing in severe LV dysfunction. It is also necessary to monitor for proarrhythmia—QT prolongation and torsades de pointes. Note that the active metabolite, N-acetyl procainamide (NAPA), may accumulate to toxic levels and cause renal failure.

Ibutilide is a class III potassium channel–blocking agent. In one study, it was shown to be more efficacious than procainamide in converting short-term AF/flutter to SR. Usual dosing is 1 mg IV over 10 minutes, which can be repeated after another 10 minutes. One should monitor for QT prolongation and torsades de pointes.

Amiodarone in its IV form is useful for patients who cannot take oral medications, though it is more expensive. It may be helpful for hemodynamically unstable patients with recurrent AF despite cardioversion or other antiarrhythmic drugs, for whom rate control is refractory to conventional

AV nodal–blocking drugs, or who are intolerant of standard antiarrhythmic or rate-controlling drugs as a result of negative inotropy. Rapid oral loading of amiodarone can usually also be achieved in patients with intact gastrointestinal function (Table 28.3).

TABLE
28.3 Pharmacologic Conversion Regimens

Drug	Route	Dose	Success Rate
Quinidine	PO	200–324 mg t.i.d. to 1.5 g/d	48%–86%
Procainamide	IV	1 g over 20–30 min	48%–65%
Propafenone	PO	600 mg	55%–87%
	IV	2 mg/kg over 10 min	40%–90%
Flecainide	PO	300 mg	90%
	IV	2 mg/kg over 10 min	65%–90%
Amiodarone	IV	1.2 g over 24 h	45%–85%
Sotalol	PO	80–160 mg, then 160–360 mg/d	52%
Dofetilide	PO	125–500 µg b.i.d. based on CrCl	30%
Ibutilide	IV	1 mg over 10 min, repeat in 10 min PRN	31%

Maintenance of Sinus Rhythm

Maintenance of SR often requires an antiarrhythmic agent, particularly in patients with frequent or persistent AF, underlying CV disease, enlarged atria, or other continuing disease factors that predispose to AF. Common antiarrhythmic agents available that can be effective in maintaining SR include class IA (procainamide, disopyramide), IC (flecainide, propafenone), and III (sotalol, dronedarone, amiodarone, dofetilide). A substudy of the AFFIRM trial demonstrated that amiodarone is more effective at 1 year for the maintenance of SR than sotalol or other class I agents (Table 28.4).

TABLE
28.4 Drugs for Maintenance of SR

Antiarrhythmic Drug	Dose	% Maintenance SR (6–12 mo)	Side Effects/Comments
Class IA			
Quinidine	200–400 mg PO t.i.d.–q.i.d.	30%–79%	↑ QT, proarrhythmia/TdP, potential ↑ AV node conduction, diarrhea, nausea, ↑ digoxin levels, thrombocytopenia
Procainamide	10–15 mg/kg IV at ≤ 50 mg/min or 2–6 g/d PO in b.i.d. or q.i.d. sustained release	N/A	↓ BP, CHF, drug-induced lupus, agranulocytosis; active metabolite NAPA with class III activity accumulates in renal failure
Disopyramide	100–300 mg PO t.i.d.	44%–67%	Anticholinergic effects (e.g., urinary retention, dry eyes/mouth), CHF
Class IC			
Flecainide	50–200 mg PO b.i.d.	34%–81%	Proarrhythmia visual disturbance, dizziness, CHF, avoid in CAD/LV dysfunction
Propafenone	150–300 mg t.i.d.	30%–76%	CHF, avoid in CAD/LV dysfunction
Class III			
Sotalol	80–240 mg b.i.d.	37%–70%	CHF, bronchospasm, bradycardia, ↑ QT proarrhythmia/TdP
Amiodarone	600–1,600 mg/d loading in divided doses, 100–400 mg daily maintenance	40%–79%	Pulmonary toxicity, bradycardia hyper- or hypothyroidism, hepatic toxicity, GI (nausea, constipation), neurologic, dermatologic, and ophthalmologic side effects, drug interactions
Dronedarone	150 mg twice daily	36%	Diarrhea, nausea, and vomiting
Dofetilide	CrCl (mL/min) >60: 500 µg b.i.d. 40–60: 250 µg b.i.d. 20–40: 125 µg b.i.d.	58%–71%	Exclude CrCl <20 mL/min, ↑ QT, proarrhythmia/TdP, headache, muscle cramps

TdP, torsades de pointes; BP, blood pressure; CHF, congestive heart failure; CAD, coronary artery disease; LV, left ventricular.

CLASS IA ANTIARRHYTHMIC DRUGS

Class IA antiarrhythmic drugs:

- Delay fast sodium channel–mediated conduction with a depression of phase 0
- Prolong repolarization
- Are associated with an incidence of torsade de pointes
- Can enhance AV nodal conduction, potentially increasing ventricular rates during AF
- Usually require concomitant use of AV nodal–blocking agents.

These drugs are usually not used chronically because of their potential proarrhythmic effects.

Quinidine

The use of quinidine is limited by proarrhythmia concerns and is thus rarely used. There is a higher risk in patients on diuretics and those with electrolyte depletion. From a meta-analysis by Coplen et al. (1990), the proportion of patients remaining in SR on quinidine at 1 year was 50% (control, 25%), but total mortality was 2.9% (control, 0.8%). Only 7 of 12 patients in the quinidine group, however, died of cardiac causes. Note that in-hospital initiation or systematic QT interval assessment may not have been followed for many of the studies in this analysis. The SPAF trial 1991 showed increased mortality on antiarrhythmic therapy, which usually consisted of quinidine, with risk seen in patients with a history of CHF. Because of the potential for proarrhythmia, including torsades de pointes, in-hospital initiation is recommended, with continuous ECG monitoring and assessment of QT interval. Quinidine increases serum digoxin levels, so concomitant digoxin dosage usually should be decreased. Other adverse effects of quinidine include gastrointestinal symptoms, particularly diarrhea.

Procainamide

Procainamide, given intravenously, is often a first-line antiarrhythmic agent for AF after cardiac surgery. Its long-term use is usually limited by a high incidence of drug-induced lupus; however, long-term controlled trials are not available.

Disopyramide

Disopyramide has been shown to be effective for maintenance of SR in approximately 50% of patients over a follow-up of 6 to 12 months. Its use is limited, however, because of its anticholinergic side effects and, in older males, urinary retention. Disopyramide is also negatively inotropic and thus has a niche use as a second-line option in patients with AF and hypertrophic cardiomyopathy with dynamic LVOT obstruction.

CLASS IC ANTIARRHYTHMIC DRUGS

The class IC antiarrhythmic drugs markedly slow sodium channel–mediated conduction, with a marked depression of phase 0, but only a slight effect on repolarization.

Flecainide and propafenone have been shown to be equivalent in efficacy in comparative studies. Proarrhythmia, however, in the form of a wide-complex tachycardia due to ventricular tachycardia or slow atrial flutter with 1:1 AV conduction can occur with these agents. They are usually avoided in patients with CAD or impaired ventricular function.

Patients with underlying heart disease may be at higher risk for proarrhythmia with class IC drugs. The Cardiac Arrhythmia Suppression Trial (CAST) reported increased mortality in patients treated with flecainide and encainide for ventricular arrhythmias after MI.

Flecainide

Flecainide has been shown to be effective in the treatment of AF and is usually well tolerated. Noncardiac effects include visual disturbances, dizziness, and paresthesias.

Propafenone

Propafenone has weak beta-blocking activity and is effective in the treatment of AF. It is available in a slow-release form that can be taken twice daily.

CLASS III ANTIARRHYTHMIC DRUGS

Class III antiarrhythmic drugs are potassium channel blockers that prolong repolarization.

Amiodarone

Amiodarone affects multiple ion channels. Its sodium and potassium channel effects include increased refractoriness in the atria, AV node, and ventricles. It also has noncompetitive beta-blocking and calcium channel–blocking activity. The drug inhibits phospholipase and antagonizes thyroid hormone but is effective against AF and has been reported to be superior to sotalol and quinidine, as well as to flecainide, in a meta-analysis.

Amiodarone has a long half-life, requiring weeks to months to achieve steady state. When used long-term, however, it has a potential for organ toxicity. It can cause significant bradycardia, but proarrhythmia is uncommon. The risk for pulmonary toxicity appears to be dose related. Other potential side effects include hypothyroidism or hyperthyroidism, liver function test elevation or toxicity, skin changes and photosensitivity, peripheral neuropathy, and, very rarely, optic neuritis. While amiodarone is known to prolong the QTc interval, Torsades de Pointes is rare. The usual maintenance dose of amiodarone for atrial arrhythmias is 100 to 200 mg daily. Of

note, preoperative administration of amiodarone reduces the incidence of AF in patients undergoing cardiac surgery. As such prophylactic administration of amiodarone for patients at high risk of postoperative AF is reasonable.

Sotalol

Sotalol is a nonselective beta-blocker with class III activity that is effective in AF. It has significant beta-blocking activity with potential for bradycardia and negative inotropic effects that can lead to exacerbation of heart failure. Monitoring for QT interval prolongation and torsade de pointes is recommended. The d-isomer of sotalol (D-sotalol) studied in the Survival with Oral D-Sotalol Trial (SWORD) increased mortality in patients after MI and was withdrawn from development.

Dofetilide

Dofetilide is a potent inhibitor of I_{kr}, the rapid component of the delayed rectifier. In the DIAMOND trials of patients after MI or with CHF, it did not increase mortality and was found to be beneficial in maintaining SR. In-hospital initiation is mandated, and dosage should be adjusted in the presence of renal insufficiency. Common practice is to check an ECG 2 hours after the first five or six doses to monitor for significant QTc prolongation. Patients must be vigilant not to combine dofetilide (as well as any other QTc prolonging antiarrythmic) with other QTc prolonging drugs (e.g., certain antibiotics, antipsychotics) as the incidence of Torsades de Pointes can rise substantially with these combinations.

Dronedarone

Dronedarone is a deiodinated derivative of amiodarone that was recently approved for use in patients with AF. In development of the drug, the hope was that by doing away with the iodinated portion of the compound, the side effect profile would be improved compared to amiodarone without losing efficacy. In multiple clinical trials, the endocrinologic, neurologic, and pulmonary toxicity of amiodarone were not present with dronedarone. Compared to amiodarone, however, dronedarone was shown to be substantially less efficacious at preventing recurrences of AF.

Dronedarone is metabolized by the P-450 system in the liver primarily by (CYP) 3A4 and is highly bound to plasma proteins; therefore, the steady-state terminal elimination is approximately 30 hours compared to 58 days for amiodarone. In pooled data from the DAFNE, EURIDIS, ADONIS, and ATHENA trials, dronedarone was shown to delay recurrence of AF modestly compared to placebo. The DIONYSOS trial compared the efficacy and safety of dronedarone compared to amiodarone for at least 6 months for the maintenance of SR in patients with AF. This study showed that dronedarone was less efficacious in limiting recurrences of AF compared to

amiodarone but had fewer discontinuations due to drug intolerance. ATHENA and ANDROMEDA were large randomized trials which evaluated the safety of dronedarone. The ANDROMEDA trial enrolled patients with recently symptomatic decompensated heart failure who may or may not have had AF. This study was stopped early due to excess mortality in patients on dronedarone. Caution is warranted with the use of dronedarone in patients with heart failure in general, and the use of the drug in patients with NYHA class IV heart failure or class II or III heart failure with recent decompensation is contraindicated (black box warning by the FDA).

ANTIARRHYTHMIC DRUG SELECTION

The decision to use an antiarrhythmic drug should include consideration of frequency and duration of the arrhythmia symptoms, reversibility of the arrhythmia, and the presence of structural heart disease. In addition, the risk of side effects, including organ toxicity and proarrhythmia, should be weighed against the benefits and efficacy rates of the drugs.

Approach to Antiarrhythmic Drug Selection

Consider:

- Frequency and duration of AF
- Symptoms
- Reversibility
- Structural heart disease
- Risk of side effects
- Proarrhythmia
- Organ toxicity
- Age and activity level
- Assessment of risk versus benefits
- Efficacy

Frequency, Duration, and Symptoms

First Episode After a first episode, the future pattern of recurrence cannot be predicted. The success rate and rate of recurrence are more favorable on an antiarrhythmic drug, but antiarrhythmic drug therapy may not be necessary after a first occurrence, unless factors such as structural heart disease, large atria, or advanced age suggest a high risk of recurrence.

A first episode can be converted either pharmacologically or electrically. If there

are early recurrences of AF after cardioversion, then consider prescribing an antiarrhythmic drug. One may also consider stopping the antiarrhythmic drug after a few weeks or months.

Recurring, Paroxysmal Atrial Fibrillation For recurring, paroxysmal AF, assess the frequency and associated symptoms. If the patient is asymptomatic, consider a rate control strategy. If the patient is symptomatic, consider further rate control or addition of an antiarrhythmic drug.

For infrequent episodes in a patient with a normal heart, consider intermittent drug therapy also known as the "pill in a pocket approach" with the use of class IC agents (single oral dose of 300 mg of flecainide or 600 mg of propafenone) during an attack. The first time such a strategy is to be used however should be in a monitored setting (the patient comes to the ER or to clinic to administer the dose while monitored). For frequent symptomatic episodes, consider a rhythm control strategy with a daily administered antiarrhythmic drug.

Chronic, Persistent Atrial Fibrillation For persistent AF, assess the duration of the AF, atrial size, symptoms, and anticoagulation status. Based on this assessment, one may want to consider cardioversion. Antiarrhythmic therapy may also be required for successful conversion and maintenance of SR at least short term, if not chronically.

Structural Heart Disease

Patients with CAD and/or ventricular dysfunction are at higher risk of proarrhythmia. For these patients:

- Avoid class IC drugs (based on the CAST trial).
- In patients with hypertension and substantial left ventricular hypertrophy (LVH), the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend amiodarone as first-line therapy. Dronedarone is also an option.
- In patients with CAD, sotalol or dofetilide are first-line options. Amiodarone is a second-line agent given its side effect profile.
- In patients with heart failure, amiodarone and dofetilide are the agents of choice. Dronedarone can be used, but cautiously, in any patient with a history of heart failure. In patients with class IV heart failure or in those with a recent heart failure exacerbation, dronedarone is strictly contraindicated.
- Sotalol can be used in patients with LV dysfunction so long as they can tolerate the negative inotropic effects of its beta-blocking activity.

Other Drug Considerations—Efficacy, Organ Toxicity, and Proarrhythmia

Efficacy Class IA and class IC drugs have efficacy rates of approximately 50% in maintaining SR at 6 months. The class III drugs have slightly higher efficacy rates (50% to 70%).

Side Effects Side effects are common with the use of antiarrhythmic agents. The side effect profile and risk for organ toxicity often limits continuation, although not necessarily, initiation of a particular drug.

- Amiodarone has significant potential for organ toxicity. The risk is dose and duration related, and side effects often limit its use, particularly in younger patients.
- Sotalol has negative inotropy, negative chronotropy, and bronchospastic side effects.
- Procainamide has a high frequency of drug-induced lupus, which seriously limits its long-term use. There is also a small risk of agranulocytosis.
- Quinidine has a small risk of agranulocytosis, thrombocytopenia, and/or lupus.

Proarrhythmic Risk Patients with normal hearts and non–life-threatening AF are at low risk for proarrhythmia. They may be treated with drugs with the lowest risk of proarrhythmia or organ toxicity. For these seasons, class IC drugs are often used as the first line of treatment. Class IA drugs and sotalol (class III) are lower-tier choices. Patients with CAD or ventricular dysfunction are at higher risk for proarrhythmia from class IC drugs, so one should consider dofetilide, sotalol, or amiodarone for these patients. Risk factors for proarrhythmia include structural heart disease, LV dysfunction, CHF, prior MI or CAD, LVH, female gender, prior torsades de pointes or CHF (amiodarone), and older age.

INPATIENT VERSUS OUTPATIENT INITIATION OF ANTIARRHYTHMIC DRUGS

The choice between initiating antiarrhythmic drug therapy on an inpatient or outpatient basis remains controversial, but inpatient initiation is usually recommended for:

- Patients with LV dysfunction
- Patients with persistent AF
- Patients at risk for proarrhythmia (see above risk factors)
- Class IA and III antiarrhythmic agents other than amiodarone: dofetilide (mandated in-hospital initiation), sotalol, quinidine, procainamide, or disopyramide
- CHF patients with a history of torsades de pointes starting amiodarone
- Prior history of proarrhythmia

- Prolonged QT interval at baseline when initiating class IA and class III drugs
- Propensity to bradycardia
- History of ventricular arrhythmias in a patient with significant LV dysfunction and no ICD

ANTITHRMOBOTIC DRUG SELECTION

Chronic Anticoagulation and Antithrombotic Therapy

AF is associated with thromboembolic events and stroke. It is one of the most potent risk factors for stroke in the elderly and is the most common cause of cardiogenic stroke. The risk of stroke in nonvalvular AF varies with age and the presence of concomitant CV disease and other risk factors. In general, patients with nonvalvular AF have about a sixfold increased risk of stroke.

In patients younger than age 65 years and without hypertension or CV disease, the risk of stroke is low. A meta-analysis of five of the major primary prevention trials for stroke in AF indicated that the risk of stroke is approximately 1% per year for patients under age 65 without risk factors of hypertension, diabetes, or prior stroke or transient ischemic attack (TIA). For patients who are older or who have risk factors for stroke or concomitant CV disease, the risk of stroke is approximately 3% to 5% per year. Older patients (>75 years old) with risk factors for stroke are at higher risk (8% per year).

Most strokes associated with AF appear to result from cardiac emboli, presumably from thrombi formed most commonly in the left atrial appendage, a small, finger-like outpouching of the left atrium adjacent to the mitral valve. Patients with paroxysmal AF have a stroke rate of 3.7% per year with events clustered at the onset of the arrhythmia. The incidence of embolism is 6.8% in the first month and decreases to 2% per year over the subsequent 5 years. Patients with paroxysmal AF appear to be at similar risk as patients with chronic, persistent AF and generally are treated similarly with regard to anticoagulation. Patients with a single AF event, with no other risk factors or structural heart disease and <65 years old have a low stroke event rate of 1% per year. The incidence of stroke in patients with AF taking placebo versus aspirin alone and in patients taking aspirin versus coumadin are shown in Tables 28.5 and 28.6, respectively.

TABLE
28.5 Stroke/Thromboembolism Reduction in AF: Aspirin versus Control

	Aspirin	Control	RRR%	*p* Value
AFASAKI	5.2	6.2	16	NS
SPAFI	3.6	6.3	42	0.02
EAFT	15.5	19.0	17	0.12
AFI	6.3	8.1	21	0.05
ESPS2	13.8	20.7	33	0.16

RRR%, relative risk ratio (percent).

AFASAKI, atrial fibrillation, aspirin, anticoagulation study; SPAFI, stroke prevention in atrial fibrillation; EAFT, European atrial fibrillation trial; AFI, atrial fibrillation investigators; ESPS2, European stroke prevention study 2.

TABLE
28.6 Stroke/Thromboembolism Reduction in AF Warfarin versus Aspirin

	Warfarin	Aspirin	RRR%	*p* Value
AFASAKI	2.7	6.2	48	<0.05
SPAF2				
≤ 75	1.3	1.9	48	0.24
>75	3.6	4.8	33	0.39
EAFT	NA	NA	40	0.008
AFASAK2	3.4	2.7	–21	NS
	Low Dose			
	Warfarin	Warfarin + Aspirin	RRR%	p Value
SPAF3	1.9	7.9	74	<0.0001
AFASAK2	3.4	3.2	–6	NS

RRR%, relative risk ratio (percent); AFASAKI, atrial fibrillation, aspirin, anticoagulation study; SPAF2, stroke prevention in atrial fibrillation phase 2; EAFT, European atrial fibrillation trial; AFASAK2, atrial fibrillation, aspirin, anticoagulation study phase 2.

Several large clinical trials have identified multiple risk factors for stroke when AF is present:

- TIA or previous stroke
- Diabetes Mellitus
- Hypertension
- Age >75 years
- LV dysfunction
- Increased left atrial size
- Rheumatic mitral valve disease
- Prosthetic valves

- Mitral annular calcification
- Increased wall thickness
- Thyrotoxicosis
- Peripheral vascular disease

CHADS II SCORE

The CHADS II score is a well-known, commonly used index used to gauge stroke risk in patients with nonrheumatic AF. CHADS stands for: Congestive heart failure (active within the last 100 days or evidence of LV dysfunction), Hypertension (blood pressure consistently above 140/90 mm Hg or treated hypertension on medication), Age (≥75 years), Diabetes Mellitus, and a history of Stroke (prior stroke or TIA). In the score the first 4 variables are counted as 1 point and a history of stroke or TIA 2 points. In patients with a CHADS II score of 0, the stroke risk is very low and daily aspirin is indicated. For a score of 1, either aspirin or Coumadin is appropriate. In patients with scores ≥ 2 daily coumadin is indicated for an international normalizing ratio (INR) between 2 and 3 (Table 28.7). For the boards, it is important not just to know the CHADS II scoring system, but the nuances as well:

TABLE
28.7 CHADS II Score Annual Risk of Stroke

CHADS II Score	Stroke Risk %	95% CI	RRR%	*p* Value
0	1.9	1.2–3.0	56	< 0.05
1	2.8	2.0–3.8	67	0.01
2	4.0	3.1–5.1	86	0.002
3	5.9	4.6–7.3	26	0.25
4	8.5	6.3–11.1	79	0.001
5	12.5	8.2–17.5	68	<0.001
6	18.2	10.5–27.4	47	0.001

RRR%, relative risk ratio (percent).

- It is not applicable to patients with rheumatic heart disease and mitral stenosis (they should receive anticoagulation with Coumadin despite a low CHADS II score).
- Patients with AF and thyrotoxicosis are thought to be at a high stroke risk; therefore, full anticoagulation with coumadin is indicated even with a low CHADS score. Of note, once the thyrotoxic state has been treated the CHADS II score is applicable.
- Patients with hypertrophic cardiomyopathy are at higher risk of stroke with AF and require therapeutic Coumadin (INR 2.0 to 3.0) even in the absence of other risk

factors.

- Knowing how hypertension, CHF, and age are defined is important (e.g., a patient with treated hypertension counts).
- If aspirin is deemed to be appropriate, a dose of 81 to 325 mg is acceptable per ACC guidelines.

Recommendations for Anticoagulation in Patients Undergoing Cardioversion

1. The risk of emboli after cardioversion is 0.6% to 5.6% without and 0.8% to 1% with anticoagulation.
2. Per the anticoagulation recommendations of the ACC/AHA/Heart Rhythm Society (HRS):
   - For AF >48 hours in duration, anticoagulate with warfarin (target INR 2.5, range 2.0 to 3.0) for 3 weeks before elective cardioversion.
   - Continue warfarin until SR has been maintained for 4 weeks (allows time for mechanical atrial transport to resume and for possible recurrence of AF).
   - A transesophageal echocardiography (TEE) protocol may be substituted for conventional therapy; however, intravenous heparin is required post cardioversion until the INR has risen to ≥2.0. Warfarin should be continued until SR has been maintained for at least 4 weeks.
3. Consideration should be given to managing anticoagulation for atrial flutter similar to that for AF.
4. Long-term anticoagulation beyond 4 weeks after cardioversion may be considered depending on patient risk factors for stroke.
5. Heparin anticoagulation followed by oral anticoagulation for 4 weeks is indicated for patients requiring emergency cardioversion for hemodynamic instability.
6. For AF of <48 hours duration, the risk of embolism after cardioversion appears to be low, but pericardioversion anticoagulation is recommended (from Albers et al., 2001).
7. In patients with AF who do not have a mechanical valve, it is reasonable to interrupt anticoagulation for up to 1 week without substituting heparin for surgical or diagnostic procedures that carry a risk of bleeding.

ROLE OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY

The ACUTE trial compared conventional anticoagulation versus a TEE-guided approach before cardioversion. It randomized 1,222 patients to conventional anticoagulation with therapeutic warfarin for 3 weeks prior to cardioversion or to a

TEE-guided approach. There was no significant difference in thromboembolic complications occurring after cardioversion between the two arms.

Oral X A Inhibitors

On October 19, 2010, the U.S. Food and Drug administration approved the oral factor X A inhibitor, dabigatran, for use in nonvalvular AF. Dabigatran etexilate is a low-molecular prodrug that is converted to its active form, dabigatran, which is a competitive and reversible direct inhibitor of the active site of thrombin, the final effector in the coagulation cascade. The drug is 80% cleared by the kidneys and prolongs the activated partial thromboplastin (aPTT) with little effect on the prothrombin time and INR. One of the major advantages of dabigatran over Coumadin is that it does not require blood testing for monitoring. The RE-LY trial randomized 18,113 patients with nonvalvular AF and at least 1 additional risk factor for stroke to warfarin, dabigatran (150 mg twice daily), or dabigatran (110 mg twice daily). Compared to warfarin, dabigatran at a dose of 150 mg twice daily was more effective at preventing stroke or embolic events than warfarin with similar bleeding profiles. Of note, the rate of MI was higher in both dabigatran doses compared to warfarin, an effect that will need to be monitored in the future. Dose reduction is needed in patients with renal impairment. It is useful as an alternative to warfarin for the prevention of systemic thromboembolism in patients with risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance <15 mL/min), or advanced liver disease (impaired baseline clotting function).

NONPHARMACOLOGIC MANAGEMENT OF ATRIAL FIBRILLATION AND FLUTTER

Electrical cardioversion is the most effective method of conversion to SR and is the method of choice for hemodynamically
compromising AF. It is necessary, however, to evaluate the need for anticoagulation before cardioversion.

For elective direct-current cardioversion:

- Fast for at least 6 to 8 hours.
- Correct electrolyte imbalances.
- Exclude toxic drug levels.
- Generally, hold digoxin the morning of the procedure.

Electrode positioning should assure an appropriate vector for atrial defibrillation:

- Anterior–posterior
- R subclavicular/parasternal–L posterior patch position

Sedation could be achieved with a short-acting anesthetic (e.g., etomidate, methohexital, or propofol). Vital signs, ECG, respiratory status, and pulse oximetry must be closely monitored. In performing the procedure, synchronize to the QRS complex to minimize risk of inducing ventricular fibrillation. Atrial flutter may require less energy for successful cardioversion (e.g. 50 to 100 J monophasic) than atrial fibrillation (e.g. 200 J monophasic). If atrial pacing electrodes are present, atrial overdrive pacing may be attempted to terminate atrial flutter. Internal cardioversion may be used for AF that is refractory to standard external cardioversion. In this case, high-energy (200 to 360 J) transcatheter direct-current shocks are used. Lower energies (2 to 10 J) have been successful using catheters placed in the right atrium and coronary sinus.

Recently, biphasic external defibrillation has largely supplanted the use of monophasic defibrillation. Biphasic defibrillators deliver current in two directions. In the first phase, the current moves from one paddle to the other similar to that of monophasic defibrillation. During the second phase, the current reverses direction. While the underlying physiologic mechanism is not fully understood, it is clear that biphasic waveforms lower the electrical threshold for successful defibrillation. Typical starting energies for electrical cardioversion of AF using biphasic wave forms are between 100 and 200 J.

AV NODE ABLATION

Complete AV nodal (or His bundle) ablation with implantation of a permanent rate-responsive pacemaker was initially achieved with direct-current ablation. Now it is performed primarily using radiofrequency catheter ablation methods. The procedure is successful in up to 100% of patients, and most experience significant symptomatic improvement. Complete ablation is most appropriate and successful for patients whose symptoms are secondary to difficult-to-control rapid ventricular rates. AF patients who have undergone AV node junctional ablation and have a severely depressed ejection fraction should have a biventricular pacemaker implanted (PAVE study).

Advantages of complete AV node ablation include:

- High rate of procedural success, nearing 100%
- Only a low rate of recurrent rapid ventricular conduction (0% to 14%)
- Improvement in symptoms and quality of life reported in 84% to 100% of patients
- Ventricular dysfunction also shown to improve

Disadvantages of complete AV node ablation are

- Dependence on a permanent pacemaker
- Lack of effects on AV synchrony
- No reduction in risk of thromboembolism

A possible small risk of late sudden death, primarily reported after direct-current ablation, has been reported, although the deaths may have been related to significant underlying structural heart disease. Increased cardiac output has been reported with regularization of ventricular rates, which would be achieved by complete AV junction ablation, but might not be attained after successful modification alone.

CATHETER ABLATION OF ATRIAL ARRHYTHMIAS

Radiofrequency catheter ablation may be used for the ablation of supraventricular tachycardias (SVTs) that may degenerate to AF. Ablation of atrial flutter consists of application of radiofrequency energy along a line from the tricuspid annulus to the IVC and/or from the coronary sinus os to the IVC and can effectively prevent the occurrence of typical, isthmus-dependent atrial flutter in approximately 90% of patients. It has been used successfully in patients with concomitant AF that can be controlled with antiarrhythmic medication but whose recurrences on medication may be in the form of atrial flutter, often occurring at a slow atrial rate that may facilitate 1:1 AV conduction. Atypical atrial flutter or tachycardias arising from the right or left atria have also been successfully ablated, particularly those associated with atrial scars or incisions.

ABLATION OF ATRIAL FIBRILLATION

Pulmonary Vein Isolation

The large majority of triggers for AF arise from pulmonary vein ostial regions. PVI seeks to electrically isolate the pulmonary veins via circumferential ablation around the respective antra therefore preventing triggers arising in the veins to initiate AF. This procedure typically involves one or more transseptal punctures in the interatrial septum through which a circular lasso catheter and an ablation catheter are placed. While the procedure varies significantly according to operator, many electrophysiologists use intracardiac echocardiography (ICE) to identify the pulmonary vein ostia. Additionally, electroanatomic mapping systems are often used to supplement the ICE images. The highest success rates tend to be in paroxysmal lone AF and may be substantially lower in AF associated with other cardiac disease, especially in patients with marked atrial scarring. Often, more than one PVI is needed to achieve long-term success since recovery of conduction out of the pulmonary veins is common.

While the incidence of complications from PVI at experienced centers is low, the risk of symptomatic pulmonary vein stenosis (PVS) is approximately 1% to 2%. The

diagnosis of PVS requires a high level of suspicion as symptoms are often nonspecific. New onset shortness of breath, cough, or hemoptysis in a patient having undergone a PVI in the past should raise consideration of the diagnosis. A CT scan of the chest with contrast is useful for diagnosis. According to the 2011 AHA, ACC, HRS guidelines for AF, PVI is indicated in selected patients with significantly symptomatic, paroxysmal AF who have failed treatment with an antiarrhythmic drug and have normal or mildly dilated left atria, normal or mildly reduced LV function, and no severe pulmonary disease. In patients with heart failure and drug refractory AF, PVI was found to be superior to AV node ablation with biventricular pacing in terms of symptoms, exercise tolerance, and ejection fraction improvement.

Maze Procedure

The maze procedure is a surgical technique that divides the atria into "mazelike" corridors and blind alleys that limit the development of reentry by limiting available path length. Part of its success may be due to the PVI that is part of the operation. In some cases, atrial transport function may be preserved but reduced. A high degree of curative success (>80% to 90%) has been reported, but the procedure has had limited use and has been reserved primarily for patients with symptomatic refractory AF or performed in conjunction with mitral valve surgery. Surgical and minisurgical approaches to isolating the PV ostia are being developed that may accomplish the same results as catheter-based approaches.

Pacemaker Therapy

Permanent pacing may become necessary for sick sinus syndrome, tachy-brady syndromes, bradyarrhythmias occurring as a result of drug therapy, or after AV junction ablation. Mode-switching algorithms can change operation from dual-chamber pacing to single-chamber (VVI or VVIR) or DDIR pacing at the onset of atrial arrhythmias. Today's pacemakers also provide atrial overdrive pacing algorithms.

Studies suggest that dual-chamber or atrial pacing that maintains AV synchrony may reduce the incidence of AF when compared to single-chamber ventricular pacing. These studies have consisted largely of patients with sick sinus syndrome who require permanent pacing. A prospective randomized trial of atrial versus ventricular pacing in 225 patients with sick sinus syndrome reported the frequency of AF and the thromboembolic event rate to be higher in the ventricular-paced group. However, another randomized study showed no difference in outcome.

Although most studies have been nonrandomized, comparisons of patients with physiologic dual-chamber, atrial synchronous (DDD, DDI, or AAI) pacing versus ventricular paced (VVI) modes suggest a decreased incidence in the development of AF in the physiologically paced groups. AF that occurs via vagally mediated mechanisms has also been successfully controlled by atrial overdrive pacing.

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QUESTIONS AND ANSWERS

Questions

1. Which of the following antiarrhythmic medications are appropriate for use in patients with significant left ventricular (LV) hypertrophy due to hypertension?
   a. Flecainide
   b. Sotalol
   c. Propafenone
   d. Amiodarone
   e. Quinidine

2. Which of the following is true of electrical cardioversion of atrial fibrillation (AF)?
   a. 360 J is an appropriate starting energy level for biphasic defibrillation.
   b. Biphasic defibrillation has been shown to lower the electrical threshold for successful defibrillation.
   c. It is safe in patients with digoxin toxicity.
   d. External defibrillation is not safe in patients with coexisting internal cardiac defibrillators; rather,

defibrillation from the device is preferable.
e. Defibrillation should be unsynchronized.

3. A 77-year-old female has paroxysmal AF, treated hypertension on medications, COPD, and treated hyperthyroidism (she is currently euthyroid).
   a. An appropriate anticoagulation strategy would be:
   b. None
   c. Aspirin 81 mg
   d. Aspirin 325 mg
   e. Coumadin for an INR of 2.5 to 3.5
   f. Coumadin for an INR of 2.0 to 3.0

4. All of the following medications are appropriate therapies for patients with hemodynamically stable pre-excited AF except:
   a. Amiodarone
   b. Ibutilide
   c. Procainamide
   d. Disopyramide
   e. Digoxin

5. A 50-year-old woman with a history of breast cancer, Menier disease, and poorly treated hyperthyroidism presents with paroxysmal AF with rapid ventricular rates. She has no history of valvular heart disease and her CHADS II score is 0. Appropriate pharmacologic therapies include:
   a. Aspirin alone
   b. Aspirin plus a beta blocker
   c. Coumadin for an INR of 2.0 to 3.0 alone
   d. Coumadin for an INR of 2.0 to 3.0 with a beta blocker
   e. Coumadin for an INR of 2.5 to 3.5 with a beta blocker

Answers

1. Answer D: Per current ACC/AHA/HRS guidelines, amiodarone is the only acceptable pharmacologic option for the treatment of atrial fibrillation in patients with hypertension and significant left ventricular hypertrophy.

2. Answer B: Biphasic defibrillation has been shown to lower defibrillation thresholds in patients with a trial fibrillation. Cardioversion should be performed in a synchronized mode and is safe in patients with intracardiac devices. Cardioversion should not be performed in digoxin toxicity due to the risk of provoking ventricular arrhythmias.

3. Answer E: This patients CHADS II score is two by age and the presence of hypertension. The patient's annual risk of stroke risk is approximately 4.0%. The patient should receive oral anticoagulation with the goal INR between 2 and 3.

4. Answer E: Digoxin should not be used in patients with pre-excited atrial fibrillation as it can cause slowing in the AV node which could lead to increased conduction down the accessory pathway leading to very fast ventricular rates and possible ventricular fibrillation.

5. Answer D: Despite the patient's CHADS II score, the patient has untreated hyperthyroidism which increases the risk of stroke substantially. The patient should receive anticoagulation for an IRN between 2 and 3.

CHAPTER

Supraventricular Tachycardias

Christopher P. Ingelmo and P. Peter Borek

Supraventricular tachycardias (SVTs) continue to be the most common as well as most diverse type of cardiac arrhythmias. SVTs occur in all age-groups and are associated with a wide range of etiologies, heart rates, frequency, and severity of heart disease. The numerous potential mechanisms and variety of descriptive adjectives for these arrhythmias make establishing a succinct classification system difficult. Approaches to classification of SVT include (a) clinical behavior (i.e., paroxysmal, persistent, permanent, sustained, nonsustained and chronic), (b) mechanism (i.e., ectopic, reentrant, reciprocating, slow/fast, fast/slow, orthodromic, and antidromic), (c) electrocardiographic appearance (i.e., narrow or wide QRS), and finally (d) location (i.e., sinus, atrial, and atrioventricular [AV] nodal/junctional). These types of classifications may provide important information in the diagnosis and treatment of SVTs. Clinicians often have difficulty determining a consistent and inclusive comprehensive management algorithm that may be applied to all forms of SVTs. This chapter briefly reviews the most common SVTs and also provides a concise approach to diagnosis that incorporates all four methods of classification.

Symptoms of SVT may range from none to profoundly disabling. SVT generally presents with a variety of symptoms, the most common of which is palpitations. Palpitations may be accompanied by shortness of breath, chest pain, lightheadedness, near-syncope, and/or syncope. The cardiac evaluation of palpitations may include electrocardiography, ambulatory Holter monitoring, cardiac event recording, transtelephonic monitoring, and, less commonly, an implantable loop recorder. The goals of this diagnostic process are twofold. First, it is necessary to document the arrhythmia. Second, it is helpful to correlate symptoms with the documented arrhythmia. Although ambulatory Holter monitoring is easy to obtain and thus frequently ordered for patients with suspected SVT, its diagnostic yield is very low. Symptoms and simultaneous electrocardiographic abnormalities are observed in only 2% to 13% of 24-hour ambulatory Holter monitors. In contrast, patient-activated cardiac event

recorders provide a greater yield and are more cost-effective than ambulatory Holter monitoring in the correlation of arrhythmia with transient symptoms.[1]

Implantable loop recorders are placed subcutaneously at a parasternal chest site, similar to a pacemaker. These monitors can record arrhythmias for more than a year. They record when activated by an external trigger or following automatic programmed parameters within the device. Because implantation of this device is considered invasive, it is reserved for patients with severe symptoms associated with presumed tachyarrhythmic episodes or those with very rare occurrences that are difficult to diagnose with less invasive testing modalities.

APPROACHING SUPRAVENTRICULAR TACHYCARDIA: AV NODE DEPENDENT VERSUS ATRIAL AND SINUS NODE DEPENDENT

In terms of evaluating arrhythmias based on site of origin, there are three types of SVT: (a) sinus node dependent (sinus tachycardia, inappropriate sinus tachycardia, and sinus node reentry), (b) atrial dependent (atrial tachycardia, atrial flutter, and atrial fibrillation), and (c) AV node/junction dependent (atrioventricular node reentry tachycardia [AVNRT] and atrioventricular reciprocating tachycardia [AVRT]). The first step in classifying SVTs is to differentiate sinus and atrial tachycardias from AV node/junctional tachycardias.[2,3] This difference is easiest to see if the tachycardia is observed during changes in AV node conduction. AV node conduction can be altered by a change in vagal tone or with medications such as calcium channel blockers or adenosine. If spontaneous changes in vagal tone do not change AV node conduction, maneuvers may be performed to prolong AV node conduction and refractoriness. Physiologic maneuvers include deep breathing, carotid sinus massage, the strain phase of the Valsalva maneuver, and facial immersion. Carotid sinus massage increases vagal tone and is easily performed at the bedside. In older patients, it is important to exclude the presence of significant carotid artery atherosclerotic disease before performing carotid sinus massage. The “diving reflex” may be applied with pediatric patients. This can be done by placing a plastic bag filled with ice water on the patient ’s face for 15 to 20 seconds. Though this maneuver may be effective, it is less well tolerated and therefore not frequently used.

If physiologic maneuvers are unsuccessful, drugs may be used to alter AV node conduction. Edrophonium chloride (Tensilon) was used classically because its potent vagotonic effect creates temporary AV node block; however, it is often poorly tolerated and therefore is no longer commonly used. Verapamil and diltiazem can also be used to create temporary AV node block. These calcium channel–blocking medications have a slow onset, allowing for a “gentler” diagnosis than sudden AV node block. However, calcium channel blockers have potential for side effects such as hypotension. Adenosine

is the most commonly used drug for this purpose because of its extremely short half-life. Adenosine provides a very transient AV nodal block. This effect is maximized when it is administered in a rapid intravenous bolus via a central vein. Care must be taken when administered in patients with bronchospasm as it may exacerbate their reactive airway disease.

Observing tachycardia behavior during slowed AV nodal conduction or AV block may help differentiate between sinus/atrial and AV nodal/junctional tachycardias. Perpetuation of the tachycardia, despite AV block occurs primarily with atrial/sinus tachycardias (Fig. 29.1). Termination of the tachycardia as a result of AV block often implicates the AV node as an essential part of the tachycardia circuit (thus an AV node/junctional-dependent tachycardia). There are rare exceptions to this rule. First, some atrial tachycardias terminate with adenosine administration. However, these atrial tachycardias often slow gradually before terminating, as compared to AV node–dependent arrhythmias, which terminate suddenly. Additionally, if the tachycardia breaks spontaneously, examining the termination can provide insight as to whether the tachycardia is atrial/sinus or AV nodal/junctional. If the tachycardia terminates with a P wave that is not followed by a QRS (Fig. 29.2), it is most consistent with an AV nodal/junctional-dependent tachycardia. This is best explained by understanding that if the rhythm had been an atrial tachycardia, it would have had to terminate at the atrial focus and develop AV block simultaneously, which is very unlikely.

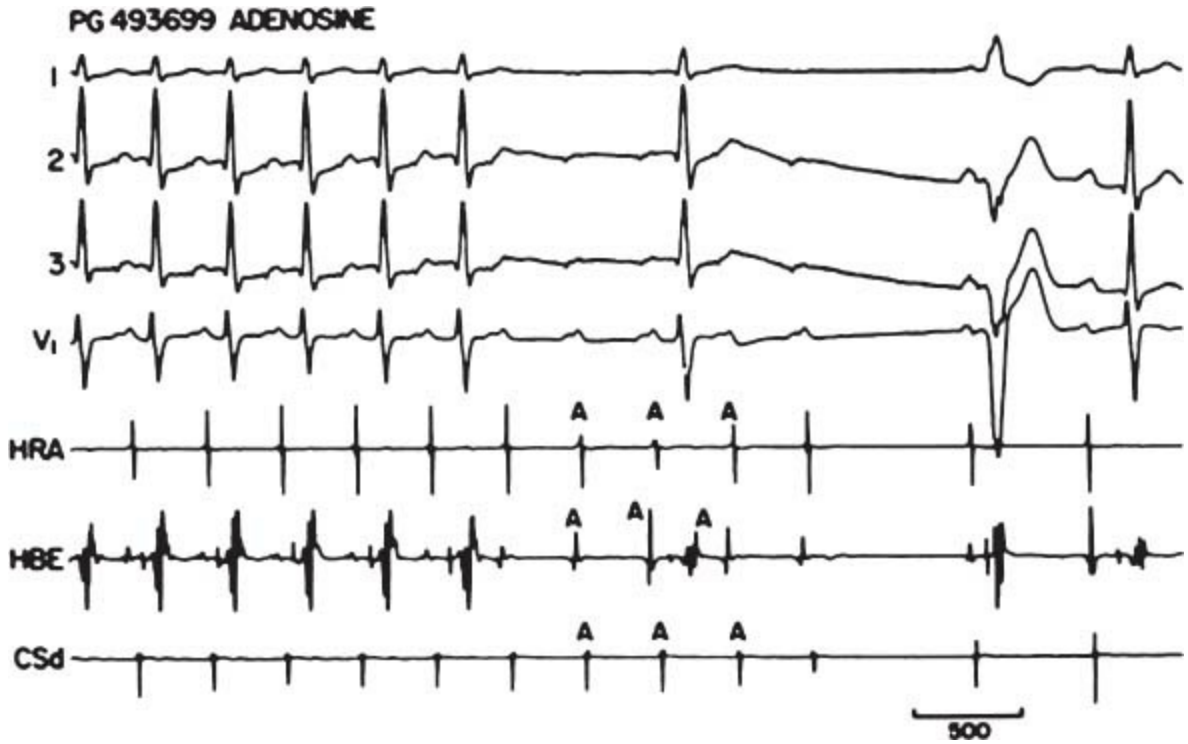

FIGURE 29.1 Atrial tachycardia terminating following the administration of adenosine demonstrating continuation of the atrial tachycardia despite block in the AV node. This would imply that the tachycardia is not AV nodal dependent.

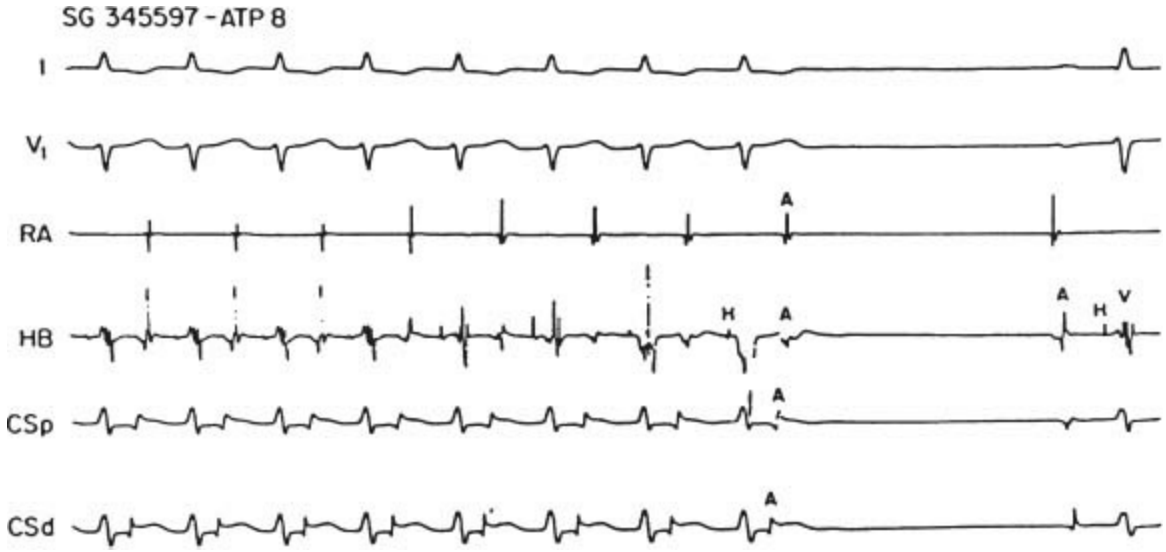

FIGURE 29.2 AV nodal/junctional-dependent tachycardia.

Other electrocardiographic findings are helpful in distinguishing sinus/atrial-dependent from AV nodal/junctional-dependent tachycardia. The P-wave axis indicates the origin of atrial depolarization, which may help differentiate sinus/atrial from AV junction tachycardia. A "high to low" activation sequence is manifested by a surface electrocardiogram positive P-wave deflection in the inferior leads. This is most consistent with a sinus or high atrial tachycardia. AV junctional tachycardias must activate the atria from the area at the AV ring (often near the AV node), leading to "low to high" activation and negative P-waves in the inferior leads.

If the tachycardia appears to have a 1:1 P:QRS relationship, examining the relationship of the R wave to the following P wave may provide additional information to differentiate between sinus/atrial versus AV nodal/junctional tachycardias. If the distance from the R to the following P wave is >50% of the R–R distance, the tachycardia is termed "short RP". If the distance from the R to the following P is <50% of the R—R distance, the tachycardia is termed "long RP" A short RP interval is more often seen in AV nodal/junctional-dependent tachycardias (AVNRT and AVRT) and a long RP interval is more often seen in sinus/atrial tachycardias. However, this rule also has exceptions that should be noted. Long RP tachycardias, though typically indicative of sinus/atrial dependence, can be seen in atypical (fast–slow) AVNRT or in an unusual form of AVRT that occurs with an accessory pathway (AP) that displays decremental properties. This is seen in the permanent form of junctional reciprocating tachycardia (PJRT). Also, sinus or ectopic tachycardias with a long first-degree AV block may present with a short R–P interval.

In <50% of patients, an appreciable P wave may not be clearly distinct from the QRS. This is because the P wave is hidden within the QRS complex or because the rate and artifact of the tachycardia mask the P wave. In typical AV node reentrant tachycardia the P wave generally occurs simultaneously with the QRS. In this

arrhythmia, the P wave is often inscribed in the terminal portion of the QRS and results in pseudo-R ' deflection in V_1 or S wave in II, III, and aVF. However, appreciation of this change may require comparison of this QRS during tachycardia with the QRS when in normal sinus rhythm (Fig. 29.3).

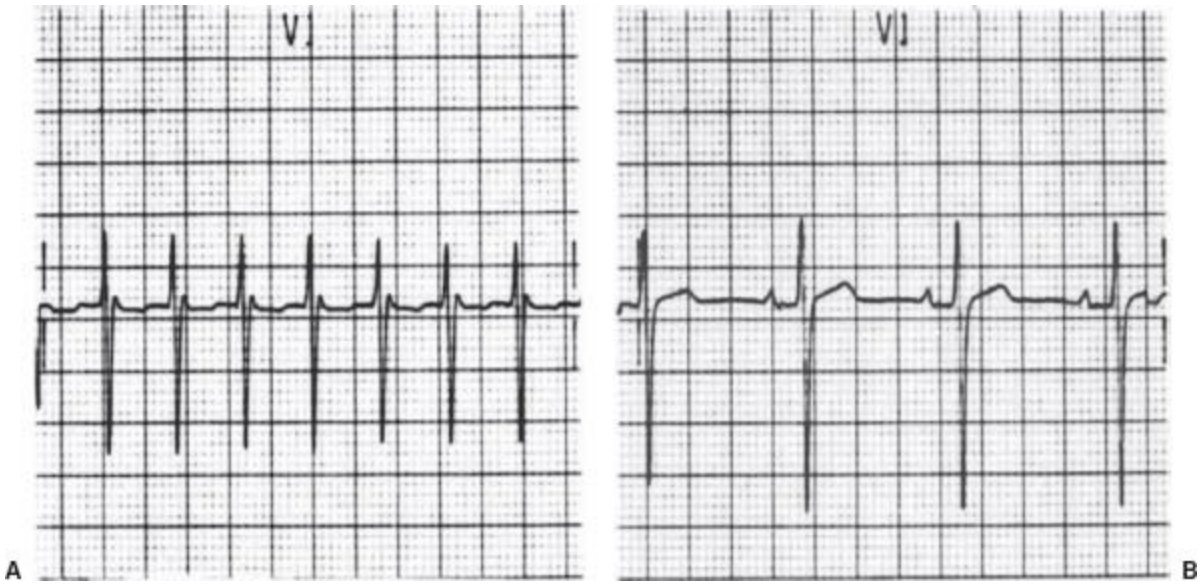

FIGURE 29.3 A: ECG in typical AV node re-entrant tachycardia. **B:** ECG in normal sinus rhythm.

AV NODE-DEPENDENT TACHYCARDIAS: AVNRT VERSUS AVRT

Once the above methods lead to establishing that the rhythm is AV nodal dependent, further evaluation is needed to determine what type of AV nodal tachycardia is present. AV node–dependent tachycardias include (a) AVNRT and (b) AVRT using an AP.

AV Nodal Reentry Tachycardia

Clinical Presentation and Diagnosis

In patients without ventricular pre-excitation in sinus rhythm, typical AVNRT is the most common mechanism of SVT, accounting for >60% of presenting SVTs.[4–6] As shown in Table 29.1, AVNRT is seen in children as well as in the elderly; however, it is most common in the fourth decade. This arrhythmia affects women more often than men, as women represent two-thirds of the patients with AVNRT. This arrhythmia is not associated with structural heart disease. Although palpitations are the primary symptom of this arrhythmia, syncope and near-syncope have been observed, most notably in elderly patients. Because the right atrium is activated nearly simultaneously with the right ventricle, it is often contracting against a closed tricuspid valve, causing many patients to feel neck fullness. Canon A waves can be seen on physical exam. Because

this is an AV node–dependent arrhythmia, termination can be achieved with AV nodal blockade. Onset and termination are characteristically abrupt. AVNRT is often triggered by a premature atrial beat which finds the fast pathway refractory and conducts down the slow pathway with associated PR prolongation consistent with dual AV node physiology AVNRT typically terminates with a retrograde P wave (negative P-wave axis in the inferior leads) without a subsequent QRS indicating AV block and dependence of the tachycardia on AV nodal conduction. Because the majority of the reentry circuit is within the AV node, the atrial and ventricular activation are nearly simultaneous; thus, this is a "short RP" tachycardia. The retrograde P wave is frequently hidden within the QRS complex.

TABLE
29.1 Narrow-QRS Tachycardia: Clinical and Electrophysiologic Characteristics

	Common AVN Reentry	Orthodromic Tachycardia	Long-RP Tachycardia	Atrial
Age (y)	56 ± 19	35 ± 15	56 ± 24	61.5 ± 6
Range	19–80	19–56	22–78	56–70
Female gender (%)	70	54	50	50
Cycle length (ms)	357.5 ± 56.8	321.25 ± 60	510 ± 10	373.3 ± 37.3
Range	230–450	220–420	500–520	320–400
P polarity (%)	—	—	100%	70%
Typical P location (%)	100	42	100	70
QRS alternation (%)	8	36	0	0

Diagnostic categories listed in the table represent the final diagnosis made at electrophysiology study. P polarity was not identifiable in AV node reentry and orthodromic tachycardia.

Mechanism

The electrophysiologic circuit of AVNRT uses regions of tissue within or adjacent to the AV node that possess different electrophysiologic properties. Patients with AVNRT have dual AV nodal physiology. Within or near the AV node there is a fast conducting pathway with a long refractory period and a slower conducting pathway with a shorter refractory period. In typical AVNRT (slow–fast form) there is antegrade conduction over the slower pathway and retrograde conduction over the fast pathway (Fig. 29.4). AVNRT typically initiates with a premature atrial beat that arrives at the AV node when the fast pathway is still refractory (longer refractory time), but the slow pathway is able to conduct antegrade. However, because of the slower conduction, by the time the impulse arrives to the compact AV node, the fast pathway has recovered and is able to conduct retrograde back up to the atrium. Thus, typical AVNRT is down the slow pathway and up the fast pathway. Because the atria are activated via the fast pathway,

the retrograde P wave is very close to (or buried within) the QRS. As mentioned previously, ECG lead V_1 may reveal a pseudo-R prime pattern due to deformation of the terminal portion of the QRS complex by the retrograde P wave. This ECG finding is very specific for AVNRT.

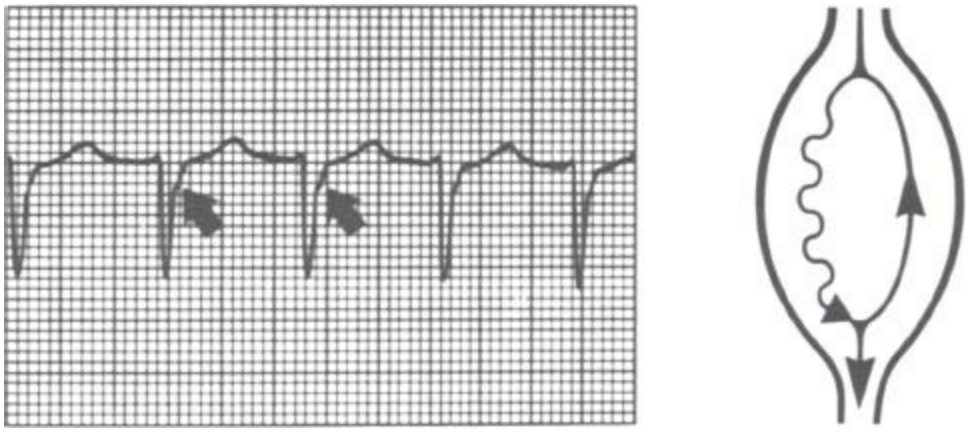

FIGURE 29.4 Typical AVNRT denoting superimposed P waves and retrograde atrial depolarization (arrows).

In the unusual variety or "atypical" AVNRT, antegrade conduction occurs over the fast pathway and retrograde conduction over the slow or intermediate pathway. Though this "atypical" form uses a similar mechanism (dual AV node physiology), although in reverse, it results in a long RP (retrograde slow conduction) and a short PR (fast antegrade conduction) interval. This atypical AVNRT is still AV node dependent and thus may terminate with adenosine or during any change in AV nodal conduction properties.

Treatment

Because both typical and atypical AVNRT are manifestations of dual AV node physiology, they are treated in the same fashion. Patients with unstable hemodynamics should undergo immediate cardioversion. In the acute setting, a hemodynamically stable patient is typically responsive to vagal maneuvers or adenosine. If those are not successful at terminating the tachycardia then an intravenous formulation of beta-blockers and calcium channel blockers may be utilized. If the patient has recurrent arrhythmic episodes, longer-acting medications that alter AV node conduction (including beta-blockers and calcium antagonists) may be used. Though medications can be successful, catheter ablation is considered the treatment of choice. Ablation is a Class I recommendation for patients with one or more episodes of AVNRT who desire resolution of the arrhythmia and patients with recurrent symptomatic or poorly tolerated AVNRT episodes. Catheter ablation of either form of AV node reentry consists of an anatomic ablation of the slow pathway located at the posterior input to the AV node. This area is most often bordered by the coronary sinus and the tendon of Todaro

posteriorly and the tricuspid annulus anteriorly. Once identified, radiofrequency or cryotherapy ablation or modification of the slow pathway is performed to the point where tachycardia is no longer inducible.

AV Reciprocating Tachycardia and Ventricular Pre-excitation (Wolff–Parkinson–White Syndrome)

Clinical Presentation and Diagnosis

Accessory AV connections or pathways may also participate in AV nodal–dependent reentrant arrhythmias. The presence of such an AP may be apparent by surface ECG. Because of the rapid and nondecremental conduction properties of these pathways, they may "pre-excite" the ventricle. Ventricular pre-excitation results in a short PR interval and slurring of the upstroke of the QRS ("delta wave"). This ECG abnormality is termed Wolff–Parkinson–White (WPW) pattern. The term WPW syndrome is reserved for patients who also have clinical SVT. It is estimated that 1 to 1.5 in 1,000 ECGs show a WPW pattern. Population-based studies have indicated that 50% to 60% of patients with WPW pattern demonstrate symptoms that may include palpitations or more severe symptoms such as syncope.[7] Approximately 85% of such symptomatic patients have AV reentrant tachycardia using the AV node as the antegrade limb and the AP as the retrograde limb of the circuit.[8,9] Approximately 30% to 40% of patients with WPW are capable of sustaining atrial fibrillation.

This type of tachycardia is not only dependent on the AV node but requires the presence of an AP. This pathway provides an additional connection between the atria and ventricles, other than the AV node. The term "pre-excitation" stems from the fact that the ventricle receives electrical activation from both the AV node-His-Purkinje system (AVN-HPS) and the AP Because antegrade conduction via the AP is not decremental as with the AV node, the ventricle is activated via the pathway before the AVN-HPS activation. This pre-excitation is represented by the delta wave on the ECG. When there is evidence of ventricular pre-excitation by ECG at baseline, the AP is described as "manifest." This pre-excitation tends to be more evident at more rapid atrial rates, when AV nodal conduction is slowed, making preexcitation even more apparent. Occasionally, conduction through the AV node is preferred to that over the AP. This may be secondary to slow or poor antegrade conduction in the AP or to the location of the pathway. In these patients there may be minimal or no delta wave on the ECG, as the ventricle is predominantly or completely activated via the AV node. The AP is still present and may be able to conduct retrograde (and thus be able to cause tachycardia), but it is not evident in sinus rhythm. These APs are termed "concealed."

It is important to remember that the presence of an AP does not always indicate that this pathway is a critical part of the presenting SVT. For this reason it is important first to determine the role of the AV node (dependent or independent) in the presenting SVT. APs provide only an additional connection between the atria and ventricles. Patients

with an AP and even a history of WPW syndrome may also have other SVTs (i.e., AVNRT) that have no relationship to the AP.

Accessory Pathways

APs may be located along either the mitral or tricuspid annuli. These pathways consist of a bundle of myocardial muscle that bypasses the AV groove with direct insertion on the ventricular myocardium of the right or left ventricle. On rare occasions, the lower insertion is in proximity or attached to the branches of the right bundle. As shown in Table 29.2, of all APs, almost half are located on the left side of the heart along the mitral annulus, nearly one-third are in the posteroseptal region, and the remainder are at the right anteroseptal region or the right lateral wall of the tricuspid annulus.

TABLE
29.2 Distribution of Most APs

	Left Lateral (%)	Posteroseptal (%)	Right Anterior (%)	Right Lateral (%)
Gallagher (1978)	47	27	9	17
Milstein (1987)	51	32	14	3

Multiple electrocardiographic algorithms have been proposed to diagnose the location of the AP from surface 12-lead ECGs (Fig. 29.5).[9–14] Unfortunately, no algorithm has proven entirely reliable. A general and easy classification proposed by Rosenbaum and Hecht[15] describes a "type A pattern," with a positive delta wave and QRS in the precordial leads (Fig. 29.6), which is usually associated with a left lateral AP, and a "type B pattern," with a left bundle branch block-type QRS morphology in the precordial leads, which is usually associated with a right-sided pathway (Fig. 29.7).

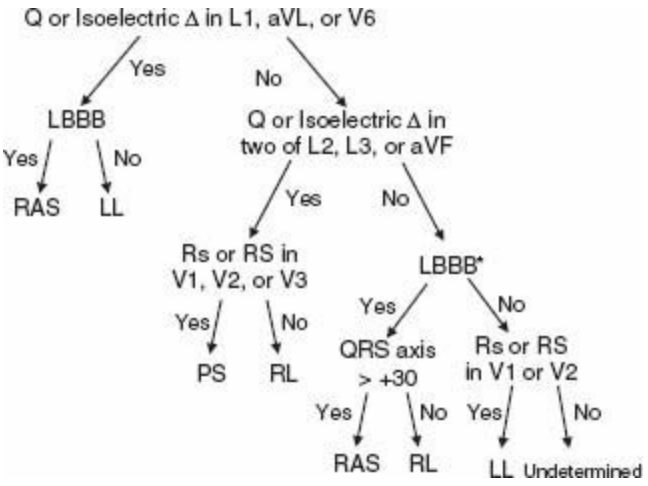

FIGURE 29.5 Milstein 's algorithm for localization of APs. LL, left lateral; PS, posteroseptal; RAS, right anteroseptal; RL, right lateral. *LBBB, +QRS LL, rS V, and V_2. (Reprinted from Milstein S, Sharma AD, Guiraudon

GM, et al. An algorithm for the electrocardiographic localization of accessory pathways in the Wolff–Parkinson–White syndrome. Pacing Clin Electrophysiol. 1987;10(3 pt 1): 555–563, with permission from John Wiley and Sons.)

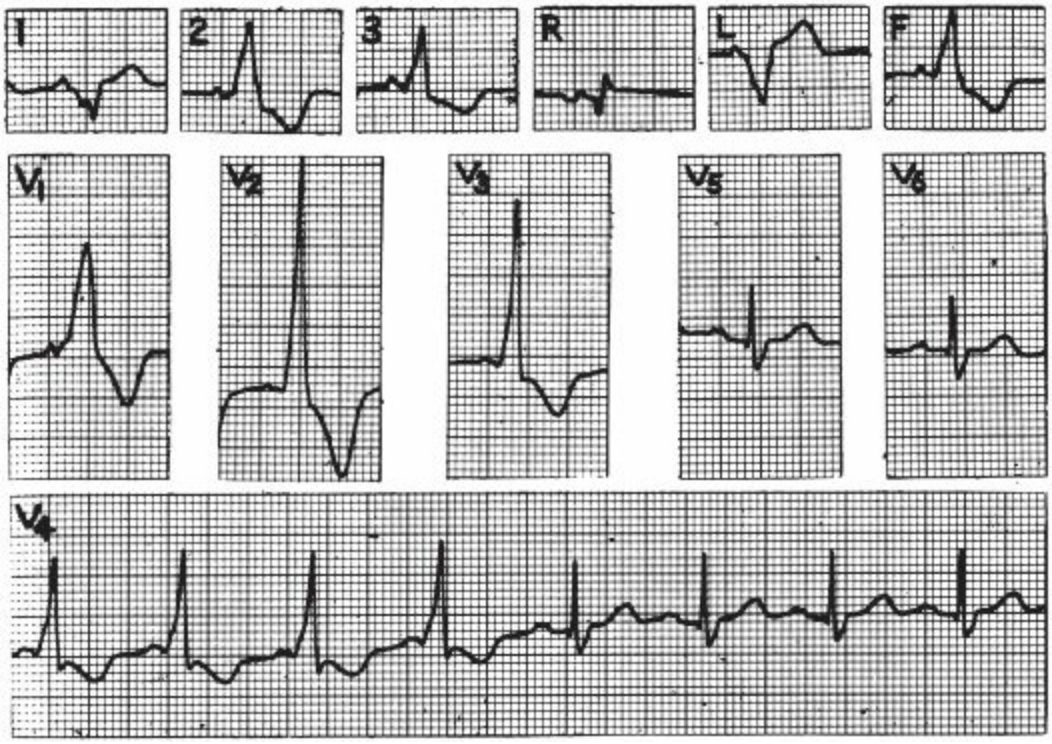

FIGURE 29.6 Type A accessory pathway.

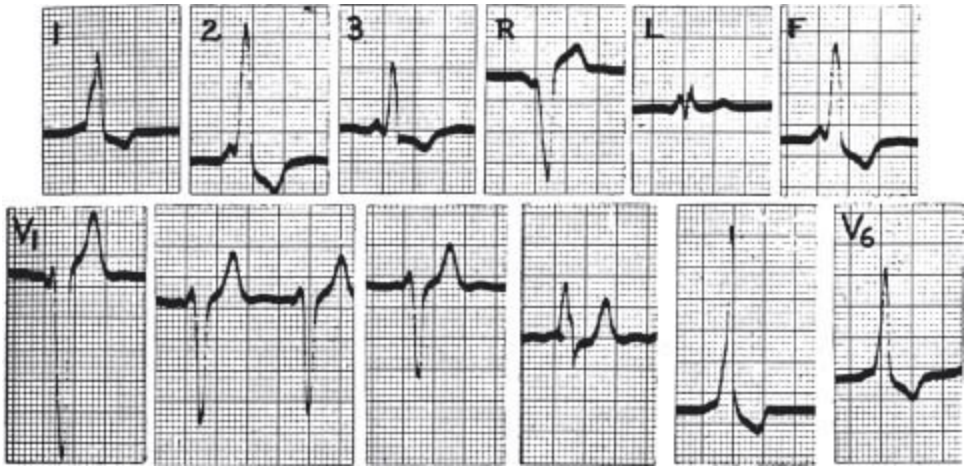

FIGURE 29.7 Type B accessory pathway.

Mechanism

AVRT is a reentrant arrhythmia. In AVRT, one limb of the reentry circuit is the AV node and the other limb is the AP. The clinical importance of APs and pre-excitation reside primarily in their predisposition to tachyarrhythmias. The conduction properties of the AP (speed of conduction and recovery) determine the likelihood of developing a reentrant circuit arrhythmia. The direction of the circuit differentiates the two types of

AVRT: orthodromic AVRT and antidromic AVRT. Orthodromic reciprocating tachycardia (ORT) comprises the majority of the reciprocating tachycardias associated with WPW syndrome. The antegrade limb of this reentrant circuit is the AV node, whereas the retrograde limb is the AP. Because the ventricle is activated via the AV node, the QRS complex is narrow. Though it is rare, antidromic reciprocating tachycardia (ART) uses the AP as the antegrade limb and the AV node as the retrograde limb. Because the ventricle is activated via the AP, the QRS complex is wide (maximal pre-excitation).

Electrophysiologic Characteristics and Diagnostic Maneuvers

ORT is typically characterized by a short RP and a long PR interval as the circuit is conducting up the AP and down the AV node. Because conduction from the atria to the ventricles is via the AV node, the QRS morphology during tachycardia should be similar (in the absence of aberration) to the QRS morphology during normal sinus rhythm.

Though algorithms based on the surface ECG are notoriously inconsistent, behavior of the AP during tachycardia can provide clinicians with hints as to the location of the pathway. For example, spontaneous or induced functional bundle branch block during ORT can yield a diagnostically useful phenomenon. As demonstrated in Figure. 29.8A,B, if the bundle branch block is ipsilateral to a free wall bypass tract, the retrograde reentrant impulse is compelled to traverse a greater distance from the His–Purkinje fibers via the AP and to the atrium. As a result, the global VA conduction time during the tachycardia must increase (usually by at least 35 milliseconds). The tachycardia cycle length may also increase such that the rate of the tachycardia may become slower. In contrast, if the bundle branch block is contralateral to a free wall bypass tract, there is no change in the distance the retrograde reentrant impulse has to travel to reach the atrium. Thus there is no effect on the tachycardia cycle length. Therefore, an SVT that slows with the development of bundle branch block should invoke suspicion that the tachycardia is ORT using an AP located ipsilateral to the site of bundle branch block.

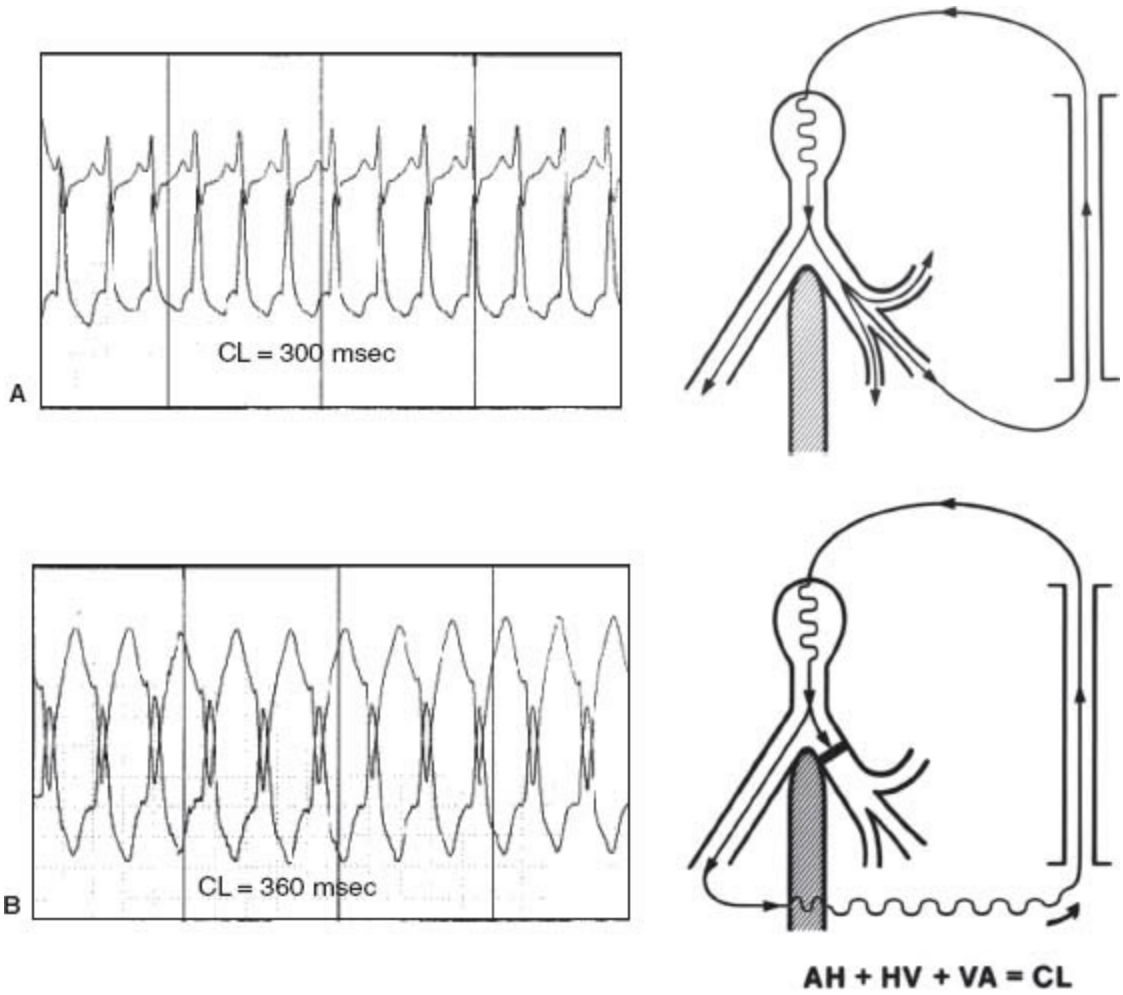

FIGURE 29.8 A - A narrow complex tachycardia utilizing the ipsilateral bundle (left bundle) antegrade and accessory pathway retrograde. Note the cycle length of the tachycardia and compare to **B** where the tachycardia now utilizes the contralateral bundle as the left bundle is blocked. This may result in prolongation of the cycle length of the tachycardia and is diagnostic of the location of the pathway.

Exceptions and Rare Forms of AVRT

Occasionally, patients present with an incessant ORT in which retrograde conduction up the AP is decremental.

Though it is rare, this type of AP is associated with a tachycardia called the PJRT. PJRT typically uses a concealed posteroseptal AP with a long conduction time and decremental AV node–like properties. These decremental properties prolong the time between the R and P, often making it a "long RP" tachycardia rather than the typical "short RP." Because of the incessant nature of this arrhythmia, it has been associated with tachycardia-induced cardiomyopathy. Tachycardia-induced cardiomyopathy is not related to any one specific SVT, but is associated with any incessant or persistent tachycardia.

Antidromic tachycardia is the least common arrhythmia associated with WPW syndrome, occurring in only 5% to 10% of patients. This tachycardia is characterized by

a wide QRS complex that is fully pre-excited with a regular R–R interval. If the diagnosis of WPW is not recognized, this tachycardia may be mistaken for ventricular tachycardia.

Uncommonly, patients may have more than one AP. In these cases there are multiple potential reentrant arrhythmia circuits. Of these patients, 33% to 60% will present with antidromic tachycardia. Even less common is a tachycardia involving two APs as both the antegrade and retrograde limbs of the circuit, without any involvement of the AV node. In these very rare cases, the tachycardia does not terminate with AV node blockade. In patients with more than one pathway, more likely scenarios are one pathway involved in either ORT or ART with the AV node as one limb of the circuit, and the other pathways as "bystanders." The term "bystander" describes accessory AV pathways that exist, but that are not part of the tachycardia circuit. The typical use of the term "bystander conduction" involves a wide-complex pre-excited SVT that is due to typical AVNRT (antegrade fast AV nodal pathway conduction and retrograde slow AV nodal pathway conduction) with concomitant antegrade conduction through the AP producing the wide-complex QRS pattern.

Occasionally, the presence of multiple APs will become apparent only after the dominant pathway has been ablated. The Ebstein anomaly is associated with WPW syndrome in 6% to 26% of patients with this congenital heart defect. In addition, 40% to 55% of patients with WPW and the Ebstein anomaly have multiple APs.[16]

Treatment

Treatment of a patient with WPW syndrome (presence of an AP and tachycardia) may involve both drug therapy and catheter ablation. In the acute setting, patients with ORT (conduction down the AV node and thus a narrow QRS complex) can be treated with AV nodal-blocking agents such as adenosine and vagal maneuvers. Chronic treatment may be directed at any essential component of the circuit. Administration of calcium channel antagonists or beta-adrenergic blockers affects the AV node, whereas antiarrhythmic drugs including flecainide, propafenone, quinidine, procainamide, and amiodarone may be chosen to target the AP. More invasive options such as catheter ablation therapy of the AP play a more prominent role in management of WPW syndrome. Catheter ablation is a Class I recommendation for patients with WPW syndrome with or without atrial fibrillation as well as patients with no evidence of pre-excitation by Electrocardiogram (EKG) but poorly tolerated AVRT episodes. With newer computerized mapping technologies, the acute success rate nears 100%, with a <1% risk of significant complications. However, pathway location may play a role in risk during ablative procedures in that some right anteroseptal pathways are very close to the AV node, increasing the possibility of disruption of normal conduction during ablation.

Wolff–Parkinson–White Syndrome and Sudden Cardiac Death

In contrast, in patients presenting with pre-excited tachycardia, adenosine and AV node-blocking agents are absolutely contraindicated. In these rhythms, the ventricles are being activated antegrade via the AP Often these rhythms are atrial arrhythmias (atrial tachycardia, atrial fibrillation, and atrial flutter) that are conducting predominantly down the AP (and partially down the AV node). In these scenarios, the "bystander" AP is conducting the tachycardia to the ventricle. If an AV-blocking agent is administered, conduction may be exclusively through the AP Because these pathways typically do not have protective decremental properties as the AV node does, rhythms such as atrial flutter/fibrillation (>300 beats/min [bpm]) may be conducted to the ventricle in a 1:1 fashion (Fig. 29.9). AV conduction at that rate may degenerate rapidly into ventricular fibrillation and subsequent cardiac arrest. In these patients, procainamide, flecainide, propafenone, or amiodarone should be considered. In case of atrial fibrillation/flutter with rapid response and hemodynamic instability, electrical direct-current cardioversion is the treatment of choice.

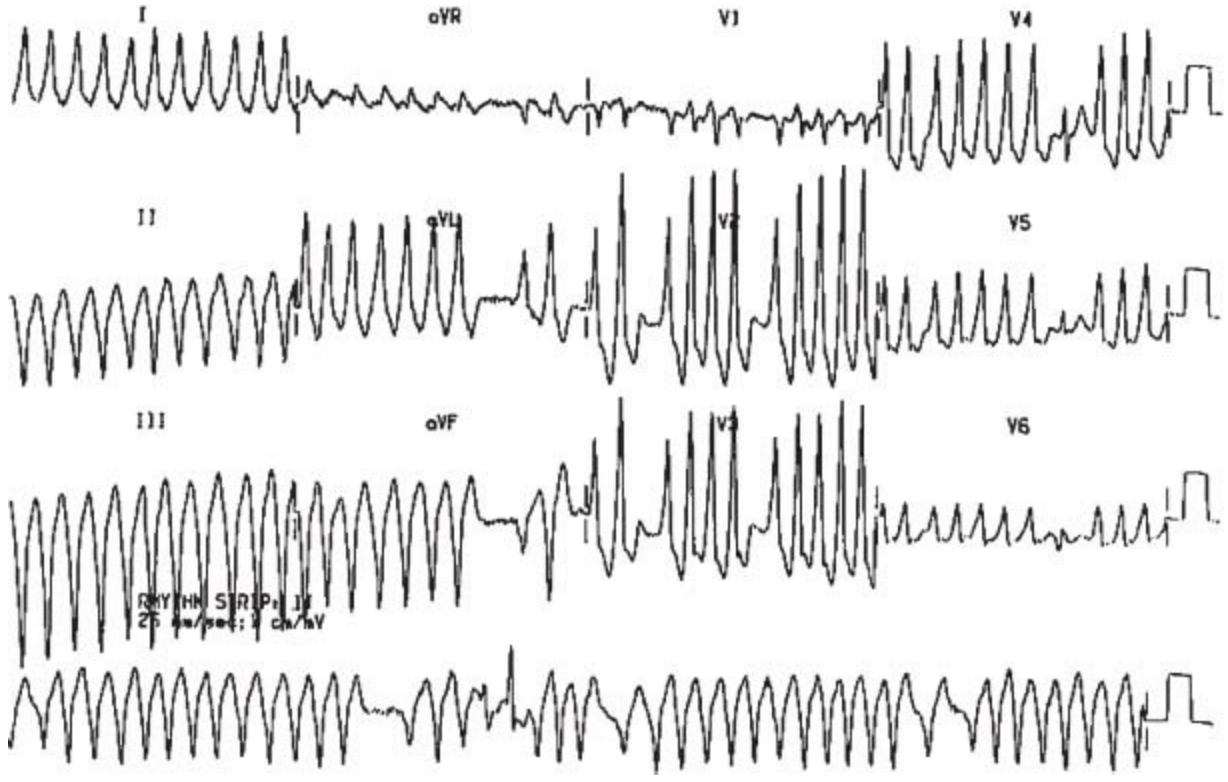

FIGURE 29.9 Atrial arrhythmia in WPW syndrome.

As shown in Table 29.3, atrial fibrillation may be a coexisting or presenting arrhythmia in about 20% to 40% of patients with WPW syndrome. Atrial fibrillation in the presence of an AP with rapid antegrade conduction can result in degeneration to ventricular fibrillation and subsequently result in sudden cardiac death. The risk of

sudden death for patients with WPW syndrome is not clear but is definitely not very high. Population-based studies suggest an incidence of 0.15% per year, and sudden death occurs almost exclusively in previously symptomatic patients.[7]

TABLE
29.3 Tachyarrhythmias in 161 WPW Patients

RT1	89
RT + AF1	32
AF	15
RT + AF + VF	13
AF + VF	5
VF	4
RT + VF	3
Total WPWs	161

RT, reciprocating tachycardia; AF, atrial fibrillation; VF, ventricular fibrillation.

This occasional occurrence of ventricular fibrillation as the initial manifestation of WPW syndrome has stimulated interest in the possibility of identifying asymptomatic patients who may be at risk for this complication. These patients possess antegrade conducting APs (pre-excitation during normal sinus rhythm) and no symptoms of SVT. Screening these patients involves evaluating the conduction properties of the AP. An easy and noninvasive method is to observe for intermittent ventricular pre-excitation by electrocardiogram, which may involve supervised treadmill stress testing or simply ambulatory Holter monitoring during the patient ’s daily activities. This intermittent pre-excitation refers to the abrupt loss of pre-excitation or the delta wave from one beat to the next. This phenomenon suggests an AP that is incapable of extremely rapid antegrade conduction and therefore carries a low risk for sudden cardiac death.[17]

If normalization of the QRS is not observed during Holter monitoring or during exercise, electrophysiologic evaluation must be considered to assess the conduction property of the AP. The most direct method for such risk stratification is the induction of atrial fibrillation in an electrophysiologic laboratory setting and the determination of the shortest R–R interval. This provides information as to the antegrade conduction capabilities of the AP. Studies have shown that patients with WPW syndrome who experienced and survived an episode of sudden cardiac death had the shortest R–R intervals.[18] A shortest R–R interval of >250 milliseconds indicates an AP that is incapable of dangerously rapid antegrade conduction. However, caution should be exercised about drawing conclusions if the shortest R–R interval is <250 milliseconds, as this does not necessarily confer a high risk of sudden death for a patient with WPW syndrome. The positive predictive value of this finding is only 20%. Therefore, the finding of a shortest R–R interval <250 milliseconds may mean simply that the patient

cannot be told that he or she is excluded from the small subset of patients with WPW syndrome who will ultimately experience sudden cardiac death.

In addition, because of the very high cure rates achievable with catheter ablation, this approach may be the best treatment option for patients involved in high-performance physical activity or with specific jobs, such as pilots or bus/truck drivers. In symptomatic patients with WPW syndrome, particularly those with frequent SVT, catheter ablation may be considered as the first-line treatment option.

In general, chronic treatment of AV nodal–dependent SVTs includes AV nodal–blocking medications (beta-adrenergic blockers and/or calcium channel antagonists) and catheter ablation. In general, it is recommended that the more invasive strategy of catheter ablation be reserved for those patients in whom medical therapy has failed or is poorly tolerated. However, there is evidence to support the consideration of catheter ablation as a first-line therapy for patients with frequent episodes of SVT, as catheter ablation in these patients is more effective and more cost-effective than medical therapy over time.

Radiofrequency catheter ablation of SVT has been shown to be cost-effective and to improve quality of life for patients with WPW syndrome who survive cardiac arrest or who experience SVT or atrial fibrillation[19] and for highly symptomatic patients with AV nodal reentrant tachycardia or AV reentrant tachycardia using a concealed AP.[20]

ATRIAL-DEPENDENT ARRHYTHMIAS

There are three predominant types of atrial-dependent arrhythmias: (a) atrial tachycardia, (b) atrial flutter, and (c) atrial fibrillation. This section discusses the first two; the third, atrial fibrillation, is discussed elsewhere in this textbook.

Atrial Tachycardia

Clinical Presentation and Diagnosis

Atrial tachycardias require only the atrium for the initiation and maintenance of the arrhythmias. It is found in all age-groups and has a wide range of potential mechanisms and clinical presentation. Atrial tachycardia can be completely asymptomatic in some individuals versus recurrent and disabling in others. Short episodes of atrial tachycardia may be seen on ambulatory Holter monitoring in 2% to 6% of normal young subjects and in up to 29% of older subjects. The majority of these episodes are asymptomatic and do not require treatment. However, in about 10% of patients, atrial tachycardia is associated with significant symptoms. As shown in Table 29.1, atrial tachycardia is more prevalent in older patients and is common in patients with underlying heart disease.

Mechanisms

There are several possible mechanisms for atrial tachycardia. Automatic or focal atrial tachycardias typically originate from a discrete area within the atria. Most commonly they originate from the right atrium in the crista terminalis region, but they can be located anywhere within the atria. They are often incessant and unresponsive to medical therapy. In fact, the incessant nature of automatic atrial tachycardia may predispose these patients to tachycardia-mediated cardiomyopathy.

Another distinct mechanism is multifocal atrial tachycardia (MAT). MAT is a SVT characterized by multiple P-wave morphologies, a varying PR interval, and an irregular ventricular response. Though the mechanism is not well understood, many feel that it is the result of multiple automatic or triggered foci driving the atria at different rates. It is distinct from atrial fibrillation in that there are well-defined P waves. By definition, there are at least three distinct P-wave morphologies and thus at least three different sources of atrial depolarization.

Treatment

As with most arrhythmias, treatment approaches for atrial tachycardia are twofold: (a) medication and (b) catheter ablation. Medications such as beta-adrenergic blockers and calcium channel antagonists can be used, although most ectopic atrial tachycardias and reentrant atrial tachycardias are not terminated or prevented by these drugs. These medications can be considered in the acute setting to control the ventricular response by decreasing AV conduction. Unfortunately, they often do little to slow or control the actual atrial focus. Other agents, including Class IA, IC, and Class III drugs are more effective in maintaining sinus rhythm or terminating the arrhythmia. Catheter ablative procedures are an alternative treatment strategy for patients in whom medical therapy fails.

MAT is most often observed in chronically ill patients, frequently those with respiratory failure or chronic pulmonary or cardiac disease. It has also been associated with digoxin toxicity, electrolytic imbalance (hypokalemia and hypomagnesemia), acute myocardial infarction, and mitral valve disease. Intravenous verapamil, intravenous potassium and magnesium have been used in the acute treatment of this arrhythmia, but with limited success. Low doses of beta-adrenergic antagonists have also been suggested but may be problematic in the majority of patients with chronic lung disease. Long-term treatment usually involves the use of a calcium channel antagonist, often requiring relatively high doses. However, the most effective therapy for MAT is treatment of the underlying medical condition or abnormality, such as treatment of bronchospasm and hypoxemia and correction of electrolyte disturbances. Cardioversion is generally ineffective for this arrhythmia disorder. Targeted catheter ablation is not effective. AV node ablation and permanent pacing may be considered in cases that are refractory to conventional medical therapy.

Atrial Flutter

Clinical Presentation and Diagnosis

Atrial flutter is a reentrant atrial tachycardia. Patients with atrial flutter can be divided into two categories: (a) those with previous ablation or cardiac surgery and (b) those with no previous ablation or cardiac surgery. Atrial flutters typically present with a regular atrial rhythm up to 300 to 350 bpm conducting to the ventricle at various rates but often at a constant multiple of the atrial rate (2:1, 4:1, etc.). Patients may be asymptomatic or with symptoms ranging from palpitations to syncope and even heart failure. The classic EKG for typical atrial flutter is characterized by negative sawtooth waves in the inferior leads with no isoelectric interval, positive flutter waves in V_1 and V_2 and negative flutter waves in V_5 and V_6 (Fig. 29.10). Atrial flutter is often a precursor to atrial fibrillation with up to 25% to 35% of patients who undergo atrial flutter ablation developing atrial fibrillation in the future.[21]

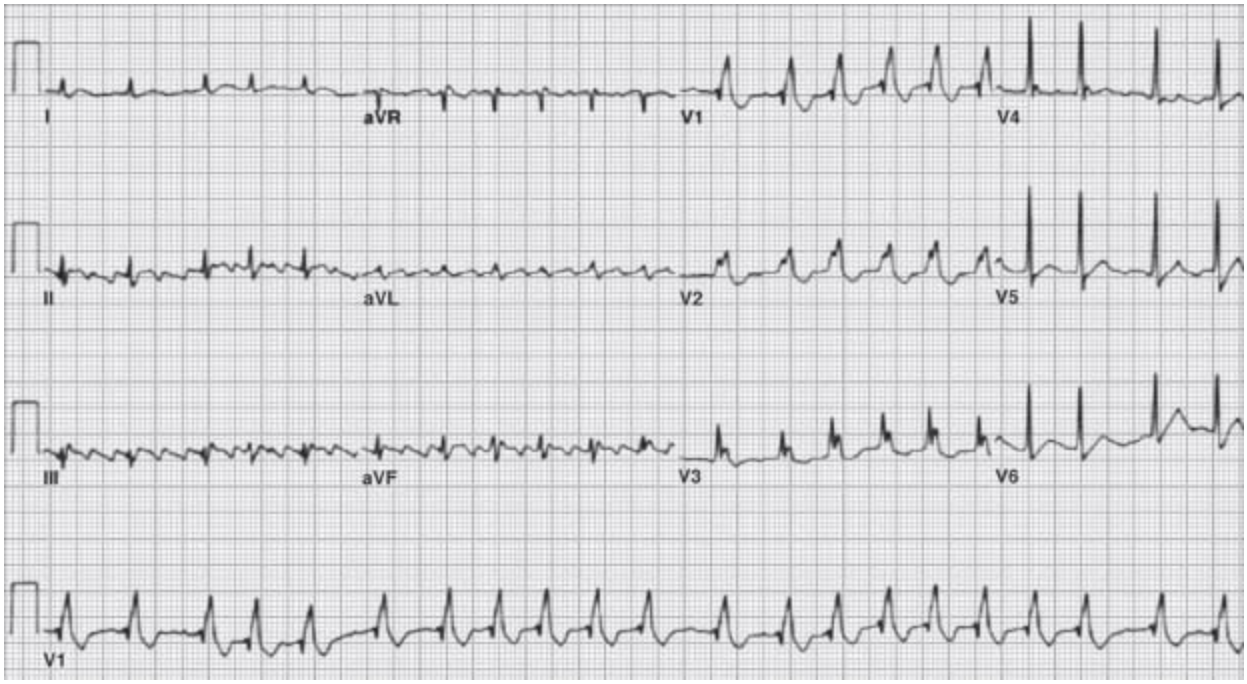

FIGURE 29.10 Typical sawtooth pattern of flutter waves.

Mechanism

Atrial flutter involves a reentrant circuit and is typically dependent on conduction through the caval-tricuspid isthmus. Atrial flutter circuits rotate around areas of nonconducting tissue within the atrium. In patients with no history of previous ablation or cardiac surgery, the area of nonconducting tissue is typically anatomic (nonconducting tissue such as the valve rings or great vessels). Typical right atrial flutter most commonly takes a “counterclockwise” rotation as it courses around the

crista terminalis, through the isthmus between the tricuspid valve and inferior vena cava, up the septum, and back around to the crista. This circuit may occur in the opposite direction in a "clockwise" direction.

In patients with a previous history of ablation or cardiac surgery, the area of nonconducting tissue is usually a site of scar from previous incisions or radiofrequency lesions. Common sites include the right atriotomy scar, the septum, perimitral valve, and near areas of previously ablated tissue.

Treatment

Like other atrial-dependent rhythms, atrial flutter is often difficult to manage medically. Beta-adrenergic blockade and calcium channel antagonists are options that can be used in the acute setting to slow conduction via the AV node and thus slow the ventricular response. Antiarrhythmic medications may also be used; however, the use of Class IC agents (flecainide, propafenone) may slow the cycle length of the flutter, permitting 1:1 AV conduction. Because of this risk, AV nodal–blocking agents (beta-blockers or calcium channel antagonists) should always be given in addition to Class IC agents. In contrast, Class III drugs may terminate and prevent atrial flutter by prolonging atrial refractoriness. Catheter ablation may be an option for many patients. With use of the newer computerized mapping technology, improved mapping of the reentrant circuit has increased success rates. During catheter ablation the goal is to interrupt the circuit in such a way that reentry cannot perpetuate. In typical isthmus-dependent right atrial flutter, a line of block with ablative lesions can be employed between two nonconducting structures (e.g., the tricuspid valve and the inferior vena cava). Once this is in place, the milieu for reentry ceases to exist.

SINUS-DEPENDENT ARRHYTHMIAS

Sinus-dependent tachycardias are rare forms of atrial tachycardias that originate at or within the area of the sinus node. These arrhythmias include sinus node reentrant tachycardia and inappropriate sinus tachycardia. Both need to be differentiated from physiologic sinus tachycardia, which is an increase of heart rate secondary to either cardiac or noncardiac etiology. In the latter form, treatment of the underlying disease may result in resolution of the sinus tachycardia. Occasionally, it is desirable to slow sinus tachycardia for symptomatic relief while the underlying etiology is being addressed. For example, beta-adrenergic blockers may be useful for thyrotoxicosis or for sinus tachycardia associated with acute myocardial infarction in the absence of heart failure. However, both sinus node reentrant tachycardia and inappropriate sinus tachycardia are arrhythmias that generally behave differently than normal sinus tachycardia. These tachycardias, characterized by a P-wave morphology similar to that observed during normal sinus rhythm, persist without any physiologic cause. Sinus node

reentry is a reentry mechanism within the sinus node and is usually observed in older patients with concomitant heart disease. In contrast, inappropriate sinus tachycardia in both the chronic and paroxysmal forms is observed mostly in young adult women.

Treatment of these arrhythmias is often very difficult. Like most tachycardias, rate control with medications such as beta-blockers and calcium channel antagonists may be used. Antiarrhythmic drug therapy has not been shown to be highly effective for these tachycardias but may be considered. When medical treatment is ineffective, catheter ablation may be considered. However, particularly for inappropriate sinus tachycardia, success with sinus node modification has been limited and should not be considered primary therapy. These arrhythmias are rare, and evaluation should focus on elucidating a possible physiologic mechanism (i.e., thyroid disease). Inappropriate sinus tachycardia should be differentiated from a specific syndrome called postural orthostatic tachycardia syndrome (POTS), which is characterized by orthostatic hypotension and 40 to 50 beats increase in the heart rate within 10 minutes after assuming a standing position. This is important in that POTS is managed medically, with catheter ablation contraindicated.

CONCLUSION

SVT is a descriptive diagnosis with varying pathologies, mechanisms, and treatments. Many of these underlying mechanisms can be determined from the surface electrocardiogram and via utilization of bedside maneuvers. It is important to implement a systematic approach to SVT, not only to define the underlying mechanism but also to provide rapid, effective, and appropriate treatment (Fig. 29.11).

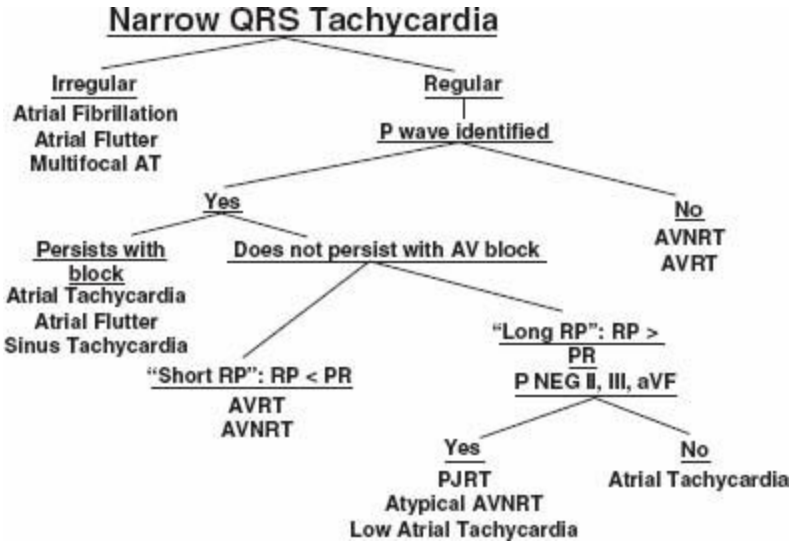

FIGURE 29.11 Algorithm for treatment of SVT.

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QUESTIONS AND ANSWERS

Questions

1. A 44-year-old patient with no previous cardiovascular history, who presents with a wide-QRS, irregular, and fast tachycardia (on ECG) is best treated with:
   a. Lidocaine
   b. Procainamide
   c. Metoprolol
   d. Diltiazem

2. Catheter ablation is an established and well-accepted treatment for each of the following tachycardia types except:
   a. AV node reentry
   b. AV reentry
   c. Permanent junctional tachycardia
   d. Sinus tachycardia

2. Which of the following forms of congenital heart disease is commonly associated with Wolff–Parkinson–White (WPW) syndrome?
   a. Aortic stenosis
   b. Ebstein anomaly
   c. Pulmonary stenosis
   d. Atrial septal defect

2. Which of the following supraventricular tachycardias (SVTs) is associated with tachycardia-induced cardiomyopathy?
   a. Permanent junctional tachycardia
   b. Incessant atrial tachycardia
   c. Atrial flutter with rapid ventricular response
   d. All of the choices

2. Which test would you consider for an asymptomatic 31-year-old man with intermittent pre-excitation?
   a. Holter monitoring
   b. Electrophysiologic study
   c. Exercise test
   d. Catheter ablation
   e. None of the choices

2. Conduction block in the atrioventricular (AV) node without termination of the tachycardia is compatible with all of the following mechanisms except:
   a. Atrial tachycardia
   b. AV reentry tachycardia
   c. Atrial flutter
   d. Sinus tachycardia

2. The initial manifestations of WPW syndrome include which of the following?
   a. Atrial fibrillation
   b. AV reentry tachycardia

c. Ventricular fibrillation
d. Wide-QRS tachycardia
e. All of the choices

2. Administration of metoprolol is more likely to terminate:
a. Sinus tachycardia
b. Atrial tachycardia
c. Atrial fibrillation
d. AV reentry tachycardia

2. Which of the following is the treatment of choice to terminate a narrow-QRS tachycardia?
a. Metoprolol
b. Diltiazem
c. Adenosine
d. Procainamide
e. Cardioversion

2. For a patient with WPW syndrome who presents with a regular wide-QRS tachycardia, all of the following are possible treatment choices except:
a. Procainamide
b. Cardioversion
c. Amiodarone
d. Ibutilide
e. Adenosine

2. Transesophageal recording may help in establishing the diagnosis in which of the following SVTs?
a. Atrial tachycardia
b. AV node reentrant tachycardia
c. AV reentrant tachycardia
d. Atrial flutter
e. All of the choices

2. A decrease in the tachycardia rate with development of bundle branch block is consistent with:
a. Atrial tachycardia
b. AV node reentry
c. AV reentry
d. Sinus tachycardia

2. The presence of an r prime in V_1 during narrow-QRS tachycardia is suggestive of:
a. AV reentry
b. AV node reentry
c. Rate-dependent bundle branch block
d. Atrial tachycardia

2. The best therapy for multifocal atrial tachycardia (MAT) is:
a. Digoxin
b. Diltiazem
c. Metoprolol
d. Flecainide
e. Treatment of the underlying disorder

Answers

1. Answer B: This patient has atrial fibrillation with pre-excited QRS and should be treated with procainamide. AV node–blocking agents are absolutely contradicted because they will favor conduction

over the accessory pathway with increased risk of degeneration into ventricular fibrillation.

2. Answer D: Catheter ablation is an established therapy for all the arrhythmias listed except sinus tachycardia.

3. Answer B: Ebstein Anomaly is associated with WPW in 6% of patients with this congenital anomaly.

4. Answer D: All tachycardias of incessant nature can cause tachycardia-induced cardiomyopathy.

5. Answer E: No further investigation or treatment is indicated for an asymptomatic patient with intermittent pre-excitation.

6. Answer B: The only tachycardia that cannot sustain with conduction block in the AV node is AV reentry.

7. Answer E: All of the choices are possible arrhythmias in WPW syndrome.

8. Answer D: Sinus tachycardia will slow down but not terminate. Atrial tachycardia and atrial fibrillation will not be affected by metoprolol.

9. Answer C: Adenosine is the best acute treatment for narrow-QRS tachycardia.

10. Answer E: Adenosine and AV node–blocking agents are contraindicated in pre-excited arrhythmias.

11. Answer E: Transesophageal recording can provide information that is helpful in establishing a diagnosis in all of the SVTs listed.

12. Answer C: AV reentry due to an accessory bypass tract ipsilateral to the bundle branch block is the only arrhythmia associated with the above behavior.

13. Answer B: The correct answer is AV node reentry.

14. Answer E: No drug therapy will be effective for MAT if the underlying disorder is not corrected.

CHAPTER

Wide-Complex Tachycardia: Ventricular Tachycardia versus Supraventricular Tachycardia

Roy Chung and Walid Saliba

Wide-complex tachycardia (WCT) is defined as a tachyarrhythmia with a rate >100 beats/min (bpm) and a QRS duration >120 milliseconds on a 12-lead electrocardiogram (ECG). Utilizing the ECG, the correct mechanistic diagnosis of a WCT rhythm is often difficult. Besides being an intellectual exercise, it is very important to establish the correct diagnosis in order to deliver appropriate acute therapy and to plan subsequent long-term patient management. Several criteria and algorithms have been developed to help distinguish among different causes of WCT. When used individually, none of these criteria reaches 100% specificity; however, when properly applied together and in conjunction with the clinical history and presentation, the algorithms serve as a guide to the correct diagnosis in the majority of the cases.

WCT can result from either a ventricular or a supraventricular mechanism. Ventricular tachycardia (VT) originates below the level of the His bundle. Supraventricular tachycardia (SVT) originates in or involves structures above the His bundle. SVT may involve atrial tachycardia, atrial fibrillation, atrial flutter, atrioventricular (AV) node reentrant tachycardia (Fig. 30.1), or AV reentrant tachycardia. AV reentrant tachycardia may be either orthodromic reentrant tachycardia or antidromic reentrant tachycardia (Fig. 30.2). Orthodromic reentrant tachycardia occurs when antegrade ventricular conduction occurs via the AV node and retrograde conduction to the atrium is via the accessory pathway. Antidromic reentrant tachycardia occurs when ventricular antegrade conduction occurs over the accessory pathway and retrograde conduction occurs via the AV node.

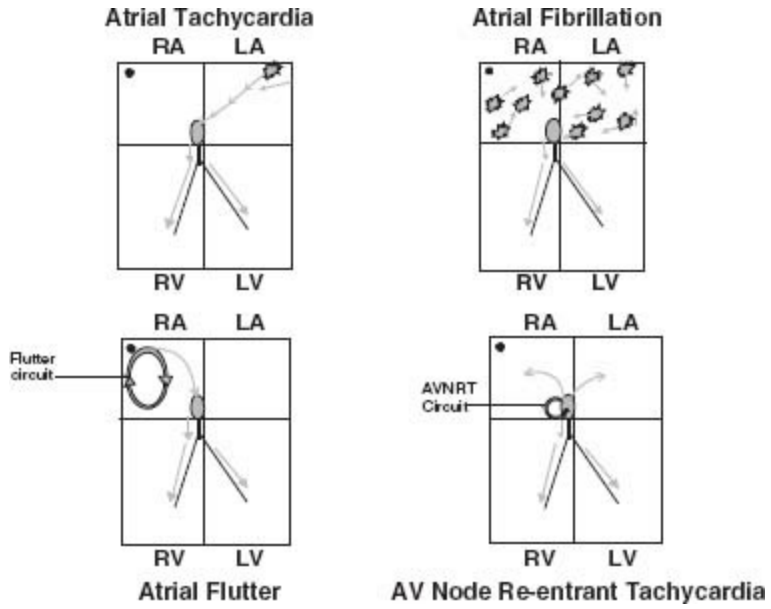

FIGURE 30.1 Supraventricular tachycardia.

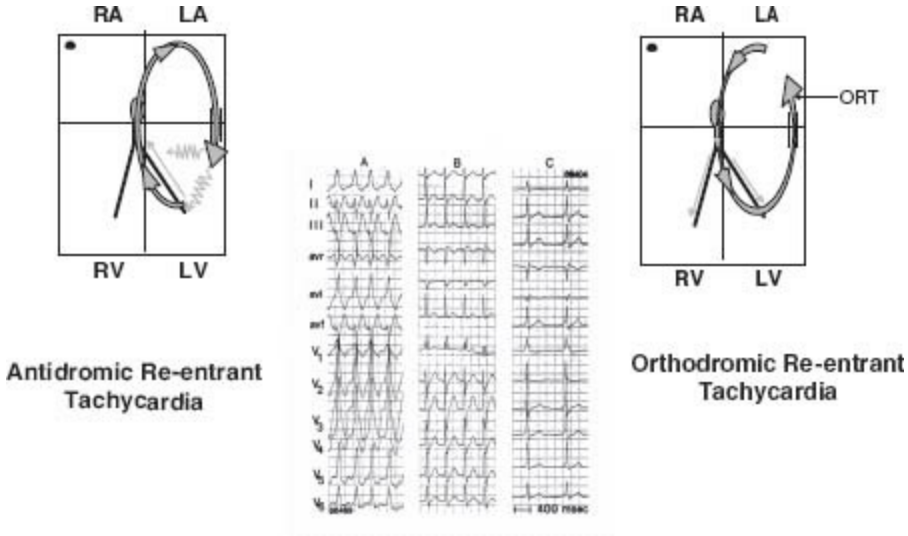

FIGURE 30.2 AV reentrant tachycardia.

DIFFERENTIAL DIAGNOSIS

WCT can occur by three different mechanisms:

1. VT is the most common cause of WCT in the general population, accounting for >80% of all cases. It is even more common in patients with structural heart disease, and it may occur in 98% of patients with a prior history of a myocardial infarction. VT may be either monomorphic or polymorphic. Monomorphic VT occurs when the QRS morphology is stable and uniform, whereas polymorphic VT occurs when the QRS complexes vary in morphology.
2. The second mechanism of WCT occurs when the tachycardia originates above the

ventricle and has abnormal ventricular activation, also known as SVT with aberrancy. It accounts for 15% to 20% of all cases of WCT and includes a variety of disorders.

a. The first example is SVT with bundle branch block aberration, which may be either a right bundle branch block (RBBB) or a left bundle branch block (LBBB) morphology (Fig. 30.3). Activation of the ventricle through the His–Purkinje system (His bundle and both bundle branches) results in a narrow QRS complex. Activation of the ventricle unilaterally via one bundle branch results in a wide QRS complex, because activation of the remainder of the ventricular myocardium is dependent on slow myocardial conduction. Aberration occurs when there are abnormalities of intraventricular conduction in response to changing heart rate, and when the conduction over the His–Purkinje conduction system is delayed or blocked in either the right or left bundle branch. RBBB is more common, occurring in 80% of cases. The aberration may be fixed, occurring in normal sinus rhythm at a slow heart rate, or it may be functional and present only during tachycardia.

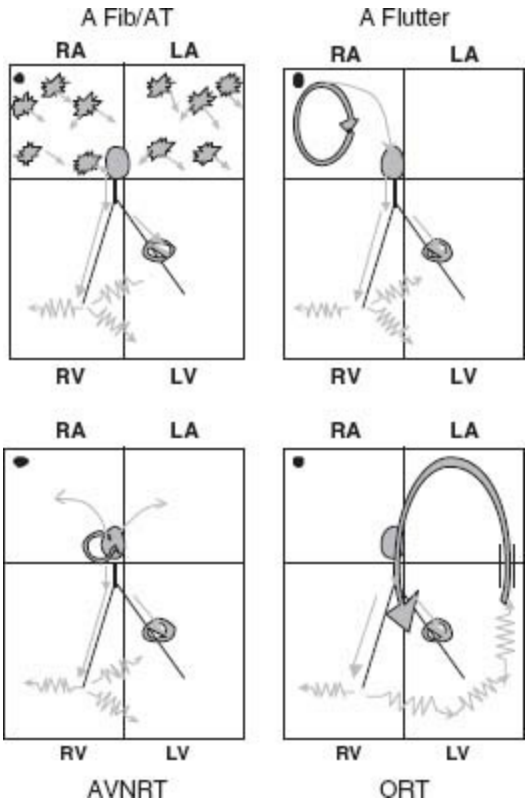

FIGURE 30.3 SVT with bundle branch block.

b. SVT with antegrade conduction via an accessory pathway, such as in Wolff–Parkinson–White syndrome, accounts for 1% to 5% of all WCT. The accessory pathway is an anomalous AV connection that inserts directly into ventricular

myocardium at the base of the ventricle along the mitral or tricuspid valve annulus. Ventricular activation is initiated at this insertion point and is termed ventricular pre-excitation. Pre-excited tachycardia can occur with SVT with antegrade conduction via the accessory pathway. The accessory pathway is not part of the tachycardia circuit and is not essential for its perpetuation. The other form of pre-excited tachycardia can occur with antidromic reciprocating tachycardia, in which the accessory pathway is part of the tachycardia circuit (Fig. 30.4).

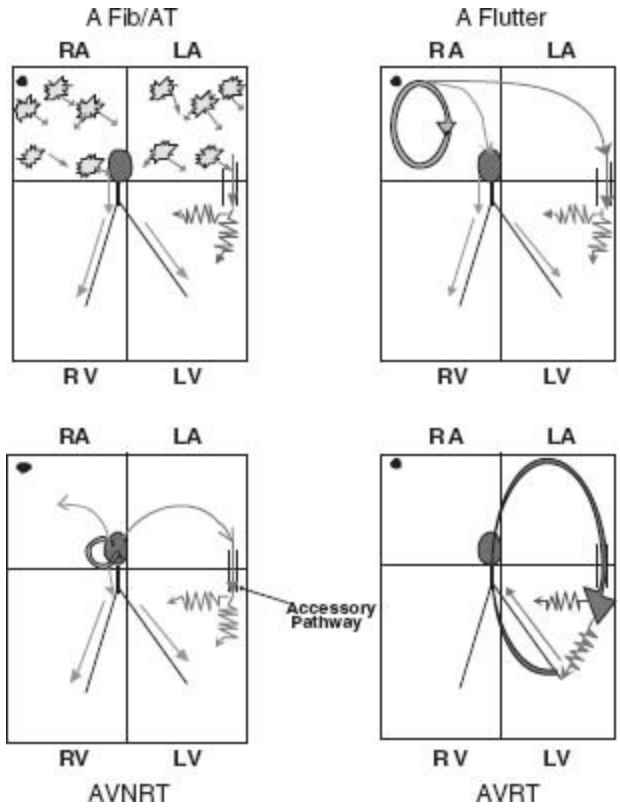

FIGURE 30.4 SVT with pre-excitation.

c. Another form of WCT is SVT with an intraventricular conduction delay. This can occur in patients with cardiomyopathy, corrected congenital heart disease such as tetralogy of Fallot, or Ebstein anomaly, in which myocardial conduction is further impaired. The conduction abnormality is usually apparent during normal sinus rhythm.

d. Some medications are capable of producing nonspecific widening of the QRS complex during SVT. These include Na^+ channel blockers, especially Class IC agents (flecainide, encainide), less so Class IA antiarrhythmics (quinidine, procainamide, disopyramide), and amiodarone. The most common example is a patient with atrial flutter being treated with flecainide. Flecainide can induce flutter rate slowing to permit 1:1 AV nodal conduction and a secondary increase

in the ventricular rate with a wide QRS complex. This is as a result of the slow ventricular conduction in response to the Na^+channel blockade. This can be easily and erroneously interpreted as VT (Fig. 30.5).

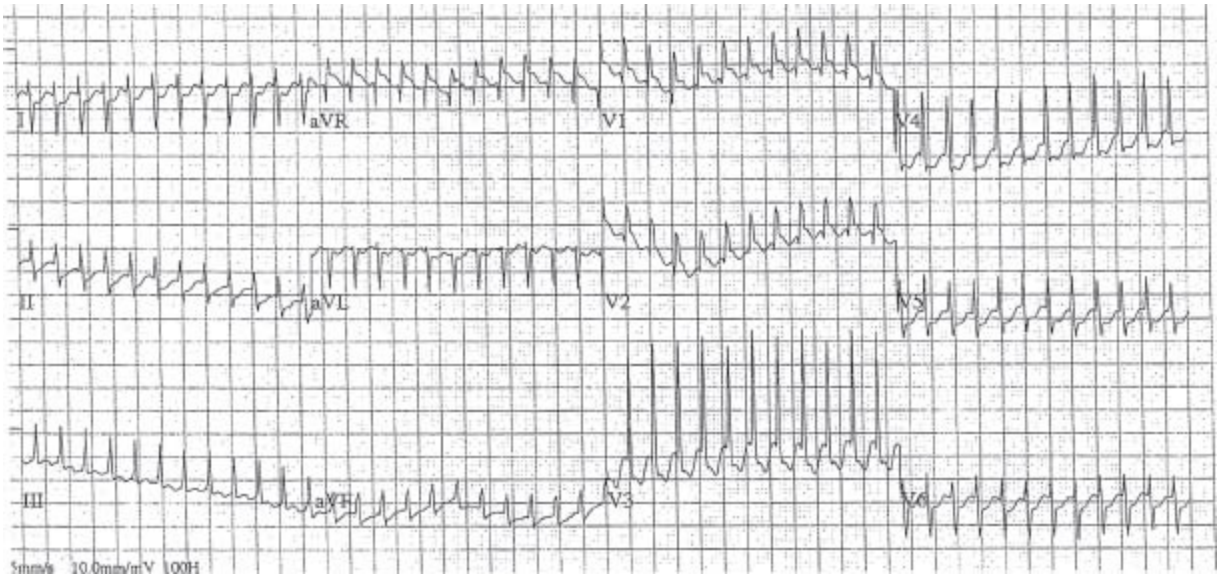

FIGURE 30.5 Atrial Flutter with 1:1 conduction.

e. Electrolyte abnormalities such as hyperkalemia can cause widening of the QRS complex and can be mistakenly interpreted as VT. The morphology is typically LBBB.

3. Ventricular paced rhythms can also mimic WCT (Fig. 30.6). Most pacemakers are dual chamber, with a lead in the right atrium and one in the right ventricle. Pacing of the right ventricle causes an LBBB QRS morphology. The surface ECG representation of the pacing stimulus is less apparent with the use of bipolar pacing modes and a resultant decrease in the energy requirement for reliable ventricular pacing. Therefore the pacing spike may be overlooked or even absent from ECG tracings. A wide QRS tachycardia can occur in any SVT with atrial tracking, in which the ventricle is paced in response to atrial sensing. In these cases, it is essential to obtain an adequate history and to analyze a previous ECG to evaluate the baseline morphology of the QRS complex.

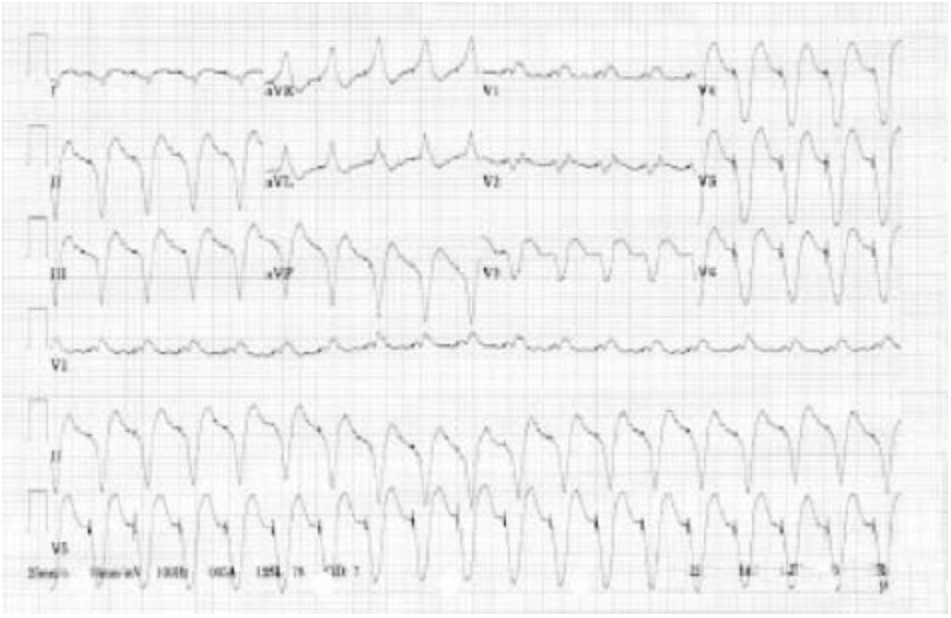

FIGURE 30.6 Ventricular paced tachycardia.

4. Pacemaker-mediated tachycardia can also produce a WCT. The pacemaker is itself responsible for the tachycardia when ventricular pacing results in retrograde conduction to the atrium. The pacemaker senses the atrial conduction, resulting in ventricular pacing, which in turn is followed by retrograde conduction to the atrium, resulting in "endless loop tachycardia" (Fig. 30.7).

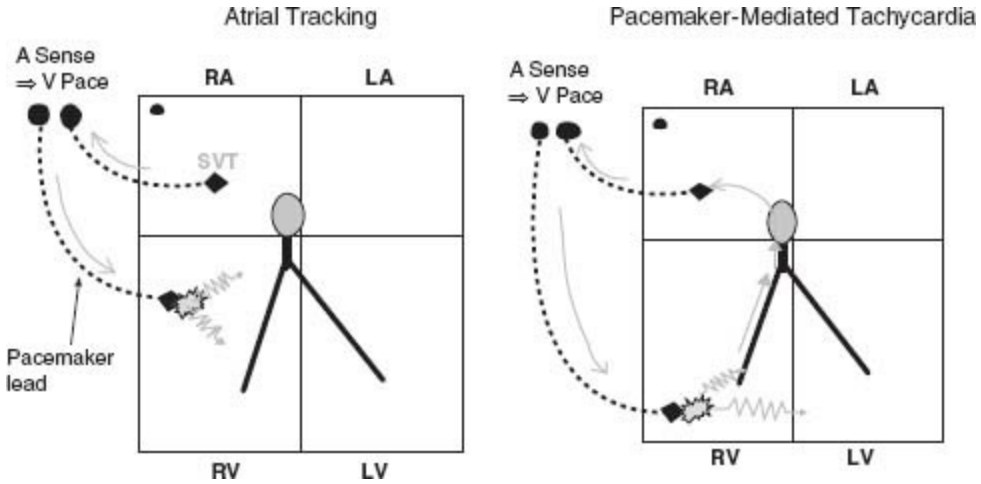

FIGURE 30.7 Ventricular paced tachycardia. **Left:** Atrial tracking. **Right:** Pacemaker-mediated tachycardia.

5. Lastly, artifacts from recording equipment problems (such as fast-sweep speed recording) or from external repetitive motion (such as brushing teeth) can present as "WCT" (Fig. 30.8).

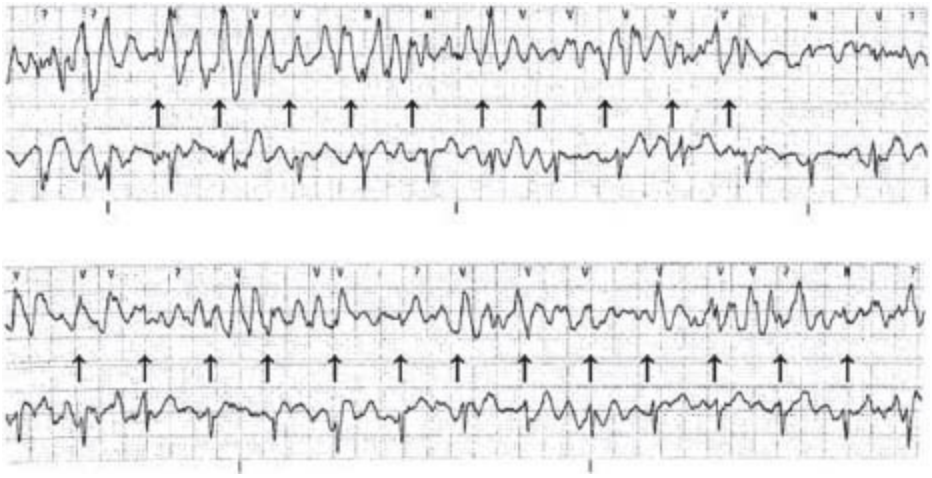

FIGURE 30.8 Artifact mimicking WCT.

DIAGNOSIS

Clinical Presentation

In order to diagnose the etiology of the WCT, it is important to evaluate the clinical presentation. As mentioned before, obtaining an accurate patient history is crucial in formulating an accurate rhythm diagnosis. A prior history of heart disease, myocardial infarction, or congestive heart failure makes the diagnosis of VT highly suggestive as the cause of the WCT. Akhtar et al. have reported that the positive predictive value of a WCT representing VT in a patient with a prior history of myocardial infarction is 98%. Tchou reported that of patients who had a prior myocardial infarction and a first episode of tachycardia occurring after the infarction, 28 of 29 patients presented with VT and were diagnosed correctly. The older the patient is, the more likely that the tachycardia is ventricular; however there is a significant overlap with SVT patients. It is also helpful to know if there is any presence of congenital heart disease, or if the patient has a pacemaker or defibrillator. Knowing that the patient has an implantable cardioverter-defibrillator (ICD) raises a concern for pacemaker-associated tachycardia, but more important, the presence of the device suggests that the patient has risk factors for VT. A history of a prior similar episode may also be useful. The first occurrence of the arrhythmia after a myocardial infarction is highly suggestive of VT, whereas SVT may be more likely if there is recurrence of the arrhythmia over several years. The presence of other medical conditions can point to a diagnosis of WCT. For example, in a patient with renal failure, the WCT may be attributable to hyperkalemia. In a patient with known peripheral vascular disease, the WCT may be indicative of VT, because such patients are likely to have underlying coronary artery disease.

Knowing what medications the patient is taking, especially cardiac medications, is vital when evaluating WCT. It is important to identify medications that prolong the QT interval, such as dofetilide, sotalol, quinidine, and erythromycin, which can all cause

torsade de pointes, a form of polymorphic VT. Electrolyte abnormalities caused by certain medications such as diuretics (hypokalemia and hypomagnesemia) or angiotensin-converting enzyme (ACE) inhibitors (hyperkalemia) may predispose to VT. Patients who are on digoxin are more susceptible to an arrhythmia when hypokalemia is present. The most common arrhythmias are monomorphic VT, bidirectional tachycardia, and junctional tachycardia, and typically occur when the plasma digoxin concentration is >2.0 ng/mL. As stated earlier, Class IC agents can cause rate-related aberrant conduction during SVT. Symptoms such as palpitations, lightheadedness, or chest pain are generally not useful in evaluating the etiology of the WCT.

One of the priorities in evaluating a patient with WCT is determining if the patient is hemodynamically stable or unstable. This requires knowing the patient's blood pressure and heart rate. In a patient who is unstable, emergency cardioversion is required and the mechanism of the arrhythmia may not necessarily be known. VT can be present when the patient is hemodynamically stable and should not be mistaken for SVT, lest the patient be given inappropriate medical therapy (such as adenosine or verapamil) that can lead to hemodynamic compromise with VT. When the patient is hemodynamically stable, a more detailed physical exam can be performed. Inspection of the chest can point to underlying cardiovascular disease when there is a sternal incision, a pacemaker, or defibrillator.

AV dissociation occurs in 60% to 75% of patients with VT and is a result of the atria and ventricles depolarizing independently. It almost never occurs in SVT. This finding is usually identifiable on the surface ECG. However, it is also possible to make this diagnosis on physical exam by assessing the jugular venous pulsation. Cannon A waves are irregular pulsations that are of greater amplitude than the normal jugular venous waves, and occur intermittently when the atrium and ventricle contract simultaneously. When the tachycardia rate is slower, there can be variable intensity of the first heart sound. However, evaluating this may not be practical in an acute situation.

Laboratory tests should be performed for patients with WCT to determine potassium and magnesium levels. If the patient is on digoxin, it is also important to obtain the serum digoxin level. If a chest x-ray is available, one can readily identify the presence of a pacemaker, defibrillator, or sternal wires that might point to underlying structural heart disease.

Provocative Maneuvers

Certain bedside maneuvers can be performed to distinguish VT from SVT. The Valsalva maneuver or carotid sinus massage enhances vagal tone, which depresses sinus nodal and AV nodal activity. These maneuvers will slow the heart rate during sinus tachycardia, but once they are completed, the heart rate will increase again. If the patient is in SVT, these maneuvers may terminate the rhythm. If the patient is in an atrial tachycardia or flutter, the rhythm will persist though the ventricular rate may be slower,

thus uncovering the background atrial activity. These maneuvers can also elicit VA conduction block, which can induce AV dissociation during VT.

Certain medications can be used to diagnose the tachyarrhythmias. For example, adenosine, given in 6- to 12-mg boluses intravenously during WCT, can result in one of the following scenarios:

1. The tachycardia terminates, making it more likely to be supraventricular in etiology, invoking AV node participation. Some atrial tachycardias may also terminate with adenosine.
2. AV block occurs, uncovering the background atrial activity such as atrial tachycardia, flutter, or fibrillation, thus allowing the diagnosis of an atrial tachyarrhythmia.
3. If 1:1 AV association is present and evident during WCT, adenosine-induced AV block results in AV dissociation, thus making the diagnosis VT

Adenosine has a short half-life of about 10 seconds. However, it has to be used with caution, because it may cause hemodynamic compromise in a patient with VT. Some paroxysmal VT in structurally normal hearts may terminate with adenosine.

Termination of the rhythm with lidocaine suggests VT as the mechanism. Amiodarone and procainamide, however, will not diagnose the rhythm if the WCT is terminated. Beta-blockers may be given as well. They can terminate SVT or uncover AV dissociation during VT in a manner similar to adenosine. It is important that verapamil not be given if the diagnosis is in question, because it can lead to significant hemodynamic compromise in VT and induce ventricular fibrillation and cardiac arrest.

ECG Criteria

The most reliable way to differentiate VT from SVT is by evaluating the ECG. A 12-lead ECG is more helpful than a rhythm strip. A rhythm strip may be additive as a result of analyzing the beginning and termination of the tachycardia. A previous ECG during a normal rhythm will help to identify the baseline QRS morphology and the presence of Q waves that might suggest a prior myocardial infarction. Ventricular pre-excitation may be suggested if there is the presence of delta waves.

There are several ECG criteria and different algorithms that may be used to differentiate VT from SVT in WCT:

1. The tachycardia rate has no diagnostic value in determining the mechanism of the WCT.
2. Regularity of the RR intervals is also not a useful criterion, because VT can be irregular in patients on antiarrhythmic medications.
3. QRS-complex duration can be useful in differentiating VT from SVT. The WCT is

more suggestive of VT when the QRS duration is >140 milliseconds with an RBBB morphology and >160 milliseconds with an LBBB morphology. A study by Wellens showed that all of 70 patients with WCT due to SVT had QRS-complex durations <140 milliseconds, whereas 66% of patients with WCT due to VT had QRS-complex duration >140 milliseconds. Another study, by Akhtar, showed that 15% of patients with VT had QRS-complex duration <140 milliseconds and that QRS duration >140 milliseconds with RBBB pattern or >160 milliseconds with LBBB pattern correlates with VT. Wide QRS-complex duration can still be seen with pre-excitation, ventricular pacing, use of antiarrhythmic drugs, and marked baseline intraventricular conduction delays. VT in structurally normal hearts may have a relatively narrow QRS complex in a case with idiopathic left ventricular VT.

4. The QRS-complex axis may also be helpful in diagnosing WCT. A right superior QRS-complex axis in the frontal plane is more suggestive of VT. Presence of LBBB and right-axis deviation is also almost always due to VT. Presence of Q waves that are also present in normal sinus rhythm suggests prior myocardial infarction, which makes the diagnosis of VT more likely. Pseudo-Q waves can be seen in SVT, which represents retrograde atrial activation.
5. QRS-complex concordance in the precordial leads is highly predictive of VT, with a specificity as high as 90% or greater. The sensitivity is low because it is only present in <20% of patients with VT. Concordance occurs when all the QRS complexes in the precordial leads (V_1 to V_6) have the same polarity, either positive or negative (Fig. 30.9). It is important to remember that 1% to 2% of patients with pre-excited tachycardia involving left lateral accessory pathways possess positive QRS-complex concordance.

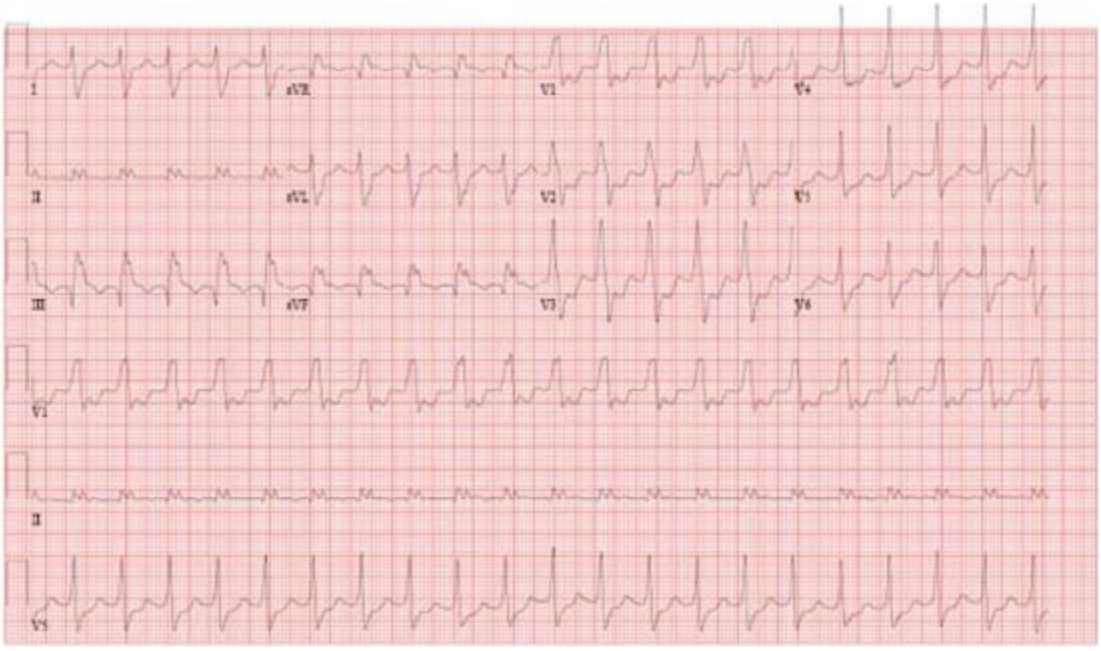

FIGURE 30.9 VT: QRS concordance.

6. AV dissociation is the most useful criterion to distinguish VT from SVT (Fig. 30.10). It occurs in up to 60% of patients with VT but is apparent on the surface ECG in only 20% to 30% of patients. The specificity is 99%, but again, the sensitivity is only 20%. AV dissociation occurs in <1% of all SVTs. Several methods can be used to maximize atrial recordings, such as using an esophageal lead, utilizing temporary epicardial atrial pacemaker wires post–cardiac surgery, changing arm lead position, and utilizing a pacemaker programmer for atrial and ventricular electrogram display in patients with permanent dual-chamber devices. Thirty percent of VT patients may have 1:1 AV association, and this cannot be differentiated from SVT. Transient AV dissociation can be elicited with carotid sinus massage or IV adenosine, which helps to confirm the diagnosis of VT.

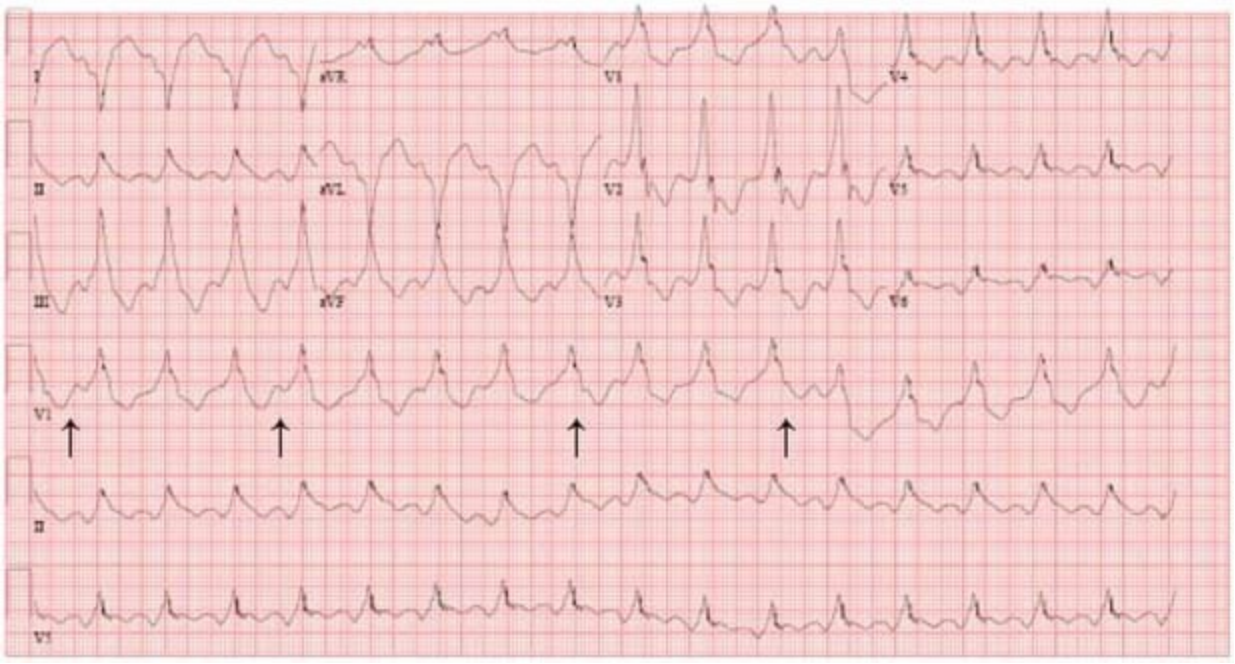

FIGURE 30.10 VT: AV dissociation.

7. The presence of capture and fusion complexes on an ECG during WCT makes the diagnosis of VT more likely. A ventricular fusion complex results from simultaneous activation of the ventricle by two or more impulses originating from the same or different chambers of the heart. An example is the fusion of a ventricular impulse with a sinus or other supraventricular conducted impulse, or another ventricular impulse. The resulting QRS-complex morphology is variable and depends on the relative contribution of each of the sources of ventricular activation. During WCT, a change in the morphology of the QRS complex is indicative of fusion and suggests the diagnosis of VT. A fusion complex is not pathognomonic for

VT and can occur when a premature ventricular contraction occurs during SVT with aberrancy. A capture complex is a ventricular QRS complex that results from conduction of a supraventricular impulse to the ventricle and ventricular depolarization before the ventricle is depolarized by the VT circuit. It is usually a narrower complex and is identical to the sinus QRS complex. It indicates that the normal conduction system has temporarily captured and depolarized the ventricle before the next VT complex. Although fusion and capture complex are seen infrequently, when they are present, they strongly indicate the etiology of WCT as VT, with the specificity being 99% and the sensitivity 5% for capture complex (Fig. 30.11A,B).

FIGURE 30.11 A: Fusion complex. **B:** Fusion and capture complexes.

8. The absence of a precordial RS pattern on a 12-lead ECG is suggestive of VT. This is the first criterion in Brugada's algorithm. Brugada performed an analysis on 554 patients with WCT. Fifteen percent of all cases had an absent RS pattern, and 100% of these cases were due to VT. Though the specificity remains high (100%), the sensitivity is quite low (21%). If an RS pattern is present, an RS duration (as measured from the beginning of the R wave to the nadir of the S wave) of >100 milliseconds suggests VT (Fig. 30.12). This is the second step in Brugada's algorithm. This finding is present in 32% of patients with WCT and has a specificity of 98%. Combining these two criteria can correctly diagnose 47% of all WCT and identify 66% of all VT.

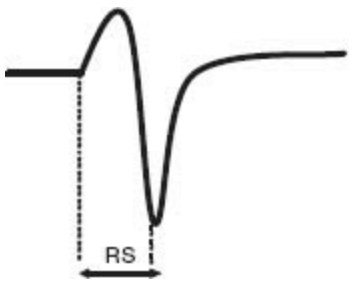

FIGURE 30.12 RS.

9. QRS morphology: Different criteria for RBBB and LBBB morphologies can also help distinguish VT from SVT (Table 30.1; Fig. 30.13). This is based predominantly on the QRS-complex analysis in the precordial leads: V_1, V_2, and V_6. If the QRS complex is predominantly positive in V_1, a "RBBB-like" pattern is observed and the corresponding morphology criteria are applied. Alternatively, if the QRS complex is predominantly negative in V_1, a "LBBB-like" pattern is observed and the corresponding morphology criteria are applied.

TABLE
30.1 Morphology Criteria

	RBBB		LBBB	
	VT	**SVT**	**VT**	**SVT**
V_1	Monophasic R R (>30 ms) + any S qR	Triphasic rSR′ rSr′ rsr′	rS (Broad r >30 ms) Notching/delay in S QS ≥ 70 ms RT taller than RS	rS, QS (rapid downstroke)
V_6	RS (R < S) QS, Qrs QR Monophasic R	Triphasic Rs RS (R > S) qRs	QR, QS QrS, qR Rr′	rR′ Monophasic R No Q waves

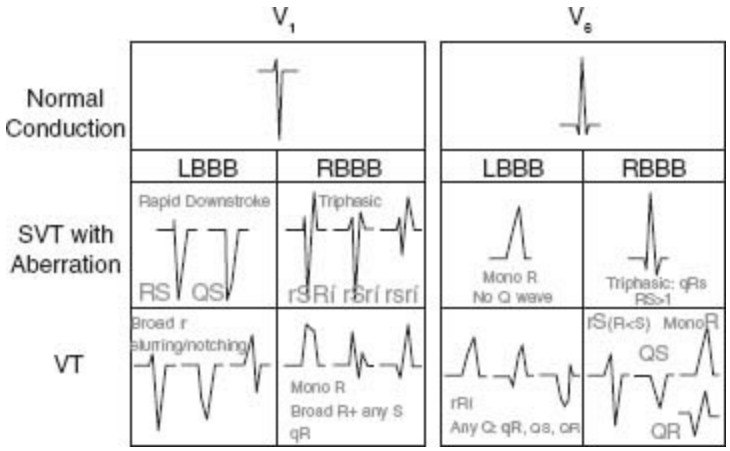

FIGURE 30.13 Morphology criteria.

ALGORITHMS

The most commonly used approach for the differential diagnosis of WCT is the aforementioned algorithm by Brugada (Fig. 30.14). This algorithm is comprised of four steps and has a sensitivity of 98.7% and a specificity of 96.5%. The four sequential steps assess for the presence of RS QRS complexes in the precordial leads, the RS interval, AV dissociation, and specific morphology criteria for VT in V_1 and V_6 (Fig.

30.15).

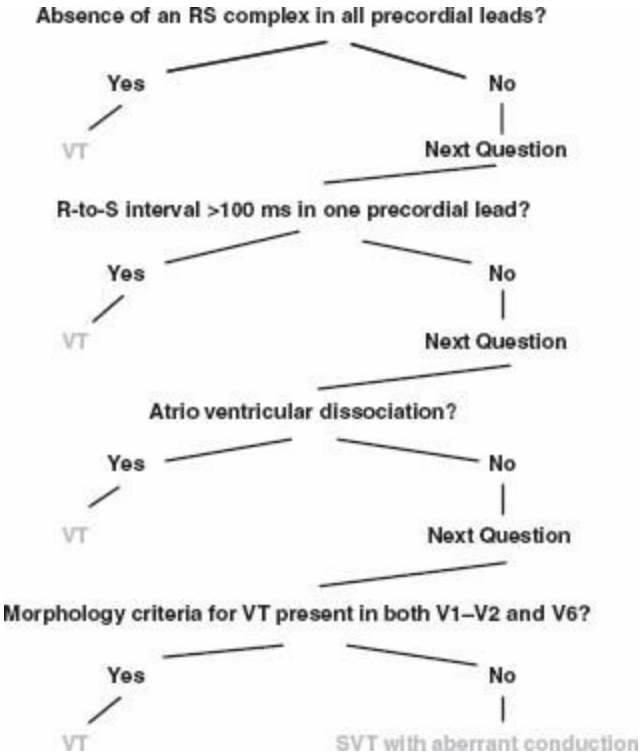

FIGURE 30.14 Brugada's criteria I.

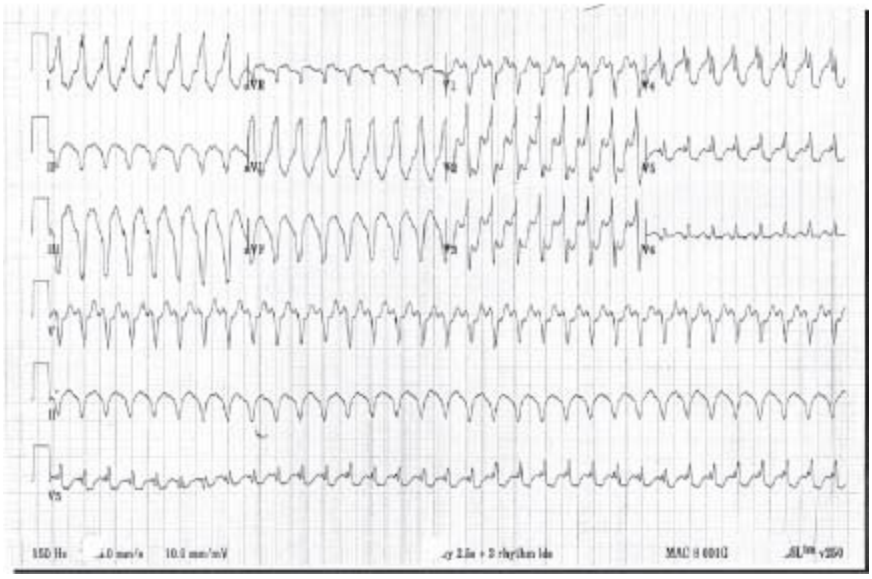

FIGURE 30.15 This ECG shows an RS pattern in V_1 to V_5. The RS interval measures 140 milliseconds in V_4, which suggests a diagnosis of VT with 98% specificity.

A second-level algorithm (Brugada's criteria II) helps to distinguish VT from pre-excited SVT. This algorithm has three steps and has a sensitivity of 75% and specificity of 100% Figs. 30.16 and 30.17).

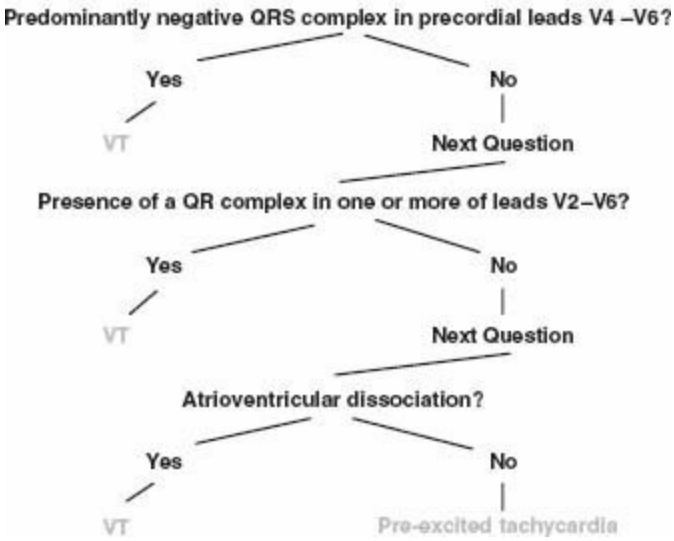

FIGURE 30.16 Brugada's criteria II.

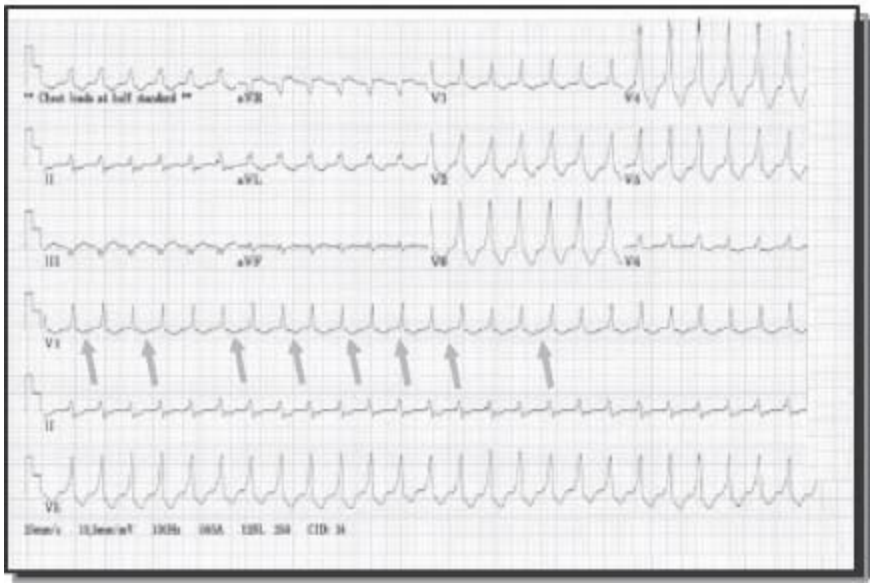

FIGURE 30.17 ECG: AV dissociation.

SPECIAL CASES

There are other miscellaneous ECG criteria that can help differentiate VT from SVT:

- When the QRS complex during WCT is narrower than in normal sinus rhythm, it is more suggestive of VT.
- The WCT is more likely to be VT if there is contralateral bundle branch block in normal sinus rhythm rather than during the WCT.
- Although regularity in itself does not help to distinguish SVT from VT, rapid irregular WCT with beat-to-beat QRS-duration variation is suggestive of atrial

fibrillation with WPW (Fig. 30.18)

- Misdiagnosis of SVT as VT using morphology criteria can occur when the WCT is a result of pre-excited tachycardia or a paced ventricular rhythm.
- VT can be misdiagnosed as SVT in cases of bundle branch reentrant VT (BBR-VT). This occurs when ventricular activation begins via the RBBB and produces a LBBB QRS morphology. The conduction spreads transseptally to retrogradely, reentering the LBBB and establishing the reentry circuit of BBR-VT. Following the morphology criteria for LBBB QRS complexes will lead to an incorrect diagnosis of SVT with LBBB aberrancy. However, if AV dissociation is present, the correct diagnosis of VT will be made.
- A narrow QRS VT can occur with QRS durations <140 milliseconds. This can occur in 12% of VTs. A possible explanation is when the origin of the VT comes from the septum, which causes simultaneous spread of ventricular activation. Such is the case when idiopathic left VT (fascicular VT) is present. This type of VT can be terminated with IV verapamil and is therefore misdiagnosed as SVT.

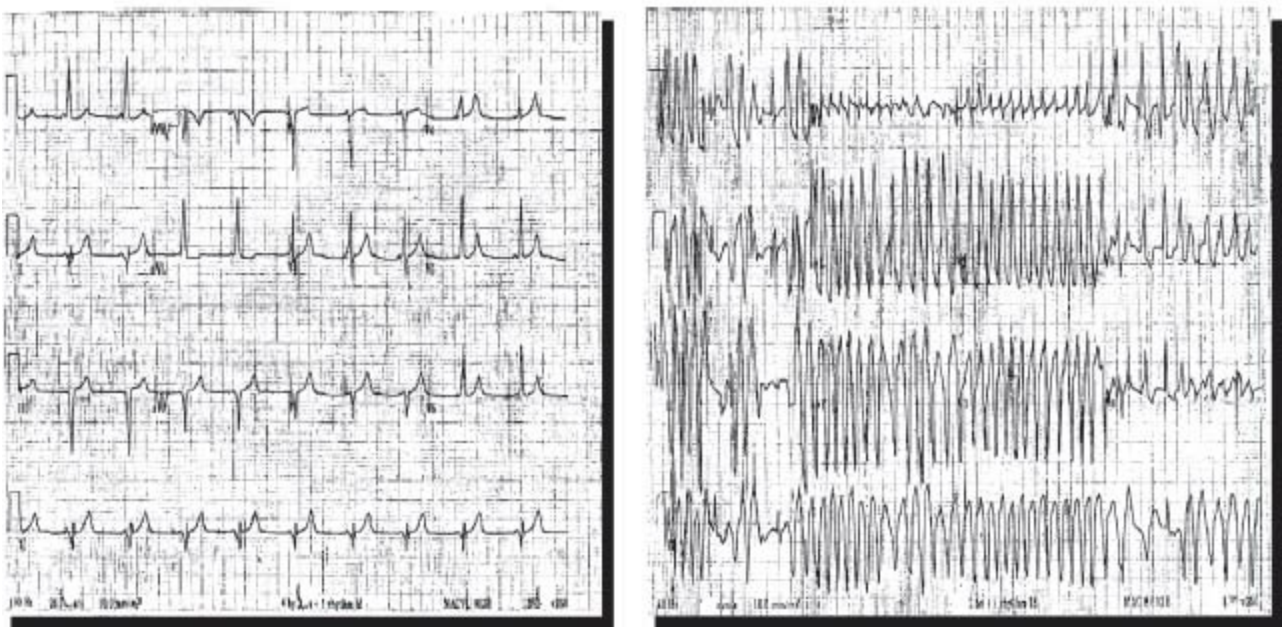

FIGURE 30.18 Examples of other ECG criteria.

CONCLUSIONS

Despite multiple diagnostic tools, the determination of WCT etiology can be difficult. Morphology criteria are difficult to remember with certainty. The widespread use of antiarrhythmic medications with secondary intraventricular conduction delay has reduced the accuracy of currently available algorithms. Certain key points that should be committed to memory:

- If the configuration of the WCT is not compatible with aberration, then it is likely to be VT.
- If structural heart disease is present, WCT is most likely VT.
- Certain type of treatments (verapamil, adenosine) can potentially worsen the patient's situation. So if the diagnosis remains in question, treat it as though it is VT.
- Using morphology criteria, pre-excited tachycardias and paced ventricular rhythms may be easily mistaken for VT.
- AV dissociation remains the most important and most specific criterion for the diagnosis of VT.
- In some situations, "I don't know" is the correct answer. In these cases, an electrophysiology study may be necessary for an accurate arrhythmic diagnosis.

ACKNOWLEDGEMENT

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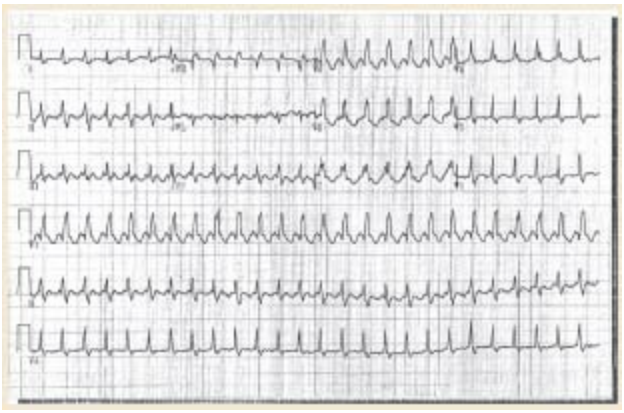
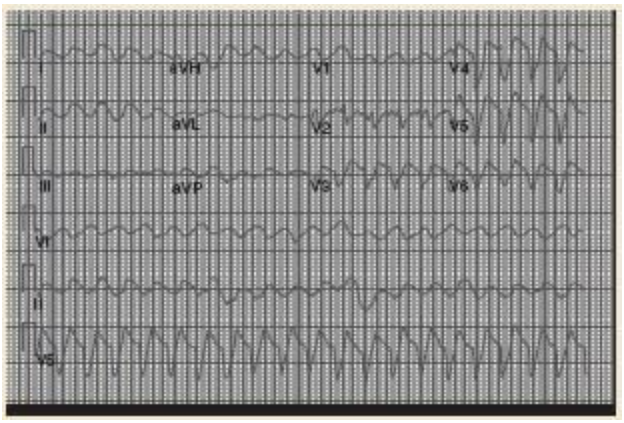
Wide-Complex Tachycardia: Ventricular tachycardia (VT) versus supraventricular tachycardia (SVT) Worksheet

1. QRS-Complex Duration
   VT: QRS >140 ms for right bundle branch block (RBBB),
   QRS >160 ms for left bundle branch block (LBBB)
2. QRS-Complex Axis
   VT: right superior
3. Capture and Fusion Complexes
4. QRS Precordial Concordance
5. WCT: Brugada's Criteria I
   Step 1. Absence of an RS complex in all pre-cordial leads?
   Step 2. R-to-S interval >100 ms in one pre-cordial lead?
   Step 3. AV dissociation?
   Step 4. Morphology criteria for VT present in both V1 to V2 and V6?

	RBBB morphology VT		SVT
V_1	Monophasic R R (>30 ms) + any S qR	V_1	Triphasic rSR′, rSr′ rR′, rsr′
V_6	RS (R < S) QS, Qrs	V_6	Triphasic Rs, RS (R > S)
	LBBB morphology VT		SVT
V_1	rS: Broad r > 30 ms Notching/delay in S QS ≥ 70 ms RT taller than RS	V_1	rS, QS (rapid downstroke)
V_6	QR, QS, QrS, qR Rr′	V_6	rR′ Monophasic R No Q waves

6. WCT: Brugada's Criteria II
   Step1. Predominantly negative QRS complex in precordial leads V4 to V6?
   Step2. Presence of a QR complex in one or more of leads V2 to V6?
   Step3. Atrioventricular dissociation?
7. Diagnosis: ECG Criteria Miscellaneous Conditions
   1. QRS complex during WCT narrower than during NSR: suggests VT.
   2. Contralateral BBB in NSR and WCT: suggests VT.
   3. Rapid irregular WCT + beat-to-beat QRS-to-QRS interval variation: atrial fibrillation with WPW.
8. Special Cases
   1. Misclassification of SVT for VT: Pre-excited tachycardia, paced ventricular rhythm.
   2. Misclassification of VT for SVT: BBR-VT (without evidence of AV dissociation).
   3. Narrow QRS VT: ILV-VT




I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1
II
V5

CHAPTER

Pacemakers and Defibrillators

Khaldoun G. Tarakji and Bruce L. Wilkoff

CARDIAC PACING

Cardiac pacing is the only definitive therapy for symptomatic bradycardia. Whether iatrogenic, ischemic, or intrinsic conduction system disease is present, cardiac pacing can be a temporary bridge to recovery, a backup safety therapy, or a permanent therapy, depending on the clinical scenario. What follows is a review of major topics in cardiac pacing.

Indications

Indications for cardiac pacing vary with the clinical scenario. The major determinant of need for permanent pacing is the anticipated duration of the pacing indication. For example, symptomatic bradycardia associated with a toxic ingestion of a nodal blocking drug (e.g., digitalis) can be anticipated to resolve as the drug is cleared. Temporary pacing may be indicated in the short term, but a permanent device should not be needed. Alternatively, a transient neurocardiogenic (cardioinhibitory) bradycardic episode may resolve spontaneously, and temporary pacing should not be needed. However, if episodes recur on medical therapy to the point of causing recurrent syncope, a permanent pacemaker is indicated to protect the patient from subsequent syncopal episodes.

Temporary Pacing

In the emergency department setting, transcutaneous pacing can be used as a bridge to a more definitive transvenous temporary pacing system in the setting of symptomatic bradycardia of any etiology with hemodynamic compromise.

In the critical care setting, temporary pacing can be a life saving bridge to recovery or, further, to a definitive therapy for the underlying cause of bradycardia. The indications can roughly be divided into those related to ischemia, and all other

categories.

Acute myocardial infarction can be associated with bradycardia due to either sinus bradycardia, which does not require therapy unless it is causing hemodynamic compromise, or due to AV block or intraventricular block. AV block can be (a) intranodal, which is usually associated with inferoposterior infarcts (right coronary artery [RCA] 90%, left circumflex artery [LCX] 10%), manifests as first degree or Mobitz I pattern, is usually transient with benign prognosis, and rarely requires temporary pacing and almost never requires permanent pacing, or (b) infranodal, which is usually associated with anteroseptal infarcts (left anterior descending artery [LAD]), manifests as Mobitz II or third- degree block, is usually transient but may persist, and carries a poor prognosis as it signifies extensive infarction; it often requires temporary pacing and if it persists permanent pacing.

In general, "high-degree" heart block such as Mobitz type II second-degree heart block and third-degree heart block warrant temporary pacing during the acute phase of anterior (LAD territory) infarcts or inferior (RCA territory) infarcts. Further, new bifascicular block or alternating bundle branch block reflects ischemia within the interventricular septum and warrants temporary pacing as a backup in case of progression to complete heart block. Refractory bradycardia in the setting of an infarct in any territory necessitates temporary pacing.

In the absence of an acute myocardial infarction, symptomatic bradycardia with or without AV dissociation and third-degree AV block with ventricular escape warrant temporary pacing. Backup pacing indications include temporary ventricular pacing during right heart catheterization in the setting of preexisting left bundle branch block (LBBB), new bundle branch block or AV block in the setting of endocarditis, and essential pharmacologic therapies that may induce or exacerbate bradycardia.

Temporary pacing systems with temporary epicardial atrial and ventricular wires are routinely used in the setting of open heart surgery. These systems are used to optimize cardiac output coming off cardiopulmonary bypass, and subsequently as a backup system in case AV nodal conduction block occurs postoperatively, especially in the setting of valvular heart surgery.

Permanent Pacing

The indications for permanent pacing are listed in detail in the ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices). This document is summarized in Table 31.1.

TABLE

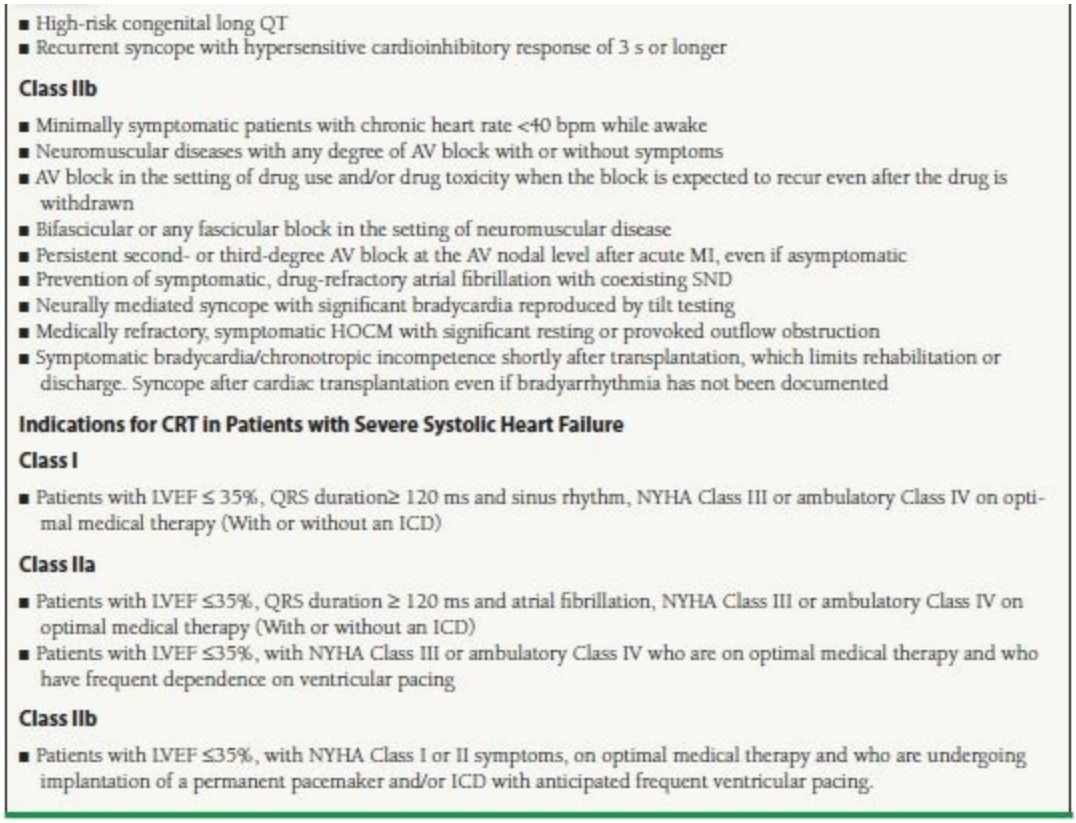
31.1 Indications for Permanent Pacemakers

Class I

- Symptomatic SND
- Symptomatic chronotropic incompetence
- Symptomatic sinus bradycardia secondary to required drug therapy for medical conditions
- Symptomatic third-degree AV block and advanced second-degree AV block including heart failure symptoms or ventricular arrhythmias presumed to be due to AV block
- Asymptomatic patients with third-degree AV block and advanced second-degree AV block in sinus rhythm with documented periods of asystole ≥3 s or any escape rate <40 bpm, or with an escape that is below the AV node
- Asymptomatic patients with third-degree AV block and advanced second-degree AV block in atrial fibrillation and bradycardia with 1 or more pauses ≥5 s
- Third-degree AV block and advanced second-degree AV block after catheter ablation of the AV junction or post cardiac surgery when it is not expected to resolve
- Neuromuscular disease associated with AV block, such as Erb's dystrophy, myotonic muscular dystrophy, Kearns–Sayre syndrome, peroneal muscular atrophy with or without symptoms
- Any second-degree AV block with symptomatic bradycardia
- Asymptomatic patients with persistent third-degree AV block with average awake rates of 40 bpm or faster if cardiomegaly or left ventricular dysfunction is present or if the site of block is below the AV node
- Second or third-degree AV block during exercise in the absence of myocardial ischemia
- Chronic bifascicular block with advanced second-degree AV block or intermittent third-degree AV block, or type II second-degree AV block, or alternating bundle branch block
- After acute phase of myocardial infarction:
  - Persistent second-degree AV block in the His–Purkinje system with alternating bundle branch block or third-degree AV block within or below the His–Purkinje system after ST-elevation myocardial infarction
  - Transient advanced second- or third-degree infranodal AV block and associated bundle branch block. (If site of block is uncertain, EPS may be needed)
  - Persistent and symptomatic second- or third-degree AV block
- Recurrent syncope with spontaneous carotid sinus stimulation and carotid sinus pressure that induces ventricular asystole of more than 3 s
- Documented pause-dependent VT with or without QT prolongation
- Symptomatic bradycardia/chronotropic incompetence after cardiac transplantation

Class IIa

- SND with heart rate <40 bpm when a clear association between severe symptoms of bradycardia and actual presence of bradycardia has not been documented
- Syncope of unexplained origin and SND discovered or provoked in EPS
- Asymptomatic third-degree AV block with average awake V rate ≥40 bpm without cardiomegaly
- Asymptomatic second-degree AV block at intra- or infra-His level at EPS
- First- or second-degree AV block with symptoms similar to pacemaker syndrome or hemodynamic compromise
- Asymptomatic type II second-degree AV block with a narrow QRS. When type II second-degree AV block occurs with a wide QRS, including isolated RBBB, pacing becomes Class I
- Bifascicular block with syncope not attributable to AV block when other causes excluded, especially VT
- Bifascicular block with prolonged HV interval (≥100 ms) at EPS or evidence of pacing-induced infra-His block that is not physiologic



- High-risk congenital long QT
- Recurrent syncope with hypersensitive cardioinhibitory response of 3 s or longer

Class IIb

- Minimally symptomatic patients with chronic heart rate <40 bpm while awake
- Neuromuscular diseases with any degree of AV block with or without symptoms
- AV block in the setting of drug use and/or drug toxicity when the block is expected to recur even after the drug is withdrawn
- Bifascicular or any fascicular block in the setting of neuromuscular disease
- Persistent second- or third-degree AV block at the AV nodal level after acute MI, even if asymptomatic
- Prevention of symptomatic, drug-refractory atrial fibrillation with coexisting SND
- Neurally mediated syncope with significant bradycardia reproduced by tilt testing
- Medically refractory, symptomatic HOCM with significant resting or provoked outflow obstruction
- Symptomatic bradycardia/chronotropic incompetence shortly after transplantation, which limits rehabilitation or discharge. Syncope after cardiac transplantation even if bradyarrhythmia has not been documented

Indications for CRT in Patients with Severe Systolic Heart Failure

Class I

- Patients with LVEF ≤ 35%, QRS duration≥ 120 ms and sinus rhythm, NYHA Class III or ambulatory Class IV on optimal medical therapy (With or without an ICD)

Class IIa

- Patients with LVEF ≤35%, QRS duration ≥ 120 ms and atrial fibrillation, NYHA Class III or ambulatory Class IV on optimal medical therapy (With or without an ICD)
- Patients with LVEF ≤35%, with NYHA Class III or ambulatory Class IV who are on optimal medical therapy and who have frequent dependence on ventricular pacing

Class IIb

- Patients with LVEF ≤35%, with NYHA Class I or II symptoms, on optimal medical therapy and who are undergoing implantation of a permanent pacemaker and/or ICD with anticipated frequent ventricular pacing.

AV atrioventricular; MI, myocardial infarction; SND, sinus node dysfunction; VT, ventricular tachycardia; LV left ventricular; EPS, electrophysiology study; CRT, cardiac resynchronization therapy; NYHA, New York Heart Association; HV Histo ventricular conduction time; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; HOCM, hypertrophic obstructive cardiomyopathy.

From Writing Committee Members Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices). Circulation. 2008;117:2820-2840, with permission.

Device Features

Single-chamber devices that only pace the ventricle or atrium have fallen by the wayside in favor of more sophisticated atrioventricular pacing devices that have the ability to track the sinus node rate when appropriate and pace the ventricle after a set delay. They also switch modes to ventricular backup pacing when the atrial signal falls outside of set parameters, as in paroxysmal atrial fibrillation and sick sinus syndrome. Further, cardiac resynchronization therapy (CRT) with biventricular pacing has a significant beneficial role in patients with symptomatic heart failure (New York Heart Association [NYHA] Class III and ambulatory Class IV) and evidence of left ventricular dysynchrony (EF ≤ 35% and wide QRS duration ≥120 milliseconds). Despite the predominance of dual-chamber pacemakers, there are increasing data suggesting that right ventricular stimulation increases the incidence of heart failure, hospitalization, and death in various patient subsets. However, if the ventricle needs to

be stimulated, the vast majority of patients tolerate right ventricular stimulation, as dual-chamber stimulation is preferred over sole ventricular stimulation. Figure 31.1 shows a schematic of pacemaker timing cycles.

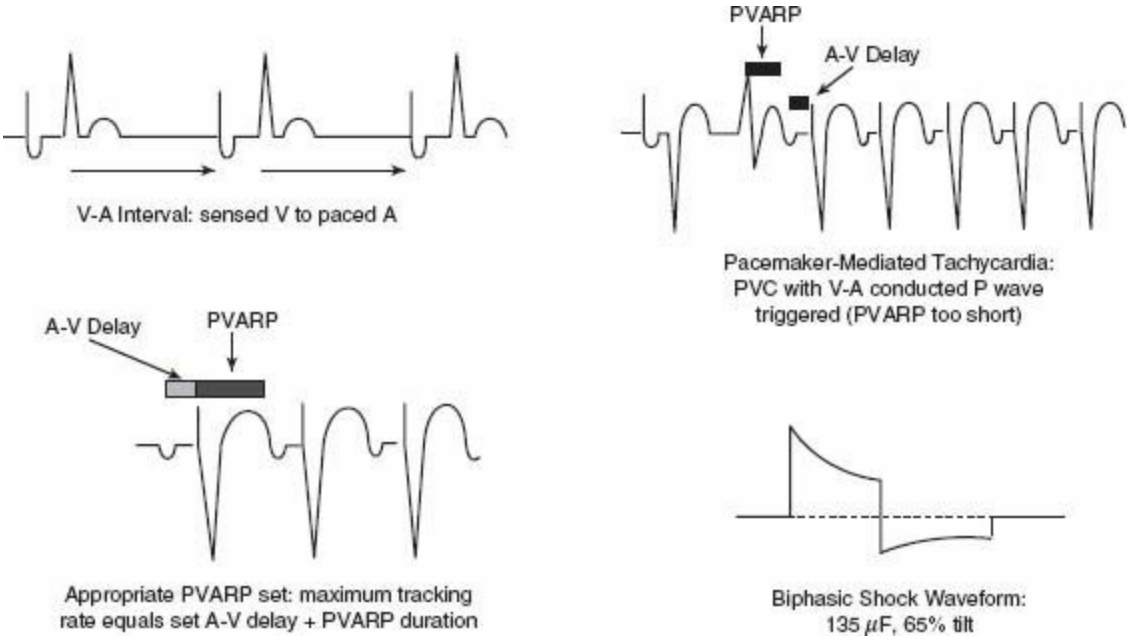


FIGURE 31.1 Schematic of important device timing cycles and impulses.

Rate-Adaptive Pacing

A variety of methods have been employed to allow for implantable pacemakers to increase their pacing rate in the setting of metabolic demand for increased cardiac output. The most commonly employed methods include activity sensors (vibration, acceleration), or minute ventilation sensors. Other sensors include peak endocardial oxygen sensors and right ventricle (RV) impedance-based sensors, which have the advantages of responding to nonexertional stimuli (emotions). These techniques utilize vibration, acceleration, minute ventilation, or other measurements as a surrogate for increased metabolic demand for oxygen delivery. In patients with chronotropic incompetence, or the inability to increase cardiac output in response to exercise, rate-adaptive devices can utilize these surrogates to increase the pacing rate and therefore increase cardiac output.

There are advantages and disadvantages to each type of sensor system. Vibration sensors and accelerometers provide an almost immediate rise in rate and therefore cardiac output when they detect activity. However, they can be "fooled" by stimuli external to the patient that mimics patient activity (i.e., turbulence during flight, etc.). The accelerometer tends to respond more specifically to patient activity than does the motion sensor. The advantage of the minute ventilation sensor is that it responds specifically to the patient's respiratory rate—a parameter that is controlled by the

brainstem. Although this parameter perhaps more reliably reflects the degree of patient exertion, it tends to lag behind the initiation of strenuous activity. Dual-sensor systems that utilize data collected from more than one sensor modality may actually be best suited for effective rate-adaptive pacing.

Mode Switching

Another feature of dual-chamber cardiac pacemakers that allows the devices to respond to changes in the physiology of the patient is mode switching. Mode switching is the ability of the device to revert to a separate, backup pacing mode in the event that the primary pacing mode no longer best serves the patient's pacing need. For example, in a patient with AV nodal block, a dual-chamber device may be programmed to sense or track the patient's intrinsic sinoatrial rate and to pace the ventricle after a set delay within the range of 60 to 120 beats/min (bpm). If the atria begin to fibrillate, the sensed atrial rate would exceed the rate parameter and the device would switch modes to a backup ventricular-only mode with a set rate sufficient to prevent hemodynamic compromise. If the patient reverted to sinus rhythm subsequently, the device would recognize the atrial rate back within the set parameter range and switch back to the primary mode, tracking the atrium and pacing the ventricle. Mode switching allows for the maximum responsiveness to the patient's intrinsic rhythm. These devices are most commonly programmed DDDR and revert to VVIR during periods of high atrial rates.

Other Programmable Features

Modern pacemakers now include a myriad of programmable features to better match the patient's physiologic status. They can be programmed to pace at a lower "sleep" rate during typical sleeping hours, with absence of strenuous activity confirmed by the devices metabolic sensing system. Programmable pulse width and output allow the programmer to optimize the impulse specifications to ensure capture while preserving battery power. Diagnostic information and event data including mode-switching data can be stored and retrieved later to assess for the presence and prevalence of atrial arrhythmias and other events. Atrial and ventricular electrograms can be obtained and stored. Device status data can also be retrieved, including battery usage and projected battery life given current settings.

Leads

The pacing leads conduct the electrical pacing impulse to the myocardium, and conduct the intrinsic electrical activity of the myocardium to the sense amplifiers within the device. Unipolar leads have a single electrode at their tip, and therefore they direct current from their tip to the can of the device through the patient's tissues, or vice versa. For this reason, problems such as pectoral, intercostal, or diaphragmatic stimulation are

more likely to occur, particularly in implants requiring higher outputs to capture the ventricle. Bipolar leads have two electrodes with close proximity at their tip and direct current proximal to distal or distal to proximal over much smaller distances. These leads can achieve capture of the myocardium with lower output energies and thus are more efficient. They are capable of unipolar function as well, but with the same limitations as standard unipolar leads. Of note, bipolar leads are by necessity larger and stiffer than unipolar leads, and have been historically more prone to mechanical failures than unipolar leads.

Coronary sinus leads are small, highly flexible unipolar or bipolar leads. They can be directed from the right atrium via the coronary sinus into a branch cardiac vein for the purpose of pacing the left ventricle in synchrony with the RV in patients with ventricular dysfunction and delayed intraventricular conduction, usually manifest as a LBBB.

Epicardial leads can be placed surgically using minimally invasive techniques or during open heart surgery for another indication and subsequently utilized instead of transvenous leads for standard pacing or more commonly for CRT (biventricular pacing). Often two leads are placed at the time of surgery and one of the two is subsequently utilized for biventricular pacing, depending on the thresholds and pacing characteristics of each at the time of device implant.

A variety of fixation techniques are utilized to maintain the contact of the lead tip with the myocardium. Active fixation leads employ a fixed extended or retractable screw to engage the myocardium. These systems allow for better localization of the lead tip at the desired site of implantation during deployment of the fixation helix. Passive fixation systems utilize plastic projections near the distal electrode that entrap in the trabeculations of the right ventricle or the right atrial appendage to maintain the position of the lead. As lead implants “mature” over time, pacing thresholds tend first to rise due to inflammation and then improve as healing continues and the inflammation resolves. Most leads have a small amount of steroid impregnated at the lead tip that reduces the size of the fibrotic tissue capsule and reduces the chronic thresholds.

Basic Concepts of Impulses and Timing

Following is a review of some basic concepts in pacemaker theory that are central to an understanding of the clinical application of pacing technology.

Stimulation threshold: The minimum amount of electrical energy that consistently produces a cardiac depolarization. The energy is a combination of voltage and pulse duration. It can be expressed in terms of amplitude (milliamperes or volts), pulse duration (milliseconds), charge (microcoulombs), or energy (microjoules).

Voltage output: The amount of voltage being delivered to the heart every time the pacemaker emits a stimulus. It is expressed in volts.

Pulse width (or pulse duration): The length in milliseconds the voltage is delivered to the heart.

Strength-duration curve: The hyperbolic relationship between the voltage output and the pulse width that defines the stimulation threshold (Fig. 31.2).

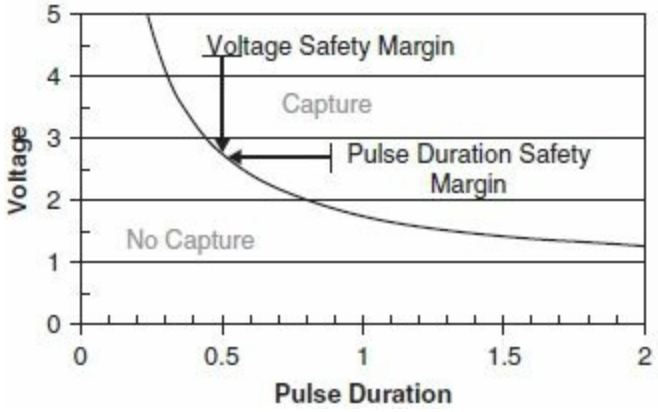


FIGURE 31.2 The strength–duration curve.

Sensing: Sensing occurs when the electrical wave front through the myocardium passes directly underneath the electrode

Atrial sensitivity: A programmed parameter that defines the largest signal that will be ignored by the device and thus determines which signals are detected by the pacemaker or implantable cardioverter/defibrillator (ICD) in the atrial channel. Atrial sensing in the dual-chamber pacing mode, DDD, will inhibit the atrial stimulus which would occur at the end of the atrial escape interval (V-to-A interval), initiate the AV interval, and trigger the ventricular output at the end of the AV interval.

Ventricular sensitivity: A programmed parameter that defines the largest signal that will be ignored by the device and thus determines which signals are detected by the pacemaker or ICD in the ventricular channel. Ventricular sensing in the dual-chamber pacing mode, DDD, will inhibit both atrial and ventricular stimuli that were scheduled to be output at the end of the atrial escape interval (atrial) or AV interval (ventricle) and initiate a new atrial escape interval (V-to-A interval).

Atrial oversensing: Sensing on the atrial channel that occurs due to signals on the atrial lead either related to signals originating outside the atrium, such as far-field ventricular signals, myopotentials from the pectoralis major muscle or diaphragm, or from noise originating from a dysfunctional lead (insulation or conductor fractures or a loose set screw). Depending on the mode of pacing, atrial oversensing will either inhibit or trigger atrial and/or ventricular stimuli.

Ventricular oversensing: Sensing on the ventricular channel that occurs due to signals on the ventricular lead either relating to signals originating outside the ventricle, such as myopotentials from the pectoralis major muscle in a unipolar lead system or from lead dysfunction secondary to insulation or conductor fracture or loose set screws. Sometimes the ventricular channel will oversense the atrial paced output and inhibit the ventricular output. This is called crosstalk inhibition and is usually prevented by a blanking of the ventricular sensing amplifier during the atrial paced outputs.

Chronotropic competence: The ability to match cardiac output to the metabolic needs of the body by appropriate modification of the heart rate.

Minimum rate: Also called the escape rate, this is the slowest rate at which the pacemaker will allow the heart to beat. The minimum paced rate is calculated by the ventricular paced or sensed event to atrial paced output interval plus the programmed A–V delay measured in milliseconds and converted to rate by dividing 60,000 by that sum.

V–A interval: Also called the atrial escape interval, this is calculated by subtracting the paced AV interval from the minimum rate interval. It is initiated by a paced or sensed ventricular event and concludes with a paced atrial event or is interrupted by either an atrial or ventricular sensed event.

A–V delay: This programmed interval is initiated by an atrial sensed or paced event and is terminated with a ventricular paced stimulus unless interrupted by a ventricular sensed event (either a conducted beat through the AV node or a premature ventricular beat). Often AV delays initiated by sensed atrial events are programmed to be shorter than AV delays initiated by atrial paced events.

Upper rate limit: The fastest rate at which the ventricular channel can track intrinsic P waves or, in the case of rate-adaptive pacing on the basis of a sensor, the fastest rate at which the ventricular channel can track the sensor rate

algorithm. The atrial tracking or upper rate limit is constrained by dividing 60,000 by the sum of the sensed AV delay and the postventricular atrial refractory period (PVARP).

PVARP: This is the Post-Ventricular Atrial Refractory Period. The PVARP is the timeframe during which the atrial channel is refractory after either a paced or sensed (R wave) ventricular event. Its purpose is to prevent atrial sensing and tracking of any V–A (retrograde) conduction of ventricular events to the atrium that would trigger a pacemaker-mediated tachycardia (see later).

Programming

Device programming has become more complex as dual- chamber pacing systems have become ubiquitous and biventricular pacing is becoming common place. It is important to note that the basic parameters discussed above can usually be derived with caliper measurements of the intervals observed on a 12-lead electrocardiogram (ECG) or rhythm strip. Following is a concise review of programming codes and timing cycles that provide the underpinnings of device programming.

Codes

A standard coding system has been adopted to delineate the basic settings of the device as follows: The first designation is the chamber paced, the second designation is the chamber sensed, the third designation is the device response to a sensed event, and the final designation reflects the rate-adaptive status of the device. There is a fifth position in the code that was originally used to indicate the antitachycardia response that the device will provide during a tachycardia, but now indicates whether multisite pacing is present or not. Table 31.2 reviews the mode codes in detail.

TABLE
31.2 Mode Codes for Cardiac Pacemakers

I Chamber (s) Paced	II Chamber (s) Sensed	III Response to Sensed Event	IV Program Rate Response	V Multisite Pacing
O: none	O: none	O: none	O: none	O: none
A: atrium	A: atrium	I: inhibited	S: simple	A: atrium
V: ventricle	V: ventricle	T: triggered	M: multiple	V: ventricle
D: dual (A + V)	D: dual (A + V)	D: dual (T + I)	C: communicating	D: dual (A + V)
S: single	S: single	—	R: rate response	—

As an example, a DDIR pacemaker can pace in both the atrium and the ventricle, and sense activity in both the atrium and the ventricle. Further, it will inhibit upon sensing intrinsic activity, and it has rate-adaptive functionality as well. A VOO device will pace the ventricle asynchronously, without sensing intrinsic activity.

Timing Cycles

When a dual-chamber device paces the atrium, the ventricular channel is blanked for a

period of 20 to 40 milliseconds as a safety feature to prevent inhibition of the ventricular channel by far-field (ventricular) sensing of the atrial paced output. The blanking period prevents "crosstalk inhibition," which could cause, in patients with complete lack of AV conduction, a string of atrial paced events and ventricular asystole. After the blanking period, the ventricular channel is open to sensed events. Typically, the first 100 milliseconds is the safety alert period. If, during this alert period a sensed event occurs, then the AV interval is abbreviated, usually to 120 milliseconds. This abbreviated AV delay is designed to prevent pacing during the vulnerable period of the ventricle, for instance, when the sensed event is caused by a premature ventricular depolarization. During the remainder of the AV delay (after the blanking and safety alert period), any sensed ventricular event will cause the ventricular output to be inhibited and reinitiate the atrial escape interval. If by the end of the programmed AV interval no event has been sensed, the device will pace the ventricle. After every paced or sensed ventricular event, a PVARP is initiated. During this period, the atrial channel is refractory to detecting atrial activity. The purpose of the PVARP is to prevent detection of atrial activity produced by retrograde conduction through the AV node. Without making the atrium refractory to retrograde atrial events (V-to-A conducted beats) an endless loop cycle can be set up that continues until the retrograde conduction fails. This endless loop tachycardia is one of several types of pacemaker-mediated tachycardia (see Fig. 31.1 for a schematic of pacemaker timing cycles in comparison to the surface ECG).

Diagnostics

Modern pacing devices are capable of storing tremendous amounts of data and reporting data in a variety of usable formats. Following is a brief review of device diagnostics and their applications.

Histograms. Histograms are a statistical report of a parameter describing the relative frequency of an event relative to time, heart rate, or another parameter. Histograms do not correlate symptoms to specific events, and from them one can only infer cause and effect (Fig. 31.3).

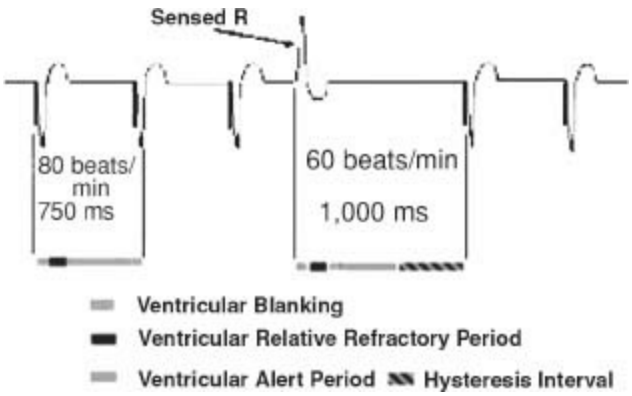


FIGURE 31.3 Histogram: ventricular hysteresis.

Trends. Trends evaluate the progression of a parameter over time. They are not a statistical representation but instead describe the correlation of an activity over time with symptoms. Trends can document concurrence of patient and rhythm events if interrogated quickly after the event occurs. Trends require extrapolation to connect patient and rhythm events. (See Fig. 31.3).

Event monitoring: Event monitoring captures an exact record of an event as characterized by electrograms, marker channel, and intervals. These monitored records are not statistical reflections of data but the actual recordings. Therefore, they can capture the relationship of symptoms and objective data. They require neither inference nor extrapolation (see Fig. 31.3).

Troubleshooting and Complications

Device troubleshooting most often involves interrogation of the device and adjustment of the pacing mode or timing cycles in order to optimize device function. Further, device interrogation using a programmer can reveal diagnostic information about the integrity of the leads, status of the battery, and performance of the device's algorithms, including the behavior of the rate-adaptive sensor function. A review of some specific device troubleshooting issues follows.

Endless Loop Tachycardia

Endless loop tachycardia is a type of pacemaker-mediated tachycardia specific to dual-chamber devices programmed to the VDD or DDD mode. Endless loop tachycardia is triggered by the atrial channel sensing retrograde conduction of a paced ventricular impulse. In response to the sensed event, the ventricle is paced again after the set AV interval, and retrograde conduction to the atrium recurs. As the atrium senses the retrograde V–A signal, the cycle begins again. The phenomenon is terminated by either applying a magnet to the device, thus reverting the device to nominal asynchronous pacing, or by reprogramming the device to lengthen the PVARP so that the atrial channel is refractory during the retrograde (V–A) conduction.

Pacemaker Syndrome

The so-called pacemaker syndrome is a constellation of physical symptoms and signs associated with loss of AV synchrony, most commonly associated with VVI pacing. Affected patients suffer weakness, dizziness, light-headedness, dyspnea on exertion, and sometimes even orthopnea and dyspnea at rest, independent of their underlying ventricular function. The symptoms result from ventricular pacing, typically with retrograde atrial conduction, which produces atrial contraction against a closed AV valve. The decrease in efficiency associated with loss of atrial kick as well as the increased back pressure within the pulmonary circuit both contribute to the symptomatology. Similar symptoms and physiology can result from atrial pacing with delayed AV conduction. The result is also related to atrial contraction against a closed AV valve. The treatment for pacemaker syndrome is device upgrade to a dual-chamber

device. An atrial tracking ventricular pacemaker eliminates the physiologic underpinnings of pacemaker syndrome and typically alleviates the symptoms.

Lead Fracture/Failure

Lead fracture is the term used to describe failures in the integrity of the lead wires, insulation, and/or coil. Fractures often occur at the ingress of the lead into the thorax within the subclavian vein as it passes between the clavicle and the first rib, particularly at the suture sleeve, due to tight ligatures or a sharp angulation of the lead in the pacemaker pocket. Crush injuries and chronic abrasion at this site are common etiologies of lead fracture. Disruption of the insulation causes a reduction of the pacing impedance and is often manifest by intermittent oversensing and either failure to produce a paced output or failure to capture the heart. Disruption of the lead conductor causes an increase in the pacing impedance and can also be manifest by intermittent oversensing and failure either to produce a paced output or to capture the heart. After the ECG, the chest x-ray is often the first diagnostic modality to reveal a lead fracture. Device interrogation typically suggests the diagnosis (abnormally high or low lead impedance, as noted above).

Infection/Erosion

Device infection occurs most commonly from bacterial contamination at the time of device implantation. Most infections do not present within the first month after implantation but are manifest within the first 2 years after implantation. Some infections can be indolent and persist for years before becoming apparent. The most commonly responsible organisms are Staphylococcus species, with gram-negative organisms occurring predominantly in diabetic patients or those otherwise immunocompromised. Physical findings associated with device infection may range from normal pocket appearance to mildly erythematous overlying tissue, to a swollen, boggy pocket and incision line. Occasionally a device will erode through the skin in the setting of a chronic device infection. When the pocket appears normal, the infection is typically endovascular and is unmasked by the presence of fevers and positive blood cultures along with supportive findings from transesophageal echo or chest CT scan. Less commonly, device infection can occur secondary to bacterial endocarditis or other bloodstream infection. Vegetations can sometimes be observed on the leads, most commonly utilizing transesophageal echocardiography.

The treatment for device infection with or without endocarditis is with antibiotics and device and lead extraction. The replacement device cannot be reimplanted at the time of device and lead extraction but should be delayed for few days or longer until it is deemed appropriate from the infectious disease stand point. Not all patients require immediate reimplant after extraction and the indication should be reinvestigated prior to reimplant. The reimplant is usually performed on the contralateral side.

Extraction

The most compelling reason for lead extraction is device–related infection, either localized to the pocket or endovascular with associated bacteremia or endocarditis. Multiple leads can compromise the venous flow, risking subclavian or superior vena cava (SVC) occlusion with symptoms, or prevent the addition of leads for upgrade to an ICD or BiV system. Lead extraction can range from simply applying traction to a recently implanted lead, to the use of mechanical, electrosurgical, or excimer laser extraction sheaths to facilitate the removal of fibrosed leads from the endovas cular surface. Lead extraction using these devices can be complicated by serious bleeding complications l eading to tamponade and even death, and are thus best relegated to experienced operators in large volume centers.

IMPLANTABLE CARDIOVERTER- DEFIBRILLATORS

ICDs initiated a new era in the treatment of ventricular tachyarrhythmias. In contrast to modern devices, the early ICD systems were implanted via thoracotomy with epicardial placement of defibrillating patches and sensing electrodes and abdominal implantation of the device can. The devices themselves had no programmability, no significant diagnostics, and an abbreviated battery life of about 1 year. Patients requiring permanent pacing had to have a separate pacing device implanted. Over time, ICD components have been reduced in size, allowing for prepectoral implantation with transvenous leads, possess bradycardia and antitachycardia pacing (ATP), and hundreds of programmable parameters, diagnostics, and event storage, all while device longevity has expanded to 5 to 7 years. The devices now have full pacing and resynchronization capabilities as well.

Indications

Indications for implantation of ICDs have expanded greatly over the past decade, based on data collected from the major ICD trials and are summarized in Table 31.3. It is very important to note that all these indications require a reasonable expectation of survival with an acceptable functional status for at least 1 year. ICDs are not indicated for patients with incessant ventricular tachycardia (VT) or ventricular fibrillation (VF), NYHA Class IV patients with drug refractory heart failure who are not transplant candidates or candidates for a CRT device, patients with significant psychiatric illnesses, when VF or VT is amenable to surgical or catheter ablation (e.g., atrial arrhythmias associated with Wolf–Parkinson–White (WPW) syndrome, right ventricular outflow tract (RVOT) or left ventricular outflow tract (LVOT), idiopathic VT in the absence of structural heart disease), or patients with ventricular arrhythmias due to a completely reversible disorder in the absence of structural heart disease.

TABLE
31.3 Indications for ICDs

Class I

- Survivors of a cardiac arrest due to VF or hemodynamically unstable sustained VT after exclusion of any reversible causes
- Structural heart disease and spontaneous sustained VT
- Syncope of undetermined origin and inducible sustained unstable VT or VF at EPS
- LVEF ≤35% due to prior MI who are at least 40 days post MI and are NYHA Class II or III
- LVEF ≤40% due to prior MI, with nonsustained VT and inducible VF or sustained VT at EP study
- LVEF ≤35% in nonischemic DCM and NYHA Class II or III

Class IIa

- Unexplained syncope, significant LV dysfunction, and nonischemic DCM
- Sustained VT and normal or near-normal ventricular function
- HCM with one or more major risk factors for SCD
- Arrhythmogenic right ventricular dysplasia/cardiomyopathy who have 1 or more risk factor for SCD
- Long QT syndrome with syncope and/or VT while on beta blockers
- Nonhospitalized patients awaiting transplantation
- Brugada syndrome with syncope or documented VT that has not resulted in cardiac arrest
- Catecholaminergic polymorphic VT with syncope and/or documented VT while receiving beta blockers
- Cardiac sarcoidosis, giant cell myocarditis, or Chagas disease

Class IIb

- LVEF ≤35% in nonischemic DCM and NYHA Class I
- Long QT syndrome and risk factors for SCD
- Syncope with structural heart disease in whom thorough invasive and noninvasive testing have failed to define a cause
- Familial cardiomyopathy associated with SCD
- LV noncompaction syndrome

VF, ventricular fibrillation; VT, ventricular tachycardia; EPS, electrophysiology study; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death; DCM, dilated cardiomyopathy.

The Center for Medicare and Medicaid Services (CMS) published updated guidelines in 2005 for reimbursement for ICD implantation, recognizing the data from the primary and secondary prevention trials of ICDs with and without capacity for cardiac resynchronization. The practical (reimbursed) indications for ICD implantation are listed in Table 31.4.

TABLE
31.4 CMS-Approved (Reimbursed) Indications for ICD Therapy

- Documented VF arrest not due to a reversible cause
- Documented sustained VT, spontaneous or induced by EPS, not associated with an acute MI or reversible cause
- Documented familial or inherited conditions with a high risk of life-threatening VT (e.g., long QT, HCM)
- Coronary artery disease with prior MI (More than 40 d prior to ICD insertion), LVEF ≤35%, and inducible VT or VF at EPS
- Documented prior MI and LVEF ≤30%, except NYHA Class IV, shock, MI within 40 d or CABG/PCI within 90 d, or any noncardiac disease associated with <1-y survival
- Ischemic heart disease, prior MI, NYHA Class II–III symptoms, LVEF ≤35%
- DCM >9 mo duration, LVEF ≤35%, NYHA Class II–III symptoms
- DCM >3 mo duration, LVEF ≤35%, NYHA Class II–III symptoms if enrolled in an approved clinical trial or approved national registry

VF, ventricular fibrillation; VT, ventricular tachycardia; EPS, electrophysiology study; MI, myocardial infarction; HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; DCM, dilated cardiomyopathy.

Providers must be able to justify the medical necessity of devices other than single-lead devices.

Devices

The current generation of ICDs includes single-chamber VVI devices, dual-chamber devices with fully programmable pacing capabilities, and CRT devices capable of biventricular pacing and antitachycardia therapies. As technology has progressed, these devices have become smaller, with better longevity and greater programmability. The diagnostics available allow for extensive troubleshooting and event monitoring.

Lead Systems

Typically, single-chamber ICD systems are implanted using active- or passive-fixation multipolar leads with shocking coils that lie in the RV apposed to the endocardium as well as the SVC. With this configuration, the device can deliver energy from the RV (+) coil to the SVC (-) coil or vice versa, or from either coil (+) to the ICD can (-) itself or vice versa. Various investigations have demonstrated that defibrillation thresholds (DFTs) can be reduced using optimal polarity and an "active can" configuration.

ICDs can be attached to epicardial leads or patches implanted during surgery. These leads are typically placed using minimally invasive techniques for patients with high DFTs or during open heart surgery performed for other indications. Subcutaneous arrays and even azygous vein leads can be placed. Virtually all ICDs are implanted with transvenous in lieu of surgically placed leads.

Dual-chamber devices possess an atrial lead in addition to the ventricular shocking coil lead. The atrial lead is typically a standard bipolar pacing lead without a shocking coil and plays no role in defibrillation.

Implantation

The most common site for device implantation is the left prepectoral space. This site

gives access to the left subclavian vein for transvenous lead placement. Especially in "active can" configurations, this site of implantation allows for lower DFTs as the path for energy transmission from can to coil or vice versa traverses the LV myocardium. In the case of prior device infection, scarring, subclavian stenosis, or mastectomy on the left side, the right prepectoral space may be used. Lead implantation technique is much like that used for standard pacing lead implantation; however, there is an impetus to implant the lead tip at the RV apex so that the RV shocking coil rests completely within the right ventricle.

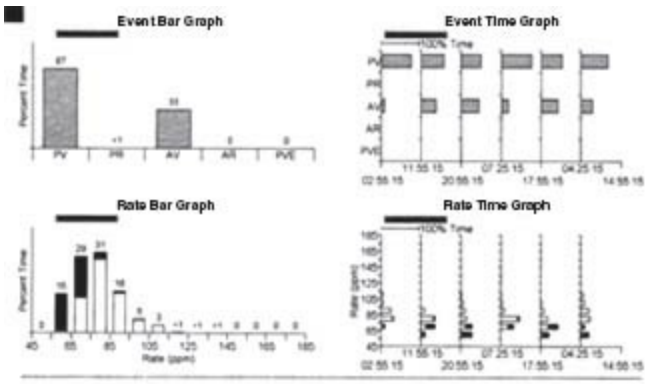
Device Function

Detection

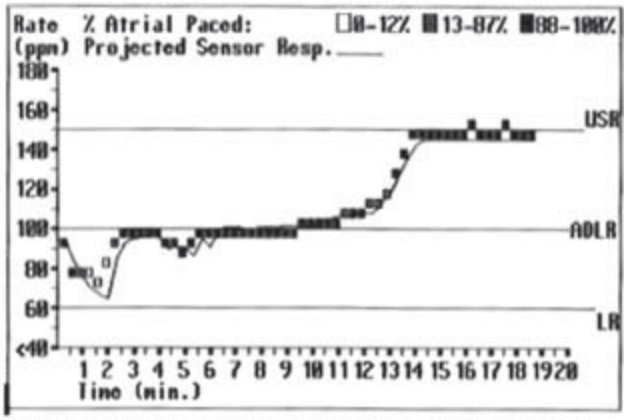
ICDs have a variety of programmed routines designed to aid in the detection and verification of VT and VF, and to minimize the number of inappropriately delivered therapies. The device must be able to sense low-amplitude high-rate signals in VF, while not oversensing far-field atrial activity or ventricular repolarization. Appropriate sensing thresholds must be achieved at the time of implantation, or the device cannot be relied on to appropriately detect and treat malignant ventricular arrhythmias.

Detection algorithms utilize counters, and detection criteria are based on signal counts registered faster than the tachycardia threshold criterion programmed into the device. For example, if an ICD is programmed to detect VT at cycle lengths of less than 400 milliseconds and the device senses consecutive R waves with a cycle length of 390 milliseconds, it begins to count consecutive R waves until it reaches the programmed detection criterion, perhaps 15 beats. If the device detects 15 consecutive R waves with cycle length <400 milliseconds, it registers a VT event and administers therapy. VF is a more unstable arrhythmia, with shorter cycle lengths, and smaller and more variable wavelet amplitudes. The device cannot be assured of sensing consecutive signals to meet the VF criterion, so the criterion is often programmed to detect VF if 15 of 20 R waves are detected with a cycle length below the VF threshold cycle length.

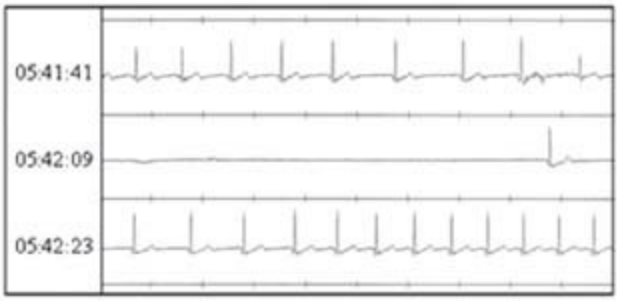
Single-chamber devices use these cycle length criteria in addition to analyzing the suddenness of arrhythmia onset, the duration and persistence of the arrhythmia, and the morphology of the sensed R waves. Dual-chamber devices have the advantage of being able to compare ventricular sensed activity to atrial sensed activity, so rates and relationship of A to V can be compared in the detection criteria. Further, dual-chamber devices can detect AV dissociation. So the detection algorithms can be more sophisticated and potentially more accurate in the detection of VT requiring therapy and the discrimination of SVT or AF not requiring ICD therapy (Fig. 31.4).



1. A device histogram reflecting time spent in pacing mode and rate



2. A Trend reflecting atrial pacing rates over a period of time



3. An event recording revealing a long sinus pause

FIGURE 31.4 Device diagnostics: histograms, trends, and event monitoring.

For example, a dual-chamber device set to apply VT therapies at ventricular cycle lengths of 400 milliseconds or less may detect VT as in the previous example while at the same time detecting atrial signals with a cycle length of 200 milliseconds. Recognizing the atrial tachycardia (flutter) and the 2:1 ventricular response, the device monitors but does not "detect and treat" VT. If, in the same example, the device senses atrial signals with a cycle length of 400 milliseconds, it monitors the sinus tachycardia or SVT but does not deliver therapy for VT.

Therapies

The therapy for VF is defibrillation upon detection with consecutive high-energy shocks

pending redetection until the arrhythmia is terminated. Upon meeting the detection criteria, the device begins to charge its capacitor to the programmed output for the initial shock. Upon completion of capacitor charging, the device then rechecks for the presence of the arrhythmia and if present, it delivers the shock. After the initial shock, the device monitors for arrhythmia meeting criteria and if present, it charges again, typically to a higher or maximum output. If after charging the arrhythmia persists, the device again delivers therapy. The cycle continues until the arrhythmia is terminated.

Therapies for VT include low-energy synchronized cardioversion as well as ATP. The advantage of ATP is that it is painless and is not often perceived by the patient. When an ATP device detects VT, it can deliver a programmed burst of pacing impulses at a cycle length just shorter than the detected arrhythmia in an attempt to interrupt the reentrant VT circuit. After the burst, the device monitors for persistence of the arrhythmia. If VT persists, further bursts of ATP can be delivered, followed if necessary by low- or high- output cardioversion. ATP bursts can be programmed at a fixed cycle length representing a percentage of the VT cycle length, or at a progressively shorter (accelerating) cycle length for a programmed number of pulses. The number of ATP attempts prior to administration of shocks can be programmed too. Low-output cardioversion shocks are typically synchronized to the intrinsic R wave of the VT. Based on a variety of investigations, ATP is not inferior to low-energy cardioversion in terms of efficacy, and because it is painless, it has become the preferred therapy for "slow VT." In addition, recent data have documented that faster tachyarrhythmias, between 200 and 250 bpm, can be successfully pace terminated approximately 50% of the time.

Waveforms

The shock waveform for VT and VF is the same: a prolonged (relative to a pacing impulse) biphasic waveform lasting 5 to 20 milliseconds. The waveform is a truncated exponential decay voltage wave with a drop from the initial voltage to the trailing-edge voltage, called the tilt. A typical tilt is a 65% reduction of the voltage at the end of the first phase of the biphasic pulse. Then the capacitor polarity is reversed, producing a leading-edge negative voltage for the second phase equal to the trailing-edge positive voltage of the first phase. The second phase also has a tilt and is truncated after a few milliseconds. Biphasic waveforms with second phases equal to or shorter in duration than the first phase have been associated with significantly lower DFTs as compared with monophasic waveforms. Thus, all current production ICDs utilize a biphasic waveform (Fig. 31.5).

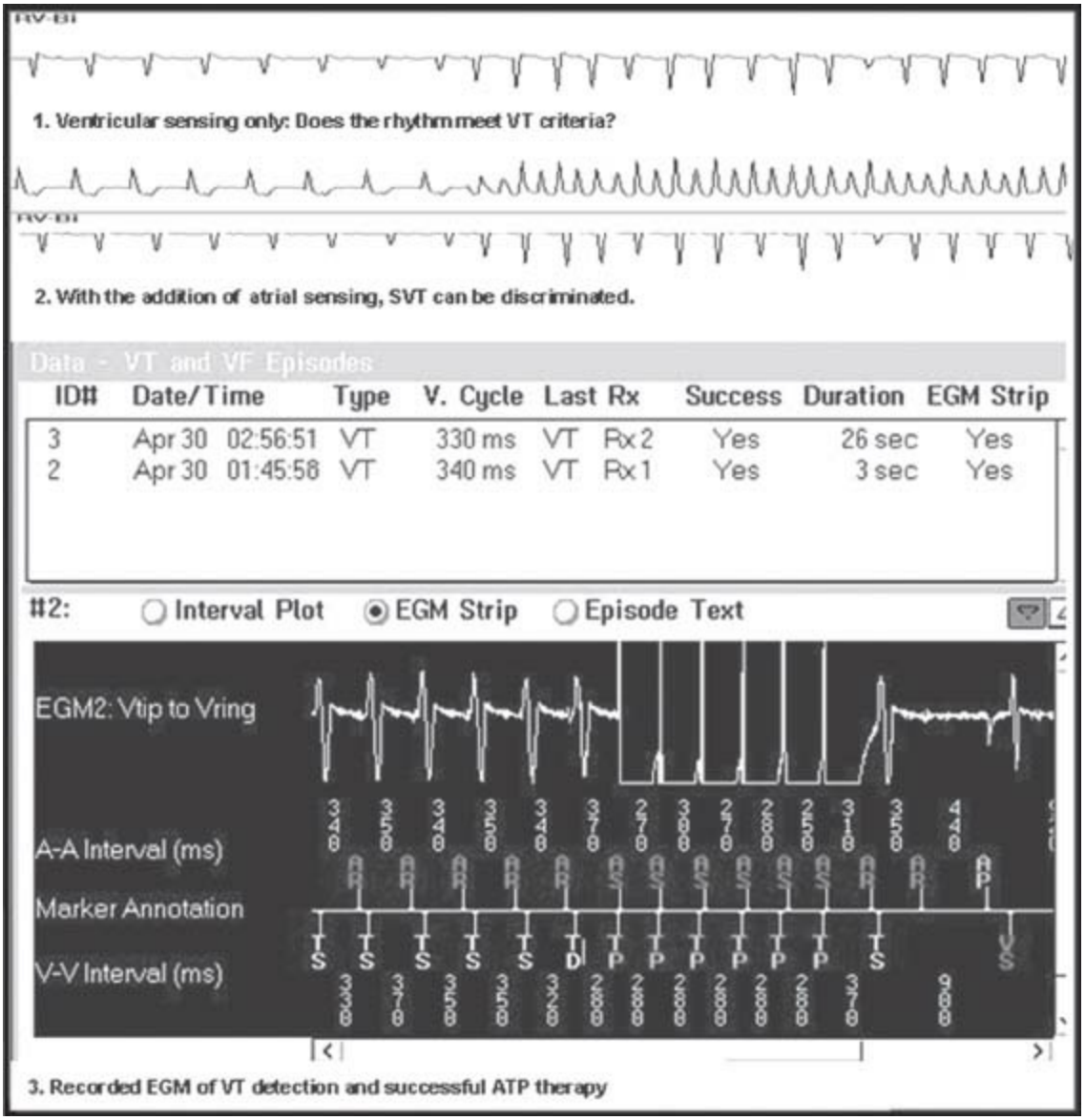


FIGURE 31.5 ICD detection: dual-chamber discrimination and event report.

Polarity

Modern ICDs have the programmability to add or subtract various electrodes from the circuit (can or SVC electrode) or change the initial (positive or negative) polarity of the leads and the can, as well as the polarity of the waveform. Polarity changes are sometimes undertaken to reduce DFTs in patients with high DFTs.

Programming

Device programming for ICDs involves programming pacing modes as well as detection parameters and therapies for VT and VF. Modern ICDs have full pacing capabilities and, depending on the device and indication for implantation, may be programmed for ventricular backup pacing, dual-chamber tracking and pacing, and even resynchronization pacing. The following review focuses on the antiarrhythmia features

of ICDs. Refer to the pacing section of the chapter for more on pacemaker programming.

Detection Criteria

Therapies for VT and VF are administered only after detection criteria are met. Therefore, the criteria programming is critical for optimal device function. The concepts of arrhythmia detection have been presented previously. What remains is the actual interface programming between the device and the physician. As a practical matter, the detection criteria sets are typically divided into VT parameters and VF parameters. The VT parameters may further be broken down into "slow" VT and "fast" VT zones, based on the premise that slower VT may be more amenable to painless therapies (ATP) and faster VT may be more prone to acceleration or failure of ATP to convert the rhythm back to the baseline rhythm. Furthermore, "monitor zones" can be established so that rhythms in a given rate zone can be recorded as "events" and retrieved later for analysis. So the task of the device programmer is to match the detection criteria and therapies to the anticipated needs of the patient.

> For example, if an 80-year-old patient with prior myocardial infarction and LV dysfunction has a device implanted after a documented VT episode with a VT cycle length of 380 milliseconds, and the patient is now being treated with amiodarone and long-acting beta-blockers, the physician programmer may opt for VVI backup pacing at 40 bpm, a "slow VT" zone of 400 to 320 milliseconds, and a "fast VT" zone of 319 to 290 milliseconds, with a VF zone of anything <290 milliseconds. Therapies may include three attempts at ATP at 81% of the VT cycle length, followed by 20, 30 J, maximum output shocks if ATP fails to convert the "slow" VT. The fast VT zone may be programmed for 20, 30 J, maximum output for six shocks, and the VF zone may be programmed likewise, 20, 30 J, maximum output for six shocks.

Now suppose the patient goes home and comes back to the Emergency Department with "weakness" but has received no shocks as far as he can tell. Telemetry reveals NSR 60 bpm. Interrogation of the device reveals normal function and no recorded events. Perhaps the patient is having VT that has now slowed below the detection criteria as a result of the addition of negative chronotropes and antiarrhythmic drugs.

Another patient with a similar profile but no history of arrhythmia may have a single-chamber device implanted for primary prevention. In this case, the physician programming the device may simply try to protect the patient from any arrhythmia reasonably anticipated to be inappropriately fast and hemodynamically unstable, and set a single zone below 320 milliseconds with six maximum output shocks.

Therapies—Antitachycardia Pacing

ATP as described previously is typically programmed to be administered in a burst of constant cycle length impulses or as a "ramp" of decreasing cycle length impulses. Typically, the device is programmed to initial ATP at a cycle length of 80% to 85% of the arrhythmia cycle length. No benefit has been demonstrated of "ramp" ATP over static cycle length ATP, and both achieve termination of VT in up to 90% of attempts.

Typical bursts are 8 to 12 impulses, with reapplication of detection criteria after the burst to redetect persistent arrhythmias. Posttherapy criteria are often less stringent than initial detection criteria so as to shorten time to redetection and retreatment of persistent arrhythmias. The programmer decides the number of attempts at ATP prior to reverting to a cardioversion strategy, but typically several attempts at ATP are made before administering shocks in an initial program. Rates of acceleration of VT are low, in the 1% to 3% range, but are quite variable among patients, among cycle lengths, and among morphologies of tachycardias within a single patient.

Therapies—Cardioversion and Defibrillation

Low-energy synchronized cardioversion may be programmed for detected VT with outputs typically between 5 and 20 J. These synchronized therapies are preferred because they are effective, have shorter charge times, and are less likely to cause VF via a R-on-T mechanism, thus preventing some syncopal events. If the ATP or low-energy shocks are unsuccessful or accelerate the rhythm to VF, then the device delivers high-energy synchronized shocks. Devices can be programmed to deliver five or six distinct therapies in sequence, each often more aggressive than the previous therapy. Therapies delivered at or above the DFT have a high probability of converting the rhythm back to baseline, with repeat therapies sometimes necessary to convert successfully.

Troubleshooting

High Defibrillation Thresholds

Because delivered therapies convert the malignant rhythm as a probability function based on delivered energy in excess of the defibrillation threshold or DFT, it is important to estimate the DFT at the time of device implantation. Initial device therapies are typically programmed with a margin of safety above the estimated DFT to increase the chance of conversion with the first shock delivered. A variety of scenarios can lead to high DFTs, but they can be divided into device-related and patient-related categories.

Device-related causes of high DFTs may include inappropriate lead positioning at implantation or subsequent dislodgement of the lead. Loose header screw or lead failure/fracture may result in high-impedance failure of defibrillation. Inappropriate shocking vector, as in the case of an active can system implanted in the right prepectoral pocket, may result in unacceptably high DFTs. In this case, a subcutaneous shocking electrode on the left side or an azygous vein shocking coil could be implanted and the system reprogrammed to shock from RV to azygous or vice versa or from RV to subcutaneous array or vice versa. Waveform morphology, polarity, and tilt may also be reprogrammed if the device nominal setting leads to high DFTs.

Patient-related characteristics that may lead to higher DFTs include the use of drugs

that may increase the DFT, including Class I agents, nonselective beta-blockers, nondihydropyridine calcium antagonists, and especially amiodar-one. Hypoxia and ischemia may both lead to refractory VF and failure of internal and even high-energy external shocks, so it is imperative that these clinical parameters be treated and optimized prior to elective DFT testing. A potential procedural complication, pneumothorax, may affect DFTs in active can configurations when air is interposed between the heart and the device. Recognition of this phenomenon is critical so that the situation is remedied prior to repositioning of leads or addition of extra coils or arrays. Finally, multiple prior attempts at defibrillation may raise DFTs during subsequent attempts within a brief period of time. Retesting hours to days after implantation may reveal lower DFTs than initially observed at implantation.

Evaluating Inappropriate Shocks

The evaluation of an ICD shock begins with an appropriate history and physical examination focusing on the circumstances of the discharge in question and the integrity of the device implantation and the patient's cardiopulmonary status. The history should assess for antecedent anginal and presyncopal symptoms, dyspnea, nausea/vomiting/diarrhea, and other potential causes of electrolyte imbalances as well as external factors such as proximity to sources of electromagnetic interference (EMI). The physical examination should assess for decompensated heart failure, rate and regularity of rhythm, trauma to the device, or the anatomic location of the leads (often beneath the clavicle).

Interrogation of the device is paramount, and evaluation of stored events and electrograms should reveal the nature of the episode during which the therapy was administered. If the therapy was appropriate, one should determine whether it was successful and assess potential reasons why subsequent therapies may have been required. If the therapy was inappropriate, a determination should be made as to whether it was in response to a conducted supraventricular arrhythmia, a far-field oversensing of myopotentials or atrial arrhythmias, or noise from lead fracture or failure.

Failure to Detect

The most common cause of failure to detect ventricular arrhythmias is inappropriate programming of tachycardia zones and detection criteria. Very often a device is implanted and antiarrhythmic drug therapy is initiated at the same time. Subsequent symptomatic arrhythmias may occur at rates lower than observed prior to implantation and initiation of drug therapy, as a consequence of drug therapy. The resulting scenario is that of an implanted device blinded to the culprit arrhythmia because of the programmed tachycardia zone. Ventricular arrhythmias can therefore be slowed into a rate range where physiologically normal tachycardia may occur. An example might be

an athlete with an ICD implanted for symptomatic Brugada syndrome. The patient could potentially have physiologic sinus tachycardia below the 400- to 380-millisecond range, but could also develop VT with a similar cycle length. Detection algorithms utilizing atrial channel activity would be imperative in discriminating malignant ventricular arrhythmias in this patient.

ICD Management during Surgical Procedures and MRI Scanning

The ICD detection algorithms can be "spoofed" by high- frequency signals such as those delivered during electrocautery use intraoperatively. As a result, inappropriate therapies could be delivered by the device during a surgical procedure. Device detection can be turned off through the use of a device programmer or a magnet applied to the implant site, so long as telemetry monitoring and external defibrillation are available during the procedure.

MRI scanners can be a source of EMI in addition to inactivating device therapies while the patient is inside the scanner. This vulnerability of the devices to MRI effects makes them a contraindication to perform these studies. However, sometimes the importance of MRI could outweigh the risks, but this should be assessed on a case-by-case basis and under controlled and monitored situations. New pacemaker devices that are MRI compatible have been recently approved for clinical use and postmarketing evaluation of these devices is of utmost importance.

SUMMARY OF IMPORTANT ISSUES FOR THE BOARD EXAMINATION

The issues discussed in this chapter are the technical aspects of pacemaker and defibrillator therapy. All of the issues discussed are important for patient care, but for the examination, the indications for pacemaker and defibrillator implantation and the supporting multicenter clinical trials are of primary importance. In addition, pacemaker electrocardiography, which depends on understanding the basic timing cycles and intervals, is likely to be both important to the cardiologist in practice as well as in test material. In a parallel way, evaluation of the appropriateness of defibrillator therapy, ATP and shock therapies, determining the presence or absence of a ventricular or supraventricular arrhythmia, lead dysfunction, and the appropriateness of the programmed parameters, as well as the effectiveness of the therapy, are central to patient care and for the examination. A list of essential facts is provided as bulleted points.

Essential Facts

- Ohm's law: Voltage = current × resistance (V = IR).
- All pacemaker intervals are initiated and terminated by a sensed event (usually silent

to the ECG) or by a pacemaker output (usually apparent on the ECG).

- Pacemakers make decisions on a beat-to-beat basis, on the basis of the current interval and not as a result of the heart rate. Therefore each beat and each interval must be analyzed separately.
- Conversion of intervals to rate equivalents or back are done as follows:
- Pacemaker magnets close the "reed switch". Closing the "reed switch" will almost always disable sensing for pacemakers and cause the pacemaker to function at a fixed rate regardless of the intrinsic rhythm.
- Pacemaker magnets, when placed over an ICD, will disable detection and therapy of tachyarrhythmias. This is most commonly only temporary, i.e., while the magnet is over the "reed switch". However, in some devices, depending on the programming of the device, it can turn off arrhythmia detection and therapy until the device is reprogrammed.

$$\text{Heart rate (beats/min)} = \frac{60{,}000}{\text{cycle length (ms)}}$$

$$\text{Cycle length (ms)} = \frac{60{,}000}{\text{heart rate (beats/min)}}$$

SUGGESTED READINGS

Ellenbogen KA, Kay GN, Lau CP, et al. Clinical Cardiac Pacing and Defibrillation and resynchronization. 3rd ed. Philadelphia: Saunders; 2007.

Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices). Circulation. 2008;117:e350–e408.

QUESTION AND ANSWERS

Questions

1. The AV delay is 200 milliseconds and the time from a paced QRS to the next atrial paced event is 800 milliseconds. To what basic or lower rate has the pacemaker been programmed?
   a. 100 beats/min (bpm)
   b. 90 bpm
   c. 80 bpm
   d. 70 bpm
   e. 60 bpm
2. The sensed AV interval is 150 milliseconds and the PVARP (postventricular atrial refractory period) is 350 milliseconds. What is the most rapid atrial rate that the pacemaker can track 1:1?
   a. 300 bpm
   b. 250 bpm
   c. 200 bpm

d. 150 bpm
e. 120 bpm

3. A pacemaker-dependent 65-year-old woman says that her activity-sensing pacemaker programmed to the DDDR mode (unipolar) makes her heart race every time she sweeps the floor. Which of the following could remedy the patient's situation?
   a. Increase the rate response slope.
   b. Program the atrial channel to bipolar paced configuration.
   c. Program the ventricular channel to bipolar sensed configuration.
   d. Decrease the atrial sensitivity from 1 to 3 mV.
   e. Decrease the ventricular sensitivity from 1 to 4 mV.

4. The VVI pacemaker is programmed to a lower rate of 80 bpm. There are PVCs and usually the heart rate is paced at 80 bpm, but intermittently there are intervals between intrinsic R waves of 960 milliseconds. Which of the following could be the explanation for the electrocardiographic findings?
   a. Paced bipolar impedance of 300 W
   b. Hysteresis rate of 60 bpm
   c. Sleep rate of 55 bpm
   d. Paced unipolar impedance of 250 W
   e. PVC response

5. Which of the following scenarios is NOT an indication for an implantable cardioverter-defibrillator (ICD) insertion?
   a. A 45-year-old man with history of myocardial infarction 2 years ago, left ventricular ejection fraction (LVEF) 25%, New York Heart Association (NYHA) Class I
   b. A 33-year-old woman, with nonischemic cardiomyopathy, LVEF 35%, NYHA Class III
   c. A 65-year-old man with history of prior MI, who presents with syncope and found to be in incessant VT requiring IV lidocaine and multiple external shocks
   d. A 69-year-old man with history of MI, LVEF 45%, who survived VF cardiac arrest that required external shock
   e. A 55-year-old man with history of MI, nonsus- tained VT, LVEF 37%, with inducible sustained VT during EPS

Answers

1. Answer E: The cycle length consists of the AV interval + VA interval. These two intervals added together and converted to a heart rate yield the lower rate or base rate programmed for this pacemaker patient.

200 ms + 800 ms = 1,000 ms = cycle length
Base heart rate = 60,000/1,000 ms = 60 bpm

Note that the AV interval can be dynamically shortened (based on the sensor and/or the atrial rate) and there can be a shortening of the AV interval if there is a sensed P wave instead of an atrial paced beat. In addition, the rate of the pacemaker can be increased with apparent increases in the base rate if the sensor detects a need to increase the paced rate.

2. Answer E: The maximal rate at which a DDD pacemaker can track an atrial rhythm is limited by the shortest interval in which the atrium can be detected. By adding together the PV interval (the AV interval initiated by a P wave and terminated with a ventricular pacemaker output) and the PVARP (the time during which the atrium cannot sense another P wave after a ventricular sensed or paced event), the total refractory period can be calculated. That interval converted to a heart rate is the maximal rate at which the pacemaker can participate in producing a paced rhythm. Both the PV delay and the PVARP can vary on the basis of atrial rate and sensor rate, but in this example the intervals are fixed. Thus,

AV interval + PVARP = 150 ms + 350 ms = 500 ms

Converting this to heart rate, we see that the maximal paced rate = 60,000/500 milliseconds = 120 bpm. To increase the upper tracking rate it would be necessary to shorten the sensed AV interval, the

PVARP, or enable rate-adaptive shortening of these intervals.

3. Answer D:.This woman is using her upper body, which has the potential to activate her activity sensor and to produce myopotentials from use of the pectoralis major muscle. Increasing the rate response slope will increase the heart rate related to her activity. Programming the atrium to bipolar paced configuration would not impact her heart rate but could help if her complaint was secondary to stimulation of the pectoral muscles. Programming the ventricle to bipolar sensed configuration would reduce the likelihood that the ventricular channel would detect myopotentials, because the muscle would no longer be within the antennae being sensed by the ventricle. Sensed events on the ventricular channel would inhibit ventricular output and could be responsible for syncope due to bradycardia. Decreasing the ventricular sensitivity would potentially decrease the likelihood that myopotentials would be sensed, but this would cause inhibition of the ventricular output and a decreased heart rate. Decreasing the atrial sensitivity from 1 to 3 mV will likely decrease the probability of sensing myopotentials on the atrial channel. These atrial sensed events would have been tracked to the ventricle and cause the patient to perceive a tachycardia rhythm.

4. Answer B: The rate of 80 bpm needs to be converted to an interval. Cycle length = 60,000/80 = 750 milliseconds. The interval of 960 is longer than the 750 (80 bpm). Longer intervals than the lower rate (base rate) of the pacemaker suggest (a) inhibition, (b) failure of output by the pacemaker (lead or generator related), or (c) an algorithm that explains the particular circumstance. A paced bipolar impedance of 300 Q is relatively low, but normal. If this represented a marked drop from previous measurements, then it is possible that there is a short within the pacing lead. The hysteresis rate of 60 bpm translates to a sensed escape interval of 1,000 milliseconds. This could explain the ECG as long as the paced intervals between ventricular events were 750 milliseconds. If the ECG findings occurred only at night, then intervals of 960 milliseconds would be normal, but would not explain the other paced intervals at 750 milliseconds. A unipolar pacing impedance cannot be too low to work. This is low but does not explain the findings. PVC responses can extend the PVARP to avoid initiating a pacemaker-mediated tachycardia but would not change the escape interval of the pacemaker.

5. Answer C: All the scenarios mentioned represent Class I indication for insertion of an ICD. Incessant VT is a contraindication to insertion of an ICD as this will lead to multiple ICD shocks. Ruling out any reversible causes (ischemia, electrolyte imbalances) and controlling the VT with medication or ablation procedure should be performed first prior to insertion of an ICD.

CHAPTER

Syncope

Fredrick J. Jaeger

This chapter focuses on core material related to the evaluation of patients who present with syncope of unknown origin. It reviews the indications and contraindications for various salient procedures and diagnostic maneuvers to evaluate patients who present with syncope. Highlighted among these are head-up tilt table testing to provoke and confirm neurocardiogenic syncope and electro-physiologic testing to assess for atrioventricular (AV) node and sinoatrial (SA) node dysfunction and inducibility of supraventricular tachycardia (SVT) and ventricular tachycardia (VT), which could be responsible for recurrent syncope. It is critical, in this era of evidence-based medicine and quality outcomes, health maintenance organizations (HMOs), diagnosis-related groups (DRGs), and limitations of diagnostic testing availability, that a concise, logical, streamlined approach to the evaluation of patients with syncope be employed. Several useful algorithms can be found in the literature (Fig. 32.1).[1] Recently, it was proposed that emergency departments adopt a streamlined approach to syncope patients that will allow more efficient utilization of resources, identifying high-risk patients and avoiding unnecessary admissions for low-risk patients.[2]

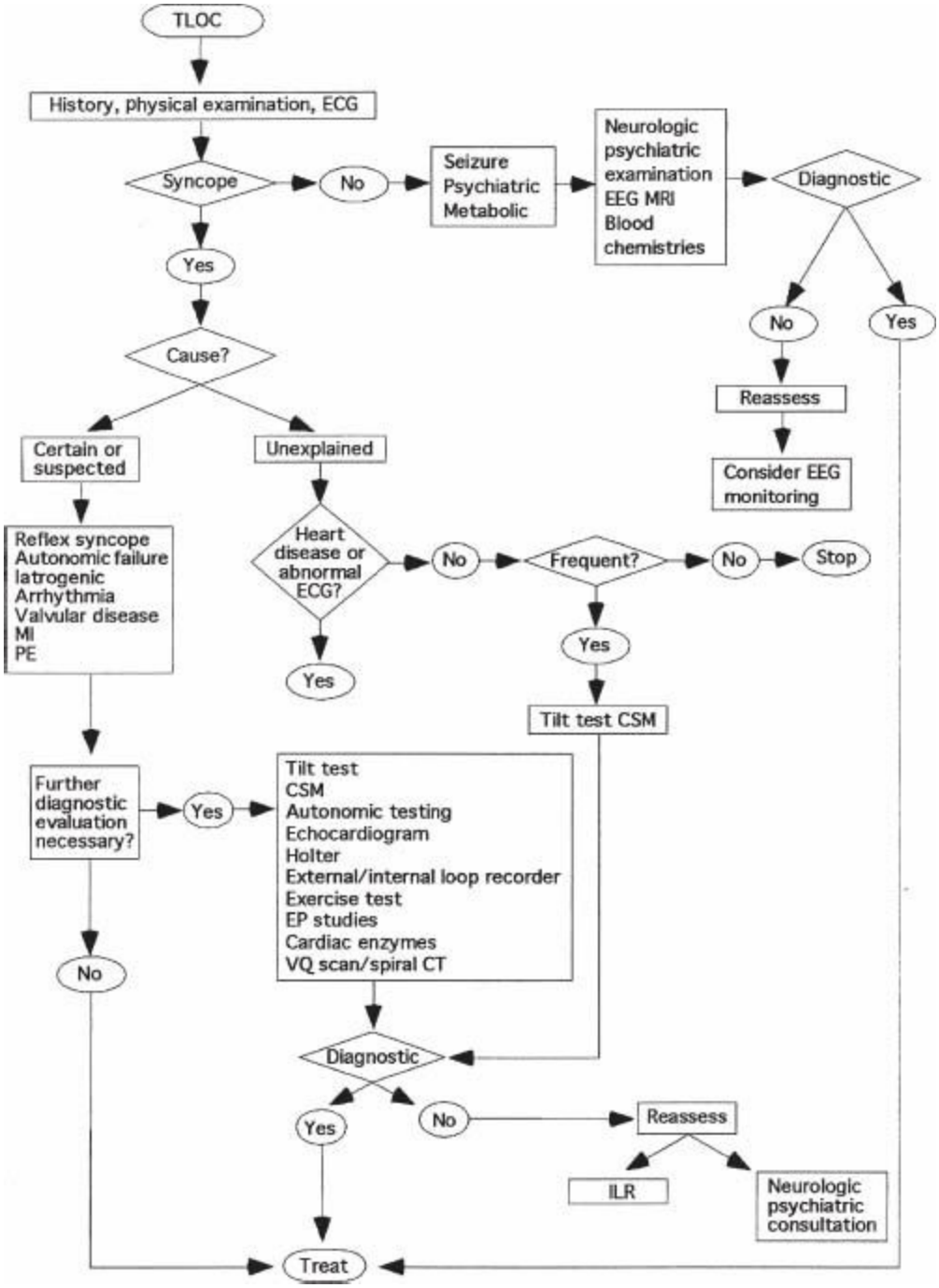


FIGURE 32.1 Example of diagnostic algorithm for patients with LOC. TLOC, transient loss of consciousness; ECG, electrocardiogram; EEG, electroencephalogram; MRI, magnetic resonance imaging; MI, myocardial infarction; PE, pulmonary embolism; CSM, carotid sinus massage; EP studies, electrophysiologic studies; VQ scan, ventilation perfusion scan; CT, computed tomography; ILR, insertable loop recorder. (Reprinted from Kaufmann H, Wieling W. Syncope: a clinically guided diagnostic algorithm. Clin Auton Res. 2004(Suppl 1);14:i87–i90, with permission.)

Syncope, defined as the transient loss of consciousness (LOC) with complete reversibility without subsequent focal neurologic deficit, is a frequent clinical conundrum for cardiologists, internists, and electrophysiologists.[3,4] The approach to the syncopal patient is comprised of several algorithms, the aggressiveness of which depends on the seriousness of the syncopal spells, and the presence or absence of

structural heart disease. Although the most common etiology of all syncope from all causes and in all groups is probably benign vasovagal syncope, a syncopal event in a patient with significant coronary disease, prior myocardial infarction (MI), severe left ventricular (LV) dysfunction, congestive heart failure, or in the context of known complex ventricular arrhythmias may be malignant and a harbinger of subsequent sudden cardiac death.

EPIDEMIOLOGY OF SYNCOPE

In the early 1980s, it was recognized that syncope is a common reason for emergency room visits and admissions.[5] Many of these patients were suspected to have either reflex or neurocardiogenic/vasovagal syncope, but testing was limited. Simultaneously, techniques of electrophysiologic testing were being developed, ambulatory monitoring was in its infancy, and tilt table tests were still a research tool. Then, as today, the workup for patients with unexplained syncope was extremely expensive. Even with recent constraints, DRGs, and so on, the evaluation of patients with syncope still has been estimated to be $1 billion annually. Although syncope for the most part was probably suspected to be due to underlying neurocardiogenic syncope, in the 1980s, there was no good test or "gold standard" to determine which patients were susceptible or truly vasovagal. When the tilt table was introduced and recognized as a valuable electrophysiologic modality, it entered intense and extensive utilization. The late 1980s and early 1990s represent the probable zenith of its use. Between 1992 and 1994, tilt table procedures escalated from approximately 6,000 to 14,000 per year. Recent years have seen a downtrend in the number of tilt table tests being performed, particularly as our clinical acumen has become better at identifying patients who are experiencing vasovagal syncope. Patients with syncope and a normal heart virtually always have underlying vasovagal syncope, even despite a negative tilt table test. Given the constraints of limited reproducibility, specificity, and sensitivity, tilt table tests, although still frequently performed, are reserved for those patients who meet specific criteria of recurrent syncope, for which no ready explanation can be provided. Although tilt table numbers have declined for suspected vasovagal syncope, the last few years have seen a burgeoning of requests to investigate for underlying dysautonomias such as postural orthostatic tachycardia syndrome (POTS).

In general, determination of the underlying etiology for syncope is almost always largely presumptive. Rarely do spontaneous clinical events occur during cardiac or telemetric monitoring. The goal in the evaluation of syncope is therefore not only to determine a likely underlying diagnosis with a relative degree of certainty and alacrity but also to ensure that no life-threatening entities are responsible. Diagnostic studies such as head up tilt table tests and electrophysiologic studies (EPS) are merely tools to examine various components of the autonomic nervous system and the cardiac electrical

system, and the results must be interpreted with cautious skepticism. Although it is reassuring to convince oneself of a relatively benign type of syncope, as in vasovagal, it is axiomatic that the patient should always be assumed to have more malignant underlying causes of syncope until proven otherwise. Merely assuming that a positive tilt table test explains syncope in a patient with an ejection fraction (EF) of 25% from known coronary artery disease is clearly clinically inappropriate and fraught with danger. To further confound the differential diagnosis, many patients have syncope that is multifactorial. For example, an elderly patient with tendency toward sinus node dysfunction and carotid sinus hypersensitivity may also be on medications that result in hypovolemia and an inclination toward orthostatic hypotension (OH). All can lead to syncope.

Syncope results from the many potential causes of cerebral hypoperfusion, and textbooks and review articles frequently display long, comprehensive lists of possible etiologies of syncope (Table 32.1).[6] In general, these lists can be synthesized and concentrated into five potential causes: (a) reflex syncope, of which vasovagal is the index hallmark and most common cause; (b) OH; (c) arrhythmic syncope; (d) mechanical structural disease such as coronary artery obstructive and valvular cardiac disease; and (e) cerebro-vascular causes. Using this framework and a precise definition of syncope differentiates it from other causes of LOC, including transient ischemic attacks (TIAs) and strokes, hypoglycemia and other metabolic causes, seizure disorders, psychogenic syncope, or vertebral basilar insufficiency (drop attacks). Traditionally, etiologies of syncope have also been even more broadly divided into cardiac and noncardiac causes. This simple paradigm has been utilized to predict clinical outcomes and prognosis. Cardiac causes of syncope may lead to increased mortality compared to noncardiac causes, in which the prognosis is normal and survival is assured.[7] However, there is certainly considerable overlap between the cardiac and noncardiac causes. For example, it is now understood that aortic stenosis can cause syncope not only from heart block, or fixed cardiac output, but through reflex mechanisms similar to the Bezold–Jarisch reflex.[8]

TABLE
32.1 Causes of Syncope

Neurally mediated (reflex)
Vasovagal syncope (common faint)
  Classical
  Nonclassical
Carotid sinus syncope
Situational syncope
  Acute hemorrhage
  Cough, sneeze
  Gastrointestinal stimulation (swallow, defecation, visceral pain)
  Micturition (postmicturition)
  Postexercise
  Postprandial
  Other (e.g., brass instrument playing, weightlifting)
Glossopharyngeal neuralgia
Orthostatic hypotension
Autonomic failure
  PAF syndromes (e.g., pure autonomic failure, multiple-system atrophy, PD with autonomic failure)
  Secondary autonomic failure syndromes (e.g., diabetic neuropathy, amyloid neuropathy)
Postexercise
Postprandial
Drug (and alcohol)-induced orthostatic syncope
Volume depletion
  Hemorrhage, diarrhea, Addison disease
Cardiac arrhythmias as primary cause
Sinus node dysfunction (including bradycardia/tachycardia syndrome)
AV conduction system disease
Paroxysmal supraventricular and ventricular tachycardias
Inherited syndromes (e.g., LQTS, Brugada syndrome)
Implanted device (pacemaker, ICD) malfunction
Drug-induced proarrhythmias
Structural cardiac or cardiopulmonary disease
Cardiac valvular disease
Acute MI/ischemia
Obstructive cardiomyopathy
Atrial myxoma
Acute aortic dissection
Pericardial disease/tamponade
Pulmonary embolus/pulmonary hypertension
Cerebrovascular
Vascular steal syndromes

From Brignole M, Lavagna I, Paolo A, et al. Guidelines on management (diagnosis and treatment) of syncope—update 2004. Europace. 2004;6:467–537, by permission of Oxford University Press.

It is often difficult to differentiate an episode of true syncope from other causes of LOC. These include seizure disorders or epilepsy, metabolic abnormalities, cerebral vascular accidents (CVAs) or TIAs, and factitious syncope/pseudoseizures or conversion reactions. The prototypical tonic–clonic movements of epilepsy are well known. Aura, urinary incontinence, and tongue biting are also frequently reported during seizures. Prior head trauma and concussion also may suggest seizures as the cause of LOC. Syncope is frequently accompanied by a few involuntary movements of the head and extremities, which can mimic a seizure disorder. This has been termed “convulsive

syncope" and "anoxic seizures" and results from loss of oxygen to the central nervous system (CNS) and brainstem motor centers, and does not reflect an epileptiform phenomenon. These jerking movements are also frequently observed during ventricular fibrillation induced during electrophysiologic testing or during tilt-induced profound vasovagal episodes. Witnesses to clinical episodes of syncope also frequently report similar movements and ascribe them to seizures. Even trained medical personnel may be quick to assume, incorrectly, that seizures are occurring in these situations.

HISTORY

When a patient presents with syncope of unknown origin, the single most important piece of information is the history. Specific detailed questioning regarding the presence or absence of structural heart disease, valvular heart disease, coronary artery disease, previous MIs, prior syncope,[9] family history, and so on can quickly delineate the high-risk patient from those at low risk. Historical factors related to a syncopal event can also help point in a specific direction. Situational syncope during phlebotomy, during prolonged standing, in a dentist's office, in a restaurant, in church, following alcohol ingestion, and so on is almost universally vasovagal or neurocardiogenic. The presence of prodromal symptoms, such as nausea or diaphoresis, usually also heralds the onset of the vasovagal reflex. Frequently, the patient with vasovagal syncope may have postsyncopal symptoms that can last from hours to a day or so, including weakness, nausea, fatigue, and a tendency to recurrent syncope.

In contrast, a lack of prodrome or presence of previous MI or heart failure certainly points to a more malignant etiology of syncope, usually mandating hospital admission. Complete and immediate recovery after a syncopal event suggests an arrhythmic etiology, such as VT, SVT, or AV block. Injuries are uncommon with vasovagal syncope, as the patient usually tends to crumble to the ground, rather than fall abruptly. In contrast, severe injuries and automobile accidents are suggestive of a more serious arrhythmic etiology such as extreme tachycardia or bradycardia.

Calkins et al.[10] have retrospectively evaluated the value of the history and the differentiation of patients with recurring syncope. Eighty patients with recurrent syncope undergoing a complete evaluation were provided comprehensive questionnaires focusing on the features of their syncopal spells. Patients underwent extensive electrophysiologic testing, tilt table testing, and ambulatory recording when appropriate, with the diagnosis confirmed in these 80 patients. The origin of syncope was broadly broken down into two varieties: relatively benign syncope due to vasovagal or neurocardiogenic etiology versus a more serious type of syncope due to underlying AV block or VT. As expected, symptoms prior to the onset of syncope, such as blurred vision, palpitations, nausea, and generalized warmth or diaphoresis, were more consistent with neurocardiogenic syncope. Similar symptoms after the syncopal event

were also more consistent with neurocardiogenic syncope. In contrast, little or no warning prior to the syncopal event was more consistent with AV block or VT. Patients with AV block or VT tended to be older and of male gender, owing to the predominance of atherosclerotic disease. In addition, patients with more dangerous syncope etiologies generally reported no prior episodes, specifically having less than two episodes of syncope in their lifetime. These features, together with a history, can help determine whether a patient requires admission for further investigation.

CLINICAL FEATURES OF SYNCOPE

Often, witnesses to the syncopal event can provide other clues as to the possible cause, particularly regarding the duration of syncope. Prolonged episodes of unresponsiveness, such as 7 to 10 minutes or more, are unlikely to be due to vasovagal or arrhythmic etiologies and instead suggest neurologic processes. Sudden LOC followed by fairly quick resumption of consciousness suggests tachyarrhythmias, such as VT, SVT, or atrial fibrillation with a post conversion pause. Patients who experience vasovagal syncope frequently have several minutes of prodromal symptoms, followed by LOC. The episode of unconsciousness with vasovagal syncope varies but may last 3 to 4 minutes, particularly if the patient cannot be rendered supine. A patient with vasovagal syncope may arouse slowly, with considerable confusion and postsyncopal vagal symptoms.

PHYSICAL EXAMINATION

The physical examination of patients with syncope is generally directed toward cardiac auscultation for the presence of valvular disease, carotid bruits, assessment of pulses, irregular pulse and heart rhythm. For patients with vasovagal syncope, the physical exam and the cardiovascular exam will generally be entirely normal. However, the presence of murmurs, S_3 or S_4 gallops, and displaced point of maximal intensity (PMI) may point to the presence of LV dysfunction. Similarly, bigeminal rhythms and trigeminy may also suggest the presence of LV dysfunction in a patient with syncope. Findings of congestive heart failure, jugular venous distention, hepatojugular reflux, hepatosplenomegaly, and bibasilar pulmonary rales also point to the presence of LV dysfunction in a patient with syncope. The finding of atrial fibrillation on physical examination or during electrocardiography (ECG) is very important and suggests tachybrady syndrome or sick sinus syndrome. Gross neurologic evaluation showing evidence of lateralization or focal neurologic deficits is also important, suggesting either cardioembolic phenomena from atrial fibrillation or carotid atherosclerotic disease, both of which can cause episodic LOC.

Carotid sinus massage can be performed safely at the bedside, but is contraindicated

in the presence of carotid bruits, known carotid stenosis, TIAs, and CVAs. During ECG monitoring, sequential bilateral gentle carotid massage can be performed for 5 to 10 seconds, with the patient in a supine, slightly elevated head position. Positive responses consist of cardioinhibitory pauses >3 seconds. Patients with true carotid sinus syndrome frequently show an instantaneous and abrupt response with a prolonged cardioinhibitory response to massage with LOC.

Careful observations of postural responses of blood pressure and heart rate are often useful when evaluating patients with syncope. The presence of marked OH in patients with syncope is highly suggestive. OH is defined as a systolic blood pressure decline of >20 to 30 mm Hg or a diastolic blood pressure decline of >10 mm Hg. These can either be elicited immediately on assuming an upright posture from supine baseline or occur more gradually at 1 to 3 minutes. OH is very common, particularly in the elderly, and may be multifactorial, often resulting from medications (diuretics, vasodilators, etc.) and intrinsic dysfunction of autonomic reflexes that can occur with aging, strokes, diabetes, alcohol use, and atherosclerosis of cardiopulmonary, aortic arch, and carotid sinus baroreceptors. Marked abrupt or instantaneous OH is particularly prominent in multisystem atrophy (MSA, previously called Shy–Dragger syndrome) or in pure or primary autonomic failure (PAF, previously called Bradbury–Eggleston syndrome). Patients with MSA may exhibit features of Parkinson disease (PD), but PD itself is an important etiology for OH as well, either from intrinsic autonomic failure or from antiparkinson medications.[11] Patients with PD often experience unexplained falls, which may result from OH, gait disturbances, or "on—off" phenomena.

DIAGNOSTIC TESTING FOR SYNCOPE

Laboratory investigation for syncope of undetermined etiology begins with an ECG to identify arrhythmias or previous MIs. The presence of Q waves indicative of previous MI, long QT interval, left bundle branch block, ventricular pre-excitation, or left anterior hemiblock are all significant and may suggest the need for further invasive investigation. Syncope in a patient with trifascicular block (Fig. 32.2) is a Class IIA indication for implantation of a permanent pacemaker.[12,13] Signal-averaged ECG, although once touted as a major advancement in diagnostic capability for syncope, is now reserved largely for the detection of late potentials, predominantly in patients with transient ventricular ectopy, which may signify underlying arrhythmogenic right ventricular cardiomyopathy (ARVC). Unfortunately, most of these patients have an intrinsic QRS abnormality consistent with a right bundle branch block, which makes the signal-averaged ECG less specific.

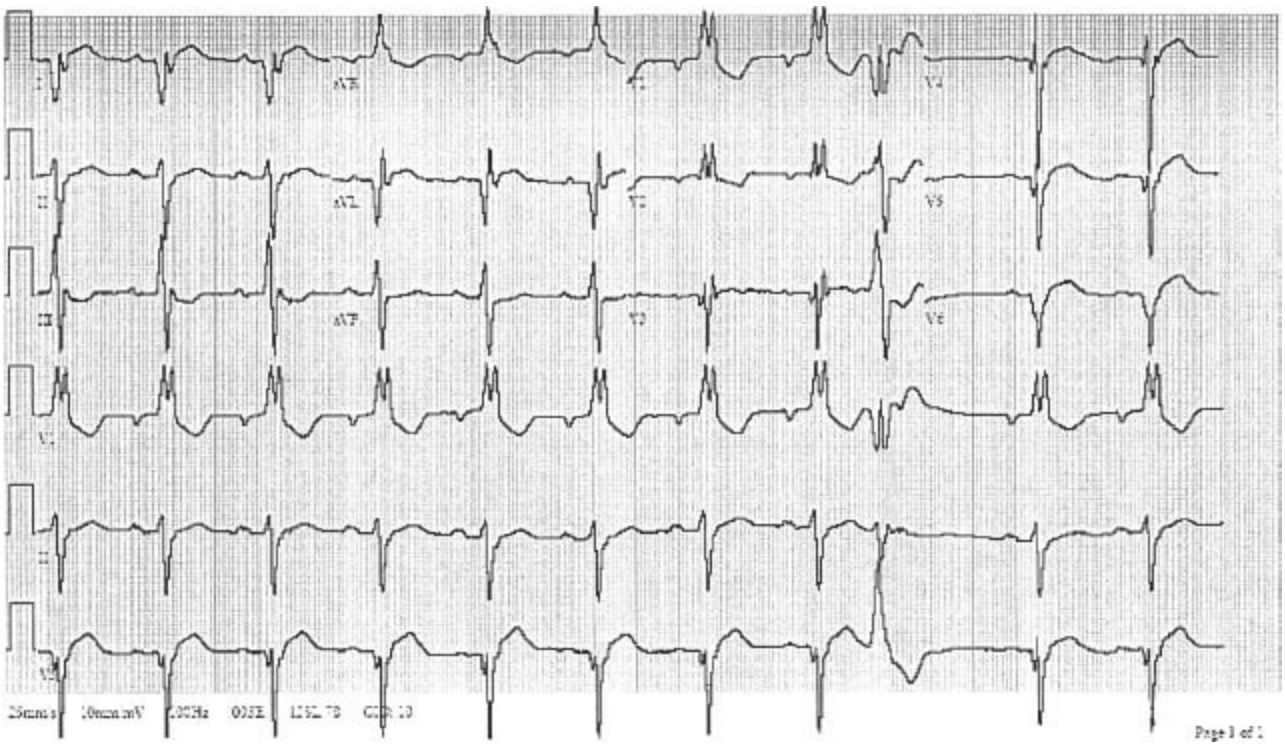


FIGURE 32.2 Complete right bundle branch block, left anterior hemiblock, and first-degree AV block, the so-called trifascicular block. This finding in patients with syncope suggests intermittent high-degree AV block and may indicate a need for a permanent pacemaker.

Stress Testing and Echocardiography

When clinically indicated, particularly with physical findings or an ECG suggesting the presence of structural heart disease, initial testing often includes functional studies to assess for an ischemic etiology. Echocardiography is useful to assess for mechanical or structural lesions, such as hypertrophic cardiomyopathy, aortic stenosis, occult LV systolic dysfunction, or in the case of ARVC or RV dysfunction. Routine incorporation of these modalities is costly and unnecessary in the vast majority of syncope cases, particularly when the clinical history, ECG, and physical examination are normal and suggest a benign cause.

Ambulatory Electrocardiographic Monitoring

Ambulatory electrocardiographic monitoring as a baseline may be helpful, particularly for those patients with recurrent syncopal episodes, and may disclose paroxysmal atrial fibrillation, SVT, or nonsustained VT. Routine Holter monitoring in the absence of structural heart disease is frequently unrewarding. Systems utilizing event-recording technology, such as the King of Hearts (Instromedix) and others may be more helpful to disclose intermittent episodes of bradyor tachyarrhythmias. Newer wireless and bluetooth devices (e.g., Lifewatch—Instromedix, Cardionet) can provide full disclosure with continuous EKG monitoring to a central monitoring station for immediate reporting, and are collectively termed mobile cardiac outpatient telemetry (MCOT). (Fig. 32.3).

These devices, however, are quite costly and are not indicated for high-risk cohorts.

FIGURE 32.3 Cardionet ambulatory arrhythmia monitor.

Ambulatory blood pressure monitor devices are also available and are frequently utilized for patients suspected of having intermittent orthostasis. However, these devices can be quite clumsy and burdensome, and often do not react quickly enough to record substantive data. Future ambulatory and implantable ECG event recorders currently in development may also allow simultaneous blood pressure recording.

Implantable Loop Recorders

The implantable loop recorder (ILR) (Fig. 32.4) (Medtronic— Reveal, St Jude Medical —Confirm) was designed specifically for patients with infrequent syncopal episodes in which Holter monitoring or 30-day event recordings fail to demonstrate the etiology of their syncope. The ideal patient is one who has recurrent syncope, palpitations, or suspected SVT once or twice a year, escaping conventional monitoring.

FIGURE 32.4 Reveal (Medtronic) ILR.

Current indications are for patients with syncope of undetermined etiology with a structurally normal heart. It should not be implanted in high-risk patients with syncope and severe LV dysfunction. It has also been used in patients with fleeting or suspected SVTs for whom electrophysiologic testing is contemplated. An emerging indication is for patients who have drug-refractory seizures in whom an arrhythmic etiology from either tachy- or bradycardia is suspected.

Several studies have utilized the ILR in their diagnostic algorithms to determine the cause of syncope. The Randomized Assessment of Syncope Trial (RAST) evaluated 60 patients randomized through either the conventional diagnostic paradigm of electrophysiologic testing, tilt table test, and extensive recording or accelerated loop recorder implants.[14–16] Follow-up was for 1 year. Patients with loop recorder implants had an earlier time to diagnosis. The International Study of Syncope of Undetermined Etiology (ISSUE) investigators examined the use of the loop recorder implant in several important patient subgroups, including those with: (a) syncope and a normal heart that had a negative tilt table test; (b) syncope and a bundle branch block and a negative EPS; and (c) syncope with cardiomyopathy and a negative EPS. The first cohorts of the ISSUE study consisted of 82 patients with syncope and a negative tilt and 29 patients with syncope and a positive tilt.[17] Both groups received ILRs. During follow-up, there was an approximate 34% syncope recurrence rate in both groups despite treatment. Interrogation of the ILRs showed that the underlying electrocardiographic abnormalities during syncope were consistent with a vasovagal etiology in the vast majority of patients. This suggested that in patients with a normal heart, syncope is still most likely due to underlying vasovagal phenomena, despite a negative tilt test. With this observation, as well as others on tilt test limitations, it has become apparent that the tilt table test may be superfluous in the evaluation of patients with syncope and a normal heart. The ISSUE study further went on to implant loop recorders in patients who had bundle branch block, syncope, and a negative electrophysiologic test, including a challenge with Ajmaline.[18] During follow-up, syncope recurred in >40% of patients, and the most common finding was AV block or asystole, although sinus arrest was also observed. Therefore, this supported the current practice of implanting pacemakers in patients with syncope, normal LV function, and bundle branch block, which is currently a Class IIA indication. Finally, the ISSUE investigators implanted loop recorders in

patients with ischemic and dilated cardiomyopathies and syncope following a negative EPS.[19] These patients usually now receive a defibrillator. A total of 35 patients were implanted with loop recorders following a negative EPS. During a relatively short follow-up of 6 ± 5 months, there was a 17% recurrence of syncope, predominately due to bradyarrhythmias. No VT was observed, although the follow-up was short. Therefore, it still would be prudent to consider implanting a defibrillator in patients with severe LV dysfunction and syncope.

Recently, the ILR was utilized to disclose a new, previously poorly defined entity of prolonged paroxysmal high-degree or complete AV block in patients with recurrent syncope, otherwise normal hearts, normal EKGs without evidence of significant conduction abnormality, and no evidence that these episodes were due to a vagal etiology.[20] These patients were observed to have varying degrees of transient high-degree AV block causing near syncope and were then treated with permanent pacemakers which eliminated their episodes. The actual prevalence of this disorder is unknown, but it certainly highlights the value of early utilization of ILRs in diagnostic paradigms.

No further investigations are probably required in a patient with historical absence of structural heart disease who has a normal ECG and a single episode of syncope that is typically vasovagal. However, if there are risk factors for coronary artery disease, such as a male aged >50 years, additional testing frequently includes assessment of LV function with an echocardiogram as well as an exercise test. In the absence of structural heart disease, for a single episode of syncope without malignant features, no other testing is typically required. However, if any of the above significant indicators of structural heart disease are present, then further investigation such as Holter monitoring and possibly EPS are warranted. The finding of nonsustained VT in the presence of LV dysfunction, and an EF <40%, especially in the setting of syncope, is indicative of the need for electrophysiologic testing and defibrillator implantation.

Electrophysiologic Testing

For patients who present with syncope of undetermined etiology, electrophysiologic testing has been described as the “gold standard” for demonstration of supraventricular and ventricular arrhythmias, AV nodal or His–Purkinje disease, and bradyarrhythmias, all of which can be responsible for syncope. Indications for electrophysiologic testing in patients with syncope are given in Table 32.2.[21] This procedure, introduced clinically in the late 1970s, involves the insertion of several intravascular catheters to record intracardiac atrial electrograms, His potentials, and ventricular electrograms. Atrial and ventricular programmed electrical stimulation may induce sustained monomorphic VT or SVT. Measurement of AV node refractoriness and Wenckebach cycle length may demonstrate significant AV nodal disease that could be responsible for

intermittent Mobitz type I, II, or high-degree AV block, particularly in elderly patients. Similarly, a prolonged His–ventricular (HV) interval suggests that syncope may be due to heart block. His–Purkinje conduction can be challenged by administration of IV procainamide with subsequent marked HV prolongation.[22] In general, electrophysiologic testing is less helpful in the evaluation of the sinus node (Table 32.3). Occasionally, sinus node recovery times (SNRTs) can demonstrate prolonged pauses indicative of sinus node dysfunction. Attempted induction of sustained monomorphic ventricular tachycardia (SMVT) consists of programmed electrical stimulation of the right ventricle at two sites (RV apex and RV outflow tract), usually with sequential repetitive drive trains of 400 to 600 milliseconds followed by one, two, or three ventricular extrastimuli. Other protocols attempt to induce SMVT by using more rapid repetitive bursts (300 to 350 milliseconds) in the ventricle. The finding of SMVT is significant and suggests the need for an implantable cardioverter-defibrillator (ICD).

TABLE
32.2 Clinical Features Suggesting Need for Electrophysiologic Testing of Patients with Syncope

Indication	AHA/ACC Class
1. Patients with symptomatic, severe AS	I
2. Patients with severe AS undergoing open heart or aortic surgery for another reason	I
3. Patients with severe AS and LVEF < 50%	I
4. Patients with moderate AS undergoing open heart or aortic surgery for another reason	IIa
5. Asymptomatic patients with severe AS and high likelihood of rapid progression (age, calcification, CAD)	IIb
Hypotension with exercise	IIb
"Extremely severe" AS with AVA <0.6 cm^2, mean gradient >60 mm Hg, and jet velocity >5 m/s if operative mortality <1%	IIb
6. Patients with mild AS undergoing coronary artery bypass graft (CABG) with risk of rapid progression (i.e. moderate to severe valve calcification)	IIb
7. Asymptomatic patients with severe AS and none of the above	III

TABLE

32.3 Electrophysiology Study—Components

SNRTS
AV node function—effective refractory period, Wenckebach of AV node
His–Purkinje assessment—measurement of HV intervals
  Infra-His block—procainamide challenges
  Intra-His block
Inducibility of SVT
Inducibility of VT
Atrial fibrillation, postconversion pauses
Brugada syndrome—pharmacologic challenge with intravenous procainamide

Almost every tachyarrhythmia is amenable to some form of radiofrequency catheter ablation. AV nodal reentry, AV reentry via accessory pathways, and atrial tachycardias are frequently mapped and ablated in a straightforward fashion. In previous decades, EPS was performed much more frequently for syncope evaluation than it is at present. Current clinical practice reserves EPS for a few select cases, such as patients with LV dysfunction, suspected SVTs, conduction abnormalities, and those who may be candidates for radiofrequency ablation. Rarely is EPS performed for syncope in patients with normal hearts and normal ECGs, given the likelihood of a vasovagal cause in this patient subset. Patients who present with syncope in the presence of LV dysfunction, a previous MI, or an EF < 35% to 40% qualify for empiric ICDs given the MADIT 2 and SCD-Heft data.[23] There are still several clinical situations in which EPS is performed to evaluate syncope patients (see Table 32.2). American College of Cardiology/American Heart Association (ACC/AHA) guidelines are listed in Table 32.4.

TABLE
32.4 Guidelines for EPS for Patients with Syncope

Class I: General agreement

Patients with suspected structural heart disease and syncope that remains unexplained after appropriate evaluation

Class II: Less certain, but accepted

Patients with recurrent unexplained syncope without structural heart disease and with a negative head-up tilt test

Class III: Not indicated

Patients with a known cause of syncope for whom treatment will not be guided by electrophysiologic testing

From Zipes DP, DiMarco JP, Gillette PC, et al. Guidelines for clinical intracardiac electrophysiological and catheter ablation procedures: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Intracardiac Electrophysiologic and Catheter Ablation Procedures), developed in collaboration with the North American Society of Pacing and Electrophysiology. J Am Coll Cardiol. 1995;26: 555–573, with permission from Elsevier.

SPECIFIC ETIOLOGIES OF SYNCOPE

Neurally Mediated Syncope

Vasovagal syncope (also called neurocardiogenic syncope, empty heart syndrome, and ventricular syncope) is the most common of the neurally mediated syncopes. All of these syndromes result from disturbances or perturbations of the autonomic nervous system. A partial list of some of the more commonly observed neurally mediated syncopes is given in Table 32.5. Syncope arising from aortic stenosis or hypertrophic obstructive cardiomyopathy is felt to have a significant neurally mediated component and may precipitate the stimulation of C fibers in the posterior left ventricle in a fashion similar to vasovagal syncope (Bezold–Jarisch reflex).[8] In addition, it is suspected that in patients with syncope due to recurrent atrial fibrillation, SVT, or VT, there may also be a neurally mediated component in which atrial vasodepressor reflexes result in significant vasodepression, causing a drop in blood pressure and contributing to the LOC independent of a low cardiac output.

TABLE
32.5 Neurally Mediated Syncope

Vasovagal/neurocardiogenic syncope
Carotid sinus syncope
Tussive/cough syncope
Glossopharyngeal neuralgia/deglutition syncope (Elias)
Pallid breath-holding spells (Jaeger)
Aortic stenosis
Hypertrophic obstructive cardiomyopathy
Pacemaker syncope
Syncope secondary to pulmonary hypertension
Micturition syncope
"Mess trick"/fainting lark-self—induced hyperventilation and Valsalva syncope
Diving reflex—reflex bradycardia/vasoconstriction, especially in cold water, causing LOC
Syncope with atrial fibrillation, SVT, and VT—may have a neurally mediated component resulting from atrial fibrillation vasodepressor reflexes

Symptoms preceding the vasovagal response are typical and can serve as clues to the nature of the syncopal spell. Vagal symptoms such as diaphoresis, nausea, vomiting, and diarrhea are common both before and after the syncopal spell. The patient may be observed to be very pale, and may complain of either being cold or excessively warm. Frequently, patients report presyncopal loss of vision, which may persist for a variable amount of time. This has been described as "graying out." Tinnitus or loss of hearing is frequently described as occurring prior to the syncopal event. Patients can be observed, both spontaneously and during head-up tilt table tests, to be hyperventilating and may complain of shortness of breath, representing an autonomic trigger reflex. The onset of yawning during a head-up tilt table test can often herald the onset of a vasovagal event. Sinus tachycardia associated with the episode may be perceived as palpitations and be confused with SVT, or may mimic a chest discomfort complaint.

During unconsciousness, patients may be observed to experience generalized myoclonic jerking, the so-called anoxic seizure or convulsive syncope. This may mimic the features of epilepsy to both medical and nonmedical bystanders, and may complicate the differential diagnosis. When patients awaken, there may be a slight confusion, which can also mimic a postictal state. If patients try to ambulate too quickly, they may experience another episode of syncope.

The most common precipitant of vasovagal syncope is from so-called noxious stimuli, such as flight or fight, pain, venipuncture, fear, or anxiety. Other situations in which marked venous pooling or sequestration of blood volume in lower extremities or splanchnics takes place may also precipitate the vasovagal response. These include prolonged rigid standing, as in soldiers at attention; pregnancy, in which the gravid uterus prevents venous return from the inferior vena cava (IVC) compression; or from inadequate venous return, such as in hypovolemia, diuretic treatment, anemia, or acute

hemorrhage. Prolonged bed rest, as in patients recovering from illness, can also lead to a propensity for vasovagal syncope. It has been known for several decades that astronauts returning from even brief exposure to microgravity are also predisposed to a vasovagal-type syndrome. The "first-dose phenomenon," such as occurs with certain vasodilators and nitrates, has also been shown to precipitate a vasovagal-type response, as does beta-blocker withdrawal.[3]

The clinical scenario of typical vasovagal syncope begins with abrupt vasodepression, followed by a marked cardioinhibitory response. Similar to cardioinhibitory responses observed during carotid sinus hypersensitivity testing, cardioinhibitory responses can also occur during head-up tilt table testing. These include sinus pauses of 3.5 seconds or more, as well as junctional rhythm, marked sinus bradycardia, or also commonly AV block of the first-, second-, or even third-degree variety. Less commonly, vasodepressor syncope occurs in which an isolated drop in blood pressure accompanies the syndrome. Even during pure vasodepressor syncope and hypotension, the heart rate can be observed to be inappropriate for the degree of hypotension. Cardioinhibitory responses that accompany vasovagal syncope have also been called "extrinsic sick sinus syndrome" and are myriad. We have frequently observed prolonged episodes of asystole, incidentally recorded by monitoring. Asystolic events occurring during vasovagal syncope can also be observed during phlebotomy-provoked fainting. Reflex asystolic pauses are occasionally mistaken for intrinsic SA or AV node disease and may promulgate erroneous consideration and referral for a permanent pacemaker. However, reflex-mediated asystolic pauses are benign, with a favorable prognosis, and pacemaker implantation is not usually necessary.[24] Other types of brady-arrhythmia can be observed both clinically during vasovagal syncope and during tilt table testing, including junctional bradycardia, marked sinus bradycardia, and first-, second-, or third-degree AV block. A unique form of atrial fibrillation can be initiated by or cause a vasovagal response. This form of atrial fibrillation is felt to be vagal in origin, resulting from marked parasympathetically mediated heterogeneity of atrial refractoriness, leading to precipitation of atrial fibrillation. The heightened or augmented parasympathetic autonomic status can then trigger concomitant vasovagal fainting.[3]

The natural history of recurrent vasovagal syncope is heterogenous, but some clinical observations merit specific mention. Vasovagal episodes tend to cluster. It is not uncommon for patients to have relative quiescence of their episodes of syncope, only to have episodes reemerge with increasing frequency, particularly around times of major life stressors. Patients with previously recurrent vasovagal syncope may have no further episodes following an initial positive tilt table test. In this respect, demonstration of the underlying etiology provides reassurance to the patient of the relatively benign nature of the syncope and may have a therapeutic affect. The occurrence of frequent spontaneous resolution of vasovagal syncope, even in untreated

patients, can make the evaluation of the efficacy of subsequent pharmacologic interventions spurious. Similarly, up to 75% of patients may have a negative tilt table test on subsequent tests performed months or years later, which makes obtaining reproducibility difficult. Natale et al.[25] observed 54 patients with neurocardiogenic syncope who declined treatment. During follow-up, nearly 70% of the patients had no further episodes.

The pathophysiology of vasovagal syncope historically has been attributed to the activation of C fibers in the posterior and inferior wall of the left ventricle during a vigorous contraction of a relatively empty ventricle (Bezold–Jarisch reflex).[8] This initiates a reflex-mediated sympathetic withdrawal, leaving the heightened parasympathetic activation relatively unopposed. Withdrawal of sympathetic activation causes peripheral arterial and arteriolar vasodilation and hypotension, and the parasympathetic predominance causes bradycardia (Fig. 32.5).[26] This concept has been challenged by the observation of a vasovagal-type response in cardiac transplant patients, who presumably would not have intact afferent and efferent innervations capable of propagating the vasovagal reflex.[27] Alternative theories for vasovagal pathogenesis have been proposed, including various neurohumoral and neuroendocrine peptides, epinephrine, and the ubiquitous nitric oxide.[28] There also appears to be a genetic predisposition to vasovagal susceptibility. Patients with fainting episodes frequently report that their parents or siblings also were fainters. As yet, no specific gene markers have been identified. A recent intriguing but highly conjectural proposal to explain genetic origins of the vasovagal response was that during the times of humans as hunter–gatherer–warriors, the tendency to faint, especially during battles, may have afforded a survival benefit by feigning death and avoiding mortal wounds. This has been called the “Paleolithic threat hypothesis.”[29]

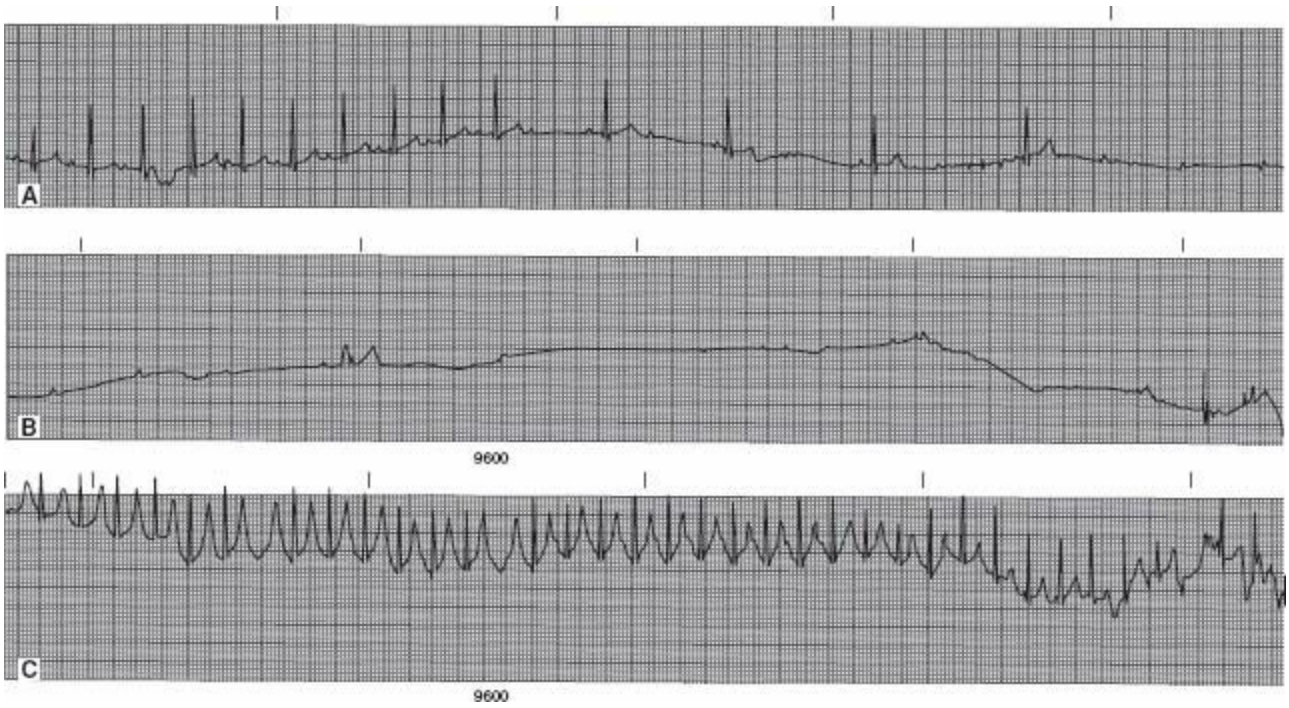


FIGURE 32.5 Example of prolonged asystole and cardioinhibitory response during a vasovagal syncope provoked by tilt table testing.

Vasovagal syncope can be divided into two categories: a relatively benign form in which patients have a recognized precipitating stimulus and a more malignant variety in which there is no recognized stimulus, but the patient may have prolonged asystole and severe injuries, with loss of driving privileges and employment.[30] This latter variety is frequently found to have some underlying autonomic abnormalities or blood volume distribution abnormalities, such as hypovolemia or marked venous pooling. In many cases, no abnormalities can be found. Future advances in the understanding and treatment of vasovagal syncope will require a better delineation of the pathophysiology.

Head-Up Tilt Testing for Vasovagal Syncope

The head-up tilt table test was initially devised in the mid-1980s as a research tool for the evaluation of postural reflexes. Subsequently, it was recognized as an important clinical tool to induce and provoke vasovagal syncope in susceptible individuals, thereby establishing a diagnosis. In the 1980s and early 1990s, extensive and divergent tilt table protocols were proposed for vasovagal syncope provocation, including protocols with 90-degree tilt for up to 90 minutes and those using tilt tables with saddle support. Some of these protocols were extremely effective at inducing the vasovagal response but possessed spurious specificity. Recently, several consensus panels have convened to standardize the nomenclature and head-up tilt protocol, which currently consists of at least 30 minutes of 70-degree tilt. Higher degrees of tilt (80 to 90 degrees) or more prolonged tilting durations may decrease specificity. Following an initial drug-

free tilt test, intravenous administration of the β-agonist isoproterenol can increase the yield but may sacrifice specificity.[31,32] An ACC expert panel document regarding tilt table testing for assessing syncope has established indications,[31] including recurrent syncope that is thought to be vasovagal but has not been clearly demonstrated to be so. In general, the tilt table test is not utilized in patients with structural heart disease until other causes of syncope have been excluded. Tilt table testing may also be appropriate for patients with a single syncope spell, if they are felt to be high risk—that is, the syncope resulted in, for example, injury or an automobile accident, or for a patient with a high-risk occupation. Furthermore, tilt table testing may be helpful for patients who are demonstrated to have intermittent episodes of AV block, sinus bradycardia asystole, and in whom the intrinsic form of sick sinus syndrome could be present. Tilt table testing is probably not indicated for a patient with structural heart disease, a patient with a single episode of syncope with typical classic clinical features, or in whom other causes of syncope have been demonstrated. There are several specific indications for tilt table testing, including the differentiation of convulsive syncope or anoxic seizures from true epilepsy; in evaluating a patient with unexplained falls, faints, or injuries; to assess the impact of autonomic dysfunction or neuropathies; or to determine the presence of OH. Although it has been speculated that tilt table testing may be helpful in assessing efficacy of therapy, it is not highly predictive.

In addition to these indications, our center frequently utilizes tilt table testing to assess for the presence of overt or covert OH and to gauge response to therapy. Frequently, the orthostatic response is relatively latent and can only be observed after a prolonged period of upright posture. These nonvasovagal drops in blood pressure are often caused by medication, venous pooling, or autonomic insufficiency.

Proposed tilt table testing protocols include adjunctive pharmacologic challenges with edrophonium, adenosine,[33] clomipramine, or sublingual nitroglycerin (The Italian Protocol)[6,34] to accelerate onset of vasovagal syncope.

Vasovagal Syncope—Pharmacologic Therapy

The initial treatment for vasovagal syncope consists of reassurance, recognition, and avoidance of precipitating factors, expansion of salt and fluid intake, and avoidance of sympathomimetics (cold remedies, caffeine, and tobacco), dehydration, and alcohol. Patients can be instructed to recognize the premonitory symptoms of vasovagal faint plus a few techniques to avoid syncope, such as immediately assuming a supine position with elevated and moving legs to increase venous return. During their prodromal phase, fainters are frequently incorrectly admonished by onlookers to “put their head between their legs” or “go outside to get some fresh air.” Such actions universally result in syncope and are to be discouraged. Although it has not been rigorously tested, repetitive coughing has been observed to abort the faint, and recently a variety of leg crossing and

arm movements have also been proposed.[35] When episodes are recurrent and recalcitrant to these simple maneuvers, pharmacologic treatment is often required. Initial empiric therapy usually consists of beta-blockers, serotonin reuptake inhibitors, α…agonists (Midodrine, ProAmatine),[36] anticholinergics, or volume expanders such as Florinef (Table 32.6).[37,38] Despite extensive observational reports on the efficacy of many medications for the prevention of vasovagal syncope, there are few randomized studies challenging their use.[34] Emerging treatment modalities include tilt table training, in which the patient is taught a technique to perform several times daily that simulates the effects of tilt table testing. This approach has shown significant promise in initial reports and is thought to work by allowing postural reflexes to accommodate to the recurrent postural changes, thereby decreasing venous pooling and attenuating and down regulating certain cardiopulmonary baroreceptors, thus increasing the individual's resistance to vasovagal syncope.[39] As mentioned, this simple exercise may be more effective than medications for vasovagal prophylaxis, but its use is limited by the substantial time commitment and required compliance.

TABLE
32.6 Vasovagal Syncope: Pharmacologic Therapy

Hydrofludrocortisone—mineralocorticoid
Beta Blockers
Serotonin and serotonin norepinephrine reuptake inhibitors
Anticholinergics—levsin, transdermal scopolamine
Theophylline—adenosine receptor blockade
α-Agonists—phenylephrine, pseudoephedrine, midodrine
Calcium channel blockers
Epogen, DDAVP—(Grubb)

Beta-Blockers for Vasovagal Syncope

Beta-blockers have long been the mainstay of initial pharmacologic therapy for patients with recurrent vasovagal syncope. Only recently has beta-blockade been subjected to the rigors of clinical trials. In fact, several trials have not shown any significant improvement in the nature of syncope or frequency of syncope in patients treated with beta-blockers compared to placebo.[35] Nevertheless, beta-blockers are frequently prescribed, particularly when the patient has sinus tachycardia or POTS preceding the vasovagal response as observed on a tilt table test. The mechanism of action is linked to the drugs' negative inotropic and chronotropic properties, which decrease LV contraction, avoid mechanoreceptor C-fiber activation, and inhibit the precipitation of

Bezold–Jarisch reflex. They may also help to partially offset reflex-mediated vasodepression by leaving ambient α-receptor–mediated vasoconstriction unopposed. It has also been suggested that beta-blockers may have a CNS effect, working by central serotonin-blocking activity. There has been increased concern about the utilization of beta-blockers in that they may transform relatively benign vasovagal episodes into more malignant occurrences by suppressing intrinsic escape cardiac pacemaker activity and inhibiting automaticity.

Treatment of Vasovagal Syncope

Based on the results of a few additional diagnostic tests performed at our facility, we are also able to further guide pharmacologic therapy. We frequently perform blood volume determination using a radioiodine technique, thereby assessing the autonomic reflexes and the degree of venous pooling. If patients are found to have significant hypovolemia from the blood volume determination, then therapy starts with a high-salt diet and Florinef. If the hemodynamic reflexes reveal a hyperkinetic circulation, as seen in POTS, then beta-blockade is the preferred initial therapy. If there is failure of vasoconstriction during upright posture, then vasoconstricting α-agonist medications (midodrine) are initial therapy. Marked venous pooling is frequently found, especially in sedentary patients, and support stocking therapy as well as physical exercise and reconditioning of leg muscles are prescribed. Finally, young patients are frequently "hypervagal," and power spectrum analysis can show a predominance of the vagal component, suggesting some benefit with anticholinergic therapy. Often, severe cases have been found to have multiple abnormalities and to require multiple drug therapy.

Pacemakers for Vasovagal Syncope

For patients with recurrent episodes of syncope that are refractory to pharmacologic therapy, for those who have high-risk occupations, or for those who experience prolonged asystole on head-up tilt table tests, the implantation of a permanent pacemaker with rate-drop algorithms has been a long-time but controversial option.[40] Evidence for the efficacy of pacing for vasovagal syncope came from large retrospective studies in small, nonrandomized cohorts. In the early to mid-1990s, several studies were proposed to examine this potential therapeutic modality. It was recognized that although cardioinhibitory components of the vasovagal response were frequently observed, they occurred later in the response, only after very profound hypotension had occurred. Therefore, pacing only when the heart rate was low was superfluous and probably already too late to abort or prevent the faint. Several proposed pacemaker designs were evaluated in the hopes that earlier detection would help ameliorate the fainting process. One was designed to tachypace at high rates (>90

to 100 beats/min) when it detected a rapidly falling heart rate. It was hoped that rapid pacing would bolster or preserve cardiac output and maintain consciousness. The multicenter VPS trial randomized patients with vasovagal syncope to a permanent pacemaker with rate-drop technology or to conventional (i.e., pharmacologic) therapy.[41] The results demonstrated a dramatic reduction in syncopal recurrences in the pacemaker group. For a brief time after the publication of this trial, pacemakers became a more prevalent component of vasovagal syncope therapy. However, the VPS2 trial, in which patients were randomized to backup pacing only versus pacemakers with rate drop actively programmed, failed to show any benefit from the rate-drop capability and again relegated pacemaker implantation for vasovagal syncope to a relatively last resort in highly selected patients.[3,41,42]

An alternative to pacemakers with rate-drop algorithms for patients with neurocardiogenic syncope is available in pacemakers from Biotronik. This pacing modality termed "closed loop stimulation" (CLS) uses local intracardiac impedance measurements which mirror the dP/dt, and in theory can detect augmented inotrope and cardiac contractility which could herald an impending vasovagal event, then allowing for a period of rapid pacing. The INVASY trial (inotrope controlled pacing in vasovagal syncope) implanted pacemakers with CLS in 50 patients with recurrent neurocardiogenic and vasovagal syncope.[43] Patients who received pacemaker CLS showed a tremendous reduction in their syncopal events. Certainly this presents promising alternatives for some patients with recalcitrant vasovagal syncope but clearly further studies need to be performed.

Therefore, given the high rate of spontaneous resolution in the long term, patients can be reassured as to the general eventual favorable prognosis with vasovagal syncope. Pharmacologic therapy is therefore provided as a temporary or short-term solution. Despite the considerable efforts of aggressive pharmacologic therapy and pacemakers, up to 20% to 30% of patients continue to experience recurrent syncope due to vasovagal phenomena.

Postural Orthostatic Tachycardia Syndrome

POTS is an emerging but poorly understood syndrome. Patients present with the perception of exaggerated heart rate responses to tilt and exercise, with palpitations, light-headedness, and syncope.[44] This syndrome is different from the inappropriate sinus tachycardia syndrome,[14] which may result from intrinsic sinus node hypersensitivity or ectopic atrial tachyarrhythmias. In addition to heart rate responses, patients may have multisystem complaints, including chronic fatigue-type syndrome,[45] fibromyalgia, cognitive dysfunctions (Brain Fog), sleep disorders, gastrointestinal and genitourinary abnormalities suggesting a form, albeit mild, of autonomic dysfunction, the so-called partial dysautonomia. This syndrome may overlap such historical syndromes

as mitral valve prolapse syndrome, the hyper-β-adrenergic circulatory state, hyperkinetic heart syndrome, soldier's heart, DeCosta syndrome, and neurocirculatory asthenia. They do have a vasovagal susceptibility, particularly on tilt table testing, although syncope frequently occurs during extreme sinus tachycardia without demonstrable cardioinhibitory responses. Therefore these patients appear to experience a more unusual form of vasodepressor syncope, particularly on a tilt table test. Several distinct varieties of POTS due to various underlying etiologies exist, and there are probably heterogeneous cases due to multiple causes, such as mild autonomic dysfunction, hypovolemia, excessive venous pooling, catecholamine hypersensitivity, norepinephrine transporter deficiency, and many other causes.[11] Treatment can be very difficult and challenging, relying on volume expanders and beta-blockers or calcium channel blockers, selective serotonin reuptake inhibitors (SSRIs), and a host of relatively investigational and off-label medications.[11]

Whatever the mechanism is for patients with POTS or orthostatic intolerance, concomitant exercise intolerance and subsequent deconditioning certainly leads to exacerbation of symptoms. Recently it was reported that aggressive reconditioning and physical therapy for patients with postural orthostatic tachycardia can lead to significant symptom amelioration and improvement. Exercises that avoid the aggravation from gravity were utilized in an aggressive protocol consisting of a rowing machine, aquatherapy, water walking, etc. in patients with orthostatic tachycardia. In a relatively short-time such as several months, many patients showed dramatic improvement, where previously aggressive pharmacologic and nonpharmacologic approaches had not been helpful. An additional interesting finding in this study was that POTS patients had significantly decreased LV mass, which may explain their borderline hemodynamics, and a tendency for sinus tachycardia. This observation of a smaller heart was termed "The Grinch syndrome" by these investigators.[46] Based on this groundbreaking observation, all patients experiencing dysautonomia should pursue aggressive attempts at physical therapy, cardiac rehabilitation, and reconditioning. Certainly, all patients with POTS should augment fluids and salt with at least 5 to 7 g sodium daily, 1 or 2 L of electrolyte-type sports drinks, compression stockings, and elevation of the head of the bed 4 to 6 inches which can help expand blood volume, and improve orthostasis.

Carotid Sinus Syndrome

Although it is not as common as recurrent vasovagal syncope, carotid sinus syndrome accounts for a significant proportion of syncopal events, particularly in elderly patients. Carotid sinus syndrome results when an overactive or hypersensitive carotid reflex precipitates sudden bradycardia, pauses, or asystole, frequently with a vasodepressor reflex. Episodes may be precipitated by maneuvers that activate the carotid sinus reflex. Often gentle or mild pressure can elicit this exquisitely sensitive reflex. Activities such

as tying a necktie, a tight collar, head turning, and forced exhalation as in playing an instrument may precipitate the reflex. Carotid sinus hypersensitivity is common, considering the definition of a 3-second or longer pause with carotid sinus massage. This reflex is particularly common in patients with coronary artery disease and may reflect the extent of coronary atherosclerosis. Carotid sinus syndrome is defined by clinically recurring episodes of syncope confirmed secondary to carotid sinus hypersensitivity. It has been suggested that alterations in the carotid baroreceptors are responsible for the syndrome and reflex. Recent work has focused on alterations in the mechanoreceptors and proprioceptive receptors in the surrounding denervated sternocleidomastoid muscles.[47] Treatment for the majority of cases of carotid sinus syndrome, particularly when accompanied by the typical cardioinhibitory responses, is comprised of a DDD permanent pacemaker. The accompanying vasodepressor reflex frequently requires the addition of a high-salt diet and volume expander plus the elimination of potential offending medications such as diuretics.

Neurally Mediated Syncope Syndromes

Less common examples of neurally mediated syncope involve various situations with diverse autonomic nervous system inputs. Tussive or cough syncope can be seen in chronic obstructive pulmonary disease (COPD) patients and may occur during violent paroxysms of coughing. This may result from decreased cardiac output from markedly increased intrathoracic pressure or a Valsalva-type precipitation of bradycardia or heart block. There may also be marked turbulence of cerebral vascular blood flow and intracranial pressure during these severe cough episodes. Deglutition syncope, glossopharyngeal neuralgia,[48] micturition, and defecation syncope are also reflex syncope episodes that presumably initiate a bradycardic and vasodepressor response. Pacemaker syndrome, which was more frequently observed during the previous decades of VVI pacing, results from atrial vasodepressor reflexes precipitated during retrograde conduction from ventricular pacing with subsequent atrial activation on a closed AV valve, causing canon A waves. These vigorous atrial systoles cause transient hypotension, which may result in syncope. As mentioned previously, aortic stenosis and hypertrophic cardiomyopathy may cause syncope through a fixed cardiac output but may also precipitate the Bezold–Jarisch reflex in a manner similar to a vasovagal cause. Pallid breath-holding spells are unique episodes of syncope, which occur in very young children following a minor injury or startle, after which they hold their breath, becoming pale and faint.[49,50] This is probably an infant or pediatric form of vasovagal syncope.

Orthostatic Hypotension in the Elderly

The elderly can be particularly susceptible to marked fluctuations in systemic blood pressure. They are frequently sedentary, leading to attenuation of their postural reflexes.

They may demonstrate supine systolic hypertension and hypotension when upright. Patients may frequently experience marked drops in blood pressure, particularly postprandially, with blood volume sequestration in the splanchnics and abdomen.

Arrhythmias as a Cause of Syncope

Virtually any tachy-or bradyarrhythmia can cause symptomatic light-headedness, hypotension, and syncope. This is particularly true in the setting of significant LV dysfunction. Sustained monomorphic or polymorphic ventricular tachycardia in the presence of severe LV dysfunction is an ominous cause of syncope and can quickly progress to lethal ventricular fibrillation. VT in a normal heart is an unusual cause of syncope, although it is now understood that syncope can result from normal heart VT as well as SVT via the recruitment of vasodepressor-type reflexes akin to vasovagal responses. Sick sinus syndrome, paroxysmal atrial fibrillation with significant postconversion pauses, as well as Mobitz type II and complete heart block are also important causes of syncope. Electrophysiologic testing (see section on electrophysiologic testing) and ambulatory monitors are important tools to obtain symptom–syncope correlation. Based on the results of the Madit II, SCD Heft, and Definite trials, patients with depressed LV function from any cause, that is, EF < 35%, should receive ICDs for primary prevention. A patient presenting with syncope who meets these criteria should be presumed to have had VT as the cause and should receive an ICD in an expedited fashion.

Long QT Syndrome

The long QT syndrome (LQTS) is a genetically transmitted disorder of cardiac ion channels, which results in intermittent or persistent prolongation of the QT interval, predisposing to a specific type of ventricular tachyarrhythmia called torsades de pointes (Fig. 32.6).[51] Many distinct subtypes have been described and can be associated with congenital deafness (Jervell–Lange–Nielsen) or with normal hearing (Romano–Ward). Ventricular tachyarrhythmias may be precipitated by bradycardia or catecholamine surges. These ventricular arrhythmias may provoke a syncopal event, and can be associated with sudden cardiac death. Family members of confirmed cases should be carefully evaluated for this disorder. Treatment may consist of beta-blockade, pacemakers, or ICDs. Careful examination of the ECG is paramount in all patients, particularly in young patients with a family history of syncope. Normal QT intervals have been described for males and females. Many drugs have been described that prolong the QT interval and may unmask covert patients.[6]

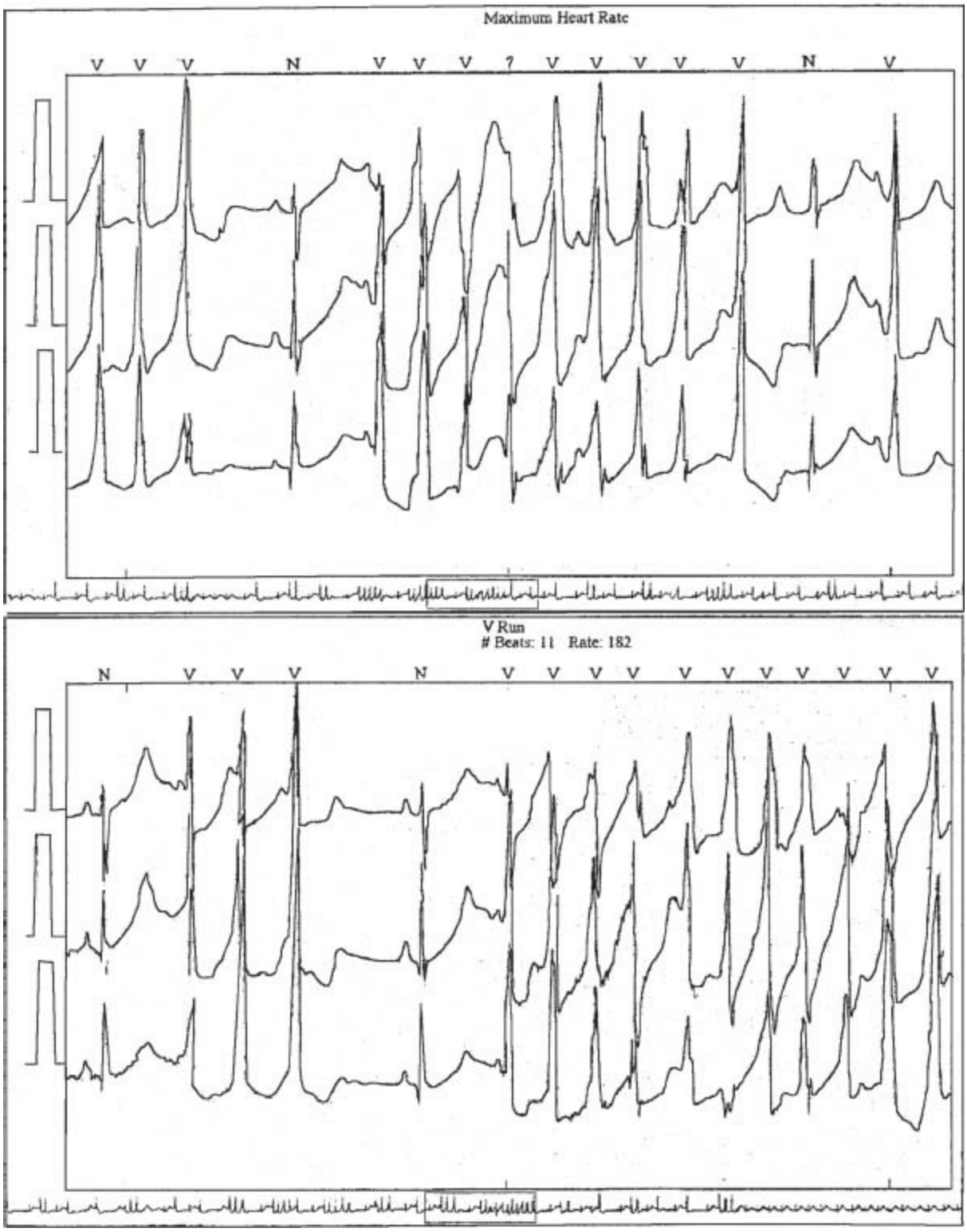


FIGURE 32.6 LQTS and polymorphic VT in a young patient presenting with syncope.

Syncope and Dilated Cardiomyopathy

Much attention has been focused on the specific clinical scenario of syncope in a patient with a dilated, nonischemic cardiomyopathy. Syncope in patients with dilated cardiomyopathy (DCM) has long been understood to be a poor prognostic sign and

portends high mortality, perhaps 50% at 1 year. Electrophysiology testing has poor sensitivity in this group for the provocation of SMVT. Several studies have proposed empiric defibrillators for these patients, and it is now a Class II indication. The recent adoption of SCD-Heft and Definite study guidelines for the implantation of ICDs in DCM patients with an EF < 35% has rendered previous arguments for empiric ICDs moot.

Brugada Syndrome and Arrhythmogenic Right Ventricular Cardiomyopathy

Brugada syndrome is a recently described arrhythmic disorder in which patients are susceptible to ventricular fibrillation and sudden death.[52] Patients may present as survivors of sudden cardiac death but may also have symptoms related to transient VT such as palpitations and syncope. Their hearts are structurally normal. The ECG characteristically demonstrates ST-segment elevation and right bundle branch block in the precordial leads (Fig. 32.7). This disorder is most likely due to a genetic abnormality of cardiac ion channels (channelopathy). Brugada syndrome is endemic in Asia, where it is a recognized cause of sudden death and has been observed to occur in families. Sudden death occurs frequently at night, during sleep. Patients with suspicious but nondiagnostic ECGs can be further evaluated in the electrophysiologic laboratory with sodium channel blockade medications such as intravenous procainamide or ajmaline, which may precipitate the characteristic ECG pattern. Flecainide, usually prescribed for atrial arrhythmia, has also been observed to provoke this ECG pattern in otherwise unsuspected patients. Patients diagnosed with Brugada syndrome should receive a defibrillator if they are symptomatic or if there is a family history of sudden cardiac death.

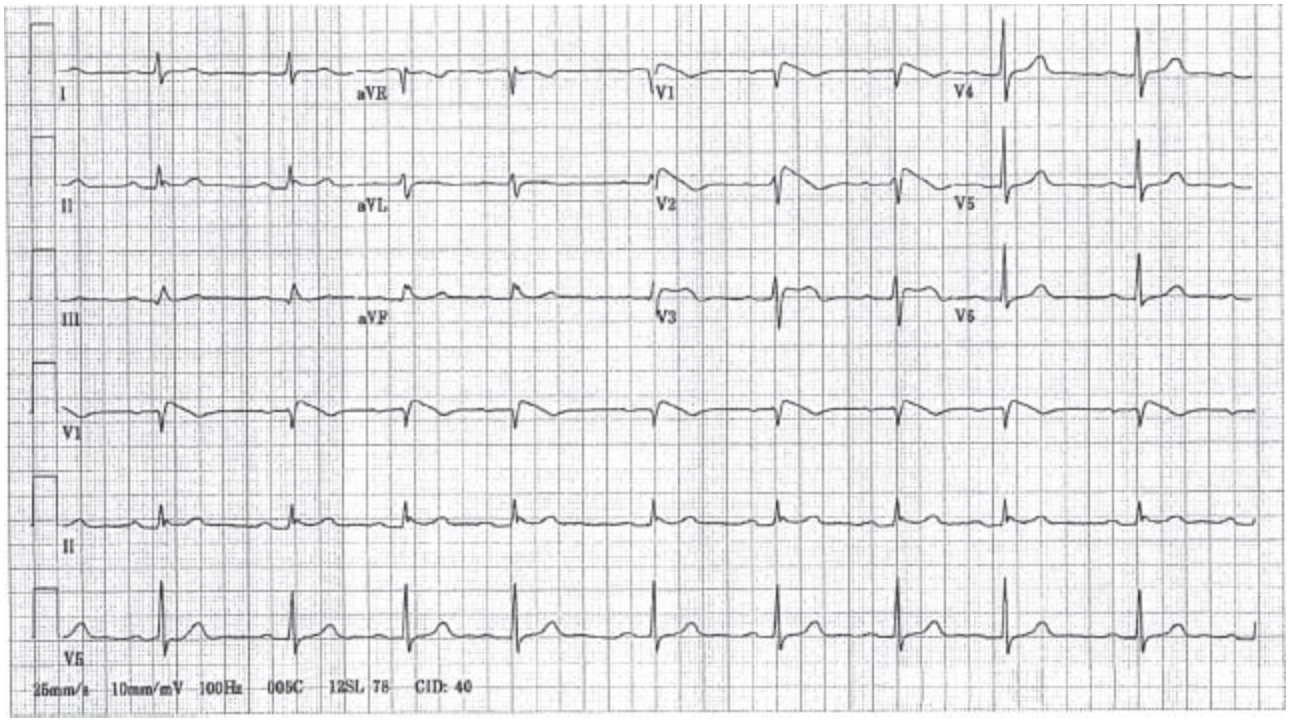


FIGURE 32.7 ECG findings of right bundle branch block and precordial ST-segment elevation suggestive of Brugada syndrome.

ARVC results from a genetic abnormality of right ventricular myocardium, replaced and infiltrated with fat and fibrous tissue.[53] Patients may experience frequent PVCs and VT, resulting in syncope. Characteristic findings on a CT or MRI are fatty infiltration of the right ventricular myocardium. ECG may show complete or incomplete right bundle branch block, a juvenile T-wave pattern, or an epsilon wave. Major and minor criteria have been proposed to establish the diagnosis.[(53)] Patients with symptomatic ARVC should receive a defibrillator and frequently require antiarrhythmic medications (sotalol, amiodarone) to decrease the frequency of ICD shocks.

DRIVING AND SYNCOPE

Syncope while driving can have life-threatening consequences for operators, passengers, and other motorists. Patients with syncope are frequently instructed to refrain from driving until a definitive diagnosis is established and successful treatment assured. An expert consensus panel has summarized their suggestions based on specific syncope etiologies and the expected recurrence rates after appropriate therapy is implemented.[54] In patients with vasovagal syncope, it is recommended that no driving be done for 3 months following what appears to be successful therapy. Patients with syncope due to VT who receive an ICD should refrain from private driving for an appropriate probationary period; approximately 6 or 7 months, as LOC can occur very quickly during VT before the ICD can detect, charge, shock, and terminate. Commercial driving is probably best avoided by patients with ICDs.

CONCLUSIONS

The evaluation of the patient with syncope requires a thoughtful and logical approach to avoid the pitfalls of unnecessary testing. Syncope in the presence of significant structural heart disease suggests a need for expedited hospitalized evaluation. If significant LV dysfunction is found, this frequently proceeds to a defibrillator. Neurocardiogenic or vasovagal syncope, although extremely common, remains a therapeutic challenge. Improved treatment modalities and pharmacologic interventions will require a better understanding of the epidemiology and pathophysiology. The role of tilt table testing in the evaluation of patients with syncope is evolving, and it is hoped that a uniformity of tilt table methodology and testing indications will soon be promulgated and adopted. The role of permanent pacemakers for vasovagal syncope remains uncertain. Improved monitoring technologies for syncope will enhance diagnostic capabilities. Implantable devices that monitor heart rate and blood pressure will greatly enhance the ability to diagnose patients accurately.

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QUESTIONS AND ANSWERS

Questions

1. An 83-year-old man comes to see you in your office complaining of three episodes of abrupt loss of consciousness (LOC) in the last year. His PMH is negative. His internist recently performed a stress

echo test and Holter monitoring that were normal. His electrocardiography (ECG) reveals “trifascicular block.” What is the next step?
   a. Perform electrophysiologic studies (EPS), and if negative, implant a Reveal device.
   b. Perform EPS, and if negative, implant an implantable cardioverter-defibrillator (ICD).
   c. Consider EPS for ventricular tachycardia (VT), and if negative, recommend a pacemaker.
   d. Schedule a tilt test.

2. A 57-year-old man with dilated cardiomyopathy (DCM) presents to the emergency department with a facial laceration. He reports that he was urinating during the night and suddenly lost consciousness, falling and sustaining the injury. He felt fine before and after the event. He has an ejection fraction (EF) of 25% secondary to probable viral myocarditis. His ECG reveals IVCD and occasional multifocal PVCs. What is the next step?
   a. Discharge from the emergency department with a 48-hour Holter monitor.
   b. Admit, perform EPS, and if negative, implant a Reveal device.
   c. Schedule an outpatient tilt test.
   d. Admit, perform EPS, and if negative, offer an ICD.

3. A 21-year-old female college student presents to her local emergency department because she fainted twice earlier that day. She reports that the first episode occurred while she was in the shower. It was preceded by nausea with diaphoresis, followed by sudden LOC. After she awoke on the floor, she felt very nauseated, diaphoretic, and vomited. She tried to stand but fainted again. She is otherwise healthy but has had the “flu” for 3 days. You are asked to consult. Her PMH, ECG, physical exam, and lab are normal. She had previously fainted once, while donating blood at a blood drive. What tests should you order?
   a. Tilt test
   b. Holter monitoring
   c. Stress echo test
   d. None of the choices

4. Treatment for vasovagal syncope usually involves avoiding offending stimuli, dehydration, and prolonged standing; improving or decreasing venous pooling; and high-salt and high-fluid diet. For recurrent episodes, pharmacologic therapy is often employed. Initial pharmacologic therapy consists of all of the following except:
   a. Beta-blockers
   b. Disopyramide
   c. Serotonin reuptake inhibitors
   d. Florinef

5. Carotid sinus syndrome is probably the second most common cause of neurally mediated syncope. It results from hypersensitivity of the carotid reflex and causes marked bradycardia and, frequently, concomitant hypotension. All of the following are true regarding the features and treatment of carotid hypersensitivity except:
   a. The finding of carotid sinus hypersensitivity is extremely specific for the presence of carotid sinus hypersensitivity and syndrome, and mandates pacemaker implantation.
   b. Pacemaker implantation has been shown to significantly reduce the number of syncopal spells.
   c. Patients with recurrent unexplained falls or injuries should be considered to have a neurally mediated syncopal etiology such as carotid sinus hypersensitivity and be tested either with carotid sinus massage testing or tilt table testing.
   d. Carotid sinus hypersensitivity syndrome may result from abnormal proprioception and baroreceptor responses, in the carotid artery and the surrounding sternocleidomastoid.

6. A 20-year-old female college student, education major, presents complaining of recurrent dizziness, fatigue, light-headedness, palpitations, shortness of breath, and chest pain. This all began acutely several weeks ago. She was otherwise previously healthy and athletic. Her electrocardiogram shows normal sinus rhythm and heart rate in the 70s. During postural checks in the office, her heart rate

goes to120 beats/min. Her physical exam is unremarkable although the patient is somewhat thin. What is the likely diagnosis?
   a. Inappropriate sinus tachycardia
   b. Vasovagal syncope
   c. Hyperthyroidism
   d. Postural orthostatic tachycardia syndrome

7. To confirm the diagnosis on the patient above, which of the following tests would not be initially performed?
   a. Comprehensive blood work, CBC electrolytes, TSH
   b. Electrophysiologic testing
   c. Holter monitoring
   d. Tilt table testing

8. A variety of pharmacologic and nonpharmacologic therapies have been proposed for patients with partial dysautonomia syndromes such as postural orthostatic tachycardia syndrome (POTS). Which of the following would not be an appropriate initial therapy?
   a. 5 to 7 g sodium diet/commensurate with electrolytes/compression stockings
   b. Graduated exercise program initially consisting of rowing machine, aqua therapy, recumbent bike
   c. 4 to 6 inches elevation of the head of the bed
   d. High-dose beta-blockade

9. A 79-year-old male presents following an episode of syncope while backing his car out of the driveway. He turned his head to look behind him, put the car in the motion, doesn't recall what happened next and found himself on the lawn. The car was still running. There was no tongue biting or incontinence. He has no known arrhythmias but had an angioplasty without stenting years prior. His EKG shows normal sinus rhythm and is otherwise normal. An echo shows normal LV size and function. He is currently free of chest pain. Which of the following diagnoses are suggested by his history?
   a. Acute myocardial infarction (MI)
   b. Ventricular tachycardia
   c. Carotid sinus syncope
   d. Sick sinus syndrome

10. A 76-year-old male presents with recurrent syncope. His examination reveals supine hypertension and severe systolic and diastolic orthostatic hypotension (OH). He has no arrhythmias, no evidence of structural heart disease, but is relatively bradycardic. He has a history of Parkinson's and takes Sinemet. Which of the following therapies are appropriate for initial treatment?
   a. Thigh high or waist compression stockings
   b. 4 to 6 inches elevation of the head of the bed
   c. Physical therapy to improve orthostatic tolerance
   d. Augmented fluid and salt
   e. All of the choices

Answers

1. Answer C: The presence of trifascicular or bifascicular block on the ECG suggests that the underlying etiology of syncope may be intermittent heart block, Mobitz type II, third-degree heart block, the so-called Stokes–Adams block. Given a normal stress echo test and normal LV function, electrophysiologic testing will likely be negative for ventricular tachycardia. Based on current American College of Cardiology/American Heart Association (ACC/AHA) guidelines, when no other cause for syncope is found, pacemaker implantation is indicated for syncope that has not been demonstrated to be due to AV block.

2. Answer D: Syncope in a patient with DCM is a very poor prognostic sign. Electrophysiologic testing has a low negative predictive value and therefore cannot be wholly relied on to screen patients who need

a defibrillator. Implantation of a defibrillator remains a Class IIB indication in the presence of “advanced structural heart disease” denoting severe ischemic or nonischemic cardiomyopathy. In addition, based on the EF alone, the patient qualifies for ICD implantation according to the recent Definite and SCD-Heft data.

3. Answer D: Patients who present with a typical vasovagal episode with a classic prodrome and sequelae, who are otherwise healthy, probably require no other diagnostic testing or therapy, as the most unlikely etiology is vasovagal syncope. Tilt table testing is indicated only if the syncope becomes recurrent, or after single episodes of syncope with atypical features or for a high-risk patient.

4. Answer B: Disopyramide (Norpace) is a type IA sodium channel antiarrhythmic medication. It was proposed to be effective for vasovagal syncope based on its negative inotropic and anticholinergic effects. However, in a very well-designed study, using disopyramide loading and repeat tilt table tests, no efficacy was found. In addition, there is genuine concern for proarrhythmia in using the antiarrhythmic agents for treatment of a relatively benign disorder. Therefore, disopyramide may have a role for some patients, but it should not be used as initial therapy.

5. Answer A: Although the finding of carotid sinus hypersensitivity in a patient with recurrent syncope is highly suggestive, without the presence of the clinical syndrome the finding is relatively nonspecific. Carotid sinus hypersensitivity has been shown to be prevalent in patients with coronary disease and other forms of atherosclerotic disease as well. The sine qua non for carotid sinus syndrome is demonstration of carotid sinus hypersensitivity during carotid sinus massage, and a clinical scenario consistent with syncope resulting from direct stimulation of the carotid sinus baro and vagal reflex.

6. Answer D: POTS or postural orthostatic tachycardia syndrome is a poorly understood subacute dysautonomia with myriad symptoms, the hallmark of which is tachycardia with minimal exertion. Inappropriate sinus tachycardia, although possibly reflecting dysautonomia is frequently characterized by incessantly high heart rates. Although patients with POTS may be more susceptible to fainting, those solely with vasovagal propensity are usually not tachycardic.

7. Answer B: Electrophysiologic testing although frequently employed for documented or suspected supraventricular tachycardia (SVT) would not be revealing in patients with postural orthostatic tachycardia. Routine laboratory analysis, although frequently unremarkable, is certainly an appropriate component of initial evaluation of a patient with a sinus tachycardia syndrome. The sine qua non or gold standard for the diagnosis of postural orthostatic tachycardia is the tilt table test showing a heart rate increase of over 30 from baseline or over 120 beats within the first 10 minutes.

8. Answer D: Recent studies have supported the idea that nonpharmacologic approaches, particularly aggressive exercise programs are superior to medical therapy. Patients with orthostatic intolerance frequently do not tolerate beta-blockers, and if utilized, the dosage is ideally minimal.

9. Answer C: Syncope that occurs following movements of the head, pressure on the neck, Valsalva, etc., suggests the possibility of carotid sinus hypersensitivity which can be evaluated performing carotid sinus massage, in patients with no history of TIAs or cerebral vascular accidents (CVAs), and no carotid bruits. Carotid sinus hypersensitivity testing can reveal pauses of >3 seconds but can also reveal a vasodepressor reflex contributing to syncope. Carotid sinus syndrome is treated with a permanent pacemaker.

10. Answer E: The combination of supine hypertension and orthostatic hypotension is extremely clinically challenging scenario requiring multiple pharmacologic and nonpharmacologic interventions and extensive serial evaluation. Initial approaches as delineated above frequently can improve symptoms. However this syndrome tends to be progressive and ultimately requires pharmacologic approaches such as Florinef, and midodrine, which can be particularly problematic given the hypertension. Beta blockers may be helpful by leaving alpha receptors unopposed and actually improving vasoconstriction. However bradycardia can occur requiring permanent pacers. Patients with advanced central nervous system (CNS) disorders such as Parkinson’s may respond to Mestinon as well.

CHAPTER

Aortic and Pulmonary Valve Disease

Amar Krishnaswamy and Brian P. Griffin

NORMAL AORTIC VALVE ANATOMY

Normal aortic valves are tricuspid—with right, left, and noncoronary cusps—and have a valve area of 2 to 3 cm^2. However, congenital variations in this anatomy are relatively common, particularly bicuspid valves. Most commonly, bicuspid valves result from fusion of the right and left coronary cusps, although any two cusps may be fused. More rare are unicuspid and quadricuspid valves, with one and four cusps, respectively (Fig. 33.1). Although some congenitally abnormal valves function normally and are clinically silent, they more frequently result in symptomatic aortic stenosis (AS) or aortic insufficiency (AI) by middle age.

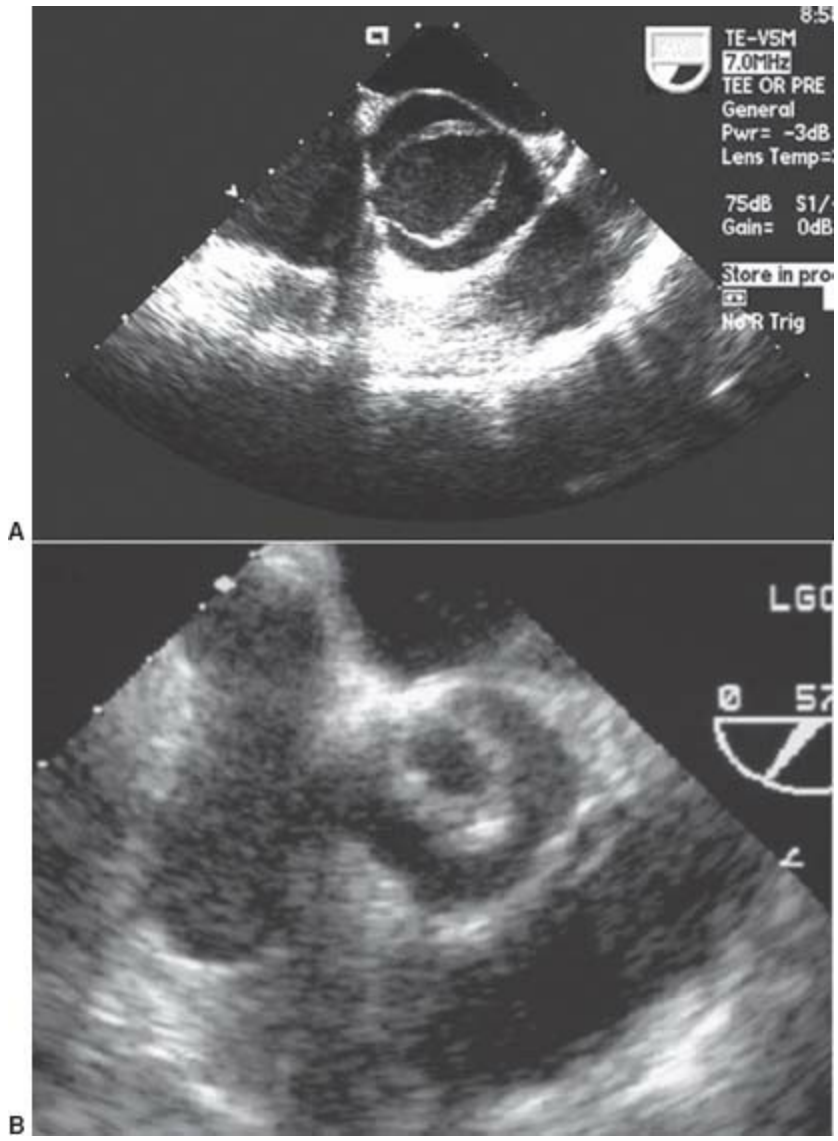

FIGURE 33.1 Transesophageal echocardiography short-axis images of bicuspid aortic valve **(A)** and unicuspid valve**(B)**

AORTIC STENOSIS

AS is one of the most frequent valve pathologies encountered in clinical cardiology. The etiology can be varied and may include subvalvular, valvular, or supravalvular lesions, but the pathophysiologic and hemodynamic responses to fixed outflow obstruction are usually predictable.

Pathophysiology of Aortic Stenosis

AS, regardless of degree, creates a pressure overload on the left ventricle (LV). Over time, the ventricle develops a compensatory concentric hypertrophy, which allows LV wall stress, or afterload, to remain normal, despite increased systolic pressures. This relationship is expressed by the law of Laplace, which states that wall stress is

proportional to the chamber radius divided by its thickness. Thus, in compensated AS, left ventricular hypertrophy (LVH) functions to normalize after load and helps to maintain normal LV contractile function. The hypertrophy does, however, lead to increased LV mass and end-diastolic pressures, which in turn may precipitate diastolic heart dysfunction and myocardial ischemia. The degree of hypertrophy may vary dramatically among individuals, and gender differences have also been noted. Classically, women develop more hypertrophy with a small-to-normal LV cavity size, whereas men develop a lesser degree of hypertrophy, a dilated LV cavity, and earlier systolic dysfunction.[1] Ultimately, compensatory mechanisms fail and patients develop symptoms due to progressive diastolic dysfunction, systolic dysfunction, compromised cardiac output, or myocardial ischemia.

Etiologies of Aortic Stenosis

There are multiple etiologies of AS, the most common of which are discussed below.

Degenerative AS is the most common etiology of AS in the United States. Once believed to be a passive process of calcification due to years of "wear and tear," degenerative AS is now understood to be a dynamic process involving a robust inflammatory response of macrophages, T cells, and fibroblasts. The exact precipitants for AS are not clear, but observational evidence suggests the process may share some risk factors with atherosclerosis. In retrospective studies, statins have attenuated progression of AS[2,3]; however, no prospective studies have shown that medical therapy is effective in delaying progression of AS.

Rheumatic heart disease is a common cause of AS in less developed countries, but its incidence in developing countries has declined over the past 30 years.

Congenital valve disease may result in bicuspid or unicuspid valves, which are a frequent cause of symptomatic AS in younger patients (see Fig. 33.1). Bicuspid valves (BAV) have a prevalence of 1% to 2% in the population and are associated with other congenital abnormalities (especially coarctation) in 20% of cases. Up to 80% of patients with coarctation have BAV. Bicuspid valves are also associated with aortic root dilatation and an aortopathy that resembles cystic medial necrosis. Unicuspid valves are inherently stenotic and usually cause symptoms by the third decade of life. Like bicuspid valves, unicuspid valves also are associated with an aortopathy.

Radiation heart disease may occur in patients who have a history of mediastinal radiation as treatment for lymphoma, breast, or esophageal cancers. The risk of valve disease is increased in patients who have received >30 Gy of radiation and generally presents 15 to 20 years after exposure. There is a greater tendency toward aortic valve disease, followed by mitral and then tricuspid valve disease. Due to this distribution of valve involvement, it is thought that flow may play a role in the valvular disease. Usually, radiation-associated aortic disease is mixed stenosis and regurgitation. Subvalvular AS is a rare form of AS and may be due to a tunnel of muscular tissue or a

discrete band or membrane. Sub-valvular stenosis should be suspected in any patient who has symptoms of AS or high LV outflow velocities on echo cardiography but whose aortic valve is structurally normal. Sub-valvular stenosis also presents as a component of the Shone complex: multiple left-sided heart obstructions, including supravalvular mitral stenosis, parachute mitral valve, subvalvular AS, BAV, and aortic coarctation. Additionally, subaortic stenosis may be associated with a patent ductus and ventricular septal defects (VSDs). Over time, the jet from subvalvular stenosis will damage the native aortic valve and will lead to AI. For this reason, early surgical repair of asymptomatic subvalvular stenosis is often recommended. Supravalvular AS is a rare variant of AS that is classically associated with Williams syndrome (child-like facies, peripheral pulmonary stenosis, hypercalcemia) and familial dyslipidemias. A mutation in the gene for elastin has been linked to Williams syndrome. Other cardiovascular associations of supravalvular stenosis include coarctation of the thoracic or abdominal aorta and renal artery stenosis.

Clinical Findings in Aortic Stenosis

The history of patients with AS varies with the etiology of the stenosis. Patients with rheumatic heart disease or bicuspid aortic valves frequently have a long history of a heart murmur. They also are more likely to present with symptomatic disease at a younger age. In contrast, patients with degenerative AS usually are older, in their seventh or eighth decade, and may present with symptoms without prior knowledge of aortic valve pathology.

The symptoms of AS are most frequently the direct result of the heart's compensatory changes. Initially, patients develop diastolic heart dysfunction, which often manifests as exertional dyspnea. With stress, patients with AS may become significantly symptomatic because their cardiac output cannot augment adequately and left ventricular end-diastolic pressure (LVFDP) markedly increases. Dyspnea and early fatigability result. As the AS progresses, the classic symptoms of angina, syncope, and heart failure develop. This triad of symptoms has been well studied and allows a rough estimate of disease severity and prognosis: if untreated, survival in patients with angina approximates 5 years, with syncope is 3 years, and with heart failure is <2 years.

Angina is very common in severe AS and may be due to concomitant coronary disease, demand ischemia, or both. Interestingly, up to 50% of patients with angina and severe AS have no obstructive coronary disease. The angina is usually typical substernal pain, worsened with exertion or stress, and relieved with rest. Anginal equivalents, such as dyspnea on exertion, are also common. Syncope or presyncope most often results from exertional cerebral hypoperfusion; with exercise, the systemic arterial tree vasodilates, but the cardiac output remains relatively fixed. Arrhythmias may also precipitate syncope, especially atrial fibrillation or ventricular tachycardia. Congestive heart failure (CHF) symptoms such as pulmonary edema, paroxysmal

nocturnal dyspnea, and orthopnea are late findings in AS and signify advanced disease with very poor prognosis if untreated.

Less common manifestations of AS include cardiac cachexia in very advanced cases and gastrointestinal bleeds from atriovenous (AV) malformations (Heyde Syndrome). Cardiac cachexia and debilitation result from a profound, longstanding low-output state. The mechanism for gastrointestinal bleeding from arteriovenous malformations is presumed to be destruction of large multimers of von Willebrand factor as they are sheared through the aortic valve. These larger multimers are apparently critical to the initial phases of hemostasis.

The Physical Exam

Vascular Findings The carotid pulsations in patients with severe AS are characterized by a delayed and weakened upstroke, the pulsus parvus et tardus. In long-standing critical AS, the peripheral pulses also may be weak, and signs of poor perfusion may be present.

Cardiac Findings On palpation, one may feel a systolic thrill in cases of severe AS. The apex may be laterally displaced if the heart has begun to dilate. The cardiac exam in AS is notable for a crescendo-decrescendo murmur, heard best in the right upper sternal border (RUSB) and radiating to the carotids. Occasionally, the murmur may instead radiate to the apex and mimic mitral regurgitation (MR); this is known as the Gallavardin phenomenon. As AS progresses, the murmur peaks increasingly later in systole until S_2 is obliterated, suggesting severe disease. The grade of the murmur correlates with severity of the stenosis, and the presence of a thrill (Grade IV/VI) suggests critical stenosis. An S_4 is also frequently appreciated. An ejection click suggests the presence of a bicuspid aortic valve.

The physical exam may be useful in differentiating valvular AS from hypertrophic cardiomyopathy (HCM) and subaortic stenosis. In HCM, the carotid pulsation is on time and is bifid, with a two-component, “spike and dome” contour. This is caused by the presystolic closure of the aortic valve. The point of maximal cardiac impulse (PMI) pulsation in HCM patients classically has three components, which correspond to atrial filling and the two components of systolic ejection. The murmur in HCM can be differentiated from AS by several maneuvers. Decreasing either preload or afterload will accentuate the murmur of HCM, but will soften the murmur of valvular AS. Thus, a Valsalva maneuver or arising from squatting to standing will accentuate a HCM murmur, but will decrease the murmur of AS. Amyl nitrate will similarly decrease afterload and preload, resulting in marked increase in the HCM murmur.

The murmur of subvalvular stenosis resembles valvular AS. Clues that the murmur might be due to subvalvular stenosis include a younger patient age, the presence of AI, and the absence of an ejection click. In supravalvular AS, blood flow preferentially is

directed into the innominate artery, so the murmur of supravalvular stenosis classically radiates to the right neck and subclavian and may be associated with a thrill over the right carotid. The blood pressure in the right arm may be slightly higher than in the left. Careful auscultation of the lung fields may reveal murmurs associated with peripheral pulmonary stenosis.

Key Diagnostic Studies

Electrocardiogram The electrocardiogram (ECG) in patients with severe AS may show LVH with concomitant strain pattern, left atrial (LA) abnormality, or interventricular conduction delay. Transient third-degree heart block has been described, and has been ascribed to aortic annular calcification impinging on the AV nodal conduction system.

Chest X-Ray The chest x-ray (CXR) is often normal in patients with AS, especially because LVH frequently is unaccompanied by dilation early in the disease. With advanced disease, LVH and enlargement, aortic dilation, and aortic valvular calcification may be appreciated.

Transthoracic Echocardiogram Echocardiography has become the gold standard for diagnosis and quantification of aortic valve disease. Key data that are attained from a transthoracic echocardiogram (TTF) assessment include the following.

LV Size and Systolic Function. Systolic function is usually normal until late in the disease. The LV will show variable hypertrophy, with overall normal size.

Diastolic Function. Early in the disease process, LV compliance decreases and the atrial component of diastolic filling becomes increasingly prominent. Over time, LA pressure rises, and ultimately, patients with long-standing AS may develop restrictive diastolic filling patterns.

Assessing Aortic Valve Morphology. Echocardiography is paramount in identifying the etiology of AS. Standard transthoracic images usually can identify bicuspid or unicuspid valves, can suggest a rheumatic etiology, or can quantify the degree of valvular calcification.

Assessing the Severity of AS. There are several methods to estimate the severity of AS. Multiple methods should be used in each patient to ensure accurate data.

Jet velocity: Peak aortic valve jet velocity provides a rough measure of valve severity and also provides a measure of prognosis. A normal outflow velocity is approximately 1 m/s. Studies have suggested that asymptomatic patients with outflow gradients in excess of 4 m/s will most likely develop symptoms within 2 years.[4]

Valve gradients: Peak transaortic valve gradients can be estimated using the jet velocity and the modified Bernoulli equation: peak gradient = $4v^2$, where v is the peak velocity across the valve. Mean gradients are calculated using the velocity time integral (VTI).

Aortic valve area (AVA): AVA most frequently is estimated using planimetry on a

parasternal short-axis image of the aortic valve or by using the continuity equation (Fig. 33.2).

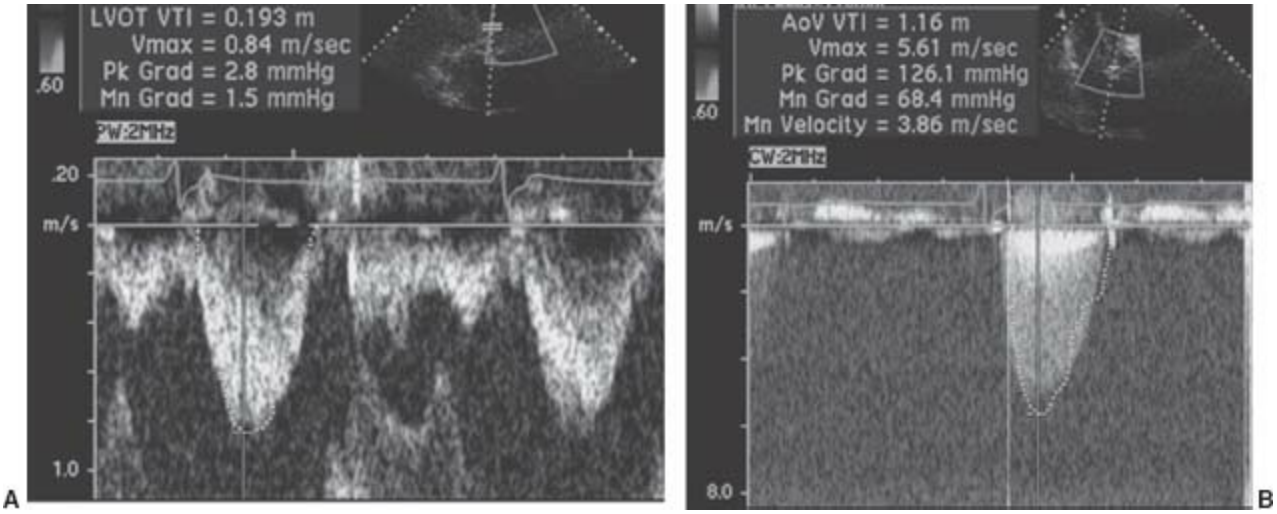

FIGURE 33.2 Pulse-wave Doppler flow through the LVOT **(A)** and continuous-wave Doppler flow through the aortic valve **(B).** The continuous-wave flow allows simple calculation of the peak transaortic gradient: peak = $4v^2$, where v is equal to the maximum flow across the aortic valve. In this case, v = 5.6 m/s, and the peak gradient is given as 126 mm Hg. The AVA can be calculated from the continuity equation, $A_{LVOT}(VTI)_{LVot} = A_{AV}(VTI)_{AV}$, where A is area and VTI is the velocity time integral, or the flow velocity integrated over the systolic ejection period. In this example, assuming the LVOT diameter is 2 cm,

$$\begin{aligned} A_{AV} &= A_{LVOT}(VTI)_{LVOT} / (VTI)_{AV} \\ &= 3.14\ cm^2(0.193\ m) / (1.16\ m) \\ &= 0.55\ cm^2 \end{aligned}$$

The dimensionless index: The dimensionless index refers to the ratio of the left ventricular outflow VTI to the aortic valve VTI. This ratio allows for a quick, semiquantitative assessment of valve stenosis. An index <25% is consistent with severe stenosis.

Several caveats must be kept in mind when using echocardiography to assess the severity of AS. First, Doppler echocardiography can underestimate the peak AS gradient if the echo beam is not accurately aligned with the aortic outflow. Therefore, multiple echo windows must be assessed to find the highest transvalvular velocities. Additionally, the modified Bernoulli equation assumes a left ventricular outflow tract (LVOT) velocity of 1 m/s, which may not always be true. If the true LVOT velocity is >1 m/s, then the modified Bernoulli equation will overestimate stenosis severity. Finally, continuous-wave Doppler cannot assess stenoses in series, such as dynamic LVOT obstruction and valvular AS, or subvalvular and valvular AS. In such instances, the use of the continuity equation can be erroneous. Care must also be taken not to confuse the Doppler signals of AS and MR. Generally, MR velocity is 4 to 5 m/s, and the Doppler signal begins at the start of systole (i.e., no period of isovolumic

contraction).

Invasive Assessment of the Aortic Stenosis

Echocardiography usually is sufficient to determine the severity of AS; however, invasive assessment of AS is sometimes necessary, particularly in cases in which clinical symptoms are not congruent with echo data (see American College of Cardiology/American Heart Association [ACC/AHA] Guidelines[5]). During right heart catheterization, Fick cardiac outputs are preferable to thermodilution because they are more reliable in low-output states. During left heart catheterization, simultaneously measured LV and ascending aortic pressures are ideal, although a pullback gradient may be used if the patient is in sinus rhythm. The femoral artery waveform should not be used to estimate aortic pressures. The AVA can be estimated with the Hakki equation: AVA = CO/√(peak or mean transvalvular gradient). A formal calculation can be done with the Gorlin equation (Fig. 33.3).

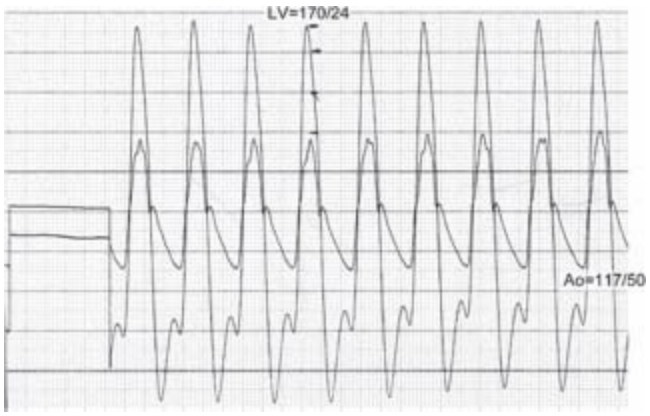

FIGURE 33.3 Simultaneous pressure recordings of the LV and aorta. Peak-to-peak gradient is approximately 53 mm Hg. If one knows the cardiac output (CO), the AVA can be estimated with the Hakki equation: AVA = CO/(peak gradient)$^{1/2}$. Assume that the CO = 4 L/m. Then

$$\begin{aligned} \text{AVA} &= 4/(53)^{1/2} \\ &= 4/7.2 \\ &= 0.55\ \text{cm}^2 \end{aligned}$$

(Courtesy of D. Vivek.)

Invasive hemodynamic assessment measures a peak LV-to-peak aortic gradient across the aortic valve, which is invariably lower than the peak gradient on echocardiography. This is due to the fact that Doppler echocardiography measures the peak instantaneous velocity. The mean transvalvular gradients by echo and catheterization correlate well, however. Occasionally, Doppler gradients greatly exceed gradients on catheterization, which may be due to the phenomenon of pressure recovery. In effect, substantial turbulent flow of blood through the valve may cause the pressure in the aorta to be artificially low immediately distal to the valve. Several

centimeters into the proximal aorta, however, laminar flow is restored, and pressure "recovers." Doppler echocardiography detects the maximum pressure gradient between the LV and the proximal aorta. Pressure recovery usually is not an issue with native aortic valves but can be problematic especially with smaller prosthetic valves.

Classifications of Severity of Aortic Stenosis

Normal AVA: 2 to 3 cm^2

Mild AS: AVA > 1.5 cm^2, mean gradient <25 mm Hg

Moderate AS: 1.0 to 1.5 cm^2, mean gradient 25 to 40 mm Hg

Severe AS: <1.0 cm^2, mean gradient >40 mm Hg

Treatment of Patients with Aortic Stenosis

Asymptomatic Patients

Patients with AS who have no symptoms may be managed expectantly, as the risk of adverse events—for example, sudden death, cardiac death, or all-cause mortality—is very low in asymptomatic patients.[6] Endocarditis prophylaxis is no longer indicated for patients with AS, though is reasonable (Class IIa) for patients with previous endocarditis or prosthetic material.[7] Vasodilators should be used with extreme caution due to concerns of diminishing preload. The ACC guidelines provide a Class I indication for serial echocardiography every 3 to 5 years for patients with mild AS, and every 1 to 2 years for patients with moderate AS. For patients with severe AS, surveillance echocardiography is recommended on an annual basis, or even more frequently if clinically indicated.[5] Stress echocardiography may be helpful in assessing patients with asymptomatic AS to evaluate functional capacity and assess for abnormal blood-pressure response or unrecognized symptoms (Class IIb indication). Patients with symptomatic AS should not have stress testing (Class III).

Patients with mild AS are encouraged to keep physically active and may participate in competitive sports. For patients with moderate AS, aerobic activity is permissible; however, competitive contact sports or heavy lifting is not advised. Patients with severe AS should not engage in strenuous activity or competitive sports.

Progression of AS is highly variable, but on average, valve area decreases approximately 0.1 cm^2/y. Progression of AS has been associated with risk factors for coronary artery disease (CAD) (diabetes, hypercholesterolemia, hypertension) in observational studies, and thus treatments of these conditions may be important is AS therapy as well. A more rapid rate of change (>0.3 m/s/y increase in velocity)[8] or a peak jet velocity >4 m/s suggest that patients have <2 years before symptoms will develop.[4,8] Heavily calcified valves are also associated with a higher likelihood of symptomatic disease.

Any patient with severe AS should be aware that dyspnea, angina, or presyncope merits prompt evaluation. Symptoms of AS may be insidious, however, and patients may be unaware of a decline in functional capacity. In such cases, stress echocardiography can be useful to assess functional capacity, ventricular function, transvalvular gradients with stress, and the pulmonary artery (PA) pressure responses to stress. Such variables may alter the threshold to pursue aortic valve replacement (AVR).

Patients with Rheumatic Fever

Rheumatic fever is an important cause of both aortic and mitral valve disease. Its prevalence has decreased over the past 30 years, largely because of better diagnosis and treatment of group A streptococcal pharyngitis. Acute rheumatic fever is recognized as a serious complication of pharyngeal streptococcal infections, and is due to an autoimmune phenomenon triggered by group A streptococcal M proteins, which mimic cardiac myosin.

Primary prevention of rheumatic fever includes prompt diagnosis of group A streptococcal infections and treatment with appropriate antibiotics, usually a penicillin derivative or macrolide. Patients who develop acute rheumatic fever require long-term secondary prophylaxis, usually with monthly intramuscular injections of benzathine penicillin (Table 33.1).

TABLE
33.1 Recommendations for Secondary Prophylaxis of Rheumatic Fever

Indication	Recommendation
1. Rheumatic fever with carditis and persistent valvular disease	>10 y or at least until age 40, whichever is longer. Consider life-long prophylaxis if high risk (e.g., health care worker, teacher)
2. Rheumatic fever with carditis but without valve disease	10 y or "well into adulthood," whichever is longer.
3. Rheumatic fever without carditis or valve disease	5 y or until age 21, whichever is longer.

From Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease) Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and

Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;52:e1-e142, with permission from Elsevier.

Symptomatic Patients

For patients with severe AS who develop symptoms, experience a decline in LV systolic function <50%, or are undergoing other open heart surgery (OHS), AVR is recommended as a Class I indication.[5] The risk of AVR increases with patient age; however, because the prognosis for untreated, severe symptomatic AS is abysmal, chronologic age alone should not be used to exclude patients from valve surgery. Low ejection fraction, heart failure, renal failure, female gender, and atrial fibrillation also are adverse predictors in patients undergoing aortic valve surgery. Transcatheter aortic valve implantation (TAVI) has emerged as an attractive alternative procedure to surgical AVR, and initial results in patients unable to undergo surgery are promising.[9]

AVR is reasonable (Class IIa) for patients with moderate AS undergoing OHS for a different reason, and may be considered (Class IIb) for patients with asymptomatic severe AS and abnormal exercise testing or features concerning for rapid progression (age, calcification, and CAD). AVR may also be considered (Class IIb) for patients with asymptomatic and "extremely severe" AS (AVA <0.6 cm ^{2}, mean gradient >60 mm Hg, or jet velocity >5 m/s) if the operative mortality is <1% (Table 33.2).[5]

TABLE
33.2 Indications for Aortic Valve Surgery in Patients with Severe AS

Indication	AHA/ACC Class
1. Patients with symptomatic, severe AS	I
2. Patients with severe AS undergoing open heart or aortic surgery for another reason	I
3. Patients with severe AS and LVEF < 50%	I
4. Patients with moderate AS undergoing open heart or aortic surgery for another reason	IIa
5. Asymptomatic patients with severe AS and high likelihood of rapid progression (age, calcification, CAD)	IIb
Hypotension with exercise	IIb
"Extremely severe" AS with AVA <0.6 cm^2, mean gradient >60 mm Hg, and jet velocity >5 m/s if operative mortality <1%	IIb
6. Patients with mild AS undergoing coronary artery bypass graft (CABG) with risk of rapid progression (i.e. moderate to severe valve calcification)	IIb
7. Asymptomatic patients with severe AS and none of the above	III

From Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease) Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;52:e1-e142, with permission from Elsevier.

Valve Replacement Options

Mechanical Valves Mechanical prostheses have excellent longevity but require systemic anticoagulation. For patients with normal ejection fractions, contemporary bileaflet or single-leaflet valves require an INR of 2 to 3. Older-generation valves should be anticoagulated to an INR of 2.5 to 3.5. Additionally, any patient with atrial fibrillation, depressed LV function, prior thromboembolism, or a hypercoagulable state should have a target INR of 2.5 to 3.5. Mechanical valves should especially be considered in younger patients (<65 years of age), patients with renal disease, and those with calcium-handling metabolic disorders. Younger women who wish to have children are better served with a biologic valve until after their child-bearing years.

Biologic Valves Porcine valve or bovine pericardial tissue valves do not require anticoagulation, but have shorter life spans than mechanical valves. In older patients, tissue valves may be expected to last 10 to 15 years, but have an expected lifespan of

<10 years in younger patients. Therefore, tissue valves should be considered for patients >age 65 years, and in patients for whom anticoagulation is problematic. All patients with tissue valves should be treated with aspirin (81 mg daily).

Homografts Cadaveric homografts are the valve of choice for patients with active infective endocarditis because they may resist infection more than tissue or mechanical valves. Additionally, they do not require long-term anticoagulation. However, the durability of homografts is no better than that of tissue valves and reoperation is much more challenging with homografts than with mechanical or other tissue valves.

Ross Procedure The Ross procedure transplants the pulmonic valve into the aortic position and places a homograft in the pulmonic position. This operation may be appropriate at experienced centers for younger patients who have not completed their growth cycle, as studies suggest that the native pulmonic valve (autograft) may grow with the patient when implanted at the aortic position. However, in the long term it creates double-valve pathology from a single-valve problem, and therefore has a limited role in aortic valve disease.

Balloon Valvuloplasty Balloon aortic valvuloplasty may be a very effective therapy for children or very young adults with congenital, noncalcific AS (Table 33.3). In adults with severe AS, however, the results of BAV are not durable. Patients may experience short-term (<6 months) symptomatic and hemodynamic benefit from balloon valvuloplasty; however, most redevelop significant symptoms by 6 to 12 months postprocedure. BAV may be considered (Class IIb) for palliation in nonsurgical patients or for temporizing symptoms until a definitive valve surgery can be performed —for example, in patients with cardiogenic shock who are too ill to undergo immediate surgery. The guidelines do not recommend BAV for patients with asymptomatic severe AS undergoing noncardiac surgery. In contemporary practice, BAV has become more commonplace as a strategy for bridging patients until TAVI can be performed as part of a clinical trial. Current guideline indications for valvuloplasty in adult, calcific AS are limited and are listed in Table 33.4.

TABLE
33.3 Recommendations for Balloon Valvuloplasty in Young Patients with Noncalcific AS

Class I

1. Transthoracic echocardiography is indicated for baseline evaluation of LV size and function, RV and left atrial size, pulmonary artery pressure, and severity of MR (Table 34.4) in any patient suspected of having MR. *(Level of Evidence: C)*
2. Transthoracic echocardiography is indicated for delineation of the mechanism of MR. *(Level of Evidence: B)*
3. Transthoracic echocardiography is indicated for annual or semiannual surveillance of LV function (estimated by ejection fraction and end-systolic dimension) in asymptomatic patients with moderate to severe MR. *(Level of Evidence: C)*
4. Transthoracic echocardiography is indicated in patients with MR to evaluate the MV apparatus and LV function after a change in signs or symptoms. *(Level of Evidence: C)*
5. Transthoracic echocardiography is indicated to evaluate LV size and function and MV hemodynamics in the initial evaluation after MV replacement or MV repair. *(Level of Evidence: C)*

Class IIa

1. Exercise Doppler echocardiography is reasonable in asymptomatic patients with severe MR to assess exercise tolerance and the effects of exercise on pulmonary artery pressure and MR severity. *(Level of Evidence: C)*

Class III

1. Transthoracic echocardiography is not indicated for routine follow-up evaluation of asymptomatic patients with mild MR and normal LV size and systolic function. *(Level of Evidence: C)*

From Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease) Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;52:e1-e142, with permission from Elsevier.

TABLE
33.4 Indications for Balloon Valvuloplasty in Adult Patients with Severe, Calcific AS

Indication	ACC/AHA Class
1. Temporizing hemodynamically unstable patients who are at high risk for AVR until definitive valve surgery can be performed	IIb
2. Palliation therapy for patients who are not operative candidates	IIb
3. Asymptomatic patients with severe AS requiring urgent non-cardiac surgery	III
4. Alternative to AVR	III

From Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease) Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;52:e1-e142, with permission from Elsevier.

Transcatheter Aortic Valve Implantation More than one-third of patients with severe AS may be denied surgical AVR due to advanced age, significant LV dysfunction, previous chest surgery or radiation, or other comorbidities. TAVI has emerged as a therapeutic option for patients who present a high surgical risk. Currently used devices include the Edwards Sapien Valve (Edwards Lifesciences) and CoreValve ReValving System (Medtronic). These bioprosthetic valves sit within a stent and are deployed across the native aortic valve. Valve implantation is usually conducted via a transfemoral or transapical approach. Results of the PARTNER (Placement of Aortic Transcatheter Valves) trial cohort randomized to medical therapy versus TAVI showed a remarkable, 20% absolute mortality decrease with TAVI (30.7 vs. 50.7%, p 0.001).[9] Results of the TAVI versus surgical AVR cohort are eagerly anticipated. Both the Sapien and CoreValve have received the European Conformity (CE) Mark. In the United States, however, the Sapien valve is placed only under the auspices of ongoing clinical trials, and trials of the CoreValve are yet to begin in the United States. 0.001).[9] Results of the TAVI versus surgical AVR cohort are eagerly anticipated. Both the Sapien and CoreValve have received the European Conformity (CE) Mark. In the United States, however, the Sapien valve is placed only under the auspices of ongoing clinical trials, and trials of the CoreValve are yet to begin in the United States.

LOW-GRADIENT AORTIC STENOSIS VERSUS PSEUDOSTENOSIS

Patients with "low-flow, low gradient" AS typically have a left ventricular ejection fraction (LVEF) <35%, mean gradient <30 mm Hg, and calculated AVA < 1 cm ^{2}, and present a challenging diagnostic dilemma. Because gradients across the valve are proportional to flow and inversely proportional to valve area, an abnormally low flow state can cause low gradients regardless of valve stenosis. In patients who have LV dysfunction, low transvalvular gradients, and suspected severe AS, it is critically important to determine if the poor cardiac output is due in part to severe AS, because these patients will benefit from AVR. However, if there is intrinsic myocardial dysfunction, the LV may not generate sufficient flow to maximally open a mildly stenotic valve. In such patients, the measured gradients may overestimate stenotic severity, leading to "pseudostenosis." These patients have a poor prognosis and do not require AVR.

Dobutamine echocardiography has been used to differentiate low-gradient AS from pseudostenosis and to assess LV contractile reserve. In the presence of true stenosis, dobutamine will increase or normalize cardiac output, improve LV contractile function and ejection fraction, and lead to increased transvalvular gradients. In true AS, the dimensionless index and valve area will not change significantly with increased cardiac output. The presence of LV contractile reserve is also an important prognosticator, as the operative mortality of patients with contractile reserve is far better than those without (11% vs. 62% for AVR + CABG).[10]

Conversely, in patients with pseudostenosis, an increase in cardiac output will augment LVOT velocities more so than transvalvular velocities, leading to an increase in both the dimensionless index and the calculated valve area. Therefore, after administration of dobutamine, indications to proceed to AVR include a significant increase in transvalvular gradients, an increase in LVEF > 5%, and no significant change in the dimensionless index or calculated AVA.

AORTIC INSUFFICIENCY

Pathophysiology of Aortic Insufficiency

Whereas AS is purely an LV pressure overload, AI provokes both pressure and volume overload, creating the largest increase in afterload of any valvular condition. The volume overload is a direct result of the AI. In turn, the regurgitation leads to an increased stroke volume through a relatively fixed outflow orifice and into the relatively high-pressure aorta, resulting in chronic pressure overload. Initially, LV compliance rises and the cavity dilates to maintain adequate forward stroke volume. Concomitantly, the LV hypertrophies eccentrically to minimize wall stress. LVEDP thus remains normal early in the disease. As the AI progresses, the ventricle progressively dilates and outpaces hypertrophy, leading to increased end-diastolic pressure (EDP) and after-load. Ultimately, the LVEF declines, and irreversible myocardial dysfunction results.

Etiology of Aortic Insufficiency

It is useful to divide causes of AI into primary (valvular) and secondary (aortic) causes.

Valvular Causes of Aortic Insufficiency

Bicuspid aortic valves are a common cause of AI, and especially are associated with aortic root dilatation.

Infective endocarditis can cause acute AI, particularly in patients with preexisting valve pathology, such as a bicuspid valve.

Rheumatic heart disease can cause AS, AI, or a combination of both.

Radiation heart disease can cause AS, AI, or a combination of both.

Subaortic stenosis is a rare cause of severe AI. The turbulent jet flow caused by the subvalvular stenosis frequently leads to progressive destruction of the aortic valve.

Drugs: Anorectic drugs such as fenfluramine and phentermine have been shown to cause thickening of aortic and mitral valve leaflets, leading to regurgitation. Likewise, ergots have been shown to cause a similar pathology.

Secondary Causes of Aortic Insufficiency

Aortic root dilatation: There are multiple causes of aortic root dilatation that may lead to severe AI. Some of the most clinically relevant include bicuspid aortic valve and Marfan disease, both of which cause root dilatation via cystic medial necrosis. Aortitis due to syphilis and collagen-vascular disease (e.g., Takayasu disease, ankylosing spondylitis, giant cell arteritis) also may precipitate AI.

Aortic dissection: Type A aortic dissections are a major cause of severe acute AI.

VSD: Supracristal VSDs can lead to AI by causing aortic leaflet prolapse. Even if they are small, these VSDs should be closed early on to prevent aortic valve pathology.

Clinical Findings

Acute Aortic Insufficiency

Acute AI most often results from infective endocarditis, trauma, or aortic dissection. On history, patients may have conditions that predispose them to these complications, such as a bicuspid valve, Marfan disease, or a known aortic aneurysm. The physical exam frequently shows profound hemodynamic compromise, with hypotension, tachycardia, and heart failure. It may be difficult to appreciate a diastolic murmur, because aortic diastolic pressure and LVEDP equilibrate very rapidly. Thus, unlike chronic AI, the murmur is only early diastolic. Because the LV does not have time to dilate and increase stroke volume, physical findings of a displaced PMI and wide pulse pressure are absent.

Chronic Aortic Insufficiency

Chronic AI, even when severe, is usually well tolerated for many years. Thus, many patients have AI diagnosed before the onset of symptoms. Early symptoms most often include dyspnea on exertion and a decline in exercise capacity. More progressive disease may lead to frank symptoms of heart failure, particularly as the LV function begins to decline. As with AS, patients with chronic AI may develop angina, regardless of obstructive coronary lesions.

Physical Exam

Vascular Findings

The peripheral vascular hallmark of severe AI is a widened pulse pressure characterized by a brisk systolic upstroke followed by a rapid diastolic collapse, which corresponds to reversal of flow in the aorta. Multiple eponyms have been ascribed to this phenomenon, and include Corrigan pulses (“waterhammer” carotid pulsation) and Quincke pulses (systolic blushing of the nail beds). A bisferiens carotid pulsation, with

two systolic peaks, may also be appreciated in severe AI.

Cardiac Findings

On palpation, one may appreciate a laterally displaced PMI or a thrill. The classic AI auscultatory signs include a diminished mitral closing sound, and a decrescendo, blowing, holodiastolic murmur, appreciated best at end-expiration with the patient leaning forward. Classically, a diastolic murmur at the right sternal border indicates aortic dilation with secondary AI, and a left sternal border (LSB) location indicates primary valvular AI. A soft systolic murmur may also be heard at the aortic position as a result of increased flow across the valve. Occasionally, severe AI creates a lowpitched, mitral stenosis–like murmur, the Austin–Flint murmur. The exact mechanism of this murmur is not clear, but it occurs when the AI jet hits the anterior leaflet of the mitral valve. An ejection click suggests a bicuspid valve.

Key Studies

Electrocardiogram

The ECG classically shows LVH.

Chest X-Ray

Chronic severe AI leads to an increase in LV size and mass. Thus, the CXR frequently shows cardiomegaly with an enlarged LV. The aorta may be aneurysmal in patients with secondary AI.

Echocardiography

As with most valvular disease, the most useful noninvasive assessment is with Doppler echocardiography. When assessing a patient with substantial AI, there are several key considerations.

1. LV size and ejection fraction: In patients with severe, asymptomatic AI, both LV size and function must be carefully monitored, because both parameters may guide decisions for valve surgery.
2. Aortic pathology: Particularly in patients with secondary AI, a careful assessment for aortic pathology is mandatory. In many patients, progressive dilation of the aorta dictates AVR and aortic surgery before the AI becomes severe.
3. Aortic valve morphology: Careful assessment of the valve itself may give clues to the etiology of regurgitation. Bicuspid valves, leaflet prolapse, presence of vegetations, and rheumatic canges all can be diagnosed or suggested by transthoracic images.

4. Assessing the severity of AI: There are multiple methods for assessing AI severity. No single measurement is definitive, so several methods should be used to evaluate the AI severity.
   a. Regurgitant jet width (vena contracta) in the parasternal long-axis view: A vena contracta width >50% of the LVOT width suggests severe AI.
   b. Presence of a proximal isovelocity surface area (PISA): a PISA suggests at least moderate AI, and allows calculation of a regurgitant orifice area (ROA). An ROA >0.3 cm^2 suggests severe AI.
   c. Pressure half-time (PHT): PHT refers to how fast the pressure gradient across the aortic valve in diastole is reduced by half. Rapid reduction in the pressure gradient (PHT < 250 milliseconds) suggests severe AI, whereas slow degradation of the gradient (PHT > 400 milliseconds) suggests milder disease. PHT is dependent on multiple variables, including systemic vascular resistance and LV and aortic compliance, and thus changes in these variables reduce the utility of PHT.
   d. Diastolic flow reversal in the descending aorta: If the reversed flow is pan-diastolic and exceeds 25 cm/s, severe AI is likely (Fig. 33.4).
   e. M-mode echocardiography: On classic M-mode imaging, fluttering of the mitral valve is seen with moderate to severe AI. Fluttering may be seen in both acute and chronic AI. In severe acute AI, premature closure of the mitral valve is also seen. Diastolic MR may be noted on color M-mode or color Doppler (Fig. 33.5).

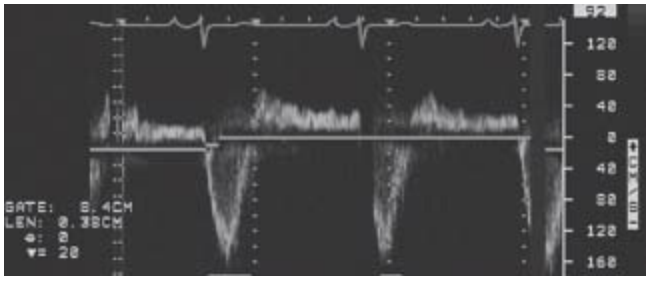

FIGURE 33.4 Continuous-wave Doppler flow profile in the descending aorta, showing flow reversal at approximately 30 cm/s. This profile suggests severe AI.

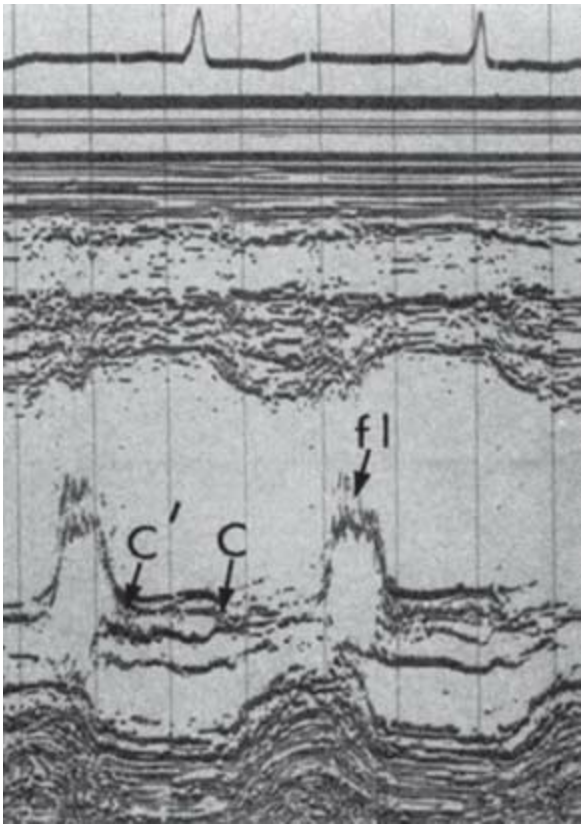

FIGURE 33.5 M-mode image through the mitral valve in a patient with severe acute AI. Classic findings shown include fluttering of the anterior leaflet (fl) and early closure of the mitral valve (c').

Treatment of Aortic Insufficiency

Acute Aortic Insufficiency

Because acute severe AI is poorly tolerated, emergency or urgent surgery is advised. If a delay is necessary before surgery, IV vasodilators become the treatment of choice. Increasing the heart rate will decrease the diastolic period, and may temporize the hemodynamic effects of acute severe AI. Intra-aortic balloon pumps are absolutely contraindicated in severe AI.

Chronic Aortic Insufficiency

Asymptomatic Patients Chronic AI is usually well tolerated for years before symptoms develop. In asymptomatic patients with normal LV function and severe compensated AI, the progression rate to symptoms is 4% per year, and the progression to LV dysfunction is 1.3% per year. The risk of sudden death is very low in asymptomatic patients (<0.2% per year). Once LV dysfunction develops, symptoms will likely follow within 3 years. Once symptoms develop, the rate of mortality increases to 10% per year.

Medical Treatment

Medical therapy for patients with severe AI includes afterload reduction with

vasodilators in certain situations. Vasodilators carry an ACC/AHA Class I recommendation for patients with severe AI and symptoms of LV dysfunction who are unable to undergo surgery, and a Class IIa recommendation for short-term therapy prior to AVR.[5] They also should be used in patients with AI who have hypertension. Vasodilators may be considered (Class IIb) in asymptomatic patients with severe AI and normal LV function but LV cavity dilation. They are not indicated (Class III) for patients with mild or moderate AI and normal LV function (Table 33.5). Dihydropyridine calcium channel blockers are first-line agents, although angiotensin receptor inhibitors (ACE) inhibitors are frequently used as well. Endocarditis prophylaxis is no longer indicated for patients with AI, though is reasonable (Class IIa) for patients with previous endocarditis or prosthetic material.[7] For patients with mild–moderate AI, yearly exams and biannual echocardiograms are sufficient follow-up if clinical symptoms are stable. For patients with severe AI, follow-up with echocardiography should be done every 6 months with a close eye toward declining LV function and/or LV cavity dilation.

TABLE
33.5 Indications for Vasodilator Therapy in Patients with Severe AI

Indication	ACC/AHA Class
1. Severe AI with LV dysfunction when surgery is not possible	I
2. Short-term therapy for patients with LV dysfunction prior to AVR	IIa
3. Severe asymptomatic AI with normal systolic function, but LV dilation	IIb
4. Long-term therapy in asymptomatic patients with normal systolic function and mild–moderate AI	III
5. Long-term therapy in asymptomatic patients with LV dysfunction who are otherwise candidates for AVR	III
6. Long-term therapy in symptomatic patients who are otherwise candidates for AVR	

From Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease) Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and

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For patients with mild–moderate secondary AI due to aortic root dilatation (>4.5 cm), beta-blockers can be used carefully to decrease aortic wall stress. Relative bradycardia, however, may worsen the AI.

Indications for Surgery

Patients with severe AI who have symptoms, LV dilatation or dysfunction, or (in the case of secondary AI) who have enlarging aortas should undergo valve surgery. ACC/AHA indications for aortic valve surgery for AI are listed in Table 33.6.[5] Class I indications for AVR include symptomatic patients with severe AI (irrespective of LV function), asymptomatic patients with LV dysfunction (EF < 50%), or patients with severe AR undergoing CABG or aortic surgery. AVR is reasonable (Class IIa) for asymptomatic patients with severe AI and normal LV function but evidence of LV dilation (left ventricular internal dimension in diastole [LVIDd] >7.5 cm or left ventricular internal dimension in systole [LVIDs] >5.5 cm). Patients with moderate AI undergoing CABG or aortic surgery may be considered for AVR (Class IIb), as well as asymptomatic patients with severe AR and LV dilation (LVIDd >7.0 cm or LVIDs >5.0 cm) if there is evidence of progressive dilation, decreasing exercise tolerance, or abnormal hemodynamic response to exercise.

TABLE
33.6 Indications for Aortic Valve Surgery in Patients with Al

Indication	AHA/ACC Class
1. Patients with severe symptomatic AI	I
2. Patients with severe asymptomatic AI and LVEF <50%	I
3. Patients with severe AI undergoing open heart or aortic surgery	I
4. Patients with severe asymptomatic AI and normal LV function but severe LV dilation (LVIDd > 7.5 cm or LVIDs >5.5 cm)	IIa
5. Patients with moderate AI undergoing open heart or aortic surgery	IIb
6. Asymptomatic patients with normal EF and moderate LV cavity dilatation (LVEDd 70–75 mm, ESD 50–55 mm)	IIb
7. Patients with asymptomatic severe AI and normal LV function without LV cavity dilation (LVIDd <7.0 cm or LVIDs < 5.0 cm)	III

From Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease) Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;52:e1–e142, with permission from Elsevier.

For patients with aortic root dilatation and significant AI, progression of the aortic diameter >45 mm is generally accepted as an indication (Class IIa) for aortic root and aortic valve surgery.[5] Lower thresholds (>40 mm) may be considered (Class IIb) for patients with Marfan syndrome or bicuspid aortic valves, particularly if the rate of aortic dilatation is accelerating (>0.5 cm/year).[11]

Surgical options for AI include valve repair or replacement. Valve repair may be considered for noncalcified bicuspid valves with substantial AI. Repair results for regurgitant t rileaflet valves have been disappointing. For valve replacement, the decision to use mechanical versus bioprosthetic valves is based on a number of considerations (see discussion above, for AS). By guidelines, patients younger than age 65 years, and patients with end-stage renal disease or other disorders that affect calcium metabolism, should receive mechanical valves.

PULMONIC VALVE DISEASE

Pulmonic Stenosis

Pulmonic stenosis (PS) is nearly always a congenital defect, although very rare cases of acquired disease have been reported with rheumatic heart disease, carcinoid heart disease, and rubella. PS may be a component of more complex congenital diseases, where it is often associated with a VSD; most frequently, however, PS is an isolated congenital defect.[12] Noonan syndrome is classically associated with isolated PS.

PS may be due to valve doming in the setting of commissural thickening, valve dysplasia in the setting of valve thickening and annular hypoplasia, or unicuspid/bicuspid valve pathology (often seen with tetralogy of Fallot).

History and Physical Exam

Symptoms with PS are rare unless the transvalvular gradient exceeds 50 mm Hg, so mild–moderate stenosis is often subclinical. When symptoms are present, they relate to decreased cardiac output and usually include fatigue, dyspnea on exertion, and decreased functional capacity. With more severe disease, presyncope and syncope may develop.

The hallmark of PS on jugular venous examination is a prominent A wave, which reflects increased right ventricular (RV) end-diastolic pressure.

The classic auscultatory findings include a widely split S_2, and a crescendo–decrescendo systolic murmur at the pulmonic position. When murmurs are associated with peripheral pulmonary stenoses, they may be heard over the lateral chest wall, the axillae, or in the back. An ejection click may also be appreciated, which moves earlier in systole as the severity of stenosis increases. Signs of severe stenosis include a late-peaking systolic murmur, decreasing intensity of P_2, and the complete disappearance of the ejection click. Unlike other right-sided valvular lesions, respiration tends to decrease the intensity of the murmur. Clinical signs of right ventricular hypertrophy (RVH) or RV failure do not present until late in the disease.

Diagnostic Studies

The CXR classically shows asymmetric PA enlargement, with a prominent left PA. The heart size is usually normal.

The key finding on echocardiography is the transpulmonic gradient, which is calculated from the peak jet velocity across the pulmonic valve. PS is likely to be severe when the pulmonic jet velocity exceeds 3 m/s (estimated peak gradient 36 mm Hg), at which point cardiac catheterization is recommended (Class I) for further evaluation and consideration of balloon valvuloplasty. Follow-up echocardiography is recommended for surveillance every 5 to 10 years.

Cardiac catheterization is recommended for patients whose echocardiogram is suggestive of severe PS (Class I). Guidelines for treatment (i.e., balloon valvuloplasty)

are based upon peak-to-peak gradient across the PV obtained at catheterization.

Treatment of Pulmonic Stenosis

Endocarditis prophylaxis is no longer indicated for patients with PS, but is reasonable (Class IIa) for patients with cyanotic congenital heart disease or prosthetic material.[7] For patients with elevated gradients or with symptoms, balloon valvotomy is the treatment of choice. Indications for balloon valvotomy are listed in Table 33.7. Class I indications for intervention include symptoms with a peak-to-peak gradient at catheterization of >30 mm Hg, or a peak-to-peak gradient >40 mm Hg even without symptoms. Balloon valvotomy for PS with a peak-to-peak gradient 30 to 39 mm Hg is reasonable (Class IIb).[5]

TABLE
33.7 Recommendations for Valve Intervention in Patients with PS

Indication	AHA/ACC Class
1. Symptomatic PS with peak-to-peak gradient >30 mm Hg	I
2. Asymptomatic PS with peak-to-peak gradient:	
>40 mm Hg	I
30–39 mm Hg	IIb
<30 mm Hg	III

From Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease) Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;52:e1–e142, with permission from Elsevier.

Pulmonary Insufficiency

The main etiologies of significant pulmonary insufficiency (PI) are annular dilation due to pulmonary hypertension, dilation of the PA (which may be idiopathic or secondary to Marfan syndrome), a late complication of tetralogy of Fallot repair, or a primary valve disorder, caused by carcinoid, rheumatic disease, or endocarditis.

Mild PI is quite common in normal hearts, and even moderately severe PI is hemodynamically well tolerated. Over long periods of time, however, severe PI may create a volume and pressure overload on the RV, which leads eventually to RV dilation and failure.

Physical Findings

Pulmonic insufficiency is frequently very difficult to appreciate on physical exam, particularly if the pulmonary pressures are normal. On chest palpation, one may appreciate a hyperdynamic RV. On auscultation, PI may be heard as a low-pitched diastolic murmur along the LSB, which accentuates with respiration.

In the setting of pulmonary hypertension, PI results in a Graham–Steel murmur, a high-pitched, decrescendo murmur heard best along the LSB. It immediately follows an accentuated P_2. With respiration, this murmur also increases in intensity.

Diagnostic Studies

The CXR may variably show RV enlargement.

Key data to be obtained from transthoracic echocardiography include RV size and function, PA size and pressures, and the degree of PI. Stress echocardiography may be used to assess RV function and reserve.

Treatment for Pulmonary Insufficiency

PI usually requires valve surgery only if there is progressive evidence of RV dilatation and failure. Biologic prostheses or homografts are favored because of lower associated thrombotic risk as compared to mechanical prostheses at this position.

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QUESTIONS AND ANSWERS

Questions

1. A 42-year-old man with hypertension, but no prior cardiac history, presents with increasing dyspnea on exertion. Physical exam reveals a heart rate of 75 beats/min (bpm) and blood pressure of 175/67. The jugular venous pattern (JVP) is unremarkable. S_1 is soft, S_2 is normal, and there is an early systolic sound. There is a soft II/VI systolic ejection murmur (SEM) at right upper sternal border (RUSB) radiating to the neck, and a III/VI decrescendo, holodiastolic murmur near LLSB. There is also a low-pitched diastolic rumble heard at the apex. The PMI is laterally displaced. Carotid pulsations are brisk and have a rapid upstroke, immediately followed by a second systolic pulsation. Femoral pulses are normal, and are slightly delayed compared to the radial pulse.
   Which of the following findings would you not expect to see on transthoracic echocardiography?
   a. Fluttering of the anterior mitral leaflet on M-mode echocardiography
   b. Mitral stenosis
   c. Bicuspid aortic valve,
   d. Dilated left ventricle (LV) cavity
   e. Coarctation of the aorta

2. You see a 17-year-old male adolescent in clinic, who is referred to you for evaluation of a murmur. He is well developed and physically active. His heart rate is 62 beats/min (bpm), and his blood pressure is 110/70. His JVP is normal. The cardiac exam shows normal S_1 and S_2. There is no third heart sound. There is a III/VI SEM at the RUSB, which radiates to the carotids, and a soft diastolic murmur along the left sternal border (LSB). With Valsalva, the murmur softens. The carotid pulses are slightly delayed. Which of the following diagnoses is most likely?
   a. Bicuspid aortic valve
   b. Supravalvular aortic stenosis (AS)
   c. Subvalvular AS
   d. Hypertrophic cardiomyopathy (HCM)

3. You see a 25-year-old woman in clinic for a murmur. She is mildly mentally retarded but is sociable and conversational. Her eyes are widely spaced and her ears are low set. Her neck is webbed, and you note that she is rather short. Her JVP has a prominent A wave. She has a pectus excavatum deformity of her chest. Cardiac exam reveals a sternal lift and a III/VI SEM at the LUSB, radiating to the left neck, which decreases with inspiration. You cannot appreciate any clicks. Which of the following statements is not true regarding this woman's condition?
   a. The mode of transmission is autosomal dominant.

b. The genetic defect is linked to elastin.
c. This valvular abnormality is not easily treated with valvuloplasty.
d. ASD is a commonly associated cardiac abnormality.

4. A 75-year-old man with prior bypass surgery is referred to you for shortness of breath and heart failure symptoms. He has a past history of hypertension and chronic obstructive pulmonary disease (COPD). His FEV_1 is 1.6 L. He also complains of occasional exertional angina. A recent adenosine nuclear scan revealed a fixed defect in the inferior wall, but no reversible defects. On gated images, the ejection fraction was 25%.

On physical exam, his heart rate is 80 bpm and his blood pressure is 110/80. He appears fatigued and somewhat frail. His JVP is elevated to 10 cm. He has bibasilar rales on pulmonary exam. Cardiac exam shows a normal S, and a paradoxically split S_2. There is a harsh III/VI systolic ejection murmur at the left sternal border (LSB), which peaks very late in systole and radiates to the carotids. A II/VI holosystolic murmur is appreciated at the apex that radiates to the axilla. Carotid pulsations are delayed.

You order an echocardiogram that confirms the severe LV systolic dysfunction. His LV is mildly dilated. The entire inferior and basal posterior walls are akinetic and thinned. The LAD and LCx territory is hypokinetic and hypertrophied. The aortic valve is heavily calcified and has poor leaflet excursion. Peak and mean gradients across the aortic valve are 27 and 17 mm Hg, respectively. By continuity, the aortic valve area (AVA) is 0.8 cm^2. There is 2+ mitral regurgitation (MR) due to posterior leaflet restriction. What is your next step in this patient's management?

a. Suggest left heart catheterization to pursue percutaneous balloon valvuloplasty.
b. Refer for cardiac surgery for aortic valve replacement (AVR) and MV repair.
c. Institute diuretic therapy and afterload reduction to treat his congestive heart failure (CHF).
d. Order dobutamine stress echocardiography.

5. A 37-year-old woman with an active history of IV drug abuse presents to the emergency department with abrupt-onset shortness of breath. She is tachycardic to 110 bpm and has a systolic blood pressure of 95 mm Hg. Her boyfriend reports that over the past 7 days she has been febrile and anorectic. He also adds that the patient was "born with an abnormal" aortic valve. Which of the following findings is inconsistent with acute aortic insufficiency (AI)?
   a. Diminished S_1 on auscultation
   b. Diastolic MR on echocardiography
   c. A holodiastolic murmur heard at the LSB.
   d. Premature closure of the mitral valve on two dimensional (2-D) echocardiography

6. Which of the following patients requires endocarditis prophylaxis?
   a. A 34-year-old man with bicuspid aortic valve (AV) and moderate AS undergoing dental extraction
   b. A 43-year-old man with mechanical AVR undergoing routine colonoscopy
   c. A 65-year-old woman with bioprosthetic AVR undergoing dental extraction
   d. All of the choices
   e. B and C

7. Which of the following patients would meet criteria for AVR?
   a. A 70-year-old woman undergoing CABG with normal left ventricular ejection fraction (LVEF) and Pk/Mn AV gradients of 45/25 mm Hg
   b. A 35-year-old man with bicuspid aortic valve and asymptomatic severe AI, normal LV systolic function, and LVIDs 6.0 cm
   c. A 75-year-old asymptomatic man with AVA 0.8 cm^2, Pk/Mn AV gradients 80/50 mm Hg, normal LV function, and moderate concentric left ventricular hypertrophy (LVH)
   d. A and B
   e. All of the choices

8. Which of the following patient(s) is/are not indicated for balloon aortic valvuloplasty?

a. An 85-year-old woman with severe symptomatic AS who is unwilling to undergo AVR
b. A 75-year-old man with severe AS and exertional dyspnea who is unable to undergo surgical AVR due to comorbid conditions
c. An 80-year-old man with severe AS who requires surgery for an incarcerated hernia
d. A 78-year-old woman with severe AS and cardiogenic shock
e. A and C

9. Which of the following scenarios describes appropriate, guideline-indicated follow-up of a patient with AS?
   a. Annual transthoracic echocardiogram (TTE) in a 34-year-old woman with bicuspid AV and mean AV gradient 30 mm Hg
   b. TTE every 2 years in a 60-year-old man with mean AV gradient 18 mm Hg
   c. TTE every 2 years in an asymptomatic 73-year-old woman with mean AV gradient 45 mm Hg
   d. Stress TTE in a 68-year-old symptomatic man with mean AV gradient 40 mm Hg

10. A patient comes to see you in clinic due to exertional dyspnea. His PMD was concerned due to a harsh systolic murmur heard on exam. On your exam, there is a harsh, 3/6 systolic murmur heard at the apex radiating to the axilla. Carotid exam reveals preserved upstrokes and no bruits. Based on your exam, you diagnose severe MR. You obtain an echocardiogram. The result is reported as normal LVEF with mild concentric LVH and severe AS with Pk/Mn gradients of 100/60 mm Hg. What is the likely source of discrepancy between your physical exam and the echocardiogram?
    a. The findings are not discrepant; the murmur in patients with severe AS may be heard at the apex and is known as Gallavardin phenomenon.
    b. The continuous wave (CW) Doppler signal measured on the echocardiogram begins at the onset of ventricular systole as seen on the rhythm strip.
    c. The CW Doppler signal measured on the echocardiogram begins approximately 80 milliseconds after the onset of ventricular systole seen on the rhythm strip.
    d. The murmur heard on exam is the Austin-Flint murmur and is therefore confirmatory of the echocardiographic findings.

Answers

1. Answer B: This patient is fairly young and has hypertension with a wide pulse pressure. The cardiac exam suggests a diagnosis of bicuspid aortic valve (younger patient with AI and an ejection click) with significant AI. The holodiastolic murmur is characteristic of chronic AI, and the displaced PMI suggests longstanding disease that has dilated the LV. Likewise, bounding carotids and a bisferiens pulse are classic findings of AI. BAV usually results from fusion of the right and left coronary cusp leaflets, which then causes a posteriorly directed AI jet. This jet frequently hits the anterior leaflet of the mitral valve, which is manifested on M-mode echocardiography as fluttering of the anterior mitral leaflet and on exam as an Austin–Flint murmur. A history of hypertension in a young patient with AI should prompt an evaluation for aortic coarctation, because up to 20% of patients with BAV also have coarctation. On physical exam, the slightly weaker and delayed femoral pulsations suggest that coarctation might be present.

2. Answer C: This patient has typical exam findings of subvalvular stenosis. In practice, subvalvular stenosis can easily be mistaken for native-valve AS. In younger patients, bicuspid or unicuspid valves are the main differential diagnoses—both of which can have findings of AS and AI. However, the absence of any ejection sound argues against aortic valvular pathology. HCM should also be considered in a patient this age; the slight delay in the carotids and the failure of the murmur to augment with Valsalva make HCM less likely.

3. Answer B: This patient has Noonan syndrome, an autosomal dominant disease characterized by mild mental retardation, characteristic facial features, and a variety of cardiac abnormalities—the most common of which are pulmonary stenosis, peripheral pulmonary stenosis, ASDs, and HCM. The physical exam findings are typical of pulmonic stenosis (PS) with increased A wave, RV left, and a systolic ejection murmur. Unlike other cases of congenital PS, patients with Noonan syndrome tend to

have dysplastic pulmonary leaflets that do not cause an ejection click. They also are frequently not amenable to balloon valvuloplasty. Mutations in the gene for elastin are associated with supravalvular AS.

4. Answer D: This patient has low-gradient AS with moderately severe LV dysfunction. His chief complaint is consistent with AS, but could be secondary to CHF or COPD. His physical exam, with narrow pulse pressure, paradoxically split S_2, and SEM radiating to the carotids, all suggest AS. Loss of A_2 is also consistent with severe AS. The nuclear stress test argues against ischemia. A relatively small fixed defect on nuclear study and preserved wall thickness in the left coronary territory both suggest that the LV dysfunction may be out of proportion to coronary artery disease (CAD), and may be secondary to valvular disease. For patients with low-gradient AS, dobutamine echo can be very helpful in assessing true stenosis versus pseudostenosis. In this patient, we would expect dobutamine to result in an increased EF (contractile reserve), increased gradients across the valve, and a valve area that remained severe. If he has pseudostenosis and a cardiomyopathy unrelated to the valve disease, dobutamine will increase cardiac output but will not result in significant increases in the transaortic gradient or AVA. Patients with LV dysfunction who have contractile reserve and severe AS should undergo AVR. This patient has no contraindications to surgery, and thus valvuloplasty should not be considered definitive treatment.

5. Answer C: Acute AI typically has a brief, early diastolic murmur. Rapid equilibration of aortic and LVED pressures causes termination of the murmur by middiastole. All of the remaining answers are typical of acute AI. A diminished S_1 may be seen in acute or chronic AI.

6. Answer C: The guidelines provide a Class IIa indication for endocarditis prophylaxis in patients with prosthetic valve material undergoing dental procedures that disrupt the gingiva or the periapical region or perforate the oral mucosa. Bicuspid AS alone is no longer an indication for prophylaxis in the most recent endocarditis guidelines. Nondental procedures (TEE, EGD, colonoscopy) do not require prophylaxis without active infection.

7. Answer D: In patients with moderate AS who are undergoing open heart surgery (OHS), it is reasonable (Class IIa) to perform concomitant AVR. In asymptomatic patients with severe AI, the presence of LV cavity dilation (LVIDd > 7.5 cm, LVIDs >5.5 cm) is a reasonable indication (Class IIa) for AVR even in the presence of normal LV function. Patients with asymptomatic severe AS may be considered (Class IIb) for isolated AVR if the AS is thought to be "extremely severe" on the basis of AVA < 0.6 cm^2, mean gradient >60 mm Hg, or peak AV jet velocity >5 m/s; the patient in (c) does not meet these criteria and is therefore a Class III (not recommended) indication for AVR.

8. Answer E: Balloon aortic vavuloplasty may be considered (Class IIb) as a palliative treatment for symptomatic patients with severe AS unable to undergo traditional surgical AVR, or as a bridging strategy for patients who are too high risk for surgical AVR at a given point in time. It is not indicated (Class III), however, for patients as an alternative to surgical AVR (a) or for patients requiring urgent noncardiac surgery (c). Utmost caution is required on the part of the anesthesia team to avoid hypotension in patients with severe AS undergoing noncardiac surgery, as preload dependence is imperative in maintaining hemodynamic stability.

9. Answer A: The ACC guidelines provide a Class I indication for serial echocardiography every 3 to 5 years for patients with mild AS and every 1 to 2 years for patients with moderate AS. For patients with severe AS, surveillance echocardiography is recommended on an annual basis, or even more frequently if clinically indicated. Patients with symptomatic AS should not have stress testing (Class III).

10. Answer B: A common misinterpretation during echocardiography is the mistaken sampling by CW Doppler of the MR envelope as the aortic outflow. MR velocity is usually in the range of 4 to 5 m/s and characteristically begins at the time of ventricular systole. In contrast, aortic outflow begins after the period of isovulmetric contraction, which on average is approximately 80 milliseconds. Gallavardin phenomenon is present when the musical component of the AS murmur is heard at the apex; it does not typically radiate to the axilla, and this patient did not have evidence of AS. The Austin-Flint murmur is a diastolic murmur of MS heard in patients with severe AI and is thought to be due to premature closure of the MV during diastole due to the eccentric jet of AI hitting the anterior MV leaflet.

CHAPTER

Mitral and Tricuspid Valve Disease

William J. Stewart

Mitral valve disease is a common valvular abnormality, resulting from various etiologies and having well-understood, varied, and interesting clinical manifestations. Tricuspid valve disease is less common, occurring most often as a functional result of left-sided heart disease and/or pulmonary hypertension.

MITRAL VALVE ANATOMY

The mitral valve apparatus consists of anterior and posterior leaflets, chordae tendineae, anterolateral and posteromedial papillary muscles, and mitral annulus. To be inclusive, it also includes the atrial and ventricular myocardium. Mitral valve dysfunction may result from aberrations of any portion of the mitral valve apparatus, as a result of mechanical, traumatic, infectious, degenerative, congenital, or metabolic causes.

MITRAL VALVE PROLAPSE

Mitral valve prolapse (MVP) is found in approximately 2% of the population and is equally common in men and women. It is the most common cause of mitral regurgitation (MR) in the United States. Most such patients have a minor amount of MR and therefore a benign prognosis, with no significant cardiovascular symptoms or manifestations such as congestive heart failure. The diagnosis of MVP is made usually by bedside physical examination, finding a mid-to-late systolic click or multiple clicks, sometimes associated with a late systolic or pansystolic murmur. The murmur becomes earlier and louder with standing and the Valsalva maneuver, resulting from reduction in preload, which brings the mitral leaflets closer together before left ventricular (LV) contraction. The murmur of mitral prolapse becomes softer and later with squatting due to an increase in preload.

The diagnosis of MVP is best confirmed echocardio-graphically. The best two-dimensional (2-D) echocardiogram criterion is leaflet displacement beyond the line of the mitral annulus in the long-axis view. Because of the saddleshaped configuration of the mitral valve, caution must be taken when MVP is diagnosed only from parasternal long-axis, apical four-chamber, and apical two-chamber views. M-mode criteria require 2 or 3 mm of displacement, either as late systolic or holosystolic hammocking (Fig. 34.1). The presence of an eccentric jet direction of MR makes the diagnosis of MVP more likely. In general, prolapse with leaflet thickness >5 mm is considered "classic" MVP, whereas prolapse with thinner valve leaflets is considered "nonclassic prolapse."

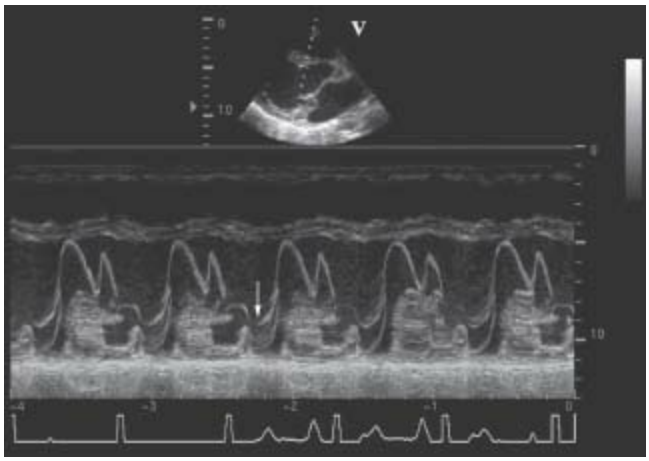


FIGURE 34.1 M-mode echocardiography showing late-systolic prolapse (arrow) of the mitral valve.

Accepted indications for performing echocardiographic study in mitral prolapse include establishing the diagnosis, determining the severity of MR, evaluating leaflet morphology, and defining LV size and function.[1] The list implies that echocardiography should be used when it can add information to findings available from history and the physical examination. Indications for echocardiography may also include exclusion of MVP in patients diagnosed with MVP when there is no clinical evidence to support the diagnosis (Table 34.1). Subsequent or serial echocardiograms are not usually necessary if the patient is asymptomatic, unless there are clinical indications of severe or worsening MR.

TABLE
34.1 Evaluation and Management of the Asymptomatic Patient in MVP

Class I

1. Echocardiography is indicated for the diagnosis of MVP and assessment of MR, leaflet morphology, and ventricular compensation in asymptomatic patients with physical signs of MVP. *(Level of Evidence: B)*

Class IIa

1. Echocardiography can effectively exclude MVP in asymptomatic patients who have been diagnosed without clinical evidence to support the diagnosis. *(Level of Evidence: C)*
2. Echocardiography can be effective for risk stratification in asymptomatic patients with physical signs of MVP or known MVP. *(Level of Evidence: C)*

Class III

1. Echocardiography is not indicated to exclude MVP in asymptomatic patients with ill-defined symptoms in the absence of a constellation of clinical symptoms or physical findings suggestive of MVP or a positive family history. *(Level of Evidence: B)*
2. Routine repetition of echocardiography is not indicated for the asymptomatic patient who has MVP and no MR or MVP and mild MR with no changes in clinical signs or symptoms. *(Level of Evidence: C)*

From Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2006;48:e1–e148, with permission from Elsevier.

Most patients with mitral prolapse, even if there is a murmur, or if the echocardiogram shows significant MR, do not need antibiotic prophylaxis for endocarditis. Although that has been common practice prior to new guidelines that were published several years ago, the newest guidelines do not advise prophylaxis for native valve disease. Prophylaxis during procedures likely to cause bacteremia (including teeth cleaning) is recommended if the patient has had previous endocarditis or if a prosthetic valve has been implanted (Table 34.2).

TABLE
34.2 Recommendations for Infective Endocarditis Prophylaxis in Valvular Heart Disease

Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa:

- Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair. *(Level of Evidence: B)*
- Patients with previous infective endocarditis. *(Level of Evidence: B)*
- Patients with CHD. *(Level of Evidence: B)*
- Unrepaired cyanotic CHD, including palliative shunts and conduits. *(Level of Evidence: B)*
- Completely repaired congenital heart defect repaired with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure. *(Level of Evidence: B)*
- Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (both of which inhibit endothelialization). *(Level of Evidence: B)*
- Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve. *(Level of Evidence: C*

Adapted from Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Valvular Heart Disease). J Am Coll Cardiol. 2008;52:e1-e142; Wilson W Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2007;116:1736-1754. Ref. (5,6).

The natural history of MVP is frequently benign. Follow-up studies in large population samples show that most patients with MVP do quite well, and most do not develop any significant congestive heart failure, atrial fibrillation (AF), stroke, or syncope. After a prolonged asymptomatic interval, a small percentage of patients with MVP develop more severe MR, ruptured mitral valve chordae (flail), left atrial and ventricular enlargement, or AF.[2] In addition, with gradual progression of MR, LV dilatation and dysfunction may occur, leading to congestive heart failure. A substantial negative effect on survival has been seen in patients who develop LV dysfunction, AF, left atrial enlargement, age >50 years, and flail mitral leaflet. Recently, quantitatively severe regurgitation has also been associated with adverse prognosis.[3,4]

The development of infective endocarditis in patients with MVP is another mechanism of increase in MR. Predictors of infective endocarditis in patients with MVP include male gender, age >45 years, the presence of MR, and leaflet thickening and redundancy Patients with MVP with significant MR also have a small but significantly increased risk of sudden death, most likely secondary to ventricular tachyarrhythmias, which may be predicted by concomitant systolic dysfunction.

MVP has been associated with a pattern of multiple nonspecific symptoms such as palpitations, atypical chest pain, syncope, and anxiety, and this constellation has been

frequently termed the “mitral valve prolapse syndrome.” No such associations have been found in multiple studies, but a small group of patients may have a complex set of symptoms associated with MVP For example, a few studies have shown a pattern of autonomic dysfunction, with increased catecholamines and decreased vagal tone, in patients with MVP.

The mainstay of medical management of patients with MVP is reassurance. Beta-blockers are the treatment of choice for patients with increased adrenergic symptoms such as palpitations, chest pain, or anxiety, though some of these effects may be the placebo effect. In patients with MVP and transient ischemic attacks (TIAs) or stroke, the treatment is usually just aspirin (81 to 325 mg/d). Warfarin may be indicated in some patients with MVP and recurrent TIA or stroke. In addition, in patients with AF, there should be a low threshold for instituting anticoagulation, individualized for the patient’s risks of stroke versus bleeding. Surgery for MVP is only a consideration in patients with more severe MR, similar to other forms of nonischemic MR, which is discussed later.

ACUTE MITRAL REGURGITATION

Acute MR is an uncommon medical condition of grave importance, requiring urgent medical and often surgical intervention. Acute MR also occurs due to disruption of mitral valve leaflets, chordae tendineae, or papillary muscles that may result from infective endocarditis, acute myocardial infarction, trauma, or rheumatic fever. The most common cause is probably acute myocardial ischemia leading to acute LV enlargement, severe MR, and acute pulmonary edema.

High left atrial pressure and reduced left atrial compliance secondary to severe MR are the mechanisms of pulmonary edema. A less common complication of severe acute MR is reduced forward flow with cardiogenic shock. Acute MR usually presents as sudden and marked increase in congestive heart failure symptoms, with weakness, fatigue, dyspnea, and sometimes respiratory failure and shock. Peripheral vasoconstriction, pallor, and diaphoresis are usually associated presenting signs. In some patients, a loud systolic murmur and a diastolic rumble or third heart sound are heard. In others, a very soft murmur or no murmur is heard, because the severity of MR and the lack of atrial compliance lead to midsystolic equalization of pressures between the left atrium and ventricle midway through systole. In addition, the acute nature of the condition obscures the mitral murmur by other aspects of the patient’s distress, including orthopnea, precluding a good exam in the left lateral decubitus position.

Echocardiography is the diagnostic procedure of choice. In acute coronary syndromes, emergency catheterization and cardiac surgery are life saving. There is little need for contrast LV angiography, except in cases where there is discrepancy in clinical and noninvasive findings. In some cases, hemodynamic measurements and monitoring may also be helpful in management.

Acute MR after myocardial infarction is discussed in detail in another chapter of this book. It is the cause of about 7% of cases of cardiogenic shock after myocardial infarction. The onset of the MR is most commonly between days 2 and 7 after myocardial infarction. The MR in most patients, like our example at the beginning of this chapter, involve a functional mechanism, from apical tethering of normal leaflets as a consequence of acute LV dysfunction and enlargement. Focal infarction most commonly involves the posteromedial papillary muscle, because it derives its blood supply solely from one artery, the right coronary artery. In contrast, the anterolateral papillary muscle has a dual blood supply, often derived partly from the circumflex and partly from left anterior descending artery. Despite the devastating effects of acute severe MR, the infarct size is not always large, with some smaller infarctions (<25% of LV), with a mild to moderate enzyme leak.

Hemodynamic stabilization with prompt surgical intervention is the most effective therapy for most cases of acute MR. Vasodilator therapy with intravenous nitroprusside and nitroglycerin may lead to decreased MR, increased forward flow, and reduced pulmonary congestion. Intra-aortic balloon pump (IABP) counterpulsation is also effective in reducing regurgitant volume and LV filling pressure, while increasing forward output and mean arterial pressure, and is frequently used for initial stabilization, as a bridge to prompt surgical intervention. However, if appreciable aortic regurgitation (AR) is present, IABP is contraindicated because it worsens the AR.

CHRONIC MITRAL REGURGITATION

The physiology of MR includes a number of classical features (Fig. 34.2). The patient with MR of any cause usually has a pansystolic murmur, best audible at the apex, often radiating to the axilla. In severe MR, this murmur also may be heard in the left paravertebral area of the back. The pulmonic component of the second heart sound may be louder than normal if there is pulmonary hypertension. An inflow sound (a third heart sound or an early diastolic rumble) at the apex may be heard in some patients if the MR is severe. The apical impulse is enlarged, displaced laterally, and exaggerated, reflecting the hyperdynamic LV motion. Left atrial pressure (and pulmonary capillary wedge pressure) is elevated by the regurgitant flow, with an associated systolic V wave, though its height is not a reliable measure of the severity of MR. The left atrium and the diastolic size of the left ventricle are enlarged. As pulmonary venous pressure becomes elevated, dyspnea or even pulmonary congestion may occur. In the later phase, pulmonary hypertension may develop, causing pulmonary artery dilation, right-sided heart failure, and systemic venous congestion.

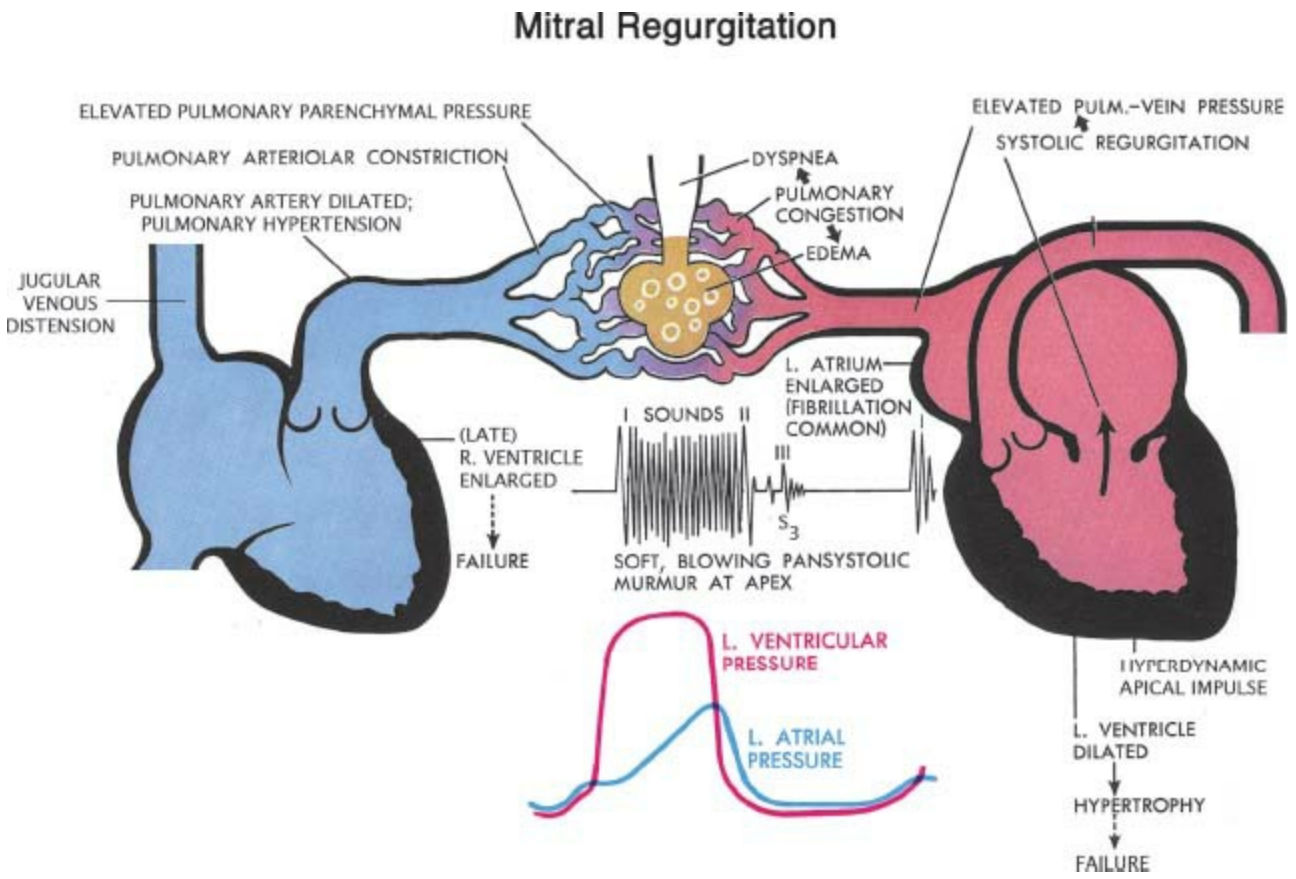


FIGURE 34.2 Schematic diagram representing pathologic complications of chronic MR. (Netter illustration adapted from www.netterimages.com. © Elsevier Inc. All rights reserved.)

Untreated chronic mitral valve abnormalities (including regurgitation or stenosis) often lead to a common endpoint, with left atrial enlargement, pulmonary hypertension, AF, and left-sided congestive heart failure. If the situation is not corrected, it may progress to include left atrial thrombosis, hemoptysis, and right-sided heart failure.[7] Cardiac output is usually normal in the early phases, but may be reduced in the later phases of the disease if the MR goes untreated.

The natural history of chronic MR may involve many years of being asymptomatic, the so-called compensated phase of MR. In early years, chronic MR leads to increased LV size and mass and increased LV end-diastolic volume associated with a normal or elevated ejection fraction. At this stage there are few or no symptoms, because the dilated and compliant left atrium and LV allow accommodation of the regurgitant volume at normal filling pressures. However, as these mechanical changes progress, LV contractile dysfunction and hemodynamic derangements begin to occur, including pulmonary congestion, heart failure symptoms, and increases in LV end-systolic and end-diastolic diameter. Reduced forward flow is a very late occurrence.

The chest x-ray often shows left atrial enlargement with a double-density and widened carina, with no other findings early in the course of chronic MR. Later, the left ventricle dilates and there may be signs of pulmonary venous congestion. The lateral chest x-ray may show posterior protrusion of the left atrial cavity, a prominent

pulmonary trunk, or small pleural effusions.

After clinical evaluation, a transthoracic echocardiogram (TTE) is useful for determining the MR severity, mechanism, etiology, presence of flail, LV size and function, left atrial size, abnormalities of other valves, and right ventricular (RV) systolic pressure (Table 34.3). It is also useful for assessing serial changes in LV size and function and evaluating the patient after a change in symptoms. An exercise echo is often useful for determining the change with exercise in LV size, LV function, or RV systolic pressure, and for discovering inducible symptoms or arrhythmias. Occasionally a transesophageal echocardiogram may be needed to better assess the severity and etiology of MR (Table 34.4). An exercise echocardiogram is often useful for determining the severity and effect of the disease on the patient's exercise hemodynamics. It helps to detect latent myocardial dysfunction, and inducible problems not present at rest including pulmonary hypertension, arrhythmias, symptoms, and decreased ejection fraction. Cardiac catheterization for left ventriculography (Fig. 34.3) and hemodynamic measurements is helpful in rare specific conditions. Magnetic resonance imaging may also be of value, but its routine use in management of patients with chronic MR is unproven.

TABLE
34.3 Indications for Transthoracic Echocardiography in MR

Class I

1. Transthoracic echocardiography is indicated for baseline evaluation of LV size and function, RV and left atrial size, pulmonary artery pressure, and severity of MR (Table 34.4) in any patient suspected of having MR. (*Level of Evidence: C*)
2. Transthoracic echocardiography is indicated for delineation of the mechanism of MR. (*Level of Evidence: B*)
3. Transthoracic echocardiography is indicated for annual or semiannual surveillance of LV function (estimated by ejection fraction and end-systolic dimension) in asymptomatic patients with moderate to severe MR. (*Level of Evidence: C*)
4. Transthoracic echocardiography is indicated in patients with MR to evaluate the MV apparatus and LV function after a change in signs or symptoms. (*Level of Evidence: C*)
5. Transthoracic echocardiography is indicated to evaluate LV size and function and MV hemodynamics in the initial evaluation after MV replacement or MV repair. (*Level of Evidence: C*)

Class IIa

1. Exercise Doppler echocardiography is reasonable in asymptomatic patients with severe MR to assess exercise tolerance and the effects of exercise on pulmonary artery pressure and MR severity. (*Level of Evidence: C*)

Class III

1. Transthoracic echocardiography is not indicated for routine follow-up evaluation of asymptomatic patients with mild MR and normal LV size and systolic function. (*Level of Evidence: C*)

From Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol.2006;48:e1–e148, with permission from Elsevier.

TABLE
34.4 Indications for TEE in MR

Class I

1. Preoperative or intraoperative TEE is indicated to establish the anatomic basis for severe MR in patients in whom surgery is recommended to assess feasibility of repair and to guide repair. *(Level of Evidence: B)*
2. TEE is indicated for evaluation of MR patients in whom transthoracic echocardiography provides nondiagnostic information regarding severity of MR, mechanism of MR, and/or status of LV function. *(Level of Evidence: B)*

Class IIa

1. Preoperative TEE is reasonable in asymptomatic patients with severe MR who are considered for surgery to assess feasibility of repair. *(Level of Evidence: C)*

Class III

1. TEE is not indicated for routine follow-up or surveillance of asymptomatic patients with native valve MR. *(Level of Evidence: C)*

From Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2006;48: e1–e148, with permission from Elsevier.

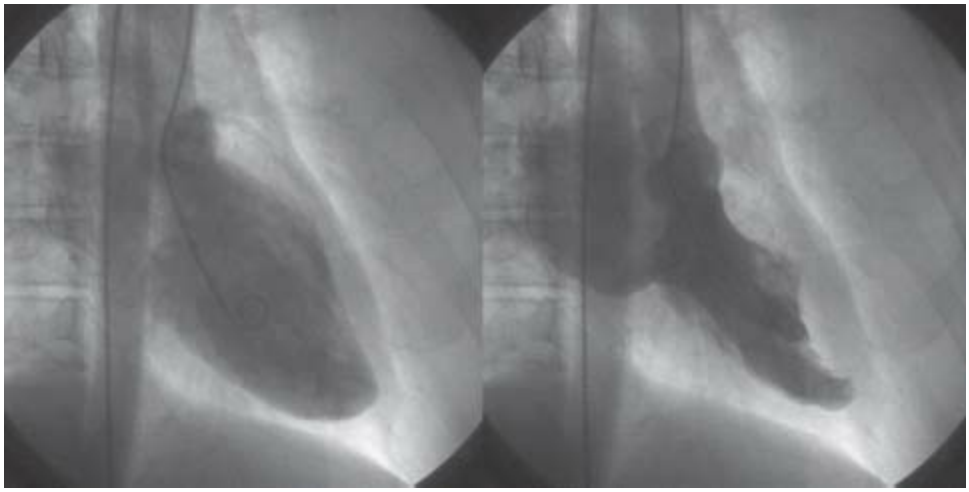


FIGURE 34.3 Left ventriculogram in the RAO projection in diastole **(left)** and systole **(right),** showing severe MR that completely fills the left atrium.

MECHANISM OF MITRAL REGURGIATION

The mechanism of MR can be determined by echocardiography by looking at leaflet motion and color Doppler jet direction.[8] First, the patient's leaflets are categorized by 2-D echocardiography into those with normal, excessive, or restricted motion. Then

additional information is gained by looking at the location, and direction of the regurgitant jet by color Doppler.

Mitral valve disease may have numerous causes, including myxomatous degeneration, ischemic, rheumatic, congenital, endocarditis, autoimmune disorders, and post radiation valve lesions. In the last half-century, there has been a remarkable increase of the frequency of myxomatous degeneration in surgical populations, with a decline in postinflammatory (rheumatic) cases, while ischemic- and infective endocarditis–associated MR have continued at a relatively low frequency.

In myxomatous degeneration, the most significant abnormality is abnormal elasticity of various portions of the mitral valvular apparatus, including the mitral annulus, chordae tendineae, and leaflets. There may be a variable amount of redundancy and enlargement of the leaflets (which, in the extreme is called Barlow syndrome) and chordae (sometimes called fibroelastic deficiency). In long-axis views, it is easy to see which leaflet is moving into the atrial side of the coaptation line in systole, indicating prolapse or flail. Additionally, the direction of the regurgitant jet provides supplemental diagnostic information (Fig. 34.4). In patients with excessive leaflet motion, the jet is directed to the opposite side of the most affected leaflet. Intercommissural views (transthoracic apical two-chamber and midesophageal transesophageal views aligned parallel to the intercommissural line at about 60 degrees multiplane angle) are useful for determining which portion of a leaflet is abnormal. Parasternal short axis and the "surgeon's view" from the left atrium by three dimensional (3-D) echo also is helpful in appreciating the exact location of various lesions (Fig. 34.5) and differentiating the presence of multiple mitral abnormalities.

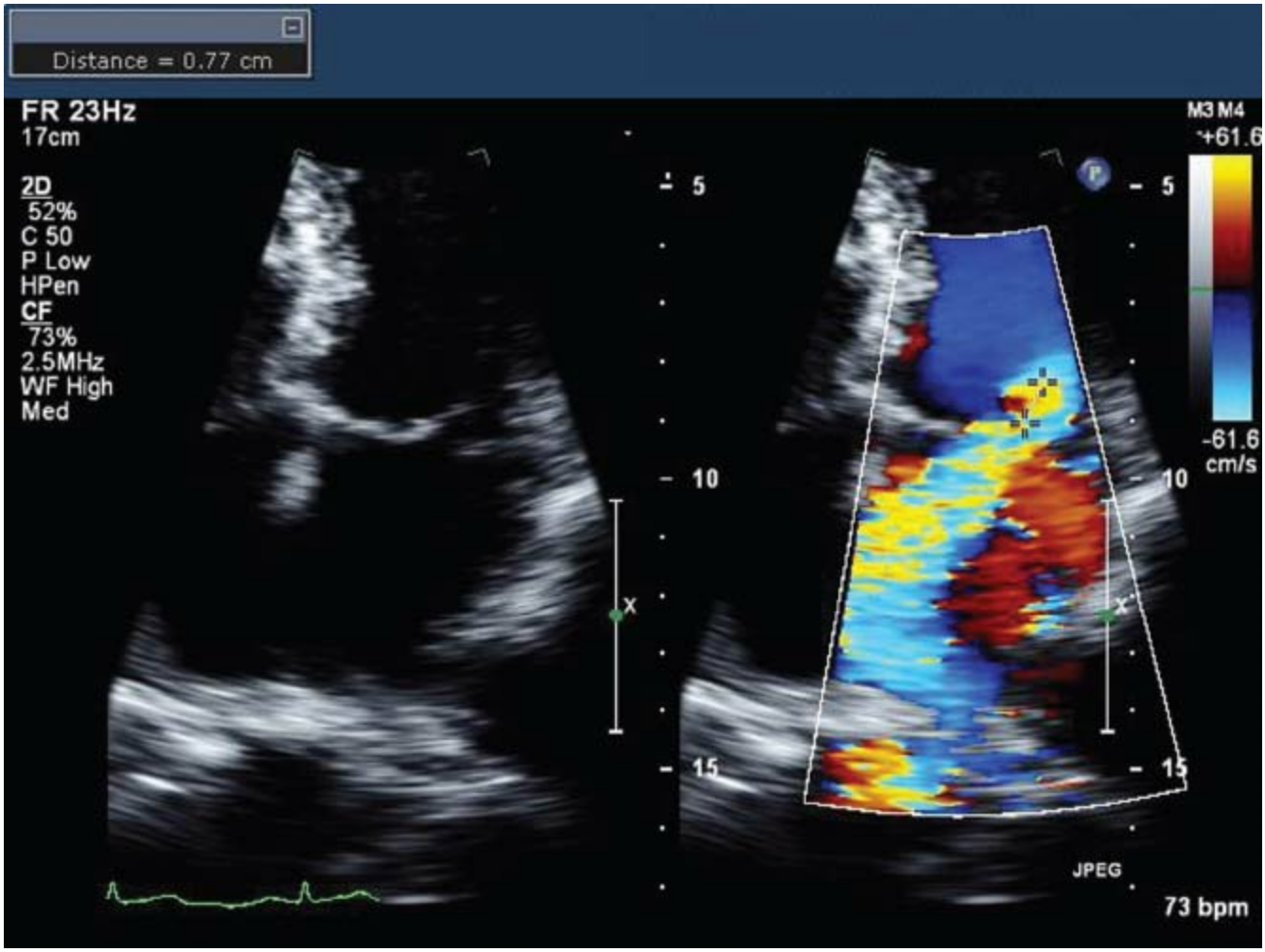


FIGURE 34.4 Transthoracic apical four-chamber 2-D echo image **(left)** and color Doppler image **(right)** in a patient with posterior leaflet flail. Note that the MR jet is deflected to the opposite (anteromedial) side of the left atrium by the unsupported posterior leaflet. Also note the flow convergence on the LV side of the jet, with a measured aliasing radius of 0.77 cm, from which a ROA of 0.46 cm^2 was calculated, based on a measured MR maximum velocity of 505 cm/s.

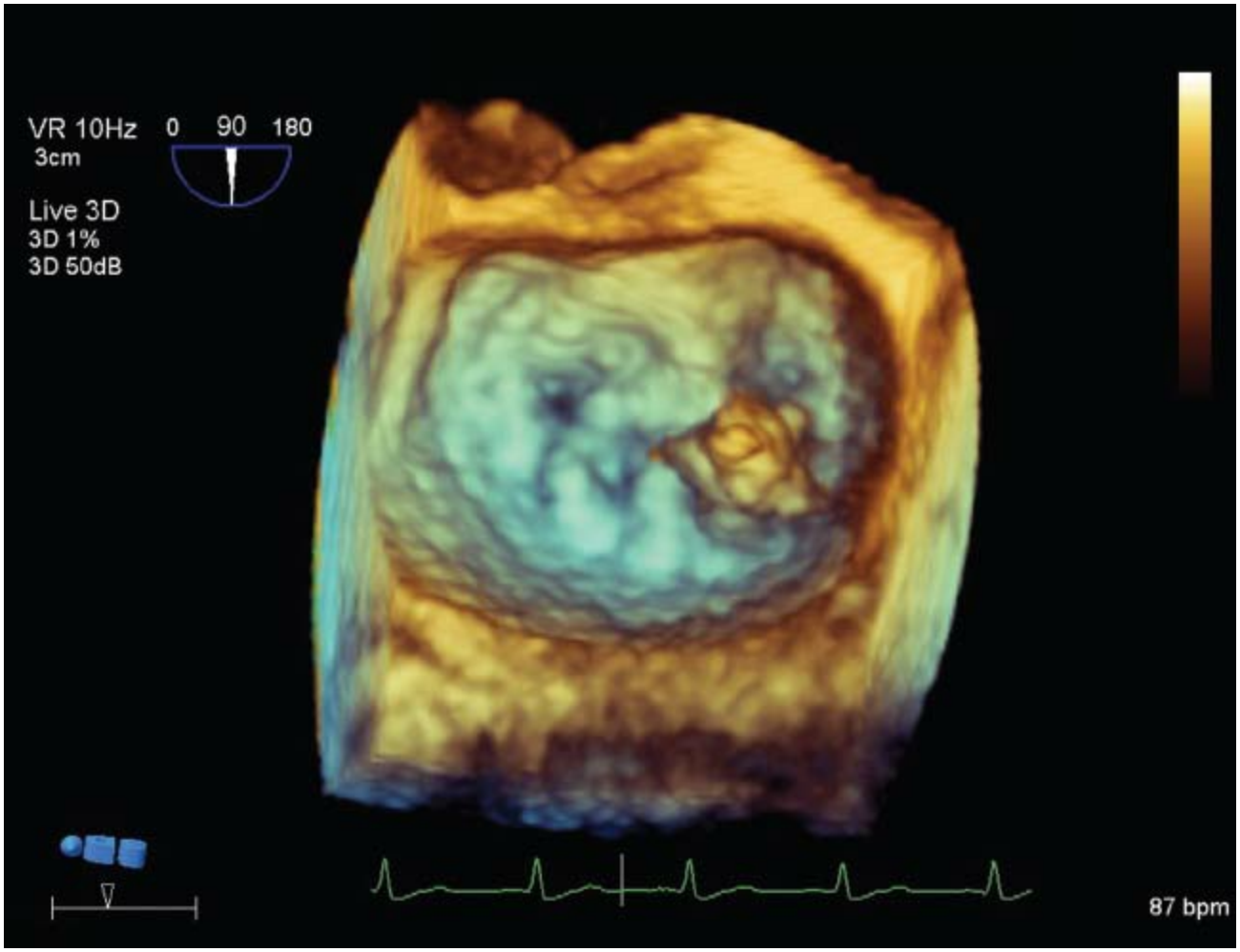


FIGURE 34.5 Transesophageal 3-D echo image using the "surgeon's view," showing that the morphology of the mitral valve causing regurgitation involved a flail portion (possible vegetation) located at the medial commissure (to the right on the image).

Rheumatic heart disease is characterized by leaflet thickening, diastolic mitral doming, valvular and subvalvular fibrosis, and various degrees of systolic and diastolic restriction of leaflet motion. In most cases of restriction involving both leaflets, the jet of MR is central. In some patients, the posterior leaflet is more restricted and the jet direction is posterior.

Ischemic MR most commonly represents "functional MR," which results from remodeling, enlargement, and "sphericalization" of the left ventricle. Functional MR from nonischemic cardiomyopathy is very similar. Both are caused by "apical tethering" of normal leaflets (Fig. 34.6). The length of mitral tissue, including the leaflets, chordae, and papillary muscle, is fixed. As the left ventricle dilates, often after myocardial infarction, the LV wall and papillary muscles are displaced outward, which tethers all or part of the mitral leaflets downward away from the left atrium, reducing the amount of leaflet tissue available for coaptation. In many cases, the result is MR, with a central, or in some cases, a posterior jet direction. In rare cases, a focal infarction may cause elongation or disruption of the papillary muscle, leading to excessive leaflet motion

(often involving both leaflets) most commonly the medial side of both leaflets from medial papillary muscle abnormalities.

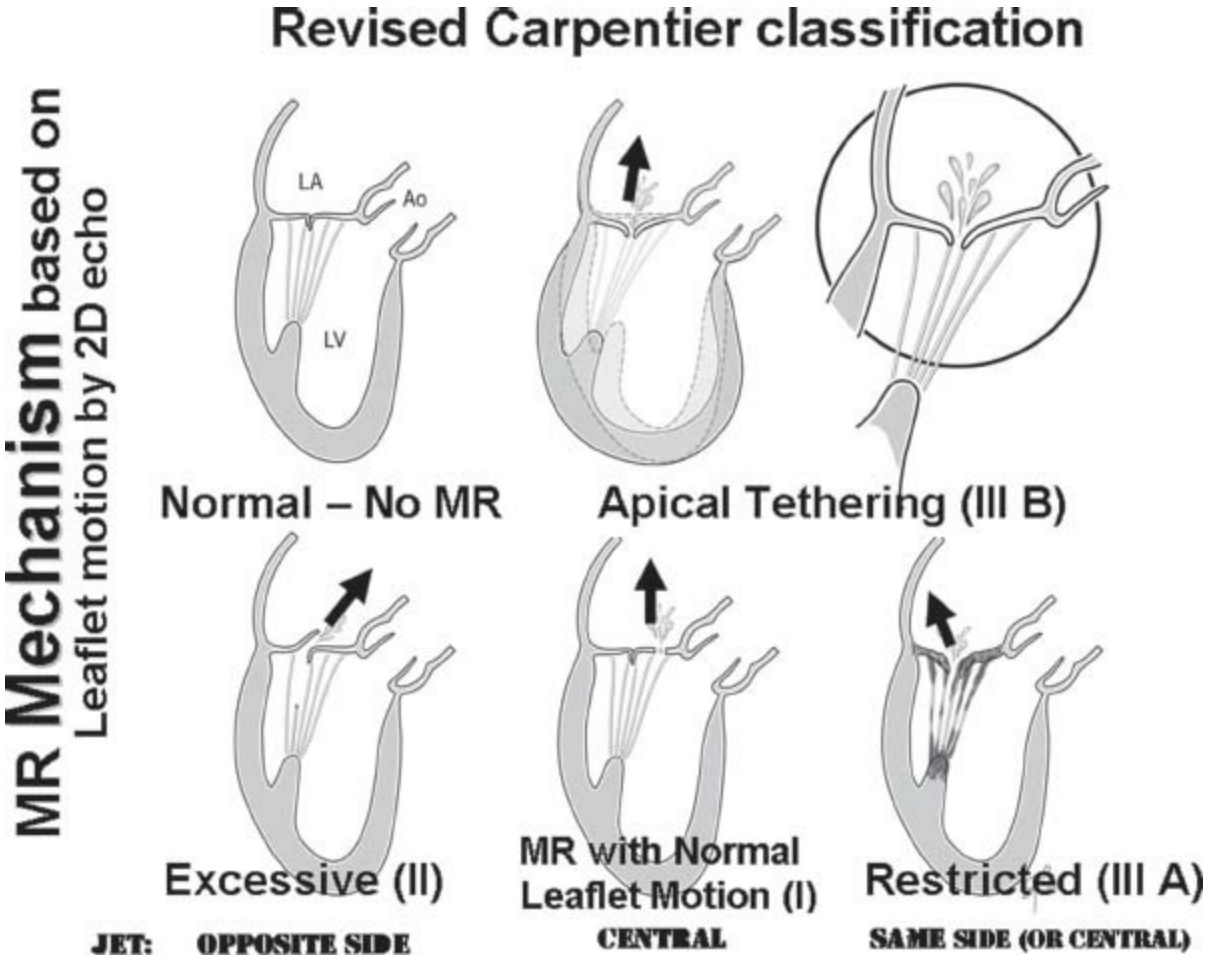


FIGURE 34.6 Artist's renderings of the mechanisms of MR defined by determination of leaflet motion by echo imaging (similar to the Carpentier classification (I, II, IIIa, and IIIb) and determination of jet direction using color Doppler. Apical tethering, often from ischemic heart disease, due to LV enlargement (Carpentier Class IIIb) is often called "functional" MR. Though the annulus may be dilated in proportion to the ventricular enlargement, the primary problem is the ventricle, not the annular dilation.

Mitral valve endocarditis can cause leaflet or chordal disruption, flail, and perforations. These often cause MR with associated nodular hypermobile densities (vegetations) that are the echocardiographic hallmarks of the disease. Care should be taken to look at adjacent valves and the perivalvular tissue looking for abscess formation or paravalvular leakage. MR secondary to the phospholipid antibody syndrome (the Lupus anticoagulant) is associated with symmetric thickening of leaflets, noninfected vegetations, and, at a later stage of the disease, fibrosis and leaflet restriction.

QUANTITATION OF MITRAL REGURGITATION

MR may be quantitated using a variety of echo and Doppler methods, including spatial

mapping, flow convergence, pulmonary vein velocity patterns, vena contracta width, continuous-wave Doppler density and shape, and quantitation of antegrade valvular flow volumes. It is best to use a "weighted average" of multiple methods, emphasizing more the methods that have good-quality data in that patient.[9]

The flow convergence method, also called the proximal isovelocity surface area (PISA) method, involves assessing the color images on the LV side of the MR (Fig. 34.7).[10]

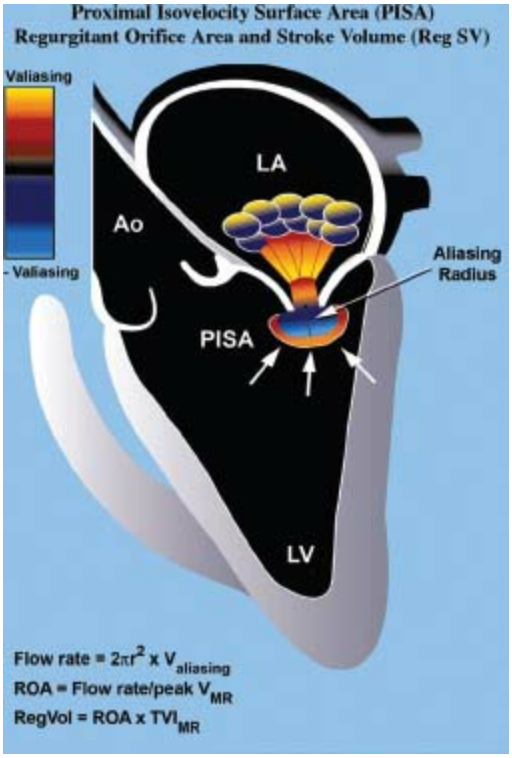


FIGURE 34.7 Method of quantifying the severity of MR using the PISA method (see text for details). (Adapted from Savage RM, Aronson S, Thomas JD, et al. Comprehensive Textbook of Intraoperative Transesophageal Echocardiography. Lippincott Williams & Wilkins. Chapter 28, 2005:512.)

This flow convergence zone is the location where the blood is accelerating, as the flow stream narrows progressively to the regurgitant orifice, where there is a pressure drop from LV pressure to left atrial pressure. Color Doppler tracks the location of increases in velocity on the LV side of the regurgitant orifice and shows this as color aliasing in the proximal convergence zone. When the shape of the aliasing contour is hemispheric, one can calculate the surface area of the aliasing hemisphere from the radius of the hemisphere. Flow can therefore be calculated from the aliasing velocity (v), extracted from the "color bar" (reflecting machine settings), and the measured radius (R) measured from the center of the jet to the transition of color aliasing. When this is combined with the maximum velocity, the maximum systolic area of the regurgitant orifice can be calculated according to the formula $2\pi R^2 v$ divided by maximum systolic velocity through the valve (V_{max}) obtained by continuous-wave Doppler. The advantage

of this formula is that it calculates the actual size of the regurgitant lesion, a fundamental parameter of valve integrity, which is less load dependent than other parameters. A maximum instantaneous regurgitant orifice area (ROA) > 0.4 cm^2 is indicative of severe regurgitation, whereas <0.2 cm^2 is considered mild.

Pulmonary vein flow profiles (Fig. 34.8) are also useful for determination of severity of MR.[11] The normal pulmonary vein pattern includes a velocity during ventricular systole that is higher than antegrade velocity during diastole, a pattern that persists in mild and sometimes moderate MR. When the regurgitation is moderate or moderately severe, the systolic velocity of pulmonary vein flow becomes blunted, with systolic velocity less than diastolic velocity. With even more MR, there is cessation of systolic flow. In patients with severe MR, in one or the other pulmonary vein profile, there is often reversal of systolic flow, with retrograde flow occurring, away from the left atrium during ventricular systole. This occurs because of the large V wave during ventricular systole in the left atrial pressure, which transiently becomes higher than pulmonary parenchymal pressure.

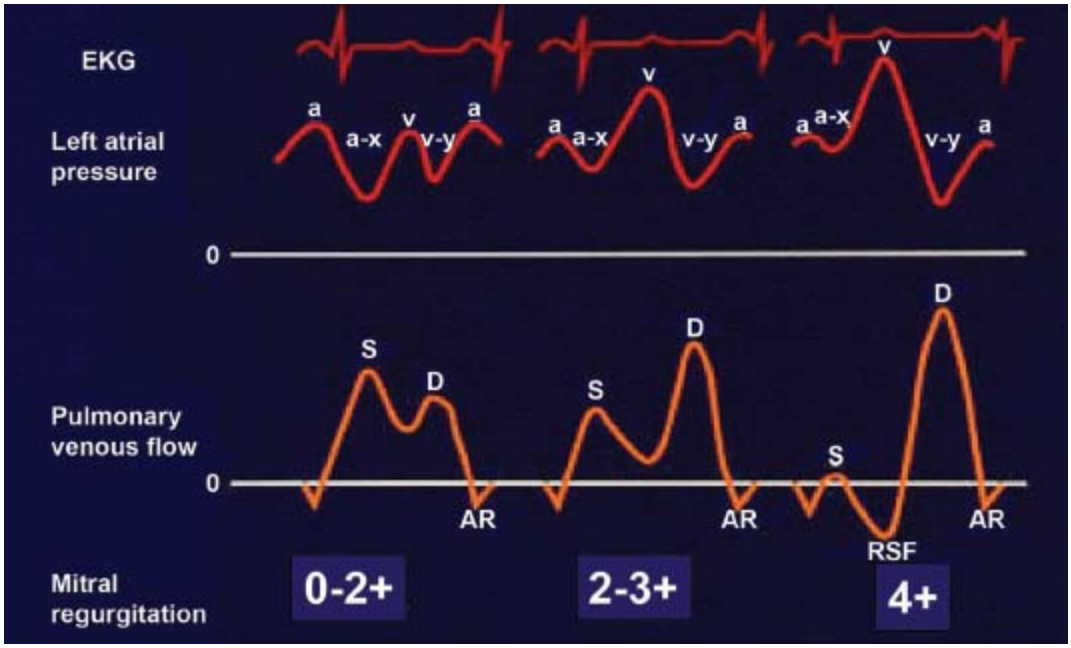


FIGURE 34.8 Stylistic ECGs, left atrial pressure waveforms, and pulmonary vein pulsed Doppler velocity recordings, in three patients: normal or mild or moderate MR (on the left), moderately severe or 2 to 3+ MR (in the middle); and severe, 4+ MR (on the right). Note the reversal of systolic flow (RSF) associated with severe MR, which results from the systolic V wave in the left atrial pressure. (Adapted from Klein AL, Obarski TP, Stewart WJ, et al. Transesophageal Doppler echocardiography of pulmonary venous flow: A new marker of mitral regurgitation severity. J Am Coll Cardiol. 1991;18:518–526.)

Medical management of patients with MR includes diuresis to correct any volume overload. Rate and rhythm control, often with beta-blockers, is often needed because many patients have AF. Aggressive blood-pressure control and risk-factor modification should be a routine part of management of these patients.

There are no large randomized studies comparing surgical with medical management of MR. Patients who have symptoms due to the MR should undergo surgery before LV dysfunction occurs.[1] There are no randomized surgical studies in asymptomatic patients with severe MR. If the patient has repairable MR that is truly severe quantitatively, American College of Cardiology/American Heart Association (ACC/AHA) guidelines (Table 34.5) state that mitral valve surgery should be recommended if the patient has developed any decrease in LV ejection fraction (LVEF), significant dilation of end-systolic LV size (>4.5 cm systolic diameter), AF, or significant pulmonary hypertension. In addition, many centers recommend mitral valve surgery for selected patients with severe MR when they also have a flail mitral leaflet,[12] or when there is exercise echo evidence of "latent LV dysfunction," defined by a declining EF or increasing end systolic volume (ESV) with exercise.[13,14]

TABLE
34.5 Indications for Mitral Valve Operation

Class I

1. MV surgery is recommended for the symptomatic patient with acute severe MR.* *(Level of Evidence: B)*
2. MV surgery is beneficial for patients with chronic severe MR* and NYHA functional Class II, III, or IV symptoms in the absence of severe LV dysfunction (severe LV dysfunction is defined as ejection fraction <0.30) and/or end-systolic dimension >55 mm. *(Level of Evidence: B)*
3. MV surgery is beneficial for asymptomatic patients with chronic severe MR* and mild to moderate LV dysfunction, ejection fraction 0.30 to 0.60, and/or end-systolic dimension ≥40 mm. *(Level of Evidence: B)*
4. MV repair is recommended over MV replacement in the majority of patients with severe chronic MR* who require surgery, and patients should be referred to surgical centers experienced in MV repair. *(Level of Evidence: C)*

Class IIa

1. MV repair is reasonable in experienced surgical centers for asymptomatic patients with chronic severe MR* with preserved LV function (ejection fraction >0.60 and end-systolic dimension <40 mm) in whom the likelihood of successful repair without residual MR is >90%. *(Level of Evidence: B)*
2. MV surgery is reasonable for asymptomatic patients with chronic severe MR,* preserved LV function, and new onset of AF. *(Level of Evidence: C)*
3. MV surgery is reasonable for asymptomatic patients with chronic severe MR,* preserved LV function, and pulmonary hypertension (pulmonary artery systolic pressure >50 mm Hg at rest or >60 mm Hg with exercise). *(Level of Evidence: C)*
4. MV surgery is reasonable for patients with chronic severe MR* due to a primary abnormality of the mitral apparatus and NYHA functional Class III–IV symptoms and severe LV dysfunction (ejection fraction < 0.30 and/or end-systolic dimension > 55 mm) in whom MV repair is highly likely. *(Level of Evidence: C)*

Class IIb

MV repair may be considered for patients with chronic severe secondary MR* due to severe LV dysfunction (ejection fraction <0.30) who have persistent NYHA functional Class III–IV symptoms despite optimal therapy for heart failure, including biventricular pacing. *(Level of Evidence: C)*

Class III

1. MV surgery is not indicated for asymptomatic patients with MR and preserved LV function (ejection fraction >0.60 and end-systolic dimension <40 mm) in whom significant doubt about the feasibility of repair exists. *(Level of Evidence: C)*
2. Isolated MV surgery is not indicated for patients with mild or moderate MR. *(Level of Evidence: C)*

From Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2006;48:e1–e148, with permission from Elsevier.

Guidelines do not advocate mitral valve surgery for patients with ejection fraction <30%. However, selected symptomatic patients with severe LV dysfunction may benefit from mitral valve operation, particularly if they have moderate ventricular dilation and

very severe regurgitation (Fig. 34.10).

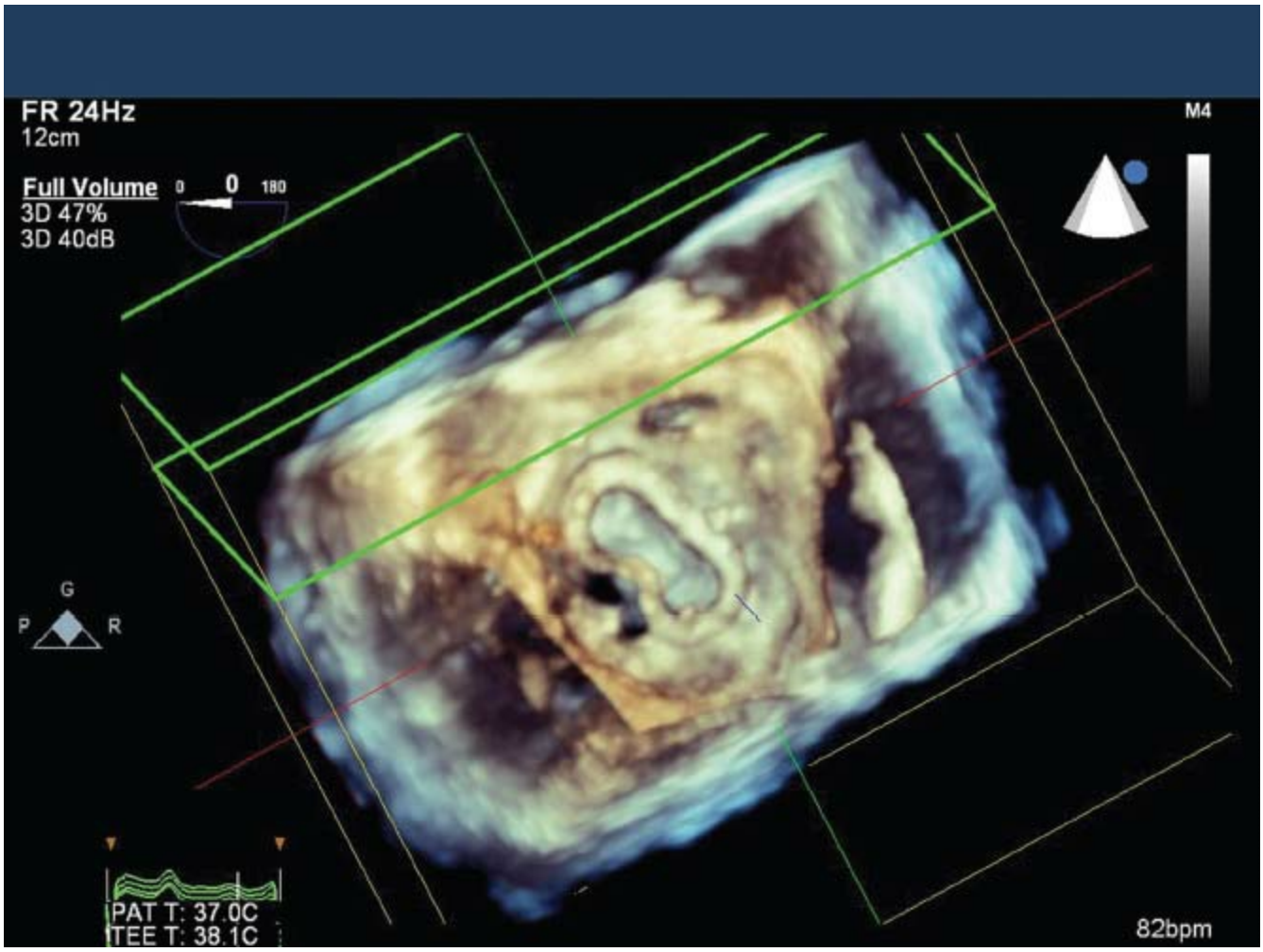


FIGURE 34.9 Transesophageal 3D image in the "surgeon's view", of a patient who had recurrence of mitral regurgitation after initially successful repair with a Geoform ™ mitral annuloplasty. Note the focal dehiscence of the ring, visible as the dark space just outside its mid posterior portion where the ring is indented inward by design.

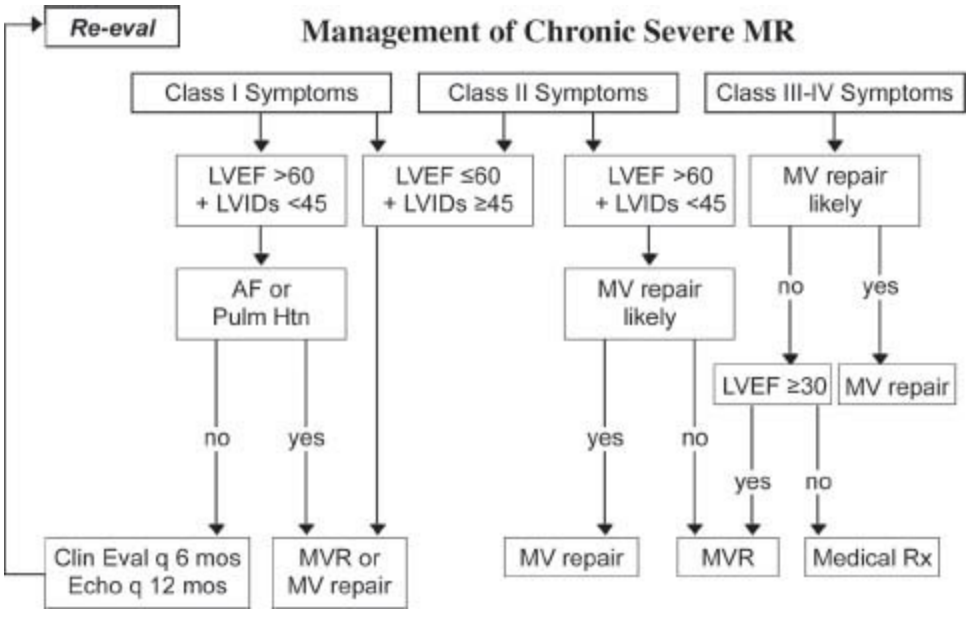


FIGURE 34.10 Flow chart summarizing management of chronic MR. (Adapted from Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2006;48:e1–e148.)

Mitral valve repair is now the surgical management of choice for most cases of MR, which does not require anticoagulation as do mechanical mitral prostheses.[7] In addition, repair preserves the mitral apparatus and leads to improved LV function and survival compared to mitral valve replacement (MVR) when the chordal are not preserved. However, for many conditions, such as rheumatic mitral valve disease or in those with significant subvalvular thickening and major loss of leaflet substance, MVR is the best option, because repair may not be feasible or durable with 0.5 to 1% of patients returning for reoperation per year after initially successful repair (figure 34.9). If so, the prosthesis should be implanted with preservation of the mitral valve chordal apparatus, as much as feasible.

Based on the guidelines, cardiac catheterization is indicated in patients with angina or previous myocardial infarction, individuals with one or more cardiac risk factors, and when ischemia is the cause of MR.[1] As long as there is no clinical suspicion of coronary artery disease, asymptomatic males <40 years of age, and asymptomatic females <50 years of age, do not need to undergo preoperative coronary angiography because of low likelihood of significant coronary disease (Table 34.6).

TABLE
34.6 Indications for Cardiac Catheterization in MR

Class I

1. Left ventriculography and hemodynamic measurements are indicated when noninvasive tests are inconclusive regarding severity of MR, LV function, or the need for surgery. *(Level of Evidence: C)*
2. Hemodynamic measurements are indicated when pulmonary artery pressure is out of proportion to the severity of MR as assessed by noninvasive testing. *(Level of Evidence: C)*
3. Left ventriculography and hemodynamic measurements are indicated when there is a discrepancy between clinical and noninvasive findings regarding severity of MR. *(Level of Evidence: C)*
4. Coronary angiography is indicated before MV repair or MV replacement in patients at risk for CAD. *(Level of Evidence: C)*

Class III

1. Left ventriculography and hemodynamic measurements are not indicated in patients with MR in whom valve surgery is not contemplated. *(Level of Evidence: C)*

Adapted from Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of

Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2006;48:e1–e148.

MITRAL VALVE STENOSIS

The primary cause of mitral stenosis (MS) is rheumatic heart disease, a chronic, postinfectious, inflammatory condition that leads to fusion and fibrosis of commissural, cuspal, and chordal portions of the mitral valve apparatus. Less commonly, MS is a complication of malignant carcinoid, radiation, systemic lupus erythematosus, rheumatoid arthritis, Whipple disease, and other rare connective tissue diseases. The mitral valve area of a normal person is 4.0 to 5.0 cm^2. Symptomatic mitral valve stenosis occurs when the valve area is less than about 1.5 cm^2. The first symptoms are mild exercise intolerance or dyspnea. The difficulties accelerate when the patient develops AF, particularly if the ventricular rate is rapid. The natural history of MS is a life-long,continuous, and slow process (Fig. 34.11) of progressive fibrosis of the mitral valve. In western countries, it usually takes 20 to 40 years after occurrence of a streptococcus infection and rheumatic fever for the patient to develop symptoms of rheumatic mitral valve disease. In underdeveloped countries where strep organisms are more virulent, this interval is much shorter. Dyspnea with exertion may occur several years before the patient experiences decompensated heart failure. Patients with MS and AF occasionally present with neurologic sequela, due to embolization of clot, occurring due to blood stasis in the left atrium. With progression of disease and increased left atrial pressure, orthopnea, paroxysmal nocturnal dyspnea, and occasionally hemoptysis may occur.

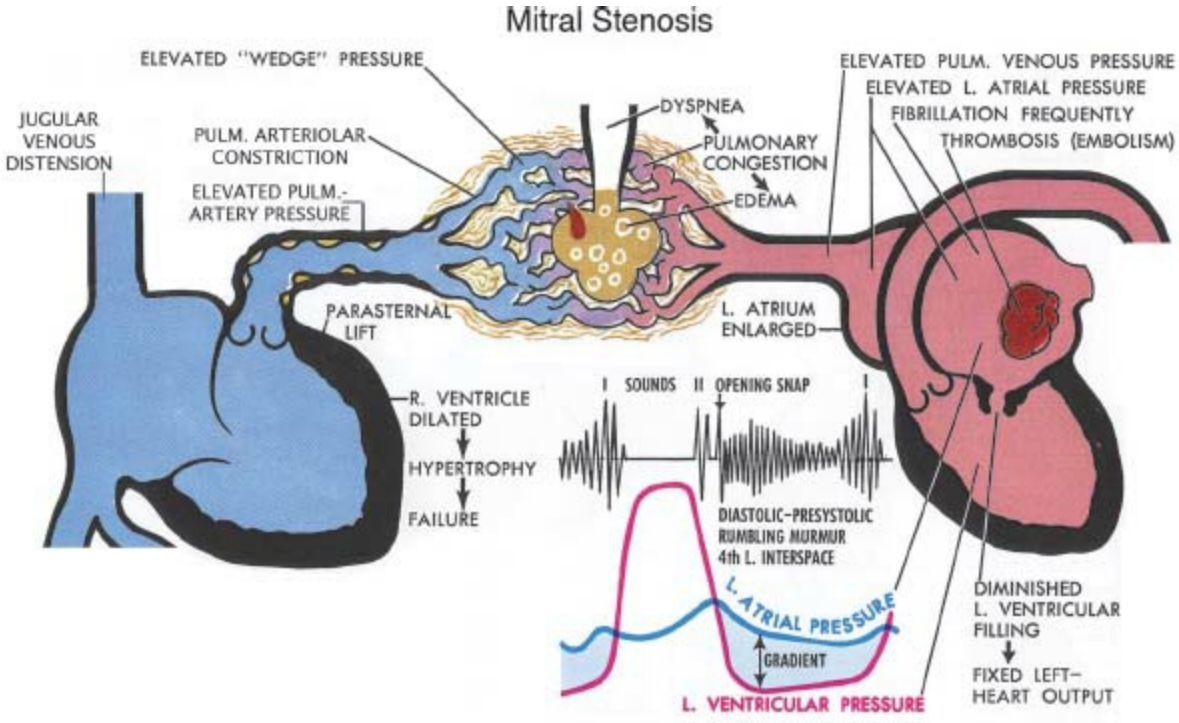


FIGURE 34.11 Schematic diagram representing pathologic complications of MS. (Netter illustration adapted from www.netterimages.com. © Elsevier Inc. All rights reserved.)

A loud first heart sound, an opening snap (OS), and a diastolic rumble are the classic auscultatory features of MS. The intensity of the pulmonic component of second heart sound is important in the bedside estimate of the severity of secondary pulmonary hypertension. The OS is caused by sudden tensing of the valve leaflet under the greater than usual diastolic gradient. The OS may occur between 50 and 120 milliseconds after the A_2 component of the second heart sound. The time between A_2 and OS is inversely associated with severity of MS; therefore, a short A_2-OS interval is a bedside indication of severe MS, due to the gradient occurring on the more steep descending slope of LV pressure curve. However, patients with severe immobility of the mitral valve, despite significant MS, often have no OS, or it is soft in intensity.

The electrocardiographic (ECG) features of MS include left atrial enlargement, the so-called P mitrale, in patients in sinus rhythm, and occasionally right axis deviation or RV enlargement. AF is a frequent arrhythmia in these patients. Radiographic features of MS included the enlarged left atrium, enlarged pulmonary arteries, mitral valve calcium, and signs of congestive heart failure such as Kerley B lines.

Although the history, physical exam, chest x-ray (Fig. 34.12), and ECG may suggest MS, 2-D echo and Doppler echocardiography are the tools of choice for its diagnosis. The characteristic findings of MS on the 2-D echo are restriction of diastolic motion, with doming in diastole of the anterior and posterior leaflets (Fig. 34.13). There is often contraction and fibrosis of the various components of the mitral apparatus, often with thickening of the submitral chordae and papillary muscles. In the parasternal short-axis view, the mitral valve can be planimetered to determine the effective mitral valve area. To do so, one must scan up and down the mitral valve short axis, searching for the place where the early diastolic (maximum in time) orifice size is smallest (i.e., smallest in space) (Fig. 34.14). In order to provide accurate measurements, the gain settings must not be too high or too low. In addition, echo imaging is useful for assessing the degree of valve thickening, decreased mobility, calcification, and subvalvular disease (the "splittability index" or Wilkin score), which helps to predict the success and durability of percutaneous balloon valvotomy versus surgical options.[15] Echo is also essential for exclusion of other valvular lesions, because it is common for patients with rheumatic mitral disease to have concomitant aortic and/or tricuspid valve disease.

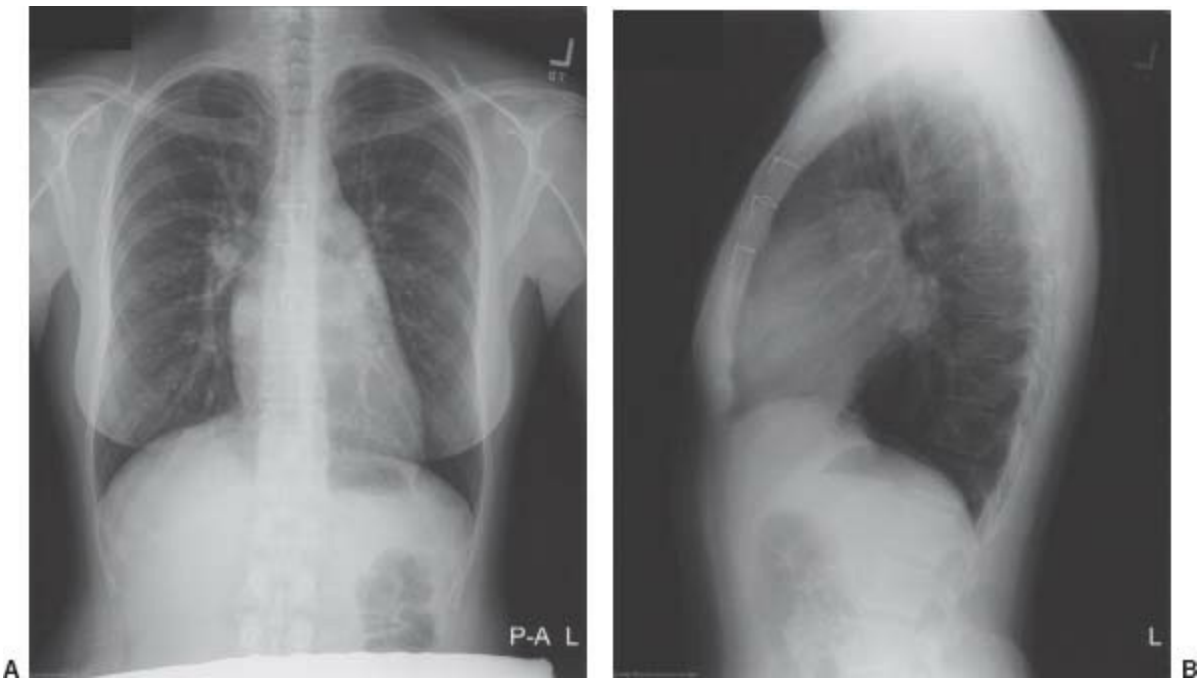


FIGURE 34-12 Posteroanterior chest x-ray **(A)** showing typical features of rheumatic MS, with an enlarged left atrium (note the widened carina and round double density), and prominent bilateral pulmonary artery shadows, with normal LV size. This patient was not in heart failure at the time of the study. Lateral chest x-ray **(B)** showing prominent pulmonary arteries and left atrial enlargement protruding from the cardiac silhouette posteriorly. This patient had midsternal wires from a previous thoracotomy.

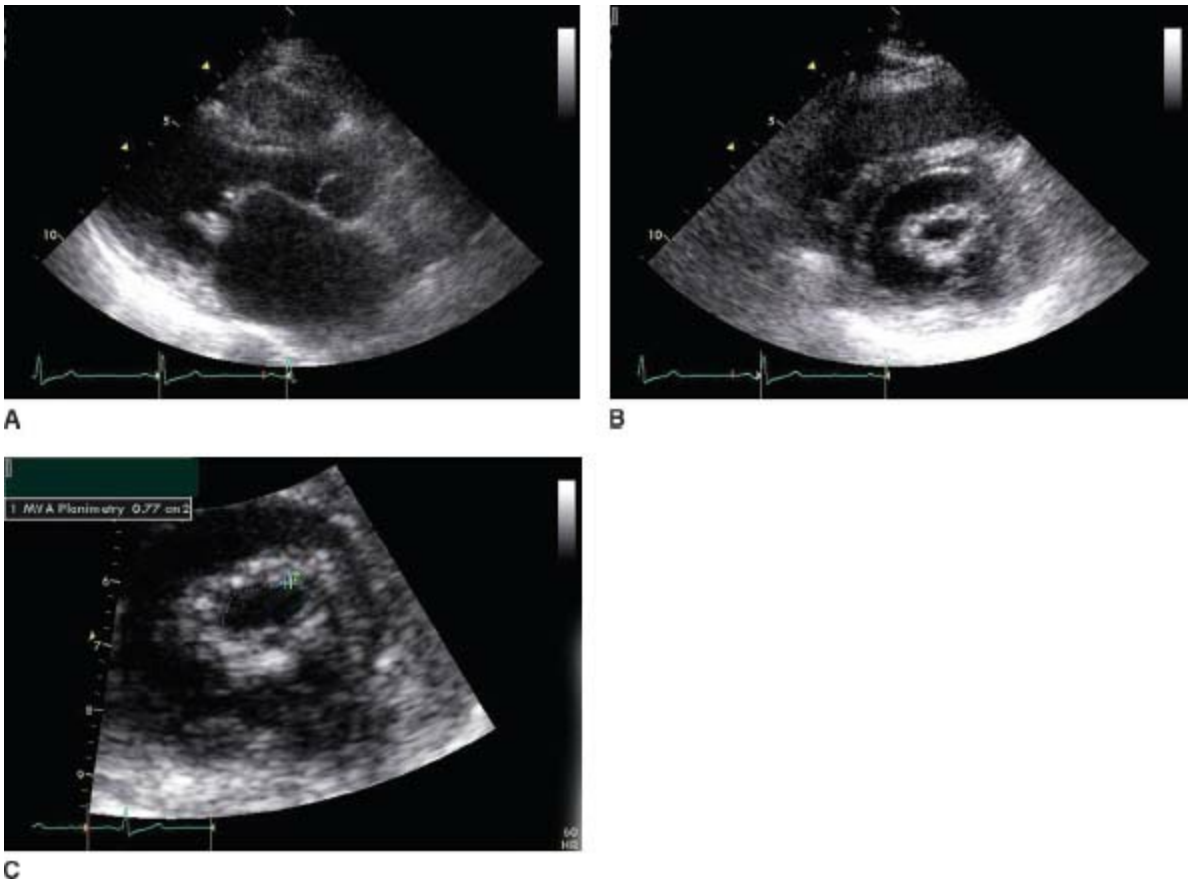


FIGURE 34.13 Diastolic stop frames from 2-D echo parasternal long-axis **(A)** and short-axis **(B)** views of a patient

with severe rheumatic mitral valve stenosis. Note the diastolic doming and the leaflet thickening of the mitral valve; as well as left atrial enlargement and normal LV size. In **(C),** a magnified view of the maximum diastolic opening of the valve has been planimetered, finding a mitral valve area of 0.77 cm^2, indicating severe stenosis.

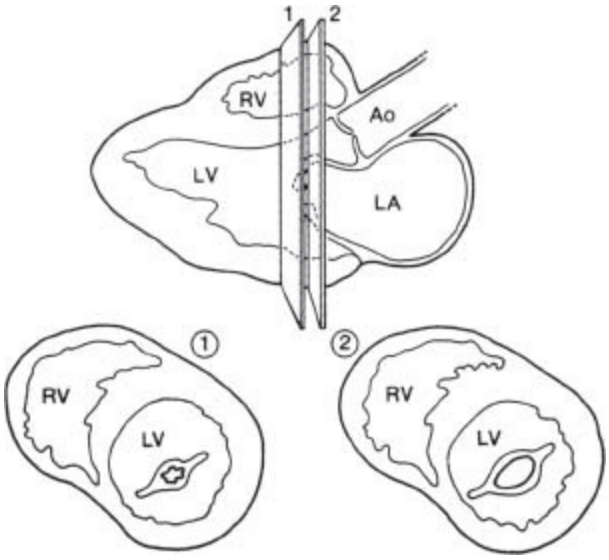


FIGURE 34.14 Artistic diagram of the parasternal long-axis transthoracic image **(top),** illustrating the technique of obtaining the various parasternal short axis transthoracic images (lower two diagrams). Planimetry to measure the flow-limiting valve area of MS would obtain a smaller orifice area in the image plane (1) on the lower left, than in image plane (2) on the lower right, because of the funnel-shaped mitral valve. RV, right ventricle. (Adapted from Salcedo E. Atlas of Echocardiography. W. B. Saunders, Philadelphia. 1985:73.)

Apical (transthoracic echo) or midesophageal (transesophageal echo) windows for recording of diastolic antegrade mitral velocity (V) are useful for quantitation of severity. Doppler accurately estimates mean mitral gradient, mitral valve area, and estimation of RV systolic pressure. The mean mitral gradient is the temporal average of instantaneous gradients throughout diastole, using the modified Bernoulli equation ($4V^2$). However, this particular measurement is very subject to changes with increased heart rate, which reduces the diastolic interval and increases the mean mitral gradient. It is also subject to concomitant MR (which increases antegrade flow) and other changes in cardiac output (with low cardiac output causing a lower mitral gradient). Severity of MS can also be judged using the mitral pressure half-time (PHT— the time in milliseconds that it takes for the maximum transmitral velocity to fall to 71% of its initial velocity (V_{max} divided by the square root of 2). Mitral valve area is calculated from the formula: 220/PHT (Fig. 34.15). In general, a valve area of 4 to 6 cm^2 is normal, 1.6 to 2.0 cm^2 is mild, 1.1 to 1.5 cm^2 is moderate, and $\leq$1.0 cm^2 is severe MS (Fig. 34.16). Estimation of RV systolic pressure is made from the maximum tricuspid regurgitation (TR) velocity.

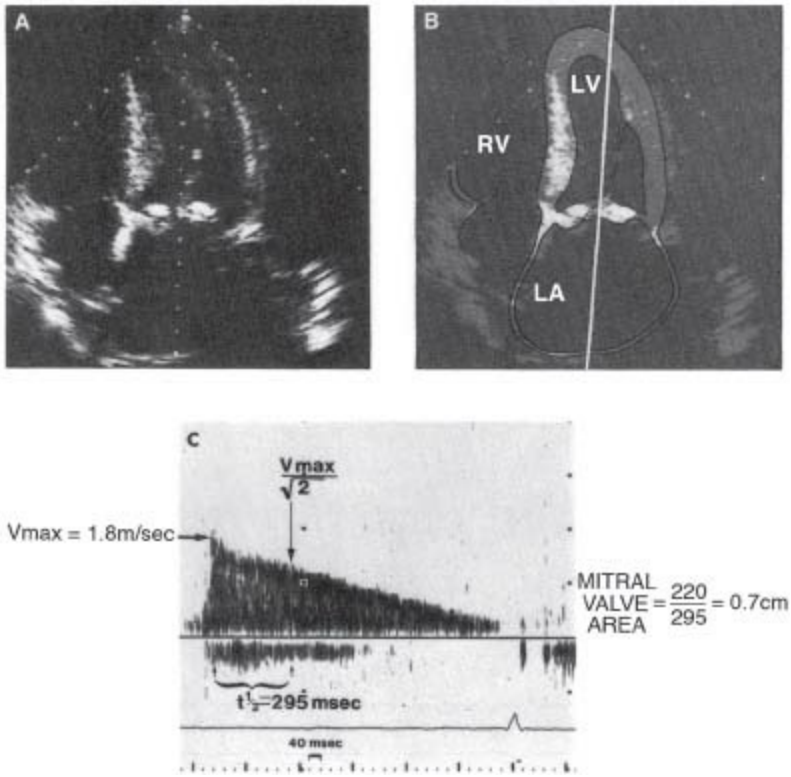


FIGURE 34.15 Apical four-chamber echo image **(A)** and matching artistic drawing **(B)** from which was recorded a continuous-wave Doppler of mitral antegrade velocity **(C)** in MS. PHT ($t_{1/2}$), measured as 295 ms, is divided into 220 milliseconds, to derive the mitral valve area, in square centimeters. (Adapted from Stewart et al. in Pohost GM Cardiac Imaging. Chicago: Yearbook Inc.; 1986:76.)

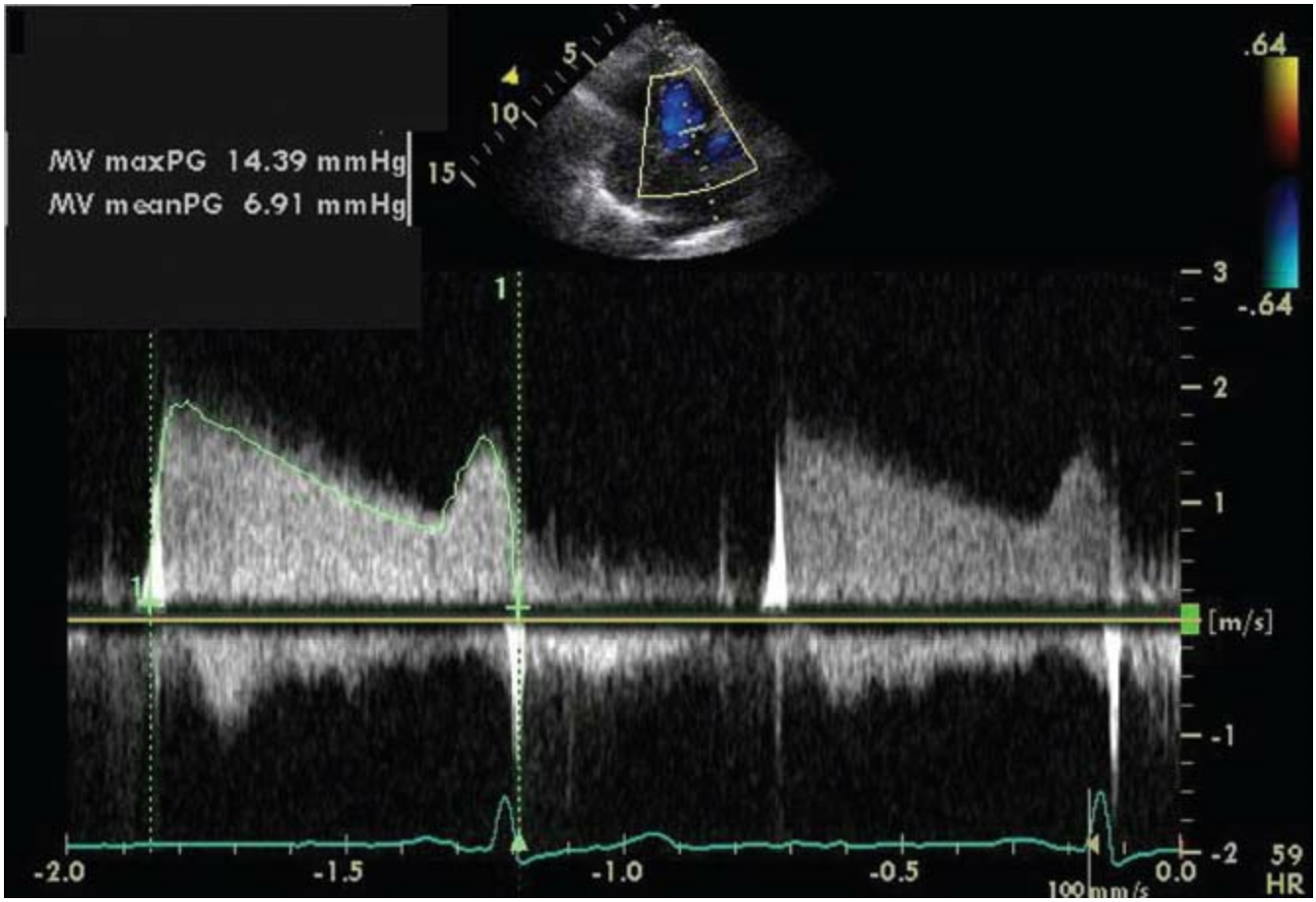


FIGURE 34.16 Continuous-wave Doppler recordings from apical four-chamber view of the same patient shown in Figure 34.13, showing in **A:** planimetry of the maximum velocity envelope to determine mean diastolic mitral gradient (6.9 mm Hg); and in **B:** measurement of the pressure half-time (271 milliseconds), indicating severe MS with a relatively low cardiac output.

Although often supplanted by a complete Doppler study, an invasive right and left heart catheterization should be reserved for patients with discrepancy between Doppler-derived hemodynamics and clinical symptoms or when there is elevation of pulmonary artery pressures out of proportion to mitral valve area or diastolic gradients (Table 34.7). Simultaneous Doppler and catheterization studies, using a transseptal measurement of left atrial pressure, have revealed that Doppler-derived mean mitral gradients and PHTs are accurate in most circumstances. Use of the pulmonary capillary wedge technique may overestimate the mitral gradient because of incomplete wedging and hence overestimation of the left atrial pressure.

TABLE
34.7 Indications for Echocardiography in MS

Class I

1. Echocardiography should be performed in patients for the diagnosis of MS, assessment of hemodynamic severity (mean gradient, MV area, and pulmonary artery pressure), assessment of concomitant valvular lesions, and assessment of valve morphology (to determine suitability for percutaneous mitral balloon valvotomy). *(Level of Evidence: B)*
2. Echocardiography should be performed for reevaluation in patients with known MS and changing symptoms or signs. *(Level of Evidence: B)*
3. Echocardiography should be performed for assessment of the hemodynamic response of the mean gradient and pulmonary artery pressure by exercise Doppler echocardiography in patients with MS when there is a discrepancy between resting Doppler echocardiographic findings, clinical findings, symptoms, and signs. *(Level of Evidence: C)*
4. TEE in MS should be performed to assess the presence or absence of left atrial thrombus and to further evaluate the severity of MR in patients considered for percutaneous mitral balloon valvotomy. *(Level of Evidence: C)*
5. TEE in MS should be performed to evaluate MV morphology and hemodynamics in patients when transthoracic echocardiography provides suboptimal data. *(Level of Evidence: C)*

Class IIa

Echocardiography is reasonable in the reevaluation of asymptomatic patients with MS and stable clinical findings to assess pulmonary artery pressure (for those with severe MS, every year; moderate MS, every 1–2 y; and mild MS, every 3–5 y). *(Level of Evidence: C)*

Class III

TEE in the patient with MS is not indicated for routine evaluation of MV morphology and hemodynamics when complete transthoracic echocardiographic data are satisfactory. *(Level of Evidence: C)*

From Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2006;48: e1–e148, with permission from Elsevier.

Medical management of patients with MS often should include aggressive anticoagulation in patients at high risk. Patients who have AF or previous systemic embolic events should definitely be anticoagulated with warfarin. The ACC/AHA guidelines recommend anticoagulation in all patients with MS with paroxysmal or chronic AF and in those with prior embolic events (Table 34.8).

TABLE
34.8 Medical Therapy for Prevention of Systemic Embolization in MS

Class I

1. Anticoagulation is indicated in patients with MS and AF (paroxysmal, persistent, or permanent). *(Level of Evidence: B)*
2. Anticoagulation is indicated in patients with MS and a prior embolic event, even in sinus rhythm. *(Level of Evidence: B)*
3. Anticoagulation is indicated in patients with MS with left atrial thrombus. *(Level of Evidence: B)*

Class IIb

1. Anticoagulation may be considered for asymptomatic patients with severe MS and left atrial dimension ≥55 mm by echocardiography.* *(Level of Evidence: B)*
2. Anticoagulation may be considered for patients with severe MS, an enlarged left atrium, and spontaneous contrast on echocardiography. *(Level of Evidence: C)*

From Bonow RO, Carabello BA, Chatteq'ee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2006;48: e1–e148, with permission from Elsevier.

Patients with moderate or greater degree of MS should avoid strenuous physical activity sufficient to cause severe symptoms. In those with exertional symptoms, beta-blockers or calcium channel blockers may be beneficial to increase the duration of diastole, especially if symptoms occur with rapid heart rate. Salt restriction and diuretic use are necessary components for management of pulmonary congestion in these patients. The incidence of AF is around 30% to 40% in patients with MS.

AF causes loss of the atrial component of ventricular filling. When AF is rapid, there is also a decrease in percentage of time per minute of diastolic filling, increasing the average gradient across the stenotic mitral valve, because the mitral flow spends a greater portion of its time in the "early" portion of diastole when velocity is higher. Therefore, anything that accelerates ventricular rate has deleterious hemodynamic consequences in MS. In patients with rapid AF and hemodynamic instability or evidence of shock with ongoing end-organ underperfusion, direct-current cardioversion should be performed without delay.

At the onset of AF in any patient with MS, rapid assessment and management with agents such as beta-blockers, calcium channel blockers, or intravenous digoxin may be necessary. In general, stable patients should undergo transesophageal echocardiography (TEE) to look for thrombus, or be anticoagulated for 3 weeks prior to cardioversion and after the cardioversion, often indefinitely, due to the risk of recurrent embolization.

The decision to intervene with surgery or catheterbased therapy in patients with MS depends largely on the severity of symptoms, but also depends on the quantitative severity of MS, the level of pulmonary hypertension, the history of atrial arrhythmias, and thromboembolic complications. Congestive heart failure that is New York Heart

Association (NYHA) Class II or above, with severe MS, <1.0 cm^2 valve area, is a clear indication for intervention. The presence of pulmonary hypertension, with systolic pressures above 55 at rest or above 60 mm Hg with exercise, is considered an indication for intervention even without symptoms.

Based on these criteria, intervention may take the form of balloon valvotomy, open commissurotomy, or MVR (Table 34.9). Balloon valvotomy is a therapeutic technique, done through a transseptal catheterization, that can accomplish enlargement of the mitral orifice in selected patients with MS who have suitable anatomy. Balloon valvotomy is more likely to be feasible if the echo-derived "splittability index" is below about 9. Balloon valvotomy is reasonably safe and has results similar to that of open mitral commissurotomy. Prior to a transcatheter therapeutic procedure, transesophageal echo is warranted to exclude left atrial thrombus and moderately severe (3+ on a scale of 4+) or more MR, both of which are contraindications to the balloon valvotomy technique. In general, mitral valve area typically doubles with a successful balloon valvotomy procedure in which both commissures are split.

TABLE
34.9 Indications for Percutaneous Mitral Balloon Valvotomy In MS

Class I

1. Percutaneous mitral balloon valvotomy is effective for symptomatic patients (NYHA functional Class II, III, or IV), with moderate or severe MS* and valve morphology favorable for percutaneous mitral balloon valvotomy in the absence of left atrial thrombus or moderate to severe MR. *(Level of Evidence: A)*
2. Percutaneous mitral balloon valvotomy is effective for asymptomatic patients with moderate or severe MS* and valve morphology that is favorable for percutaneous mitral balloon valvotomy who have pulmonary hypertension (pulmonary artery systolic pressure >50 mm Hg at rest or >60 mm Hg with exercise) in the absence of left atrial thrombus or moderate to severe MR. *(Level of Evidence: C)*

Class IIa

Percutaneous mitral balloon valvotomy is reasonable for patients with moderate or severe MS* who have a nonpliable calcified valve, are in NYHA functional Class III–IV, and are either not candidates for surgery or are at high risk for surgery. *(Level of Evidence: C)*

Class IIb

1. Percutaneous mitral balloon valvotomy may be considered for asymptomatic patients with moderate or severe MS* and valve morphology favorable for percutaneous mitral balloon valvotomy who have new onset of AF in the absence of left atrial thrombus or moderate to severe MR. *(Level of Evidence: C)*
2. Percutaneous mitral balloon valvotomy may be considered for symptomatic patients (NYHA functional Class II, III, or IV) with MV area >1.5 cm^2 if there is evidence of hemodynamically significant MS based on pulmonary artery systolic pressure >60 mm Hg, pulmonary artery wedge pressure of 25 mm Hg or more, or mean MV gradient >15 mm Hg during exercise. *(Level of Evidence: C)*
3. Percutaneous mitral balloon valvotomy may be considered as an alternative to surgery for patients with moderate or severe MS who have a nonpliable calcified valve and are in NYHA Class III–IV. *(Level of Evidence: C)*

Class III

1. Percutaneous mitral balloon valvotomy is not indicated for patients with mild MS. *(Level of Evidence: C)*
2. Percutaneous mitral balloon valvotomy should not be performed in patients with moderate to severe MR or left atrial thrombus. *(Level of Evidence: C)*

From Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2006;48: e1–e148, with permission from Elsevier.

Patients with a left atrial thrombus, significant MR, or a high echo splittability index should be considered for valve repair or valve replacement rather than balloon procedures. Mitral valve repair can be accomplished in selected patients with MS, particularly when the valve has a moderate or lower splittability index, and is the procedure of choice when there is concomitant substantial MR, especially if there is a contraindication to anticoagulation.

MVR is an alternative procedure for patients who are not candidates for

percutaneous mitral valvotomy or surgical commissurotomy (Table 34.10). MVR is the surgery of choice in patients with heavily calcified, immobile, fibrotic valves with a high splittability index, where percutaneous mitral valvotomy or surgical commissurotomy may not be feasible, may leave the patient with substantial dysfunction, or may be prone to recurrence of dysfunction. Traditionally a mechanical valve is used for most patients having mitral replacement who are <50 to 60 years of age, whereas older patients undergo bioprosthetic valve replacement.

TABLE
34.10 Indications for Surgery for MS

Class I

1. MV surgery (repair if possible) is indicated in patients with symptomatic (NYHA functional Class III–IV) moderate or severe MS* when (a) percutaneous mitral balloon valvotomy is unavailable, (b) percutaneous mitral balloon valvotomy is contraindicated because of left atrial thrombus despite anticoagulation or because concomitant moderate to severe MR is present, or (c) the valve morphology is not favorable for percutaneous mitral balloon valvotomy in a patient with acceptable operative risk. *(Level of Evidence: B)*
2. Symptomatic patients with moderate to severe MS* who also have moderate to severe MR should receive MV replacement, unless valve repair is possible at the time of surgery. *(Level of Evidence: C)*

Class IIa

MV replacement is reasonable for patients with severe MS* and severe pulmonary hypertension (pulmonary artery systolic pressure >60) with NYHA functional Class I–II symptoms who are not considered candidates for percutaneous mitral balloon valvotomy or surgical MV repair. *(Level of Evidence: C)*

Class IIb

MV repair may be considered for asymptomatic patients with moderate or severe MS* who have had recurrent embolic events while receiving adequate anticoagulation and who have valve morphology favorable for repair. *(Level of Evidence: C)*

Class III

1. MV repair for MS is not indicated for patients with mild MS. *(Level of Evidence: C)*
2. Closed commissurotomy should not be performed in patients undergoing MV repair; open commissurotomy is the preferred approach. *(Level of Evidence: C)*

From Bonow RO, Carabello BA, Chatteq'ee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2006;48: e1–e148, with permission from Elsevier.

TRICUSPID VALVE REGURGITATION

TR is a very common valvular abnormality, but it is often mild or moderate in severity,

and in those cases, usually asymptomatic. In severe TR, right-sided heart failure often occurs, and the patients develop ascites, hepatic congestion, and peripheral edema (Fig. 34.17). In addition, patients may complain of fatigue, shortness of breath, and exercise intolerance as a result of an inability to augment cardiac output because of the severe TR.

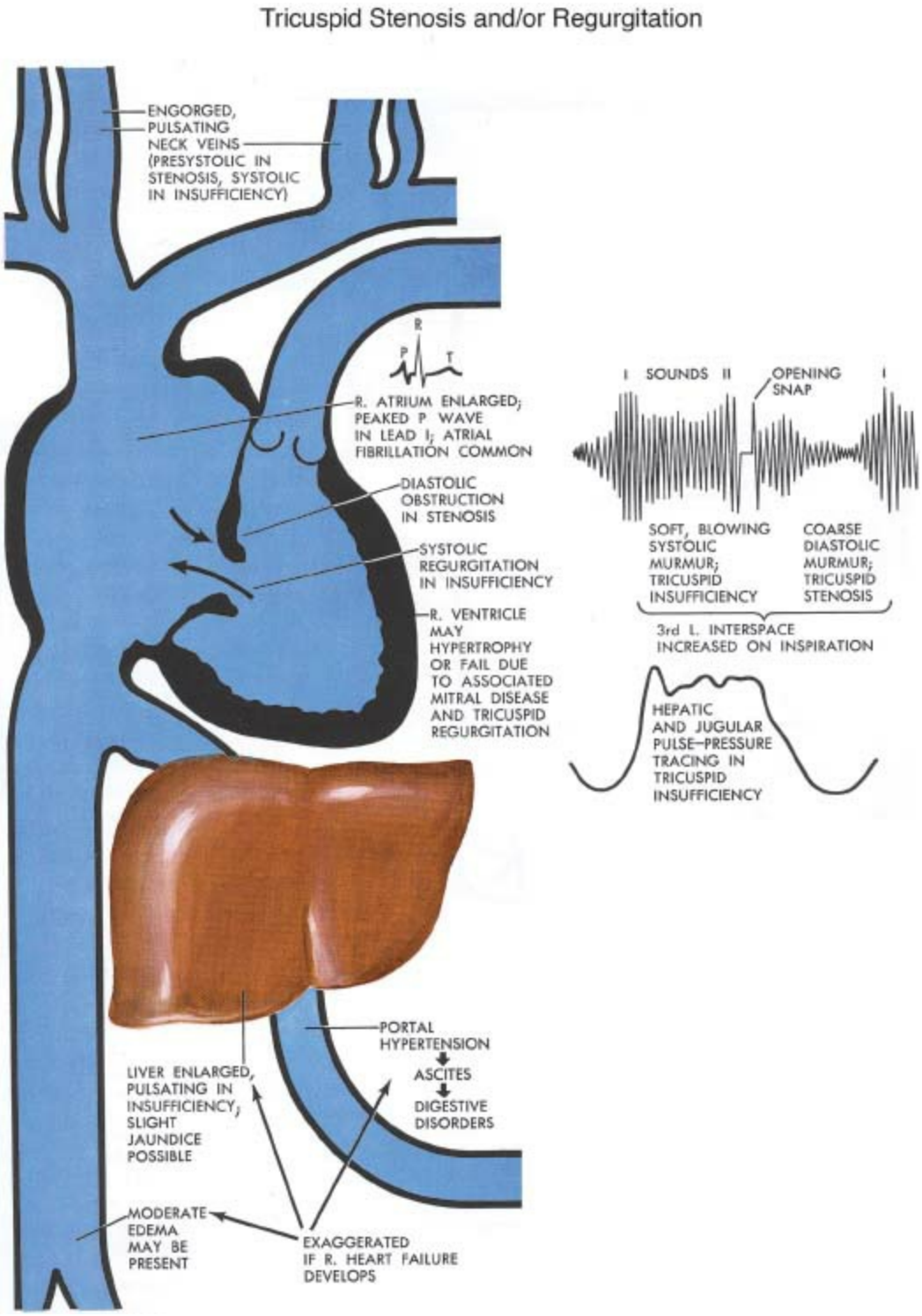
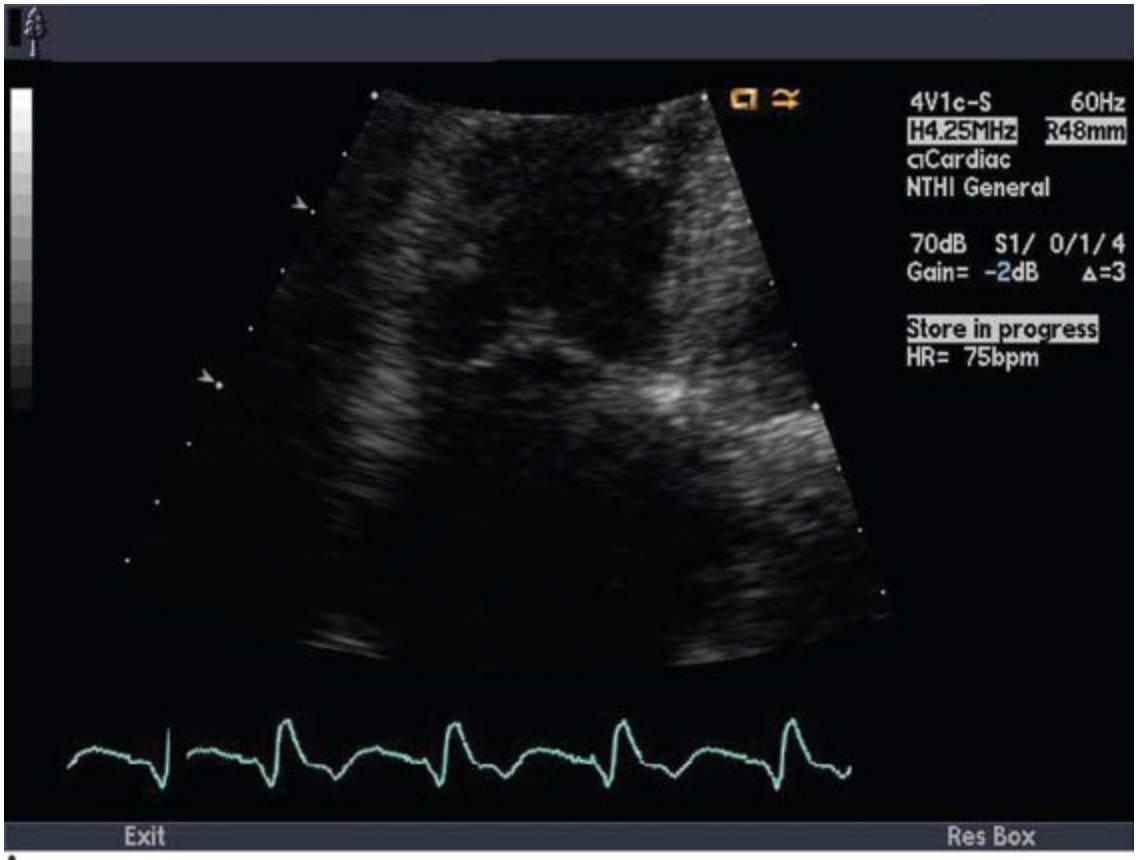


FIGURE 34.17 Schematic diagram representing pathologic complications of tricuspid stenosis and regurgitation. (Netter illustration adapted from www.netterimages.com. © Elsevier Inc. All rights reserved.)

On physical exam, patients often have distended jugular veins, leg and pedal edema, and an enlarged liver. The jugular vein profile and the right atrial pressure waveforms show a positive systolic V wave from the effects of the TR. On cardiac auscultation, there may or may not be a holosystolic murmur, which may be high pitched, much lower pitched, or absent. The murmur is often heard best at the right or left sternal border, and classically increases with inhalation, though this is not a reliable finding. Maneuvers that increase venous return, such as leg raising, augment the intensity of the TR murmur. In severe TR, an S_3 or an early diastolic rumble may be heard. When there is associated pulmonary hypertension, the second heart sound may be loud. Palpation of the heart often reveals a RV lift or heave. Palpation of the liver reveals pulsatile hepatomegaly, which may achieve vast proportions. In severe, long-standing TR, chronic passive congestion of the liver occurs, and the patient may develop numerous secondary phenomena. These include abdominal bloating and tenderness, early satiety, jaundice, ascites, and other "digestive symptoms." Variable diffuse elevations of blood tests of liver function, cardiac cirrhosis, and progressive cachexia may also occur. Many patients with severe TR have been misdiagnosed as having various gastrointestinal disorders.

The most useful diagnostic modality is echocardiography. Color Doppler can define the severity and presence of the regurgitant flow (Fig. 34.18). Care should be give to the Nyquist setting in color imaging, as severe intrinsic TR may be low velocity and may not show color aliasing at the usual Nyquist settings. Two-dimensional echocardiography may identify other structural abnormalities involved in the etiology of the TR, such as leaflet prolapse, flail, fibrosis, or annular dilation. Enlargement of the right atrium and RV is common as is RV dysfunction. Other findings include paradoxical septal motion as a result of RV diastolic overload, and reversal of flow during ventricular systole in the inferior vena cava or hepatic veins by pulsed Doppler. Continuouswave Doppler is used to define the severity of pulmonary hypertension.



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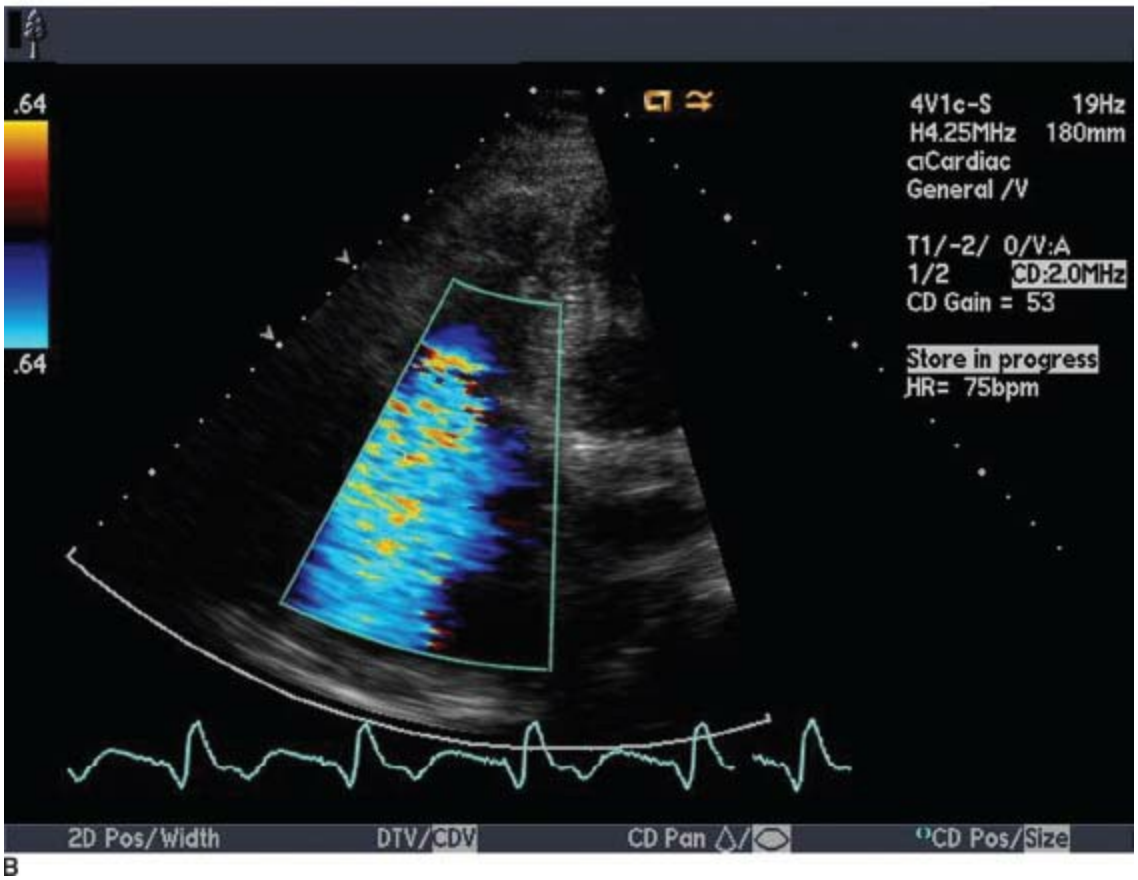


B

FIGURE 34.18 Transthoracic apical four-chamber systolic 2-D echo image **(A)** and color flow Doppler image **(B)** of

a patient with severe TR due to apical tethering of tricuspid leaflets resulting from left-sided valve disease.

There are no specific ECG changes associated with TR; however, with severe pulmonary hypertension, the ECG pattern of RV hypertrophy may be seen. When right atrial enlargement is present, the ECG may show large P waves in the pattern "P pulmonale," but in the chronic phase, most patients have AF. Chest x-ray often reveals cardiomegaly due to RV and right atrial enlargement, coupled with the findings that reflect their left-sided heart disease, if present.

Regarding etiology, the most common type of TR is termed "functional," because it results from RV and tricuspid annular dilatation. Any cause of pulmonary hypertension may cause this type of TR, including left-sided heart failure due to LV dysfunction, MS or regurgitation, or less commonly, aortic valve disease. Functional TR also results from RV hypertension or enlargement caused by intrinsic pulmonary disease, primary pulmonary hypertension, pulmonic valve abnormalities, or left-to-right shunts. Right heart dilation also occurs directly as a result of various disorders of the RV myocardium, including RV infarction or dilated cardiomyopathy.

Regurgitation from intrinsic tricuspid valvular dysfunction is less common than functional TR. These etiologies include infective endocarditis, myxomatous degeneration (prolapse), rheumatic fever, congenital Ebstein anomaly, carcinoid syndrome, papillary muscle dysfunction or rupture, connective tissue disorders, trauma (including myocardial biopsy), rupture of chordae tendineae, marantic endocarditis, and endomyocardial fibrosis.

Treatment of TR involves correcting the primary cause. For example, if a correctable cause of acute or chronic pulmonary hypertension can be found, TR may improve or resolve. For example, diuresis of a patient in left heart failure may also diminish the severity of TR. Rhythm and rate control also are beneficial to patient well-being in appropriate patients. In some patients, vasodilator therapy may help by dilation of venous capacitance beds, or by reducing pulmonary arteriolar resistance.

Annuloplasty is the most frequent surgical treatment used for TR. However, when valve leaflets themselves are destroyed or diseased, a prosthesis is needed, and a biologic valve is usually used as there is a high prevalence of valve thrombosis with mechanical valves in the tricuspid position. The indications for tricuspid valve surgery are listed in Table 34.11. In patients with mitral valve dysfunction and TR requiring surgery,the improvement in pulmonary hypertension may relieve the RV dilation sufficient to correct the TR. However, there should be low threshold for annuloplasty; any patient with moderate 2+ TR or more on a scale of 4+ at any time prior to surgery may be a surgical candidate.

TABLE
34.11 Management of TR

Class I

Tricuspid valve repair is beneficial for severe TR in patients with MV disease requiring MV surgery. *(Level of Evidence: B)*

Class IIa

1. Tricuspid valve replacement or annuloplasty is reasonable for severe primary TR when symptomatic. *(Level of Evidence: C)*
2. Tricuspid valve replacement is reasonable for severe TR secondary to diseased/abnormal tricuspid valve leaflets not amenable to annuloplasty or repair. *(Level of Evidence: C)*

Class IIb

Tricuspid annuloplasty may be considered for less than severe TR in patients undergoing MV surgery when there is pulmonary hypertension or tricuspid annular dilatation. *(Level of Evidence: C)*

Class III

1. Tricuspid valve replacement or annuloplasty is not indicated in asymptomatic patients with TR whose pulmonary artery systolic pressure is <60 mm Hg in the presence of a normal MV. *(Level of Evidence: C)*
2. Tricuspid valve replacement or annuloplasty is not indicated in patients with mild primary TR. *(Level of Evidence: C)*

Adapted from Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2006;48:e1–e148.

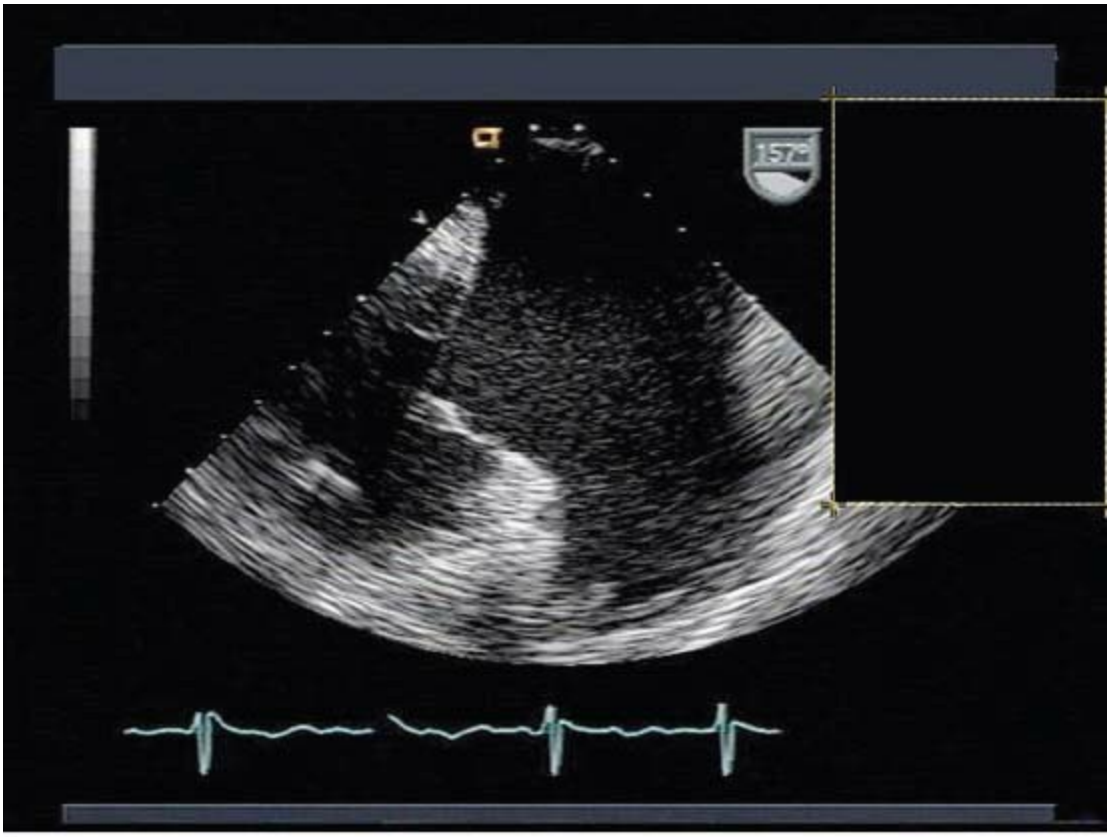
TRICUSPID VALVE STENOSIS

The primary cause of tricuspid valve stenosis (TS) is rheumatic heart disease and is almost always accompanied by severe TR. Stenosis is a consequence of chronic rheumatic fibrosis, as discussed above for MS, occurring for many years after the episode of acute rheumatic fever. It is almost never seen as an isolated valvular lesion and frequently presents later in the phase of rheumatic mitral and aortic valve disease. By the time TS is apparent, most patients have a long history of heart failure and most have already had mitral valve disease long enough to have had one or more cardiac surgical procedures, mostly on the mitral valve.

The symptoms and hemodynamic effects of TS are typically those of severe chronic right-sided congestive failure, and cannot be distinguished easily from those resulting from TR, and the frequent concomitant mitral and aortic valve dysfunction. Patients present with right-sided heart failure, with chronic and progressive symptoms of dyspnea, weakness, fatigue, edema, and anorexia. Common physical exam findings include elevated jugular venous pressure, a RV lift, ascites, peripheral edema, and a parasternal diastolic rumble. There is seldom a tricuspid OS. Electrocardiogram shows

AF in most patients. The rare patient in sinus rhythm has abnormal P waves from left and right atrial enlargement. Chest x-ray often shows massive cardiomegaly, where the dilated right atrium is eclipsed by severe left atrial enlargement.

The findings by echocardiography include diastolic doming, thickening, and restricted motion of tricuspid leaflets (Fig. 34.19). Valve area and pressure gradients can be obtained by Doppler echocardiography, similar to MS, although the accuracy of these measurements is not as well validated.



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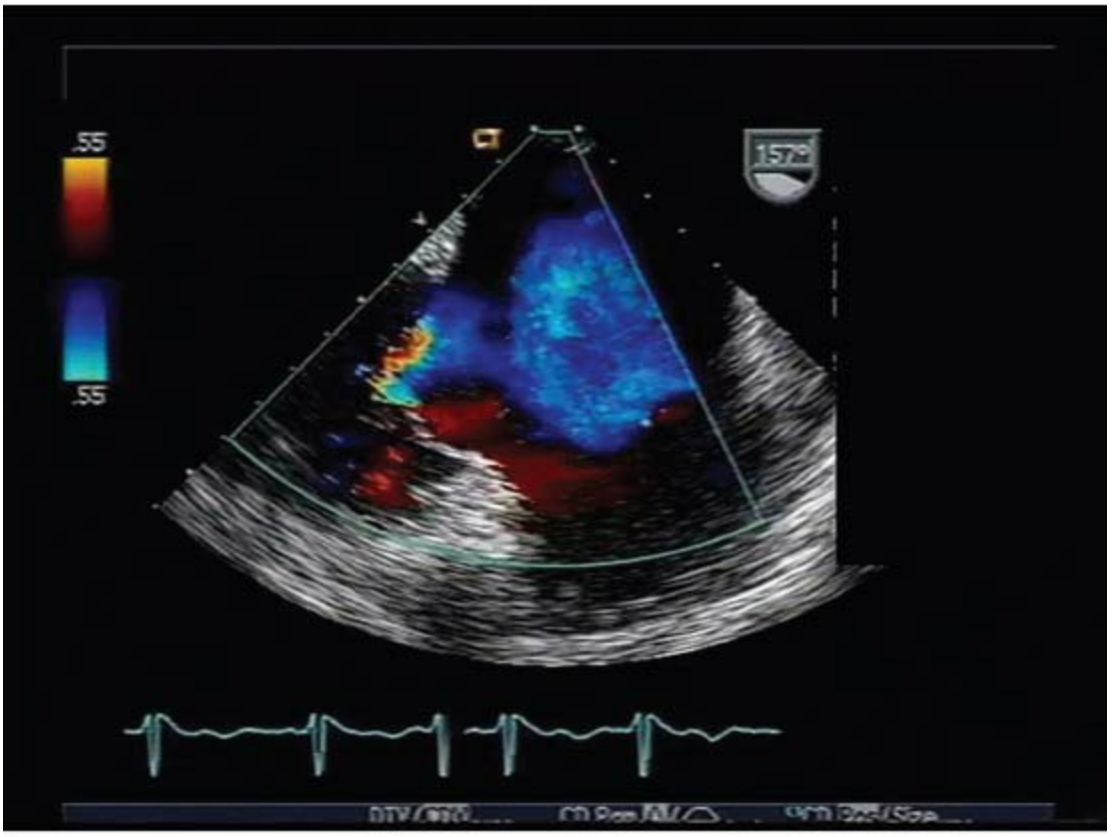

B

FIGURE 34.19 Midesophageal diastolic 2-D image **(A)** and color flow image **(B)** in a patient with severe rheumatic tricuspid stenosis, showing the diastolic doming, leaflet thickening, and restricted motion. The severely enlarged right

atrium is shown. The patient was under evaluation for reoperation, with recurrence of right and left heart failure after three previous mitral valve operations.

Surgical correction is the mainstay of therapy, and this is clinically successful primarily when combined with mitral and/or aortic valve surgery. Correcting the tricuspid valve without fixing the left-sided problems may lead to pulmonary congestion and edema. Open or balloon valvotomy, especially to relieve the fusion at the commissure between the anterior and septal leaflets and between the posterior and septal leaflets, can relieve the stenosis, but the clinical results are often poor because of persistence of TR. Often tricuspid valve replacement, usually with a bioprosthesis, is necessary to treat the patient with significant TS–TR adequately.

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QUESTIONS AND ANSWERS

Questions

1. Mitral valve regurgitation is not associated with which of the following?
   a. Heart failure
   b. Atrial fibrillation (AF)
   c. Stroke
   d. Pulmonary hypertension
   e. Increased pulse pressure
2. What is the effect of successful mitral regurgitation (MR) repair on left ventricular ejection fraction (LVEF)?
   a. Stays the same
   b. Goes up
   c. Goes down
3. What level of instantaneous regurgitant orifice area (ROA) is the criterion for severe (4+) MR?
   a. >60 mL
   b. >0.4 cm^2
   c. >200 mL/s
   d. >400 mm^2
   e. >0.6 cm^2
4. What is the most common etiology of tricuspid regurgitation (TR)?
   a. Rheumatic disease
   b. Prolapse or flail
   c. Trauma
   d. Carcinoid
   e. Left-sided heart failure
5. A 55-year-old man has posterior mitral valve prolapse (MVP) that was detected on a recent physical exam. His MR is anteriorly directed and his ROA measures 0.5 cm^2 on proximal convergence method. He has an LVEF of 50%, normal pulmonary artery pressures, and can run 3 miles every other day without difficulty. He has never experienced AF to his knowledge. His left ventricular (LV) end systolic dimension is 4.2 cm and his LV end diastolic dimension is 6 cm. His left atrial diameter is 4.5 cm. What do you recommend now?
   a. Watchful waiting with repeat echocardiogram in a year
   b. Mitral valve replacement (MVR) with a bioprosthesis given his age
   c. MVR with a mechanical valve given his age

d. Mitral valve repair within the next few months
e. Afterload reduction with an angiotensin-converting enzyme (ACE) inhibitor and careful monitoring of his LV function

6. A 70-year-old woman with long-standing mitral stenosis (MS) comes to see you. She claims that she is perfectly fine and can do all her activities of daily living. Her family who accompany her suggest that she has gradually reduced her activities and is now house bound. The valve is heavily calcified and her mean gradient across it is 6 mm Hg by echocardiography. There is 2+ MR. The pulmonary artery pressure is 50 mm Hg systolic. Her other valves are thickened but not stenotic. She has 3+ TR. She has long-standing AF that is rate controlled. She is taking coumadin, digoxin, and a beta-blocker. The next step in her evaluation is:
   a. Start furosemide to reduce her filling pressures.
   b. Do a stress echocardiogram to assess her functional capacity and change in valve gradients, regurgitation, and pulmonary pressures with stress.
   c. Recommend cardiac catheterization to measure her intracardiac pressures invasively.
   d. Perform transesophageal echocardiography (TEE) to better assess her MS.
   e. Recommend balloon valvuloplasty now to improve her valve gradients.

7. A 45-year-old woman presents with increasing weight gain and abdominal fullness for a number of months. She sustained a motor vehicle accident about 6 months ago and had a major injury to her chest. She had made a reasonable recovery but is now limited. On examination, she is in normal sinus rhythm. Her venous pressure wave is prominent and elevated. She has a Grade 3/6 systolic murmur at the right sternal border. She has abdominal distention with hepatomegaly. She has 3+ pitting edema bilaterally. The most likely cause of her problems is:
   a. Carcinoid syndrome with resultant severe TR
   b. Right heart failure from respiratory insufficiency following her traumatic injury to the chest
   c. Constrictive pericarditis consequent on her chest injury
   d. Ischemic injury to the right coronary artery and ruptured papillary muscle to the tricuspid valve
   e. Traumatic chordal rupture of tricuspid valve leaflet with severe TR

8. The following is true about tricuspid stenosis:
   a. It often occurs as an isolated lesion independent of other valve involvement.
   b. Balloon valvuloplasty is the treatment of choice in most situations.
   c. If mitral valve disease is present, tricuspid stenosis is usually evident before mitral valve disease is manifest.
   d. Is often accompanied by severe TR.
   e. Often an audible opening snap (OS) is present over the tricuspid valve.

9. A 55-year-old woman has severe symptomatic MS and has a valve area of 0.8 cm^2. She has 2+ MR, moderate aortic regurgitation (AR), and a splittability score of 11. She had an open commissurotomy in the past. Which of the following statements is most likely to be correct?
   a. She should not undergo mitral balloon valvuloplasty as the degree of MR and splittability score are absolute contraindications to the procedure.
   b. You tell her that balloon mitral valvuloplasty is unlikely to be successful because of her prior commissurotomy.
   c. You tell her that balloon mitral valvuloplasty may be attempted but she is unlikely to have an optimal result based on her splittability score and her prior commissurotomy but may provide symptomatic relief.
   d. You recommend watchful waiting as she will likely improve with an exercise program.
   e. You tell her that her only option is MVR and that this will be a low-risk procedure with estimated mortality of <1%.

10. Which of the following statements with regard to MVP is true?
   a. It is more common in women than in men.
   b. It is best diagnosed from the apical four-chamber echocardiographic image plane.

c. Men are more likely to have significant complications including surgery on the mitral valve than women.
d. Leaflet thickening when present has no adverse effect.
e. Most patients with MVP will eventually progress to severe MR and need for surgery.

Answers

1. Answer E: AR is associated with increased pulse pressure due to the excess run-off of flow back into the LV in diastole. Prior to end-stage MR with secondary abnormalities, the cardiac output and forward stroke volume are normal. Arterial pressure is usually normal, and pulse pressure is normal. All the other choices are in some circumstances associated with MR, including the development of left atrial thrombi, often from concomitant AF, leading to systemic embolization.

2. Answer C: In a study by Leung et al.[13] of 139 patients with isolated MR and no evidence of coronary artery disease, of whom 74 underwent uncomplicated valve repair, MR repair was associated with decreased LVEF and end-diastolic volume. However, end-systolic volume was preserved. This can be understood as relief of the chronic state of increased chronic excess stroke volume present when the MR is causing redundant mitral valve inflow, over LV outflow. In other words, chronic MR is often associated with an ejection fraction that overestimates true myocardial function.

3. Answer B: The following cut points have been established for severe MR when using proximal isovelocity surface area (PISA) to calculate instantaneous ROA:

<0.19 cm^2 is mild

0.2 to 0.29 cm^2 is moderate

0.3 to 0.39 cm^2 is moderately severe

>0.4 cm^2 is severe

4. Answer E: The most common etiology of TR is left-sided heart disease.

5. Answer D: He has severe MR with ROA > 0.5 cm^2. He now has LV dysfunction as his LVEF is 50%. This should be at least 60% in someone with severe MR and normal LV function and is a Class I indication for surgical intervention. Mitral valve repair is favored over MVR in the treatment of MR when feasible as long-term outcomes are generally better and LV function is more likely to be preserved postoperatively with repair. Waiting further in this man may only cause his contractile function to deteriorate further. There is no evidence that afterload reduction or any other medical therapy will alter the natural history of MR. Either a mechanical or bioprosthetic valve might be reasonable choices in this individual if repair were not feasible.

6. Answer B: This lady has mixed MS and regurgitation and significant pulmonary hypertension. She has a heavily calcified mitral valve with moderate mitral gradients. The first thing to establish with her is how severely limited she is and whether the mitral valve is contributing to this. A stress echocardiogram will allow her functional capacity and her hemodynamic changes on exercise be determined. In some patients with mixed mitral valve disease, the MR may worsen on exercise and lead to a significant increase in the pulmonary artery pressures. TEE is useful in evaluating MR but planimetry of the mitral valve is often difficult with TEE. Cardiac catheterization is very useful in evaluating the hemodynamics of mitral valve disease but will not give an assessment as to how limited the patient is. This is crucial for decision making as to the best options for her.

7. Answer E: Traumatic injury to the tricuspid valve may occur following a motor vehicle accident and can present insidiously with severe TR and right heart failure. Surgical repair is usually feasible and curative.

8. Answer D: Tricuspid stenosis is relatively uncommon and is almost always seen in the setting of significant rheumatic mitral valve disease. It usually manifests late often with accompanying significant TR. Balloon valvuloplasty is feasible in some instances but is rarely considered because of concomitant

severe TR.

9. Answer C: Balloon valvuloplasty is not contraindicated based on either the splittability score or a history of prior commissurotomy or 2+ MR. The results are less likely to be optimal in this situation but may afford symptomatic relief. It is unlikely that her symptoms will improve with exercise as she has critical MS. MVR will have a >1% risk given her prior surgical procedure.

10. Answer C: MVP is equally prevalent in men and women but men are more likely to have complications such as endocarditis and significant MR. In most patients, mitral prolapse is a benign condition and does not require surgery. Mitral valve thickening of > 5 mm— classic mitral prolapse- is more likely to have a complicated course. Mitral prolapse is best detected and diagnosed on the long-axis views and not the apical four-chamber echocardiographic view because the saddle shape of the mitral annulus may lead to apparent but factitious prolapse on the apical four-chamber view.

CHAPTER

Infective Endocarditis

Peter Zimbwa and Steven M. Gordon

Over the last three decades, the overall incidence of infective endocarditis (IE) and the associated mortality have remained constant, between 1.7 and 6.2 per 100,000 people per year, and between 10% and 30%, respectively.[1–4] The clinical spectrum of IE has, however, undergone dramatic changes. These changes are noted in:

- The at-risk population
- The underlying susceptible cardiac lesions
- The etiologic pathogens
- The clinical presentation
- The diagnostic evaluation
- The antimicrobial agents
- The recommendations for prophylaxis

In industrialized countries, the population at risk for IE has become older, parallel to an ageing population. The attendant degenerative valve lesions such as calcific aortic stenosis and myxomatous mitral regurgitation (MR) have superseded rheumatic heart disease as the primary risk factors for IE. In developing countries where antibiotic use is not as widespread, however, rheumatic heart disease remains the key risk factor for IE. Invasive medical interventions, particularly with intravascular catheters, hemodialysis, and cardiac implantable electronic devices, have led to the emergence and prominence of health care–associated (nosocomial) IE. There has also been growth in those at risk in industrialized countries among injection drug users (IDU), and patients with prosthetic valves. The etiologic pathogens have remained largely unchanged, with viridans streptococci and staphylococci species accounting for the majority of cases. However, their relative contributions and antibiotic sensitivities have changed, mirroring the risk factors. For instance, the majority of cases in the 1960s and

1970s were caused by viridans streptococci, and 15% of cases were due to staphylococci. More recently, staphylococci have surpassed streptococci as the most common cause of IE accounting for 31% of the cases, whereas viridans streptococci were identified in 17%.[2] In most urban areas, IDU may account for the majority of IE that is most commonly caused by Staphylococcus aureus.[3,11] Such patients tend to be younger and present more acutely with fever and sepsis syndromes rather than as the classic Oslerian subacute and chronic presentation of fever of unknown origin, with regurgitant valvulitis, splinter hemorrhages (Fig. 35.1), Osler nodes (Fig. 35.2), Janeway lesions (Fig. 35.3), or Roth spots.

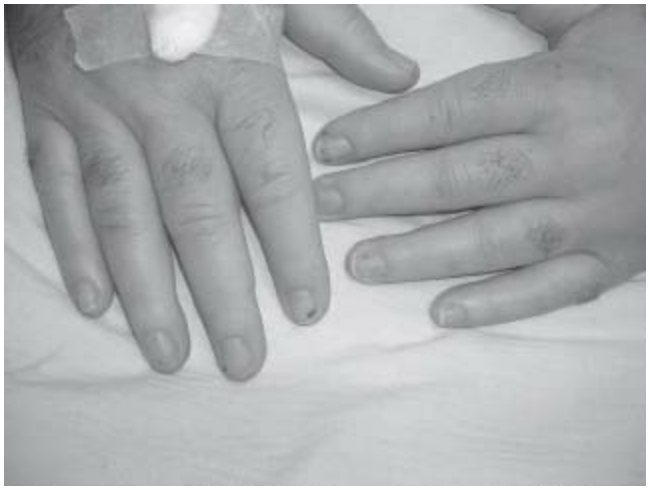

FIGURE 35.1 Splinter hemorrhages.

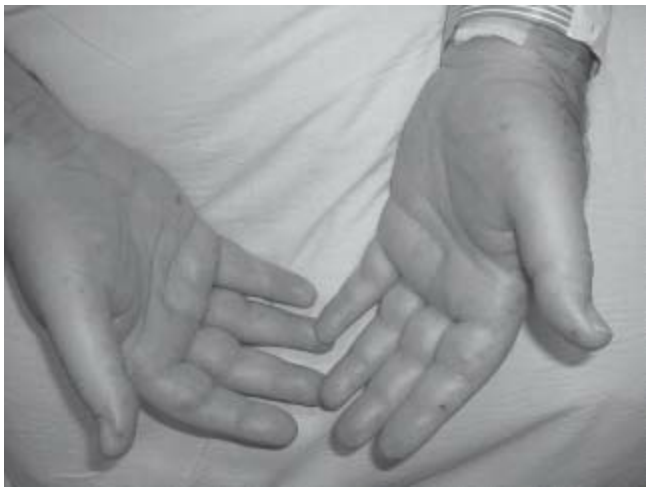

FIGURE 35.2 Osler nodes

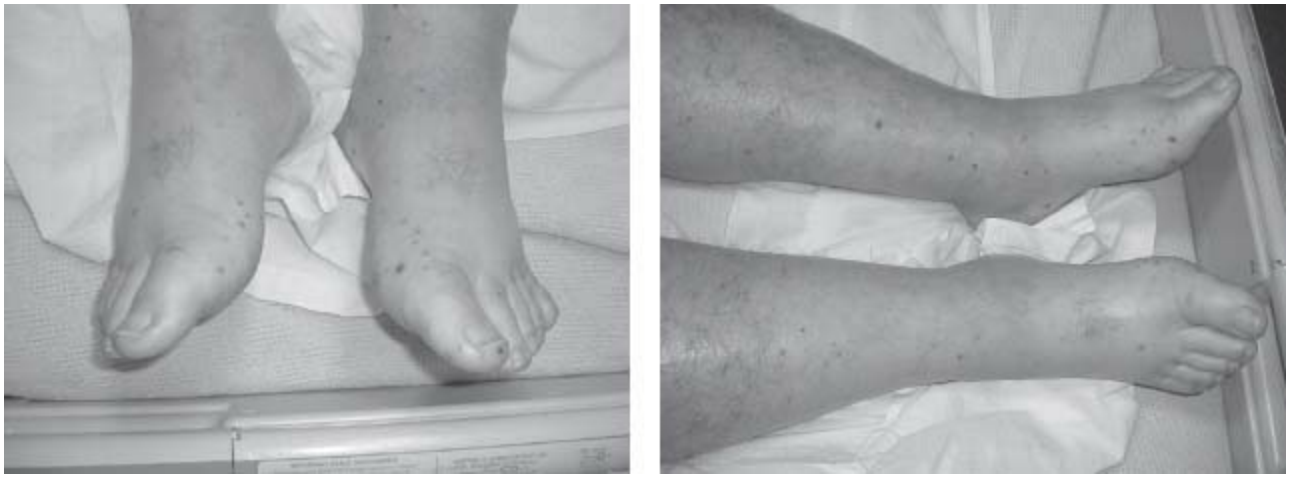

FIGURE 35.3 Janeway lesions.

The International Collaboration on Endocarditis–Prospective Cohort Study (ICE-PCS), Murdoch and coinvestigators[2] prospectively collected data on 2,781 patients with definite IE by the modified Duke criteria at 58 hospitals in 25 countries from June 1, 2000, through September 1, 2005. The median age of the cohort was 57.9 years, and 72.1% had native valve endocarditis (NVE). Most patients (77%) presented early (within 30 days) with few of the classic features of IE. Recent health care exposure was found in 25% of patients. S. aureus was the most common pathogen (31.2%). Left-sided IE was more common (mitral valve 41.1%, aortic valve 37.6%). Common complications included stroke (16.9%), embolization other than stroke (22.6%), heart failure (32.3%), and intracardiac abscess (14.4%). Surgical therapy was common (48.2%), and in-hospital mortality was high (17.7%). Increased risk of in-hospital death was associated with prosthetic valves (PV), older age, pulmonary edema, S. aureus, coagulase-negative staphylococcal infection, mitral valve vegetation, and paravalvular complications. Viridans streptococcal infection and surgery were associated with a decreased risk.

DEFINITIONS

IE is defined as a microbial infection of the endocardium. Acute and subacute endocarditis are further subdivisions based on the tempo and severity of the infection[1] with subacute presentation usually defined as >2 months of symptoms before diagnosis. Prosthetic valve endocarditis within 12 months after valve surgery is defined as early and is often caused by drug-resistant, surgery-related pathogens, such as methicillin-resistant Staphylococcus aureus (MRSA).[1] Infections that are acquired after this period, presumably after endothelialization of the valve prosthesis, are defined as late. Late PV is more likely caused by the same set of pathogens that cause NVE, such as oral streptococci, and the HACEK group (Haemophilus species, Aggregatibacter (formerly

Act-inobacillus) actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella species).[1] Hospital-acquired IE has been defined as either IE with onset of symptoms >72 hours after hospitalization or IE occurring from 4 to 8 weeks after discharge from the hospital if an invasive procedure was performed during hospitalization.[5]

EPIDEMIOLOGY

IE is uncommon. The incidence of community-acquired NVE has remained between 1.7 and 6.2 per 100,000 person-years over the last three decades. The associated mortality has also remained unchanged (between 10% and 30%) over the same period.[1–4] While three decades ago, IE was mainly a complication of rheumatic heart disease in children and young adults, in the industrialized world, IE is now mainly seen in much older adults rendered vulnerable by new risk factors including degenerative heart valve disease, valve prostheses, hemodialysis, intravascular catheters, cardiac implantable electronic devices, and IDU.[1–4]

Left-sided IE is more frequent than right-sided IE, accounting for over two-thirds of NVE.[2,6] Prosthetic valve endocarditis of the left side has the worst prognosis, associated with mortality that can exceed 40%.[5–7] The cumulative risk for PV increases with duration of the prosthesis, reported to be approximately 1% at 1 year and 2% to 3% at 5 years.[8,9] Right-sided IE commonly occurs in the setting of IDU, indwelling central venous catheter, cardiac implantable electronic devices, congenital heart disease (CHD), and human immunodeficiency virus (HIV) infection.[10,11] The incidence of IE associated with IDU is 150 to 2,000 per 100,000 person-years with in-hospital mortality <10%.[1] Although its prognosis is generally better than that of left-sided IE, in patients with acquired immunodeficiency syndrome (AIDS), mortality of right heart endocarditis can reach 50%.[12,13]

Hospital-acquired IE constitutes 9% to 29% of all cases and has increased in frequency in recent years owing to greater use of invasive procedures.[14,15] MRSA, coagulase-negative staphylococci, and gram-negative bacilli tend to predominate as causative agents, with mortality rates as high as 40% to 60%. Fowler et al.[16] recruited 324 patients with S. aureus bacteremia caused by an infected intravascular device to define patient and bacterial characteristics associated with the development of hematogenous complications (including endocarditis). On multivariable analysis, symptom duration, hemodialysis dependence, presence of a long-term intravascular catheter, or a noncatheter device, and infection with MRSA placed the patients at a higher risk of developing hematogenous complications.

RISK FACTORS

Important risk factors for IE include:

- Degenerative valvular heart disease
- Prosthetic heart valves
- Increased exposure to nosocomial bacteremia
- Poor dental hygiene
- Long-term hemodialysis
- Injection drug use
- HIV infection

PATHOGENESIS

Four main mechanisms are responsible for the initiation and localization of infection of the endocardium:

1. A previously damaged cardiac valve or a situation in which a jet effect is produced by blood flowing from a region of high pressure to one of low pressure
2. A sterile platelet fibrin thrombus
3. A pathogen in the bloodstream
4. High titer of agglutinating antibody for the infecting organism

Damaged endocardium results in exposure of the underlying extracellular matrix proteins, which engenders thrombosis with production of tissue factor, and the deposition of fibrin and platelets.[17] Pathogens then adhere to the damaged endothelium and set up infection via adhesins which include proteins and polysaccharides collectively known as Microbial Surface Component Reacting with Adhesive Matrix Molecules (MSCRAMMs).[18] In experimental IE using animal models, both the magnitude of bacterial inoculum and the adhesive properties of bacteria were important in determining the likelihood of subsequent infection.[19] Inoculating animals with bacterial bolus injections between 10^5 and 10^7 colony-forming units (CFU)/mL induced IE.[20] Veloso et al.[21] tested whether IE could also be induced by injecting the same absolute number of bacteria but at a very low level. They found that such low-grade continuous infusion (over >10 hours) was as infective as high-grade bolus infusion, confirming that perhaps the most critical factor for IE induction is total bacterial burden, rather than peak bacterial concentration. Transient, recurrent, low-grade, and short duration (1 to 100 CFU/mL for <10 minutes) bacteremia occurs during chewing and brushing teeth.[22] Such “normal” cumulative exposure exceeds a single tooth extraction

by the order of 10^5.[23,24] This likely explains why most cases of IE occur without antecedent dental procedures and why health care-associated IE arises from recurrent health care–related bacteremia,[25,26] a point for consideration in IE prophylaxis.

MICROBIOLOGY

In recent times, staphylococci, particularly S. aureus, have overtaken viridans streptococci as the most common cause of IE.[1,2] In the future, we foresee a further shift in IE being caused by S. aureus. Coagulase-negative staphylococci are the most common pathogens in early PV[1] Staphylococcus lugdunensis, a coagulase-negative organism, tends to cause a particularly virulent form of IE with high rates of perivalvular extension and metastatic seeding.[1] The most common streptococci isolated from patients with IE are Streptococcus sanguis, Streptococcus bovis, Streptococcus mutans, and Streptococcus mitis.[1] Endocarditis by group D streptococci, mainly Streptococcus gallolyticus, previously known as S. bovis, is prevalent among the elderly and is associated with preexisting colonic lesions.[1] Polymicrobial IE is encountered most often in the setting of IDU and is uncommon.[1]

The HACEK group are gram-negative aerobic organisms associated with the so-called "culture-negative" IE and are now readily identified by blood culture systems. Culture-negative IE accounts for around 10% of most reported series of IE.[2] The most common cause of culture-negative endocarditis is prior administration of antibiotics. To overcome this problem, special blood culture media containing charcoal have been devised to inhibit the effects of antibiotics.[27] When blood cultures from patients with IE remain negative at 48 to 72 hours, the laboratory should be alerted for prolonged incubation or for plating of subcultures on enriched media. A list of organisms that cause culture-negative endocarditis is provided in Table 35.1. A comparison of microorganisms identified in published series of blood culture-negative IE shows that the most common etiologies are Bartonella species, Coxiella burnetti, and Tropheryma whipplei.[28]

TABLE
35.1 Organisms Causing Culture-Negative Endocarditis

Organism	Approach
Abiotrophia species (previously classified as nutritionally variant streptococci)	Grow in thioglycolate medium of blood culture and as satellite colonies around *S. aureus* on blood agar or on medium supplemented with pyridoxal hydrochloride or L-cysteine
Bartonella species (usually *Bartonella hensla* or *B. quintane*)	Serologic tests Lysis-centrifugation system for blood cultures PCR of valve or embolized vegetations; special culture techniques available, but organisms are slow growing and may require a month or more for isolation
Coxiella burnetii (Q fever)	Serologic tests PCR, Giemsa stain, or immunohistologic techniques on operative specimens
HACEK organisms	Blood cultures positive by day 7; occasionally require prolonged incubation and subculturing
Chlamydia species (usually *Chlamydia psittaci*)	Culture from blood has been described Serologic tests Direct staining of tissue with use of fluorescent monoclonal antibody
Tropheryma whippleii	Histologic examination (silver and PAS stains) of excised heart valve; PCR or culture of vegetation
Legionella species	Subculture from blood cultures, lysis-centrifugation pellet from blood cultures or operative specimens on BCYE agar; direct detection on heart valves with fluorescent antibody Serologic tests
Brucella species (usually *Brucella melitensis* or *B. abortus*)	Serologic tests Prolonged incubation of standard or lysis-centrifugation blood cultures
Fungi	Regular blood cultures often positive for *Candida* species; lysis-centrifugation system with specific fungal medium can increase yield; testing urine for *H. capsulatum* antigen or serum for *Cryptococcus neoformans* polysaccharide capsular antigen can be helpful Accessible lesions (such as emboli) should be cultured and examined histologically for fungi

PCR, polymerase chain reaction; HACEK organisms Haemophilus species (H. parainfluenzae, H. aphrophilus, and H. paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae; PAS, periodic acid–Schiff; BCYE, buffered charcoal yeast extract.

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Bartonella species are fastidious gram-negative coccobacilli that are mainly transmitted by arthropod vectors. Bartonella henselae infections occur following exposure to cats or cat fleas and are associated with various diseases including cat-scratch disease, meningoencephalitis, bacillary angiomatosis, peliosis hepatitis as well as a subacute IE. Among the 24 known Bartonella species, most cases of IE are caused by B. henselae or Bartonella quintana and account for approximately 1% to 3% of IE cases and 9% to 10% of culture-negative IE.

C. burnetii is the cause of Q fever and is a common cause of IE in parts of the world where sheep, cattle, and goats are birthed.[29] Coxiella tends to infect prosthetic valves or previously damaged aortic and mitral valves and causes small subendothelial vegetations that are often missed by echocardiography. The organism resides in the acidic phagolysosome, where antibiotic activity may be inhibited.

Tropheryma whipplei is a rod-shaped bacterium that is identified as PAS-positive microorganism inside the macrophages.[30] It is the causative pathogen for Whipple disease characterized by chronic enteritis with malabsorption, arthritis,

lymphadenopathy, uveitis, encephalitis, and dementia. It can also cause culture-negative endocarditis. Diagnosis is best achieved by polymerase chain reaction (PCR).

Brucellae are zoonotic infections.[31] Humans are infected through the ingestion of contaminated meat or unpasteurized milk, the inhalation of infectious aerosols, or direct contact with infected tissues. This is mainly a disease of farmers, abattoir workers, veterinarians, and shepherds. Because vegetations are large and valve destruction commonly occurs, most patients require a combination of antimicrobial therapy and valve replacement. Legionella IE often presents as a febrile illness present over many months.[32] Most patients have prosthetic valves. Embolic events are unusual with this organism. Pseudomonas aeruginosa is a rare cause of IE and occurs in the setting of IDU.[2]

Fungal IE is usually caused by Candida species but may also include other species such as Aspergillus and Histoplasmosis capsulatum.[33] It usually manifests as bulky vegetations, perivalvular extension of infection, metastatic seeding, and embolization to large blood vessels. Predisposing factors for fungal IE are IDU, prolonged antibiotic therapy, immunosuppression, intravenous catheters, cardiac implantable electronic devices, prior or concomitant bacterial endocarditis, and disseminated fungal infection. The rate of recovery of filamentous fungi such as Aspergillus is <30% even with the lysis centrifugation system.

The Important Role of Staphlococcus aureus Bacteremia

The issue of IE in patients with prosthetic valves and S. aureus bacteremia has been recently addressed in two studies. Fowler et al.[16] found that 42 of 324 (13%) patients with S. aureus bacteremia caused by intravascular device infection developed a hematogenous complication. Of these 42 patients, 31 (74%) had IE. In a prospective study by El-Ahdab et al.,[34] approximately 50% of patients with prosthetic valves who developed S. aureus bacteremia had definite endocarditis. The mortality rate was high (60%) in those patients who were managed medically. The authors recommend that all such patients undergo transesophageal echocardiography (TEE) whenever possible.

CLINICAL FEATURES

IE is a systemic disease with protean manifestations. In 1885, William Osler presented the first comprehensive description of endocarditis during three Gulstonian Lectures at the Royal College of Physicians in the United Kingdom. Emanuel Libman later associated the valvular lesions with bacteremia in 1906.[1] In patients presenting with classic features such as bacteremia or fungemia, active valvulitis, peripheral emboli, and immunologic vascular phenomena, the diagnosis of IE is straightforward. Fever is the most common symptom and sign; however, it may be absent in patients with

congestive heart failure (CHF), severe debility, chronic renal or liver failure, previous use of antimicrobial drugs, or IE caused by less virulent organisms. Other common symptoms of subacute IE include anorexia, weight loss, malaise, and night sweats. Musculoskeletal complaints are an early symptom in subacute IE, ranging from low-back pain and myalgias to frank septic arthritis. A chronic wasting disease similar to that seen in HIV or cancer may develop in a proportion of patients with subacute IE. Pulmonary findings such as pneumonia may be the dominant feature in isolated right-sided IE. The onset of nosocomial IE is usually acute, and signs of endocarditis are infrequent.

The presentation of IE often includes extracardiac manifestations or findings that are associated with intracardiac extension of infection. Most patients with IE have a heart murmur (most commonly preexisting). A murmur or other evidence of valvular disease, especially aortic regurgitation (AR) or MR, may be a common sign in subacute IE. Patients may have petechiae on the skin, conjunctivae, or oral mucosa, as well as splenomegaly and other peripheral manifestations.

Skin lesions often provide a clue to IE diagnosis. Splinter hemorrhages (see Fig. 35.1) are 1 to 2 mm subungual brown streaks and are of greater significance when seen in the proximal nail bed rather than distal splinters that are usually related to trauma, such as that incurred while gardening. Osler nodes (see Fig. 35.2) are red, painful, indurated lesions between 2 and 15 mm, found on the palms and soles. Janeway lesions (see Fig. 35.3) are red, painless macules that appear on the palms and soles. Roth spots are boat-shaped retinal hemorrhages with a pale center. Embolization of small vegetations to the distal extremities may result in "blue toe syndrome," which resolves in most cases without sequelae. Acute IE presents as severe sepsis with high fevers, lethargy, rapid cardiac deterioration, and shock. In acute AR, signs such as a widened pulse pressure are not usually present. In acute MR, a fourth heart sound may develop rather than the typical third heart sound seen in chronic MR. A rapid destruction of left-sided valves occurs leading to heart failure and circulatory collapse. Heart failure may result from valvular destruction, myocardial abscess, myocardial ischemia from vegetation embolization of the coronary circulation, arrhythmia such as atrial fibrillation, and sepsis.

Metastatic infection and vegetation embolization in IE can occur in virtually any organ, resulting in an acutely ischemic limb, a splenic infarct causing referred left shoulder pain from diaphragmatic irritation, a kidney infarct causing flank pain, etc. Brain complications of IE include cerebral vascular accident (CVA) from vegetation embolization or ruptured cerebral mycotic aneurysm (MA) that usually presents with intracranial hemorrhage. Anyone with a fever and a stroke should have blood cultures and be evaluated for possible IE. Symptoms and signs of cerebral involvement may be subtle however, including lethargy, confusion, and frank psychosis. Renal failure may occur from severe sepsis, embolization, immune complex deposition with acute post

infectious glomerulonephritis, or may arise from therapy with antibiotics such as gentamicin. Prosthetic valve endocarditis may be manifested as an indolent illness with low-grade fever or it can be an acute febrile and toxic illness. The high frequency of invasive infection in PV results in higher rates of new or changing murmurs and of CHF. Unexplained fever in a patient with a prosthetic valve should prompt careful evaluation for PV[35]

DIAGNOSIS

A substantial proportion of patients with IE do not present with the classic Oslerian manifestations because of the acute nature of their illness. The diagnosis of IE requires a high index of suspicion, as well as the assimilation of clinical, laboratory, electrocardiographic, and echocardiographic data. Nonspecific laboratory abnormalities may be present, including anemia, leukocytosis, and elevated erythrocyte sedimentation rate and C-reactive protein level, and abnormal urinalysis with hematuria, proteinuria, or red cell casts. New electrocardiographic abnormalities may arise including AV or bundle-branch block, particularly in the setting of aortic-valve endocarditis with perivalvular invasion and aortic root abscess formation. Such patients need close cardiac monitoring.

The Duke Criteria

The variability of illness in IE mandates a diagnostic strategy that is both sensitive and specific. In 1981, Von Reyn et al. [36] proposed very stringent Beth Israel criteria to aid in the diagnosis of IE. In 1994, a group at Duke University proposed standardized criteria for assessing patients with suspected IE.[37] These criteria integrated factors predisposing patients to the development of IE, the blood-culture isolate and persistence of bacteremia, and echocardiographic findings with other clinical and laboratory information. In a review of the individual value of each component of the Duke criteria, the major microbiologic criteria had the highest relative importance. This further stresses the importance of obtaining adequate blood cultures in a patient suspected of having IE, preferably prior to the administration of antibiotics.

The Duke criteria classify patients into three categories: definite cases identified either clinically or pathologically, possible cases, and rejected cases. Numerous studies have validated the usefulness of the Duke criteria.[38–43] Misclassification of culture-negative cases, the increasing role of TEE, the relative risk of endocarditis in S. aureus bacteremia, and the overly broad categorization of cases as “possible” were problems with the original criteria. A modified version of the Duke criteria has recently been proposed.[44] (Table 35.2).

TABLE
35.2 Modified Duke Criteria

Criteria	Comments
Major criteria	
Microbiologic	
Typical microorganism isolated from two separate blood cultures: viridans streptococci, *S. bovis*, HACEK group, *S. aureus*, or community-acquired enterococcal bacteremia without a primary focus	In patients with possible IE, at least two sets of cultures of blood collected by separate venipunctures should be obtained within the first 1–2 h of presentation. Patients with cardiovascular collapse should have three cultures of blood obtained at 5–10 min intervals and thereafter receive empirical antibiotic therapy.
or	
Microorganism consistent with IE isolated from persistently positive blood cultures	
or	
Single positive blood culture for *C. burnetii* or phase 1 IgG antibody titer to *C. burnetii* >1:800	*C. burnetii* is not readily cultivated in most clinical microbiology laboratories.
Evidence of endocardial involvement	
New valvular regurgitation (increase or change in preexisting murmur not sufficient)	
or	
Positive echocardiogram (transesophageal echocardiogram recommended in patients who have a prosthetic valve, who are rated as having at least possible IE by clinical criteria, or who have complicated IE)	Three echocardiographic findings quality as major criteria: a discrete, echogenic, oscillating intracardiac mass located at a site of endocardial injury; a periannular abscess; and a new dehiscence of a prosthetic valve.
Minor criteria	
Predisposition to IE that includes certain cardiac conditions and injection drug use	Cardiac abnormalities that are associated with IE are classified into three groups: High-risk conditions: previous IE,** aortic valve disease, rheumatic heart disease, prosthetic heart valve, coarctation of the aorta, and complex cyanotic CHDs Moderate risk conditions: mitral valve prolapse with valvular regurgitation or leaflet thickening, isolated mitral stenosis, tricuspid valve disease, pulmonary stenosis, and hypertrophic cardiomyopathy Low or no risk conditions: secundum atrial septal defect, ischemic heart disease, previous coronary artery bypass graft surgery, and mitral valve prolapse with thin leaflets in the absence of regurgitation
Fever	Temperature >38°C (100.4°F)
Vascular phenomena	Petechiae and splinter hemorrhages are excluded. None of the peripheral lesions are pathognomonic for IE.
Immunologic phenomena	Presence of rheumatoid factor, glomerulonephritis, Osler nodes, or Roth spots
Microbiologic findings	Positive blood cultures that do not meet the major criteria Serologic evidence of active infection; single isolates of coagulase-negative staphylococci and organisms that very rarely cause IE are excluded from this category.

Cases are defined clinically as definite if they fulfill two major criteria, one major criterion plus three minor criteria, or five minor criteria; they are defined as possible if they fulfill one major and one minor criterion, or three minor criteria. HACEK, Haemophilus species (H. parainfluenzae, H. aphriphilus, and H. paraphrophilus), A. actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae.

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Blood Cultures

Blood cultures are excellent traditional tools, not only for diagnosis, but also for the determination of antibiotic susceptibility to guide therapy. According to Towns and Reller,[27] best practice guidelines for blood cultures include:

- Obtaining blood cultures before starting antimicrobials whenever possible
- Exercising strict aseptic technique and optimal skin preparation when collecting blood cultures
- In acute presentations, obtaining at least two or preferably three sets of blood cultures rapidly within 5 to 10 minutes of each other prior to starting antibiotic therapy
- In subacute presentations, obtaining three separate sets of blood cultures spaced 30 minutes apart
- Obtaining 20 mL of blood for each sample drawn (for adults)

Role of PCR Amplification in Clinical Specimens

The diagnosis of IE is straightforward in a patient with typical signs and symptoms and a positive blood culture with a characteristic microorganism. It can be more difficult when blood cultures are sterile, either because of prior antimicrobial therapy or because of the fastidious nature of the pathogen. More recently, a range of microorganisms including T. whipplei, C. burnetii, B. henselae, and B. quintana have been identified using a broad-range PCR in valvular specimens. Using universal primers, species-specific genetic sequences can be identified directly from tissue samples. This technique is culture independent, and almost all bacteria can be detected in a single reaction. Species-specific PCR primers are also available for many bacterial genera, including T. whipplei, Chlamydia, Brucella, Legionella, mycobacteria, and Mycoplasma.

In a recent study by Greub et al.[45] culture, histologic examination, and broad-range PCR were performed on valve samples taken from 127 patients with definite and possible IE (determined prior to valve surgery according to modified Duke criteria) and from 118 patients without IE. The sensitivity of PCR was 61%, that of histology 63%, and that of valve culture 13%. The specificity of both PCR and histology was 100%.

Echocardiography

Echocardiography is key in the management of IE. It is used for the diagnosis of IE and the detection of cardiac complications in order to inform the need and timing of surgical intervention. Intraoperative echocardiography is used to guide the surgeon. Transthoracic echocardiography (TTE) is rapid and noninvasive. It has excellent specificity for vegetations (98%).[46] However, TTE may produce suboptimal images in up to 20% of adult patients because of obesity, chronic obstructive pulmonary disease, or chest-wall deformities; the overall sensitivity for vegetations may be <60% to 70%.[46] Additionally, TTE cannot exclude several important aspects of IE, including infection on prosthetic valves, periannular abscess, leaflet perforation, and fistulae.[46]

TEE utilizes a probe juxtaposed to the heart with less interference from interposed tissues. It also utilizes higher ultrasonic frequencies. This produces images with higher spatial resolution. It is however more costly and invasive, with small but finite risk, the worst being esophageal perforation. TEE increases the sensitivity for detecting vegetations to 75% to 95% while maintaining specificity of 85% to 98%.[46,47–49] It is particularly useful in patients with prosthetic valves and for the evaluation of myocardial invasion.[50] TEE is more sensitive (76% to 100%) and more specific (94%) than TTE for defining perivalvular extension of IE and the presence of a myocardial abscess.[51–53] It is more sensitive than TTE for identifying valve perforations.[54] A TEE with spectral and color-flow Doppler techniques can also demonstrate fistulas, pseudoaneurysms, or abscess cavities. A negative TEE has a negative predictive value for IE of over 92%.[46] Recent guidelines suggest that among patients with suspected IE, TTE should be used in the evaluation of those with native valves who are good candidates for imaging.[55,56] In fact, the appropriate use of echocardiography depends on the probability of IE. If this probability is low, a negative TTE is a cost-effective and clinically satisfactory way to rule out IE.[57] For patients with intermediate probability of IE endocarditic, initial use of TEE is more cost-effective and diagnostically efficient than initial use of TTE, which, if negative, is followed by TEE.[57] Intermediate probability patients include those with unexplained bacteremia and gram-positive cocci, those with catheter-associated S. aureus bacteremia, and those admitted with fever or bacteremia in the setting of recent IDU. The category of low prior probability includes patients with gram-negative bacteremia with a clear noncardiac source and patients with a firm alternate diagnosis or those in whom the “endocarditis” syndrome resolved within 4 days.

There has been controversy whether vegetation size as measured by echocardiography is a prognostic indicator for embolism or even an indication for surgery. Di Salvo et al.[58] in a study of 178 patients with IE reported that those with vegetations >1 cm or those with “highly mobile” vegetations may need to be considered for early surgery irrespective of their response to antimicrobials, the presence of valve destruction, or heart failure. On the other hand, De Castro et al.[59] reported no relationship between vegetation size and the risk of embolization in a study involving 57 patients. Echocardiographic features that suggest potential need for surgical intervention are shown in Table 35.3.

TABLE
35.3 Echocardiographic Features that Suggest Potential HBMl Need for Surgical Intervention

Vegetation
Persistent vegetation after systemic embolization
Anterior mitral leaflet vegetation, particularly with size >10 mm[a]
1 embolic event during first 2 wks of antimicrobial therapy[a]
Increase in vegetation size despite appropriate antimicrobial therapy[a,b]
Valvular dysfunction
Acute aortic or mitral insufficiency with signs of ventricular failure[b]
Heart failure unresponsive to medical therapy[b]
Valve perforation or rupture[b]
Perivalvular extension
Valvular dehiscence, rupture, or fistula[b]
New heart block[b,c]
Large abscess or extension of abscess despite appropriate antimicrobial therapy[b]

see text for more complete discussion of indications for surgery based on vegetation characterizations.

[a]Surgery may be required because of risk of embolization.

[b]Surgery may be required because of heart failure or failure of medical therapy.

[c]Echocardiography should not be the primary modality used to detect or monitor heart block.

From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. Circulation. 2005;111:e394–e434, with permission.

COMPLICATIONS

Certain conditions place patients at increased risk for complications from IE. These are summarized in Table 35.4. Complications of IE may be classified as

TABLE
35.4 Clinical Situations Constituting High Risk for Complications for IE

Prosthetic cardiac valves
Left-sided IE
Staphylococcus aureus IE
Fungal IE
Previous IE
Prolonged clinical symptoms (≥)
Cyanotic CHD
Patients with systemic to pulmonary shunts
Poor clinical response to antimicrobial therapy

Reproduced from Bayer AS, Bolger AF, Taubert KA, et al. Diagnosis and management of infective endocarditis and its complications. Circulation. 1998;98(25):2936–2948, with permission.

- Cardiac including CHF, paravalvular extension
- Neurologic including stroke
- Systemic emboli including splenic abscess

- MAs, intracranial and extracranial

CHF may develop acutely as a result of valve perforation, rupture of mitral chordae, mechanical blockage of valve orifice by bulky vegetation, fistulization of cardiac chambers, coronary vegetation embolization, or arrhythmia.[1] It may occur in a more gradual fashion as result of worsening valvular insufficiency. Heart failure as a result of IE is associated with a grave prognosis and delaying surgery to the point of total ventricular decompensation increases operative mortality. In addition, poor surgical outcomes are portended by renal insufficiency and advanced age.[59] Aortic valve infection is more commonly associated with CHF than mitral valve infection. The left ventricle alone bears the brunt of the volume overload in the case of acute aortic insufficiency (AI) as opposed to acute MR where the left atrium and the pulmonary vascular bed accommodate the regurgitant volume. Hence, new-onset, moderate to severe AI due to IE usually requires surgery. The indications for surgery in right-sided IE are less clear-cut. Tricuspid and pulmonary regurgitation are well tolerated as long as there is no preexisting pulmonary vascular resistance. Extension of infection beyond the valve annulus is associated with higher mortality, more frequent CHF, and the need for surgery. This complication occurs in 10% to 40% of all NVE,[59] and in 56% to 100% of all PV[60] In native aortic valve IE, the extension tends to happen at the weakest portion of the annulus, which resides near the membranous septum and AV node. This is why abscesses and heart block are more frequent in this location.[48] Clinical parameters or the size of the vegetation do not predict the possibility of periannular extension. Development of new AV block has a 77% positive predictive value for abscess formation, but the sensitivity is only 42%.[60] Urgent surgery is usually indicated for this condition and involves drainage of abscess cavities, excision of necrotic tissue, and closure of fistulous tracts in addition to valve replacement.[61]

Neurologic complications develop in up to 40% of all patients with IE,[1] and over half of those requiring admission to intensive care units. Sonneville et al.[62] reported that among 198 patients with definite left-sided IE, 108 (55%) experienced at least 1 neurologic complication. These may include embolic stroke with or without hemorrhage, ruptured intracranial MA, transient ischemic attack, meningitis, and encephalopathy.[1,62] Factors independently associated with neurologic complications were S. aureus IE, mitral valve IE, and nonneurologic emboli.[62] The majority of emboli lodge in the middle cerebral artery (MCA) distribution.[48] The management of a patient with neurologic complications in the acute phase of IE is controversial. Any patient with IE and neurologic symptoms should have preoperative imaging (CT or MRI of the head). Four vessel cerebral angiograms may also be indicated if MA is suspected (usually after rupture causing CNS hemorrhage). A ruptured MA should be clipped, resected, or embolized prior to cardiac surgery for IE.[63] In patients with a hemorrhagic

infarct, the current recommendation is to wait for 2 to 3 weeks between the neurologic event and cardiac surgery because of the risk of intracranial bleeding during anticoagulation with cardiopulmonary bypass, or post cardiac surgery indications.[63,64]

Systemic embolization most commonly involves the spleen, kidney, liver, and the iliac or mesenteric arteries.[1] Splenic abscess is a rare complication of IE and develops as a result of bacteremic seeding of a bland infarct caused by a splenic artery embolus, or by direct seeding of the splenic tissue by an infected vegetation.[48] It occurs in 5% of all splenic infarctions, with viridans streptococci and S. aureus being the major causes. The diagnosis must be suspected in any patient with IE and flank, back or abdominal tenderness in the left upper quadrant or left shoulder (from diaphragmatic irritation).[48] Abdominal CT and MRI are the most sensitive modalities to diagnose this complication, and definitive treatment is splenectomy with antibiotics before valve surgery, unless valve replacement is more urgent.[48]

MAs may be intra- or extracranial. They are uncommon complications of IE and result from septic embolization of vegetations first to the vasa vasorum, then into the intima, and finally through the outer layer of the vessel wall. The commonest sites are the branching points of arteries and occur, in decreasing order, in intracranial arteries, visceral arteries, and arteries of the lower and upper extremities. Intracranial MA occurs in 1.2% to 5% of patients with IE and carry a high mortality rate of 60%. The bifurcations of the distal MCA are the most commonly involved arteries. Symptoms may include severe headache, altered mental status, hemianopia, or cranial neuropathies. Sudden hemorrhage may occur in the absence of other premonitory symptoms.[1,48] Routine screening for intracranial MA is not recommended in the absence of neurologic symptoms or signs. Contrast-enhanced CT, MRI, and MRA are all useful techniques to diagnose intracranial MA, but the current gold standard is 4-vessel cerebral angiography. Decisions concerning the medical versus surgical treatment of intracranial MA need to be tailored according to the individual patient. A single intracranial MA distal to the first bifurcation of a major intracranial artery should be monitored closely with serial angiograms and must be excised if it enlarges or bleeds. In the case of multiple aneurysms, close monitoring is required with angiograms or CTs and if more than one aneurysm enlarges, prompt surgical excision is required.[48] A less invasive alternative to surgery, especially in distally or peripherally located aneurysms is coil embolization.[65] Extracranial MA are often asymptomatic. However, the appearance of a new, painful, pulsatile mass with IE should prompt the diagnosis of extracranial MAs. Hematuria and hypertension should suggest the rupture of a renal artery MA. Massive bloody diarrhea should suggest the rupture of an intrab-dominal MA into the bowel. Hematemesis, hematobilia, and jaundice should suggest rupture of a hepatic artery MA. Mortality in patients with IE is high and revascularization should be established through extra-anatomic routes via uninfected tissue planes. Long-term, suppressive antibiotic

therapy will probably be required as patients are at high risk of recurrence of infection especially in the interposed vascular grafts in previously infected areas.

TREATMENT

Certain principles are important when considering treatment of IE.[65] The regimen must be bactericidal. Prolonged therapy is often necessary. Vancomycin is less rapidly bactericidal than semisynthetic penicillins and first-generation cephalosporins. IE is one of the situations where skin testing should be performed on patients with a questionable history of immediate hypersensitivity reactions to penicillin. The American Heart Association[46] and European Society of Cardiology[56] have published guidelines for the treatment of adults with IE due to streptococci, enterococci, staphylococci, and HACEK microorganisms. These are summarized in Table 35.5.

TABLE
35.5 Therapy of NVE Caused by Highly Penicillin-Susceptible Viridans Group Streptococci and S.bovis

Regimen	Dosage[a] and Route	Duration (wk)	Strength of Recommendation	Comments
Aqueous crystalline penicillin G sodium	12–18 million U/24 h IV, either continuously or in 4 or 6 equally divided doses	4	IA	Preferred in most patients >65 y or patients with impairment of eighth cranial nerve function or renal function
or				
Ceftriaxone sodium	2 g/24 h IV/IM in 1 dose *Pediatric dose*[b]: penicillin 200,000 U/kg per 24 h IV in 4–6 equally divided doses; ceftriaxone 100 mg/kg per 24 h IV/IM in 1 dose	4	IA	
Aqueous crystalline penicillin G sodium	12–18 million U/24 h IV either continuously or in 6 equally divided doses	2	IB	2-wk regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of <20 mL/min, impaired eighth cranial nerve function, or *Abiotrophia*, *Granulicatella*, or *Gemella* spp. infection; gentamicin dosage should be adjusted to achieve peak serum concentration of 3–4 μg/mL and trough serum concentration of <1 μg/mL when 3 divided doses are used; nomogram used for single daily dosing[d]
or				
Ceftriaxone sodium	2 g/24 h IV/IM in 1 dose	2	IB	
plus				
Gentamicin sulfate[c]	3 mg/kg per 24 h IV/IM in 1 dose *Pediatric dose*: penicillin 200,000 U/kg per 24 h IV in 4–6 equally divided doses; ceftriaxone 100 mg/kg per 24 h IV/IM in 1 dose; gentamicin 3 mg/kg per 24 h IV/IM in 1 dose or 3 equally divided doses[e]	2		
Vancomycin hydrochloride[f]	30 mg/kg per 24 h IV in 2 equally divided doses not to exceed 2 g/24 h unless concentrations in serum are inappropriately low *Pediatric dose*: 40 mg/kg per 24 h IV in 2–3 equally divided doses	4	IB	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dosage should be adjusted to obtain peak (1 h after infusion completed) serum concentration of 30–45 μg/mL and a trough concentration range of 10–15 μg/mL

MIC 0.12 μg/mL.

[a]Dosages recommended are for patients with normal renal function.

[b]Pediatric dose should not exceed that of a normal adult.

[c]Other potentially nephrotoxic drugs (e.g., nonsteroidal anti-inflammatory drugs) should be used with caution in patients receiving gentamicin therapy.

[d]See reference 280 in full statement.

[e]Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of IE exist.

[f]Vancomycin dosages should be infused during course of at least 1 h to reduce risk of histamine-release "red

man" syndrome. From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. Circulation. 2005;111:e394–e434, with permission.

Caveats for the Common Causes of IE

Minimum inhibitory concentrations (MIC) should be determined for streptococci against penicillin as treatment is dependent on the values obtained.[1] A 2-week regimen[65] may be appropriate in certain situations such as those cases of uncomplicated IE caused by highly penicillin-susceptible viridans streptococci, S. bovis in those patients at low risk for complications from gentamicin therapy. For patients allergic to beta-lactams, vancomycin is an effective alternative. Enterococcus faecium and E. fecalis[46,56] are the two major enterococcal causes of IE. These organisms are relatively resistant to penicillin, expanded spectrum penicillins, and vancomycin. They are also uniformly resistant to cephalosporins and relatively resistant to aminoglycosides. The combination of penicillin, vancomycin, or ampicillin with aminoglycosides is necessary to exhibit a synergistic bactericidal effect on these isolates and standard therapy should continue for 4 weeks. All enterococcal isolates causing IE must be screened for antimicrobial susceptibility against penicillin, ampicillin, vancomycin, gentamicin, and streptomycin. Optimal therapy has not been determined for isolates with high level resistance to both gentamicin and streptomycin. For organisms with intrinsic high-level resistance to penicillin (MIC >16 μg/mL), vancomycin is the preferred agent for combination. Vancomycin may enhance the nephrotoxic potential of amoniglycosides. Serum levels of aminoglycosides should be carefully monitored during therapy of enterococcal endocarditis. Peak levels of gentamicin should not exceed 3 and trough levels should not exceed 1. Note that these levels are not as high as those when aminoglycosides are used in the synergistic treatment of gram-negative systemic infections.

Daptomycin has proven in vitro activity against MRSA, methicillin resistant Staphylococcal epidermidis (MRSE), glycopeptide-intermediate S. aureus, and Vancomycin-resistant enterococcus (VRE) faecium in an in vitro pharmacodynamic model with simulated endocardial vegetations.[66] For methicillin-susceptible staphylococci NVE,[67] nafcillin or oxacillin must be used with a brief 3 to 5 day course of gentamicin. Though the aminoglycoside offered no significant mortality or morbidity benefit, it shortened the duration of positive blood cultures in a multicenter collaborative study while harmful side effects were reduced. For methicillin-susceptible staphylococcal IE in prosthetic valves, nafcillin or oxacillin with rifampin for 6 weeks plus gentamicin for the first 2 weeks is recommended. For methicillin-resistant staphylococcal native valve IE, vancomycin, usually with gentamicin added for the first 3 to 5 days of therapy is the standard. For methicillin-resistant staphylococcal IE on prosthetic valves, combination therapy is advocated with vancomycin and rifampin for 6 weeks plus gentamicin for the first 2 weeks.[68] The benefit of rifampin[69] in MRSA endocarditis has been derived from the ability of this drug to sterilize "foreign

body infection" in experimental animal model. Coagulase-negative staphylococci are now the commonest cause of PV, particularly in the first 12 months following surgery. The organisms are usually methicillin resistant, and treatment should be the combination described. If the organism is resistant to gentamicin, an aminoglycoside to which susceptibility is demonstrated should be chosen. If the isolate is resistant to all aminoglycosides, this component should be omitted from the regimen. In the situation of right-sided native valve IE[70,71] caused by methicillin-susceptible S. aureus in IDUs, limited data suggest that a 2-week course of nafcillin or oxacillin with gentamicin may be sufficient. This regimen may not be suitable in IDUs with left-sided IE, metastatic IE such as lung abscess, underlying HIV, or vegetations >1 to 2 cm.

HACEK organisms[72] should be considered ampicillin resistant and monotherapy with this drug is no longer recommended. Limited data suggest that a third generation cephalosporin such as ceftriaxone or cefotaxime sodium should be used for 4 weeks in native valve and for 6 weeks in PV Aztreonam, trimethoprim/sulfameth-oxazole, or the fluoroquinolones are the recommended alternative agents for patients with HACEK IE unable to tolerate cephalosporins.

Caveats for the Uncommon Causes of IE

C. burnetii[73] IE is usually treated with a combination of doxycycline and rifampin, trimethoprim-sulfamethoxazole, or fluoroquinolones. The optimal duration of therapy is unknown. Valve replacement is only indicated for CHF, PV, or uncontrolled infection. Many experts recommend long-term and possibly indefinite therapy in this setting. Yet others have suggested a minimum of 3 years of therapy once phase I IgG antibody titers drop to <1:4,000 and phase I IgA antibody is undetectable. Few patients with Brucella[31] IE have been cured with antimicrobial therapy alone. Most require valve replacement in addition to the following: doxycycline plus either streptomycin or gentamicin OR doxycycline plus either trimethoprim/sulfamethoxazole or rifampin. Again, the optimal duration of therapy is unknown, but authorities recommend this regimen for 8 weeks to 10 months following valve replacement. In Legionella[32] IE, cure has been obtained by prolonged parenteral therapy with either doxycycline or erythromycin followed by an oral course for a prolonged period. The total duration of therapy is usually 6 to 17 months. Pseudomonas aeruginosa[74] IE of the right side usually requires the combination of high doses of an antipseudomonal penicillin (piperacillin) and an aminoglycoside (tobramycin). Left-sided Pseudomonas IE rarely responds to medical therapy alone and surgery is considered mandatory. In fungal IE[59] caused by Aspergillus or Candida species, Amphotericin B has poor penetration into vegetations. Most vegetations are bulky and metastatic complications, including periannular extension and embolization to large blood vessels are frequent. Virtually all complicated cases of Candida IE need surgery, and mortality is 90% to 100% in Aspergillus IE without surgery.

INDICATIONS FOR SURGERY IN INFECTIVE ENDOCARDITIS

Surgery is frequently required in patients with IE particularly when complicated by perivalvular and myocardial abscess and valvular dysfunction. The decision regarding surgery in the treatment of IE is multidisciplinary with input from an experienced cardiothoracic cardiac surgeon, a cardiologist, and an infectious disease clinician. It should be individualized per patient. Surgical therapy in IE has contributed to the overall decrease in mortality, especially in patients with CHF, complicated perivalvular extension, and in PV[46,56,59,63,64] The general preoperative condition of the patient, chronic hemodialysis, ongoing antibiotic treatment, timing of surgery, surgical techniques, postoperative care, and follow-up are important influences of outcome. Preoperative New York Heart Association (NYHA) class, age, and preoperative renal failure are the variables that foretell operative mortality in logistic regression analysis. The following table summarizes the indications for surgical intervention in IE (Table 35.6).

TABLE
35.6 Indications for Surgery in Patients with IE

Indication	Evidence Based
Emergency indication for cardiac surgery (same day)	
1. Acute AR with early closure of mitral valve	A
2. Rupture of a sinus Valsalva aneurysm into the right heart chamber	A
3. Rupture into the pericardium	A
Urgent indication for cardiac surgery (within 1–2 d)	
4. Valvular obstruction	A
5. Unstable prosthesis	A
6. Acute AR or MR with heart failure, NYHA III–IV	A
7. Septal perforation	A
8. Evidence of annular or aortic abscess, sinus or aortic true or false aneurysm, fistula formation, or new-onset conduction disturbances	A
9. Major embolism + mobile vegetation >10 mm + appropriate antibiotic therapy <7–10 d	B
10. Mobile vegetation >15 mm + appropriate antibiotic therapy <7–10 d	C
11. No effective antimicrobial therapy available	A
Elective indication for cardiac surgery (earlier is usually better)	
12. Staphylococcal prosthetic valve endocarditis	B
13. Early prosthetic valve endocarditis (≤2 mo after surgery)	B
14. Evidence of progressive paravalvular prosthetic leak	A
15. Evidence of valve dysfunction and persistent infection after 7–10 d of appropriate antibiotic therapy, as indicated by presence of fever or bacteremia, provided there are no noncardiac causes for infection	A
16. Fungal endocarditis caused by a mold	A
17. Fungal endocarditis caused by a yeast	B
18. Infection with difficult-to-treat organisms	B
19. Vegetation growing larger during antibiotic therapy >7 d	C

A, strong evidence or general agreement that cardiac surgery is useful and effective; AR, aortic regurgitation; B, inconclusive or conflicting evidence or a divergence of opinion about the usefulness/efficacy of cardiac surgery, but weight of evidence/opinion of the majority is in favor; C, inconclusive or conflicting evidence or a divergence of opinion; lack of clear consensus on the basis of evidence/opinion of the majority. MR, mitral regurgitation; NYHA, New York Heart Association classification.

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PROPHYLAXIS

IE is a disease characterized by high morbidity and mortality that should be prevented whenever possible. In the absence of controlled prospective studies and therefore based largely on expert opinion, the American Heart Association[75] and the European Society of Cardiology[56] recently revised their guidelines for IE prophylaxis. The absence of epidemiologic correlations between dental or other procedures and ensuing IE led them to recommend prophylaxis only to those patients at highest risk by virtue of their underlying cardiac conditions, when undergoing procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa (Table 35.7). Prophylaxis is no longer recommended for patients who undergo a genitourinary or gastrointestinal tract procedure.

TABLE
35.7 Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Endocarditis for which Prophylaxis with Dental Procedures is Reasonable

Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
Previous IE
CHD
■ Unrepaired cyanotic CHD, including palliative shunts and conduits
■ Completely repaired CHD with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 mo after the procedure
■ Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
Cardiac transplantation recipients who develop cardiac valvulopathy

Note that antibiotic prophylaxis is not recommended for procedures on the genitourinary or gastrointestinal tracts, if indication for prophylaxis implicates only endocarditis prevention. (Adapted from Habib G, Hoen B, Tornos P, et al. ESC Committee for Practice Guidelines. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J. 2009;30(19):2369–2413, and Nishimura RA, Carabello BA, Faxon DP, et al. ACC/AHA 2008 Guideline update on valvular heart disease: focused update on infective endocarditis: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;52(8):676–685.)

CONCLUSIONS

IE remains an important disease characterized by high morbidity and mortality. Over the last three decades, the overall incidence of IE and the associated mortality have remained constant. Dramatic changes have however occurred in the at-risk population, underlying susceptible cardiac lesions, etiologic pathogens, diagnostic evaluation, clinical presentation, antimicrobial agents, and recommendations for prophylaxis. It is a complex systemic disease that requires close multispecialty collaboration in order to effect its successful management. Even with advanced diagnostic and management strategies in the 21st century, it still is a life-threatening disease.

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QUESTIONS AND ANSWERS

Questions

1. All of the following are true statements except:
   a. By definition, “early” prosthetic valve endocarditis refers to the development of infection within 60

days of surgery.
b. Aztreonam is not an acceptable alternative for the treatment of HACEK endocarditis.
c. Gram-negative bacilli are important pathogens causing hospital-acquired endocarditis.
d. Endocarditis with Streptococcus bovis should prompt a search for a colonic neoplasm.
e. Surgery is often necessary in infective endocarditis (IE) with Brucella organisms.

2. Which of the following is true?
a. Mitral valve prolapse without mitral regurgitation (MR) is a risk factor for the development of IE.
b. Mechanical valves are at higher risk than bio-prosthetic valves for IE during the first 90 days following surgery. 7
c. MSSA is the most common causative agent of health care-acquired endocarditis in the United States.
d. Hemodialysis patients are at higher risk for Staphylococcus aureus bacteremia and health care-associated IE.
e. Rheumatic valvulitis is still the most common predisposing factor for IE in the elderly in developed nations.

3. All of the following are correctly matched associations except:
a. Brucella—abattoir workers
b. Coxiella—sheep farmers
c. Pseudomonas IE—injection drug users (IDU)
d. Fungal IE—prolonged antibiotic exposure
e. HACEK IE—veterinarians

4. The cutoff minimum inhibitory concentrations (MIC) for a penicillin-susceptible Streptococcus viridans is:
a. ≤0.5 μg/mL
b. ≤0.05 μg/mL
c. ≤0.01 μg/mL
d. ≥1 μg/mL
e. ≤0.12 μg/mL

5. Regarding the complications of IE, all of the following are true except:
a. Four-vessel cerebral angiography is the current gold standard for diagnosing intracranial mycotic aneurysms (MAs).
b. Mitral valve infection is a more common cause of congestive heart failure (CHF) in IE than aortic valve infection.
c. The definitive treatment of a splenic abscess resulting from embolization in IE is splenectomy.
d. Transthoracic echocardiogram is inferior to transesophageal echocardiogram in detecting paravalvular extension of IE.
e. Extracranial MAs are more common in the visceral arteries than in the upper-extremity arteries.

6. Wich of the following is associated with a lower complication rate in a patient with endocarditis?
a. Streptocoocus viridans infection
b. Perivalvular abscess
c. Methicillin resistant Staphylococcal aureus (MSSA) infection
d. Older age
e. Pulmonary edema

7. Which of the following is not considered an indication for surgical intervention in endocarditis?
a. Persistent bacteremia and increasing size of vegetation despite appropriate bactericidal antibiotic therapy
b. Mitral valve vegetation of 4 mm in a patient with moderate MR who remains culture negative on appropriate antibiotic therapy
c. Aortic valve endocarditis with an episode of congestive failure with severe aortic regurgitation (AR)

d. Mobile vegetation on the mitral valve that is 10 mm long in a patient with a recent episode of homonymous hemianopsia
e. Mobile mitral vegetation of >15 mm in length despite a 2 week course of appropriate antibiotic therapy

8. Which of the following is considered an appropriate indication for antibiotic prophylaxis against endocarditis?
a. Patient with severe aortic stenosis undergoing a dental extraction
b. Atrial septal defect patient undergoing colonoscopy
c. Patient with prosthetic mitral valve undergoing dental cleaning
d. Patient with mitral valve prolapse and moderate MR undergoing cystoscopy
e. Patient with mitral valve repair with a prosthetic ring and mild residual MR undergoing transurethral resection of prostate

9. Which of the following causes of endocarditis usually require serologic testing for definitive diagnosis rather than blood cultures?
a. Coxiella burnetti
b. Streptococcus viridans
c. Streptococcus bovis
d. Psedomonas aeruginosa
e. HACEK organisms

10. Which of the following statements about endocarditis in the current era is true?
a. It typically presents with a subacute course over months before presentation.
b. Enterococcus is the most common organism implicated.
c. Surgery is required in <20% of cases.
d. Right-sided valve lesions now predominate.
e. Heart failure is the most likely cardiac complication.

Answers

1. Answer A: Early-onset prosthetic valve endocarditis is usually attributed to pathogens from perioperative contamination (health care-associated), and therefore within 60 days from implant of the valve. Aztreonam (gram-negative organism only) will not be active against HACEK organisms. Staphylococcus aureus is the most common health care-associated cause of IE (not gram-negative organisms). Brucella IE almost always requires surgery for cure.

2. Answer D: Staphylococcus aureus is recognized as the most common health care-associated pathogen causing IE. Patients receiving hemodialysis with indwelling vascular catheters are at particular risk for S. aureus bacteremia and subsequent endocarditis.[76] Mitral valve prolapse without regurgitation is not a high-risk condition for IE. Methicillin-resistant S. aureus is more common than methicillin-susceptible S. aureus as a cause of nosocomial IE in the United States. There is no significant difference in the incidence of PV for mechanical valves and bioprosthetic valves during the first 90 days following surgery. Rheumatic valvulitis is not the most common predisposing factor for IE in the developed world.

3. Answer E: HACEK organisms are not particularly associated with veterinarians. Brucella is a zoonosis and associated with abattoir workers. Similarly, C. burnetii (agent of Q fever) is associated with parturient sheep. Pseudomonas has been associated with injected drug users (contamination with processing), and nosocomial fungal IE can follow prolonged antibiotic use (risk factor for fungemia).

4. Answer E: The NCCLS cutoff for S. viridans penicillin susceptibility is 0.12 mg/mL.

5. Answer B: Mitral valve IE is not more often associated with complications of CHF than aortic valve IE. MRA is not as sensitive as four-vessel angiogram for detection of MAs.

6. Answer A: All of the other factors increase the risk of a complicated course and mortality in IE.

7. Answer B: Moderate MR with moderate size vegetation does not mandate surgical intervention. All of the other scenarios are considered indications for surgical intervention.

8. Answer C: The revised guidelines now recommend antibiotic prophylaxis only in high-risk instances such as with prosthetic valves, uncorrected complex congenital heart disease (CHD), or a history of previous endocarditis. Prophylaxis is no longer recommended for genitourinary or gastrointestinal procedures.

9. Answer A: Coxiella burnetti, the pathogen responsible for Q fever endocarditis requires serologic testing for diagnosis in most instances as most laboratories are not set up to grow it in culture. The other organisms usually grow in blood culture though delayed culture is common with HACEK organisms.

10. Answer E: The presentation now is less classical and subacute and occurs within 30 days of onset typically. Staphylococcus aureus is the most common infecting organism and surgery may be required in up to 50% of cases. Left-sided valve lesions predominate and heart failure is the most common cardiac complication.

CHAPTER

Prosthetic Valvular Disease

Lawrence Lazar and James Thomas

There are two major classes of prosthetic valves, mechanical and bioprosthetic (Fig. 36.1). Each specific valve within these groups has unique features that provide differences in hemodynamics, durability, and thromboembolic risk.

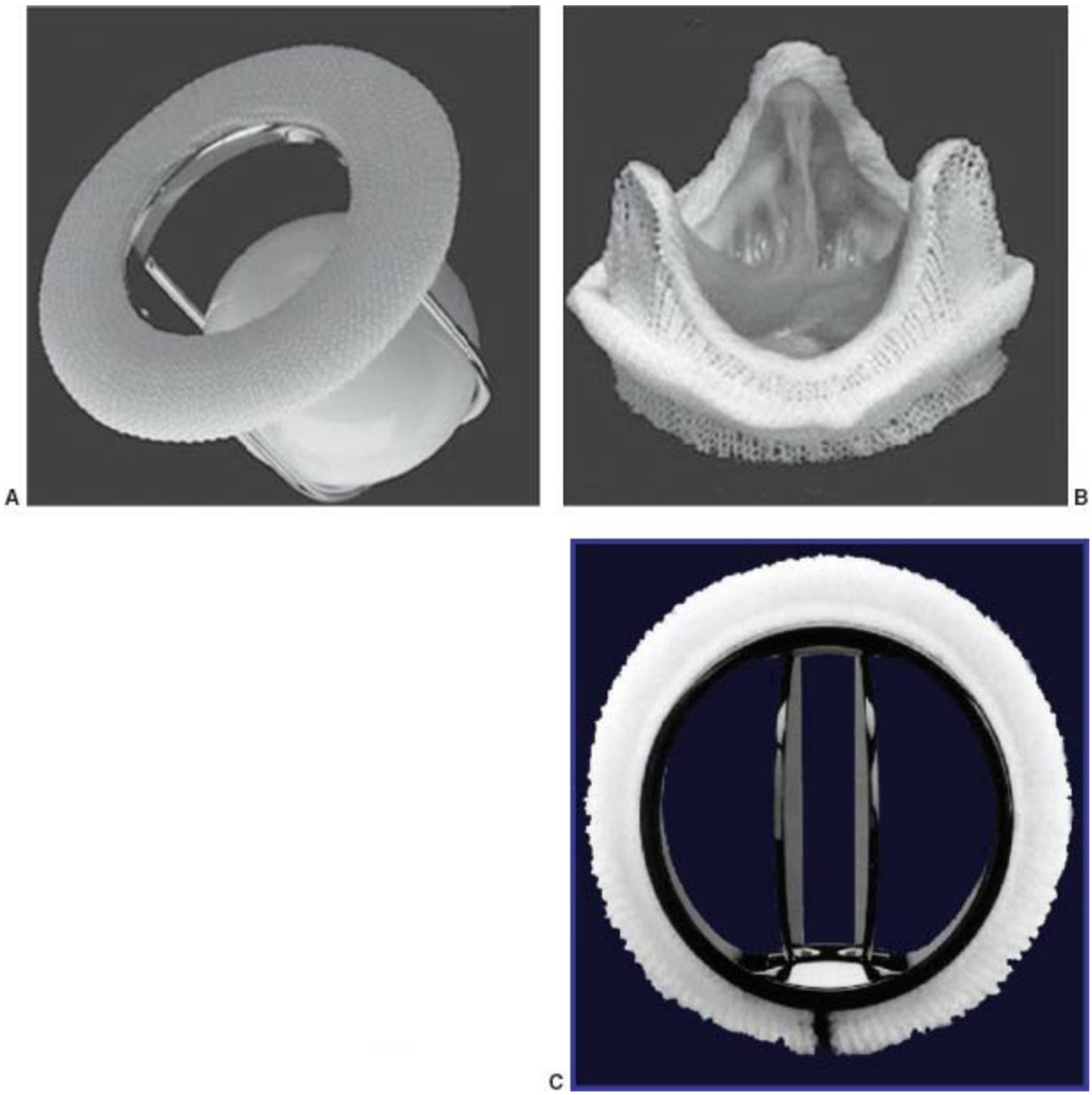


FIGURE 36.1 **A**:Ball-in-cage valve. **B**:Bioprosthetic valve. **C**:Bileaflet mechanical valve.

MECHANICAL VALVES

The three main types of mechanical valves available are bileaflet, tilting disc, and ball-in-cage. Bileaflet tilting disc valves include the St. Jude's Medical (see Fig. 36.1A), Carbomedics, and On-X valves. The symmetric flow across the bileaflet system provides excellent hemodynamics, with lower transvalvular pressure gradients at any outer diameter or cardiac output than the tilting disc valves or ball-in-cage types. Along with lower rates of mechanical failure or thromboembolism, bileaflet valves are currently the most commonly used mechanical prostheses worldwide.

Single tilting disc valves such as the Bjork–Shiley (see Fig. 36.1B) or Medtronic Hall valves consist of a metallic sewing ring attached to a tilting disc that rotates about

an off-centered pivot axis. Some models of the convexoconcave Bjork–Shiley valve demonstrated a high degree of strut fracture (2% per year) and embolization of the disc, resulting in withdrawal of these valves from the market, and prophylactic valve replacement in those whose risk of embolization exceeded the risk of reoperation. Valves at particular risk for this are larger valves in the mitral position implanted in younger patients. Since no Bjork–Shiley valve has been implanted in more than 20 years, the at-risk population is getting quite small. The earlier tilting disc valves also have greater thrombosis risk than newer Medtronic-Hall valves, in which a small orifice in the center permits regurgitant flow to "wash" potentially thrombogenic material from the disc.

The Starr–Edwards valve (see Fig. 36.1C) is the prototypical ball-in-cage valve. Ball-in-cage valves demonstrate a less favorable hemodynamic profile and a higher incidence of thromboembolic complications. Despite these limitations, however, some Starr–Edwards valves have performed for over 40 years.

BIOPROSTHETIC VALVES

Bioprosthetic valves fall into one of two categories: heterografts, such as Carpentier–Edwards (CE, see Fig. 36.1D), which are non–human tissue valves, and homografts, which are cadaveric human aortic valves within a small portion of the donor's aortic root for support. Compared to mechanical valves, bioprosthetic valves require less anticoagulation, but they are less durable. Stented heterografts are manufactured from porcine valvular tissue (e.g., Medtronic Mosaic valve) or bovine pericardium (e.g., CE Perimount valve). With improvements in design and preseration techniques, currently produced bovine and porcine valves are expected to have comparable durability. Aortic homografts are harvested from cadaveric hearts and cryopreserved. They may be implanted as isolated valves in the subcoronary position or, more commonly, with a short segment of the donor's aortic root, in which the recipient's coronary arteries are reimplanted. Although the durability of homograft prostheses may be slightly higher, they are less frequently used due to the complexity of reoperation (calcification of the root and need for reimplantation of the coronary arteries). Homografts have a reduced rate of early reinfection and are the valve of choice in aortic valve endocarditis (Fig. 36.2).

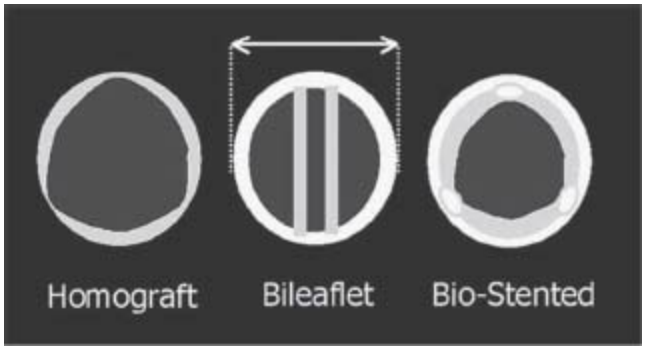


FIGURE 36.2 Although mechanical and bioprosthetic valves have similar external diameters, the figure demonstrates that the stented bioprosthetic valves have a smaller internal diameter and thus a more unfavorable hemodynamic profile.

SELECTION OF VALVE TYPE

Valve repair is preferred over replacement, when feasible. Mitral valves are much more frequently repaired, with repair offering advantages of preserving left ventricular (LV) function via conservation of the subvalvular apparatus, lower operative mortality, higher long-term survival rate, and freedom from anticoagulation. Aortic valve repair is less frequent, although possible in cases with predominant regurgitation due to prolapse or redundancy without severe stenosis or calcification.

Multiple factors need to be considered in selecting a prosthetic valve, including the age of the patient, the probability of future pregnancy, life expectancy, occupation, and lifestyle. Mechanical valves are more durable than bioprosthetic valves, but they require a commitment to chronic anticoagulation. Age recommendations differ with valve position, as bioprosthetic mitral valves deteriorate more rapidly than aortic valves. Mechanical aortic and mitral valves are generally recommended for patients younger than 60 and 65 years of age, respectively, who have no contraindications to anticoagulation and are expected to be medically compliant. The minimum age for a bioprosthesis is later for mitral than for aortic valves due to the more rapid deterioration of bioprostheses in the mitral position. The most recent valve guidelines, however, emphasize patient choice, particularly lifestyle, in valve implantation. With reduction in the risk of redo valve surgery, many patients 50 years of age or younger are opting for bioprosthetic valves.

The development of transcatheter aortic valve replacement (TAVR) is encouraging a further move toward bioprosthetic valves for younger patients: one may choose the benefits of less anticoagulation now in spite of the decreased valve durability, banking on the hope that future TAVR will carry a lower procedural risk should future valve replacement be required.

ANTICOAGULATION

Anticoagulation is a frequent topic of cardiology consultation and board testing. We review here the essentials including general guidelines for mechanical and bioprosthetic valves, therapy adjustment after thromboembolic events, perioperative management, and management in pregnancy.

1. Anticoagulation for mechanical prosthetic valves (Table 36.1). For board review purposes, recommendations are simplified here to just the Class I recommendations, except where indicated. Aortic position bileaflet and Medtronic-Hall tilting disc valves, without risk factors, may be anticoagulated to an international normalizing ratio (INR) of 2.0 to 3.0. All other aortic mechanical valves and all mitral mechanical valves should be anticoagulated to an INR of 2.5 to 3.5. Furthermore, patients with even low-risk aortic mechanical valves and any thromboembolic risk factors, such as atrial fibrillation, previous thromboembolism, hypercoagulable state, or severe systolic dysfunction (left ventricular ejection fraction [LVEF] <30%) should also be anticoagulated to 2.5 to 3.5. All patients with prosthetic valves should be on aspirin (81 mg daily).

   Rates of thromboembolism are highest with Starr–Edwards valves, followed by single tilting disc valves. Bileaflet tilting disc valves have the lowest reported rates of thromboembolism, because the built-in regurgitation acts to "clean" debris off the valve. Regardless of the type of valve, at appropriate levels of anticoagulation, the incidence of thromboembolism is <1% in those maintained on therapeutic anticoagulation. The majority of patients who experience thromboembolic complications have subtherapeutic INR at the time of the event. Currently, there is no approved use of dabigatran in anticoagulation of prosthetic heart valves (PHVs), though future trials may lead to expansion of the indication to include this.

TABLE
36.1 Recommended Anticoagulation Therapy for Patients with Prosthetic Valves

Aspirin Alone	INR 2.0–3.0 Plus Aspirin	INR 2.5–3.5 Plus Aspirin
Bioprosthesis—low risk	Bioprosthesis—high risk[a] AVR—low risk (BL, MH)	AVR—high risk[a] AVR (BS, SE) MVR (all)

INR, international normalizing ratio; AVR, aortic valve replacement; MVR, mitral valve replacement; BL, bileaflet; MH, Medtronic-Hall; BS, Bjork–Shiley; SE, Starr–Edwards.

[a]High Risk defined as atrial fibrillation, prior thromboembolism, hypercoagulable state, or severe left ventricular dysfunction (EF < 30%). From Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused update incorporated into the ACC/AHA 2006 Guidelines for the management of patients with valvular heart disease. J Am Coll Cardiol. 2008;52:e1-e142, with permission from Elsevier.

2. Anticoagulation for bioprosthetic valves. Patients with bioprosthetic aortic or mitral valves and no risk factors may be maintained on aspirin alone. Patients with risk factors should be anticoagulated to an INR of 2 to 3. As with mechanical valves, risk factors are atrial fibrillation, prior thromboembolic event, hypercoagulable state, or severe LV dysfunction (EF < 30%).

   Early postoperative anticoagulation: In the early postoperative period, the approach to anticoagulation for bioprostheses varies widely. American College of Cardiology/American Heart Association (ACC/AHA) guidelines give a class Ila recommendation to warfarin starting 2 to 4 days following surgery, after epicardial wires are removed. Bioprosthetic valve recipients without risk factors may discontinue warfarin after 3 months and continue aspirin alone. In many center, however, low-risk patients are managed entirely without warfarin.

3. Adjustment of anticoagulation after a thromboembolic event. Patients who have an embolic event while therapeutically anticoagulated should have their therapy increased as follows:
   - On Warfarin, not taking aspirin: add aspirin 81 mg daily
   - INR 2 to 3 and aspirin: Increase INR to 2.5 to 3.5.
   - INR 2.5 to 3.5 and aspirin: Increase INR to 3.5 to 4.5.
   - Aspirin alone: Add Warfarin to target INR 2 to 3. Guidelines also give options to increase dose to 325 mg daily or add clopidogrel 75 mg daily.

4. Perioperative anticoagulation for noncardiac surgery. For patients with mechanical valves who require major surgery with anticipated substantial blood loss, warfarin should be stopped 2 to 3 days prior to the procedure, to achieve an INR level of 1.5 or less, and restarted 24 hours after the surgery. For low-risk patients with bileaflet aortic valve (i.e., baseline target INR of 2 to 3), the short-term risk is so low that routine heparinization is not recommended. For all patients with a target INR of 2.5 to 3.5 (any mitral mechanical valve, aortic mechanical valves excluding bileaflet or Medtronic-Hall, or any risk factors—see Table 36.1), hospital admission is recommended with initiation of heparin when INR falls below 2.0. Postoperatively, heparin should be restarted as soon as it is considered safe and continued until therapeutic anticoagulation is achieved with warfarin. For minor procedures, in which blood loss is minimal, anticoagulation can be continued. High-dose vitamin K should not be given routinely (class III recommendation), as this may create a hypercoagulable state. Use of fresh frozen plasma is preferable in emergency situations.

5. Pregnancy. Warfarin is teratogenic between 6 and 12 weeks of gestation. Women requiring warfarin therapy who are attempting to become pregnant should have frequent pregnancy tests and cease warfarin when pregnancy is achieved. They should then use dose-adjusted subcutaneous unfractionated heparin (UFH), continuous IV UFH, or low molecular weight heparin (LMWH) for the remainder of the first trimester. Subcutaneous heparin, dosed 17,500 to 20,000 units twice daily, should be adjusted to a target activated partial thromboplastin time (aPTT) of at least twice the control, checked 6 hours after injection. LMWH is dosed twice daily, adjusted to maintain an anti-Xa level between 0.7 and 1.2 units per mL, checked 4 hours after administration. LMWH should only be used if anti-Xa levels are appropriately monitored.

   Patients may resume warfarin therapy for the second and third trimesters. As pregnancy is a hypercoagulable state, all pregnant women with mechanical valves on warfarin should be treated to a target INR of 2.5 to 3.5. In those patients who resume warfarin, it should again be discontinued 2 to 3 weeks before term and continuous UFH initiated. Low-dose aspirin can be used in conjunction with anticoagulation therapy in the second and third trimesters. Nursing mothers can safely use both heparin and warfarin, which do not appear to be secreted into breast milk.

COMPLICATIONS OF VALVE PROSTHESES

Monitoring By Echocardiography

A postoperative transthoracic echocardiogram (TTE) should be obtained either prior to discharge or within 4 weeks of discharge. Asymptomatic uncomplicated patients should follow-up annually, although routine TTEs are not indicated in the absence of a change in clinical status. In asymptomatic patients with mechanical valves, no further follow-up echocardiography is required, in the absence of other indications. In patients with bioprosthetic valves, annual TTEs may be considered after the first 5 years. Of course, a TTE is indicated in any patient with a prosthetic valve whenever there is a change in clinical status, new murmur, question of valve function, or concerns of ventricular function. Of note, cardiac magnetic resonance imaging (MRI) is safe for all available prosthetic valves, though artifact induced by metal in the valve will obscure adjacent structures.

Normally functioning mechanical and bioprosthetic valves all have gradients across them, with mean gradients up to 14 mm Hg in the aortic position (except Starr–Edwards, up to 24 mm Hg) and up to 7 mm Hg in the mitral position. Conditions with increased cardiac output such as anemia, tachycardia, pregnancy, hyperthyroidism, or severe prosthetic, leak can lead to higher-than-normal gradients and give the false impression of prosthetic stenosis. Occasionally, a high gradient across an aortic valve demonstrates

a prosthesis–patient mismatch, which is defined as <0.6 cm^2/m^2. The recently published prosthetic valve guidelines from the American Society of Echocardiography provide comprehensive normal values for all prosthetic valves in common use.

Pressure recovery can complicate measurements across bileaflet mechanical prostheses (Fig. 36.3). In this situation, flow deceleration through the gently flaring central orifice may cause Doppler to overestimate the true pressure gradient by up to one-third. This phenomenon may be particularly problematic with small mechanical bileaflet prostheses in the aortic position. Given the need to follow transvalvular gradients to exclude pannus, thrombus, or stenosis secondary to increasing calcification, it is critical to obtain a baseline echocardiogram early postoperatively for future reference.

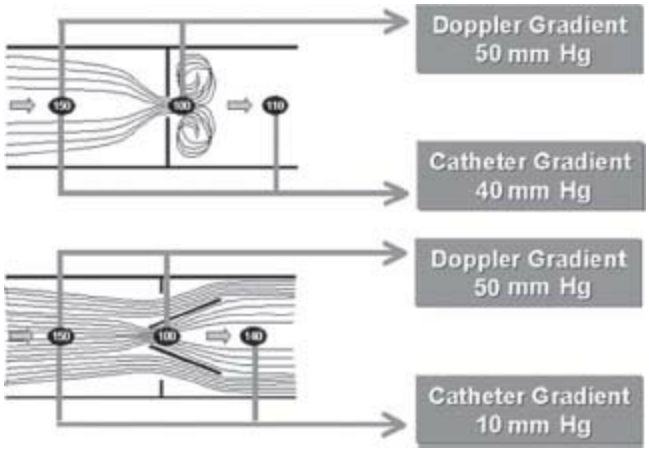


FIGURE 36.3 Demonstration of pressure recovery. The higher pressure gradient recorded through a prosthesis by Doppler overestimates the true pressure gradient as a result of flow acceleration through a narrowed orifice. Pressure recovers distally, at the position of the catheter recording. This occurs primarily with small mechanical bileaflet prostheses in the aortic position.

Mechanical valves have physiologic regurgitation from multiple jets to help clean off debris, but it should be no more than mild and should not be paravalvular in origin. Regurgitation from mechanical valves in the mitral position is often underestimated by transthoracic echocardiography because of acoustic shielding. Indirect evidence of increased flow across the valve can be obtained in the presence of severe regurgitation if peak gradients are elevated with relatively low mean gradients. Transesophageal echocardiography (TEE) remains the best way to detect and quantify prosthetic mitral regurgitation.

The diagnosis of structural valve degeneration relies primarily on echocardiographic findings, but physical exam findings can sometimes provide clues to complications (Fig. 36.4). Prosthetic valve degeneration occurs more commonly with bioprosthetic valves. The leaflets gradually become thickened and calcified, resulting in both stenosis and regurgitation. Elevated gradients across the valve support the

diagnosis and define the severity. Replacement is usually deferred until symptoms appear. Prosthetic deterioration can be more rapid for mechanical prostheses, resulting from thrombosis, encroachment by pannus, infection, or abrasion of a silastic ball occluder (Fig. 36.5). Abrupt failure can be fatal, although rare, occurring as a result of strut fracture or disc dislodgement.

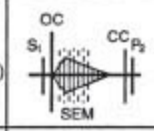
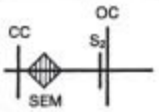
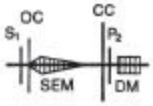
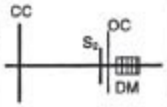
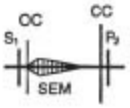
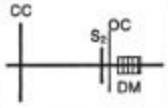
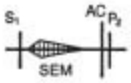
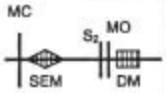
Type of Valve	Aortic Prosthesis		Mitral Prosthesis	
	Normal Findings	Abnormal Findings	Normal Findings	Abnormal Findings
Caged-Ball (Starr–Edwards)		Aortic diastolic murmur Decreased intensity of opening or closing click		Low-frequency apical diastolic murmur High-frequency holosystolic murmur
Single-Tilting-Disk (Bjork–Shiley or Medtronic–Hall		Decreased intensity of closing click		High-frequency holosystolic murmur Decreased intensity of closing click
Bileaflet-Tilting-Disk (St. Jude Medical)		Aortic diastolic murmur Decreased intensity of closing click		High-frequency holosystolic murmur Decreased intensity of closing click
Heterograft Bioprosthesis (Hancock or Carpentier–Edwards		Aortic diastolic murmur		High-frequency holosystolic murmur

FIGURE 36.4 Acoustic characteristics of various mechanical and bioprosthetic valves. (From Vongpatanasin W, Hillis LD, Lange RA. Prosthetic heart valves. N Engl J Med 1996;335:410, with permission from the Massachusetts Medical Society.)

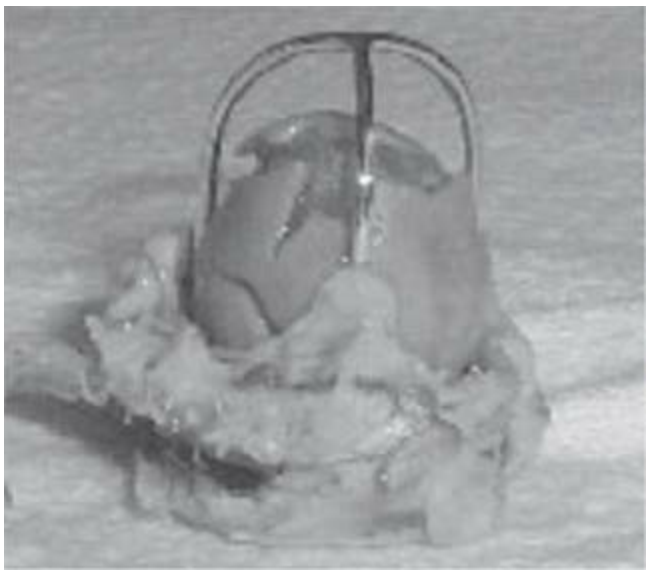


FIGURE 36.5 Starr–Edwards valve showing degeneration of silicone ball and pannus invasion of the suture ring.

The annual incidence of prosthetic valve thrombosis is approximately 0.5% to 1.5%. The highest incidence is at the tricuspid position, followed by the mitral and then

the aortic position. Thrombus is suspected in patients with acute onset of symptoms, embolic event, or inadequate anticoagulation. TEE is a useful diagnostic technique, particularly for mitral prostheses, although cinefluoroscopy and CT scanning are the tests of choice to document restriction in disk or occluder mobility. Heparin should be initiated early, and may be adequate for small (<5 mm) nonobstructive thrombi. Any evidence of valve obstruction should be met with emergent surgical consultation, and fibrinolytic therapy should be considered if surgery is not available.

Approximately 3% to 6% of patients with PVEs will experience endocarditis. PVE is typically associated with large vegetations because microorganisms are sheltered from the host defense mechanisms. Early PVE (<2 months following implantation) is typically caused by Staphylococcus epidermidis. The clinical course is often fulminating, with mortality as high as 50% to 70%. Surgery is almost universally required for effective treatment. Late PVE occurs most commonly in patients with multiple prostheses, especially involving the aortic position. Its clinical course resembles that of native-valve endocarditis, and the most common infectious agents are Staphylococcus aureus and streptococci, followed by S. epidermidis, enterococci, gram-negative bacteria, and fungal agents. The general therapy for patients with PVE is surgery, although a few patients can be treated successfully with medical therapy alone. Patients with PVE should also continue to receive anticoagulation. PVE is associated with a 50% incidence of stroke in the absence of anticoagulation, as opposed to a 10% incidence with anticoagulation, and there is no compelling evidence of increased hemorrhage with warfarin in patients with PVE. Surgery is clearly indicated in patients with persistent bacteremia despite IV antibiotics, tissue invasion or fistula formation, recurrent embolization, fungal infection, prosthetic valve dehiscence or obstruction, new or worsening heart block, or medically refractory congestive heart failure (Fig. 36.6). As discussed, the cure rates with medical therapy in PVE are considerably lower, and repeat surgery should be a consideration for all appropriate candidates who fail a trial of antibiotics. The use of antibiotic prophylaxis is recommended for all patients with prosthetic valves.

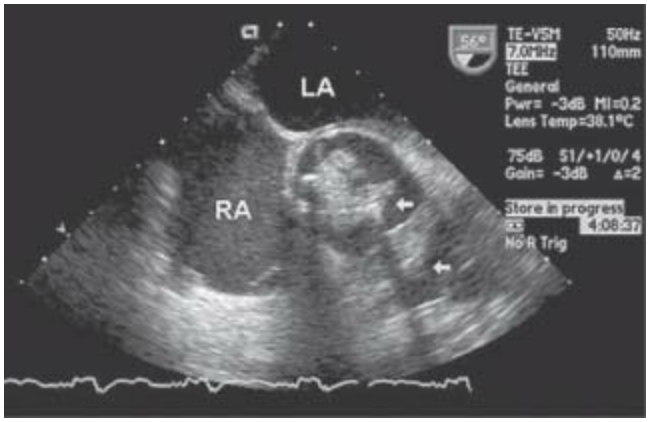


FIGURE 36.6 Prosthetic aortic valve demonstrating large vegetation and surrounding abscess. RA, right atrium; LA,

left atrium.

Subclinical hemolysis is present in many patients with mechanical valves but rarely results in significant anemia. Clinical hemolysis occurs in approximately 10% of patients with ball/disc-and-cage valves but is uncommon with normal bioprostheses or tilting disc valves. Clinical hemolysis is associated with multiple prosthetic valves, small prostheses, periprosthetic leaks, and PVE. Mechanisms involved in the generation of hemolysis include high shear stress or turbulence across the prosthesis. Diagnosis is made by various laboratory tests (elevated LDH, reticulocyte count, unconjugated bilirubin, decreased haptoglobin, and the presence of schistocytes on blood smear) and echo imaging showing abnormal rocking of the prosthesis or regurgitant jets of high shear stress such as periprosthetic regurgitant jets or those impacting on a solid surface such as the left atrial appendage. Mild anemia from hemolysis can be managed with iron, folic acid, and occasional blood transfusions. Beta-blockade and blood-pressure control may reduce the severity of hemolysis. Surgical therapy or percutaneous occlusion is recommended for those with periprosthetic leaks in patients with severe anemia requiring repeated transfusions or those with congestive heart failure.

Dehiscence of the sewing ring from the annulus may occur in the early postoperative period because of poor surgical techniques, excessive annular calcification, chronic steroid use, fragility of the valvular tissue (particularly following prior valve operations), or infections. Late dehiscence occurs mainly by infectious endocarditis. Abnormal rocking of the prosthesis on echo or cinefluoroscopy is an indication for urgent surgery, but some rocking may occur with preservation of the mitral valve apparatus.

ACKNOWLEDGMENTS

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QUESTIONS AND ANSWERS

Questions

1. Assuming no other thromboembolic risk factors, what is the recommended anticoagulation therapy for a St. Jude mitral valve?
   a. International normalizing ratio (INR) of 2 to 3 for life of valve
   b. INR of 2.5 to 3.5 for life of valve
   c. Anticoagulation therapy with INR of 2.5 to 3.5 for first 3 months, then aspirin therapy thereafter
   d. INR of 3.5 to 4.5 for life of valve
   e. INR of 3 to 4 for life of valve

2. A homograft is the preferred valve choice in which of the following clinical situations?
   a. A 45-year-old man with aortic valve endocarditis and aortic root abscess in the presence of a bicuspid aortic valve
   b. A 30-year-old man with a nonrepairable aortic bicuspid valve in the setting of severe symptomatic aortic insufficiency
   c. A 68-year-old woman with chronic lymphocytic leukemia, who has rheumatic mitral stenosis that is not amenable to valvuloplasty
   d. A 70-year-old woman with a nonrepairable aortic bicuspid valve in the setting of severe symptomatic aortic insufficiency

3. Which of the following statements regarding prosthetic valve thrombosis (PVT) is true?
   a. The annual incidence of PVT is approximately 0.5% to 1.5%.
   b. Incidence is highest for the mitral position and then the aortic position followed by the tricuspid position.
   c. Fibrinolysis is generally performed rather than surgery for left-sided prosthetic valve thrombosis.
   d. Surgery is generally considered the treatment of choice for right-sided PVT.
   e. Cinefluoroscopy is not usually reliable to determine restriction in occluder mobility at a mechanical prosthesis.

4. When assessing transvalvular gradients across a prosthetic valve, all of the following can lead to a false assessment of prosthetic valve stenosis except:
   a. Patient–prosthesis mismatch
   b. Anemia
   c. Sepsis
   d. Regurgitation
   e. Pressure recovery phenomenon

5. A 55-year-old man has a #19 mechanical tilting disc prosthesis placed 6 months ago for aortic stenosis. Initially, postoperatively, the peak and mean gradients across the prosthesis were 60/35 mm Hg (peak/mean), respectively. He now feels short of breath on minimal exertion and a repeat

transthoracic echocardiogram shows normal apparent valve function, normal LV function, and a peak and mean gradient of 70/45 mm Hg. A transesophageal echocardiography (TEE) is performed. There is no abnormal regurgitation at the valve. Valve motion appears full and no abnormal masses are seen at the valve. He is not anemic and his LDH is mildly elevated. His INR has been in the therapeutic range throughout. What is the most likely cause of his symptoms?

a. Hemolysis at the valve.
b. Pannus at the valve causing obstruction and leading to prosthetic stenosis
c. Patient–prosthesis mismatch due to inadequate sized valve for patients needs
d. Pressure recovery at the valve giving an overestimate of the true pressure gradient across the left ventricular outflow tract
e. Occult valve thrombosis

6. A 45-year-old healthy man with a mechanical double tilting disc aortic prosthesis is seen in clinic with a recent episode of transient dysphasia. He has otherwise been well and afebrile. His INRs have been therapeutic in the 2.5 to 3.0 range and coumadin is his only medication. A TTE shows normal gradients and a TEE shows normal valve motion and function. The most appropriate management now is to:

a. Increase coumadin to maintain an INR of 3.0 to 4.0.
b. Refer for surgical evaluation for bioprosthetic insertion.
c. Get blood cultures and start antibiotics intravenously.
d. Start aspirin 81 mg in addition to coumadin.
e. Consider a trial of dabigatran given the failure of therapeutic coumadin therapy.

7. A 55-year-old man has had increasing fatigue over the last several months. He has a mechanical valve at the mitral position for the last several years. His prosthetic click sounds fine and no murmur is appreciated. He has had adequate INR levels. A routine blood count shows normocytic anemia of 10 g and no leucocytosis and normal platelet count. An LDH level is 1,100 IU. A TTE shows a peak gradient of 25 and mean gradient of 10 mm Hg across the valve (previously 10/5 peak/mean mm Hg). There is considerable shielding of the left atrium but no mitral regurgitation is detected. The most appropriate test now to determine a course of action would be to

a. Perform cinefluoroscopy to exclude valve thrombosis.
b. Perform TEE to exclude a paravalvular leak.
c. Perform GI workup to determine source of GI bleeding.
d. Stop coumadin until anemia resolves.
e. Check blood cultures to exclude endocarditis.

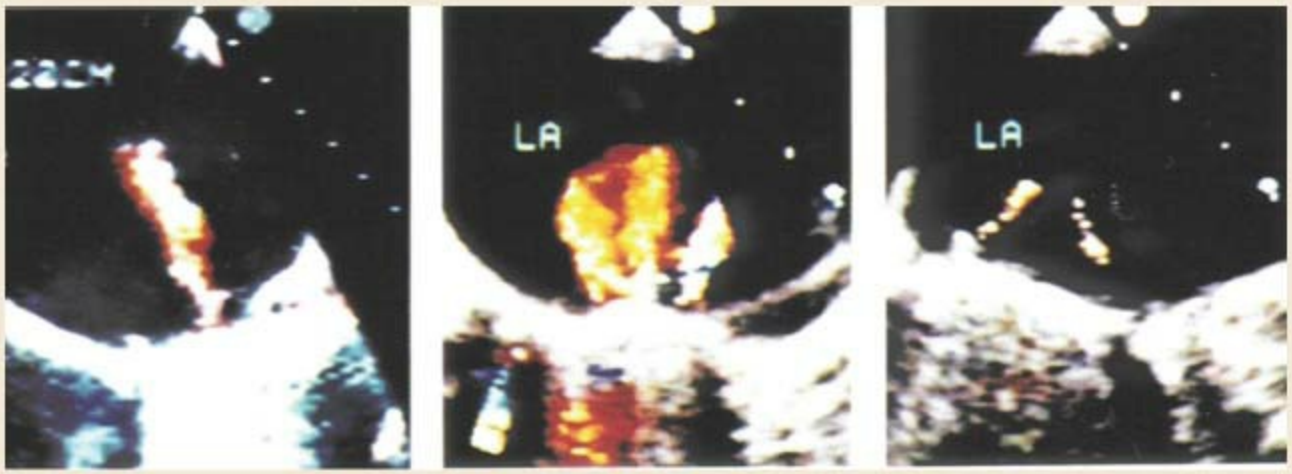
8. An 80-year-old woman has a mitral bioprosthesis that is 16 years old. You saw her 6 months ago and a transthoracic echocardiogram revealed mildly increased gradients across the prosthesis. There is some calcium on the leaflets and mild regurgitation. Her LV function is normal. Her family practitioner calls you urgently to say that she has gone into pulmonary edema unexpectedly without any fever or other illness or recent symptomatic deterioration. The most likely cause of her sudden deterioration is:

a. Atypical endocarditis
b. Acute valve thrombosis
c. Acute coronary embolism from degenerative valve
d. Patient–prosthetic mismatch
e. Flail prosthetic valve leaflet with severe acute mitral regurgitation

9. You are called to the operating room by the anesthetist who has performed a postoperative TEE on a 50-year-old man who has had a mitral bileaflet tilting disc valve placed for severe calcific mitral stenosis. The anesthetist has noted multiple small low-velocity jets emanating from the valve edges that are systolic in timing and that are relatively short in duration (see figure). The motion of the valve leaflets is normal and the patient is off bypass. Protamine has been given to reverse heparin but the jets are still present. The pressure gradients across the prosthesis are not increased. The most likely cause of these jets is:

a. Paravalvular leaks at the site of the sewing ring due to calcium impingement

b. Normal regurgitation from the valve that is of no concern
c. Prosthetic occluder impingement from a severed chord
d. Valve thrombosis
e. Pulmonary vein stenosis with high-velocity jet in left atrium



Intraoperative TEE of mitral valve prosthesis. LA: left atrium

a. Which of the following is the most likely finding in patient with severe paravalvular regurgitation at a mitral bioprosthesis and previously normal LV function?
b. Reduced LV ejection fraction
c. Increased cardiac output
d. Normal pulmonary pressure
e. Elevated peak transvalvular gradient across the bioprosthesis
f. Normal LDH levels

Answers

1. Answer B: Embolic event rates are higher for mitral valves than for aortic valves and therefore generally require higher anticoagulation therapy. Caged ball and single tilting valves also carry greater embolic risk than double tilting mechanical valves. Bioprosthetic valves generally carry the lowest risk of embolization, yet according to AMA guidelines, anticoagulation is still recommend in the first 3 months after placement, although this varies according to institution.

2. Answer A: In the setting of infection and, in particular, aortic root abscess, an aortic homograft is generally considered the best choice to prevent subsequent immediate reinfection. The durability of homografts was once thought to be superior to that of bioprosthetics, but recent experience has demonstrated this not to be the case. Furthermore, the difficulty of reoperation in such a patient (coronary reimplantation and subsequent extensive calcification) should be taken into account. A mechanical aortic valve with the lowest thromboembolic risk, such as a St. Jude or Carbomedics, is preferred in a young person, given its durability and potential to prevent future reoperation. The risk of anticoagulation for the patient must also be taken into consideration. Given the comorbidity of chronic lymphocytic leukemia, which carries a decreased life expectancy yet not imminent death, a bioprosthetic valve is probably a good option. Of course, there are surgical considerations to the placement of a bioprosthetic valve, such as the larger profile of the valve secondary to its struts. If possible, however, the risk of anticoagulation should be avoided, given the low potential for reoperation in this patient. Recent data with bovine pericardial bioprosthetic valves demonstrate a higher-than-expected durability of approximately 85% at 15 years, which may have shifted the threshold for bioprosthetic valves to many patients in their 50s and 60s. The 70-year-old woman would probably be best served by a bioprosthesis given its durability and higher risk of anticoagulation in this age group.

3. Answer A: Thrombus formation is most common at the tricuspid valve and least common at the aortic valve. Fibrinolytic therapy is considered the treatment of choice for right-sided PVT because the

consequences of distal embolization are less severe than in a left-sided prosthesis. Streptokinase and urokinase are the most common agents, and the success rate is approximately 82%, with a 12% rate of thromboembolism and 5% incidence of major bleeding for right-sided PVT. Leftsided PVT is generally considered for surgery unless the thrombus is small or the surgical risk is prohibitive as the consequences of embolization at a left-sided valve during thrombolysis may be catastrophic. Cinefluoroscopy is an excellent way to evaluate occluder motion.

4. Answer A: Patient–prosthesis mismatch implies a true physiologic stenosis that is a result of the placement of a relatively small prosthesis, typically in the aortic position, that leads to a reduction in cardiac output. All prosthetic valves have an inherent relative stenosis, but when an inappropriately small prosthesis is placed, a patient can be left with a true gradient that is similar to that prior to the operation. Anything that increases cardiac output, such as anemia, as in the postoperative period, or sepsis, will increase flow through the prosthesis and produce higher-than-normal transvalvular gradients. Similarly, increased regurgitation, such as mitral regurgitation, which is often shielded on surface echo by prosthetic valves, will increase flow across the valve and produce a picture of pseudostenosis. Pressure recovery phenomenon describes a false elevation in gradients that is obtained by echocardiography, typically as a result of high-velocity flow through the central orifice of a bileaflet mechanical valve, which dissipates in the ascending aorta.

5. Answer C: The patient has persistently high gradients across the valve since surgery and has a small prosthesis (#19) implanted. Initially, the gradients might be attributed to anemia postoperatively but have actually got higher postresolution of this. There may be an element of pressure recovery leading to high gradients at this mechanical valve but this would not account for his symptoms. No thrombus or pannus was evident at TEE and it would be unusual to have pannus ingrowth this early postoperatively. This patient may require reoperation with placement of a larger valve. The aortic annulus may have to be enlarged at the same time to fit a bigger valve. Another option may be the insertion of a stentless valve such as a homograft that has a larger orifice size for its diameter.

6. Answer D: The most appropriate treatment is to add aspirin or clopidogrel in the absence of structural abnormality at the valve and absence of other embolic source. Dabigatran is not approved for mechanical valve anticoagulation. Occasionally, surgical exploration and bioprosthetic insertion are necessary for recurrent embolization despite adequate and even supertherapeutic anticoagulation. Blood cultures are indicated if infection is suspected but not otherwise.

7. Answer B: The patient has high gradients and high LDH even for a mechanical valve. This suggests a hemolytic anemia related to the valve. The most likely cause of this is a paravalvular leak that may be hard to detect because of shielding especially if it is posteriorly directed. This will render it inaudible also. There tends to be a disproportionate increase in the peak rather than the mean gradient with concomitant regurgitation at a prosthetic valve. Hemolysis normally occurs at mechanical prostheses even in the absence of a paravalvular leak but rarely cause anemia and LDH levels are in the 300 IU range.

8. Answer E: The patient has a degenerated bioprosthesis. Valve failure at bioprostheses is rarely catastrophic but when it occurs is generally due to a flail valve leaflet leading to regurgitation. Patient–prosthetic mismatch is the presence of a valve of inadequate size to meet the hemodynamic needs of the patient. This is associated with high valve gradients that are usually present from the time of surgery. Thrombosis and embolism from bioprostheses are very rare but can occur.

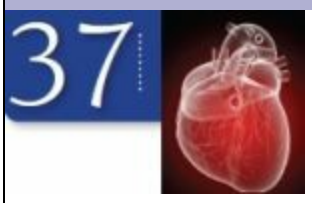
9. Answer B: These jets are what is expected normally at a double tilting disc mitral valve prosthesis. The jets emanate peripherally, are of low velocity, and frequently may not persist throughout systole. They are a design feature of the valve. Paravalvular leaks are generally larger. Valve thrombosis usually causes central regurgitation because the leaflets neither open nor close fully as does occluder impingement from a severed chord.

10. Answer D: Mitral regurgitation at a prosthesis will usually give rise to increased gradients across the valve and especially of the peak gradients because of the increased flow through the valve. Severe mitral regurgitation will usually lead to increased ejection fraction at least initially though contractile function may not have changed as the ventricle is ejecting a lot of its output back into to the low-pressure left atrium. Forward cardiac output is not usually increased though the flow through the regurgitant valve is. Paravalvular leak will typically cause some increase in LDH levels. These are not

usually elevated in bioprosthetic valves, unlike in mechanical valves where they are elevated mildly normally. Pulmonary hypertension is usually present when there is significant mitral regurgitation. With severe paravalvular leak, it is often severe.

SECTION VII ■ CORONARY ARTERY DISEASE AND CARDIAC CATHETERIZATION

CHAPTER



Evaluation of Chest Discomfort

Clay A. Cauthen and Donald A. Underwood

Chest pain or discomfort is a common complaint encountered in virtually every clinical setting: outpatient clinics, emergency departments, hospital floors, and intensive care units (ICUs). The evaluation of chest discomfort is directed by the patient history, chronicity of chest pain, the physical examination, and the clinical scenario. The differential diagnosis (Table 37.1) should remain foremost in the clinician's mind during the evaluation, with the more life-threatening problems initially excluded and the underlying diagnosis ultimately clarified. What follows is an overview of the evaluation of chest discomfort.

TABLE
37.1 Differential Diagnosis of Chest Pain

Cardiovascular	ACSs, myocarditis, pericarditis, hypertrophic cardiomyopathy (HCM) with obstruction, acute aortic dissection, aortic or mitral stenosis, aortic dissection
Pulmonary	Pulmonary embolism, pleuritis, pneumonia, tracheobronchitis, pneumothorax
Gastrointestinal	Gastroesophageal reflux, esophageal spasm, peptic ulcer disease, biliary colic, pancreatitis
Musculoskeletal	Costochondritis, spinal disease
Infection	Shingles
Psychological	Anxiety attacks

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for chest discomfort can be divided into those diseases that cause acute chest discomfort and those that cause more subacute or chronic syndromes. Further, the causes of acute chest discomfort can be further subdivided into those syndromes that are urgent, life-threatening problems requiring immediate recognition and treatment, and those that warrant a more measured approach (Table 37.2).

TABLE
37.2 Causes of Acute Chest Discomfort

Critical syndromes	Acute myocardial infarction	HCM with obstruction
	ACSs	Pulmonary embolism
	Acute aortic dissection	Spontaneous pneumothorax
	Thoracic aortic aneurysm	Boerhaave syndrome
	Critical aortic stenosis	
Stable syndromes	Pericarditis	Pneumonia
	Myocarditis	Gastroesophageal reflux disease
	Mitral stenosis	Esophageal spasm
	Pulmonary hypertension	Pancreatitis and biliary disease
	Pleuritis	Musculoskeletal syndromes

The acute, life-threatening problems in the differential diagnosis include acute myocardial infarction, acute aortic dissection, pulmonary embolism, spontaneous pneumothorax, and esophageal rupture and acute coronary syndrome (ACS). Hypertrophic obstructive cardiomyopathy with symptomatic obstruction, symptomatic aortic stenosis, and thoracic aortic aneurysm should also be considered in this group. These syndromes are each very different, and their successful recognition and treatment should likewise be individualized (Table 37.2).

Acute pericarditis and myocarditis may cause oppressive symptoms with relatively acute onset. Pulmonary hypertension causing chronic cor pulmonale may be of more insidious onset but can have acute symptoms superimposed. Pneumonia with pleuritis or pleuritis associated with other inflammatory illnesses can cause acute progressive chest discomfort, often exacerbated with inspiration or cough. Gastroesophageal disease such as reflux disease, peptic ulcer disease, and esophageal spasm may cause chest discomfort syndromes that may mimic angina pectoris. A variety of musculoskeletal injuries and inflammatory processes may cause chest wall pain syndromes of acute onset. All of these, while important causes of chest discomfort, are less critical and should therefore be pursued only after the acute, emergent diagnoses have been excluded.

Of the more chronic causes of chest discomfort, chronic stable angina is an important etiology of episodic discomfort. Clinical scenarios that may cause persistent

symptoms include chronic cor pulmonale due to chronic venous thromboembolic disease, underlying lung disease, and rheumatologic disease. These syndromes are typically addressed initially in the outpatient setting and may often be worked up on an outpatient basis.

HISTORY

The evaluation should begin with a clinical history focusing on the characteristics of the discomfort. The location, quality, radiation, severity, timing, plaintive and palliative factors, context, and associated symptoms should be carefully and thoroughly documented. These syndrome attributes will form the basis of the physical examination and inform the near-future decisions regarding further diagnostic studies. Further, the patient's medical, social, and family histories, as well as medication history, are critical to an understanding of the patient's overall risk for acute and chronic disease processes under consideration.

LOCATION

The location of the discomfort can suggest a specific diagnosis or can help differentiate between chest wall and visceral organ pathology. In the thorax, general visceral afferent pain fibers, including cardiac visceral afferent fibers, course with the corresponding sympathetic fibers back to the spinal cord segments T1—T4. Chest wall and the upper limbs have their origin in the same spinal cord segments. Thus, the central nervous system cannot clearly distinguish pain type and location (i.e., the visceral organs or chest wall). Clinically, we see that the term "chest pain" is often too specific for patients, and they will deny "chest pain" in favor of other, less-specific sensations like pressure or burning. Asking about chest "distress or discomfort" often leads to a story of typical angina pectoris when chest "pains" had been denied. In contrast, focal pains can be localized more consistently when they involve the parietal pleura or the chest wall itself. These structures have cutaneous dermatomal innervation, with inflammation or injury more commonly causing focal pain. Eliciting a careful description of the location of the pain or discomfort is critical to the overall assessment of the syndrome.

QUALITY

The quality of the sensation is, as stated above, important in identifying the involvement of the viscera of the chest, or the chest wall. Is there pain or pressure? Heaviness or burning? These are typical complaints associated with visceral inflammation or injury. However, they are not specific to a particular organ tissue. The "squeezing" of myocardial ischemia may be perceived no differently than the "squeezing" sensation of

esophageal spasm or pulmonary hypertension. Likewise, pleuritic pain, a sharp stabbing sensation often exacerbated by breathing or certain positioning, is no different than the perception of pericardial inflammation. Aortic dissection may cause a writhing, tearing, or stabbing sensation that is maximally intense at the onset and inescapable with different positioning, but has no variation with respiration. The quality of the discomfort contributes to the clinician's overall picture of the syndrome.

RADIATION

Although chest discomfort is often localized to one single spot or generalized area, it may be described as "radiating" or migrating to another location. The discomfort of angina pectoris is often described as radiating to the arms or shoulders, the neck or jaw, or the back. In contrast, the pain of aortic dissection is classically described as tearing through to the back and migrating with the dissection. The pain of pulmonary embolism may cause diffuse, nonspecific tightness or heaviness (likely due to acute right ventricle strain), evolving with time to include a focal pleural component representative of inflammation in the parietal pleura apposed to the infarcted lung tissue. This may felt to be "radiation" of pain or simply a separate component of the syndrome.

SEVERITY

The severity of symptoms can provide the clinician an indication as to the severity of the underlying pathology. Likert pain scales are often used for patient self-assessment of pain severity. Pain scales may be helpful in following the patient's response to therapy, but in life-threatening clinical scenarios such as acute aortopathies and high-risk ACSs, qualitative improvement on a pain scale should not dissuade the clinician from advancing care. In more chronic syndromes, severity assessment may be helpful in following the progression of the disease.

TIMING

The physician should make careful note of the symptom complex initial time of onset and the timing of the appearance of new symptoms as they occurred prior to presentation. The duration of symptoms may help differentiate acute ischemic injury or infarction with hours of persistent symptoms from an episode of unstable angina lasting 25 minutes. Furthermore, the duration of symptoms can be an important factor in the decision to administer certain therapies such as pharmacologic thrombolysis in acute myocardial infarction or pulmonary embolism.

PLAINTIVE AND PALLIATIVE FACTORS

An assessment of the modifying factors of the primary complaint may in some cases help inform the diagnosis. Palliation of symptoms with medication such as nitroglycerin or resolution of symptoms with rest, discontinuation of strenuous activity, or changing position (sitting up, resulting in reduced preload and oxygen need) may suggest an anginal picture. Esophageal spasm is also thought to be palliated with nitroglycerin. Conversely, in ACSs, pulmonary embolism, and chronic stable angina, exertion tends to be plaintive. So, while it is important to know what the patient has found to be palliative in his or her discomfort syndrome, it also helps to know what maneuvers may have exacerbated the symptoms.

CONTEXT

The symptom context can assist in differentiating acute musculoskeletal injuries from unstable coronary syndromes. For example, sudden symptoms waking a patient from sleep at 4 am may be more suggestive of an ACS than of a chest wall injury, whereas symptoms occurring while shoveling snow may be less clearly differentiated. Within the context of the occurrence of the symptoms should be an exploration of whether the patient has ever suffered a similar syndrome in the past. If the symptoms are recurrent, any previous studies performed to further evaluate the syndrome may be an invaluable resource. If the symptoms are new, then more aggressive evaluation may be warranted.

ASSOCIATED SYMPTOMS

A thorough exploration of associated symptoms with chest discomfort onset may help guide clinical decision making. Chest discomfort with associated dyspnea, nausea, vomiting, or diaphoresis may suggest significant autonomic and adrenergic activation, consistent with myocardial ischemia. Presyncopal or syncopal symptoms may be more concerning for ischemia-induced arrhythmias or critical aortic stenosis. Again, severity and duration of the symptoms as well as modifying factors may further clarify the picture of the larger syndrome.

MEDICAL HISTORY

An exploration of the patient's prior medical history must be done and may help identify underlying risk factors for the various disease states under consideration. Risk factors for coronary artery disease, including patient age, presence of hypertension, hyperlipidemia, diabetes, peripheral vascular disease, history of prior myocardial infarction, cerebrovascular accident, or transient ischemic attacks, all increase the likelihood of the presenting syndrome being attributable to coronary disease or acute aortic pathology. A history of estrogen use, hypercoagulable state, smoking,

immobilization, or recent surgery may all point toward venous thromboembolic disease as an underlying cause of presenting symptoms.

SOCIAL, FAMILY, AND MEDICATION HISTORY

Risk factors such as tobacco use, cocaine use, and even herbal supplement use, as in the case of ephedrine, may be helpful in further evaluating an acute chest discomfort syndrome. In addition, an assessment of the patient's family history may reveal a strong familial history of early coronary events, or aortic pathology as in the case of Marfan syndrome.

Medication history is important in assessing the new patient with chest discomfort. Medical compliance history in addition to the medications themselves and their dosing schedule may contribute to the clinical scenario, for example, a patient with chest discomfort and hypertension who was taking high-dose clonidine but ran out of medication. Rebound phenomena with **α**- and **β**-antagonists may be active issues.

PHYSICAL EXAMINATION

The physical examination should focus on findings supporting the diagnostic question and assess the suitability of any required invasive procedure. The head and neck examination should include assessment of the carotid pulses for their symmetry and quality of upstroke. The jugular veins should be observed for distention suggestive of volume overload and normal a, c, and v waves. The cardiovascular exam should be sensitive to findings consistent with the differential diagnostic acute chest discomfort possibilities under consideration.

The pulmonary examination should assess for the presence of rales suggestive of fluid overload, but also for symmetric air movement in both lungs, tracheal shift from the midline, dullness to percussion suggestive of pleural effusion, or a cardiac border percussed lateral to the apex suggesting effusion. A complete (carotid, brachial, radial, femoral, popliteal, and dorsalis pedis/posterior tibialis pulsations) survey of the peripheral vasculature should be conducted to assess symmetry of the pulse. Any bruits should be documented, as the presence of bruits in the periphery may help inform the choice of vessel for arterial access if a left heart catheterization is needed. More important, bruits raise the likelihood of coronary insufficiency as the cause of the acute chest discomfort.

The extremities should be examined for edema, evidence of chronic venous stasis, cellulitis, vascular ulcerations, cords, or Homans sign (sign of deep venous thrombosis). Furthermore, an adequate neurologic examination is critical to establish baseline neurologic deficits that may be associated with the chest discomfort syndrome. The use of agents such as sedatives, opiate analgesics, and, more important,

thrombolytics may be complicated by alterations in neurologic status.

WORKUP

The pace of the diagnostic evaluation is determined by the clinician's index of suspicion for critical acute chest disease. Chronic stable syndromes may be evaluated on an outpatient basis with diagnostic studies to rule out symptomatic obstructive coronary artery disease, gastroesophageal disease, peptic ulcer disease, and chronic lung, pericardial, or neuromuscular disease.

In the emergency department, patients presenting with acute chest discomfort are typically evaluated with an electrocardiogram (ECG) and chest x-ray. Critical evaluation of the ECG for evidence of myocardial ischemia, injury, or infarction should be conducted. A chest x-ray should be closely reviewed to assess for the presence of acute parenchymal or mediastinal changes. Serial cardiac markers and observation on telemetry may be performed in clinical observation units in patients at low risk for ACSs. After an appropriate observation period, if the biomarkers and ECG remain negative for evidence of coronary insufficiency, patients may undergo further risk stratification for coronary artery disease through exercise testing prior to discharge. Negative laboratory values and exercise stress testing during close observation is reassuring that the syndrome is unlikely to be attributable to coronary insufficiency, and an evaluation for other, less ominous causes of the chest discomfort syndrome can be pursued on an outpatient basis.

Patients at higher risk for ACS should be treated more aggressively with admission to the hospital and therapeutic anticoagulation, if not contraindicated. If suggested by the history and physical examination, ventilation/perfusion scan or helical computed tomography (CT) to rule out pulmonary embolism should be performed. CT or a transesophageal echocardiogram may be performed to assess for the presence of aortic aneurysm or dissection.

SPECIAL CIRCUMSTANCES

"Atypical chest pain" is a term used to describe a syndrome of discomfort that does not follow the classically described pattern of discomfort attributable to coronary insufficiency. The pretest risk is uncertain based on symptoms, with the clinical risk-factor profile becoming important coupled with the physical examination.

Coronary disease presenting with atypical symptoms occurs more commonly in women and in diabetics. Furthermore, the less common causes of chest discomfort, including the less common causes of myocardial ischemia, are more prevalent in women than in men. The presence of diabetes in women presenting with atypical chest discomfort appears to be the most predictive risk factor for angiographically evident

coronary artery disease, arguing that these patients should be treated more aggressively and with a high clinical suspicion for ACS than the less typical symptoms might dictate.

COCAINE-ASSOCIATED CHEST DISCOMFORT

Cocaine use is a commonly encountered comorbidity in patients presenting to the emergency department with acute chest discomfort. The initial evaluation of these patients proceeds in similar fashion to others presenting with similar complaints, save for the recognition that these patients have a higher risk for ACS and myocardial infarction. These patients are often younger and have fewer risk factors for coronary artery disease than those not using cocaine. They are at higher risk due to the increased incidence of accelerated atherosclerotic disease associated with cocaine use plus the increased incidence of coronary vasospasm. In the absence of ECG evidence of ongoing myocardial injury, cocaine-associated chest discomfort should be treated aggressively with antianginals, antiplatelet and antithrombotic therapy until the discomfort is resolved and myocardial infarction has been excluded. One caveat in the treatment of cocaine-associated chest discomfort is that the use of **β**-antagonists without **α**-antagonist activity is contraindicated because of the risk of a profound hypertensive response in the setting of unopposed **α**-activity.

VARIANT OR "PRINZMETAL" ANGINA

A small subset of patients with apparently ischemic chest discomfort and known angiographically normal coronaries suffer from transient vasospastic coronary obstruction. Patients who use tobacco, cocaine, or have other vasospastic syndromes such as Raynaud phenomenon or vascular headaches are at higher risk for variant angina. Patients present with typical anginal symptoms and ECG changes suggestive of acute injury, occurring at rest or with stress and resolving with nitrates and/or calcium antagonist therapy. Patients with recurrent episodes but without ECG changes often need provocative testing in the catheterization laboratory to confirm the diagnosis. Intracoronary ergonovine can reproduce the spasm and symptoms experienced by these patients. These patients frequently respond to therapy with long-acting nitrates and calcium antagonists, though higher than usual doses are often needed.

SUMMARY

The evaluation of chest discomfort syndromes requires the performance of a careful history and physical examination with a focus on risk factors, signs, and symptoms indicative of critical pathology. Some basic laboratory studies and testing may guide the physician toward the diagnosis or help to rule out acute life-threatening syndromes. The

pace of the evaluation is determined by the acuity of the clinical scenario and the clinical venue. In the absence of an acute syndrome, risk stratification for the presence of coronary artery disease is commonly undertaken, and further evaluation ensues.

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QUESTIONS AND ANSWERS

Questions

1. A 23-year-old peripartum female presents with substernal chest pain. Electrocardiogram (ECG) demonstrates ST elevations in II, III, and aVF. The next appropriate step is:
   a. Administer aspirin 325 mg, clopidogrel 600 mg, oxygen, nitrates, and heparin weight-adjusted bolus.
   b. Administer aspirin 650 mg, clopidogrel 300 mg, oxygen, nitrates, and heparin weight-adjusted bolus.
   c. Administer aspirin 650 mg, clopidogrel 600 mg, oxygen, nitrates, and heparin weight-adjusted bolus.
   d. Administer oxygen, beta-blocker, and order gated computed tomography (CT) of the chest.
   e. Administer oxygen, beta-blocker, and order non-gated CT of the chest.
2. A 44-year-old male with known hypertension, hyperlipidemia, and diabetes presents with chest pain that occurs with minimal exertion. Initial ECG demonstrates normal sinus rhythm with nonspecific T-wave changes laterally. Which of the following is true regarding cardiac biomarkers?
   a. For this patient who presented within 6 hours of the onset of symptoms, an early marker of cardiac injury, such as myoglobin or CK-MB subforms should be considered instead of cardiac troponin.
   b. In this patient with suspected acute coronary syndrome (ACS) and negative initial cardiac biomarkers, another sample should not be drawn since the patient is pain free.
   c. Troponin I is preferred over Troponin T due to variability in the biochemical assays.
   d. Total CK cannot be used alone with additional test such as cardiac-specific troponin when evaluating a patient with ACS.
3. A 65-year-old female with known coronary disease, previous three vessel coronary bypass grafting, poorly controlled hypertension, and chronic kidney disease stage III presents with crushing chest pain, ECG demonstrates atrial fibrillation with a ventricular rate of 82 and left ventricular hypertrophy with repolarization. The patient is admitted to the chest pain unit. Which of the following is the best approach?
   a. The patient should have serial 12-lead ECG and cardiac biomarkers, and if the biomarkers become positive, a stress test should be ordered.
   b. From the history, physical exam, 12-lead ECG and initial cardiac marker should be integrated to designate the patient as noncardiac chest pain, chronic stable angina, possible ACS, or definite ACS.
   c. Chest pain units often increase the costs incurred to health care systems as they "rule-out" low-

risk patients.
   d. Morphine sulfate intravenously should be administered before nitroglycerin to decrease symptoms of acute pulmonary congestion.

4. A 43-year-old female with no known medical history presents to local emergency department with complaints of chest pain. ECG demonstrates normal sinus rhythm, first-degree atrioventricular block, and T-wave inversion in V_5 and V_6. Serial cardiac biomarkers are within normal limits. All of the following historical descriptions would be concerning for angina except:
   a. The patient develops chest pain with moderate exertion that resolves despite continued exertion.
   b. The patient develops chest pain that occurs with change in posture, like standing from a seated position.
   c. The patient suffers from nightmares where she frequently awakes in the middle of the night with chest pain that resolves soon after awakening
   d. The patient is in the middle of a horrible divorce and has been having episodes of chest pain that last 5 to 10 seconds that are provoked by emotional distress.

5. A 52-year-old male with a bicuspid valve, moderate aortic stenosis, severe right coronary artery (RCA) disease and known aortopathy (proximal aorta measures 5.1 cm) presents with crushing chest pain to emergency room 6 weeks after mechanical aortic valve replacement, aortoplasty, and bypass grafting of the RCA. Initial set of biomarkers are within pending. ECG demonstrates ST elevation in I, II, aVL, and V_3–V_6. Chest radiograph demonstrates cardiomegaly that is unchanged from the radiograph at discharge. Echocardiogram at discharge demonstrated a moderate pericardial effusion with fibrous stranding. Which of the following is the most appropriate next step?
   a. Immediate activation of the cardiac catheterization laboratory
   b. Activation of the cardiac catheterization laboratory within 48 hours of chest pain
   c. Treatment with non-steroidal antiinflammatory drugs, colchicine, and possible steroids if pain is recurrent
   d. Echocardiography to assess for wall motion abnormalities and possible graft leak
   e. Erythrocyte sedementation rate and C reactive protein to determine level of inflammation

Answers

1. Answer D: The patient is most likely presenting with dissection. Most appropriate test for a patient who is at a higher likelihood of presenting with an acute dissection rather than ACS is a gated CT of chest or cardiac CT.

2. Answer D: Total CK must be used with a cardiacspecific biomarker such as cardiac-specific troponin and CK-MB.

3. Answer B: Patients should be triaged according to their risk stratification determined by history and physical and laboratory data.

4. Answer D: A describes chest pain that is most likely due to the walk-through phenomena where angina is relieved by recruitment of collaterals. B represents decubitus angina where a patient has chest pain due to shifts in volume distribution. C represents a patient who has nocturnal angina that is most likely due to tachyarrhythmias. Patients who experience chest pain as a result of emotion and have episodes that last <1 minute are unlikely to have true angina.

5. Answer A: The patient is most likely suffering from post pericardectomy syndrome. However, dissection and ACS need to be excluded. Activation of the cardiac catheterization lab can assess coronaries and aortic graft patency. Treatment for pericarditis is premature at this point of the evaluation. Echocardiography cannot diagnose pericarditis but could demonstrate wall motion abnormalities as well as possible dehiscence of aortic graft. Inflammatory markers are helpful for the treatment of recurrent pericarditis or augmenting the diagnosis of pericarditis.

CHAPTER

Coronary Artery Disease: Demographics and Incidence

Michael Jolly and Leslie Cho

GLOBAL BURDEN

It is widely acknowledged that cardiovascular diseases (CVDs) became the leading cause of mortality and a major cause of morbidity in adults worldwide over the course of the 20th century. Of these diseases, coronary artery or coronary heart disease (CAD) is the single most common cause, accounting for well over 42% of all CVD-related death.[1] The World Health Organization (WHO) global burden of disease (GBD) project estimates that >7 million deaths were attributable to CAD in 2004. More than 5.8 million new cases of CAD are added yearly. In order to further define the societal effects, the GBD designed a new measure to capture the effect of years of life lost as a result of both premature death and disability. This metric is termed the disability-adjusted life-year or DALY and reflects a year of healthy life lost to disease. In 2004, CAD accounted for the loss of nearly 62 million DALYs worldwide, making it the fourth leading cause overall, behind lower respiratory infections, diarrheal diseases, and depression (Table 38.1).[1]

TABLE
38.1 Worldwide Burden of CAD and CVD, 2004

	AFR	AMR	EUR	SEAR	WPR	EMR	World
Mortality in thousands							
Ischemic (CAD)	346	925	2,296	2,011	1,029	579	7,198
Cerebrovascular	425	461	1,364	1,074	2,128	254	5,712
Rheumatic	11	10	30	129	93	25	298
Hypertensive	78	151	179	156	316	103	987
All CVDs	1,175	1,969	4,767	3,875	4,094	1,163	17,073
Societal impact in millions of DALYs							
Ischemic (CAD)	3.51	6.52	16.83	21.58	7.88	6.15	62.59
Cerebrovascular	4.88	3.99	9.53	9.60	15.84	2.70	46.59
Rheumatic	0.32	0.14	0.41	2.49	1.23	0.59	5.19
Hypertensive	0.82	1.11	1.14	1.69	2.30	0.94	8.02
All CVDs	14.24	15.22	34.76	14.24	31.78	13.10	151.38

CAD, coronary artery disease; CVD, cardiovascular disease; AFR, Africa; AMR, America; EUR, Europe; SEAR, South East Asia region; WPR, Western Pacific region; EMR, Eastern Mediterranean region; DALY, disability-adjusted life years. Data obtained from the World Health Organization.

Global Temporal Trends in Coronary Artery Disease

Great strides were made in the latter half of the 20th century in the identification and management of traditional risk factors and in the therapeutics and management of acute coronary events, to combat the rising tide of coronary disease. These efforts resulted in dramatic reductions in coronary event rates and CAD-related mortality, mostly in developed countries such as those of Northern Europe. Between the mid-1980s and the mid-1990s, coronary event rates decreased roughly 23% in women and 25% in men, while CAD-related mortality decreased 34% in women and 42% in men. One-third of this reduction in CAD disease burden is attributable to improved therapeutics, whereas two-thirds is attributed to better identification and management of risk factors, leading to a decrease in acute coronary event rates.

Despite these improvements, the trend has been reversed, and we are currently in the midst of a dramatic resurgence in CAD morbidity and mortality. Between 1990 and 2020, worldwide CAD mortality is expected to increase 100% in men and 80% in women. The majority of that increase is expected to occur in the developing world, where rates of CAD mortality are expected to increase 137% in men and 120% in women, whereas in developed countries, the increases are a bit more modest, 48% in men and 29% in women. In terms of DALYs lost, the expected rise is nearly 40%, from 59 to 82 million. The basis for this astounding increase in CAD in the developing world is explained largely by the tightly linked relationship between disease prevalence and various socioeconomic factors. Reductions in mortality from infectious diseases and malnutrition paired with economic prosperity have led to longer life spans worldwide. Along with these changes, modernization and industrialization have led to a decrease in physical activity, increased availability, and consumption of a high-fat, high-calorie

diet. These observations, often termed “epidemiological transitions,” occur when a shift occurs in the predominant cause of morbidity and mortality for a given region.[2] In the developing world, all of these factors have contributed to rising rates of obesity, diabetes, and lipid disorders that are now well established in the developed, western world.

BURDEN IN THE UNITED STATES

Although the mortality rates from CAD have declined since 1968, it remains the most common manifestation of atherosclerotic CVD and the single most common cause of adult death in the United States, accounting for one of every five, and, in people over the age of 35 years, one of every three (Figs. 38.1 and 38.2; Table 38.2). CVD has accounted for more deaths in the United States than any other major cause every year since 1900 except 1918.[3] According to the American Heart Association, 406,351 people died from CAD in 2007, many at the peak of their productive lives. Currently, >16 million people are afflicted with CAD in the United States, with 1.3 million new cases of myocardial infarction (MI), or one every 25 seconds! Of this number, 785,000 represent new cases, whereas 470,000 are recurrent. By comparison, approximately 865,000 people per year suffered a MI from 1987 to 2000, 565,000 per year being new cases. Importantly, 21% of all new MIs in 2007 were symptomatically silent. In terms of societal impact, CAD accounted for the loss of roughly 6.5 million DALYs in 2004, while the estimated average number of years of life lost due to MI is 16.6. It is the leading cause of premature permanent disability, accounting for 19% of Social Security disability outlays.[3]

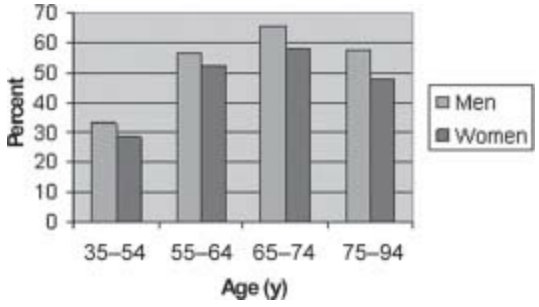

FIGURE 38.1 Proportion of CVD as CAD by age and sex, from Framingham Study, 26-year follow-up. (Reprinted from Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. Am Heart J. 1986;111(2):383–390, with permission from Elsevier.)

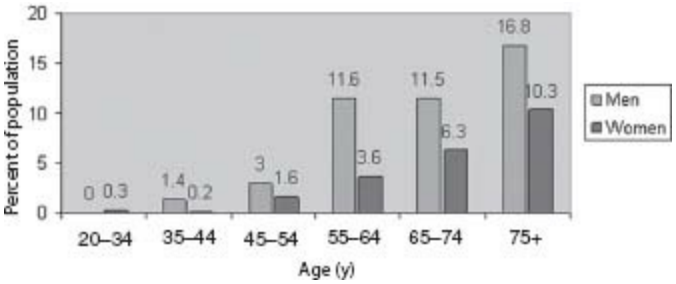

FIGURE 38.2 Prevalence of coronary heart disease by age and sex (National Health and Nutrition Examination Survey: 2005–2008. National Center for Health Statistics and National Heart, Lung, and Blood Institute. *Myocardial infarction diagnosis by expert committee based on review of hospital records.) (From Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation. 2011;123(4):e18–e209, with permission.)

TABLE
38.2 Burden of CAD in the United States, 2008

Population Group	Prevalence of CAD	Prevalence of MI	Prevalence of Angina	CAD Mortality (Thousands)[a]
Total population (%)	16.3 million	7.9 million	9 million	406
Men	8.3	4.3	3.8	216
Women	6.1	2.2	4.0	190
White men	8.5	4.3	3.8	189
White women	5.8	2.1	3.7	165
Black men	7.9	4.3	3.3	22
Black women	7.6	2.2	5.6	21
Mexican American men	6.3	3.0	3.6	—
Mexican American women	5.6	1.1	3.7	—

Data are for people age 20 years and older.

[a]Data are for people of all ages.

Roger VL, Go AS, Lloyd-Jones DM, et al.; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation. 2011;123(4):e18–e209, with permission.

Unrecognized and Silent Myocardial Ischemia and Infarction

The estimated prevalence of asymptomatic significant CAD that is detectable by stress testing or ambulatory ECG is 2% to 4% in the United States.[4] Silent ischemia is actually the most common manifestation of clinically significant CAD, even more so than angina. The prevalence of silent myocardial ischemia in men with two or more traditional coronary risk factors (smoking, hyperlipidemia, family history, diabetes, age, hypertension, age >45 years, and obesity) is upwards of 10%. Of these patients, more than half will go on to develop overt clinical manifestations of CAD and come to

medical attention. Further, often (75% in one study) these patients have multivessel disease when further investigated. In patients with known coronary disease and stable angina, the prevalence of silent ischemia is estimated to be between 25% and 50%. Additionally, 70% to 80% of ischemic episodes in patients with stable angina are silent. Unrecognized MI has two components, asymptomatic or silent MI (approximately 50%), and that which is associated with such atypical symptoms that infarction is not entertained as part of the differential (approximately 50%). One in three MIs can actually be classified as unrecognized. The long-term morbidity and mortality of silent ischemia and unrecognized MI is similar to that of recognized MI (Figs. 38.3 and 38.4).[5]

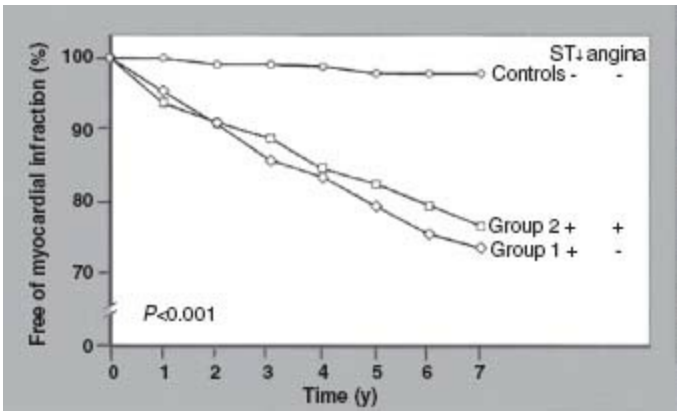

FIGURE 38.3 Outcome of patients with angina (Group 2) or silent ischemia (Group 2) and exercise-induced ST depression in the Coronary Artery Surgery Study (CASS) registry. Controls had no objective evidence of ischemia. (Reprinted from Weiner DA, Ryan TJ, McCabe CH, Ng G. Risk of developing an acute myocardial infarction or sudden cardiac death in patients with exercise induced silent myocardial ischemia: a report from the Coronary Artery Study (CASS) Registry. Am J Cardiol. 1988;62(17):1155–1158, with permission from Elsevier.)

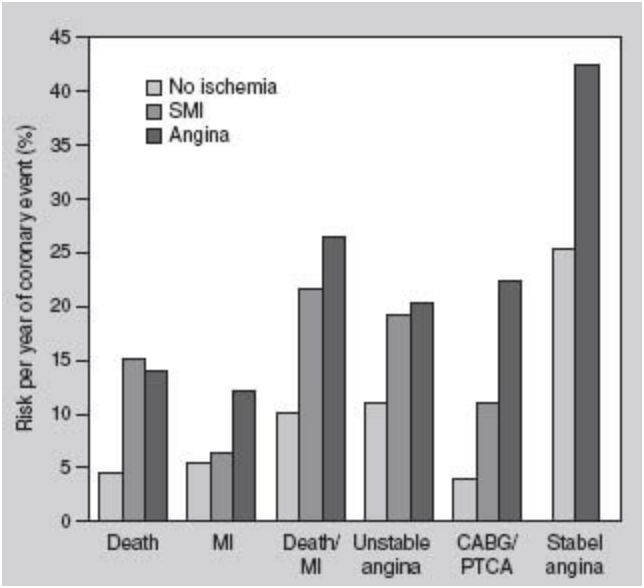

FIGURE 38.4 Long-term outcome of patients post myocardial infarction with angina versus silent ischemia versus no objective ischemia. SMI, silent myocardial ischemia; CABG, coronary artery bypass grafting; PTCA, percutaneous coronary angioplasty; MI, myocardial infarction. (With kind permission from Springer Science+Business Media:

Essential Atlas of Heart Diseases, 2005, Braunwald E.)

Diabetic and hypertensive patients seem to be most susceptible to unrecognized MI.

Age and Gender Variation

The average age of a person presenting with a first MI in the United States is 65 years for men and 70 years for women. Figures 38.2 and 38.5 provide a sense of how strongly the prevalence and incidence of CAD is influenced by age and gender. The incidence of serious manifestations of CAD, such as MI or death, more than doubles between the age ranges of 65–74 and >85 for men and nearly quadruples for women. Further, data from the Centers for Disease Control (CDC) demonstrate that 83% of people who die from CAD are 65 years or older. After age 40 years, men have a lifetime risk of developing CAD of 49%, while women have a risk of 32%. After 70 years this risk decreases to 35% for men and 24% for women.[6]

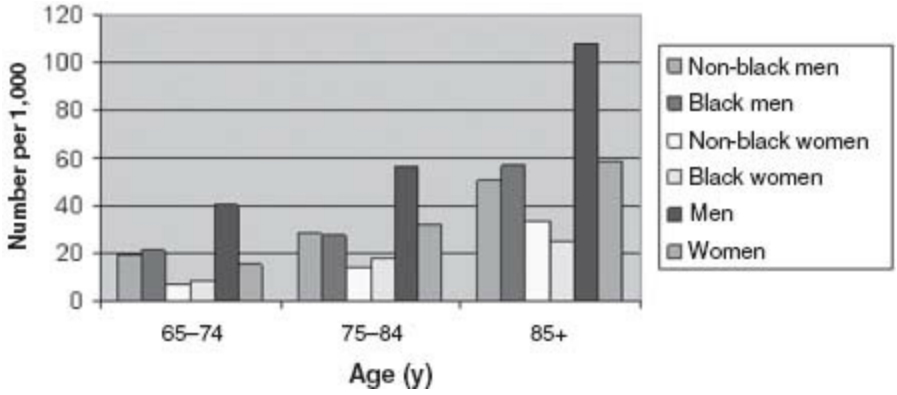

FIGURE 38.5 Incidence of myocardial infarction* by age, race, and sex (Atherosclerosis Risk in Communities Surveillance, 1987–2004). *Myocardial infarction diagnosis by expert committee based on review of hospital records. (From Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation. 2011;123(4):e18–e209, with permission.)

The incidence of any manifestation of CAD in women lags behind that in men by 10 years, whereas the incidence of MI or sudden death lags by 20 years. In fact, excluding people >75 years of age, women are much more likely to present with angina as their first manifestation of CAD, whereas men more often present with MI (Fig. 38.6). In terms of CAD mortality, gender differences narrow significantly with age. Between the ages of 45 and 64 the 1-year mortality following a first MI is 5% for white men, 14% for black men, 9% for white women, and 8% for black women. However, after the age of 65, 30% of women (white or black) will die within 1 year compared to only 25% of men (white or black).[3]

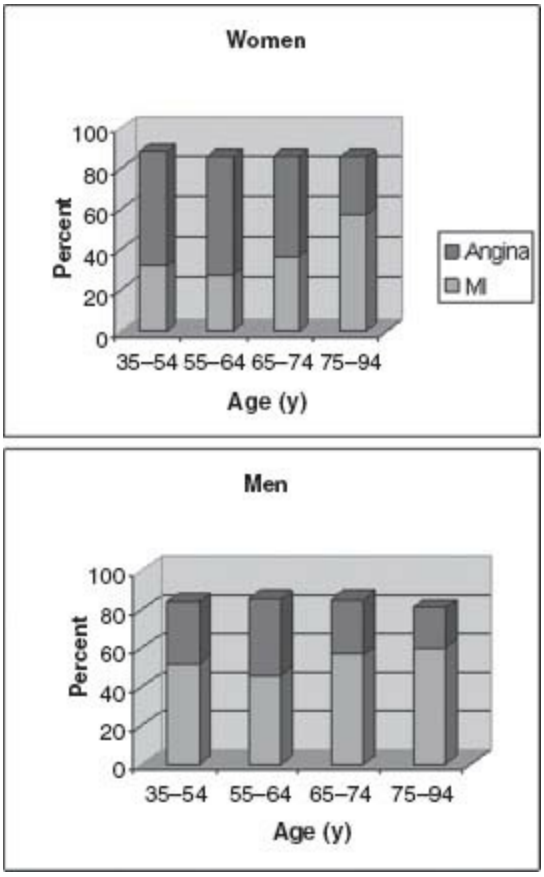

FIGURE 38.6 First manifestation of CAD in men and women by age. MI, myocardial infarction. (Reprinted from Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. Am Heart J. 1986;111(2):383–390, with permission from Elsevier.)

Finally, menopause, whether natural or surgical, has a significant influence on the incidence and severity of CAD. Indeed, the incidence of serious manifestations of CAD is rare in premenopausal women but increases more than threefold in age-matched postmenopausal women. Of note, polycystic ovarian disease increases the likelihood of premature CAD in women.[3]

Racial and Socioeconomic Disparities

CAD is the leading cause of death in the United States for every major ethnic group. The self-reported prevalence of CAD and MI and the CAD mortality rates in various racial and ethnic groups according to the latest AHA update are shown in Table 38.2 and Figure 38.7. The most conspicuous feature of these data is that the CAD mortality rate is highest among blacks overall. Indeed, the mortality rate among black Americans is 1.6 times that of whites, a ratio that has not changed since the 1950s.[7] This difference is particularly striking among younger people, aged 35 to 44 years, in whom the mortality among blacks is reported to be 50% higher than among whites. This difference disappears by age 75 years. Additionally, the incidence of CAD is particularly high among South Asians. The mortality rate among East Asians, Hispanics, and Native

Americans or Alaskans is not nearly as high as that among whites or blacks. In terms of socioeconomic differences, numerous studies have linked lower income levels, lower educational levels, and other social factors to elevated CAD risk. One recent study showed a 2.5- to 3-fold increased risk in people living in poorer neighborhoods compared with those living in higherincome neighborhoods, even after adjusting for other socioeconomic and traditional risk factors.[8]

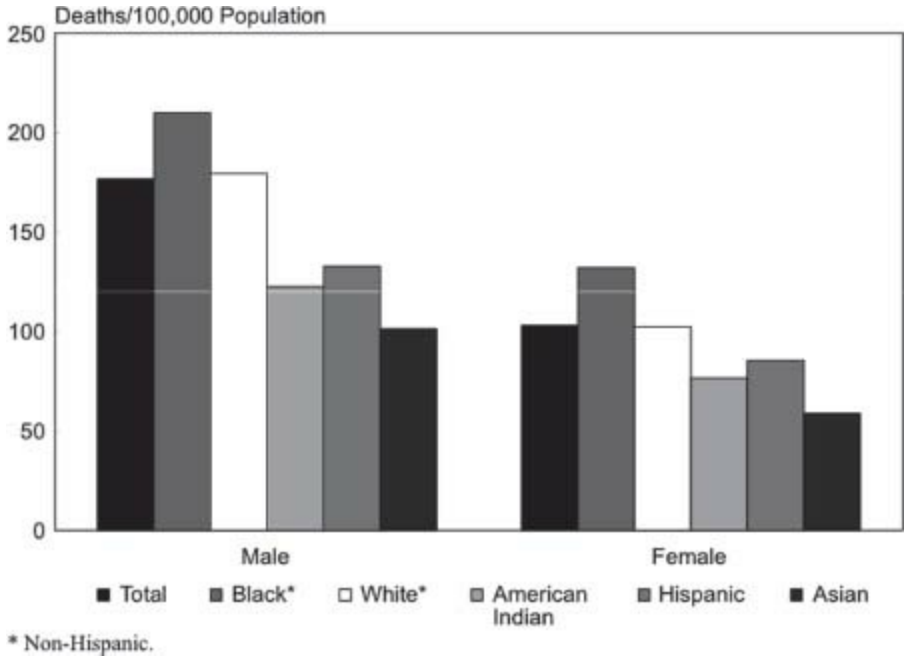

FIGURE 38.7 Age-adjusted death rates for coronary heart disease by race/ethnicity and sex, U.S., 2006. (Morbidity & Mortality: 2009 Chart Book on Cardiovascular, Lung, and Blood Diseases. 2009, National Institutes of Health.)

CAD in the Young

Symptomatic CAD in people under the age of 40 to 45 years is a fairly uncommon problem. In autopsy studies, however, the prevalence of anatomic CAD is roughly 20% in men and 8% in women aged 30 to 34 years.[3] This is consistent with the finding of a delay in manifestations of CAD in women versus men and that atherosclerosis, despite its relative rarity in the young, is a process that begins at an early age. People presenting with CAD at a young age tend to have multiple risk factors as well as a significant family history of premature CAD. Tobacco use is very common among this population; however, the prevalence of dyslipidemia is similar to those presenting later in life. Often, this population tends to have some manifestations of the metabolic syndrome, such as low HDL, elevated triglycerides, and glucose intolerance. With the current epidemics of obesity and the metabolic syndrome in the United States, it seems likely that the incidence of symptomatic CAD in young people is either on the rise currently, or soon will be.

Temporal Trends in CAD

Autopsy studies over the past few decades have shown a decreasing prevalence of anatomically significant CAD in people 59 years of age and younger in the United States. From the periods 1979 to 1983 and 1990 to 1994, the prevalence of CAD decreased from 42% to 32% among men and from 29% to 16% among women.[9] There was no change in those >60 years of age. Similarly, the incidence of clinically manifested CAD decreased from the 1970s to the 1980s. The National Health and Nutrition Examination Survey (NHANES) tracked two cohorts of patients from 1971 to 1982 and from 1982 to 1992 and found that the prevalence of CAD over these time periods decreased from 133 to 114 cases per 10,000 persons per year of followup. Over a similar time period, the overall incidence of MI remained relatively stable. However, from 2000 to 2008 the incidence of MI decreased from 287 cases per 100,000 person-years to 208 cases per 100,000 person-years, a relative decrease of 24%. This was even more impressive among patients with ST-segment elevation MI (STEMI) where from 1999 to 2008 there was a relative decrease of 62%, from 133 to only 50 cases per 100,000 persons. For non–ST-segment elevation MI (NSTEMI), the incidence actually increased between 1999 and 2004, from 155 to 202 cases per 100,000 persons, likely reflecting the newer and more sensitive troponin assays being widely utilized. Even still, the incidence of NSTEMI has been decreasing since 2004 (Fig. 38.8).[10]

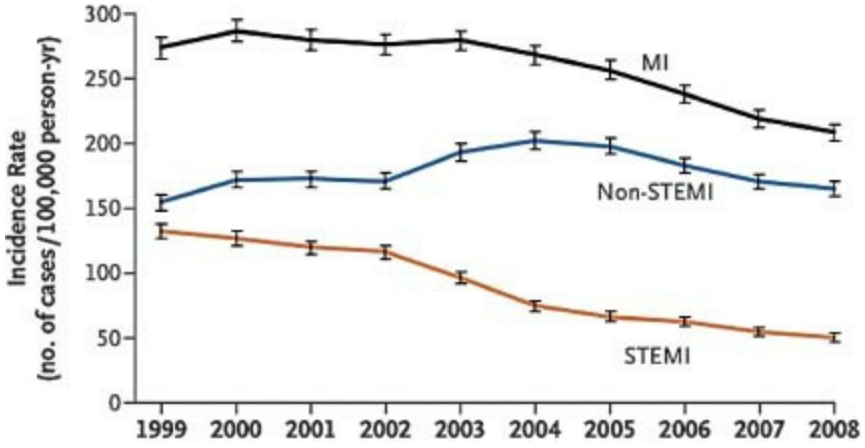

FIGURE 38.8 Age- and sex-adjusted incidence rates of acute myocardial infarction, 1999 to 2008. Bars represent 95% confidence intervals. MI denotes myocardial infarction, and STEMI ST-segment myocardial infarction. (From Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med. 2010;362(23):2155–2165, with permission from the Massachusetts Medical Society.)

In the United States, coronary heart disease mortality has declined steadily since it reached a peak in the mid-1960s (Fig. 38.9). The WHO estimated that between 1965 to 1969 and 1995 to 1997, overall CAD death rates declined 63% in men and 60% in women. Data from the Framingham study echo this, demonstrating a 59% reduction in CAD mortality and a 49% reduction in the rate of sudden cardiac death (SCD) from

1950 to 1999.[3] Additionally, from 1990 to 1999, in-hospital mortality rates for acute MI declined from 11.2% to 9.4%. However, this trend is showing signs of slowing; the CDC found only a 27% reduction from 1992 to 2002. This is likely attributable to the epidemics of obesity, diabetes, and the metabolic syndrome in the United States at the end of the twentieth century.[3]

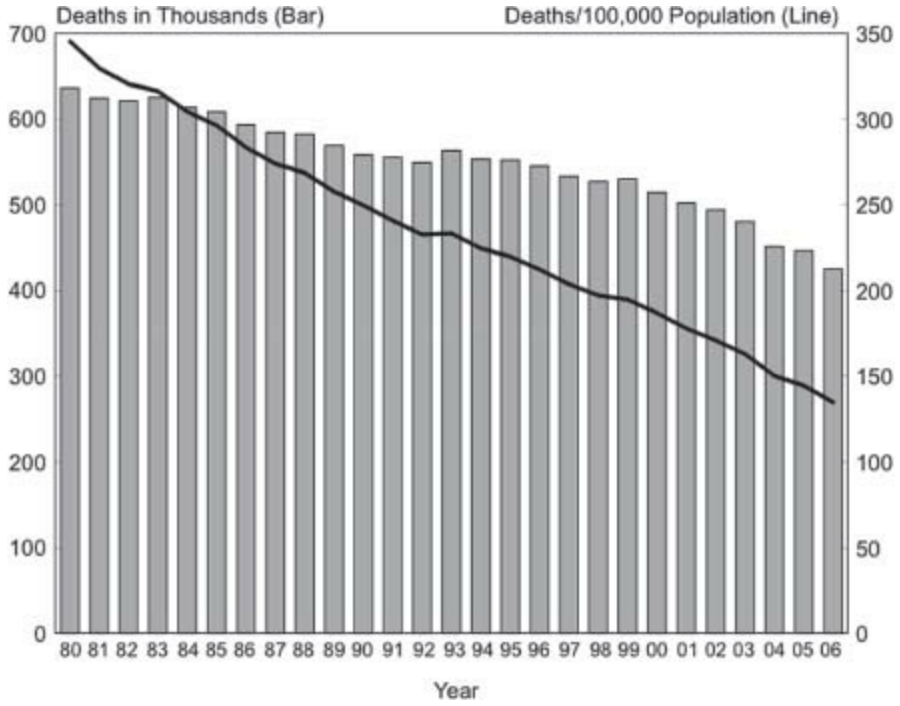

FIGURE 38.9 Age-adjusted death rates for coronary heart disease, U.S., 1980 to 2006. (Morbidity & Mortality: 2009 Chart Book on Cardiovascular, Lung, and Blood Diseases. 2009, National Institutes of Health.)

Prognosis and Risk of Sudden Cardiac Death

Once an individual has been diagnosed with stable angina, prognosis shifts to a much higher risk stratum. The risk of future events, in particular subsequent MI, is increased, whereas survival is dramatically reduced with increasing age. The effect of age at presentation on risk of future events is more profound for women than for men. Overall, however, men remain at higher risk of subsequent MI and death at all age strata (Figs. 38.10 and 38.11).[11]

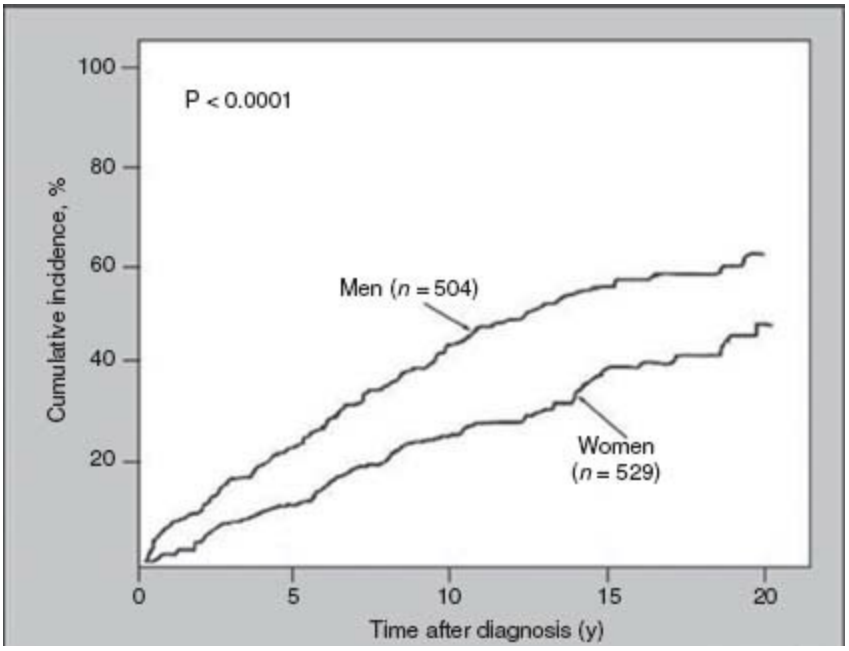

FIGURE 38.10 Risk of subsequent MI or cardiac death after being diagnosed with angina, stratified by sex. (Adapted from Orencia A, Baily K, Yaun P, et al. Effect of gender on long-term outcome of angina pectoris and myocardial infarction/sudden unexpected death. JAMA 1993;269:2392–2397)

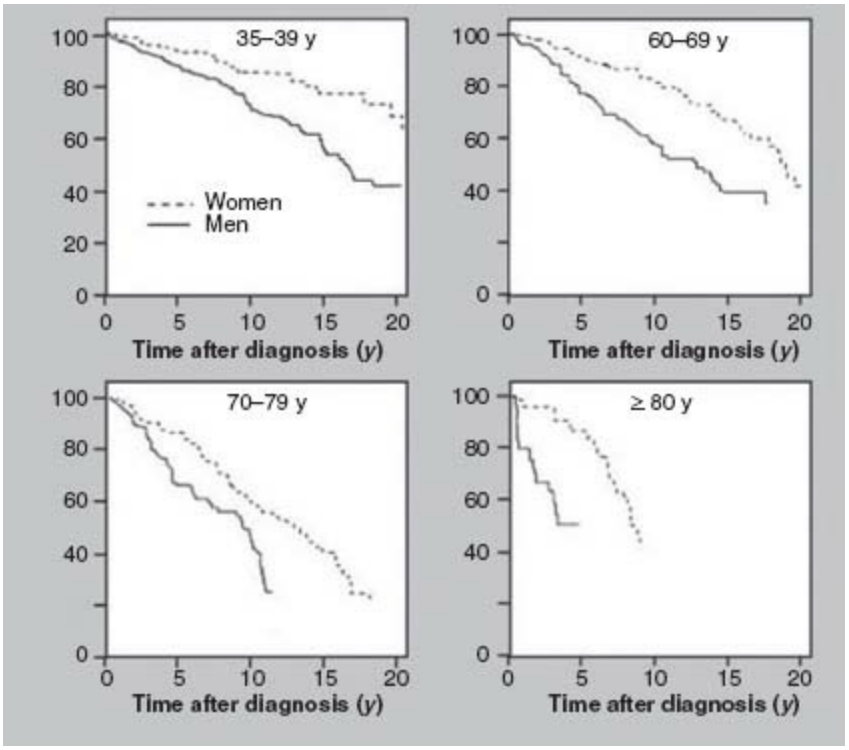

FIGURE 38.11 Long-term survival after the diagnosis of uncomplicated angina, stratified by age and sex. (Adapted from Orencia A, Bailey K, Yawn BP, et al. Effect of gender on long-term outcome of angina pectoris and myocardial infarction/sudden unexpected death. JAMA. 1993;269(18):2392.)

Survivors of acute MI have 1.5 to 15 times the morbidity and mortality rate as the general population, depending on age, gender, and clinical outcome of the inciting event.

In contrast to stable angina, the incidence of future adverse cardiovascular events in people after their initial recognized MI is, in general, higher in women than in men (Fig. 38.12). Following a recognized acute MI, the 1-year mortality rate in men is 25%, whereas in women it is significantly higher, 38%. The majority of this risk occurs within the first 30 days after the event.[3] The discrepancy between the male and female mortality and event rates can be explained by the later age and greater burden of risk factors on average at initial presentation in women.

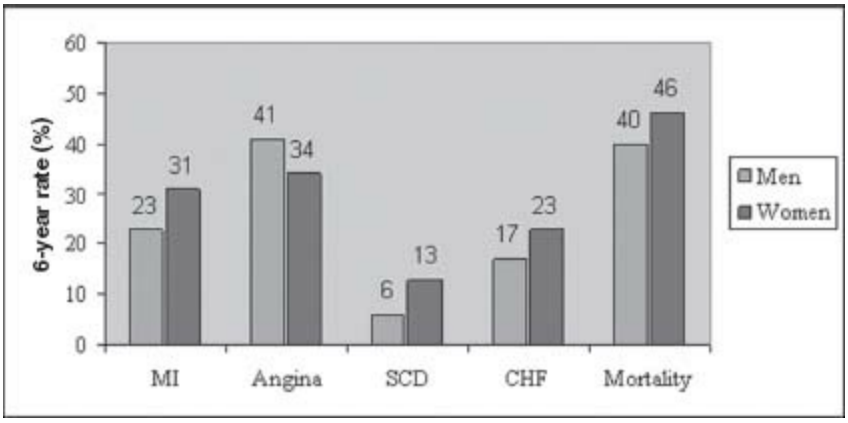

FIGURE 38.12 Prognosis after myocardial infarction, from Framingham Study, 36-year follow-up. MI, myocardial infarction; SCD, sudden cardiac death; CHF, congestive heart failure. (From Kannel WB. Prevalence, incidence, and mortality of coronary heart disease. In: Atherosclerosis and Coronary Artery Disease. Lippincott Williams & Wilkins, 1996.)

Sudden cardiac death (SCD), mostly due to out-of-hospital ventricular fibrillation, accounts for >50% of total CAD-related mortality. In the United States, there are approximately 300,000 out-of-hospital emergency medical services (EMS)-assessed cardiac arrests. Only one-third of patients treated by EMS for cardiac arrest have symptoms within 1 hour of death. The mean survival rate following ventricular fibrillation is 21%, whereas the median survival rate to hospital discharge with any first-recorded rhythm is 7.9%.[12] The risk of SCD death in a person after the index MI is four to six times higher than for the age-matched general population. This risk also varies significantly as a function of age, gender, and race. Overall, from 70% to 89% of all SCD cases occur in men, and the incidence of SCD is three to four times greater in men than in women. This disparity decreases as women age and their risk increases. Blacks have an estimated twofold higher incidence of 30-day mortality following discharge after SCD, a disparity likely related to health care access and a higher incidence of congestive heart failure.[3]

Cost and Health Care Resource Utilization

Direct and indirect costs related to coronary heart disease exceeded $177 billion in the United States in 2007. This represents nearly half of the total cost related to all CVDs,

including stroke, hypertension, and congestive heart failure, which reached a staggering $287 billion for the same year (Table 38.3). In contrast, 2007 costs related to all forms of cancer were estimated to be $219 billion. Medicare estimates that the cost of CAD-related hospitalizations exceeded $14,000 for acute MI, $12,900 for coronary atherosclerosis, and $10,600 for "other" CAD diagnoses, per discharge, in 2006.[3]

TABLE
38.3 2007 Estimated Direct and Indirect Costs (in Billions of Dollars) of EfiBI CVDs In the United States

Component	Heart Diseases[a]	Stroke	Hypertensive Disease[b]	Total CVD
Direct costs				
Hospital inpatient stays	$49.8	$17.9	$6.2	$85.7
Hospital emergency room visits	3.9	0.6	0.6	5.3
Hospital outpatient or office-based provider visits	13.7	2.5	9.8	31
Home health care	6.6	2.9	3.6	13.9
Prescribed medicines	8.5	1.3	20.4	31.4
Total expenditures	82.2	25.2	40.6	167.4
Indirect costs				
Lost productivity/mortality[c]	95.3	15.7	2.9	119.2
Grand totals[b]	177.5	40.9	43.5	286.6

[a]Includes coronary heart disease, congestive heart failure, part of hypertensive disease, cardiac dysrhythmias, rheumatic heart disease, cardiomyopathy, pulmonary heart disease, and other or ill-defined heart diseases.

[b]Costs due to hypertensive disease are limited to hypertension without heart disease

[c]Earnings of persons who died in 2007, discounted at 3%.

From Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation. 2011;123(4):e18–e209, with permission.

Despite rising overall costs, the actual number of patients hospitalized fell 42% between 1997 and 2007, from 2.1 million to 1.6 million. In 2007, it was estimated that 1.1 million diagnostic cardiac catheterizations, 1.2 million percutaneous coronary interventions, and 408,000 bypass operations were performed in the United States.

RISK FACTORS

Traditional Modifiable Risk Factors

Epidemiologic studies undertaken in the latter half of the twentieth century have firmly established links between certain demographic and clinical factors as well as social habits and the diagnosis of coronary heart disease. Among these, older age,

dyslipidemia, hypertension, tobacco smoking, male sex, diabetes mellitus, and family history of premature coronary disease are among the more common and well recognized. Risk scores, most commonly the Framingham Risk Score, have been developed using these and other risks to predict accurately the long-term risk of CAD events. More than 90% of people carrying the diagnosis of CAD have one of the following major risk factors: hypertension, hyperlipidemia, treatment for hypertension or hyperlipidemia, or diabetes. Further the INTERHEART study of >29,000 patients in 52 countries showed that >90% of the risk of an index MI is attributable to the following factors regardless of gender, ethnicity, or geography: tobacco, hyperlipidemia, hypertension, diabetes, obesity, sedentary lifestyle, alcoholism, low intake of fruits and vegetables, and psychosocial index.[3]

Tobacco

According to the AHA, in 2009 >46 million Americans 18 years of age and older are active cigarette smokers, representing nearly 21% of the total population. This constitutes 23% of all men and 18% of all women in the United States. While the total number has decreased by 3.5% since 1998, the number of new smokers every year has seemingly plateaued at approximately 2.4 million. Even more discouraging, most new smokers (58.8%) in 2008 were <18 years of age. From 1980 to 2002 the number of high school seniors who had smoked within the past month declined 12.5%, and since 1965, smoking among persons 18 years of age and older has decreased 47% overall. The prevalence of smoking is highest among white men (25%), black men (23%), white women (21%), and black women (19%). Of all ethnic groups, Asians and Hispanics had the lowest overall prevalence. Smokers have a two- to fourfold higher risk of CAD than nonsmokers, and two- to threefold higher risk of CAD-related mortality, and twofold greater risk for stroke. Even more striking, smokers have a >10-fold risk of developing peripheral artery disease than nonsmokers.[13] The INTERHEART study estimated that tobacco accounts for 36% of the population attributable risk of a first MI.[3] Importantly, it is estimated that the total estimated cost of smoking to society, including direct medical costs and lost productivity, was $193 billion per year between 2000 and 2004.

Smoking cessation has proven benefits for CAD. According to the WHO, the risk of CAD decreases by 50% 1 year after abstention, and within 15 years the relative risk of death from CAD for an ex-smoker becomes equivalent to that of a lifetime nonsmoker.

Lipids

The prevalence of lipid disorders in patients with CAD and in the general population is extraordinarily common. Of people with premature CAD, 75% to 85% have dyslipidemia. In the United States in 2008, approximately one-third of all adults >20

years of age had an LDL cholesterol ≥130 mg/dL. For further details on dyslipidemia and its effects on coronary disease, refer to Chapter 15.

Hypertension

According to AHA figures, 76 million Americans carried the diagnosis of hypertension in 2008. An additional 59 million people are classified as having prehypertension (systolic blood pressure 120 to 139 mm Hg, or diastolic blood pressure 80 to 89 mm Hg) and are at risk for overt hypertension. Systolic blood pressure, diastolic blood pressure, and pulse pressure have all been separately identified as risk factors. The prevalence of hypertension in blacks in the United States is among the highest in the world and continues to increase.[6] From 1988 to 2002, the prevalence increased from 35.8% to 41.4%.[13] According to the INTERHEART study, hypertension accounts for 18% of the population attributable risk of first MI.[3] Further details on hypertension and its cardiovascular effects are included in Chapter 52.

Diabetes Mellitus

The prevalence of physician-diagnosed and undiagnosed diabetes mellitus among adults in the United States was 25.4 million in 2008. An additional 81.5 million (37%) have prediabetes, with fasting blood glucose of 100 to <126 mg/dL. From 1990 to 2002, the prevalence of diabetes increased 61% in the United States. Mexican Americans and blacks currently have the highest rates of any ethnic group.[13] The prevalence of diabetes in individuals 40 to 74 years of age is 11.2% for whites, 18.2% for blacks, and 20.3% for Hispanics. Despite the higher prevalence in Hispanics, blacks were more likely to die from diabetes.[7] Worldwide, the prevalence among all ages is 2.8%, and it is expected to nearly double to 4.4% by 2030. Diabetes increases the risk of MI or cerebrovascular accident by two- to threefold and doubles the risk of SCD. According to the INTERHEART study, diabetes accounts for 10% of the population attributable risk of first MI.[3] In 2002 the National Cholesterol Education Program (NCEP) was compelled by these and additional statistics to elevate diabetes to the category of CAD equivalent.

Obesity and the Metabolic Syndrome

According to the AHA, over 149 million Americans (67%) were overweight or obese in 2008, with 75 million (34%) being overtly obese. Further, the prevalence of overweight and obese children has quadrupled since the 1960s, reaching 32% of all American children in 2008. Obesity has reached true epidemic proportions in the United States and shows no signs of slowing down in the near future. From 1999 to 2000 and from 2007 to 2008, the prevalence of obesity increased from 28% to 32% in adult men

and 33% to 36% adult women, respectively.[13] Mexican Americans constitute the ethnic group with the greatest prevalence. Obesity is now recognized as an independent risk factor for CAD, although it also mediates its effects through other factors that are highly associated with it, such as hypertension, insulin resistance, and hypertriglyceridemia. Obesity accounts for roughly 20% of the population attributable risk of a first MI.

The metabolic syndrome is defined by having ≥3 of the following: a fasting plasma glucose ≥100 mg/dL or undergoing drug treatment for elevated glucose, HDL cholesterol <40 mg/dL in men or <50 mg/dL in women or undergoing drug treatment for reduced high-density lipoprotein (HDL) cholesterol, triglycerides ≥150 mg/dL or undergoing drug treatment for elevated triglycerides, waist circumference ≥102 cm in men or ≥88 cm in women in the United States, or a BP ≥130 mm Hg systolic or ≥85 mm Hg diastolic or undergoing drug treatment for hypertension or antihypertensive drug treatment in a patient with a history of hypertension.[14] The age-adjusted prevalence of the metabolic syndrome in U.S. adults is 34%.[3] Among ethnic groups in the United States, Mexican Americans have the greatest prevalence. A diagnosis of metabolic syndrome carries with it an increased risk of overt diabetes mellitus, a twofold greater risk of CAD, an increased risk of CAD death.

Novel Risk Factors

In addition to the classic modifiable risk factors newer measures are emerging that are leading to new insights and confirming the role of inflammation in atherosclerosis. Not all of these factors have obvious treatments or are modifiable, and some may prove to be risk markers rather than truly play a pathophysiologic role. Among these, high-sensitivity C-reactive protein (hs-CRP) has been at the forefront, although not without controversy Levels of hs-CRP have been shown to predict the long-term risk of first MI and improve risk stratification along with serum lipids in a primary prevention setting. Even in patients who do not meet current pharmacologic treatment recommendations, the addition of statins to patients with elevated hs-CRP has been shown to decrease adverse cardiovascular events.[3] Elevated serum homocysteine levels have similarly been shown to be linked with increased risk for CAD. Levels above the 95th percentile increase the risk of MI approximately threefold. Other novel markers that may prove useful in predicting cardiovascular risk include, fibrinogen, N-terminal fragment brain natriuretic peptide, small dense lipoproteins, apolipoproteins, lipoprotein-associated phospholipase A2, lipoprotein (a), cystatin C, uric acid, alanine aminotransferase, and gamma glutamyltransferase.[15]

Finally, peripheral vascular disease (PVD) as manifested by a cerebral vascular accident (CVA), transient ischemic attack, or lower-extremity claudication significantly increases the risk of CAD and coronary events. This is somewhat intuitive, given that many of the risk factors are shared. CVA increases the risk of CAD or cardiac failure twofold, whereas intermittent claudication increases the risk two- to threefold. Carotid

intima-media thickness (IMT), a measure of carotid atherosclerotic disease as determined by ultrasound, has been shown to be predictive of future MI, even after controlling for traditional risk factors.[16] This lends further support to the role of systemic inflammation in the pathobiology of atherosclerotic vascular disease.

SUMMARY

- CVD remains the leading cause of death worldwide.
- CVD remains the leading cause of death and health care expenditures in the United States, although the mortality rates have declined over the past several decades.
- The incidence of CAD in women lags behind men by 10 years, whereas the incidence of MI in women lags behind men by 20 years.
- In general, women are more likely to present with angina, whereas men tend to present with MI as their first manifestation of CAD.
- African Americans have a CAD-related mortality rate that is 1.6 times higher than whites, a difference that is even more pronounced in younger populations.
- The incidence of NSTEMI far out numbers the incidence of STEMI, although both have been declining in recent years.
- SCD accounts for >50% of all CAD-related mortality
- The prevalence of tobacco smoking has seemingly reached a plateau of approximately 20% and still accounts for 36% of the risk of first MI.
- The prevalence of hypertension in African Americans is among the highest in the world and continues to increase.
- Obesity, diabetes, hyperlipidemia, and the metabolic syndrome are all modifiable risk factors for coronary disease that are reaching near-epidemic proportions in the United States.

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QUESTIONS AND ANSWERS

Questions

1. Which U.S. racial group has the highest mortality rate associated with coronary artery disease (CAD)?
   a. Hispanics
   b. Asians
   c. Blacks
   d. Whites

2. Which of the following regarding acute myocardial infarction (MI) in the United States is false?
   a. The incidence of ST-segment elevation MI (STEMI) has declined over the past decade.
   b. The in-hospital mortality has declined.
   c. The incidence of non-ST-segment elevation MI (NSTEMI) increased with the advent of sensitive troponin assays.
   d. Roughly 50% of all MIs are symptomatically silent.

3. Which of the following factors are associated with the epidemiologic transition of CAD becoming the leading cause of mortality in the United States during the 20th century?
   a. Reduced incidence of infectious diseases and malnutrition
   b. Increased life expectancy
   c. Industrialization with shift in the type of workrelated activities
   d. Increased availability of foods with high saturated fat content
   e. All of the above

4. Which of the following patient is more likely to die within 1 year following their first MI?
   a. A 55-year-old black man
   b. A 70-year-old white woman
   c. A 47-year-old white woman
   d. A 60-year-old black woman

5. Which of the following related to cost is true?
   a. The estimated total cost of all forms of cancer continues to exceed cardiovascular disease (CVD).
   b. The majority of CAD-related costs come from hospital emergency room visits.
   c. CAD-related costs are increasing due to increased patient hospitalizations.
   d. Lost productivity accounts for the majority of CAD-related cost.

6. Which of the following statements related to smoking is false?
   a. Smoking increases the risk of peripheral arterial disease by >10-fold.
   b. The majority of new smokers start the habit during their early 20s, often while in college.
   c. Cigarette smoking has a twofold greater risk of suffering a CVA.
   d. The overall prevalence of smokers has decreased in the United States compared to the mid 20th century.

7. Which ethnic group has the highest prevalence of diabetes?
   a. Whites
   b. Hispanics
   c. Asians
   d. Blacks

8. Which of the following is not considered a criterion for the metabolic syndrome?
   a. Having a fasting blood glucose ≥100 mg/dL
   b. Undergoing treatment for hypertension
   c. Having a body mass index (BMI) ≥ 30
   d. Triglycerides ≥150 mg/dL

9. Treatment with statins has been shown to reduce the incidence of major cardiovascular events in nonhyperlipidemic patients with which abnormal novel risk marker?
   a. High-sensitivity C-reactive protein (hs-CRP)
   b. Alanine aminotransferase
   c. NT-BNP
   d. Cystatin C

10. All of the following are true regarding sudden cardiac death (SCD) except:
   a. The incidence is higher in men than women.
   b. The median survival rate following ventricular fibrillation is approximately 21%.
   c. The risk of developing SCD is four to six times higher in patients following an index MI.
   d. The most common presenting arrhythmia for SCD is polymorphic VT.

Answers

1. Answer C: Black Americans have a mortality that is 1.6 times that of white Americans. Additionally, blacks are more likely than whites to suffer from hypertension, diabetes, and obesity.

2. Answer D: It is estimated that roughly 21% off all new acute MIs were symptomatically silent in 2007. It is thought that silent MIs are associated with worse overall outcomes, largely due delayed diagnosis and risk factor progression. The incidence of STEMI has declined over the past several decades. Between 1999 and 2004, the incidence of NSTEMI actually increased, largely due to the widespread availability of sensitive troponin assays. Since 2004, they have gradually declined.

3. Answer E: All of the mentioned factors are contributory for CAD becoming the predominant cause of death in the United States for the past century. Many of the developing world countries are currently

undergoing similar transitions with improvements in overall public health systems, cleaner water, more abundant food, and modernization and industrialization of industries. While the burden of infectious diseases and malnutrition decrease, the diseases associated with longer life such as cancer, hypertension, diabetes, and heart disease predominate.

4. Answer B: The incidence of any manifestation of CAD in women lags behind that in men by 10 years, whereas the incidence of MI or sudden death lags by 20 years. However, age is one of the strongest predictors of mortality in CAD, independent of race.

5. Answer D: Lost productivity from premature death accounts for an estimated $95 billion overall cost to society per year. This is in excess of the direct costs associated with hospitalizations, medications, outpatient visits, and emergency room visits combined. CVD expenditures exceed the cost of treating all forms of cancer. The most expensive direct expenditure for CVD comes from inpatient hospitalizations. The cost of CVD has increased despite a reduction in total yearly patient hospitalizations.

6. Answer B: The highest incidence of new smokers is observed in persons <18 years of age. According to a report from the Surgeon General, >80% of all smokers started smoking when <18 years, with the age of initiation most commonly being 14- and 15 years old. Cigarette smoking has declined in the United States when compared to the mid 20th century, however, since 2005 the prevalence seems to have plateaued at around 20%. Smoking is known to greatly increase the risk of PAD, stroke, and CAD.

7. Answer B: Hispanics have the highest prevalence of diabetes in the United States. However, mortality rates related to diabetes are highest among blacks.

8. Answer C: BMI is not part of the contemporary definition for the metabolic syndrome. However, a waist circumference ≥102 cm in men or ≥88 cm in women is included. All of the other factors are included. Of note, for each of the parameters involving glucose, hypertension, or lipids, the cutoff values are relevant only for people not already being actively treated. Once treatment has been initiated, that particular risk factor should be included in the required ≥3 for the definition.

9. Answer A: hs-CRP was shown in the large Jupiter study to be a potential modifiable risk marker when treated with rosuvastatin, even in patients without hyperlipidemia. Alanine aminotransferase, NT-BNP, and Cystatin C all have been loosely correlated with predicting adverse cardiovascular risk but not tested rigorously with regard to the effects statins have on them.

10. Answer D: The most common arrhythmia associated with SCD is VF, accounting for >50% of all CAD-related mortality. While survival following treated VF is as high as 21%, the median rate of survival to hospital discharge is <10%. Patients with documented CAD have far higher risk of developing SCD than the general population, as do patients with cardiomyopathies and other genetic predispositions.

CHAPTER

Stable Angina: Diagnosis, Risk Stratification, Medical Therapy, and Revascularization Strategies

Kellan E. Ashley and Conrad C. Simpfendorfer

The syndrome of angina pectoris, first described in 1768 by William Heberden, is most commonly the symptomatic result of fixed coronary artery obstruction and impaired endothelial vasomotor activity in patients with advanced coronary atherosclerosis. In stable angina, symptoms occur in a predictable and reproducible fashion during periods of physical or emotional stress, when increases in heart rate, cardiac contractility, and afterload increase myocardial oxygen requirements. Relief is usually brought on with rest or nitroglycerin. Symptom severity can be widely variable from patient to patient and is most commonly graded according to the Canadian Cardiovascular Society (CCS) scale (Table 39.1).[1]

TABLE
39.1 CCS Classification of Angina

Class I	No angina with ordinary physical activity. Strenuous activity may cause symptoms.
Class II	Angina causes slight limitation on ordinary physical activity.
Class III	Angina causes marked limitation on ordinary physical activity.
Class IV	Angina occurs with any physical activity and may be present at rest.

From Campeau L. Letter: grading of angina pectoris. Circulation. 1976;54(3):522–523.

The epidemiology of coronary artery disease (CAD) and stable angina has changed in the United States. As a result of improved medical and revascularization strategies, the myocardial infarction (MI) survival rate has improved, thus allowing patients to live longer with more chronic manifestations of CAD. From 1997 to 2007, the annual death

rate due to CAD decreased by 26.3%, with more than 80% of deaths in patients 65 years of age or older.[2] With the aging of the population, there has been an increase in the prevalence of CAD, with current estimates showing over 16 million Americans living with stable CAD. This represents approximately 7% of the U.S. population over 20 years of age.[2]

Despite these substantial improvements, CAD remains the number one killer of both men and women in the United States, causing about one in six deaths in 2007.[2] Stable angina pectoris remains among the most common initial clinical manifestations of CAD. Of the 16 million Americans with known CAD, an estimated 9 million live with chronic stable angina, a number that is expected to increase as the population continues to age.[2] The presence of symptomatic CAD affects quality of life negatively. It imparts significant morbidity and mortality, with estimates of just over 10% annual incidence of either a nonfatal MI or coronary death in patients presenting with stable angina.[3] While most of the early data were in men, more recent data suggest an equally poor outcome in women presenting with angina.[4]

DEFINITION OF STABLE ANGINA

Angina is defined as the sensation of chest discomfort that occurs in the setting of myocardial ischemia in the absence of myonecrosis.[5] It is traditionally described in terms of its clinical setting, characteristics (quality, location, radiation, etc.), precipitating or alleviating factors, and time course to cessation. The classic description is of substernal pressure or heaviness that can radiate to the left arm, jaw, neck, or shoulders. Chronic stable angina usually occurs due to fixed coronary obstructions of ≥50% of the diameter of the left main trunk or ≥70% of the diameter of one of the other epicardial coronary arteries and is a demand phenomenon.[5] The pain is predictable, occurring with physical activity at a known threshold or related to emotional stress. Most often, it is relieved quickly with rest and does not last longer than 10 minutes.[5] Typical stable angina meets all three of the following criteria: substernal location with the characteristic quality and duration, provoked by exertion or emotional stress, and relieved by rest or nitroglycerin.[6]

Unfortunately, classic symptoms or triggers are not present in all patients, most notably diabetics, women, and the elderly. This is referred to as atypical angina and can sometimes lead to later diagnoses and poorer outcomes.[5] Atypical angina meets two of the three characteristics listed above. Patients who do not experience any chest discomfort can still be diagnosed as having stable angina. Diabetics and the elderly are more likely to experience anginal equivalents, such as dyspnea, diaphoresis, fatigue, nausea, light-headedness, altered sensorium, or syncope.[5] It has been theorized that the lack of chest discomfort is related to altered pain perception or autonomic neuropathy.

In its most ominous form, the ischemia can be completely silent.[5] Finally, noncardiac chest pain is defined as pain that meets one or zero of the characteristics of typical angina.[6]

PATHOPHYSIOLOGY OF STABLE ANGINA

Simply put, angina occurs as the result of an imbalance between myocardial oxygen/substrate supply and demand.[5] Conditions that alter oxygen or other substrate (glucose and free fatty acids) supply can produce angina even in spite of a normal demand state. Conversely, with exercise or emotional stress, myocardial demand is increased due to increased heart rate, blood pressure, and left ventricular contractility in relation to a sympathetic nervous response. With significant CAD, the oxygen/substrate supply is fixed due to the inability of coronary autoregulation to increase coronary blood flow due to the fixed stenosis. Oxygen extraction in the coronary arteries is already at a maximum at baseline, so increased extraction cannot satisfy the imbalance between supply and demand. Thus, the patient experiences angina in these states of increased demand.[5]

DIAGNOSTIC TESTING/RISK STRATIFICATION

Evaluation of the patient with symptoms suspicious for CAD begins with assessing for the presence of CAD historical predictors, such as pain character and setting, age, gender, diabetes mellitus, smoking, hypertension, and hyperlipidemia.[7] This allows one to establish the pretest likelihood of disease and helps determine which, if any, diagnostic testing is needed. Each patient presenting with suspected stable angina should have a thorough history and physical examination as well as an electrocardiogram (ECG) (American College of Cardiology/American Heart Association [ACC/AHA] Class I recommendation).[6] There are certain features in this initial workup that can indicate a high, intermediate, or low likelihood of CAD and help to guide further evaluation (Table 39.2). In those with a significant suspicion for CAD, the spectrum of risk is broad and warrants different evaluation and treatment strategies for different levels of risk. Conversely, patients with low-risk features may warrant a more conservative and less invasive evaluation and treatment course. However, stratifying patients in this manner is not fail-safe; it is still possible to have obstructive CAD but with low-risk symptoms or features. The only way to completely rule out the presence of CAD is with a coronary angiogram.[5]

TABLE
39.2 Clinical Features and Likelihood of CAD in Patients Presenting with

Angina

High Likelihood of CAD	Intermediate Likelihood of CAD	Low Likelihood of CAD
At least one of the following:	No high risk features and one of the following:	No high or intermediate risk features and one of the following:
Rest pain that lasts longer than 20 min	Rest pain that lasts longer than 20 min but is relieved with rest or nitroglycerin	Increased frequency, severity, or duration of pain
Associated pulmonary edema	Nocturnal angina	Pain provoked at lower threshold
Associated hypotension	Age > 65 years	New onset (within 2 weeks to 2 months) angina
Associated S_3 gallop or new/worsening rales	Associated with dynamic T-wave changes	Normal ECG or minor ECG changes (i.e., T-wave flattening, T-wave inversions in leads with dominant R waves, etc.)
Rest angina with new ST-segment deviation ≥1.0 mm	New onset (≤2 weeks) angina with moderate or high likelihood of CAD	
Associated with new or worsening mitral regurgitation murmur	Resting ST-segment depression ≤1 mm in multiple leads	
	Q waves on ECG	

From Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). Circulation. 2GG3;1G7(1):149–158, with permission.

Electrocardiography

Although the 12-lead ECG is normal in more than half of patients with chronic stable angina, an ECG is a readily available first-line test that provides both diagnostic and prognostic information (ACC/AHA Class I recommendation).[6] A normal ECG at the time of diagnosis is associated with a favorable long-term prognosis, whereas abnormalities such as left ventricular hypertrophy, Q waves suggestive of prior MI, and persistent ST-segment depression identify patients at higher risk of future adverse events.[6,8] In the half of patients with a normal baseline ECG, one obtained during an episode of pain will be abnormal in another 50% of patients. Evidence of ST-segment deviation signals a high likelihood of CAD and has a more unfavorable prognosis.[6] Patients with ECG abnormalities at baseline can have "pseudonormalization" of these during a pain episode; this also indicates a high likelihood of CAD.[6] Depending on the ECG and the underlying likelihood of CAD, a decision is made to either pursue further noninvasive testing or proceed straight to a coronary angiogram.

Exercise ECG Testing

One of the oldest and most widely used noninvasive tests for CAD is the treadmill exercise ECG, because of its widespread availability, low cost, and ease of performance.[5] This is generally the first test selected to evaluate patients with an intermediate likelihood of CAD and a normal baseline ECG who are able to exercise

(ACC/AHA Class I recommendation).[6] The absolute contraindications to exercise ECG testing include hemodynamically significant arrhythmias, within the first 48 hours of MI, symptomatic heart failure, symptomatic or severe aortic stenosis, myocarditis, acute aortic dissection, and acute pulmonary embolus. There are also ECG abnormalities that are not suited for exercise ECG testing, as they make interpretation of the exercise ECG impossible. These include Wolff–Parkinson–White syndrome, paced ventricular rhythms, >1 mm resting ST-segment depression, and complete left bundle branch block (ACC/AHA Class III recommendation).[6]

In a large meta-analysis of exercise stress ECG, the mean sensitivity and specificity for detecting angiographically significant CAD were 68% and 77%, respectively.[6] Although exercise ECG is less sensitive than stress tests performed with imaging modalities, particularly in women, it remains the primary noninvasive tool for both the diagnosis and risk stratification of patients with suspected CAD and interpretable ECGs. The ACC/AHA guidelines recommend that, unless cardiac catheterization is more urgently indicated, symptomatic patients with suspected or known CAD should be considered for exercise ECG testing to assess the risk of future cardiac events and the possible need for angiography.[6] As a diagnostic tool, exercise ECG testing is most useful in patients with stable chest pain syndromes and an intermediate risk of CAD (ACC/AHA Class I recommendation). In those with a low or high pretest probability of CAD, exercise ECG has a Class IIb recommendation.[6] As a prognostic tool, it can help to identify patients with extensive atherosclerosis who would benefit from coronary angiography and possible revascularization.

In addition to the ECG portion, there are other variables that contribute to the interpretation of the test. The usual definition for a positive exercise ECG test is 1 mm or more of ST-segment elevation or horizontal or downsloping ST-segment depression at a point 60 to 80 milliseconds after the QRS complex during exercise or recovery.[6] Additionally, symptoms, exercise capacity, and hemodynamic and rhythm response to exercise should be considered.[6] The most important prognostic variables measured during exercise testing are exercise capacity, typically expressed in metabolic equivalents of task (METs), and exercise-induced ischemic ST-segment changes. The Duke Treadmill Score (DTS) integrates these two objective variables with the subjective presence or absence of anginal symptoms to generate a risk score that separates patients into high-, moderate-, and low-risk subsets (5%, 1.25%, and 0.25% annual mortality rates, respectively) (Table 39.3).[9] Patients with high-risk DTSs frequently have left main or three-vessel CAD that would benefit from revascularization, and these patients should be referred for coronary angiography. Low-risk patients, on the other hand, have an excellent prognosis that is unlikely to improve with further evaluation or revascularization and thus can be treated safely with medical therapy.

TABLE
39.3 Duke Treadmill Score

Calculation:	DTS = exercise time in minutes on the Bruce protocol – (5 × ST-segment deviation in mm) – (4 × angina index) (angina index: 0 = none, 1 = nonlimiting, and 2 = exercise limiting)
Risk stratification:	
Low risk, DTS ≥5	0.25% annual mortality
Intermediate risk, DTS –10 to +4	1.25% annual mortality
High risk, DTS ≤ –11	5.25% annual mortality

From Mark DB, Shaw L, Harrell FE Jr, et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. N Engl J Med. 1991;325(12):849–853, with permission from the Massachusetts Medical Society.

Echocardiography

Most patients undergoing a diagnostic evaluation for stable angina do not require echocardiography. More specifically, in patients with a normal ECG, no history of prior MI, and no clinical signs or symptoms of heart failure, valvular disease, or hypertrophic cardiomyopathy, it is currently contraindicated to obtain an echocardiogram (ACC/AHA Class III recommendation).[6] An exception is when there is a murmur suspicious for aortic stenosis or hypertrophic cardiomyopathy on physical exam or when the echocardiogram can be obtained during or within 30 minutes of presentation with chest pain to evaluate for regional wall motion abnormalities (ACC/AHA Class I recommendation).[6] In this setting, regional wall motion abnormalities have a positive predictive value for ischemia of approximately 50%, whereas normal studies identify patients at low risk for an acute infarction.[6,10]

Stress Testing with Nuclear or Echocardiographic Imaging

Although stress imaging modalities have greater diagnostic accuracy than exercise electrocardiography, the increased cost of these tests precludes their routine use in all patients with suspected CAD. Most commonly, nuclear (single positron emission computed tomography [SPECT] or positron emission tomography [PET]) or echocardiographic stress imaging is reserved as first-line testing in patients with abnormal baseline ECGs (i.e., pre-excitation, resting ST-segment depression ≥1 mm) or with symptoms and history of prior revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) (ACC/AHA Class I recommendation).[6] In patients with either paced ventricular rhythms or left bundle

branch block, pharmacologic stress myocardial perfusion imaging is preferred over stress echocardiography due to the difficulty with interpreting echocardiographic wall motion in these conditions (ACC/AHA Class I recommendation).[6] For patients who are unable to exercise, pharmacologic stress myocardial perfusion imaging or dobutamine stress echocardiography is equally preferred (ACC/AHA Class I recommendation).[6] For a summary of the ACC/AHA recommendations, see Table 39.4.

TABLE
39.4 ACC/AHA Recommendations for Exercise ECG Testing and Stress Imaging Studies in Stable Angina Pectoris

	Exercise ECG Testing without Imaging
Class I	For diagnosis of obstructive CAD in patients with an intermediate pretest probability of CAD
	For risk assessment and prognosis in patients undergoing initial evaluation
Class IIa	Suspected vasospastic angina
Class IIb	High pretest probability of CAD
	Low pretest probability of CAD
	Digoxin therapy with <1 mm ST-segment depression on baseline ECG
	ECG criteria for LV hypertrophy and <1 mm of ST-segment depression
Class III	Pre-excitation (Wolff–Parkinson–White) syndrome
	Electronically paced ventricular rhythm
	More than 1 mm of rest ST-segment depression
	Complete LBBB
	Risk stratification in patients with severe comorbid conditions likely to limit life expectancy or prevent revascularization
	Stress Imaging Studies
Class I	Identify the extent, severity, or location of ischemia in patients with normal ECGs
	Patients with an intermediate pretest probability of CAD with abnormal baseline ECGs (pre-excitation or ST depression >1 mm at rest) that preclude exercise ECG testing (dipyridamole or adenosine MPI preferred in patients with LBBB or electronically paced ventricular rhythm)
	Pharmacologic stress imaging in patients with an intermediate pretest probability of CAD who are unable to exercise
	Exercise myocardial perfusion imaging or exercise echocardiography in patients with prior revascularization (either PCI or CABG) (pharmacologic stress can be used for those unable to exercise.)
Class IIb	Patients with low or high pretest probability of CAD with abnormal baseline ECGs (pre-excitation or >1 mm ST-segment depression) that preclude exercise ECG testing (dipyridamole or adenosine MPI preferred in patients with LBBB or electronically paced ventricular rhythms)
	Exercise MPI or exercise echocardiography in patients with intermediate pretest probability of CAD who are taking digoxin and have <1 mm ST-segment depression on baseline ECG or have LV hypertrophy and <1 mm ST-segment depression on baseline ECG
	Exercise or dobutamine echocardiography in patients with LBBB
Class III	Exercise myocardial perfusion imaging in patients with LBBB
	Risk stratification in patients with severe comorbid conditions likely to limit life expectancy or prevent revascularization

CABG, coronary artery bypass grafting; CAD, coronary artery disease; ECG, electrocardiogram; LBBB, left bundle branch block; LV, left ventricular; MPI, myocardial perfusion imaging; PCI, percutaneous coronary intervention.

From Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). Circulation. 2003;107(1):149–158, with permission.

As mentioned, stress myocardial perfusion imaging has a higher sensitivity for the diagnosis of CAD than exercise ECG in patients with intermediate risk. The data vary depending on the population studied, but generally the sensitivity is accepted to be

around 90% for myocardial perfusion imaging.[5] Similar numbers are seen with exercise stress echocardiography (sensitivity around 85%) and dobutamine echocardiography (sensitivity around 82%).[6] The choice of test depends on both patient characteristics and local expertise in performing the different imaging modalities.

There are some special populations or situations in which exercise stress imaging should be considered over exercise ECG. Women have an overall lower prevalence of CAD than men and thus have a lower pretest probability of disease, making false-positive exercise ECGs more common. The higher sensitivity of stress imaging, therefore, could theoretically improve on the positive predictive value of the exercise ECG.[6] Additionally, elderly patients are oftentimes less able to exercise due to comorbid medical conditions or deconditioning. Therefore, pharmacologic stress imaging may be the test of choice in this population.[6] As with exercise electrocardiography, stress imaging results can also provide prognostic information, separating patients who are appropriate for medical therapy (low risk, ≤1% annual mortality) from those who may benefit from further angiographic evaluation and possible revascularization (intermediate risk, 1% to 3%; high risk, ≥3% annual mortality) (Table 39.5).[11]

TABLE
39.5 Risk Stratification Based on Findings of Noninvasive Testing

High Risk (≥3% Annual Mortality)	
Severe resting LV dysfunction (EF < 35%)	High-risk DTS (<–11)
Severe exercise LV dysfunction (EF < 35%)	Stress-induced large perfusion defect (particularly anterior)
Stress-induced, multiple moderate perfusion defects	Large fixed perfusion defect with LV dilation or increased lung uptake (Thallium-201)
Stress-induced moderate perfusion defect with LV dilation or increased lung uptake (Thallium-201)	Echocardiographic wall motion abnormality (>2 segments) developing at low dose of dobutamine (≤10 μg/kg/min) or low HR (<120 bpm)
Stress echocardiographic evidence of ischemia	
Intermediate Risk (1%–3% Annual Mortality)	
Mild/moderate resting LV dysfunction (EF 35%–49%)	Intermediate DTS (–11 < DTS < 5)
Stress-induced moderate perfusion defect without LV dilation or increased lung uptake (Thallium-201)	Limited stress echocardiographic ischemia with a wall motion abnormality only at higher doses of dobutamine involving ≤2 segments
Low Risk (≤1% Annual Mortality)	
Low-risk DTS (≥5)	Normal or small myocardial perfusion defect at rest or with stress (unless high-risk DTS or severe resting LV dysfunction)
Normal stress echocardiographic wall motion or no change of limited resting wall motion abnormalities during stress (unless high-risk DTS or severe resting LV dysfunction)	

DTS, Duke Treadmill score; EF, ejection fraction; HR, heart rate; LV, left ventricular.

From Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). Circulation. 2003;107(1):149–158, with permission.

Coronary Angiography

Coronary angiography remains the gold standard diagnostic test for CAD. Additionally, coronary angiography is able to provide anatomic definition of disease extent and severity as well as prognostic information, identifying those patients who would achieve survival benefits related to surgical revascularization. Specifically, from the early studies of CABG, patients with severe left main trunk stenosis, three-vessel disease, and two-vessel disease involving the proximal left anterior descending (LAD) coronary artery are known to derive a survival benefit with bypass surgery over medical therapy.[12]

In general, coronary angiography is performed in patients with stable chest pain

syndromes when noninvasive tests are inconclusive or cannot be performed, when clinical evaluation or noninvasive testing suggests high-risk features (see Table 39.5), and when symptoms persist despite appropriate medical therapy. Less commonly, diagnostic coronary angiography is recommended for patients in whom coronary artery spasm is suspected, those with occupations that necessitate a definitive diagnosis (e.g., pilots, police, professional athletes), and for survivors of sudden cardiac death.[13] For the list of ACC/AHA recommendations related to coronary angiography, see Table 39.6.

TABLE
39.6 ACC/AHA Recommendations for Coronary Angiography in Stable Angina Pectoris

Class I	CCS Class III or IV angina despite OMT
	High-risk criteria on clinical assessment or noninvasive testing regardless of anginal severity
	Stable angina patients with sudden cardiac death or serious ventricular arrhythmia
	Stable angina patients with congestive heart failure
Class IIa	Equivocal findings/uncertain diagnosis after noninvasive testing
	Unable to undergo noninvasive testing due to disability, illness, or morbid obesity
	Occupational requirement for a definitive diagnosis (e.g., pilots, bus drivers, police)
	CCS Class III or IV angina that improves to Class I or II with medical therapy
	Worsening abnormalities on serial noninvasive tests
	Suspected nonatherosclerotic cause for chest pain or myocardial ischemia (coronary anomaly, Kawasaki disease, primary coronary artery dissection, radiation-induced vasculopathy)
	Suspected coronary spasm where provocative testing is felt necessary
	High pretest probability of left main trunk or three-vessel CAD
Class IIb	Patients with recurrent hospitalizations for chest pain in whom a definitive diagnosis is deemed necessary
	Patients with an overriding desire for a definitive diagnosis and more than low probability of CAD
	CCS Class I or II angina with demonstrable ischemia but no high-risk features on noninvasive testing
Class III	Risk of coronary angiography outweighs the benefits.
	Patients with CCS Class I or II angina who respond to medical therapy and have no evidence of ischemia on noninvasive testing
	Patients who prefer to avoid revascularization
	Angina in patients who are not candidates for revascularization or in whom revascularization is not likely to improve quality or duration of life
	Patients with an overriding desire for a diagnosis but who are low probability of CAD

CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; OMT, optimal medical therapy.

From Scanlon PJ, Faxon DP, Audet AM, et al. ACC/AHA guidelines for coronary angiography: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography) developed in collaboration with the Society for Cardiac Angiography and Interventions. Circulation. 1999;99(17):2345–2357, with permission.

For patients determined to be at low risk of adverse events, medical therapy alone is usually sufficient and may be superior to an invasive approach. For the moderate- or high-risk subsets, there is older evidence from randomized trials that medical therapy coupled with surgical revascularization improves long-term survival over medical therapy alone.[12] Therefore, the judicious use of noninvasive and invasive studies can help establish the diagnosis of CAD while simultaneously performing the critical risk stratification that is essential in determining the appropriate risk-reducing treatment strategies, from medical therapy alone to medical therapy plus revascularization.

Conclusion

Chest pain is the most common initial presenting symptom for patients diagnosed with CAD. Although coronary angiography provides powerful prognostic information and remains the gold standard for diagnosis, noninvasive tests are often more appropriate initial tools for patients with low or intermediate clinical predictors of CAD. Even for patients with a high pretest probability of CAD, noninvasive testing can be a useful prognostic tool that allows for selection of patients who warrant further invasive evaluation.

MEDICAL TREATMENT FOR STABLE ANGINA

There are two primary goals of medical treatment for chronic stable angina: prevent MI and cardiovascular death as well as improve quality of life by decreasing anginal symptoms and occurrence of ischemia.[6] However, the process of atherosclerosis cannot be reversed by medications or by revascularization procedures. Lifestyle changes can and do influence the disease course and are most often underutilized in the treatment of patients with stable CAD.[14] Lifestyle changes are inexpensive, readily available, and very effective but require a motivated patient as well as support and emphasis from the physician. Lifestyle changes should be implemented first-line and should be complementary to medical therapy.

PCIs became increasingly more common in the late 1990s and early 2000s due to an overall favorable effect on reducing anginal symptoms in numerous studies of PCI versus medical therapy in CAD.[15–23] The early meta-analyses of these studies did not show a reduction in mortality or MI incidence compared to medical therapy alone in these patients,[24,25] even though a more recent meta-analysis did show a possible improvement in overall mortality with PCI.[26] As mentioned previously, CABG does

have clear-cut long-term survival benefits versus medical therapy alone, but only in a minority of patients with high-risk angiographic features.[12] An initial trial of medical therapy, therefore, remains the mainstay of treatment for the majority of patients with chronic, stable CAD. This is achieved through a combination of therapies that target both ischemic symptoms and modifiable risk factors known to aggravate angina and cardiovascular disease. Medications known to reduce the risk of MI and death receive the highest priority. Medications aimed at improving quality of life by reducing the frequency and severity of anginal episodes serve as important supplementary therapies.

Medical Therapy to Improve Survival

As discussed in the next section, the symptoms of angina may be effectively reduced with the use of standard antianginal medications (e.g., beta-blockers, nitrates, and calcium channel blockers [CCBs]), but these therapies have not been shown to improve survival or reduce MI incidence in patients with otherwise uncomplicated stable angina. Therefore, the management of patients with stable CAD has evolved to include a set of standard therapies directed specifically at reducing adverse clinical outcomes such as death and MI.

Antiplatelet Therapy

The benefit of aspirin in a broad spectrum of patients with both stable and unstable atherosclerotic syndromes has been well established for decades.[27] Aspirin exerts its antiplatelet effects by inhibiting cyclooxygenase, thus preventing the release of the prothrombotic platelet-aggregant thromboxane A_2. Although it does not improve symptoms, clinical trials of aspirin in patients with chronic stable angina have demonstrated risk reductions for adverse cardiac events that are of a magnitude similar to that seen in patients with unstable coronary syndromes.[27] In the Swedish Angina Pectoris Aspirin Trial,[28] the largest randomized trial of aspirin therapy for chronic stable angina, the addition of 75 mg of aspirin to sotalol resulted in a 34% reduction in the primary composite endpoint of MI and sudden death and a 22% to 32% reduction in the measured secondary vascular endpoints (vascular death, all-cause mortality, and stroke). A similar 33% reduction in adverse cardiovascular events (vascular death, stroke, and MI) was demonstrated among 2,920 patients with stable angina included in a meta-analysis performed by the Antithrombotic Trialists' Collaboration.[27] Therefore, aspirin, administered at 75 to 162 mg daily, is first-line therapy in all chronic CAD patients (ACC/AHA Class I recommendation).[29]

Thienopyridines are a second class of beneficial antiplatelet agents that exert their effects by irreversibly and selectively inhibiting the binding of adenosine diphosphate (ADP) to receptors on the platelet surface, thus preventing platelet activation. Without platelet activation, the glycoprotein IIb/IIIa receptor is unable to undergo a

conformational change, which then makes it unable to bind fibrinogen or von Willebrand factor. In this manner, platelet aggregation is inhibited. There are currently three drugs in this class on the market: ticlopidine, clopidogrel, and prasugrel. The oldest, ticlopidine, initially showed benefit in several atherosclerotic processes including post-PCI,[30–34] unstable angina,[35] and peripheral arterial disease.[36–38] However, its widespread use was limited by its side effect profile, which included a risk of neutropenia as well as thrombotic thrombocytopenic purpura.

Due to its more favorable side effect profile and reduction in cardiovascular events, clopidogrel has become the thienopyridine of choice in combination with aspirin for acute coronary syndromes,[39] ST-segment elevation MI,[40,41] and post-PCI.[42,43] However, no study has specifically addressed its effect in patients with stable angina.[6] In the Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events (CAPRIE) trial,[44] clopidogrel appeared to be more effective than aspirin, with an overall 8.7% reduction in the combined primary endpoint (MI, vascular death, or ischemic stroke), in high-risk CAD patients (i.e., those with recent MI or stroke or with symptomatic peripheral arterial disease). To date, the only setting in which clopidogrel has not been shown to improve cardiovascular outcomes is long-term primary or secondary prevention in patients with established atherosclerosis or multiple risk factors.[45]

Given the limited data for clopidogrel in stable coronary syndromes, it remains an ACC/AHA Class IIa recommendation as a replacement for aspirin in patients with a contraindication.[6]

Prasugrel, the newest member of this class, has been shown to be a more potent antiplatelet agent than clopidog-rel[46] and has been shown to be more effective in reducing cardiovascular endpoints (cardiovascular death, nonfatal MI, or nonfatal stroke) in patients with acute coronary syndromes.[47] However, prasugrel has a higher risk of major bleeding and to date has not been studied in stable CAD.

Lipid-Lowering Therapy

Lipid management has been guided for decades by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP). All NCEP ATP reports have targeted low-density lipoprotein cholesterol (LDL-C) as the driving risk factor for CAD.[48] However, prior to the third report of NCEP, most of the evidence for LDL-C lowering was based on trials of lipid-lowering agents other than HMG-CoA reductase inhibitors (statins), such as bile acid sequestrants, fibric acid derivatives, and niacin.[6,48] In 2001, the third report of the NCEP ATP was published,[49] which reviewed the data from several randomized trials of statin therapy in CAD. With these guidelines, a treatment algorithm for LDL-C was established that focused on statins as first-line agents for all patients with stable CAD. In 2004, some revisions to those recommendations were

required based on the results of several newer randomized trials not included in the original guidelines.[48]

In general, statins lower LDL-C, total cholesterol, and triglycerides (TG), while raising high-density lipoprotein cholesterol (HDL-C), all of which are favorable in cardiovascular disease. In aggregate, the randomized trials and meta-analyses of statins in primary and secondary prevention show reductions in MI, stroke, and cardiovascular death by about one-third each, as well as a reduction in total mortality by about one-fifth.[50] The ATP III algorithm categorized patients into three risk categories: (a) established coronary heart disease (CHD) or CHD risk equivalents, (b) two or more CHD risk factors, or (c) 0 to 1 CHD risk factor.[48] High risk was defined as those with CHD or CHD risk equivalents (known noncoronary atherosclerotic vascular disease, diabetes, or two or more CHD risk factors with 10-year risk for CHD > 20%).[49] According to the original NCEP ATP III report [49] and the subsequent revisions based on newer trial data,[48] statin therapy and therapeutic lifestyle changes are indicated for all stable CAD patients with an LDL-C ≥100 mg/dL, with a goal of LDL-C < 100 mg/dL (ACC/AHA Class I recommendation).[29] For patients deemed high risk, there is the optional goal of treating to a more aggressive LDL-C < 70 mg/dL or with a high-dose statin (ACC/AHA Class IIa recommendation).[29] If on-treatment LDL-C is ≥100 mg/dL, lipid-lowering therapy should be intensified (ACC/AHA Class I recommendation).[29] If the LDL-C is 70 to 100 mg/dL at baseline, it is reasonable to treat to an LDL-C <70 mg/dL (ACC/AHA Class IIa recommendation).[29] These are more aggressive goals than those set forth in the original NCEP ATP III report.

The benefit of a more aggressive lipid-lowering strategy in patients with stable CAD was definitively established by the Treating to New Targets (TNT) trial,[51] among others. In this study, aggressive cholesterol reduction with 80 mg of atorvastatin daily (mean LDL = 77 mg/dL) produced an absolute 2.2% reduction in major adverse cardiovascular events (8.7% vs. 10.9%, $p < 0.001$) compared to the more conventional 10 mg of atorvastatin daily (mean LDL = 101 mg/dL). The results of TNT, in addition to data from other trials such as Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22),[52] were the impetus for the addition of the optional LDL-C goal of <70 mg/dL in the revision of the NCEP ATP III recommendations.[48] PROVE-IT TIMI 22 showed similar benefits of very aggressive LDL-C reduction in patients with acute coronary syndromes.[52]

In addition to improving outcomes, nuclear studies have demonstrated that statin therapy improves myocardial perfusion and reduces ischemia on ambulatory ECG monitoring in stable angina patients with both high and normal serum cholesterol levels.[53] In patients with medically refractory angina that is not amenable to revascularization, aggressive lipid reduction with 80 mg daily of atorvastatin (LDL goal

< 77 mg/dL) has been shown to reduce symptoms of angina and decrease myocardial ischemic segments measured by dobutamine echocardiography when compared to more conventional therapy (LDL goal < 116 mg/dL).[54]

In addition to LDL-C, the 2007 updated chronic angina ACC/AHA guidelines focused more heavily on other lipid parameters. If TG are 200 to 499 mg/dL, non-HDL-C (calculated as total cholesterol minus HDL-C) should be <130 mg/dL (ACC/AHA Class I recommendation) and further reduction to <100 mg/dL was optional (ACC/AHA Class IIa recommendation).[29] Therapeutic options to reduce non-HDL-C are niacin or fibrate therapy in combination with statin therapy (ACC/AHA Class IIa recommendation).[29] If using a fibrate in combination with a statin, the statin dose should be kept in the lower range given the high risk for associated myopathy with the combination. If, however, the TG level is >500 mg/dL, this level should be reduced in order to prevent the development of pancreatitis; this should be done prior to the initiation of statin therapy. The therapeutic options are fibrates or niacin with a goal of non-HDL-C <130 mg/dL (ACC/AHA Class I recommendation).[29]

Renin–Angiotensin–Aldosterone System Blockade

The benefit of angiotensin-converting enzyme (ACE) inhibition in patients with diabetes and impaired left ventricular systolic function has been firmly established by multiple large-scale clinical trials that have consistently demonstrated a reduction in adverse clinical events.[6] ACE inhibitors are therefore recommended as first-line therapy indefinitely in all patients with CAD who have impaired left ventricular systolic function (left ventricular ejection fraction ≤40%) or in those with concomitant diabetes, hypertension, or chronic kidney disease (ACC/AHA Class I recommendation).[29] In patients with stable CAD and preserved left ventricular function, the data have been less consistent. Although both the Heart Outcomes Prevention Evaluation (HOPE)[55] and EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA)[56] trials demonstrated decreased mortality with ACE inhibition (ramipril and perindopril, respectively) in stable CAD patients with preserved left ventricular function, a similar population of patients in the Prevention of Events with Angiotensin Converting Enzyme inhibition (PEACE)[57] trial failed to benefit with trandolapril. In light of this data, ACE inhibitors are given a Class IIa recommendation in the most recent ACC/AHA guidelines for patients with CAD and mildly reduced or normal left ventricular function.[29]

Most of the data for the substitution of angiotensin receptor blockers (ARBs) for those intolerant to ACE inhibitors come from trials in systolic heart failure. For instance, in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-alternative study,[58] the patients with left ventricular systolic

dysfunction treated with candesartan had improvement in primary outcomes (cardiovascular mortality and admission for heart failure) over placebo. Additionally, when MI and stroke were added in a composite secondary outcome, there were reductions in secondary outcomes as well with candesartan. Notably, the population in CHARM-alternative had a medical history consistent with a stable CAD population: approximately 60% with history of MI, approximately 20% with current angina, and 15% to 25% with history of either PCI or CABG.[58] In a separate arm, CHARM-added,[59] patients with left ventricular ejection fraction ≤40% and already receiving an ACE inhibitor were randomized to additional candesartan or placebo. Again there was reduction in the primary composite endpoint (cardiovascular death and heart failure admission). Similarly, when MI and stroke were incorporated into the secondary endpoints, there was a significant reduction in those as well with candesartan.[59] Based on these data, ARBs are recommended for patients who have hypertension, have indications for but are intolerant of ACE inhibitors, have heart failure, or have had an MI with left ventricular ejection fraction ≤40% (ACC/AHA Class I recommendation).[29] Additionally, ARBs may be considered in combination with ACE inhibitors for heart failure due to left ventricular systolic dysfunction (ACC/AHA Class IIb recommendation).[29]

Aldosterone blockers, such as spironolactone and eplerenone, are also ACC/AHA Class I recommendations in post-MI patients without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a beta-blocker, have a left ventricular ejection fraction ≤40%, and have either diabetes or heart failure.[29] This recommendation was based primarily on data in left ventricular systolic dysfunction, with spironolactone from the Randomized ALdactone Evaluation Study (RALES)[60] and eplerenone in the Eplerenone Post-acute myocardial infarction Heart failure Efficacy and SUrvival Study (EPHESUS).[61]

Symptomatic Medical Therapies: Antianginals

The primary goal of antianginal therapy is to reduce coronary ischemia, thereby improving exercise capacity and overall quality of life.[6] The currently available antianginal medications work to counteract the hemodynamic effects of flow-limiting coronary stenoses by reducing myocardial oxygen requirements and/or by promoting coronary vasodilation. Each is an effective therapy for symptom relief alone but they are often used in combination for more complete symptom control. However, unlike the therapies in the previous section, none have been shown to reduce death or MI in patients with otherwise uncomplicated stable angina pectoris.

Beta-Blockers

Beta-blockers function by competitively inhibiting the physiologic actions of

catecholamines on the beta (β) receptors in the heart and vasculature. The resulting decreases in heart rate, arterial blood pressure, and myocardial contractility substantially reduce myocardial oxygen demand. Their functional benefits in stable angina have been most clearly linked to the lowering of the heart rate–blood pressure product (double product) and were definitively demonstrated by exercise studies in which beta-blocked patients experienced a delay or avoidance of ischemia onset with activity compared to baseline.[62,63] By convention, the dose of beta-blocker is therefore adjusted to lower the double product, with a goal heart rate of 55 to 60 beats/min (bpm) and exercise heart rate response <75% of the rate that precipitated ischemia on stress testing.[14]

Although nonselective beta-blockers are effective in stable angina, the majority of the antianginal effects of beta-blockers are related to their effects at the β_1 receptor, thus β_1 selective agents may be preferred. Some beta-blockers are partial agonists and are said to have intrinsic sympathomimetic activity; these are generally avoided in stable angina.[14] Several of the beta-blockers (i.e., carvedilol, labetalol.), in addition to their nonselective beta-blockade, also block catecholamines at the alpha (α) receptor (specifically α_1) and are profound vasodilators.[14] Additionally, some betablockers are said to have antiarrhythmic and other advantageous effects. Therefore, the choice of agent should be tailored to the specific needs of the patient, and the provider should be familiar with several different agents. For a list of common beta-blockers used in stable angina, see Table 39.7.

TABLE
39.7 Beta-Blockers Commonly Used to Treat Stable Angina Pectoris

Drug	Receptor Selectivity	Onset of Action	Usual Dose
Atenolol	β_1	2–4 h	50–200 mg/d
Bisoprolol	β_1	2–4 h	10 mg/d
Esmolol (IV)	β_1	9 min	50–300 μg/kg/min
Metoprolol	β_1	1–2 h	50–200 mg twice daily (extended release once daily preparation available)
Propranolol	None	1–2 h	80–120 mg twice daily
Nadolol	None	3–4 h	40–80 mg/d
Timolol	None	1–2 h	10 mg twice daily
Carvedilol	Nonselective β and selective α_1	1.0–1.5 h	3.125–25 mg twice daily
Labetalol	Nonselective β and selective α_1	2–4 h	200–600 mg twice daily

α, alpha; β, beta; IV, intravenous.

In low-risk patients with otherwise uncomplicated stable angina, beta-blockers have not consistently reduced the incidence of major ischemic cardiovascular events. However, in high-risk subsets with a history of MI or heart failure, the long-term benefit of beta-blockers in reducing death and recurrent MI has been firmly established by multiple large-scale randomized trials. Studies comparing beta-blockers with CCBs have reported similar efficacy in controlling symptoms and improving functional capacity without a measurable difference in adverse cardiovascular events.[64–69] The Total Ischemic Burden European Trial (TIBET) did show a nonsignificant trend toward a lower rate of cardiovascular death, nonfatal MI, and unstable angina with combination atenolol and nifedipine.[65] However, there was no difference noted between the two agents. Similarly, the Angina Prognosis Study in Stockholm (APSIS) trial showed no difference between metoprolol and verapamil treatment in terms of mortality, cardiovascular endpoints, and quality of life measures in patients with stable angina.[67]

The limited data directly comparing nitrates to betablockers as monotherapy for stable angina suggest superior symptomatic relief with beta-blockade.[70] Given the benefits of beta-blockers in reducing death and adverse cardiovascular events in high-risk patients (post-MI or with systolic left ventricular dysfunction) with stable angina, plus their equivalent efficacy in treating anginal symptoms, these medications are first-line antianginal agents indefinitely in all patients with stable angina, particularly if post-MI, acute coronary syndrome, or in the presence of left ventricular systolic dysfunction unless contraindicated (ACC/AHA Class I recommendation).[29] Absolute contraindications to beta-blocker therapy include severe bradycardia, high-degree atrioventricular block, sick sinus syndrome, and decompensated systolic heart failure.[6]

Calcium Channel Blockers

All CCBs are vasodilators and some have a negative chronotropic effect, overall acting to reduce myocardial oxygen demand and increase myocardial oxygen supply. This is achieved by the reduction in the transmembrane flux of calcium, either in the conduction system (negative chronotropic effect) or at the vascular level (vasodilatory effect). Although CCBs do not improve survival or reduce MI in patients with stable angina pectoris, randomized trials, as mentioned in the previous section, have demonstrated that both dihydropyridine and nondihydropyridine agents are as effective as beta-blockers for symptom relief.[64–69]

The safety of CCBs in patients with hypertension and CAD has generated significant debate following the publication of studies suggesting an increase in adverse cardiovascular outcomes among patients treated with short-acting formulations, particularly nifedipine.[71,72] Although further analysis of the published reports has failed to confirm an increased risk of adverse events,[73] the safety of shorter acting dihydropyridine CCBs remains uncertain and they should be avoided in patients with

CAD.

In contrast, slow-release or long-acting vasoselective CCBs are both safe and effective for anginal symptom relief.[74] The A Coronary disease Trial Investigating Outcome with Nifedipine GITS (ACTION) trial, a randomized study of long-acting nifedipine compared to placebo in >7,600 patients with stable angina, demonstrated a reduction in the need for coronary angiography and revascularization without an increase in mortality or adverse cardiovascular events in the long-acting nifedipine group.[75] Based on these data, long-acting CCBs are indicated as initial therapy for reduction of anginal symptoms when beta-blockers are contraindicated or not tolerated and in combination with beta-blockers when initial treatment with beta-blockers alone is not successful (ACC/AHA Class I recommendation).[6] As initial monotherapy, long-acting nondihydropyridine CCBs, in lieu of beta-blockers, are an ACC/AHA Class IIa recommendation.[6]

Generally, the nondihydropyridine CCBs are contrain-dicated in decompensated heart failure; the newer generation dihydropyridines can, however, be used in patients with left ventricular dysfunction. Bradycardia, sinus node dysfunction, and high-grade atrioventricular block are also contraindications for the use of both diltiazem and verapamil.[6] For an overview of those CCBs used in stable angina, see Table 39.8.

TABLE
39.8 CCBs Commonly Used to Treat Stable Angina Pectoris

Drug	Duration of Action	Usual Dose
	Dihydropyridines	
Nicardipine	Short	20–40 mg three times daily
Isradipine, SR	Medium	2.5–10 mg twice daily
Amlodipine	Long	5–20 mg/d
Felodipine, SR	Long	5–10 mg/d
Nifedipine, SR	Long	30–180 mg/d
	Nondihydropyridines	
Diltiazem, IR	Short	30–80 mg four times daily
Diltiazem, SR	Long	120–320 mg/d
Verapamil, IR	Short	80–160 mg three times daily
Verapamil, SR	Long	120–480 mg/d

CCB, calcium channel blocker; IR, immediate release; SR, sustained release.

Nitroglycerin and Nitrates

Nitrates are beneficial agents in stable angina due to their ability to decrease myocardial oxygen demand. This is primarily achieved by decreases in left ventricular volume and wall stress by decreasing preload via predominantly venodilation.[6,14] Nitrates also improve myocardial oxygen supply via an endothelium-independent dilation of epicardial coronary arteries. Nitrates have been in clinical use for more than 100 years and have an excellent safety profile, well-recognized side effects, and few drug interactions. In patients with stable angina pectoris, nitrates reduce symptoms as both monotherapy and in combination with beta-blockers or CCBs.[76–79] Nitrates do not improve survival or decrease the risk of MI, regardless of estimated baseline risk.[80]

Commonly used nitrate preparations in stable angina are listed in Table 39.9. Sublingual nitroglycerin tablets and spray are effective preparations and are indicated for immediate relief of angina (ACC/AHA Class I recommendation).[6] Long-acting nitrate preparations, such as isosorbide mononitrate, isosorbide dinitrate, transdermal nitroglycerin patches, and nitroglycerin ointment, are indicated for initial therapy in stable CAD when beta-blockers are contraindicated or not tolerated or in combination with beta-blockers when beta-blockers alone are ineffective (ACC/AHA Class I recommendation).[6] These long-acting agents should be administered so as to incorporate a nitrate-free interval of at least 8 hours to prevent tolerance. Additionally, nitrates should not be used in the same 24-hour period as a type 5-cyclic guanosine monophosphate-dependent phosphodiesterase inhibitor (e.g., sildenafil, tadalafil), as this can lead to severe hypotension.[14]

TABLE
39.9 Nitrate Preparations Commonly Used to Treat Stable Angina Pectoris

Drug	Route	Onset of Action	Usual Dose
Nitroglycerin	Sublingual	2–5 min	0.3–0.6 mg/dose, up to 1.5 mg total dose as needed
	Spray	2–5 min	0.4 mg, 1–2 sprays as needed, up to 3 doses 5 min apart
	Ointment, 2%	20–60 min	7.5–40 mg, 6 × 6 inches or 15 × 15 cm
	Transdermal patch	>60 min	0.2–0.8 mg/h/d, removed at night for 12-h nitrate-free period
	Intravenous	1–2 min	5–200 μg/min, titrated to symptom relief
Isosorbide dinitrate	Oral	30–60 min	5–80 mg 2–3 times daily
Isosorbide mononitrate	Oral	30–60 min	20 mg twice daily, 7–8 h apart
Isosorbide mononitrate, SR	Oral	30–60 min	30–240 mg daily

SR, sustained release.

Combination Therapy

For many patients receiving treatment for stable angina pectoris, the symptoms persist despite monotherapy, illustrating the frequent need for combination pharmacotherapy. Although not all published trials of combination therapy have demonstrated greater efficacy over monotherapy, meta-analysis data suggest that the combination of a beta-blocker and CCB allows for greater exercise tolerance when compared to either medication used alone.[81] The combination of long-acting, second-generation vasoselective dihydropyridine CCBs with beta-blockers appears to be a particularly effective antianginal regimen, as measured by indices of angina, exercise tolerance, and nitroglycerin consumption.[82] In the International Multicenter AnGina Exercise (IMAGE) study, the combination of metoprolol and nifedipine improved ischemia and exercise tolerance over either drug alone.[68]

Nitrates also improve symptoms when used in combination with beta-blockers or CCBs, as mentioned previously.[76–79] Both CCBs and long-acting nitrates are indicated in combination with beta-blockers for the initial treatment of stable angina when beta-blockers alone are ineffective (ACC/AHA Class I recommendation).[6] Extensive data with the combination of all three classes of antianginals are lacking. However, some analyses estimate that 5% to 15% of patients are refractory to even triple antianginal therapy.[83]

Ranolazine

Ranolazine is the first antianginal drug approved by the United States Food and Drug Administration (FDA) in more than 20 years and is used primarily in those patients refractory to traditional agents.[14] Ranolazine, a piperazine derivative, inhibits late sodium channels by lowering total inward sodium influx and thus the subsequent intracellular calcium overload that is associated with ischemia. Fortunately, at therapeutic levels, ranolazine does not alter fast inward sodium channels; the late inward sodium channels are inhibited in ischemic tissue only.[14] By preventing the intracellular calcium overload, there is myocardial diastolic relaxation and a rebalancing of oxygen demand and supply in the coronary vasculature.

Because ranolazine is cleared by hepatic enzymes and is also a substrate of P-glycoprotein, there are a number of important drug interactions to be aware of. Any cytochrome P 3A4 inhibitor (e.g., ketoconazole, clarithromycin, phenytoin) will raise the levels of ranolazine and can lead to side effects such as dizziness, headache, and nausea.[14] Ranolazine itself is a mild inhibitor of some cytochromes (CYP 3A4 and CYP 2D6). This can lead to increases in levels of some statins and should be a concern in patients with stable CAD. Also, because of P-glycoprotein competition, ranolazine can lead to increases in digoxin levels in patients on this medication, so dose reduction or further monitoring is usually warranted.[14] Finally, ranolazine may prolong the QT interval. Thus, patients with congenital long QT syndrome or who are on medications that prolong the QT interval should likely not receive this medication.

In preliminary trials, ranolazine showed a significant improvement in exercise duration and ischemia in patients with stable angina.[84,85] In the first of the major clinical studies, three doses of ranolazine were assessed in stable angina patients previously responsive to traditional therapies.[86] Ranolazine resulted in improvement in symptoms of angina and exercise duration as monotherapy, with the optimal dose established at 1,000 mg twice daily.[86] The subsequent trial evaluated ranolazine in combination with a beta-blocker or CCB and again showed improvement in anginal symptoms and ischemia in the patients receiving the combination therapy.[87] In the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Segment Elevation Acute Coronary Syndromes (MERLIN)-TIMI 36 trial, there was no improvement in the primary endpoint of cardiovascular death, MI, or recurrent ischemia between ranolazine and placebo in patients with non–ST-segment elevation acute coronary syndromes.[88] Further analysis showed no impact on cardiovascular death and MI, but ranolazine did show an improvement in angina and duration of exercise.[89] Currently, ranolazine use is not reflected in the ACC/AHA guidelines, as it was not FDA approved at the time of the last update.

Conclusion

Although no single class of medical therapy directed at symptom relief has proven to be

prognostically superior in the treatment of uncomplicated stable angina pectoris, beta-blockers have been shown to reduce mortality in high-risk subsets of cardiovascular disease (prior MI, heart failure, hypertension) and therefore serve as first-line agents for symptomatic treatment. CCBs and long-acting nitrates are reserved for combination therapy in patients with persistent symptoms or as second-line agents in patients who are unable to tolerate beta-blockers (see Table 39.10).

TABLE 39.10 ACC/AHA Recommendations for Pharmacotherapy in Stable Angina Pectoris

Pharmacotherapy to prevent symptoms
Beta-blockers
Class I: indefinitely in all patients with prior MI, acute coronary syndrome, or LV dysfunction with or without heart failure symptoms, unless contraindicated
Calcium channel blockers
Class I: in combination with beta-blockers when beta-blockers alone are ineffective
Class I: initial therapy in patients where beta-blockers are contraindicated or in those unable to tolerate beta-blockers
Class IIa: long-acting nondihydropyridine calcium antagonists instead of beta-blockers as initial therapy
Nitrates
Class I: long-acting nitrates in combination with beta-blockers when beta-blockers alone are ineffective
Class I: long-acting nitrates as initial therapy in patients where beta-blockers are contraindicated or in those unable to tolerate beta-blockers
Class I: Sublingual nitroglycerin or nitroglycerin spray for immediate relief of angina
Pharmacotherapy to prevent death or MI
Aspirin
Class I: indefinitely in all patients without contraindications, at a dose of 75–162 mg/d
Clopidogrel
Class IIa: in patients for whom aspirin is absolutely contraindicated
ACE inhibitors
Class I: indefinitely in patients with LV systolic dysfunction (EF ≤ 40%), HTN, DM, or CKD, unless contraindicated
Class IIa: in patients with mildly reduced or normal LV function (if risk factors are well controlled and the patient is revascularized)
Angiotensin receptor blockers
Class I: in patients who have HTN, have indications for but are intolerant of ACE inhibitors, have heart failure, or have had MI with LV EF ≤ 40%
Class IIb: in combination with ACE inhibitors in patients with heart failure due to LV systolic dysfunction
Aldosterone receptor blockers
Class I: in post-MI patients without significant renal dysfunction (creatinine <2.5 mg/dL in men and <2.0 mg/dL in women) or hyperkalemia (potassium < 5.0 mEq/L) who are already receiving therapeutic doses of an ACE inhibitor and a beta-blocker, have LV EF ≤ 40%, and have either diabetes or heart failure
Statins
Class I: LDL-C goal is <100 mg/dL.
Class I: if baseline LDL-C is ≥100 mg/dL, therapeutic lifestyle changes and LDL-lowering drug therapy should be initiated.
Class I: if on-treatment LDL-C is ≥100 mg/dL, LDL-lowering drug therapy should be intensified.
Class IIa: high-risk patients with optional LDL-C goal of <70 mg/dL
Class IIa: if baseline LDL-C is 70–100 mg/dL, it is reasonable to treat to LDL-C < 70 mg/dL.

ACE, angiotensin-converting enzyme; CKD, chronic kidney disease; DM, diabetes mellitus; EF, ejection fraction; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; MI, myocardial infarction.

From Fraker TD Jr, Fihn SD, Gibbons RJ, et al. 2007 chronic angina focused update of the ACC/AHA 2002 Guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to develop the focused update of the 2002 Guidelines for the management of patients with chronic stable angina. Circulation. 2007;116(23):2762–2772, with permission.

In addition to symptomatic treatment, it is essential that individual patient risk factors be identified and treated. The greatest emphasis should be placed on the treatment of modifiable factors that have the greatest potential for preventing disease progression and reducing the risk of future ischemic events. This includes smoking cessation, physical activity in sedentary patients, weight management, antiplatelet therapy with aspirin, and aggressive treatment of concomitant hyperlipidemia, hypertension, and diabetes mellitus.[29] Newer pharmacologic agents targeting metabolic pathways (e.g., nicorandil, trimetazidine) and sinus rate-lowering drugs (e.g., ivabradine) have unique mechanisms of action that may provide additive benefits when combined with traditional therapies, but further investigation is still required before these medications receive FDA approval.

REVASCULARIZATION IN STABLE ANGINA PECTORIS

In 2007, there were an estimated 408,000 coronary artery bypass surgeries, over 1 million diagnostic cardiac catheterizations, and just under 1.2 million inpatient PCIs in the United States.[2] Even though the overall percentage has decreased in recent years, the majority of these were performed electively in patients with stable ischemic syndromes. Despite the more widespread availability of mechanical revascularization in the management of stable angina, evidence-based medicine suggests that patients with low-risk features are best managed medically, with revascularization reserved for those with refractory symptoms or high-risk clinical and angiographic features. As both medical and revascularization therapies continue to improve, identifying the patients most likely to derive sufficient symptomatic or survival benefit to warrant the immediate risk of an invasive procedure and selecting the most appropriate mode for revascularization remain an important challenge.

Coronary Artery Bypass Grafting versus Medical Therapy

The initial studies comparing medical therapy and CABG in stable coronary disease were performed prior to the advent of percutaneous therapies and before the routine use of antiplatelet and lipid-lowering pharmacotherapies. The three largest trials were the Veterans Administration Cooperative Study (VA Study), [90,91] the Coronary Artery Surgery Study (CASS),[92] and the European Coronary Surgery Study (ECSS).[93,94] In these trials, patients with significant CAD were variably defined angiographically. Left main stenosis was generally considered significant if ≥50% in all studies. By contrast, in CASS, a stenosis of ≥70% in a major epicardial coronary artery segment was considered significant,[92] while in the others, it was ≥50%.[91,93] Either way, patients were randomized to medical therapy alone or in combination with surgical revascularization. In all three trials, patients who underwent CABG had a marked improvement in anginal symptoms, exercise tolerance, and quality of life compared to

medically treated patients.[12] Generally following CABG, angina control is more prominent early in the postoperative period and decreases over time, with more than 90% of patients free of symptoms 1 year after surgery, 78% at 5 years, and 52% at 10 years.[95] Accelerating vein graft attrition and progressive native vessel disease eventually reduce this number to around 25% by 15 years.[95]

More important than symptom relief, these early trials identified high-risk angiographic features that predicted a survival benefit with CABG. Specifically, survival was improved for patients with severe left main stenosis (≥50%), two- or three-vessel disease that included >75% proximal LAD stenosis, and three-vessel disease with abnormal left ventricular systolic function regardless of proximal LAD involvement.[6,12,96] These results were obtained across the range of the CCS angina severity scale and were independent of other clinical variables. For low-risk patients, such as those with single-vessel disease, surgical revascularization provided better angina relief, but it did not improve survival. MIs were not significantly reduced in any subgroups, regardless of risk.[96]

The data from individual trials were further bolstered by the Coronary Artery Bypass Graft Surgery Trialists Collaboration meta-analysis, which included seven randomized trials comparing CABG with medical treatment in 2,649 patients with stable coronary syndromes.[12] Although the 5-year risk of MI was not significantly reduced with CABG (24.4% with CABG vs. 30.7% with medical therapy), a survival advantage was confirmed in patients with severe left main stenosis, three-vessel disease, or two-vessel disease with proximal LAD involvement.[12] Within these subsets, the presence of left ventricular dysfunction or a strongly positive exercise test predicted an even greater absolute benefit. It is important to note that the survival advantage of bypass surgery over medical therapy does not become apparent for 2 to 3 years postoperatively, and this is thought to be due to early perioperative mortality. The benefit remains statistically significant for up to 10 years and diminishes thereafter due to a combination of accelerating vein graft attrition and the high rate of crossover of medically treated patients to CABG (around 40% of medically assigned patients in the trials underwent CABG by 10 years).[12] Long-term postoperative survival and symptoms have improved significantly over recent years with advances in medical therapies and the routine use of internal mammary artery (IMA) conduits, which have excellent long-term patency (>90% at 10 years) and result in fewer reoperations compared to surgery with vein grafts alone.[97]

A risk-stratification model, performed as part of the CABG Surgery Trialists Collaboration meta-analysis, that used clinical and angiographic variables (extent of CAD, severity of angina, left ventricular function, and severity of myocardial ischemia) demonstrated a significant survival benefit with CABG among those deemed at high risk (5-year medical treatment mortality 23% to 25.2%) and moderate risk (5-year medical

treatment mortality 11.5% to 13.9%).[12] Patients in the lowest risk category (5-year medical treatment mortality 5.5% to 6.3%) did not benefit from bypass surgery and showed a slight trend toward increased mortality with revascularization, further illustrating the need for careful patient selection.[12] Another important consideration is that the majority of the early CABG data were in men with a mean age of around 50; there is little data in women or in patients over the age of 60, thus making treatment decisions more complex for these populations.

Percutaneous Coronary Intervention versus Medical Therapy

PCI began as percutaneous transluminal coronary angioplasty (PTCA) in the late 1970s and has expanded over the years to include rotational atherectomy, laser ablative procedures, and intracoronary stents.[6] The initial data comparing PCI to medical therapy in stable CAD were limited to mostly PTCA and consisted of several small trials that enrolled very low-risk patients, primarily with single-vessel disease, mild symptoms, and preserved left ventricular function.[15,20,22,98,99]

Although PTCA generally provided greater anginal relief than medical therapy, none of the individual trials suggested a reduction in mortality or MI following percutaneous revascularization.[25] The second Randomized Intervention Treatment of Angina (RITA-2) trial, the largest study comparing PTCA to medical therapy in stable coronary disease, actually noted that the composite primary endpoint of death or nonfatal MI was increased in the revascularization arm (3.3% in the medical arm vs. 6.3% in the PTCA arm; $p = 0.02$), primarily due to an excess of periprocedural MIs in a small number of overall events.[98] An earlier meta-analysis of the six randomized trials comparing PTCA to medical therapy in 1,904 patients with stable CAD demonstrated that, while PTCA significantly improved symptoms compared to medical therapy, it did not decrease death or MI.[24] Additionally, initial treatment with PTCA resulted in significantly more bypass surgeries and a trend toward more repeat percutaneous interventions.[24] Since those initial studies, longer term follow-up has been published. The reduction in anginal symptoms in patients treated with PTCA has remained significant, while there remains no benefit in death or MI with PTCA over medical therapy alone.[16,17,21]

The advent of coronary stents was thought to be the answer to improving outcomes of PCI, especially in terms of acute vessel closure and requirement for repeat revascularization procedures. Subsequent studies variably used intracoronary bare metal stents (BMS) in comparison to medical therapy in treating patients with stable angina.[19,100,101] Again, the studies were conducted in relatively small numbers of patients, most of whom were younger (mean age about 60), with low-risk and normal left ventricular function. When combined in aggregate in a subsequent meta-analysis, there was no difference in PCI and medical therapy in terms of mortality, cardiac death or MI, nonfatal MI, CABG, or PCI during follow-up.[25]

The long awaited results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, the largest randomized trial of PCI plus optimal medical therapy (OMT) versus OMT alone in stable CAD, were published in 2007.[102] This study evaluated the occurrence of all-cause mortality and nonfatal MI in 2,287 patients followed for a median of 4.6 years. Stable CAD was defined as a stenosis of ≥70% in a proximal epicardial coronary artery with objective evidence of ischemia or a stenosis of ≥80% and classic anginal symptoms. The study used the most contemporary and aggressive medical therapy available to date with good compliance and attainment of treatment goals in both groups. There was no significant difference in the primary outcome of all-cause mortality and nonfatal MI between the PCI plus OMT versus OMT alone groups (event rates 19.0% vs. 18.5%).[102] Additionally, there was no difference in other composite secondary outcomes that included stroke or hospitalization for acute coronary syndromes. However, there was significant improvement in symptoms of angina in the PCI plus OMT group for the first 3 years, which evened out and was not statistically significant at median follow-up. Another advantage for PCI plus OMT was in need for additional revascularization (21.1% vs. 32.6% with OMT alone), which was performed for angina that was unresponsive to maximal medical therapy or for ischemia on noninvasive testing.[102] There were limitations to the COURAGE trial, however. The majority of patients were men, and very few patients had left ventricular systolic dysfunction. In addition, most of the stents used for PCI were BMS, there was a high rate of crossover in the OMT arm, and the extent of the practices in place to ensure OMT adherence is not thought to be achievable in the general population. In spite of those limitations, COURAGE does reiterate the importance of medical therapy and provide reassurance that not pursuing PCI in favor of a more conservative approach in stable patients is not detrimental.

In contrast to the overall results of the COURAGE trial, the results of the nuclear substudy were in favor of PCI plus OMT. For this nuclear substudy, 314 patients were enrolled for serial rest/stress SPECT myocardial perfusion scanning before treatment and at 6 to 18 months postrandomization.[103] The primary endpoint was more than 5% reduction in ischemic myocardium. The PCI plus OMT group had more significant reduction in ischemic burden with more patients obtaining this reduction (33% vs. 19% with OMT alone); this risk reduction was especially pronounced for those with moderate to severe pretreatment ischemia. Further, those with a reduction in ischemic myocardium had a significant improvement in mortality and subsequent MI.[103]

Thus, given the absence of evidence to suggest that percutaneous interventions improve long-term outcomes in low-risk patients with stable coronary syndromes, medical therapy is generally recommended as the initial strategy for the majority of patients with stable angina. However, for those with persistent lifestyle-limiting symptoms despite maximized medical therapy or with extensive ischemia on

noninvasive testing, percutaneous revascularization can provide symptomatic relief and improve cardiovascular outcomes.

PCI versus CABG in Single-Vessel CAD

Randomized trials of revascularization, whether surgical or percutaneous, in patients with stable single-vessel CAD have never demonstrated a survival benefit over medical therapy. Revascularization in this population is therefore generally reserved for patients with persistent symptoms despite OMT. In this low-risk population, only three small trials have directly compared surgical and percutaneous revascularization. The Medicine, Angioplasty or Surgery Study (MASS) randomized 214 patients with stable angina, >80% proximal LAD coronary stenosis, and preserved left ventricular function to medical therapy, CABG using an IMA graft, or PTCA.[20] There was no difference in survival or MI between the treatment arms at 3 years. Angina was improved compared to medical therapy following either form of revascularization, although initial CABG provided greater relief and fewer repeat procedures than initial PTCA.

The trial out of Lausanne, Switzerland, which did not include a medical treatment arm, reported similar survival and symptomatic benefit at 5-year follow-up among 134 patients with a proximal LAD stenosis randomized to PTCA or bypass surgery with an IMA graft.[104] There were also more repeat revascularization procedures in the PTCA group. Lastly, a more recent trial comparing the more contemporary approach of minimally invasive CABG with IMA versus stenting for a proximal LAD stenosis also failed to detect a difference in death or MI.[105] There were more often recurrent symptoms and repeat interventions in the PCI group, while the CABG group more often had adverse events (i.e., reoperation for graft occlusion, perioperative MI, stroke, chest wall hernia requiring surgical repair, etc.).

PCI versus CABG in Multivessel CAD

Multiple early randomized trials comparing initial PCI, consisting mostly of PTCA, versus CABG in multivessel CAD have shown that, except for the subset of patients with diabetes, the long-term risk of death or MI is equivalent with both procedures. Percutaneous revascularization, however, is consistently associated with less anginal relief and the need for repeat revascularizations. The largest single study comparing these revascularization strategies for multivessel CAD was the Bypass Angioplasty Revascularization Investigation (BARI).[106] In this study, 1,829 patients with multivessel CAD were randomized to PTCA versus CABG and followed for an average of 5.4 years. In the periprocedural time period, there was no difference in in-hospital mortality or stroke rates between the two arms; however, CABG patients had a higher incidence of perioperative MI and PTCA patients had a higher likelihood of early reintervention. Long-term follow-up evened out the rates of MI between the two treatment groups and there was no difference at 5 years. The trend for revascularization held for the follow-

up period, with PTCA patients requiring more repeat revascularization procedures (54% vs. 8% in the CABG arm), most of which occurred within the first year of follow-up. Importantly, on subgroup analysis, as initially noted in this trial and confirmed in subsequent publications, diabetic patients with multivessel disease have a significant survival benefit with surgery over PTCA (5-year survival 80.6% with CABG vs. 65.5% with PTCA, $p = 0.003$). The survival outcomes for nondiabetics were identical.

A meta-analysis published in 1995 combined the results of the available eight randomized trials at that time, which enrolled 3,371 total patients with a mean follow-up of 2.7 years.[107] There was no detected difference in mortality or MI, but the analysis did confirm that patients treated with PTCA experienced less complete relief of anginal symptoms and required more repeat revascularizations (3.3% CABG vs. 33.7% PTCA). In contrast, a later meta-analysis of 13 trials, including 7,964 patients and 4 trials in which stents were used as the initial PCI, demonstrated a significant survival advantage favoring CABG over PCI at 5 years but, with longer follow-up out to 8 years, was no longer significant.[108] Subgroup analyses suggested that the mortality reduction was limited to diabetics, while nondiabetics again had equivalent outcomes. Anginal symptoms and repeat revascularizations were again significantly reduced following CABG, but the difference was markedly attenuated in patients receiving coronary stents (repeat revascularization rates of PCI group cut in half by the use of stents).[108]

The early trials of PTCA versus CABG had important limitations. For the most part, the patient populations were younger and at lower risk. Although stenting was initially introduced for the management of complications related to PTCA and was not used in the early trials, it is now the dominant PCI modality because it significantly reduces restenosis compared with PTCA. There were four subsequent trials that evaluated PCI incorporating BMS versus CABG in multivessel CAD.[18,109-111] In the meta-analysis of the aggregate data from these 4 trials of 3,051 patients with multivessel CAD, there was no difference in the combined endpoint of death, MI, or stroke at 1 year between the groups.[112] Once again, CABG was superior in need for repeat revascularization procedures (4.4% vs. 18% in PCI patients); however, for the first time, PCI was better in relieving anginal symptoms, with 82% freedom from angina versus 77% in the CABG group ($p = 0.002$). Even though the need for repeat revascularization was still higher for percutaneous procedures, this meta-analysis showed that the gap had narrowed considerably with the use of BMS.[112]

In 2009, the results of the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) trial were published and contradicted the results of earlier trials in regard to the treatment of diabetic patients.[113] BARI-2D randomized 2,368 patients with diabetes and stable CAD to medical therapy or prompt revascularization, either by CABG or PCI. The decision of CABG or PCI, however, was at the discretion of the treating physician. At 5 years, there was no difference in mortality between medical

therapy and revascularization (survival 88.3% in revascularization group vs. 87.8% in medical therapy group). At baseline, the patients stratified to CABG over PCI had more extensive CAD, with more three-vessel CAD, proximal LAD disease, and chronic total occlusions. In spite of this, there was no difference in mortality between either the CABG or PCI arms and the medical therapy arm. While there was no difference in major cardiovascular events (death, MI, or stroke) in PCI versus medical therapy, there was significant improvement in major cardiovascular events in the CABG group over medical therapy alone. When the interaction between study group assignments was evaluated, there was a statistically significant benefit in prompt revascularization, over medical therapy, in patients selected for CABG over those stratified to PCI. There are some limitations to conclusions drawn from these data. First, this study was not designed to evaluate PCI versus CABG in diabetic patients; as mentioned previously, the patients stratified for CABG had more extensive CAD. Additionally, the use of drug-eluting stents (DES) was low (around 35%) in the PCI arm, as was the use of antiplatelet agents (around 20%). The best revascularization strategy in diabetic patients is, therefore, still an area of some debate. The ongoing Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) trial will help answer this question.[114] This study is an open-label, prospective randomized trial of PCI with DES versus CABG in diabetic patients in whom revascularization is indicated.

Also published in 2009 were the results of the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial.[115] In this study, 1,800 patients with three-vessel or left main CAD were randomized to CABG or PCI with Taxus DES. At 1 year, the rates of death and MI were similar between the two groups, while stroke was more likely to occur with CABG (2.2% vs. 0.6% with PCI) and an increased rate of repeat revascularization was more likely with PCI (13.5% vs. 5.9% with CABG). Further, the investigators used an angiographic scoring tool (the SYNTAX score) to objectify the severity of CAD. Stratified by SYNTAX score, patients with low or intermediate scores had similar rates of major adverse cardiac or cerebrovascular events whether undergoing PCI or CABG. However, in those with high SYNTAX scores, the CABG group had much lower rates of major adverse cardiac or cerebrovascular events (all-cause mortality, stroke, MI, or repeat revascularization).[115]

Conclusion

Data from randomized trials and observational registries indicate that the benefits of revascularization in stable coronary syndromes are proportional to the patient's estimated long-term risk while on medical therapy.[107,108] For low-risk patients with single-vessel CAD, medical therapy remains the initial treatment of choice, with revascularization reserved for symptom relief when medical treatment has failed. Patients with multivessel CAD are more complicated. Surgical revascularization likely

provides the best long-term survival benefit for diabetics with multivessel disease and for all patients with high-risk angiographic features, such as severe left main stenosis, three-vessel disease, or two-vessel disease involving the proximal LAD. For the remaining patients with moderate-risk multivessel disease, revascularization and medical therapy appear to provide similar outcomes. For a complete listing of the ACC/AHA recommendations for revascularization in stable angina, see Table 39.11.

TABLE
39.11 ACC/AHA Recommendations for Revascularization in Stable Angina Pectoris

Class I
CABG for >50% left main trunk stenosis
CABG for three-vessel disease, especially if abnormal LV function or diabetes
CABG for two-vessel disease with significant proximal LAD CAD and abnormal LV function (EF < 50%) or ischemia on noninvasive testing
PCI for two- or three-vessel CAD with significant proximal LAD CAD who have anatomy suitable for PCI and have normal LV function and are not diabetic
PCI or CABG for one- or two-vessel CAD without significant proximal LAD CAD but with a large area of viable myocardium and high-risk criteria on noninvasive testing
CABG for one- or two-vessel CAD without significant proximal LAD CAD in patients who have survived sudden cardiac death or sustained VT
CABG or PCI for restenosis in patients with prior PCI that is associated with a large area of viable myocardium and/or high-risk criteria on noninvasive testing
PCI or CABG for persistent symptoms despite OMT
Class IIa
Repeat CABG for multiple SVG stenoses, especially if/when significant stenosis involves a graft to LAD. PCI may be appropriate in focal stenoses or in poor candidates for reoperation.
PCI or CABG for one- or two-vessel CAD without significant proximal LAD disease but with a moderate area of viable myocardium and ischemia on noninvasive testing
PCI or CABG for one-vessel disease with significant proximal LAD disease
Class IIb
PCI (over CABG) for two- or three-vessel CAD with significant proximal LAD CAD in patients with anatomy suitable for PCI and who are diabetic or have abnormal LV function
PCI for left main disease in patients who are not operative candidates
PCI for one- or two-vessel CAD without significant proximal LAD CAD in patients who have survived sudden cardiac death or sustained VT
Class III
PCI or CABG for one- or two-vessel CAD without significant proximal LAD CAD in patients who have mild symptoms that are unlikely due to myocardial ischemia, or in patients who have not received an adequate trial of medical therapy and have only a small area of viable myocardium or have no ischemia on noninvasive testing
PCI or CABG for borderline coronary stenoses (50%–60% in locations other than the left main trunk) and no ischemia on noninvasive testing
PCI or CABG for insignificant coronary stenosis (<50% diameter)
PCI in patients with significant left main CAD who are candidates for CABG

CABG, coronary artery bypass graft; CAD, coronary artery disease; EF, ejection fraction; LAD, left anterior descending; LV, left ventricular; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; SVG, saphenous vein graft; VT, ventricular tachycardia. From Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

(Committee on the Management of Patients With Chronic Stable Angina). Circulation. 2003;107(1):149–158, with permission.

REFRACTORY ANGINA

Considerable progress has been made over the last 25 years in expanding the therapeutic options available in ischemic heart disease, including pharmacologic and revascularization therapies that improve both symptoms and prognosis. However, despite the efficacy of these treatments, there remains a subset of patients with severe symptoms who are refractory to conventional medical therapy and are deemed to be unsuitable for coronary revascularization. As many as 1.7 million patients in the United States are suffering from refractory angina pectoris, with the prevalence increasing as the population ages and patients live longer with their CAD.[14] For these patients with refractory angina, there are adjunctive invasive and noninvasive therapies available that do not improve prognosis but may serve to alleviate symptoms and improve quality of life.

Enhanced External Counterpulsation

Although the mechanisms underlying the benefits observed with enhanced external counterpulsation (EECP) in patients with stable angina pectoris remain unclear, this is an effective noninvasive option in the management of patients with refractory angina pectoris. EECP utilizes three sets of pneumatic cuffs applied to the lower extremities at the calves, lower and upper thighs that inflate sequentially from distal to proximal during diastole to provide diastolic augmentation of coronary flow and increased venous return. The cuffs deflate just before systole, reducing afterload and thereby increasing cardiac output. A standard course of EECP involves 1 hour a day for a total of 35 hours of therapy performed over 7 weeks. Observational studies have demonstrated that EECP improves anginal class, exercise tolerance, and quality of life while reducing nitroglycerin use and the severity of ischemia measured with myocardial perfusion imaging.[14] The data from these studies are further supported by a randomized, double-blind, sham-controlled study of EECP that demonstrated a reduction in angina, an increase in time to ST-segment depression during exercise, and an improvement in quality of life at 1 year (registry data suggest a benefit up to 2 years).[116] For those whose symptoms do eventually recur, a repeat course of EECP performed after 1 year may also be effective.[117] EECP is FDA approved for the treatment of refractory angina and has a Class IIb indication from the ACC/AHA.[6]

Spinal Cord Stimulation

Spinal cord stimulation (SCS) is an invasive procedure that involves the surgical placement of an epidural electrode at the level of C7 through T1 and a pulse generator in the left lower abdomen. Neuromodulation of the dorsal columns several times per

day by the device is believed to inhibit the pain-conducting impulses originating from the spinothalamic tract and lower pain perception. More recent data also show some sympatholytic activity and changes in cerebral blood flow that may explain some of its mechanisms of action.[14] The typical course of treatment consists of three 1-hour stimulations daily. Several small observational studies have demonstrated improvements in anginal class and time to onset of ST-segment depression in patients treated with SCS.[14] In a single randomized trial comparing SCS to CABG in 104 patients with stable angina, the two treatments provided equivalent symptom relief and an improved long-term quality of life.[118] Mortality was improved at 6 months with SCS and similar between the two treatment arms at 5 years.[14] Based on these results, SCS has an ACC/AHA Class IIb recommendation for patients with refractory angina.[6]

Other Miscellaneous Proposed Therapies

Several small clinical trials have investigated the use of neuromodulation with transcutaneous electrical nerve stimulation (TENS) units in patients with refractory angina. In these limited studies, patients treated with TENS demonstrated an increase in exercise tolerance, a decrease in anginal symptoms, and a reduction in ischemia noted on exercise electrocardiography.[119] Other methods undergoing investigation include low-energy electrohydraulic shock wave therapy, intermittent urokinase therapy, and intramyocardial bone marrow stem cell injection. Because clinical trial data are so limited, the most recent ACC/AHA guidelines do not specifically make recommendations on the utility of these therapies (Table 39.12).[6]

TABLE
39.12 ACC/AHA Recommendations on Therapeutic Treatment Options for Refractory Angina

EECP—Class IIb
SCS—Class IIb

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QUESTIONS AND ANSWERS

Questions

1. An 80-year-old man is referred to the Cardiovascular Medicine clinic due to symptoms consistent with stable angina. He has a history of hypertension that is well controlled on metoprolol succinate 150 mg daily. He has been experiencing stable angina for 3 months. After seeing his internist, he is now also on aspirin 81 mg daily, isosorbide mononitrate 120 mg daily, and simvastatin 40 mg daily. On exam, the heart rate is 62 beats/min and the blood pressure is 110/60 mm Hg. The cardiopulmonary exam is unremarkable. Resting electrocardiogram (ECG) is within normal limits. An exercise stress test is performed utilizing the Bruce protocol and is significant for 2-mm horizontal ST-segment depression in the inferolateral leads, as well as chest discomfort at 4 minutes that required cessation of exercise. The Duke Treadmill Score (DTS) for this patient is:
   a. −8, intermediate risk
   b. −8, high risk
   c. −10, intermediate risk
   d. −14, intermediate risk
   e. −14, high risk

2. For the patient mentioned in question 1, the next most appropriate step would be:
   a. Increase the dose of isosorbide mononitrate
   b. Increase the dose of metoprolol succinate
   c. Add nifedipine sustained release (SR)
   d. Coronary angiography
   e. Stress echocardiography

3. Which of the following statements are not true in regard to medical therapy versus percutaneous coronary intervention (PCI) for chronic stable angina?
   a. PCI is more effective than medical therapy in reducing cardiovascular mortality in patients with chronic stable angina.
   b. PCI is more effective than medical therapy for symptomatic relief of angina.
   c. PCI plus optimal medical therapy in the COURAGE trial was no more effective than optimal medical therapy alone in preventing mortality or myocardial infarction in patients with stable coronary artery disease (CAD).
   d. As evidenced by the nuclear substudy of the COURAGE trial, PCI plus optimal medical therapy is more effective than optimal medical therapy alone in reduction of ischemia in patients with stable CAD.

4. A 60-year-old man with cirrhosis presents to the Cardiovascular Medicine clinic for evaluation of stable angina. He is already on maximum doses of a long-acting nitrate and a beta-blocker. He continues to have angina and is extremely limited. His heart rate is 55 beats/min and his blood pressure is 99/62 mm Hg. His cardiopulmonary examination is normal. Stress testing with myocardial perfusion imaging is performed and reveals an exercise- induced reversible defect in the inferior wall. The left ventricular ejection fraction is normal. Coronary angiography reveals a long occlusion of the mid right coronary artery that fills via collaterals from the left anterior descending coronary artery. There is no other significant disease. You consider the addition of ranolazine given he is already maximized on a beta-blocker and a long-acting nitrate. Which of the following statements regarding ranolazine is correct?

a. There is a significant increase in the risk of lethal arrhythmias with the use of ranolazine.
b. Ranolazine would not be an option for this patient, as it would further decrease the blood pressure and heart rate.
c. Ranolazine would be contraindicated in this patient given his liver disease.
d. There is no benefit in adding ranolazine to the medical regimen of patients already receiving combination therapy with other antianginals.
e. Ranolazine is a class I recommendation by the ACC/AHA guidelines in this patient.

5. For a patient with stable coronary artery disease (CAD), which of the following statements is not true about the role of percutaneous coronary intervention (PCI) versus coronary artery bypass graft (CABG) surgery?
   a. In a patient with an 80% lesion of the left anterior descending coronary artery, there is no difference between PCI and CABG in the rates of long-term cardiovascular death or myocardial infarction.
   b. For most patients, there is no difference between PCI and CABG in terms of overall mortality.
   c. In a patient with diabetes mellitus and multivessel CAD, there is a greater reduction in mortality with CABG over PCI.
   d. In general, PCI has a higher rate of recurrent angina than CABG.
   e. In general, CABG has a lower rate of long-term myocardial infarction than PCI.

Answers

1. **Answer E:** This patient with exercise-limiting angina has a DTS of −14, which predicts a high probability of severe angiographic coronary artery disease (CAD). The DTS is calculated as follows:
   DTS = Exercise time (minutes of Bruce protocol) − (5 × maximum ST-segment deviation in mm) − (4 × angina index)
   (Angina index: 0 = none, 1 = nonlimiting angina, 2 = exercise-limiting angina)
   Patients are classified as low-, moderate-, or high-risk based on their DTS. A low-risk DTS is ≥ +5, and these patients have a low (3%) 5-year mortality rate. A high-risk DTS is considered ≤ −11. These patients carry the highest mortality rate (35% at 5 years). A moderate-risk DTS is between -10 and +4 and carries a 10% 5-year mortality rate. Generally, patients with high-risk DTS have high-risk anatomy at cardiac catheterization (left main or three-vessel disease) and would benefit from revascularization. Low-risk patients have an overall excellent prognosis that likely cannot be improved with further evaluation and revascularization.
2. **Answer D:** The patient is on maximal medical therapy and is unlikely to derive significant benefit from further titration of his current medications or addition of further antianginals. Stress imaging is not warranted at this time given his high risk Duke Treadmill Score and likelihood of deriving benefit from revascularization. Thus, coronary angiography would be indicated.
3. **Answer A:** Most of the trials comparing medical therapy to PCI confirm that PCI is more effective in relief of anginal symptoms as measured by severity of angina, the need for antianginal medications, and improved quality of life. However, there is no evidence that PCI is more effective than medical therapy in reducing major cardiac events (cardiac death or myocardial infarction). In one of the largest of the trials of patients with stable CAD, COURAGE randomized over 2,000 patients with moderately severe chronic stable angina to PCI plus optimal medical therapy or optimal medical therapy alone. After more than 4 years of follow-up, there was no difference in the two groups in terms of death or myocardial infarction. However, in the nuclear substudy of COURAGE, 314 patients were enrolled for serial rest/stress single positron emission computed tomography (SPECT) myocardial perfusion scanning before treatment and at 6 to 18 months postrandomization. In this substudy, the PCI plus optimal medical therapy group had more significant reduction in ischemic burden with more patients obtaining this reduction than in the optimal medical therapy alone group. Further, those with reduction in ischemic myocardium had a significant improvement in mortality and rate of subsequent myocardial infarction.
4. **Answer C:** Ranolazine is the first antianginal drug approved by the United States Food and Drug

Administration (FDA) in more than 20 years and is used primarily in those patients refractory to traditional agents. Ranolazine, a piperazine derivative, inhibits late sodium channels by lowering total inward sodium influx and thus the subsequent intracellular calcium overload that is associated with ischemia. Fortunately, at therapeutic levels, ranolazine does not alter fast inward sodium channels; the late inward sodium channels are inhibited in ischemic tissue only. By preventing the intracellular calcium overload, there is myocardial diastolic relaxation and a rebalancing of oxygen demand and supply in the coronary vasculature. Unlike other antianginal drugs, ranolazine has no effect on the heart rate or blood pressure. As evidenced in clinical trials, ranolazine is effective as both monotherapy or in combination with other antianginals for patients with stable angina. Because of its effects on sodium channels, there was some concern about the precipitation of lethal arrhythmias. There is a concentration-dependent prolongation of the QT interval and repolarization; however, in MERLIN-TIMI 36, there was no difference in the rates of documented arrhythmias or sudden death in patients receiving ranolazine compared to placebo. Ranolazine is metabolized in the liver (particularly cytochrome 3A); therefore, it is contraindicated in liver disease. Ranolazine is not currently reflected in the ACC/AHA guidelines for stable coronary artery disease (CAD) as it was not FDA approved at the time of the last update.

5. **Answer E:** Based on clinical trial data, for most patients there is no difference between CABG and PCI in terms of overall mortality and subsequent myocardial infarction. This is true for both single-vessel (including left anterior descending) and multivessel CAD. The populations in which CABG has been shown to improve survival over PCI are patients with diabetes mellitus or multivessel disease (bypass angioplasty revascularization investigation [BARI] trial). Clinical trial data also show that PCI is associated with more recurrent angina and repeat revascularization than CABG.

CHAPTER

Unstable Coronary Syndromes

Gus Theodos, Anthony A. Bavry, and A. Michael Lincoff

TERMINOLOGY AND OVERVIEW

The current approach to unstable or acute coronary syndromes (ACSs) recognizes a heterogeneous clinical spectrum that ranges from unstable angina (UA) and non–ST-elevation myocardial infarction (NSTEMI) to ST-elevation myocardial infarction (STEMI). ACS is one manifestation of atherothrombotic disease. Other clinical manifestations of vascular disease include ischemic/embolic stroke, transient ischemic attack, renal insufficiency/failure, and limb ischemia/claudication. There is considerable overlap in the burden of vascular disease, so the presence of atherothrombosis in one vascular bed should raise the suspicion for disease in another vascular bed. As an example, an individual who has limb claudication is also likely to have coronary artery disease and should undergo equally aggressive atherothrombotic risk factor modification.

Various classifications have been used to describe the syndrome of UA. The Braunwald classification of UA is a widely used mechanism for providing diagnostic and prognostic information about the patient. In this system, angina is divided into acute rest (class III), subacute rest (class II), or exertional angina (class I). Acute rest angina is chest pain that occurred at rest within 48 hours of presentation, while subacute rest angina is chest pain that occurred at rest within the previous month, although more than 48 hours prior to presentation. Exertional angina is chest pain that has been present for <2 months' duration that is described as new onset, severe, or accelerating in nature. This type of angina occurs with any exertion or less exertion than would normally bring about chest pain, with no rest angina for the previous 2 months. The Braunwald classification system also describes the clinical circumstances in which the angina is occurring. For example, secondary UA is caused by a clinical process that causes demand ischemia, such as gastrointestinal bleeding resulting in tachycardia. This process is in contrast to primary UA, in which supply ischemia results from plaque

rupture with partial or total coronary occlusion. Postinfarction angina is a special clinical circumstance to consider, as these patients are at higher risk for adverse cardiac outcomes.

The classification for ACS focuses on electrocardiographic (ECG) findings in the first minutes to hours of an event. This approach ensures that the most appropriate management (i.e., early invasive therapy with appropriate coronary revascularization vs. a more conservative approach) occurs as rapidly as possible. Older ACS terminology is inefficient, as it focused on the ECG findings after the completion of the coronary event. Historical terms such as Q-wave and non–Q-wave myocardial infarction (MI) should therefore be avoided.

This chapter discusses the spectrum that encompasses UA and NSTEMI, while another chapter focuses on STEMI. Other causes of chest pain syndromes such as aortic dissection, acute pericarditis, or pulmonary embolus are not discussed here. These chapters follow the American College of Cardiology/American Heart Association (ACC/AHA) guidelines (Table 40.1).

TABLE
40.1 ACC/AHA Classification for Recommendations

Class I	Conditions for which there is evidence and/or general agreement that a given procedure/treatment is useful and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure/treatment
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful

From Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol. 2007;50(7):e1–e157, with permission from Elsevier.

EPIDEMIOLOGY AND PROGNOSIS

There are over 5 million annual visits to emergency departments in this country for the evaluation of chest pain, with approximately 1.5 million hospitalizations for UA/NSTEMI. This number is expected to increase over the next decade. Atherothrombotic disease, especially ACS, significantly shortens an individual's life span. A survived acute MI shortens the expected life expectancy for a 60-year-old individual by approximately 9 years, whereas a cerebrovascular accident shortens an

individual's expected life span by about 12 years. Coronary disease is the single largest cause of mortality worldwide. This translates into approximately one of every five deaths in the United States being attributable to atherothrombotic disease. The shift in the epidemiology of coronary disease in this country, with improved overall mortality, is due to effective prevention and treatment of cardiovascular disease over the last several decades.

Most ACSs occur in individuals >65 years old, and nearly 50% occur in women. When women present with chest pain, the etiology is less likely to be secondary to obstructive coronary disease, and when coronary disease is present, it tends to be less severe than in men. In-hospital mortality of UA and NSTEMI patients is less than that of STEMI patients, although because the former are at risk for recurrent events, their long-term risk is equivalent or worse compared to STEMI patients.

CLINICAL PRESENTATION

UA and NSTEMI patients typically present with substernal chest discomfort, described as a pressure or a heavy sensation. This more accurately describes angina than terminology such as "pain." Symptoms typically last <30 minutes, although they may recur frequently throughout the day or evening upon minimal exertion. Symptoms may occur at rest. Angina that occurs with minimal exertion is usually relieved promptly with rest or nitroglycerin. Anginal equivalents include neck and jaw discomfort, although the most common anginal equivalent is worsening dyspnea upon exertion. Atypical findings such as nausea, vomiting, and fatigue are easily overlooked, although these symptoms should be considered as angina in diabetics, women, and the elderly. Findings that are typically not characteristic of myocardial ischemia include sharp/pleuritic pain, pain that has been present for several hours, and brief pain that lasts only a few seconds. Up to 20% of MI s are "silent" and occur without any appreciable symptoms.

ECG findings include transient ST elevations, ST depressions (horizontal or downsloping), T-wave inversions, or nonspecific changes. The ECG may also appear normal. Deep symmetric T-wave inversions predict higher risk than small T-wave inversions. Ischemic T waves may also have a biphasic appearance. Dynamic ECG changes that are obtained during an episode of chest pain are particularly valuable, especially if the changes resolve in the absence of symptoms. It is important to repeat the ECG frequently, as a non–ST-elevation ACS may progress to a STEMI. Conversely, initial ST elevations may resolve quickly, thus changing the focus of early management.

PATHOPHYSIOLOGY FOR PRIMARY AND SECONDARY CAUSES OF ANGINA

The above discussion assumes a primary coronary etiology for an unstable coronary syndrome. The corresponding pathophysiology for a primary ACS is most commonly felt to be rupture of a vulnerable plaque, and less commonly due to plaque erosion or calcific nodules. Vulnerable plaques overlie lipid-rich cores that are surrounded by thin fibrous caps. Exposure of the underlying plaque to blood is a potent activator of platelets and thrombus formation. This subsequently results in microembolization of platelet aggregates and intermittent coronary vasoconstriction. The fibrous cap can become unstable as a result of fissures caused by proteinases secreted by neighboring macrophages. As a plaque matures, the fibrous cap becomes thicker and more stable. Conversely, plaque erosion occurs over lesions rich in smooth muscle cells and proteoglycans. These areas have minimal amounts of inflammatory substrate. The calcific nodule refers to rupture of a dense, calcified matrix through a fibrous cap. These are commonly associated with healed plaques. An important observation has been that acute MIs do not occur at sites of severe coronary narrowing. Two-thirds of events that are caused by an acutely occluded coronary vessel are in the location of a previous mild stenosis (i.e., stenosis <50%).

Secondary causes of ACS that are responsible for demand ischemia should be screened for and corrected if present before proceeding down the appropriate ACS management algorithm. Secondary causes include hypertensive crises, anemia/hypovolemia, worsened chronic obstructive pulmonary disease/hypoxia, hyperthyroidism, arteriovenous fistula in dialysis patients, and systemic infection. Aortic stenosis and hypertrophic obstructive cardiomyopathy are cardiac diseases that may cause demand myocardial ischemia. Cocaine use is a special condition to consider, as it can produce both demand ischemia (increased heart rate and blood pressure) as well as supply ischemia (coronary vasospasm and thrombus formation).

RISK STRATIFICATION

ECG

Risk stratification is a necessary component in the initial management of coronary disease patients. The ECG is a first-line test that provides not only diagnostic but also prognostic information. Data from the Global Use Of Strategies To Open Occluded Arteries In Acute Coronary Syndromes (GUSTO IIb) trial revealed a lower 6-month survival among patients with ST depressions treated conservatively compared to STEMI patients treated with fibrinolysis. The lowest-risk ACS patients (among those with any ECG changes) were those with T-wave inversions. Patients with a completely normal ECG had the lowest overall risk. A similar analysis from the relationship between insulin sensitivity and cardiovascular disease risk (RISC) Study Group found the highest risk to be among those with ST elevations and reciprocal changes (ST depressions). The lowest risk was among those with no ST changes or nonspecific ST-

T changes.

Biomarkers

While the ECG is being performed and interpreted, blood work should be sent for analysis of complete blood count (CBC), chemistry, cardiac biomarkers, markers of inflammation and volume overload, and a lipid profile. Although it is not usually thought of for this purpose, information available from the CBC can be helpful in providing a crude measure of risk stratification. An elevated white blood cell (WBC) count has been shown to predict worse cardiac outcomes in ACS patients.

High-sensitivity C-reactive protein (hs-CRP) as a marker of inflammation provides prognostic information in unstable coronary syndromes. An elevated hs-CRP predicts a three- to fourfold increased risk for future cardiac events. This increased risk for MI can be attenuated by the use of aspirin. An hs-CRP level >3 mg/L is considered high risk, while a level >10 mg/L is considered an acute-phase response and should be repeated in 3 weeks. An elevated CRP predicts future cardiac events better than elevated cholesterol or presence of the metabolic syndrome.

An elevated troponin I or T also carries independent prognostic information. A meta-analysis showed that troponin-positive ACS patients have a fourfold increased risk for death compared to troponin-negative patients. Similarly, an analysis of the thrombolysis in myocardial infarction (TIMI) IIIb trial documented an eightfold increased risk of death at 42 days for patients with an elevated troponin I (>9 ng/mL) compared to troponinnegative patients. The 42-day mortality in patients with an elevated troponin was 7.5%, compared to 1% in those with a negative troponin.

An elevated brain natriuretic peptide (BNP) predicts increased risk for adverse cardiac events across the spectrum of ACS, although the predictive effect is greatest for UA and NSTEMI. BNP is a cardiac neurohormone synthesized in the ventricles and released as a larger peptide which is then cleaved into smaller portions including BNP and inactive N-terminal proBNP peptide (NT-proBNP). The release of BNP reflects the decompensated state of the ventricles, and it causes vasodilatation, natriuresis, and diuresis, leading to some improvement of the loading conditions of the failing heart. Even though BNP is the active hormone, both forms can be measured and serve as markers of congestive heart failure (CHF).

The combination of multiple biomarkers has incremental value. An hs-CRP combined with cardiac biomarkers (i.e., troponin I or T) and markers of pressure/volume overload (i.e., BNP) predict an increased risk for major cardiac events. In the OPUS-TIMI 16 trial there was a sixfold increased risk for 30-day cardiac events when all three markers were elevated. Similarly, in the TACTICS-TIMI 18 trial there was a 13-fold increased risk in 30-day cardiac events. So hs-CRP, troponin I or T, and BNP provide prognostic information in ACS patients. Other inflammatory markers such as CD-40 ligand are experimental, although they may have a role in the

future in predicting the overall risk for cardiac events in ACS.

Risk Scores

The TIMI risk score incorporates data derived from the TIMI 11B trial and has been validated by three additional trials. The TIMI risk score is an easily used model that has important prognostic and therapeutic implications. It incorporates seven variables that are readily available from the history, ECG, and cardiac biomarkers (Fig. 40.1). The presence of six or seven risk factors predicts a 40% incidence of death, MI, or ischemia requiring repeat revascularization by 30 days. This is in contrast to zero or one risk factor, where the 30-day cardiac event rate is <5%. The seven variables used to calculate the TIMI risk score are age ≥65 years, ≥3 coronary disease risk factors (defined as diabetes, hypertension, hyperlipidemia, use of tobacco, and family history of premature coronary disease), a known coronary stenosis of >50%, ST deviation (transient ST elevations, ST depressions, or T-wave inversions), ≥2 anginal events in the past 24 hours, aspirin use in the last 7 days, and elevated cardiac biomarkers (i.e., elevated CK-MB or troponin).

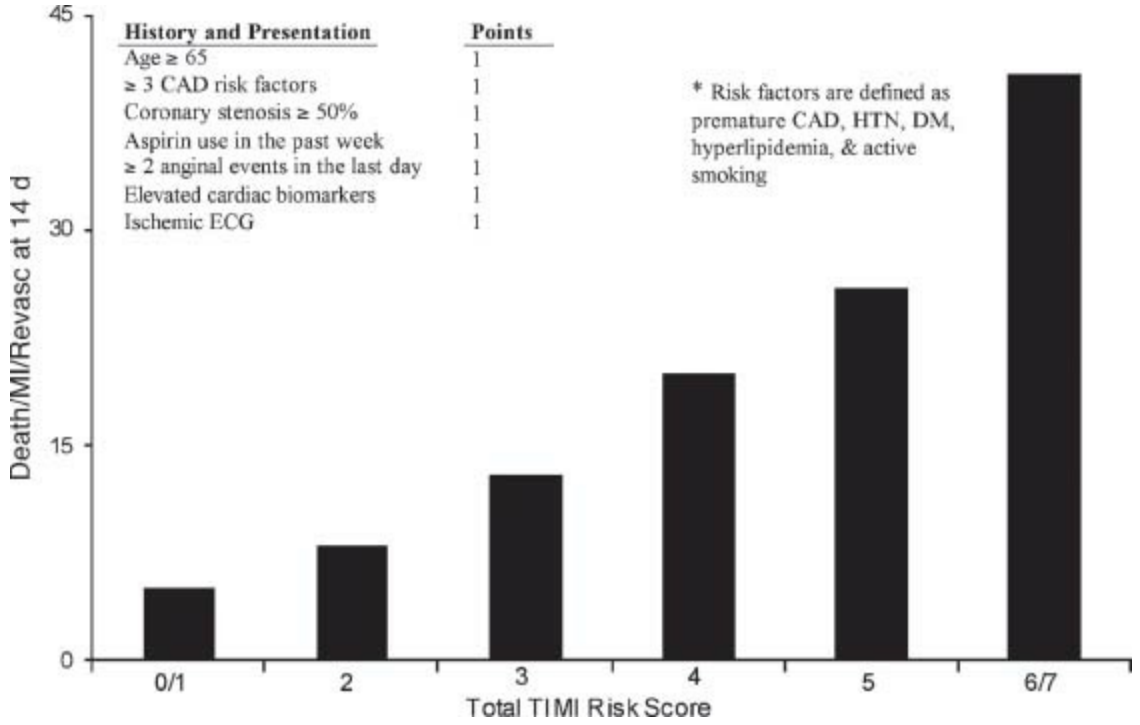


FIGURE 40.1 TIMI risk model for prediction of short-term adverse cardiac events in UA/NSTEMI patients. (Adapted from Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA. 2000;284:835–842.)

Another risk score which has been utilized extensively is the global registry of acute coronary events (GRACE) score. This score is the composite of nine variables, which, when added together, can be plotted on a nomogram to determine mortality risk from discharge to 6 months. The variables included in the score include age, history of CHF,

history of MI, heart rate and blood pressure on presentation, presence of ST-segment depression on initial ECG, serum creatinine and elevated cardiac biomarkers during hospitalization, and no percutaneous coronary intervention (PCI) performed during hospitalization.

With either scoring system in patients presenting with UA/NSTEMI, there is progressively greater benefit of more aggressive therapies as the risk score rises.

MANAGEMENT

Initial Approach

The initial assessment of UA/NSTEMI coronary syndromes includes establishing intravenous access and starting supplemental oxygen in patients who are hypoxic or who show signs of respiratory distress. Simultaneously, an ECG must be interpreted, a targeted history and physical exam taken, and cardiac biomarkers measured. Preferred cardiac biomarkers include troponin I or T and CK-MB. Total CK (without MB) should not be used to evaluate an ACS (class III recommendation).

The primary management focus during an ACS, while antithrombotic and anti-ischemic medicines are administered (Table 40.2), is to determine a patient's suitability for early invasive therapy versus conservative therapy. While fibrinolytic therapy plays an invaluable role in STEMI patients, it should not be used for the management of UA/NSTEMI unstable coronary syndromes (class III recommendation).

TABLE
40.2 Class I Anti-ischemic Recommendations

Bed rest with continuous ECG monitoring
Supplemental oxygen to keep SaO_2 > 90%
NTG (SL X 3, IV for ongoing ischemia, heart failure, hypertension)
Oral beta-blockers within 24 h for patients without HF, low-output state, risk of cardiogenic shock, markedly prolonged PR interval, second- or third-degree heart block, or severe asthma[a,b]
IABP for refractory ischemia or hemodynamic instability
ACE-I in first 24 h for heart failure or LV dysfunction (EF < 40%) after MI[c]
ARBs for those with ACE-I intolerance
Discontinuation of nonsteroidal anti-inflammatory drugs (NSAIDs)
Aspirin (continued indefinitely)[d]
Clopidogrel (loading followed by maintenance dose)[c]
The listed therapies are indicated for ongoing ischemia.

[a]Intravenous beta-blockers class IIa.

[b]Nondihydropyridine calcium channel blockers may be used when beta-blockers are not successful, or there is a contraindication to their use.

[c]ACE-I are continued when ischemia is controlled, especially for LV dysfunction or diabetes.

[d]Clopidogrel can be substituted in patients who cannot take aspirin due to hypersensitivity or major gastrointestinal intolerance.

[e]Prasugrel can be substituted if planning for PCI with risk of bleeding is low and CABG considered unlikely—class IIb recommendation.

From Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol. 2007;50(7):e1–e157, with permission from Elsevier.

Invasive Therapy

Early trials failed to show a benefit from an invasive approach in UA/NSTEMI patients. A meta-analysis performed in the current PCI era analyzed all available studies that randomized patients to early invasive therapy versus conservative management. In those studies, patients who were treated conservatively could have an angiogram performed if they had recurrent chest pain, ischemic ECG changes, a large reversible defect with noninvasive stress testing, or elevated cardiac biomarkers. Only contemporary trials that used glycoprotein (GP) IIb/IIIa inhibitors and intracoronary stents were included. Five studies, involving nearly 7,000 UA/NSTEMI patients, were analyzed. This analysis revealed a 6- to 12-month survival advantage from early invasive therapy compared to conservative management (RR = 0.80, 95% CI 0.63 to 1.03). In contrast, studies that enrolled patients before the routine use of stents and GP IIb/IIIa inhibitors revealed a harmful association from early invasive therapy (RR 1.31, 95% CI 0.98 to 1.75).

The most contemporary large-scale data on this topic derive from the Invasive versus Conservative Treatment in Unstable coronary Syndromes (ICTUS) trial, which randomized 1,200 UA/NSTEMI patients to routine invasive or selective invasive management. Patients in the selective invasive arm were treated medically and only in cases of refractory angina or a positive exercise stress test underwent coronary angiography with or without revascularization. Results at the end of 1 year and after 3 years follow-up showed there was no significant difference in the composite ischemic end point. The investigators postulate that due to the high rate of revascularization in the selective invasive therapy arm (47%), use of aggressive medical therapy in both arms (including routine use of clopidogrel in the conservative arm) and low event rate, there was little incremental benefit to be observed with an early invasive strategy. Given the results of ICTUS, the ACC/AHA guidelines recognize that an initially conservative (selective invasive) strategy may be considered as a treatment option in stabilized UA/NSTEMI patients.

Earlier trials comparing early invasive versus conservative management include third randomized intervention treatment of angina (RITA-3) and FRagmin and fast

revascularization during InStability in Coronary artery disease (FRISC II). In the RITA-3 trial, 1,810 UA/NSTEMI patients were randomized to interventional versus conservative treatment. Like ICTUS, at 1 year, death and MI rates were similar, but at 5 years, a significant reduction in death or MI emerged in the early invasive treatment arm. Benefits were seen mainly in high-risk patients. Similarly, an invasive strategy was favored at 5 years in the FRISC II trial for the primary end point of death or nonfatal MI (HR 0.81, $p = 0.009$). Here, the benefit was confined to males, nonsmokers, and patients with two or more cardiac risk factors.

A meta-analysis of seven randomized trials of management strategies in UA/NSTEMI, including ICTUS, supports the long-term benefit of an early invasive strategy. Among 8,375 patients, the incidence of all-cause mortality at 2 years was 4.9% in the early invasive group compared with 6.5% in the conservative groups (RR 0.75, 95% CI 0.63 to 0.90, $p = 0.001$), while also showing a significant reduction in nonfatal MI and hospitalization

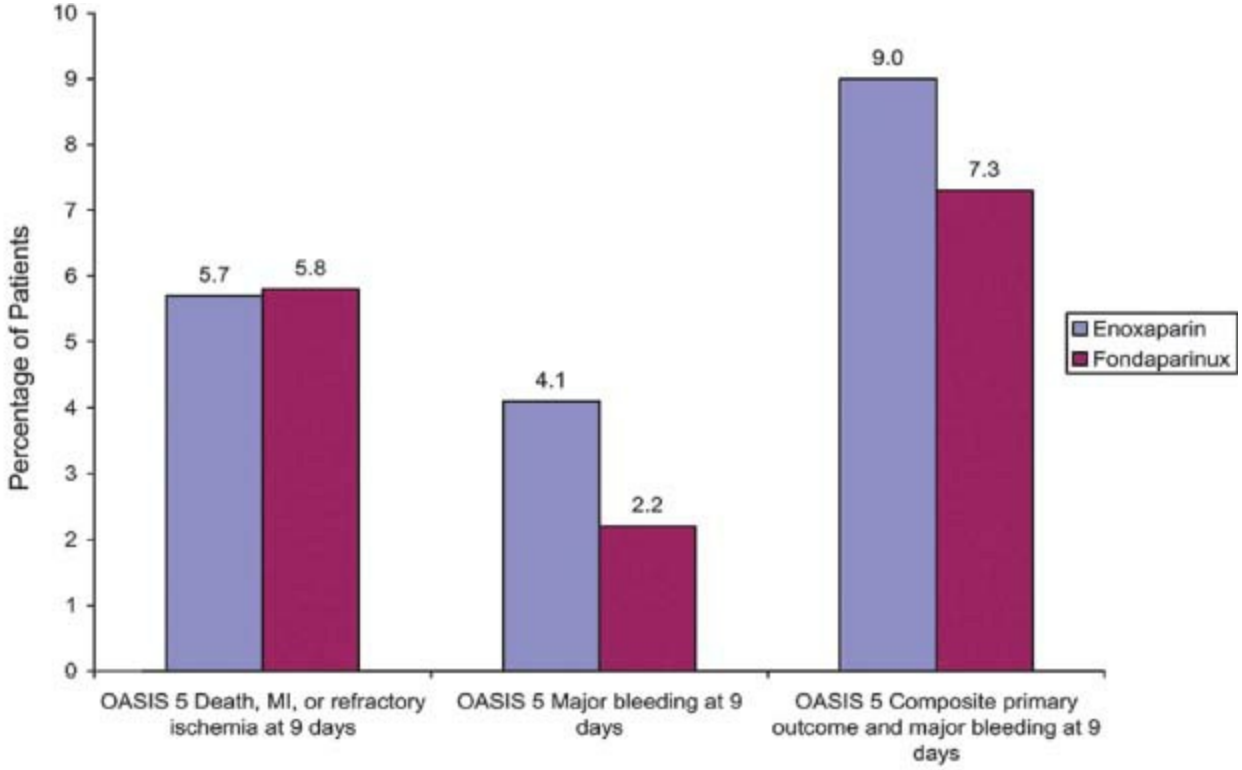
Data from the ABOARD, TIMACS, and ISAR-COOL studies helped to determine the optimal timing of the invasive strategy. These three trials, taken together with earlier studies, do provide support for a strategy of early angiography and intervention to reduce ischemic complications in patients who have been selected for an initial invasive strategy, particularly among those at high risk (defined by GRACE score >140), whereas a more delayed approach is reasonable in low- to intermediate-risk patients. The "early" time period in this context is considered to be within the first 24 hours after hospital presentation, although there is no evidence that incremental benefit is derived by angiography and intervention performed within the first few hours of hospital admission. The advantage of early intervention was achieved in the context of intensive background antithrombotic therapy.

Therefore, current ACC/AHA guidelines recommend (class I) an early invasive approach to patients with angina in the presence of heart failure symptoms (pulmonary edema, an S_3 gallop, or new mitral regurgitation), known left ventricular dysfunction, hemodynamic instability, positive noninvasive stress test (large area of ischemia), sustained ventricular tachycardia, or prior revascularization (prior coronary artery bypass grafting [CABG], or PCI within the last 6 months). The updated guidelines additionally recommend that individuals with rest angina despite intensive anti-ischemic therapy or with new ST depressions or elevated cardiac biomarkers be directed to early invasive therapy. Routine invasive therapy is discouraged in low-risk patients and those with extensive comorbidities (class III recommendation).

Intermediate-risk patients can initially be treated by either an early invasive or a conservative approach with careful monitoring for the development of high-risk features. High-risk features include refractory pain, angina with dynamic ECG changes, or elevated cardiac biomarkers. Such a change in clinical status should advance therapy to a more invasive approach along with adjunctive GP IIb/IIIa inhibitor use.

Low-risk patients can often be treated as outpatients or screened for MI with serial cardiac enzymes in a chest pain unit with a goal of early discharge. Invasive therapy is discouraged in these patients. Risk-factor modification is emphasized to all patients regardless of their risk at presentation.

Once the decision is made to perform coronary angiography, the patient's suitability for coronary revascularization is determined. Two options for revascularization are PCI (i.e., percutaneous transluminal coronary angioplasty [PTCA] and intracoronary stents) or CABG. The choice of which revascularization to perform is beyond the scope of this chapter, although several general guidelines exist. Severe left main trunk disease is usually an indication for CABG, although left main PCI can be performed in select cases (i.e., the patient is not a candidate for open heart surgery). Severe three-vessel disease or severe two-vessel disease involving the left anterior descending artery, along with left ventricular dysfunction or diabetes, also favor CABG (Fig. 40.2).



OASIS 5 (424)			
Absolute Risk Reduction	-0.1	1.9	1.7
Hazard Ratio	1.01	0.52	0.81
95% CI	0.90 to 1.13	0.44 to 0.61	0.73 to 0.89
p	0.007*	less than 0.001†	less than 0.001†

FIGURE 40.2 Revascularization strategy in UA/NSTEMI. *There is conflicting information about these patients. Most consider CABG to be preferable to PCI. CABG, coronary artery bypass graft; LAD, left anterior descending coronary artery; PCI, percutaneous coronary intervention; UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction. (From Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American

College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol. 2007;50(7):e1–e157, with permission from Elsevier.)

Antiplatelet Agents

Aspirin

Aspirin is the cornerstone of treatment for all unstable coronary syndromes unless there is a serious contraindication to its use (class I recommendation). Aspirin blocks the conversion of arachidonic acid to thromboxane A_2 by irreversibly acetylating cyclooxygenase (Fig. 40.3). Full-dose aspirin exerts maximal antiplatelet effects within 30 minutes of absorption; therefore an initial 325 mg of aspirin orally (or by rectal suppository if necessary) is given during an ACS (see Table 40.2). Low-dose aspirin (75 to 150 mg daily) is effective in primary prevention by reducing the incidence of MI. Optimal dosing of aspirin has been debated for some time, and the recently published CURRENT-OASIS 7 trial demonstrated no difference in outcome between patients treated with low-dose and high-dose aspirin, in all patients and in the PCI subgroup. This indicates that either dose can be used provided a 300-mg loading dose is used before initiation of a maintenance dose. There was an increase in minor bleeding events with high-dose aspirin, and therefore lower doses of aspirin should be used unless there is concern for recurrent ischemia. In secondary prevention, aspirin improves survival. Bleeding complications increase with increasing dosage; therefore ongoing aspirin therapy is typically an 81-mg tablet daily unless there is a compelling reason for using a higher dosage, such as mitigating the cutaneous side effects of niacin.

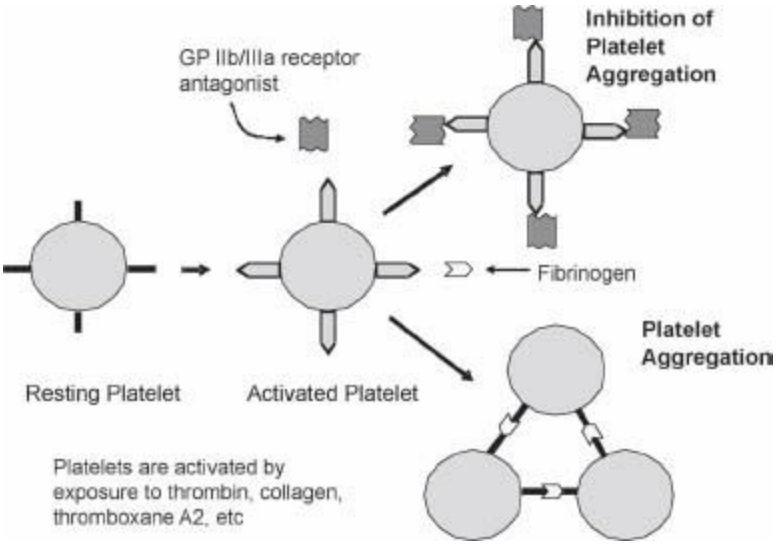


FIGURE 40.3 Schema for platelet aggregation and inhibition of platelet aggregation by GP Iib/IIIa inhibitors. Platelets are activated by adenosine diphosphate, thrombin, epinephrine, collagen, and thromboxane A2. Aspirin blocks the conversion of arachidonic acid to thromboxane A2. Clopidogrel blocks adenosine diphosphate-mediated platelet activation. GP IIb/IIIa inhibitors cause a conformational change in the GP IIib/IIIa receptor that prevents fibrinogenmediated platelet aggregation. (From Yeghiazarians Y, Braunstein JB, Askari A, Stone PH. Unstable angina pectoris. N Engl J Med. 2000;342:101-114, with permission from the Massachusetts Medical Society.)

Thienopyridines and ADP Inhibitors

Despite aspirin's proven benefit in reducing MI and death, it does not fully block platelet aggregation, especially when aggregation is induced by adenosine diphosphate (ADP). Other agents such as thienopyridines play a valuable role in the management of UA/NSTEMI patients because they complement the actions of aspirin. Thienopyridines are represented by ticlopidine, clopidogrel, and prasugrel. These agents act by inhibiting ADP receptor–mediated platelet activation. Ticagrelor has also recently been approved for use in the United States. In contrast to the other thienopyridines, ticagrelor has a binding site different from ADP, making it an allosteric antagonist, and the blockage is reversible. Newer agents, cangrelor and elinogrel, which are direct inhibitors of the ADP receptor P2Y12, are also on the horizon. Thienopyridines may be used alone if a patient has a hypersensitivity to aspirin, but they are ideally used adjunctively with aspirin. Clopidogrel is preferred over ticlopidine, given its lower incidence of neutropenia and thrombocytopenia and its rapid onset of action. A loading dose of 300 to 600 mg of clopidogrel produces maximal antiplatelet effects in 4 to 6 hours. The important studies that document the benefit of clopidogrel in unstable coronary syndromes are the CAPRIE and CURE trials.

The CAPRIE trial randomized over 19,000 vascular disease patients to receive aspirin or clopidogrel. Vascular disease was manifested as a history of ischemic stroke, MI, or symptomatic peripheral arterial disease. After nearly 2 years of follow-up, clopidogrel reduced a composite endpoint of ischemic stroke, MI, or death from vascular causes (5.3% vs. 5.8%, $p = 0.04$).

The CURE trial tested protection from ischemic events beyond that of aspirin by the addition of clopidogrel to aspirin and standard medical therapy in patients with ACS. This trial randomized over 12,000 non–ST-elevation ACS patients within 24 hours of their onset of chest pain to clopidogrel plus aspirin versus aspirin alone. Patients were eligible if they had ischemic ECG changes or elevated cardiac biomarkers. Individuals who were randomized to clopidogrel received a loading dose of 300 mg, followed by 75 mg/d for 3 to 12 months. Aspirin could be given at a dose of 75 to 325 mg/d. This was largely a conservatively treated population, as <50% of the patients underwent angiography. Among enrolled patients, <20% underwent CABG, and <25% had percutaneous coronary revascularization. Also, <10% of individuals were treated with a GP IIb/IIIa inhibitor in addition to the other antithrombotic agents. The mean duration

of treatment with clopidogrel was 9 months. A composite of cardiac outcomes was significantly reduced at 30 days (RR = 0.79, 95% CI 0.67 to 0.92) and 1 year by the regimen of clopidogrel plus aspirin versus aspirin alone (RR = 0.8, 95% CI 0.72 to 0.9, $p < 0.001$). There were trends toward reduction in each of the individual components, with the most effect on MI. The primary outcome was reduced across a range of patients regardless of whether or not they were revascularized.

Important safety data also came from the CURE trial. Major bleeding was significantly increased by the use of clopidogrel, although this did not include hemorrhagic strokes. Patients who had clopidogrel discontinued more than 5 days before CABG did not have an increase in major postoperative bleeding, while individuals whose clopidogrel was stopped within 5 days of CABG appeared to have an increase in major bleeding (9.6% in clopidogrel vs. 6.3% in placebo, RR 1.53, $p = 0.06$). Additionally, patients on clopidogrel who were treated with high-dose aspirin (325 mg/d) suffered more bleeding than individuals on approximately 81 mg/d.

The recent CURRENT-OASIS 7 trial examined dosing strategies of aspirin and clopidogrel, and determined equivalent short-term efficacy with both low and high-dose aspirin. Double-dose clopidogrel for 6 days (after a 600 mg loading dose) was associated with a significant reduction in both the primary endpoint (30 day mortality, MI, or stroke) (0.7 vs. 1.3%; HR = 0.54, 95% CI 0.39 to 0.74, $p = 0.0001$) and the secondary outcome of stent thrombosis (1.6% vs. 2.3%; HR = 0.68; 95% CI, 0.55 to 0.85; $p = 0.001$) among the 17,263 patients who underwent PCI.

Prasugrel is another drug in the thienopyridine class, and it is metabolized by the intestine and liver into its active metabolite. It is nearly completely converted to the active metabolite rapidly after ingestion and therefore inhibits ADP-induced platelet aggregation more rapidly, more consistently, and to a greater extent than do standard and higher doses of clopidogrel. The clinical benefit of this intense platelet inhibition with prasugrel was demonstrated in the TRITON-TIMI 38 study. This randomized trial compared clopidogrel and prasugrel, in addition to aspirin, in 13,608 patients with ACSs scheduled to undergo PCI. There was a significant reduction in the composite endpoint of cardiovascular death, myocardial infraction, or stroke in patients who received prasugrel versus clopidogrel (9.9% vs. 12.1%, $p < 0.001$) over 15 months. This decrease in cardiovascular outcomes was associated with a higher risk of bleeding, both TIMI major (2.4% vs. 1.8%, $p = 0.03$) and life-threatening bleeding (1.4% vs. 0.9%, $p = 0.01$). The increase in bleeding was particularly marked in certain subgroups, including patients >75 years old, patients with history of transient ischemic attack (TIA) or stroke, and those with body weight <60 kg. For this reason caution should be taken in older patients and those with low body weight, and is contraindicated in those with prior TIA or stroke. Prasugrel was also associated with a particular benefit in diabetic patients.

Clopidogrel should be considered in addition to aspirin (or alone when there is

hypersensitivity to aspirin) for all UA/NSTEMI patients when PCI is planned or for those managed conservatively (class I recommendation) (see Table 40.2). Patients with UA/NSTEMI at medium/high risk should receive dual-antiplatelet therapy on presentation. The decision on which adjunctive medication to use depends on whether it is being started before PCI (then choose clopidogrel or a GP IIb/IIIa inhibitor) or at the time of PCI (then choose clopidogrel, prasugrel, or a GP IIb/IIIa inhibitor). Prasugrel may be considered for administration on presentation, but only if PCI is planned and the perceived need for CABG is low (class IIb recommendation).

Duration of therapy with either clopidogrel or prasugrel is at least 1 month and ideally 1 year or longer. Those patients in whom a stent is placed should be treated with dual antiplatelet therapy for at least 1 month (with bare metal stents) and ideally at least 1 year (with drug-eluting stents). An important caveat with clopidogrel and prasugrel is that they likely increase the risk for major bleeding during surgery and so they should be held for at least 5 days before cardiac surgery is performed. For this reason, clopidogrel or prasugrel is often first administered on the catheterization table (loading dose) after coronary anatomy is defined and it is clear that cardiac surgery will not be required. A loading dose of clopidogrel is 300 to 600 mg, followed by a daily dose of 75 mg. A loading dose of prasugrel is 60 mg, and a daily dose is 10 mg daily. When a significant aspirin allergy exists, clopidogrel should be used in its place (class I recommendation).

Ticagrelor is a reversible nonthienopyridine direct P2Y12 receptor antagonist, and unlike clopidogrel and prasugrel, does not require metabolic activation. The platelet inhibition and patient outcomes (PLATO) study in mid-2009 found that ticagrelor reduced the incidence of the composite ischemic endpoint compared with clopidogrel (9.8% vs. 11.7%, $p < 0.001$) when used in addition to aspirin in patients with ACS. Patients given ticagrelor were less likely to die from vascular causes, heart attack, or stroke. Unlike the experience with the nonreversible prasugrel, ticagrelor therapy was associated with little increase in bleeding complications. This agent was recently approved by the United States Food and Drug Administration, but optimal time to discontinue before CABG is still under review.

Overall, ADP inhibition with thienopyridines adds to aspirin in protecting patients against ischemic events. This benefit is tempered by an increased risk of bleeding. More inhibition of ADP receptors (with higher doses of clopidogrel, prasugrel, or ticagrelor) produces better inhibition of ischemic endpoints, but the risk–benefit ratio becomes narrower with nonreversible intense agents like prasugrel. Ticagrelor may be a nearly optimal combination with aspirin, as it provides the benefit of more intense inhibition without a substantial excess of bleeding complications.

Glycoprotein IIb/IIIa Inhibitors

GP IIb/IIIa inhibitors have been shown to be effective in the management of high-risk UA/NSTEMI patients managed by early invasive therapy, particularly those who undergo PCI. GP IIb/IIIa inhibitors further complement the actions of aspirin and clopidogrel by blocking the final pathway involved in platelet activation and aggregation. Medicines in this class include eptifibatide, abciximab, and tirofiban. In individuals for whom an invasive strategy is planned, the use of a GP IIb/IIIa inhibitor reduces mortality and MI rates, albeit with an increased risk of bleeding. Accordingly, it is a class I recommendation to use a GP IIb/IIIa inhibitor as one of the potential second antiplatelet therapies that can be administered on presentation in high-risk UA/NSTEMI patients.

This information comes principally from studies that were performed prior to the widespread use of dual antiplatelet therapy with aspirin and thienopyridines. Therefore, more contemporary trials were performed to determine the use of GP IIb/IIIa inhibitors as a third antiplatelet therapy.

Prior to the widespread use of dual antiplatelet therapy with oral thienopyridines, there was more "upstream" (upon presentation and prior to angiography) use of GP IIb/IIIa inhibitors. In the more contemporary era, the EARLY ACS trial tested a strategy of routine upstream usage of eptifibatide versus delayed provisional usage in 9,492 UA/NSTEMI patients. "Upfront" clopidogrel was used in 70% of patients. The primary composite endpoint of death, MI, need for urgent revascularization or thrombotic bailout were similar between the groups, but routine upstream usage of eptifibatide was associated with increased risk of TIMI major bleeding (2.6% vs. 1.8%, $p = 0.02$).

Further evidence supporting a more selective usage of GP IIb/IIIa inhibitors comes from the ACUITY trial. Patients with moderate- or high-risk unstable coronary syndromes were randomized to receive adjunctive anticoagulation with strategies including heparin, bivalirudin, or GP IIb/IIIa inhibitors. Clopidogrel was used in 63% of patients before angiography. Patients within either of the two strategies using GP IIb/IIIa inhibitors were further randomized to routine upstream administration (upon randomization) versus deferred selective usage (in the cardiac catheterization laboratory at the time of PCI). Results again showed similar rates of ischemic endpoints with more bleeding in the routine upstream usage groups (6.1% vs. 4.9%, $p < 0.001$). See "Direct Thrombin Inhibitors" for further discussion of the ACUITY trial as it relates to bivalirudin.

The benefits of GP IIb/IIIa inhibitors in patients during (as compared with prior to) PCI were confirmed in the ISAR-REACT 2 trial. 2,022 patients with UA/NSTEMI who had been treated with a 600 mg clopidogrel bolus previously were randomized to receive abciximab versus placebo (and additional heparin) at the time of PCI. Patients who received abciximab had a reduced rate of the composite endpoint of death, MI, or urgent revascularization at 30 days (8.9% vs. 11.9%, $p < 0.05$). There were also reduced rates of the individual outcomes, with no difference in bleeding outcomes.

These studies highlight the benefit of GP IIb/IIIa inhibitors, especially in those undergoing PCI. Early upstream usage of GP IIb/IIIa inhibitors is associated with more bleeding risk than a delayed provisional approach, and should only be used when the risk–benefit ratio is appropriate. Routine use of GP IIb/IIIa inhibitors in addition to dual antiplatelet therapy should therefore be reserved for patients at particularly high risk for ischemic complications or with recurrent or refractory symptoms.

Antithrombin Therapy

Unfractionated Heparin and Low-Molecular-Weight Heparin

Heparins have been used in the management of coronary syndromes and during PCI for the last several decades. Unfractionated heparin is a glycosaminoglycan composed of polysaccharide chains which inhibit platelet aggregation and fibrin formation by causing a conformational change in antithrombin III that inhibits the activity of thrombin (factor IIa) and factor Xa. Low-molecular-weight heparins are easy to administer and do not require monitoring, and the various low-molecular-weight heparins have different ratios of anti-Xa to IIa.

Heparin and aspirin reduce death and MI in non–ST-elevation ACSs compared to treatment with aspirin alone. Therapy with unfractionated heparin is a class I recommendation in the care of intermediate- or higher-risk ACS patients. Low-molecular-weight heparin may have marginal benefit over unfractionated heparin in conservatively treated patients, and can be considered in patients who do not have renal insufficiency or when surgical revascularization is not planned within 24 hours (class IIa recommendation). For invasively treated patients, there is no clear advantage of low-molecular-weight heparin over unfractionated heparin, and institutional preference should govern the choice of a particular agent.

The dose of unfractionated heparin in conservatively treated patients is 80 U/kg bolus followed by 18 U/kg/h infusion. Heparin dosage is lowered if a patient will be managed invasively with a GP IIb/IIIa inhibitor and will be at higher risk for bleeding. The heparin dose in this case is 60 U/kg bolus (maximum 5,000 U) followed by 12 U/kg/h infusion (maximum 1,000 U/h) for a goal partial thromboplastin time (pTT) of 45 to 65. Conservative dosing for enoxaparin is 1 mg/kg subcutaneously twice a day, while the dose used in conjunction with invasive therapy is 0.75 mg/kg subcutaneously twice a day.

The large meta-analysis on GP IIb/IIIa inhibition in the setting of PCI revealed an increase in major bleeding when heparin was continued after PCI, although major adverse cardiac outcomes (MI, stroke, urgent revascularization) were not increased by stopping heparin at the time of completion of PCI. Accordingly, heparin or coumadin should not be continued post-PCI, unless there is a specific indication for their use. The routine use of coumadin in stabilized UA/NSTEMI patients is a class IIb

recommendation. An indication for continuing antithrombin therapy after PCI would be a patient with atrial fibrillation or a mechanical valve. The optimal duration of heparin in conservatively treated patients is unknown, although if patients are asymptomatic, the duration of heparin therapy usually should not exceed 48 hours. If conservatively treated patients continue to have signs of ischemia, then longer duration of heparin therapy may be indicated.

Direct Thrombin Inhibitors

In contrast to heparins, direct thrombin inhibitors (DTIs) block only factor IIa via a mechanism that does not require the action of antithrombin III. These agents overcome important limitations of heparin, including unpredictable pharmacokinetics, increased bleeding, and the potential to cause heparin-induced thrombocytopenia (HIT). Representative agents in this class of medicines include hirudin, argatroban, and bivalirudin. Older studies suggested improved cardiac outcomes and reduced bleeding risk with bivalirudin, although an increased risk of major bleeding with hirudin.

The REPLACE-2 trial expanded on these findings by examining the role of bivalirudin during contemporary PCI. Although the patients in this trial were relatively stable, some lower-risk UA patients were enrolled. This trial documented the noninferiority of bivalirudin and a provisional GP IIb/IIIa inhibitor (in ~5% of patients) compared to unfractionated heparin and a planned GP IIb/IIIa inhibitor. Additionally, bivalirudin was shown to significantly reduce the risk for major bleeding (2.4% in the bivalirudin group vs. 4.1% in the heparin group, $p < 0.001$).

In the ACUITY trial, 13,819 patients with UA/NSTEMI were randomized to one of three strategies: heparin plus GP IIb/IIIa inhibitor, bivalirudin plus GP IIb/IIIa inhibitor, or bivalirudin alone. The groups with bivalirudin plus GP IIb/IIIa inhibitor and heparin plus GP IIb/IIIa inhibitor had similar outcomes. Importantly, though, bivalirudin alone, in comparison to heparin plus GP IIb/IIIa, was associated with similar cardiac ischemic outcomes, but significantly reduced rates of major bleeding (3.0% vs. 5.7%; $p < 0.001$). These results have led to an increase in the usage of bivalirudin as alternative antithrombotic to heparin plus GP IIb/IIIa during PCI.

These trials highlight the utility of bivalirudin across in patients at different levels of risk, and confirm that it provides equal protection against ischemic events, with a significantly reduced risk of bleeding, as does heparin plus GP IIb/IIIa inhibition. Therefore, in patients with UA/NSTEMI in whom PCI is planned as a postangiography management strategy, it is a class IIa recommendation to administer bivalirudin instead of GP IIB/IIIa inhibitors. This is particularly true for patients at high bleeding risk.

Anti-Ischemic Agents

Regardless of whether a patient will be directed to an early invasive approach versus a

conservative approach, anti-ischemic medications are a priority. Nitroglycerin and beta-blockers are the first-line agents to consider (see Table 40.2). Nitroglycerin is initiated by a 0.4-mg sublingual tablet (repeated several times every 5 minutes if symptoms persist and hypotension does not develop), followed by intravenous infusion started at 10 to 20 μg/min (titrated up until resolution of symptoms or hypotension develops). An intravenous dose of 200 μg/min is considered a ceiling, although doses as high as 400 μg/min are occasionally used if needed. Sildenafil use within 24 hours of presentation is a class III recommendation to the use of nitroglycerin.

Beta-blockers are administered along with nitroglycerin and help to blunt the reflex tachycardia that may occur from its use. Beta-blockade is initiated intravenously (i.e., 5 mg metoprolol intravenously, repeated several times every 5 minutes), followed by oral administration (i.e., 25 mg metoprolol orally twice to three times per day and titrated up to effect) if there are no contraindications to its use. Contraindications include significant conduction abnormalities (marked first-degree AV block, or second/third-degree block), asthma, or decompensated heart failure. If beta-blockers are used at maximal dose or there are contraindications to their use, a nondihydropyridine (i.e., diltiazem or verapamil) may be considered to control symptoms. Morphine (1 to 5 mg intravenously) is also considered a class I anti-ischemic medication and is particularly helpful for anxious patients. Care must be taken, however, not to obscure symptoms and confound treatment of ongoing myocardial ischemia with excessive morphine doses.

If hemodynamics are well controlled with anti-ischemic medications (i.e., heart rate is 50 to 60 beats/min and systolic blood pressure is 90 to 100 mm Hg) but ischemia persists, an intra-aortic balloon pump (IABP) should be considered (class IIa recommendation). Hemodynamic instability is another class IIa indication for using an IABP in the management of UA/NSTEMI. In either scenario, the device is used as a bridge to coronary angiography or until stabilization occurs after invasive therapy has been performed.

Miscellaneous Agents

Angiotensin-converting enzyme inhibitors (ACE-I) should be considered in patients after an unstable coronary syndrome (class IIa recommendation) (Table 14.5). An ACE-I is usually not given in the first hours of an ACS, to ensure that the patient is hemodynamically stable. The presence of diabetes or left ventricular dysfunction strengthens the recommendation for an ACE-I after UA/NSTEMI (class I recommendation).

Early statin trials excluded ACS patients, although more recent studies have addressed this high-risk population. The PROVE IT-TIMI 22 trial randomized >4,000 patients within 10 days of an ACS to intensive lipid lowering (80 mg/d atorvastatin) versus moderate lipid lowering (40 mg/d pravastatin). The outcome was a composite of death, MI, ACS requiring rehospitalization, revascularization, and stroke. Follow-up

was 18 to 36 months, with a mean follow-up of 24 months. Atorvastatin was more effective in lowering cholesterol (median low-density lipoprotein [LDL] 62 mg/dL) than pravastatin (median LDL 95 mg/dL). The primary outcome was reached in 22% of the atorvastatin group and 26% of the pravastatin group, representing a 16% reduction in the hazard ratio (95% CI 5 to 26%, p = 0.005). Intensive lipid-lowering therapy appeared to beneficially lower the primary outcome as early as 30 days after enrollment. Both medications were well tolerated, with 23% of the atorvastatin group discontinuing therapy at 1 year because of an adverse event, compared to 21% for pravastatin (p = 0.3). Atorvastatin was associated with more elevations in liver enzymes (defined as alanine aminotransferase more than three times the upper limit of normal) (3.3% of the atorvastatin group, 1.1% of the pravastatin group).

DISCHARGE PLANNING AND NONINVASIVE STRESS TESTING

All stabilized UA/NSTEMI patients need aggressive riskfactor modification (including smoking cessation) and must have their discharge medicines reviewed. For intermediate- and low-risk patients managed conservatively (either hospitalized or observed in a chest pain unit), a noninvasive stress test provides important additional risk stratification (Table 40.3). A noninvasive stress test should be performed in intermediate-risk patients who have been free of chest pain and without heart failure symptoms for 2 to 3 days and in low-risk patients who have been free of chest pain and without heart failure symptoms for 12 to 24 hours. Patients who have an interpretable baseline ECG and are able to exercise should have an exercise ECG performed. Radionuclide or echocardiographic imaging should be used if there is a noninterpretable ECG (i.e., the presence of a left bundle branch block or left ventricular hypertrophy with repolarization changes). Patients who are unable to exercise should have a pharmacologic stress test.

TABLE
40.3 Noninvasive Risk Stratification

High risk (>3% annual mortality):
- Severe resting or exercise LV dysfunction (<35%)
- High-risk treadmill score (≤–11)
- Large stress perfusion defect (especially anterior)
- Multiple moderate stress perfusion defects
- Large fixed defect or moderate perfusion defect with LV dilatation or increased lung uptake
- Wall motion abnormalities (>2 segments) at low-dose dobutamine or low heart rate
- Extensive ischemia by stress echo

Intermediate risk (1%–3% annual mortality):
- Mild/moderate resting LV dysfunction
- Intermediate-risk treadmill score (–11 to 5)
- Moderate perfusion defect without LV dilatation or increased lung uptake
- Limited stress echo wall motion (≤2 segments) only at high-dose dobutamine

Low risk (<1% annual mortality):
- Low-risk treadmill score (≥5)
- Normal to small rest or stress perfusion defect
- Normal stress echo wall motion

From Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol. 2007',50(7):e1–e157, with permission from Elsevier.

SUMMARY

Patients with unstable coronary syndromes are a heterogeneous group that includes UA and NSTEMI. These patients have a high burden of atherothrombotic disease in other vascular beds and are at high risk for future adverse cardiac events. Risk stratification helps to guide therapy and should take place by one of several mechanisms during the initial assessment of the patient. The ECG is one simple and readily available diagnostic test that should be performed in all ACS patients that provides important prognostic information.

High-risk patients presenting with UA/NSTEMI benefit from early therapy with aspirin, heparin, and a thienopyridine or ADP inhibitor. Among patients receiving dual antiplatelet therapy with aspirin and a thienopyridine, routine use of upstream GP IIb/IIIa inhibitors is not advised, and should be used in a delayed, provisional manner. Alternatively, in patients with ACS for whom a thienopyridine is not employed prior to revascularization (i.e., in anticipation of possible need for cardiac surgery), GP IIb/IIIa inhibitors as a component of dual antiplatelet therapy are indicated. “Triple” antiplatelet therapy with aspirin, thienopyridine, and GP IIb/IIIa inhibition is best reserved for highest-risk patients or those with recurrent ischemia. Bivalirudin is useful as an adjunctive anticoagulant during PCI, with similar ischemic outcomes and

significantly reduced bleeding risks. Lowest-risk patients can be treated with aspirin and managed expeditiously in a chest pain unit or discharged home with noninvasive stress testing performed on an outpatient basis. In addition to antiplatelet and antithrombin agents, anti-ischemic agents should be used judiciously, with the goal of relieving ischemic symptoms and improving hemodynamics. Nitroglycerin and beta-blockers are first-line anti-ischemic medications, unless there is a contraindication to their use. Calcium channel blockers are considered second-line anti-ischemic agents. Intensive statin therapy and possibly an ACE-I (especially if the patient is diabetic or there is left ventricular dysfunction) should be part of the discharge regimen. Once ACS patients are risk stratified, stabilized, and possibly revascularized, discharge planning goals are centered on aggressive risk factor modification. Lower-risk patients who were not revascularized should have plans made for a future noninvasive stress test.

SUGGESTED READINGS

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QUESTIONS AND ANSWERS

Questions

1. All of the following are recommended mechanisms to decrease bleeding complications in the management of unstable coronary syndromes, except:
   a. Decreasing the maintenance dose of aspirin from 325 to 81 mg daily
   b. Stopping clopidogrel a minimum of 5 days prior to a major surgical procedure
   c. Stopping the routine use of heparin after percutaneous coronary intervention
   d. Withholding the loading dose of clopidogrel
   e. Reducing the dose of heparin for patients who are also on aspirin and a glycoprotein IIb/IIIa

inhibitor

2. All of the following are high-risk features of the thrombolysis in myocardial infarction (TIMI) risk score for stratifying patients with unstable coronary syndromes, except:
   a. Elevated cardiac biomarkers
   b. Age >65 years
   c. Tachycardia
   d. Ischemic electrocardiographic (ECG) changes
   e. A known coronary stenosis of more than 50%

3. All of the following therapies are class I recommendations for conservatively treated patients with unstable coronary syndromes, except:
   a. Angiotensin-converting enzyme inhibitor (ACE-I) therapy
   b. Nitrate therapy
   c. Aspirin therapy
   d. Beta-blocker therapy
   e. Clopidogrel therapy

4. All of the following are class III recommendations in: the treatment of unstable coronary syndromes, except
   a. Use of fibrinolytic therapy for non–ST-elevation acute coronary syndromes (ACSs)
   b. Use of abciximab for conservatively managed high-risk patients who continue to have ischemic symptoms
   c. The use of a low-molecular-weight heparin instead of unfractionated heparin for conservatively managed unstable coronary syndromes
   d. Use of nitroglycerin within 24 hours of sildenafil (Viagra)
   e. Invasive therapy in low-risk patients who present with a chest pain syndrome

5. Which of the following are causes of secondary angina?
   a. An anemic patient from a gastrointestinal bleed
   b. A dialysis patient with an arteriovenous fistula
   c. A dyspneic patient with underlying emphysema
   d. a and c
   e. a, b, and c

6. A 47-year-old female without known coronary artery disease (CAD) presents with two episodes of exertional angina over the past 2 weeks, and one episode of rest angina. Her cardiac risk factors include hypertension (HTN) and hyperlipidemia. Her examination and ECG are normal. Her troponin is negative.
   What is the most appropriate course of action?
   a. Discharge home with follow-up in 7 days.
   b. Immediate stress echocardiography
   c. Observe with serial cardiac biomarkers, with exercise testing before discharge.
   d. Proceed with coronary angiography and percutaneous coronary intervention (PCI) if indicated.

7. An 87-year-old male without known CAD presents with several anginal episodes at rest. ECG and examination are normal. Troponin is slightly elevated at 0.10. After discussion with the patient, you decide on an initial conservative approach. His hemoglobin is normal and his serum creatinine is 2.8 mg/dL. Which of the following is the most appropriate antiplatelet and anticoagulant strategy?
   a. ASA, clopidogrel, LMWH
   b. ASA, fondaparinux
   c. ASA, clopidogrel, UFH
   d. ASA, abciximab

8. Which of the following is an absolute contraindication to the use of prasugrel in a patient presenting

with ACS?

a. Systemic HTN with BP >160/100
b. Prior history of transient ischemic attack (TIA) or cerebrovascular accident (CVA)
c. Concomitant use of glycoprotein IIb/IIIa inhibitor
d. Weight < 60 kg
e. Age >75 years old

9. Which of the following is the most common cause of unstable angina (UA)?

a. Plaque rupture and thrombosis
b. Secondary causes (i.e., HTN)
c. Coronary vasospasm
d. Embolization of thrombus

Answers

1. Answer D: When clopidogrel is used for either invasively or conservatively managed unstable coronary syndromes, a loading dose of 300 to 600 mg should be used. Giving 75 mg of clopidogrel daily without a loading dose would require up to 7 days to reach full antiplatelet effect. All of the other listed strategies may be effective in reducing bleeding complications.

2. Answer C: Although tachycardia (and hypotension) have been identified through the PURSUIT trial to be markers of high risk, they are not part of the formal TIMI risk model. All the other variables are components of the TIMI risk score.

3. Answer A: All of the listed therapies are class I recommendations for stabilized patients with unstable coronary syndromes except ACE-I, which are a class IIa recommendation. ACE-I are strengthened to a class I recommendation if patients have diabetes or left ventricular dysfunction. Clopidogrel is a class I recommendation for both invasive and conservatively managed patients with unstable coronary syndromes.

4. Answer C: There may be a marginal benefit of low-molecular-weight heparin over unfractionated heparin for conservatively managed patients, and this strategy is a class IIa recommendation. Nitroglycerin should not be used within 24 hours from the last dose of sildenafil. Fibrinolytics should only be used for ST-elevation myocardial infarctions (STEMIs). Ideally, high-risk patients should be managed invasively, but for high-risk individuals who defer invasive therapy or who have extensive comorbidities and continue to have ischemic symptoms, the use of a glycoprotein IIb/IIIa inhibitor is a class IIa recommendation. However, eptifibatide or tirofiban should be used in this setting, while abciximab should be used only during invasive management.

5. Answer E: Anemia, arteriovenous shunting, and hypoxemia can all cause demand ischemia. Note that a left-arm arteriovenous fistula can produce shunting as well as subclavian steal in patients with a previous left internal mammary artery graft.

6. Answer C: She has UA, but class III recommendation to perform cardiac catheterization in patients with acute chest pain and low likelihood of ACS.

7. Answer C: LMWH should not be used due to the elevated creatinine. Abciximab is not indicated in early conservative strategies.

8. Answer B: Prasugrel is contraindicated in patients with prior history of TIA or CVA.

9. Answer A: Vulnerable plaques overlie lipid-rich cores that are surrounded by thin fibrous caps. Exposure of the underlying plaque to blood is a potent activator of platelets and thrombus formation

CHAPTER

Acute Myocardial Infarction

Venu Menon and Christopher M. Huff

INTRODUCTION AND EPIDEMIOLOGY OF ST-ELEVATION MYOCARDIAL INFARCTION

This chapter focuses on the diagnosis and management of ST-elevation myocardial infarction (STEMI). STEMI represents the most urgent presentation among the acute coronary syndromes (ACSs). This condition mobilizes a health care network with the aim of promptly restoring coronary perfusion in order to improve myocardial salvage and patient survival. This is a distinct clinical entity from unstable angina (UA) and non–ST-elevation myocardial infarction (NSTEMI), which were discussed in the previous chapter. In contrast to UA, which is characterized by ST depressions or T-wave inversions without elevated cardiac biomarkers, and NSTEMI, which is characterized by elevated cardiac biomarkers without ST-segment elevations, STEMI usually presents with ST elevations that are localizing in the territory of the infarcted myocardium.

Acute myocardial infarction (AMI) or onset of angina is the usual initial clinical presentation for coronary disease, although about 20% of individuals with a coronary event do not even present to the hospital. For these individuals, sudden cardiac death (SCD) due to ischemia-triggered ventricular fibrillation (VF) is the initial manifestation of symptomatic coronary disease. Unless defibrillation occurs within minutes, death ensues quickly. Fortunately, automated external defibrillators have become more available and are now found in many public places. Rates of neurologically intact survival for out-of-hospital cardiac arrest due to VF, are highly variable across the United States and are dependent on early defibrillation, effective bystander cardiopulmonary resuscitation (CPR), prompt emergency medical services (EMS) intervention, rates of revascularization, implementation of hypothermia protocols, and adequate postarrest care.

More than half a million hospital presentations per year are attributable to STEMI.

This condition is responsible for higher in-hospital mortality than UA or NSTEMI. Whereas the early management decision in UA/NSTEMI is deciding whether a patient should be directed to an early invasive approach versus conservative management, in STEMI, the focus is on rapid pharmacologic or mechanical reperfusion.

Issues such as risk stratification, fibrinolysis, primary percutaneous coronary intervention (PCI), adjunctive medical therapy, and discharge planning are discussed in the following text. A controversial issue is whether patients with suspected AMI should be directed to the nearest hospital or to a facility with cardiac catheterization and surgical capabilities. Important patient characteristics and logistical considerations are reviewed that may favor one approach over another. This chapter follows the American College of Cardiology/American Heart Association (ACC/AHA) guidelines.

CLINICAL PRESENTATION

STEMI typically presents with substernal chest discomfort that is described as a pressure or heavy sensation that lasts more than 30 minutes. Symptoms are often described as "vicelike" or "an elephant sitting on my chest." Patients may display the Levine sign by clutching their fist over their chest. STEMI is often accompanied by dyspnea, nausea, vomiting, and diaphoresis. Atypical symptoms are more common in diabetics, women, and the elderly (similar to UA/NSTEMI patients). There is a subset (~20%) of patients who have myocardial infarction (MI) in the absence of clinically recognized symptoms. Successful reperfusion is dependent on early recognition of symptoms by the patient with prompt activation of the EMS. As a goal, EMS personnel should arrive at the subject's location within 10 minutes of system activation. Unfortunately almost 40% of patients with STEMI fail to activate EMS. EMS-transported patients have significantly shorter delays in both symptom onset to arrival as well as door to reperfusion time.

DIAGNOSIS

The sine qua non for the diagnosis of STEMI is recognizing ST elevations in a typical coronary distribution or a new left bundle branch block (LBBB) in the setting of typical (or atypical) symptoms. In the NCDR ACTION registry, performance and transmission of an out-of-hospital 12-lead EKG was associated with a greater and more timely use of reperfusion therapy with a trend toward lower mortality likely because it facilitates early activation of the STEMI protocol. Waiting for cardiac biomarkers to return before making a diagnosis of AMI and initiating emergency therapy is inappropriate (class III recommendation). A brief phase before ST elevations appear is often unrecognized. This phase is characterized by hyperacute T waves in the infarct-related territory. The hyperacute electrocardiogram (ECG) findings rapidly progress to typical ST elevations.

ST elevations are usually convex or “tombstone” in appearance, although they can be concave. STEMI is diagnosed when at least 1-mm ST elevations are recognized in two or more contiguous leads. Figures 41.1 to 41.4 show various ECG examples of STEMI. Patients with STEMI in the posterior circulation can manifest with ST depression across the anterior precordial leads. In patients with initial nondiagnostic ECG findings, serial repeat EKGs are warranted.

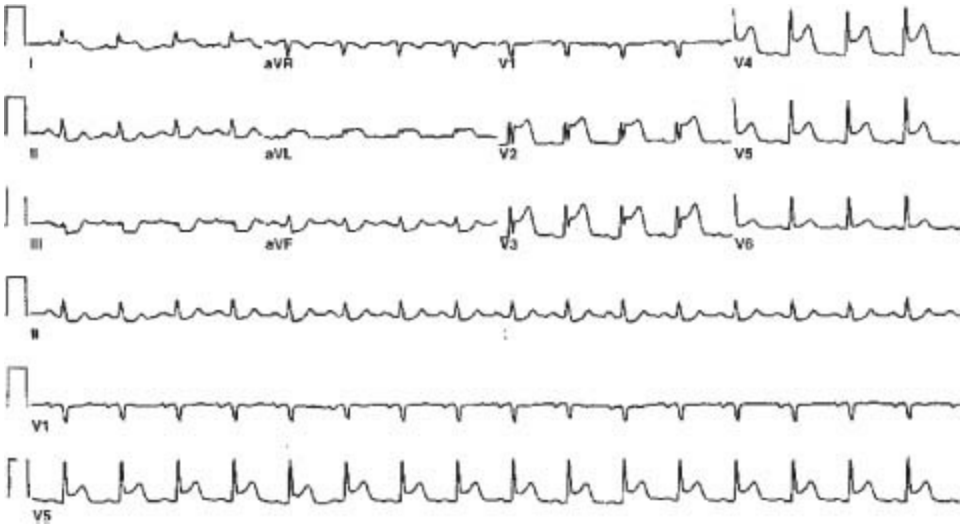

FIGURE 41.1 Anterior ST-elevartion AMI. There is also ST elevation in leads I and aVL, suggesting a left anterior descending artery occlusion proximal to a major diagonal branch.

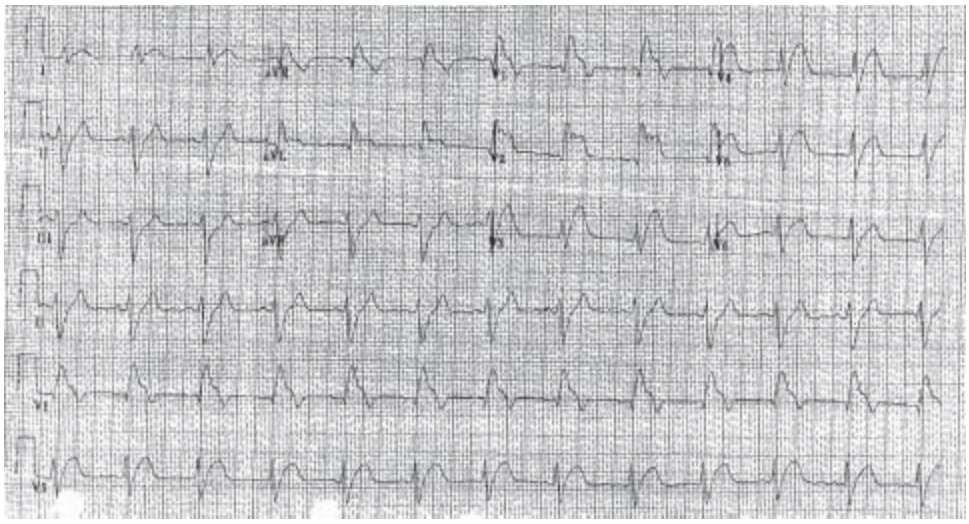

FIGURE 41.2 Anterior ST-elevation AMI. In addition to ST elevation in leads I and aVL, there is also QRS prolongation, suggesting a left anterior descending artery occlusion proximal to a major diagonal branch and a major septal perforator.

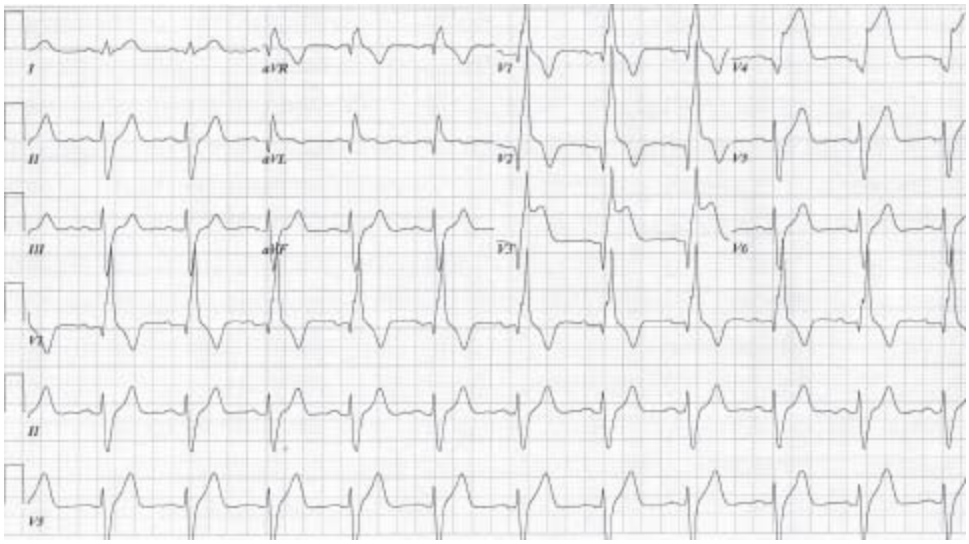

FIGURE 41.3 Anterior ST-elevation AMI in the setting of a preexisting RBBB. ST elevation is noted in leads V_3 to V_6depression and the concordance or discordance of the ST segment with the QRS.

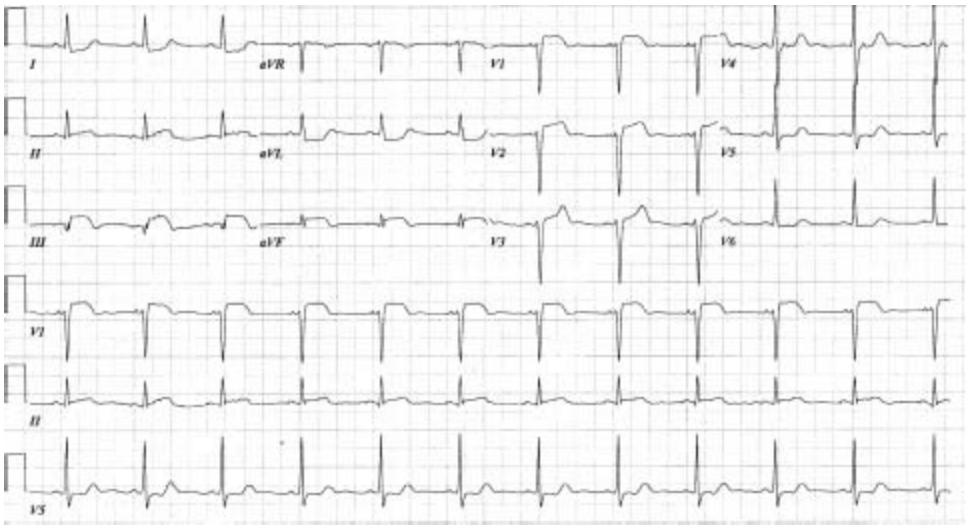

FIGURE 41.4 Inferior ST-elevation AMI. There is also ST elevation in leads V_1 to V_3, suggesting RV involvement. RV leads should also be done to confirm RV involvement (i.e., occlusion proximal to acute marginal branch).

The ECG can also help to localize the location of the coronary occlusion. For example, high lateral (i.e., I and aVL) ST elevations that accompany an anterior MI indicate a left anterior descending artery occlusion proximal to a major diagonal branch. An anterior STEMI with ST-segment elevation in lead V_1 and QRS complex prolongation indicates a left anterior descending artery occlusion proximal to a major septal perforator. Most STEMIs (70% to 80%) eventually progress into Q waves in the region of the infarcted myocardium.

Although the ECG is diagnostic in the setting of STEMI, other conditions that cause ST elevations must be simultaneously screened for and evaluated. These include acute pericarditis, hyperkalemia, left ventricular hypertrophy, early repolarization, and

ventricular aneurysm (Table 41.1).

TABLE
41.1 Differential for ST-Segment Elevation

Condition	Features
Male pattern	90% of healthy young men, most pronounced in V_2
Early repolarization	J point notching most pronounced in V_4, upright T
Left ventricular hypertrophy (LVH)	Concave, other criteria for left ventricular hypertrophy
LBBB	Concave
Acute pericarditis	Diffuse ST↑, ST↓ Avr and PR↓
Hyperkalemia	Wide QRS, peaked T, low-amplitude P, downsloping ST
Brugada syndrome	rSR′ in V_1 and V_2, downsloping ST↑ in V_1 and V_2
Pulmonary embolism	Can simulate inferior and anteroseptal AMI
Cardioversion	Pronounced transient ST↑ after DCC

From Wang K, Asinger RW, Marriott HJ. ST-segment elevation in conditions other than acute myocardial infarction. N Engl J Med. 2003;349:2128–2135, with permission from the Massachusetts Medical Society.

A posterior MI is an important STEMI equivalent. This is often seen in the setting of an inferior or inferolateral MI. The ECG findings are a tall R wave in V_1 with ST depressions in V_1 to V_2. It is critical to recognize an isolated posterior infarction as a STEMI, because patient prognosis hinges on the prompt restoration of coronary flow.

The other STEMI equivalent to consider is a new or presumably new complete LBBB. Not surprisingly, patients who present with a complete LBBB have high in-hospital mortality rates (up to 25%), in part due to the fact that they are nearly 80% less likely to receive reperfusion therapy than patients who present with recognizable ST elevations. However, even with reperfusion therapy, mortality rates are higher in patients with new complete LBBB than with ST elevation, attesting to the high-risk nature of this population. Although ischemic changes are interpretable in the context of a right bundle branch block (RBBB), this task becomes more difficult with a complete LBBB. There are criteria that can help diagnose a LBBB as an AMI with good specificity (Table 41.2), which look at the degree of ST elevation or depression and the concordance or discordance of the ST segment with the QRS.

TABLE
41.2 ECG Criteria for the Presence of AMI in the Setting of LBBB

Criterion	Score
ST elevation ≥1 mm, concordant with QRS	5
ST depression ≥1 mm, in lead V_1, V_2, or V_3	3
ST elevation ≥5 mm, discordant with QRS	2

Adapted from Sgarbossa EB, Pinski SL, Barbagelata A, et al. Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle branch block. GUSTO-1 (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) Investigators. N Engl J Med. 1996;334:481–487.

RISK STRATIFICATION

Killip Class, TIMI Risk Score, GRACE Score, ACTION-GWTG Risk Score

Since all patients with STEMI are initially eligible for reperfusion therapy, risk models are used primarily to determine prognosis and not to direct therapy as in UA/NSTEMI risk models. Initial information for risk stratification comes from the physical exam. Assessing for signs of heart failure is a useful tool for risk stratification. Patients who present with cardiogenic shock have a 30-day mortality rate of approximately 60% (Table 41.3). Cardiac biomarkers (troponin I or T and total CK and CK-MB isoenzyme) supplement the physical exam by gauging infarct size and providing additional prognostic information.

TABLE
41.3 Killip Class—30-Day Mortality

Killip Class	Characteristics	Patients (%)	Mortality (%)
I	No evidence for CHF	85	5
II	Rales, ↑ JVD, S_3	13	14
III	Pulmonary edema	1	32
IV	Cardiogenic shock	1	58

From Lee KL, Woodlief LH, Topol EJ, et al. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. GUSTO-I Investigators. Circulation. 1995;91:1659–1668, with permission from Wolters Kluwer Health.

Risk models have been created that provide clinicians with a more accurate prediction of risk. These models combine multiple variables that are most predictive for

future adverse cardiac outcomes. The thrombolysis in myocardial infarction (TIMI) risk score is an easily used and validated model that has important prognostic implications. It incorporates eight variables that are readily available from the history, physical exam, and ECG (Fig. 41.5). In a fibrinolytic treated population, a TIMI risk score of greater than eight predicts an approximately 35% incidence of death at 30 days. This is in contrast to a score of zero to one, for which the 30-day mortality rate is <2%. The strongest variable that predicts an adverse prognosis is advanced age (where age ≥75 years receives 3 points and age 65 to 74 years receives 2 points). Other variables include hypotension, tachycardia, or Killip class II to IV at presentation, history of diabetes or hypertension, low body weight, anterior ST elevation (also complete LBBB), and a time to treatment of >4 hours.

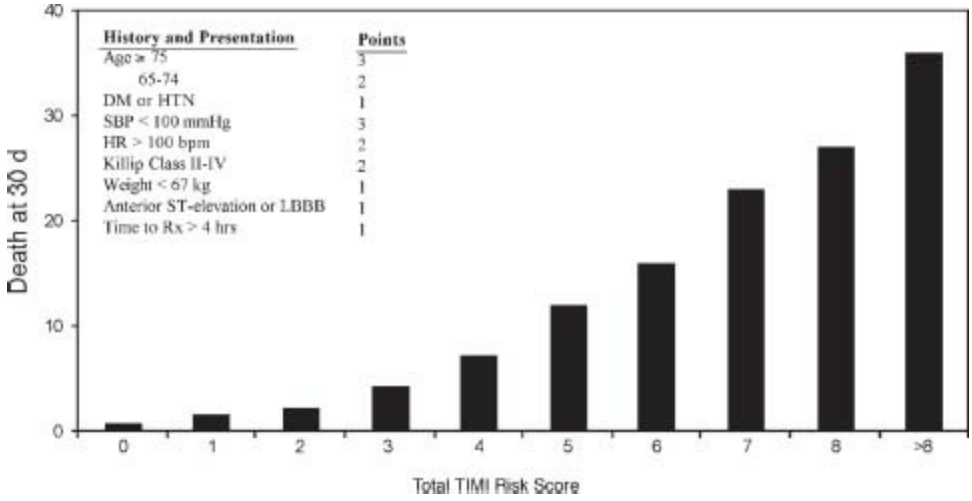

FIGURE 41.5 TIMI risk model for prediction of short-term mortality in STEMI patients. (From Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation. 2000;102:2031–2037, with permission from Wolters Kluwer Health.)

The GRACE score was designed to improve the risk prediction of in-hospital mortality in patients with ACS. It can be used in patients with ST-elevation and non–ST-elevation myocardial infarction. Risk is determined based on Killip class, systolic blood pressure, heart rate, age, creatinine level, presence or absence of cardiac arrest at admission, ST-segment deviation, and presence or absence of cardiac biomarkers. A score of ≤60 is associated with a ≤0.2% probability of in-hospital mortality whereas a score of ≥250 is associated with a ≥52% probability of in-hospital mortality.

A mortality model and risk score utilizing a contemporary set of patients is that derived from the ACTION Registry. In this validated model, patients with a risk score of <40 had an observed mortality rate of 4% compared with a 12% observed mortality rate in subjects with a score >50.

MANAGEMENT

Initial Approach

The initial assessment of a patient suspected of having an AMI is to establish intravenous access and start supplemental oxygen for individuals who are hypoxic or who show signs or respiratory distress. Simultaneously, a targeted history and physical exam should be obtained. The history and physical exam provide prognostic information, but also can suggest an alternative diagnosis and help identify mechanical complications of STEMI. It is important to rule out other causes of chest pain such as aortic dissection. Pain arising from a gall stone, renal stone, pancreatitis, esophageal dys-motility, pneumothorax, pleuritis as well as impending herpes zoster may frequently mimic this presentation.

If reperfusion with fibrinolysis is considered, the history and physical exam should screen for contraindications to its use. Because the most feared complication with the use of fibrinolytics is intracranial hemorrhage (ICH), patients with an increased risk for this complication must be identified. Risk factors for ICH are advanced age, female gender, uncontrolled hypertension, and low body weight. Patients with coagulopathies (e.g., patients on Coumadin therapy) are also at increased risk for bleeding. Absolute and relative contraindications to fibrinolysis are listed in Table 41.4.

TABLE
41.4 Contraindications to Fibrinolysis

Absolute Contraindications

Any prior intracranial hemorrhage
Known intracranial neoplasm
Active bleeding
Suspected aortic dissection
Known structural cerebral vascular lesion
Ischemic stroke within the past 3 months
Severe closed head or facial trauma within the past 3 months

Relative Contraindications

Severe hypertension on presentation (blood pressure >180/110)
History of chronic, severe, poorly controlled hypertension
History of ischemic stroke greater than 3 months before presentation, dementia, or other intracranial pathology not listed as an absolute contraindication
Traumatic or prolonged CPR (greater than 10 minutes)
Use of anticoagulation
Recent internal bleeding (within 2-4 weeks)
Pregnancy
Active peptic ulcer disease
Vascular punctures at noncompressible sites

Adapted from Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction-executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). J Am Coll Cardiol. 2004;44:671-719.

Reperfusion Therapy

Time is of paramount importance in reinstituting coronary flow. The greatest improvement on mortality comes from reperfusion within the first hour, the so-called golden hour. Reperfusion therapy can be considered up to 12 hours from the onset of chest pain and even longer in select cases. In order to facilitate rapid coronary reperfusion, a pharmacologic or mechanical approach should be decided on quickly. The current goal for door-to-lytic time is 30 minutes, whereas the goal for door-to-balloon time is 90 minutes if the patient presents to a PCI capable facility and 120 minutes if the patient requires transfer for PCI.

In general, if primary PCI can be performed immediately (i.e., the patient presents to a center capable of performing PCI), this is the preferred choice for reperfusion (class I recommendation). This information comes from a metaanalysis of 23 trials that randomized nearly 8,000 STEMI patients to fibrinolytic therapy versus primary PCI. The hospitals included in the analysis were largely experienced providers of coronary

intervention and were able to deliver mechanical reperfusion in a timely fashion, although some studies enrolled patients who were transferred for primary PCI versus given immediate fibrinolysis. This study was a contemporary analysis, as stents were used in 12 of the trials and glycoprotein (GP) IIb/IIIa inhibitors were used in eight. General inclusion criteria required that patients have ischemic symptoms within the previous 6 to 12 hours and at least 1-mm ST elevations in contiguous leads or a new/presumable new complete LBBB. Patients also needed to be candidates for fibrinolysis to be eligible for enrollment. A notable exception was the SHOCK trial, as this study enrolled patients with cardiogenic shock and chest pain within the preceding 36 hours. Since the SHOCK trial was the outlier to the overall analysis, the analysis was performed with and without this study. Most patients (76%) received fibrin-specific (i.e., t-PA) lytic agents, whereas the remainder received streptokinase. This analysis revealed a short-term survival advantage as well as a reduction in recurrent MI and hemorrhagic stroke in those who received primary PCI. Short-term mortality was 7% in the primary PCI group, compared to 9% in the fibrinolytic group ($p = 0.0002$). Long-term mortality was also significantly reduced ($p = 0.0019$). Thus, among patients who present within 12 hours of the onset of chest pain to a tertiary care center that is capable of performing primary PCI expeditiously, data supports the use of mechanical reperfusion.

When individuals present to a community hospital without primary PCI capabilities, the question becomes whether to transfer the patient to a primary PCI center or to administer immediate fibrinolysis. Fibrinolysis is limited by postlysis TIMI 3 flow of <50% at 90 minutes and risk of reocclusion, which results in inadequate myocardial salvage and heightened rates of recurrent ischemia and reinfarction. There is also a definite risk for ICH (up to 0.9% in many trials and even greater in high-risk patients). There are also numerous contraindications to consider. These limitations have led to trials that specifically addressed if delaying immediate reperfusion to allow transfer for primary PCI may be beneficial.

A subanalysis from the previously mentioned metaanalysis examined the studies that transferred patients for primary PCI versus giving immediate fibrinolytics. The mean time that was required for transfer to a primary PCI center was 39 minutes. Mortality was similar between the two groups ($p = 0.057$), although a composite outcome that included death, reinfarction, or stroke was reduced by transfer for primary PCI ($p < 0.001$).

Another meta-analysis specifically addressed this issue using available clinical trial information. This study examined only trials that randomized patients to either immediate fibrinolysis or transfer to a center capable of performing primary PCI. The inclusion criteria were similar to the previous meta-analysis: acute STEMI within 6 to 12 hours from the onset of chest pain and eligibility to receive a fibrinolytic agent. Six trials were available for analysis, involving nearly 4,000 patients. A few of these trials

deserve special comment. The AIR-PAMI study randomized patients who were high risk to one of the above reperfusion strategies. High risk was defined as age >70 years, heart rate >100 beats/min (bpm), systolic blood pressure <100 mm Hg, Killip class II/III, complete LBBB, or anterior MI. Although this was the smallest study included in the meta-analysis, there was no noticeable harm in transferring high risk patients for PCI. The CAPTIM trial was unique in that patients were randomized to a reperfusion strategy before arrival to the hospital, which enabled fibrinolytics to be given in an even more timely fashion. This was the only trial that showed a nonsignificant trend in mortality favoring fibrinolysis. The PRAGUE-2 trial examined the optimal reperfusion strategy based on time from the onset of chest pain. The study was stopped prematurely, as mortality was increased 2.5-fold among patients who presented more than 3 hours from the onset of chest pain who received fibrinolysis (15% with fibrinolysis and 6% with primary PCI, $p < 0.02$). In Patients who presented within 3 hours from the onset of chest pain, mortality was similar between the two reperfusion strategies (7.4% with fibrinolysis and 7.3% with primary PCI).

So, while transferring a STEMI patient for primary PCI versus immediately administering fibrinolysis is controversial, some patient characteristics and logistical considerations favor one approach over another. According to the 2011 ACCF/AHA/SCAI guidelines for PCI, if a patient presents with STEMI and can undergo PCI within 120 minutes of first medical contact, this is the preferred approach. Conversely, if the patient cannot receive PCI within 120 minutes of first medical contact, and there are no contraindications to fibrinolysis, fibrinolytics should be administered within 30 minutes of hospital presentation (class I recommendation). It is important to note that the effectiveness of fibrinolytics are highly time dependent with a marked efficacy when administered in the first hour following STEMI onset. Accordingly, for patients who are at high risk for bleeding or who present more than 3 hours after the onset of chest pain, transfer for primary PCI is favored. Additionally, patients who are in cardiogenic shock benefit from mechanical revascularization, but have not been shown to have a mortality reduction with fibrinolysis. Lastly, in the elderly who have an increased risk of ICH, patients with contraindications to fibrinolytics or when the diagnosis of STEMI is in doubt, PCI should be considered. When interhospital transfer for primary PCI is planned, the DIDO (door in to door out) time at the originating hospital is an important performance measure and should ideally be <30 minutes. This benchmark is associated with optimal door to balloon times and lower in-hospital mortality.

Fibrinolytic Therapy

A large body of research involving tens of thousands of patients documented the benefit of fibrinolytic therapy in reducing infarct size, preserving left ventricular function, and improving survival in AMI patients. For every 1,000 patients treated with fibrinolytics

within 1 hour of onset of symptoms, the number of lives saved is 26, while treatment within 3 to 6 hours from the onset of chest pain saves 18 lives. There is still a survival advantage from 6 to 12 hours, although it is smaller in magnitude than giving lytics closer to the onset of chest pain. Accordingly, fibrinolysis is indicated for 1 mm or more of ST elevations in contiguous leads, or a new complete LBBB within 12 hours from the onset of chest pain. Patients with stuttering infarcts may benefit from lytics up to 24 hours after the onset of chest pain. Asymptomatic patients more than 24 hours out from the onset of chest pain should not receive lytic therapy (class III recommendation).

If lytic therapy is selected, it is important to know the different agents used for fibrinolysis and which are available at a given institution. Additionally, contraindications to the use of fibrinolytics should be reviewed in every eligible patient. The choice of one agent over another is made according to hospital availability and physician experience with a given agent.

Streptokinase, a first-generation fibrinolytic agent, is capable of lysing circulating and clot-bound fibrin. Allergic reactions are common, and reexposure to streptokinase should be avoided. This is the least expensive lytic agent, at around $500 per dose. Streptokinase may not require adjunctive heparin therapy unless the patient is at high risk for emboli (i.e., atrial fibrillation or known left ventricular thrombus). Accordingly, lysis with streptokinase is associated with a slightly less ICH risk (0.5% compared to 0.7% for fibrin-specific agents). This property makes streptokinase attractive if an individual is not a candidate for PCI and is at high risk for ICH. An example would be a small, elderly, hypertensive female with a history of a remote ischemic stroke who presents with an extensive anterior MI and refuses PCI.

Fibrin-specific agents activate plasminogen directly and are relatively selective against clot-bound fibrin rather than circulating fibrinogen. Allergic reactions do not occur with these agents, as can occur with streptokinase. Fibrin-specific agents include alteplase (tPA), reteplase (rPA), and tenect-eplase (TNK-tPA). Because these fibrin-specific agents do not produce a systemically lytic state and because they activate platelets, the use of heparin therapy appears to improve and maintain vessel patency.

The GUSTO-I trial was a landmark study published in 1993 that compared streptokinase to various fibrin-specific strategies. Up until this trial there was no known advantage of one agent over another. This trial studied >40,000 patients with AMI and revealed the superiority of accelerated tPA over streptokinase. Accelerated tPA with intravenous heparin resulted in a 14% reduction in mortality and higher rates of TIMI 3 flow at 90 minutes (54% vs. 31%) compared to streptokinase-based regimens. The accelerated tPA dose is a 15-mg bolus, then 0.75 mg/kg (up to 50 mg) over 30 minutes, followed by 0.5 mg/kg over 60 minutes (up to 35 mg).

Reteplase is less fibrin-specific than alteplase. This agent is equivalent to alteplase in terms of efficacy, although it is easier to administer (two 10-mg boluses administered 30 minutes apart). Tenecteplase is the easiest lytic to administer, because it is given as

a single bolus (dose ranges from 30 to 50 mg, adjusted for body weight). See Table 41.5 for dosing. This agent is more fibrin specific and has a slower plasma clearance than the other fibrin-specific agents. The ASSENT 2 trials showed the noninferiority of tenecteplase compared to alteplase. In this trial, there was also less major bleeding with tenecteplase, and a trend toward less ICH in elderly women. Equivalent efficacy, enhanced safety, and ease of administration make tenecteplase an attractive fibrinolytic agent.

TABLE
41.5 Weight-based Dosing of Tenecteplase

Weight (kg)	Dose (mg)
<60	30
60–69	35
70–79	40
80–89	45
≥90	50

Reprinted from Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction-executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). J Am Coll Cardiol. 2004;44:671–719, with permission from Elsevier.

Percutaneous Coronary Intervention

When PCI is selected for reperfusion, eligibility criteria are the same as those used for fibrinolytics: 1 mm or more of ST elevations in contiguous leads or a new/presumably new complete LBBB within 12 hours of the onset of chest pain. A posterior MI should be treated as a STEMI equivalent. The goal of PCI is to achieve optimal revascularization of the infarct-related artery by establishing TIMI 3 flow. Multivessel revascularization at the time of primary PCI is usually not indicated (class III recommendation), except in patients with cardiogenic shock.

Several approaches to PCI exist in the setting of STEMI. Most data support the use of primary PCI. In primary PCI, fibrinolytics are not given prior to intervention. Patients either present directly to a PCI center, or they are transferred (without fibrinolysis) from a community hospital to a center capable of performing PCI. As mentioned previously, the downside in transferring a patient for primary PCI is the delay in time that is required until mechanical reperfusion can occur.

In a pharmacoinvasive strategy patients who receive fibrinolysis are transferred for early PCI regardless of reperfusion status. The TRANSFER AMI trial evaluated this strategy in high-risk STEMI patients. In TRANSFER AMI, patients who received

fibrinolysis followed by PCI within 6 hours of presentation had a 6% absolute and 46% relative reduction in the composite endpoint of death, reinfarction, recurrent ischemia, heart failure, and shock when compared with patients who received fibrinolysis followed by rescue or delayed PCI. Based on these results, patients who are high risk and receive fibrinolysis as the primary reperfusion strategy should be transferred to a PCI-capable facility as soon as possible (class IIa recommendation). Table 41.6 lists the criteria for defining high-risk patients. For low-risk patients this same management strategy is considered a class IIb recommendation.

TABLE
41.6 ACC/AHA Recommendations for Triage and Transfer for PCI: High-risk Definition

Defined in CARESS-in-AMI

1. STEMI patients with one or more of the following:
   - Extensive ST-segment elevation
   - New onset LBBB
   - Previous MI
   - Killip class > 2 or EF ≤ 35% for inferior MI
2. Anterior MI with ≥ 2 mm or more ST elevation in 2 or more leads

Defined in TRANSFER-AMI

1. ≥ 2 mm ST elevation in 2 anterior leads or ST elevation ≥ 1 mm in inferior leads with at least:
   - SBP < 100 mm Hg
   - HR > 100 bpm
   - Killip class II–III
   - ≥ 2 mm ST-segment depression in anterior leads
   - ≥ 1 mm of ST elevation in right-sided lead V_4 indicative of RV infarct

Adapted from Kushner FG, Hand M, King SB, et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update). J Am Coll Cardiol. 2009;54:2205–2241.

With facilitated PCI, all STEMI patients without a contraindication routinely receive full or half-dose fibrinolysis prior to transfer for PCI. This strategy is not favored because of negative results in the ASSENT 4 and FINESSE trials. In the ASSENT 4 trial, STEMI patients were randomized to either full-dose tenecteplase plus PCI or primary PCI with unfractionated heparin (UFH). Patients who received fibrinolysis had an increased incidence of the composite endpoint of death, cardiogenic shock, or congestive heart failure (CHF). In the FINESSE trial, STEMI patients were randomized to abciximab followed by PCI, abciximab and reteplase followed by PCI,

or primary PCI with abciximab given in the cath lab. The primary endpoint was a composite of death from all causes, VF occurring >48 hours following randomization, or cardiogenic shock and CHF within 90 days. The primary outcome did not differ between the groups, however, there was a significant increase in major and minor bleeding in the patients who received fibrinolysis. Given this, facilitated PCI is no longer recommended as a management strategy for STEMI patients.

The role of late or delayed PCI in asymptomatic individuals 12 to 24 hours after the initial event is unclear as there is a paucity of evidence. In the BRAVE 2 trial, performance of PCI in this time window was associated with a decreased infarct size on SPECT. Performance of PCI in hemodynamically stable patients with an occluded infarct artery >72 hours after the initial event is unwarranted. The OAT trial was a randomized study that enrolled patients with total occlusion of the infarct-related artery 3 to 28 days after MI. Patients were randomized to PCI with stenting and optimal medical management versus medical management alone. The primary endpoint was a composite of death, MI, and New York Heart Association (NYHA) class IV heart failure. PCI with stenting did not reduce the occurrence of death, reinfarction, or heart failure, and there was a trend toward excess reinfarction during 4 years of follow-up. Consequently, AHA recommends against PCI of an occluded infarct-related artery >24 hours after STEMI if the patient is hemodynamically stable and does not have signs of severe ischemia (class III recommendation).

Historically, STEMI patients who were selected for mechanical reperfusion underwent percutaneous transluminal coronary angioplasty (PTCA). With the advent of intracoronary stents, randomized trials were designed to determine if PCI using intracoronary stents would improve outcomes. A meta-analysis that involved nearly 3,000 patients with STEMI who were randomized to PTCA versus PCI with intracoronary stents revealed an advantage to the use of stents. This analysis documented a reduction in the composite endpoint of death, MI, and target vessel revascularization at 6 months by the use of stents (14% vs. 26%, $p < 0.0001$), a difference that was driven by a reduction in the need for target vessel revascularization. The largest trial in this analysis was the CADILLAC trial. This study showed no reduction in death or MI from the use of stents, although there was less clinical and angiographic restenosis at follow-up.

Drug-eluting stents (DES) dramatically reduce restenosis compared to bare metal stents. However, because they were not initially evaluated in patients with AMI, the use of a drug-eluting stents in this setting is considered “off-label.” Since 2005, several trials have demonstrated the benefit of drug-eluting stents in the setting of AMI. One such trial, HORIZONS-AMI, randomly assigned STEMI patients to either paclitaxel-eluting stents or bare metal stents. At 12 months, the rate of ischemia-driven target vessel revascularization was significantly lower in patients treated with paclitaxel-eluting stents. In addition, paclitaxel-eluting stents were not inferior to bare metal stents

in the rates of the combined safety endpoint of death, stroke, stent thrombosis, or reinfarction. In 2009, a meta-analysis of data from 18 registries and 13 randomized trials further supported the benefit of drug-eluting stents compared to bare metal stents in patients with STEMI. In the registries and randomized trials, drug-eluting stents significantly reduced the rate of target vessel revascularization without increasing the rate of death or MI. Accordingly, the 2011 ACCF/AHA/SCAI PCI guideline states that DES can be used as an alternative to BMS in cases where the risk of restenosis is high, as long as the patient can tolerate and comply with prolonged dual antiplatelet therapy (DAPT) (class I recommendation). Safety of DES stents, especially in the year following implantation, is closely linked to compliance with dual antiplatelet therapy. Consequently, patients who are likely to be noncompliant with dual antiplatelet therapy and those requiring an urgent noncardiac surgical intervention may benefit from placement of bare metal stents or balloon angioplasty alone.

With the success of intracoronary stents and adjunctive antiplatelet as well as antithrombotic therapy, PCI is usually successful in achieving TIMI 3 flow in the infarct-related artery in >90% of subjects. Thrombus aspiration catheters have been shown to improve ST-segment resolution and myocardial blush, and are associated with improved clinical outcomes. In the TAPAS study, patients who received aspiration thrombectomy were significantly more likely to have complete resolution of ST-segment elevation when compared with patients who underwent conventional balloon angioplasty and PCI (56.6% vs. 44.2%, $p < 0.001$). At 1 year, there was also a significant reduction in the rates of cardiac death (3.6% vs. 6.7%, $p = 0.02$) and cardiac death or nonfatal reinfarction (5.6% vs. 9.9%, $p = 0.009$). Based on current guidelines, thrombus aspiration is considered reasonable during PCI in patients with STEMI who have a high clot burden and short ischemic times.

Coronary artery bypass grafting (CABG) is still indicated for left main disease, failed PCI, or mechanical complications of infarction (e.g., myocardial rupture). Additionally, patients with three-vessel disease (or two-vessel disease that includes the proximal left anterior descending artery) in the setting of left ventricular dysfunction or diabetes may have a better clinical outcome with surgery.

Antiplatelet Agents

Just as aspirin is the cornerstone of treatment for all UA/NSTEMI patients, it is also a class I recommendation for STEMI patients (see Fig. 41.4). Aspirin is associated with a mortality benefit similar to that achieved by streptokinase. Unless there is a serious contraindication to its use, a loading dose of 162 to 325 mg of nonenteric coated aspirin is currently recommended for all STEMI patients (class I recommendation). If there is any question as to whether the patient received aspirin prior to arrival in the emergency department, another dose should be given. If the patient is vomiting, aspirin can be given by rectal suppository if necessary (at the same dose). All post-PCI STEMI patients

should receive aspirin indefinitely. Whereas previous guidelines recommended high dose aspirin for at least one month, the 2011 PCI guideline states that 81 mg of aspirin is reasonable (class IIa recommendation). When significant hypersensitivity to aspirin exists, clopidogrel should be given in its place (class I recommendation).

Thienopyridines should be used routinely in all patients with STEMI regardless of whether or not reperfusion therapy is received and should be continued for at least 1 year (class I recommendation). An important caveat with thienopyridines is the increased risk for major bleeding during surgery. It is currently recommended that clopidogrel and prasugrel be held for 5 and 7 days, respectively, prior to CABG, unless the need for urgent revascularization outweighs the risk of potential excessive bleeding (class I recommendation). In patients in whom PCI is planned, a loading dose of clopidogrel or prasugrel should be given prior to or at the time of PCI. Currently, the recommended loading dose of clopidogrel is 300 to 600 mg (class I recommendation). Although results of the CURRENT-OASIS 7 trial suggest that patients may benefit from a 600 mg clopidogrel loading dose compared to 300 mg, there is currently insufficient data to establish superior safety and efficacy of this higher loading dose. The recommended loading dose of prasugrel is 60 mg (class I recommendation).

Prasugrel is considered to be superior to clopidogrel in onset of action and potency of platelet inhibition. The TRITON-TIMI 38 investigators evaluated the efficacy and safety of prasugrel compared to clopidogrel in 13,608 patients with moderate to high-risk ACS undergoing PCI. Patients who received prasugrel had significantly fewer ischemic events, including stent thrombosis. The risk of major bleeding, including fatal hemorrhage, was higher with the use of prasugrel though overall mortality did not differ between the two groups.

Currently, the AHA/ACC guidelines do not consider one agent superior to another; however, clopidogrel is preferred in certain situations. Prasugrel is not recommended in patients with a history of transient ischemic attack (TIA) or stroke due to the risk of ICH (class III recommendation). Also, in patients who have received fibrinolysis, clopidogrel is the thienopyridine of choice. This recommendation is based on results of the CLARITY-TIMI 28 trial. This trial revealed that in STEMI patients who undergo fibrinolysis, there is a reduction in the composite endpoint of occluded infarct-related artery, death, or recurrent MI before angiography by the addition of clopidogrel to aspirin, heparin, and standard medical therapy. The recommended loading dose of clopidogrel following fibrinolysis is 300 mg if given within 24 hours of fibrinolysis and 600 mg thereafter (class I recommendation).

In patients who receive PCI, thienopyridine therapy should be continued for at least 1 year (class I recommendation). Fifteen months of therapy is preferred in patients undergoing drug-eluting stent placement (class IIb recommendation). If the risk of bleeding outweighs the potential benefit of thienopyridine therapy, earlier discontinuation should be considered. The maintenance dose of clopidogrel and

prasugrel is 75 mg and 10 mg daily, respectively.

Ticagrelor is a reversible and direct-acting oral antagonist of the platelet adenosine diphosphate receptor $P2Y_{12}$. It provides faster and greater platelet inhibition than clopidogrel, without an increase in bleeding complications. Based on results of the PLATO trial, it is now considered an acceptable alternative to clopidogrel or prasugrel (class I recommendation). PLATO was a multicenter, randomized trial that evaluated the benefit of ticagrelor compared to clopidogrel in patients with ACS. At 1 year, the primary end point, a composite of death from vascular causes, MI, or stroke, was significantly less in patients who received ticagrelor without an increase in major bleeding. Patients who receive ticagrelor should not be treated with high-dose aspirin, as high-dose aspirin has been associated with worse outcomes in these patients.

GP IIb/IIIa Inhibitors

The benefits of GP IIb/IIIa inhibition during primary PCI in the pre DAPT era are well documented. An analysis that included ADMIRAL, CADILLAC, ISAR-2, and the RAPPORT trials revealed a reduction in rates of the composite endpoint of death, recurrent MI, or target revascularization by 6 months with the adjunctive use of abciximab during PCI compared to placebo (OR = 80, 95% CI 0.67 to 0.97). The efficacy of these agents in the setting of dual oral antiplatelet therapy is less certain. The dose of abciximab is a 0.25-mg/kg intravenous bolus, followed by an infusion of 0.125 mg/kg for 12 hours. Based on the 2011 ACCF/AHA/SCAI PCI guideline treatment with abciximab, eptifibatide, or tirofiban is reasonable at the time of PCI in selected patients with STEMI (class IIa recommendation). The routine use of these agents prior to arrival in the cardiac catheterization lab is not recommended (class III recommendation).

Antithrombotic Agents

All STEMI patients should receive anticoagulant therapy, which has traditionally been unfractionated heparin (UFH). The dose of UFH varies depending on the reperfusion strategy selected. The dose is 60 U/kg as a bolus (maximum 4,000 U), followed by 12-U/kg/h infusion (maximum 1,000 U/h) to achieve a partial thromboplastin time (PTT) of 45 to 65 seconds in patients undergoing fibrinolysis or patients undergoing PCI with an adjunctive GP IIb/IIIa inhibitor. The goal of intraprocedural activated clotting time (ACT) in this case is 200 to 250 seconds. For patients undergoing PCI without adjunctive GP IIb/IIIa inhibitor, the dose of UFH is 80 U/kg as a bolus, followed by 18-U/kg/h infusion to achieve a PTT of 50 to 75 seconds and an ACT of 300 to 350 seconds during the PCI. In general, heparin should not be continued after PCI, because there is increased risk for major bleeding and no incremental benefit. Exceptions to this rule include patients at high risk for systemic emboli, such as with large anterior infarction/left ventricular thrombus and atrial fibrillation. Deep venous thrombosis

should be prevented during periods of immobilization by subcutaneous UFH, 5,000 to 7,000 U, twice to three times per day when therapeutic doses of heparin are not being used.

Bivalirudin is considered an acceptable alternative to UFH for primary PCI (class I recommendation). This recommendation is based on results of the HORIZONS AMI trial. This trial randomized 3,600 patients to either bivarlirudin and provisional GP IIb/IIIa inhibitor or UFH and planned GP IIb/IIIa inhibitor prior to primary PCI. Only 7.5% of patients in the bivalirudin group received a GP IIb/IIIa inhibitor. The primary end points were major bleeding and the 30-day rate of combined adverse clinical events (major bleeding, death, reinfarction, target-vessel revascularization, and stroke). Patients in the bivalirudin group had a significant reduction in the primary end point, most of which was due to a reduction in the rate of major bleeding. The benefit of bivalirudin was maintained at 1 year. The use of bivalirudin in the setting of fibrinolysis was evaluated in the HERO-2 trial. In this trial, 17,073 STEMI patients were randomized to streptokinase and bivalirudin or streptokinase and UFH. The primary endpoint of mortality was not reduced by bivalirudin, although reinfarction was reduced by 30% within 96 hours. There was a small increase in mild to moderate bleeding with bivalirudin. If this agent is selected, the dose is 0.75 mg/kg bolus, followed by an infusion at 1.75 mg/kg/h with a PTT not to exceed 75 seconds. Thus, according to ACC/AHA guidelines, it is reasonable to consider bivalirudin as an alternative to UFH in patients who have been treated with streptokinase and have a known heparin allergy (class IIa indication).

Fondaparinux is a synthetic heparin pentasaccharide that acts through antithrombin to selectively inhibit factor Xa. The dose is 2.5 mg/d given subcutaneously. Its efficacy in STEMI was evaluated in the OASIS-6 trial. In this trial patients were classified as stratum 1, meaning UFH was not indicated, or stratum 2, meaning UFH was indicated. Patients in stratum 1 were randomly assigned to fondaparinux or placebo. Patients in stratum 2 were randomly assigned to fondaparinux or UFH. Primary PCI was performed in 0.2% of stratum 1 patients and 53% of stratum 2 patients. Thromrbolysis was performed in 78% of stratum 1 patients and 16% of stratum 2 patients. The most common thrombolytic used was streptokinase and a quarter of patients did not receive any form of reperfusion therapy. For the entire population (strata 1 and 2), there was a significant reduction in the primary endpoint of death or reinfarction at 30 days (9.7 vs.11.2%, HR 0.86). When the strata were evaluated individually, there was a significant reduction in the primary endpoint in strata 1 (11.2% vs. 14.0%, HR 0.79) but not strata 2 (8.3% vs. 8.7%, HR 0.96). The lack of benefit in strata 2 was due to worse outcomes in patients undergoing primary PCI. The use of fondaparinux in primary PCI was associated with an increase in guiding catheter thrombosis and in coronary dissection, no reflow, and abrupt closure. Based on these results, the use of fondaparinux as the sole anticoagulant during primary PCI is a class III

recommendation. Currently, if a patient receives fondaparinux then undergoes PCI, the ACC/AHA recommends additional IV treatment with an anticoagulant that possesses anti-IIa activity such as heparin, enoxaparin, or bivalirudin. Based on results of the FUTURA/OASIS 8 trial, standard-dose heparin is preferable to low-dose heparin as there is no increase in major bleeding and a statistically significant reduction in CV death, MI, TVR, and stent or catheter thrombosis.

Low-molecular-weight heparin (LMWH) may be considered as an alternative to UFH in patients undergoing fibrinolysis (class IIb recommendation). The ASSENT-3 trial tested various antithrombotic regimens with weight-based tenecteplase. LMWH was represented by enoxaparin initiated by 30-mg intravenous bolus, followed by 1.0 mg/kg subcutaneously every 12 hours up to discharge or revascularization, for a maximum of 7 days. Tenecteplase plus enoxaparin reduced a composite endpoint of death, in-hospital reinfarction, or in-hospital refractory ischemia compared to UFH. The ExTRACT-TIMI 25 trial randomized 20,506 STEMI patients undergoing fibrinolysis to either enoxaparin throughout the index hospitalization or UFH for 48 hours. The primary endpoint was death or nonfatal MI at 30 days. The enoxaparin group had a significant reduction in the primary endpoint, primarily due to a significant reduction in reinfarction (3.0% vs. 4.5%). The enoxaparin group also had a significant reduction in urgent revascularization (2.1% vs. 2.8%). Unfortunately, the interpretation of this study is limited by the difference in duration of therapy between the two groups. The mean duration of enoxaparin therapy was 7 days, whereas the mean duration of therapy with UFH was 48 hours. Currently, based on ACC/AHA guidelines, patients who undergo reperfusion with fibrinolytics should receive anticoagulant therapy with UFH, enoxaparin, or fondaparinux for a minimum of 48 hours and preferably the duration of the index hospitalization, up to 8 days (class I recommendation). If more than 48 hours of therapy is required, enoxaparin or fondaparinux are preferable to UFH because of the risk of heparin-induced thrombocytopenia (class I recommendation). For patients undergoing PCI after having received enoxaparin, additional dosing in the cardiac catheterization lab should be based on the time at which the last dose was received. If the last dose was within 8 hours, no additional enoxaparin should be given. If the last dose was given 8 to 12 hours earlier, or if the patient has received less than 2 subcutaneous doses, an IV dose of 0.3 mg/kg should be given. If the last dose was given >12 hours earlier, another 1 mg/kg subcutaneous dose should be administered (class I recommendation). For patients who are >75 years old or who have renal insufficiency (creatinine >2.5 mg/dL for men and >2.0 mg/dL for women) the use of a LMWH is not recommended (class III recommendation).

Anti-Ischemic Agents

Nitroglycerin and beta-blockers are first-line antiischemic agents (class I recommendation). Nitroglycerin is initiated by a 0.4-mg sublingual tablet (repeated

several times every 5 minutes if symptoms persist and hypotension does not develop), followed by intravenous infusion of 10 to 20 μg/min (titrated up until resolution of symptoms or until hypotension develops). An intravenous dose of 200 μg/min is considered a ceiling, although the dose is occasionally increased to 400 μg/min if needed. Notably, large-scale randomized trials have failed to observe any reduction in mortality with nitroglycerin, and indications for this agent in the setting of STEMI are thus to relieve ischemia, hypertension, or pulmonary congestion. Nitrates should not be utilized in the setting of a suspected right ventricular (RV) infarction as venous pooling can result in significant hypotension. Sildenafil use within 24 hours of presentation is a class III recommendation against the use of nitroglycerin. Similar caution is applicable to other PDE5 inhibitors.

Beta-blockers are administered along with nitroglycrerin and help to blunt the reflex tachycardia that may occur from their use. A large body of evidence supports the use of beta-blockers (class I recommendation). A pooled analysis from the prefibrinolytic era in >24,000 patients (dominated by the ISIS-1 trial) documented a 14% reduction in 7-day mortality (23% long-term reduction) among patients who received beta-blockade. Interestingly, in the reperfusion era, only the CAPRICORN trial with carvedilol has shown a mortality reduction with a beta-blocker. Other trials in the reperfusion era have only shown reduced reinfarction or recurrent ischemia.

Oral beta-blockers should be administered in the first 24 hours to all STEMI patients without a contraindication (class I recommendation). Medical contraindications to beta-blockers include significant conduction abnormalities (marked first-degree AV block, or second/third-degree block), asthma, or decompensated heart failure. The use of beta blockade with metoprolol in the COMMIT trial was associated with an increased risk of precipitating cardiogenic shock. Blunting the heart rate in patients with compensatory tachycardia likely resulted in this finding. Current guidelines highlight caution in patients at risk for cardiac shock. Risk factors include age > 70, systolic blood pressure <120 mm Hg, heart rate > 110 or < 60 bpm, and delay in reperfusion. Patients with a contraindication to beta-blocker therapy within the first 24 hours of STEMI should be reevaluated for candidacy throughout the hospitalization (class I recommendation). If there are contraindications to beta-blocker use, a nondihydropyridine calcium channel blocker (i.e., diltiazem or verapamil) may be considered to control anginal symptoms. Morphine (1 to 5 mg intravenously) is also considered a class I anti-ischemic medication and is particularly helpful for anxious patients and to control the pain of infarction.

Secondary Prevention

Inhibition of the Renin–Angiotensin–Aldosterone System

Angiotensin-converting enzyme inhibitors (ACE-I) are indicated in all STEMI patients

with a left ventricular ejection fraction (LVEF) <40% or in patients with a preserved LVEF and hypertension, diabetes, or chronic kidney disease (class I recommendation). The ACC/AHA also recommends that ACE-I be started and continued indefinitely in any STEMI patient who is not low risk (low risk defined as normal LVEF, well-controlled cardiovascular risk factors, and revascularization has been performed). Low-risk patients recovering from STEMI have a class IIa indication for ACE-I therapy. An angiotensin receptor blocker (ARB) may be used in the place of an ACE-I in patients who are ACE-I intolerant unless there is a history of angioedema (class I recommendation). If an ARB is used, candesartan and valsartan are the preferred agents as they have demonstrated efficacy in STEMI patients.

Aldosterone blockade is also beneficial in a select group of post-MI patients. The EPHESUS trial evaluated the efficacy of long-term aldosterone blockade with eplerenone in acute MI patients with a LVEF < 40%. Patients were enrolled 3 to 14 days after acute MI. Inclusion in the study required either heart failure (rales, a third heart sound, or pulmonary congestion on chest radiography) or diabetes. Patients with a serum creatinine >2.5 or a serum potassium > 5 were excluded. Study participants were randomly assigned to eplerenone or placebo. Patients in the eplerenone group had a significant reduction in mortality (14.4% vs. 16.7%), cardiovascular mortality (12.3% vs. 14.6%), and combined cardiovascular mortality or hospitalization for cardiac events (26.7% vs. 30.0%). Currently, the ACC/AHA recommends the use of aldosterone blockade in post-MI patients who: have an EF < 40%, are already receiving therapeutic doses of ACE-I and beta-blockade, and have either heart failure or diabetes, assuming the patient does not have significant renal dysfunction or hyperkalemia (class I recommendation).

Vasopressors, Inotropes, and Antiarrhythmics

Inotropic or vasopressor agents (i.e., dopamine, dobutamine, norepinephrine) are not used routinely in the setting of STEMI, as these agents can cause increased myocardial ischemia. If possible, patients in cardiogenic shock should first receive mechanical support with an intra-aortic balloon pump (IABP). If the patient does not respond to an IABP, an inotrope or vasopressor can then be added. Dobutamine may also be used for RV infarction that does not respond to intravenous fluids.

Ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) should be treated with immediate unsynchronized electric shock. If the arrhythmia is refractory to electric shock, 300 mg of IV amiodarone should be administered followed by repeat electric shock (class IIa recommendation). When present, electrolyte and acid–base disturbances should be corrected. For shock refractory VT or VF, treatment with boluses of IV procainamide may be considered (class IIb recommendation). Prophylactic antiarrhythmic therapy in the setting of STEMI is not recommended (class III recommendation).

A patient with sustained polymorphic VT or symptomatic sustained monomorphic VT should receive unsynchronized electric shock (class I recommendation). Treatment of stable sustained monomorphic VT includes Amiodarone 150 mg IV over 10 minutes or synchronized electrical cardioversion (class I recommendation). For refractory polymorphic VT, attempts should be made to reduce adrenergic stimulation and myocardial ischemia with beta-blockers, IABP use, and reperfusion therapy (class IIa recommendation). Procainamide therapy may be considered if the VT is not associated with angina, pulmonary edema, or hypotension (class IIb recommendation).

Lipid Management

A fasting lipid profile should be checked within 24 hours of presentation in all patients with STEMI. Target LDL-C is <100 mg/dL (class I recommendation) and further reduction in LDL-C to <70 mg/dL is reasonable (class IIa recommendation). Regardless of LDL-C level HMG-CoA reductase inhibitors (statins) should be initiated in all patients with STEMI (class I recommendation). Based on clinical trial data, atorvastatin has been studied most extensively at a dose of 80 mg daily. Gemfibrozil, niacin, and fish oil should be considered for patients with a low HDL (class IIa recommendation).

Secondary Prevention—Goals

- Smoking—complete cessation and with no environmental exposure
- Blood pressure control—<140/90 and <130/80 for patients with diabetes or chronic kidney disease
- Physical activity—30 min/d, 5 d/wk (preferably 7 d/wk)
- BMI—8.5 to 24.9 kg/m^2
- Waist circumference—men < 40 inches and women <35 inches
- Diabetes management—HbA1c <7%
- Influenza vaccination—patients with cardiovascular disease should receive an annual influenza vaccination

Mechanical Devices

Intra-Aortic Balloon Pump

The use of an IABP is recommended for patients in cardiogenic shock. A pulmonary artery catheter should also be used during the management of cardiogenic shock. Shock can result from early pump failure that may respond to multivessel revascularization. Hemodynamic instability may remain after revascularization for a period of time. The differential for hemodynamic instability after revascularization includes hypovolemia, anemia, RV infarction, and mechanical complications. Mechanical complications to consider in every AMI patient with hemodynamic instability/cardiogenic shock include

papillary muscle dysfunction/rupture, ventricular septal defect, and myocardial free wall rupture with tamponade. Electrical complications may occur during the course of the AMI, either before or after reperfusion, and an IABP may be considered for unstable ventricular arrhythmias. Moreover, an IABP is indicated for patients with recurrent myocardial ischemia that is refractory to pharmacologic therapy until revascularization may be performed. Therefore the IABP is used for stabilization until revascularization, as a bridge to CABG or repair of a mechanical complication, or for continued hemodynamic instability after revascularization.

Temporary Right Ventricular Pacing

RV pacing may be indicated in the management of conduction disturbances. Bradyarrhythmias are common in the setting of inferior MIs, especially with RV involvement. If such a patient exists who does not respond to chronotropic agents such as dobutamine or dopamine, temporary RV pacing may be needed until electrical and hemodynamic stability returns. Complete heart block can be seen with anterior MIs that involve a large septal perforator branch.

Implantable Cardioverter–Defibrillator Implantation in Patients after STEMI

Several trials have been performed to evaluate the efficacy of implantable cardioverter–defibrillator (ICD) insertion in patients after MI. The following discussion outlines some of these trials and discusses the current ACC/AHA guidelines.

The DINAMIT trial evaluated the role of prophylactic ICD insertion in patients with a LVEF of $\leq$ 35% and a history of MI in the preceding 6 to 40 days. Patients with NYHA class IV heart failure, sustained VT > 48 hours after MI, and who had received CABG or three-vessel PCI as management for their MI were excluded. While the patients who received an ICD had less death due to arrhythmia compared to controls, at a mean follow-up of 30 months, there was no significant difference in all-cause mortality (7.5% vs. 6.9%). The IRIS trial also evaluated the benefit of prophylactic ICD insertion in patients with a recent MI (5 to 31 days). Results again showed no difference in all-cause mortality between patients who did and did not receive an ICD.

MADIT II evaluated the benefit of delaying ICD insertion until at least 1 month after MI. The trial enrolled 1,232 patients with a history of MI more than 30 days prior to enrollment (more than 90 days if bypass surgery was performed) and an LVEF $\leq$ 30%. Patients were randomized to prophylactic ICD implantation or standard medical therapy.

At an average follow-up of 20 months, ICD implantation significantly reduced all-cause mortality (14.2% vs. 19.8% for standard therapy). This survival benefit was entirely due to a reduction in SCD (3.8% vs. 10.0% for standard therapy).

The SCD-HeFT trial randomized 2,521 patients with ischemic or nonischemic cardiomyopathy, a LVEF ≤ 35%, and NYHA class II or III heart failure to ICD implantation, amiodarone, or placebo. At 5 years, all-cause mortality was significantly reduced in patients who received an ICD (29% vs. 36% with placebo). This benefit did not differ based on the etiology of heart failure, but was nullified in patients with NYHA class III symptoms. Amiodarone therapy was not beneficial.

Based on multiple studies, including the above trials, the current ACC/AHA guidelines for ICD insertion are as follows: An ICD should be inserted in any patient with VF or sustained hemodynamically significant VT that occurs 48 hours after acute MI (class I recommendation). This is provided that the arrhythmia is not secondary to recurrent ischemia or MI. Patients whose MI occurred at least 40 days prior, who have a LVEF of ≤ 35% and NYHA class II or III heart failure, should also receive an ICD (class I recommendation). In addition, patients with NYHA class I heart failure are candidates for ICD insertion if their LVEF is ≤ 30% at least 40 days after MI (class I recommendation). If a patient receives CABG, the LVEF and NYHA functional class should be reassessed 90 days after the procedure to determine ICD candidacy. An ICD should not be inserted in patients without ventricular arrhythmia 48 hours after STEMI and who have an LVEF > 35% 40 days after the MI or 3 months after bypass grafting (class III recommendation).

Wearable cardioverter–defibrillators have been used in patients who are considered at risk for SCD but do not meet the above criteria, such as patients waiting for reassessment of LVEF after coronary artery revascularization. The efficacy of wearable cardioverter–defibrillators was initially evaluated by a clinical trial that consisted of two components. The first component (the WEARIT study) enrolled 177 patients with a LVEF < 30% and NYHA class III or IV heart failure. The second component (the BIROAD study) enrolled 112 patients with a recent MI or recent CABG who were considered high risk for SCD but did not meet criteria for an ICD or refused implantation. At the end of the 901 patient month observational period, there were six successful and two unsuccessful defibrillation attempts. Both unsuccessful attempts were because the device was being worn incorrectly. There were six instances of SCD during the study; in five cases the device was not being worn and in one case it was being worn incorrectly. While wearable cardioverter–defibrillators are currently not recognized in the ACC/AHA guidelines, there appears to be benefit to their use in select patients.

Pericarditis

Acute pericarditis develops in 10% to 15% of AMI patients within 2 to 4 days. Pain that occurs within the first 24 hours of a STEMI is unlikely to be secondary to pericarditis. Perircardial effusion is common, although frank tamponade is infrequent. Unlike ischemic pain, pericarditic pain is more often sharp, worse with deep inspiration

and recumbency. A pericardial friction rub is helpful in making the diagnosis, although it is not always present. The ECG may show diffuse ST elevation with PR depression. The treatment consists of aspirin (650 mg, three to four times per day). Alternatively, 600 to 800 mg of ibuprofen four times per day may be used. Indomethacin is effective, although it should be avoided given its reduction in coronary blood flow and gastrointestinal toxicity. Colchicine, 0.6 mg twice a day, may be added to aspirin or ibuprofen for refractory cases. Steroids should be avoided if possible, because of the concern for increased risk of myocardial rupture.

Dressler syndrome is the finding of pleuropericarditis 1 to 2 weeks after the infarct. This inflammatory reaction occurs in 1% to 2% of AMI patients. The clinical course is usually benign, although constrictive pericarditis may result. The treatment is generally the same as for acute pericarditis.

PREDISCHARGE RISK STRATIFICATION

Stress testing is a widely used mechanism for risk stratification after AMI. In STEMI patients who do not receive a left heart catheterization, exercise testing to assess for myocardial ischemia should be performed while in the hospital or early after discharge (class I recommendation). If the patient has baseline abnormalities that prevent ECG interpretation, echocardiography or nuclear imaging should be added to standard exercise testing (class I recommendation). It should also be considered prior to the hospital discharge of STEMI patients in order to guide cardiac rehabilitation or determine the significance of a lesion seen on coronary angiography (class IIb recommendation). Exercise testing should not be performed within 2 to 3 days of STEMI or in patients with UA, decompenrsated heart failure, or life-threatening arrhythmias (class III recommendation). It should also not be used to risk stratify patients who have already received a cardiac catheterization (class III recommendation).

Every patient after an AMI should have an assessment of left ventricular function. Patients with moderate to severe left ventricular dysfunction are at higher risk for adverse events. For these individuals, the use of beta-blockers and ACE inhibitors is especially important. Additionally, the implantation of an ICD may be indicated, after a period of convalescence from an AMI.

SUMMARY

STEMI is a distinctly different clinical entity than UA/NSTEMI, with a higher early mortality. Risk models such as the TIMI and GRACE risk scores are used to determine prognosis, not to guide therapy. In STEMI there is a limited window of opportunity (generally <12 hours and preferably <3 to 6 hours) for revascularization to preserve left

ventricular function and improve survival. Primary PCI is preferred over fibrinolytic therapy if it can be performed rapidly and potentially even if there is a delay in transport to a PCI center. Certain patient characteristics and logistical considerations favor one approach over another. Fibrinolysis is a viable option if primary PCI is not available in a timely fashion. High-risk patients who receive fibrinolysis should be transferred as soon as possible to a facility that is capable of performing PCI. Failed fibrinolysis is characterized by continued ischemia, hemodyrnamic instability, or incomplete ST-segment resolution.

All STEMI patients should receive aspirin, a thienorpyridine or $P2Y_{12}$ receptor antagonist, and an anticoagulant agent such as heparin, enoxaparin, fondaparinux, or bivalirrudin. The dose of heparin varies depending on the use of adjunctive medicines. Because of the risk of coronary complications and catheter thrombosis, fondaparinux should not be used as the sole anticoagulant during PCI. Clopidogrel, prasugrel, or ticagrelor should be given to all STEMI patients who receive PCI, with the duration of therapy depending on the type of stent placed. GP IIb/IIIa inhibitors may be beneficial during PCI, although their role during fibrinolyrsis is less clear. Beta-blockers and nitrates are first-line antirischemic agents and should be used judiciously. Calcium channel blockers may be used if the patient has a significant intolerance to beta-blockers. Statins are important across the spectrum of ACSs, including STEMI. ACE inhibitors are indicated when the patient becomes hemodynamically stable (usually not before 6 hours), and are especially useful for anterior MIs, in the presence of left ventricular dysfunction, and in diabetics. ARB may be substituted if the patient is intolerant to ACE-I, unless there is a history of angioedema. Aldosterone antagonists such as eplerenone are indicated in post-MI patients who have an EF $< 40\%$, are already receiving therapeutic doses of ACE-I and beta-blockade, and have either heart failure or diabetes, assuming the patient does not have significant renal dysfunction or hyperkalemia.

AMI patients should be monitored for the development of mechanical and electrical complications. Mechanical complications are life-threatening conditions that necessitate the use of an IABP and urgent surgical repair. Electrical complications may necessitate the use of antiarrhythmics and potentially RV pacing for bradyarrhythmias. Once patients are revascularized, they should be risk stratified in order to identify residual ischemia and determine the need for future ICD implantation.

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QUESTION AND ANSWERS

Questions

1. In the TIMI risk score model, the variable that has the strongest prediction for subsequent 30-day mortality is:
   a. Low body weight (i.e., <67 kg)
   b. Tachycardia
   c. Advanced age (i.e., >75 years)
   d. Killip class II to IV at presentation
   e. Left bundle branch block (LBBB) at presentation
2. Which of the following is not included in the differential diagnosis for electrocardiographic ST elevations?

a. ST-elevation myocardial infarction (STEMI)
b. Left ventricular aneurysm
c. Hypokalemia
d. Pericarditis
e. Left ventricular hypertrophy

3. Risk factors for intracranial hemorrhage (ICH) during administration of fibrinolytics include all of the following except:
   a. Uncontrolled hypertension
   b. Advanced age
   c. Female gender
   d. Preexisting coagulopathy
   e. Morbid obesity

4. All of the following are class III recommendations except:
   a. Performing revascularization of non-infarctrelated arteries at the time of primary percutaneous coronary intervention (PCI)
   b. Waiting for cardiac biomarkers to return before making the diagnosis of a STEMI
   c. Administering fibrinolytics to asymptomatic patients more than 24 hours from the onset of chest pain
   d. The use of a low-molecular-weight heparin (LMWH) along with fibrinolytics in patients with renal insufficiency
   e. The use of an oral ACE inhibitor within 24 hours of an anterior STEMI

5. The fibrinolytic agent associated with the lowest rate of ICH is:
   a. Alteplase (tPA)
   b. Streptokinase
   c. Reteplase (rPA)
   d. Tenecteplase (TNK-tPA)

6. Fondaparinux should not be used as the sole anticoagulant during PCI because there is a risk of:
   a. Coronary artery dissection
   b. Catheter thrombosis
   c. No reflow
   d. All of the choices

7. If a patient with STEMI and normal renal function is going for primay PCI and last received enoxaparin 9 hours prior, the additional enoxaparin dose that should be given is:
   a. 0.5 mg/kg IV
   b. 0.3 mg/kg IV
   c. 1 mg/kg subcutaneously
   d. 0.3 mg/kg subcutaneously

8. Which STEMI patient has a class I indication for risk stratification by exercise stress testing before discharge?
   a. A 75-year-old male who received fibrinolysis 48 hours ago and is now chest pain free without ST elevations on his ECG
   b. A 65-year-old female who received a PCI to her left anterior descending artery 4 days ago and had no other stenosis >50% on coronary angiogram
   c. A 52-year-old male who received fibrinolysis 6 days ago and has pulmonary rales and a third heart sound on physical exam.
   d. A 68-year-old female who received thrombolysis for an inferior STEMI 4 days ago and has had intermittent atrial fibrillation

9. Which patient should receive an implantable cardioverter–defibrillator (ICD)?

a. A 65-year-old female with an anterior STEMI 24 hours ago, for which she received a PCI to her left anterior descending (LAD), who is now having multiple runs of asymptomatic sustained ventricular tachycardia (VT)
b. A 52-year-old male with a left ventricular ejection fraction (LVEF) of 35% by echocardiogram performed 60 days after coronary artery bypass grafting (CABG)
c. A 58-year-old male with a LVEF of 25% and a normal electrophysiologic study 45 days after PCI for an anterior STEMI
d. A 62-year-old female with an EF of 40% 6 months after CABG

10. What is the goal waist circumference in women after a STEMI?
a. <20 inches
b. <25 inches
c. <30 inches
d. <35 inches

Answers

1. Answer C: Advanced age (>75 years) predicts the worst outcome for 30-day mortality and receives 3 points in the risk model. The other variables listed receive 1 to 2 points each. Hypotension (i.e., systolic blood pressure <90 mm Hg) at presentation is also a high-risk variable and receives 3 points in the risk model.

2. Answer C: Among the electrolyte abnormalities, hyperkalemia, not hypokalemia can cause ST elevations that mimic STEMIs.

3. Answer E: Low body weight, not morbid obesity, is a risk factor for ICH.

4. Answer E: The use of an oral ACE inhibitor is generally recommended early in the hospital course as long as the patient is hemodynamically stable (usually at least 6 hours after presentation). In contrast, the use of an intravenous ACE inhibitor during the first 24 hours is not recommended. Non–infarct-related coronaries should not be revascularized except in the setting of cardiogenic shock. Fibrinolytics are recommended for STEMI within 12 hours from the onset of chest pain. Administering fibrinolytics 12 to 24 hours from the onset of chest pain is generally not recommended, however individuals with stuttering chest pain during this time period may still be eligible to receive fibrinolytics. In individuals with renal insufficiency who also receive fibrinolytics, the use of UFH is preferred over LMWH.

5. Answer B: Among the various fibrinolytic agents, streptokinase does not necessitate the use of heparin. This may help to explain the smaller incidence of ICH seen with this agent.

6. Answer D: The OASIS-6 trial showed that the use of fondaparinux during PCI was associated with an increased incidence of catheter thrombosis, coronary artery dissection, no reflow, and acute vessel closure.

7. Answer B: According to the ACC/AHA guidelines, if the last dose was within 8 hours, no additional enoxaparin should be given. If the last dose was given 8 to 12 hours earlier, an IV dose of 0.3 mg/kg should be given. If the last dose was given >12 earlier, another 1 mg/kg subcutaneous dose should be administered.

8. Answer D: Because this patient is over 72 hours removed from her event and has not yet received left heart catheterization, an exercise stress test is indicated to assess for inducible ischemia. Patients should not receive exercise stress testing within 48 to 72 hours of STEMI. In addition, risk stratification by exercise testing is a class III indication in patients whose coronary angiogram during PCI showed no significant stenosis other than the target lesion. Patients with unstable angina, decompensated congestive heart failure (CHF), or life-threatening arrhythmias should not receive exercise stress testing.

9. Answer C: ICD implantation is indicated if a patient is >40 days post-myocardial infarction (MI) or 90 days post-CABG and the EF is ≤ 30% (New York Heart Association [NYHA] Class I) or ≤35% (NYHA Class II or III). Ventricular fibrillation (VF) or hemodynamically significant ventricular tachycardia (VT) > 48 hours after MI is also an indication for ICD implantation.

10. Answer D: For secondary prevention following acute MI, the goal waist circumference for men is <40 inches and women is < 35 inches.

CHAPTER

Complications of Myocardial Infarction

Olcay Aksoy and E. Murat Tuzcu

Despite advances in technology and therapeutics, in-hospital mortality following acute myocardial infarction (AMI) remains high. The leading cause of death in these patients is cardiogenic shock (CGS), with an incidence of approximately 7%.[1] CGS in the AMI setting can result from severe left ventricular (LV) or right ventricular (RV) systolic dysfunction, dynamic left ventricular outflow tract (LVOT) obstruction, or mechanical complications. These mechanical complications include acute mitral regurgitation (MR) from papillary muscle rupture, tamponade from cardiac free wall rupture, and left-to-right shunting from a ventricular septal defect (VSD). Arrhythmias and inflammatory sequelae are most often less deleterious unless they occur in an unmonitored setting or in a patient who is already in shock or hemodynamically tenuous.

LEFT VENTRICULAR DYSFUNCTION COMPLICATED BY CARDIOGENIC SHOCK

Isolated LV failure accounts for the majority of shock cases following AMI. In the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) Trial and concurrent SHOCK Trial registry, predominant LV failure was the cause of CGS in 78.5% of the patients, and in-hospital mortality was 59.2%.[2] Autopsy studies have shown that those patients who develop LV failure have lost approximately 40% of their myocardial mass to necrosis.[3] This generally occurs after a large transmural myocardial infarction (MI) or following a relatively small, nontransmural event in a patient with prior ischemic damage. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) Trial that examined outcomes associated with thrombolytic therapy in 41,021 patients with acute ST-elevation myocardial infarction (STEMI), risk factors for the development of shock were advanced age, female gender, prior infarction, anterior infarction location,

and diabetes mellitus.[4]

Symptoms and Signs

Upon presentation, subjective symptoms usually do not clarify the diagnosis; however, early recognition of symptoms of malperfusion can be critical. The physical examination can be helpful. One of the most popular systems to categorize these patients is the Killip classification (Table 42.1). Shock is present if there are signs of inadequate tissue perfusion with or without hypotension, which is defined as a systolic blood pressure <90 mm Hg. Signs of inadequate tissue perfusion include altered mental status, oliguria, and chemical evidence of end-organ damage such as a rise in serum creatinine, lactate, and/or liver transaminases. Patients are often tachycardic, hypothermic, and have cool extremities. Neck vein distention can be seen, and an S_3 gallop is sometimes heard on physical examination. Peripheral edema and displacement of the point of maximal impulse is less likely unless it existed prior to the AMI.

TABLE
42.1 Killip Classification

Killip Class	Exam Findings
I	No CHF
II	Mild to moderate CHF: S_3, rales <½ posterior thorax, JVD
III	Overt pulmonary edema
IV	Cardiogenic shock

Diagnosis

In addition to the symptoms and physical findings mentioned above, the electrocardiogram (ECG) is critical in diagnosis. Anterior STEMI is the most common cause of shock in the AMI setting.[2,4] Chest x-ray (CXR) can demonstrate an enlarged cardiac silhouette, although this is rare in the acute phase if prior myocardial damage has not occurred. Varying degrees of pulmonary venous congestion and edema can be seen. Transthoracic echocardiography (TTE), though not necessary for diagnosis, should be performed urgently in patients with shock or signs of congestive heart failure (CHF) to assess the extent of LV and/or RV dysfunction and exclude mechanical complications. Right heart catheterization can also be used to confirm the diagnosis and monitor therapy. In CGS, the cardiac index is typically <2.2 L/min/m^2; the mixed venous oxygen saturation is low, typically <65%; and the pulmonary capillary wedge pressure (PCWP) is elevated, typically >18 mm Hg.

Treatment

Treatment involves a combination of revascularization, medication, and mechanical therapy. It is important to remember that mechanical complications other than isolated LV dysfunction must be ruled out in the initial phases of management. Although this can be done with TTE, transport to the catheterization laboratory and implementation of aggressive supportive measures such as placement of an intra-aortic balloon pump (IABP) should not be delayed for this purpose. It is an American College of Cardiology/American Heart Association (ACC/AHA) Class I recommendation that intra-arterial blood pressure monitoring and a Class IIa recommendation that right heart catheterization should be used to monitor patients in CGS.[5]

REVASCULARIZATION

Thrombolytic therapy has a limited effect on the high mortality rate associated with AMI complicated by CGS.[2,4] Data to support this come from the Italian Group for the Study of Streptokinase in Myocardial Infarction (GISSI), which randomized >11,000 patients with AMI to thrombolytic therapy versus no thrombolytic therapy. In both groups, the subset of patients with CGS had a 70% mortality rate.[6] Fortunately, with the advent of more aggressive and invasive strategies for the management of AMI, survival of patients with AMI complicated by CGS has improved. Although the SHOCK Trial did not show a significant reduction in 30-day mortality between patients undergoing early revascularization and those receiving initial medical stabilization, 6-month and 1-year survival were both significantly improved in those who underwent early revascularization, defined as within 18 hours of the diagnosis of shock.[2,7] Only one subgroup in this study, those 75 years of age or older, did not benefit from early revascularization at 6 months and 1 year. It is therefore an ACC/AHA Class I recommendation that patients younger than 75 years of age with an acute STEMI (including new-onset left bundle branch block) complicated by CGS undergo early revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).[5] This recommendation applies only to patients who present within 36 hours of MI onset and who can be revascularized within 18 hours of shock development. This recommendation is Class IIa for selected patients who are 75 years of age or older if they have good functional status. Therefore, treatment must be individualized in this group of patients. Whether shock is present upon arrival or manifests during the course of hospitalization, clinicians are charged with developing protocols to transfer patients to STEMI-referral centers in the event of CGS (Class I recommendation per ACC/AHA).[8]

Although the use of thrombolytic therapy has limited efficacy on the high mortality rate associated with this condition, it is acceptable in two circumstances. The first is

when the patient is not a candidate for either surgical intervention or PCI. The second is when PCI or CABG is expected to be delayed. For specific recommendations regarding thrombolytic, interventional, and surgical strategies following AMI.

MEDICAL AND MECHANICAL THERAPIES

Although prompt cardiac catheterization and percutaneous or surgical revascularization are the primary goals in patients with AMI complicated by CGS, measures to stabilize the blood pressure and achieve adequate tissue perfusion must begin immediately. If the patient does not possess signs of volume overload, therapy can begin with rapid volume expansion. If this is not corrective, or the patient has volume overload, vasopressor therapy becomes necessary. Dopamine is the drug of first choice if systolic blood pressure is more than 70 mm Hg and <100 mm Hg, and norepinephrine should be added if the patient remains hypotensive or has signs of inadequate tissue perfusion on maximum doses. It is acceptable to start with norepinephrine if the patient's blood pressure is <70 mm Hg, with an attempt to transition to dopamine once the patient's systolic blood pressure improves.[5] Epinephrine and phenylephrine are not first choices in CGS because of their significant α-agonist activity, which can lead to an increase in afterload and subsequent decrease in cardiac output. They may become necessary, however, if dopamine and norepinephrine fail to stabilize the patient. Dobutamine can also be used in patients with acute pulmonary edema with systolic blood pressure >70 mm Hg and <100 mm Hg.

Short-Term Circulatory-Assist Devices

In the reperfusion era, a large randomized trial and two large registries have shown benefit of IABP use in patients with AMI complicated by CGS. In GUSTO-I, early insertion of an IABP in conjunction with thrombolytic therapy demonstrated a trend toward lower 30-day and 1-year mortality, though the bleeding risk was higher.[9] This trial also demonstrated that patients who received no or late IABP therapy had a much higher mortality within the first 8 hours of hospitalization than those receiving IABP therapy early In the SHOCK Trial Registry and the second National Registry of Myocardial Infarction, patients who received both IABP therapy and thrombolytic therapy had a significant mortality benefit over patients who received thrombolytic therapy alone.[10,11] In addition, those who received early IABP and thrombolytic therapy in the SHOCK Trial Registry had a higher likelihood of receiving revascularization. Early IABP therapy, therefore, appears to have a mortality benefit in patients with CGS complicating AMI. This is why insertion under these circumstances remains an ACC/AHA Class I recommendation, provided no contraindications exist. These contraindications are aortic dissection, more than moderate aortic regurgitation, sepsis, bleeding diathesis, iliac or aortic atherosclerosis that impairs lower extremity blood

flow, patent ductus arteriosus, and an anatomic abnormality of the femoral artery, iliac artery, or aorta that prevents insertion.[12] IABP insertion should be performed concomitant with the early stabilization efforts discussed previously. Once in place, it may allow for weaning of both vasopressor and inotropic agents, which increase myocardial workload and are therefore not ideal in the AMI setting.

If an IABP is felt to be insufficient in producing adequate cardiac support, there are several options for patients who present with CGS with LV dysfunction and severe MR (similar to indications for IABP). Impella—a device with the inlet end in the LV and output in the aorta with its body through the aortic valve—has been developed where the blood is pumped directly from the LV into the aorta with the use of a microaxial pump in the Impella catheter that's controlled by an external console. Currently, two types of Impella are available: 2.5 and 5.0 corresponding to the maximum cardiac output produced by the device. The advantage of this device is its ability to be placed in the catheterization laboratory much like an IABP with higher cardiac output produced. A major disadvantage is the size of the sheath necessary to place the catheter, which is larger than those used for IABP placement. Preliminary studies have shown that the Impella device can be placed safely and might lead to improved aortic and coronary pressures with decreased coronary microvascular resistance.[13,14] A small randomized trial comparing the 2.5 device with IABP in the setting of CGS post-MI has shown improved hemodynamics at 30 minutes; however, it has failed to show better survival compared to IABP.[15] The Impella 5.0 device can provide larger cardiac outputs in patients when necessary; however, data are not yet available regarding outcomes. As such, no recommendations for the use of these devices are yet in the guidelines.

The Tandem Heart—a device where inflow cannula is placed in the left atrium via transseptal puncture using a venous access site and outflow cannula in the femoral artery—allows bypassing of the left ventricle with the use of a centrifugal pump. This device can provide up to 5.0 L/min of cardiac output in tandem with the heart when used percutaneously. While the Tandem Heart provides higher outputs produced than those by IABP and the Impella 2.5, the transseptal approach requires more advanced operator training which can be a limiting factor. In a small randomized study of patients with CGS in the setting of MI, use of the Tandem Heart was associated with improved hemodynamics compared to the IABP; however, mortality at 30 days was no different. Such improved hemodynamics come with a cost of increased bleeding and limb ischemia, however.[16]

There are no studies comparing the Tandem Heart with the Impella device, but the above studies have shown that when a higher level of support is necessary; both devices perform better than the IABP hemodynamically, and may be more beneficial in the critically ill when a higher level of cardiac support is necessary. Potentially higher vascular complication rates necessitate that experienced operators perform these

procedures.

Longer-Term Circulatory-Assist Devices

Decisions regarding placement of circulatory-assist devices in the AMI setting, other than the short-term devices noted above, should involve collaboration with a cardiothoracic surgeon skilled in their placement and follow-up. In addition, the medical and surgical cardiac transplantation teams should be consulted. Decisions regarding their placement are complex and involve multiple considerations in addition to the hemodynamic status of the patient. Mechanical cardiac support devices in AMI complicated by isolated LV dysfunction should be considered when patients remain hemodynamically unstable and have evidence of end-organ hypoperfusion despite IABP therapy and maximal inotropic support. In addition, surgically correctable, mechanical complications of MI must be ruled out. Other issues such as transplant candidacy, potential reversibility of cardiac dysfunction, bleeding risks, expected duration of support, and the absence or presence of biventricular dysfunction are also important. In addition, the patient's age, body habitus, and comorbid conditions must be considered.

There are a number of different circulatory-assist devices, grouped best into two categories. Extracorporeal membrane oxygenation (ECMO) is a device where the patient's circulatory and respiratory system is fully supported by way of providing cardiac support and oxygenation of the blood externally. ECMO allows for temporizing the acute hemodynamic and respiratory decline while further decisions can be made as the patient is evaluated. If a patient is subsequently refused for transplantation, he or she can be weaned from the device and removal can occur without reinstitution of cardiopulmonary bypass. These devices are useful because they allow for observation of myocardial recovery after a period of rest and provide decision time concerning transplant candidacy. The second category of devices consists of ventricular assist devices that are suitable for long-term support. These devices are inserted via cannulation of the LV which then delivers blood to the aorta for perfusion. If a patient is deemed a transplant candidate in the acute setting, some centers will immediately place this type of device. If a short-term device was used initially, switching to a long-term device can be done as well. These devices are then explanted at the time of transplant or can be used as bridge-to-decision or destination therapies.

Vasodilators

Vasodilator therapy is ideal in patients with a low cardiac output who are not hypotensive. The two drugs most frequently used in the intensive care unit (ICU) setting are nitroprusside and nitroglycerin. Nitroprusside is a direct intravenous vasodilator that produces a balanced effect on both arteries and veins. It is initiated at low doses and titrated to a mean arterial blood pressure (MAP) of 65 to 70 mm Hg. Thiocyanate and cyanide toxicity have been reported but are uncommon unless patients receive a

prolonged infusion. Patients with renal dysfunction are more prone to the former, and those with liver dysfunction, the latter. Thus, nitroprusside must be used cautiously in patients with these comorbidities. Intravenous nitroglycerin is the drug of first choice in the setting of AMI and CHF. In addition to its vasodilatory effect, it has anti-ischemic properties, plus, when compared to nitroprusside, is unlikely to cause coronary steal. If a nitroprusside infusion is initiated in a patient with low cardiac output in the setting of coronary instability, nitroglycerin should also be added to negate the potential coronary steal that can be associated with nitroprusside. Both of these drugs should be avoided in hypotensive patients.

Beta-Blockers

Intravenous beta-blockers should be avoided in patients with AMI complicated by CGS (ACC/AHA Class III recommendation).[17] Once the patient is hemodynamically stable and has been weaned from inotrope and IABP support, it is safe to institute low doses of oral beta-blockers.

Diuretics

Intravenous diuretics are frequently necessary in the setting of AMI complicated by CGS for the treatment of pulmonary edema and volume overload. These can cause hypotension and therefore measures to stabilize the blood pressure should be instituted before diuretics are administered to a hypotensive patient. If the patient is in extremis from a respiratory standpoint, intubation should be considered.

Aldosterone Antagonists

Long-term administration of aldosterone antagonist— eplerenone—should be considered as its use has been associated with improved survival in the post-MI setting in patients who develop heart failure.[18]

Angiotensin-Converting Enzyme Inhibitors and Angiotensin-II Receptor Blockers

Multiple trials studying the administration of oral angiotensin-converting enzyme inhibitors (ACE-I) during the first few days following AMI complicated by CHF have shown a decrease in both mortality and adverse cardiovascular events.[19–21] Angiotensin-II receptor blockers (ARBs) have also been shown to lower mortality and adverse cardiovascular events when instituted early in patients with AMI complicated by CHF.[22,23] Importantly, these trials did not include patients in CGS. These medications are contraindicated in patients with hypotension in the setting of AMI. Once shock has resolved, ACE-I and/or ARBs can be initiated at low doses, provided no contraindications to these drugs exist.

MECHANICAL COMPLICATIONS

Ventricular Septal Defect

VSD is a serious complication of AMI that increases the risk of mortality substantially, even in patients who have undergone urgent surgical correction. In the prethrombolytic era, its occurrence was between 1% and 2%, and it accounted for approximately 5% of AMI-related deaths. The incidence has decreased with the use of thrombolytic agents, as demonstrated in the GUSTO-I Trial, where this was 0.2%.[24] Also noteworthy, in GUSTO-I the most important predictors of VSD were advanced age, female sex, anterior infarct location, and no current smoking.[24] In addition, a history of hypertension was common among patients. Angiographically, >50% of the patients had two- and three-vessel coronary disease, and those patients with a VSD were more likely to have had total occlusion of the infarct-related artery.[24]

VSD typically presents in the first week after MI and usually within 3 to 5 days of symptom onset. It was noted to occur earlier in the GUSTO-I and SHOCK trials, with a median time of 1 day and 16 hours from MI symptom onset, respectively.[24,25] Many of the patients in both of these trials received thrombolytic therapy, which has led investigators to hypothesize that timely administration of thrombolytic therapy restores patency of the infarct-related artery, thereby preventing or limiting the extensive transmural necrosis required for ventricular septal rupture. If VSD occurs with lytics, the presentation of the VSD is earlier as the use of lytics might exacerbate the myocardial hemorrhage associated with MI.[24]

VSD occurs with equal frequency in anterior, inferior, or posterior MIs. When it occurs in the setting of a right coronary artery (RCA) or dominant left circumflex artery (LCx) occlusion, the location of the defect is typically in the posterobasal region of the septum as opposed to the apical–septal region, seen with anterior infarctions. Posterobasal ruptures are often complex, with serpiginous courses containing multiple small defects. This differs from the direct, through-and-through communication sometimes seen with apical–septal defects. Further, posterobasal VSDs are in close proximity to the mitral and tricuspid valves. These anatomic issues make surgical and percutaneous closure of posterobasal ruptures more difficult. Additionally, patients with inferior or posterobasal infarctions often present with varying degrees of RV infarction, which adds to management complexity.

Symptoms and Signs

VSD results in a left-to-right shunt that leads to RV volume overload, increased pulmonary blood flow with reduced systemic blood flow. These hemodynamic alterations often lead to shock. Patients demonstrate signs of biventricular failure that include elevated neck veins and pulmonary edema. Peripheral edema is uncommon in

the acute setting, as is displacement of the point of maximal impulse. There is often a loud, holosystolic, precordial murmur that has widespread radiation. A palpable, precordial thrill is present in >50% of these patients.[26]

Diagnosis

The physical examination is diagnostic in most patients with a VSD. The test of first choice to confirm its presence is TTE with color Doppler imaging. A basal VSD can be visualized in multiple views, including the parasternal long-axis view with medial angulation, the apical long-axis view, the subcostal long-axis view, and the parasternal short-axis view (Fig. 42.1). An apical VSD is best visualized in the apical four-chamber view, although it too can be appreciated in multiple views.

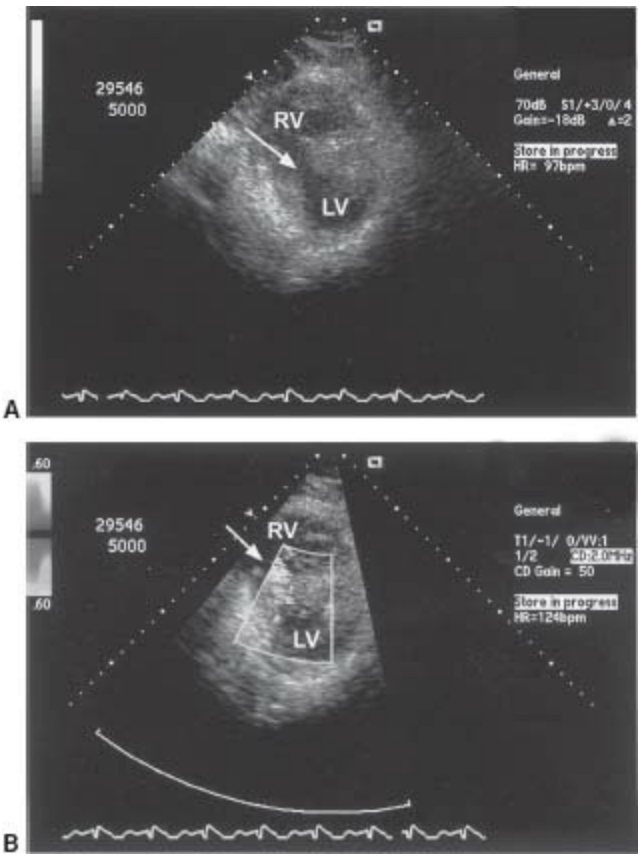

FIGURE 42.1 A: Subcostal short-axis view demonstrating an inferobasal VSD (arrow). **B:** Same view with Doppler across the defect, demonstrating a left-to-right shunt. RV, right ventricle; LV, left ventricle.

Diagnosis can be confirmed by right heart catheterization with a saturation run. This is performed by sequentially sampling blood from the pulmonary artery (PA), RV, right atrium (RA), superior vena cava (SVC), and inferior vena cava (IVC). At least a 7% step-up in the oxygen saturation from RA to PA is required to diagnose a LV to RV level. Subsequently, by using the O_2 saturation values, one can calculate the degree of

shunting, which is expressed as the ratio of pulmonary to systemic blood flow (Qp:Qs) (Fig. 42.2).

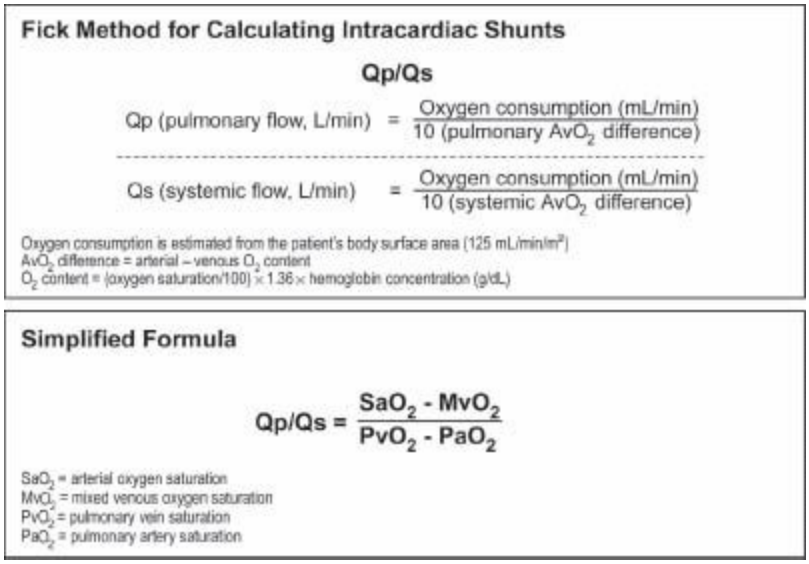

FIGURE 42.2 Calculation of left-to-right intracardiac shunts. When no shunt exists, MvO_2 = pulmonary artery saturation. When a left-to-right shunt is present, MvO_2 = the saturation in the chamber prior to the oxygen step-up. If there is no right-to-left shunt, and PvO_2 is not collected, it is assumed to be 95%.

Lastly, VSD can be diagnosed by ventriculography. Typically, the best view for this is the LAO view with cranial projection, such as LAO 60 degrees with 20 degrees of cranial angulation. This image nicely demonstrates the full length of the septum and, with contrast injection, passage of the contrast material will be seen crossing into the RV (Fig. 42.3).

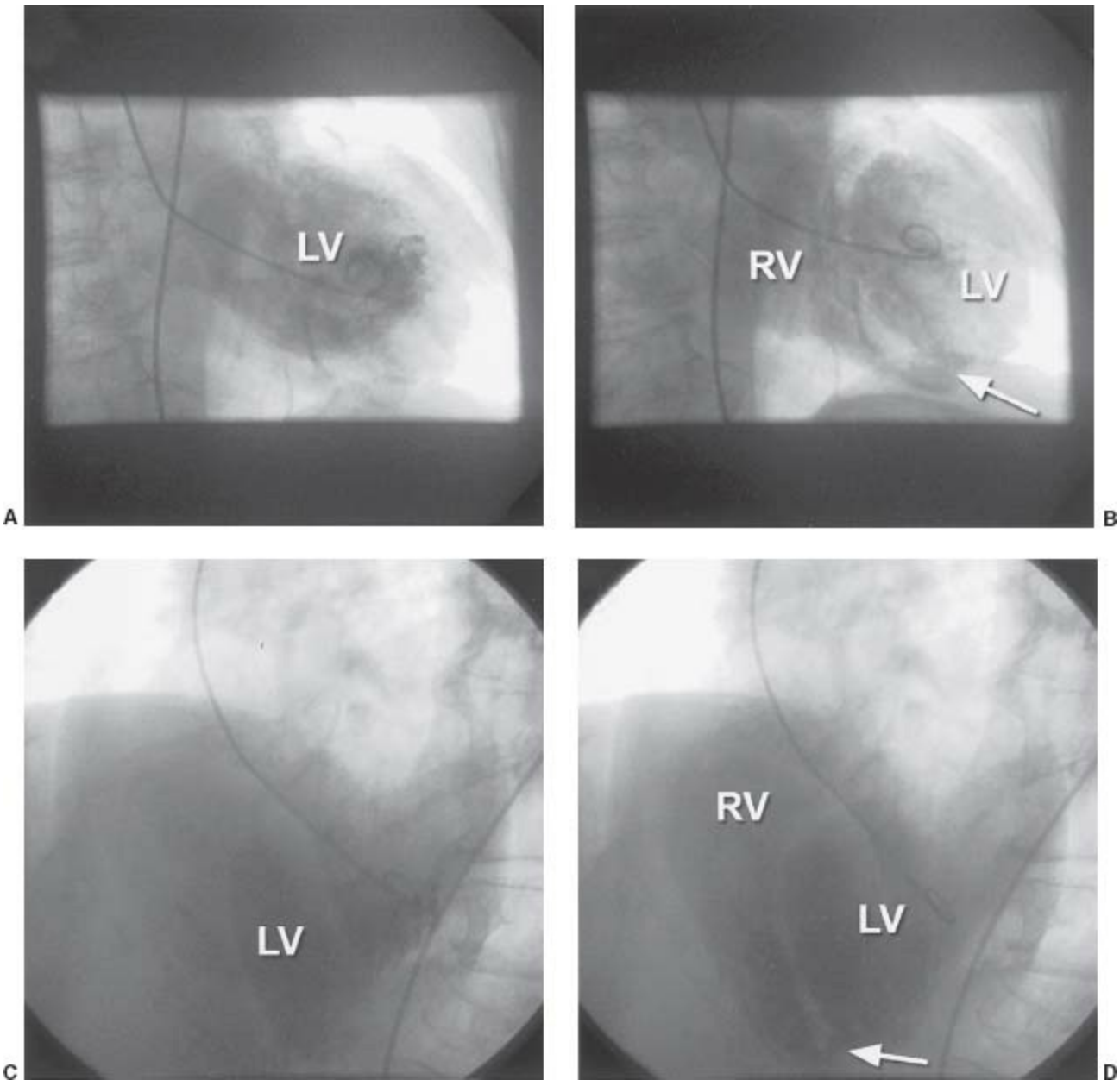

FIGURE 42.3 A: RAO 20-degree projection demonstrating filling of the left ventricle (LV). **B:** Same view demonstrating filling of the right ventricle (RV) from the LV through an inferoapical VSD (arrow). **C:** LAO 40-degree, cranial 25-degree projection demonstrating filling of the LV. **D:** Same view demonstrating filling of the RV from the LV through an inferoapical VSD (arrow).

Treatment

Emergency cardiac surgery with concomitant CABG is recommended for patients who present with VSD following AMI. This applies to both stable and unstable patients because stability can change rapidly if the necrotic edges of the defect expand abruptly. While surgical consultation is being obtained, patients should be placed in the ICU for invasive hemodynamic monitoring, initial treatment of shock, and consideration of IABP insertion. If the patient is not hypotensive, a short-acting vasodilator such as

nitroprusside can be used to optimize hemodynamics.[4] Percutaneous closure for a VSD complicating AMI has been reported in small case series.[27] It remains investigational, as patient numbers were small, follow-up was short, different devices were used, and some patients underwent closure several weeks following the acute event. This technique however might be used as a last resort in patients who are poor surgical candidates because complete closure is typically not achieved with percutaneous devices.

Even in patients who undergo emergency surgical repair, mortality at 30 days in the thrombolytic era is estimated to be approximately 50%. This is in comparison to a >90% 30-day mortality in patients managed medically.[24,25] This underscores the importance of prompt recognition, early placement of an IABP, and expeditious triage to the operating room for surgical repair.

Acute Mitral Regurgitation from Papillary Muscle Rupture or Functional Mitral Regurgitation

MR in the setting of AMI can occur for various reasons. It can result from papillary muscle rupture, which complicates 1% of AMIs and results in approximately 5% of AMI-related deaths. It can also result from abnormal coaptation of the mitral valve leaflets during systole due to dyssynchronous contraction of the LV walls. The latter may be seen in the acute setting when segmental LV wall dysfunction leads to restricted motion of the leaflet leading to MR. In the absence of early revascularization with scar formation, this type of MR might become chronic over time.

Although any degree of MR following AMI has been associated with an increase in mortality, papillary muscle rupture carries the gravest prognosis. In patients who develop severe MR, due to restrictive leaflet motion, the infarct is often extensive. In contrast, papillary muscle rupture is more often the result of a small infarction affecting the papillary muscle itself and typically occurs between the second and seventh days following AMI.[26] Rupture of the posteromedial papillary muscle in the setting of an inferior infarction is more common because it has a single vessel blood supply from the posterior descending branch of the dominant coronary artery. The anterolateral papillary muscle receives a dual blood supply from the left anterior descending (LAD) and LCx arteries, making it more resistant to necrosis.

Symptoms and Signs

Severe MR caused by papillary muscle rupture or a restrictive leaflet manifests as sudden shortness of breath followed by rapid hemodynamic deterioration. The median time to its development in the SHOCK Trial registry was 12.8 hours.[28] Also noteworthy in the SHOCK Trial Registry was that ST elevation was less frequent in those patients

with CGS and severe MR in comparison to patients with CGS caused by severe LV dysfunction without MR.[28] This important observation shows that an ECG with a relatively benign appearance in the setting of abrupt and severe hemodynamic deterioration should raise the suspicion of acute MR. Signs of shock are typically present with pulmonary rales. A precordial, systolic murmur may be heard, and its quality varies significantly from patient to patient. In some cases there is no appreciable murmur due to the rapid equilibration of pressures between the left ventricle and left atrium.

Diagnosis

Although physical examination is quite helpful, accurate diagnosis can be made by TTE or transesophageal echocardiography (TEE) with color Doppler imaging. The left ventricular ejection fraction (LVEF) may be normal or even supranormal in the case of papillary muscle rupture, as the infarcts occurring in this setting are often less extensive and the MR possesses an unloading effect on the left ventricle. If rupture has occurred, one will see the head of the papillary muscle attached to a flail mitral leaflet (Fig. 42.4).

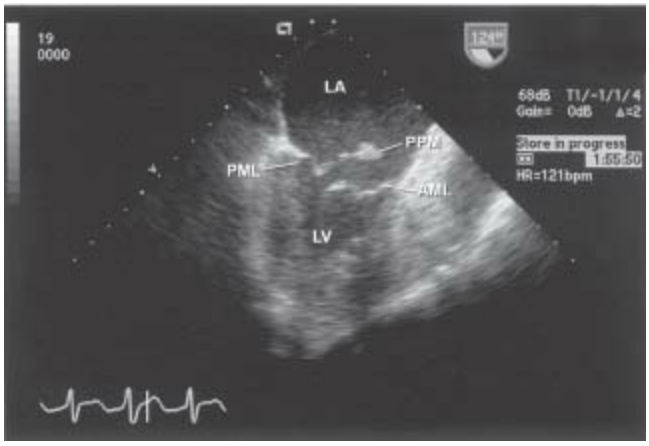

FIGURE 42.4 TEE at 124 degrees at the midesophageal level demonstrating papillary muscle rupture and a flail posterior mitral leaflet. LV, left ventricle; LA, left atrium; PML, posterior mitral leaflet; AML, anterior mitral leaflet; PPM, posterior papillary muscle.

Right heart catheterization (RHC), though important for hemodynamic monitoring and therapy in MR complicating AMI, should not be used as a diagnostic modality. It can, however, help to confirm the diagnosis. In addition to an elevated PCWP, there will often be giant V waves in the PCWP tracing (Fig. 42.5). It should be noted however that large V waves are also seen in patients with acute VSD. Left ventriculography can also confirm the diagnosis, but it is often unnecessary because echocardiography is sufficient to make both diagnostic and treatment decisions.

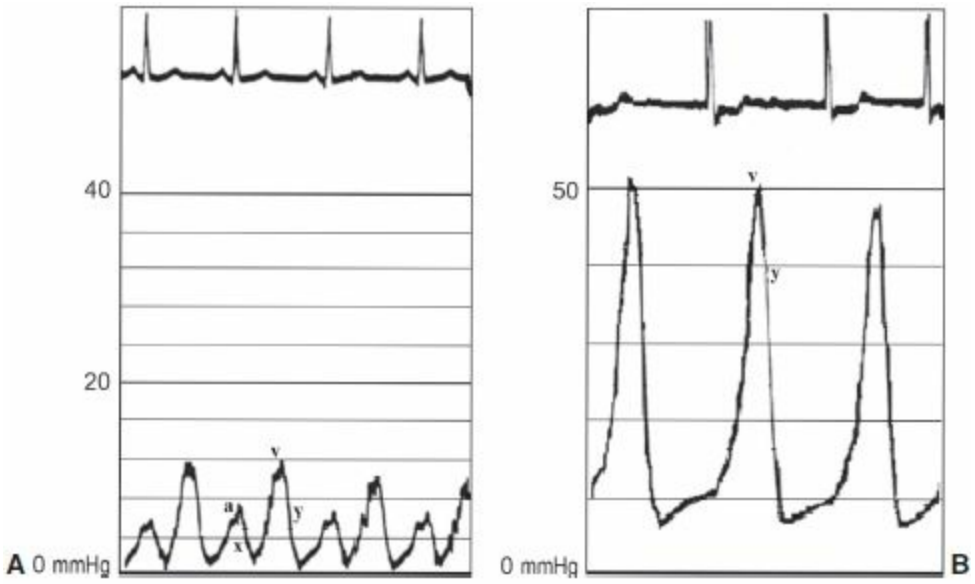

FIGURE 42.5 A: PCWP tracing representing normal waveforms during the cardiac cycle. **B:** PCWP tracing representing severe MR in a patient in atrial fibrillation. Note the giant V wave that represents regurgitant volume into the left atrium during ventricular systole.

Treatment

Stabilization efforts for papillary muscle rupture and severe restrictive leaflet-related MR are the same as those discussed for patients with CGS related to isolated LV dysfunction. With regard to medical therapy, patients who are not hypotensive can be managed with an intravenous vasodilator such as sodium nitroprusside. This will reduce LV afterload, improve cardiac output, and subsequently reduce the degree of MR and pulmonary edema. An IABP should be placed if the patient is in shock or has overt pulmonary edema. In patients with papillary muscle rupture, even if these two signs are not present, IABP therapy should be considered because stability can change rapidly.[5] Stabilization efforts should begin immediately, but not prevent rapid transport to the catheterization laboratory. Patients should be cared for in the ICU, and there is general agreement that a RHC is warranted for short-term guidance of pharmacologic and/or mechanical management of severe MR complicating AMI.[29] Diuretics should be used judiciously for relief of pulmonary edema.

Urgent cardiac surgery with concomitant CABG is indicated in all cases of AMI complicated by papillary muscle rupture (Class I ACC/AHA Recommendation).[5] Stability can change rapidly, so stabilization and triage to the operating room must be swift. In-hospital mortality in surgically treated patients is approximately 40%, substantially lower than for those treated medically.[28] In patients who survive to hospital discharge after surgery, short- and long-term survival remains excellent.

It is important to recognize that outcome of patients with even moderate MR after AMI is much worse than that without MR. Although a patient with severe MR with

restrictive leaflet may ultimately require CABG and mitral valve repair or replacement, emergency surgery may not be not necessary for the MR alone. This is because the degree of regurgitation often improves with revascularization and aggressive medical and/or mechanical therapies. If the patient's coronary anatomy is felt to require surgical revascularization, the degree of MR should be reassessed and valve repair or replacement considered.[5]

Cardiac Free Wall Rupture

Cardiac free wall rupture, though an infrequent complication of AMI, is the second leading cause of in-hospital mortality in AMI patients. Approximately half of cardiac ruptures occur within the first 5 days of AMI, and approximately 90% within the first 2 weeks. It can present in an acute or subacute fashion. The acute presentation is typically associated with hemodynamic collapse. There may not be time for life-saving emergency treatment. Subacute rupture presents more subtly, and if diagnosis is made early, prognosis with surgery is favorable.

Rupture most commonly involves the LV, but on occasion may involve the RV Although the incidence of cardiac rupture has decreased recently, there has been an increase in the incidence of in-hospital mortality following rupture. This is particularly more common in the first 2 days following AMI, in those patients who have received thrombolytic therapy.[30,31] Risk factors associated with free wall rupture have been variable across studies, but those commonly seen include: age >70 years, female gender, no history of prior MI or angina, transmural myocardial involvement, poor coronary collateral blood flow, and hypertension.[32–35]

Signs and Symptoms

The acute presentation of free wall rupture is typically one of cardiovascular collapse and electromechanical dissociation. This is commonly associated with transmural, through-and-through tears that cause abrupt tamponade. The subacute presentation is less severe, and patients slowly begin to manifest signs of CGS (see above) from tamponade. This is due to the slow egress of blood into the pericardial space from gradual or incomplete rupture of the infarcted myocardium. It can also occur when thrombus or pericardium incompletely seals off the rupture site, also known as a pseudoaneurysm, or contained rupture. Patients may experience persistent or recurrent chest pain with ST- and T-wave abnormalities. Additionally, they may experience episodes of transient hypotension, nausea, a feeling of doom, and/or have a fleeting pericardial friction rub prior to decompensation. Signs of tamponade, such as hypotension, tachycardia, and neck vein distention, may be present.

Diagnosis

In addition to the above symptoms and signs, the ECG often demonstrates persistent ST elevation and evidence of infarct extension or expansion.[35] Hemodynamics by RHC will demonstrate elevation of intracardiac pressures, along with equalization of diastolic filling pressures and a reduced cardiac output. Pulsus paradoxus can be appreciated on the intra-arterial waveform, along with blunting of the Y decent on the right atrial and pulmonary arterial pressure waveforms (Fig. 42.6). TTE will demonstrate a large pericardial effusion and signs of tamponade, including right atrial collapse during ventricular systole (Fig. 42.7), RV collapse during ventricular diastole (Fig. 42.8), respiratory variation of the tricuspid and mitral valve inflow velocities, and a plethoric IVC (see Fig. 42.7) that fails to collapse by 50% of its diameter with inspiration. It is important to note that pericardial effusion is a common finding following uncomplicated MI. Its presence should heighten one's suspicion for the possibility of subacute rupture. Serial echocardiography and close clinical observation can then be performed in order to exclude further accumulation of pericardial fluid.

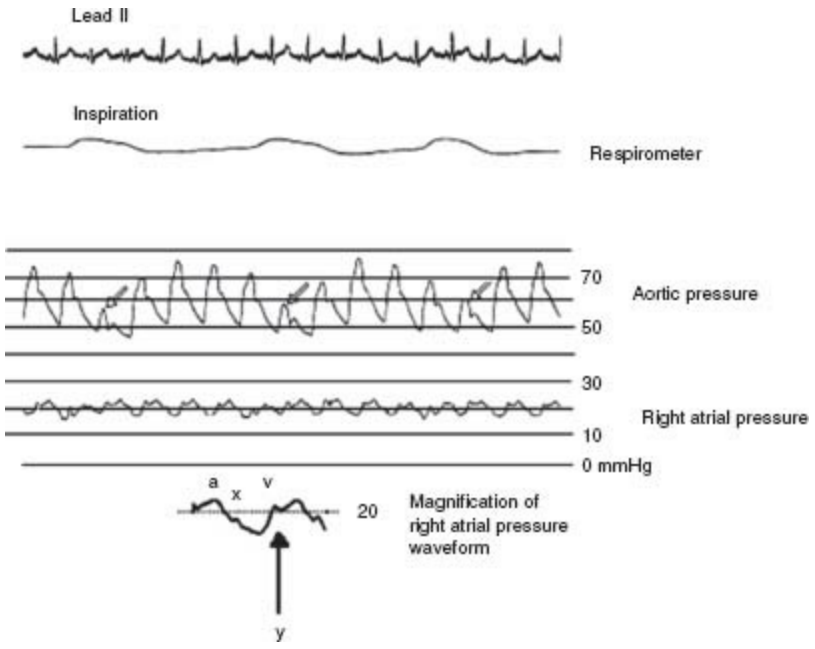

FIGURE 42.6 Hemodynamic findings in tamponade. Note that the aortic pressure tracing demonstrates hypotension and pulsus paradoxus (drop in systolic blood pressure by >10 mm Hg upon inspiration). In addition, the right atrial pressure is elevated and the y-descent is extremely blunted (arrow). a, atrial contraction; x, atrial relaxation; v, atrial filling (ventricular systole); y, atrial emptying (ventricular diastole). (Modified from Wu LA, Nishimura RA. Pulsus paradoxus. N Engl J Med. 2003;349(7):666.)

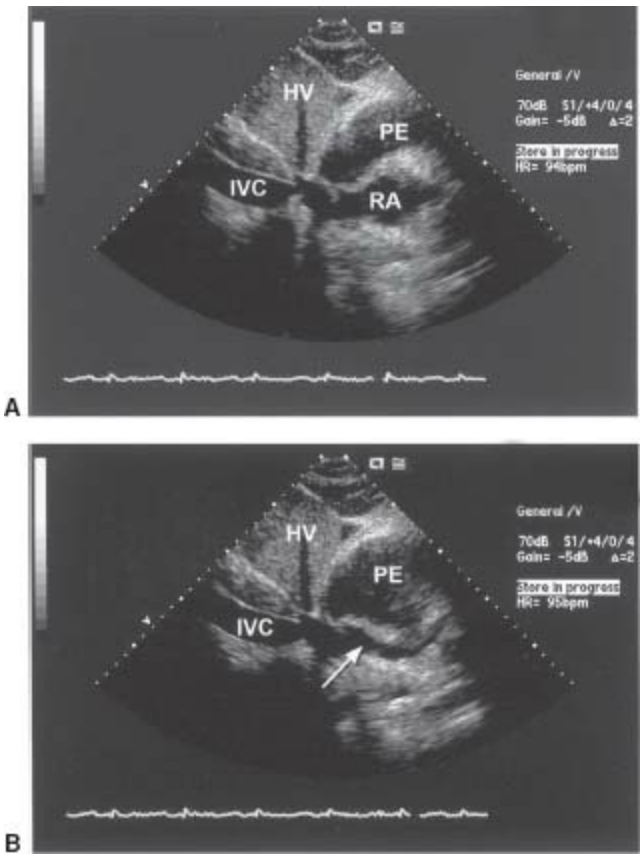

FIGURE 42.7 A: Subcostal long-axis view demonstrating a large pericardial effusion adjacent to the RA. **B:** Same view demonstrating right atrial wall inversion (arrow) during systole. Note that IVC plethora is present in both images. HV, hepatic vein; PE, pericardial effusion; RA, right atrium.

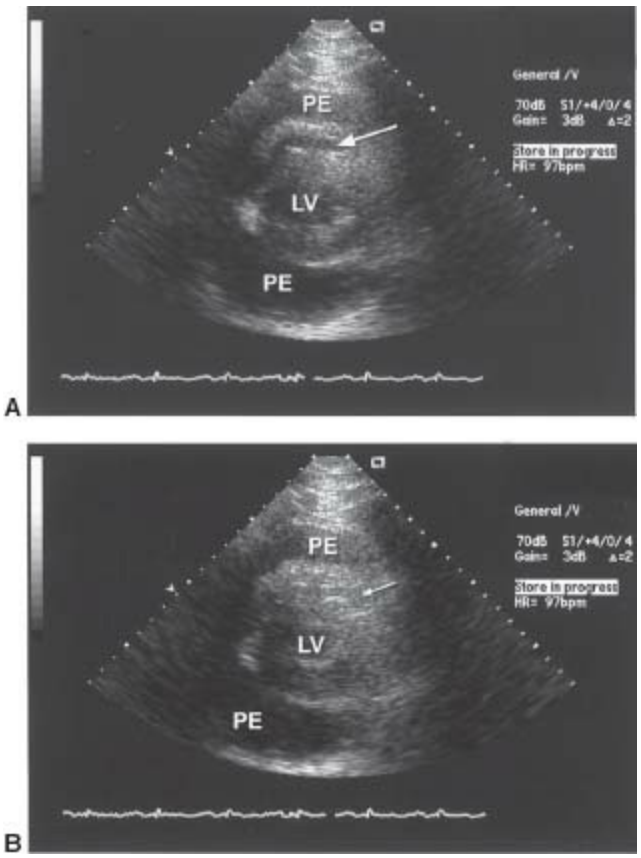

FIGURE 42.8 A: Parasternal short-axis view demonstrating that the right ventricle, while small and underfilled, remains open during systole (arrow). **B:** Same view demonstrating RV diastolic collapse (smaller arrow). LV, left ventricle; PE, pericardial effusion.

Treatment

Patients with acute or subacute rupture should be supported with intravenous fluids and, if hypotensive, with vasopressors while emergency cardiothoracic surgical consultation is obtained. Pericardiocentesis should be performed only in the operating room, as decompression of the pericardial space will result in further bleeding. If a patient is hemodynamically unstable despite treatment with fluids and vasopressors, pericardiocentesis can be performed as a last resort because decompression may be the only chance for survival.

Pseudoaneurysm

Although it is an infrequent complication of AMI, it is important to recognize a pseudoaneurysm because it is prone to rupture. It occurs when pericardial adhesions and thrombus seal off an area of myocardial rupture. Although this can happen at any location, a recent review found that the posterior wall was the most common area of involvement. This was followed by the lateral, apical, and finally inferior regions of the myocardium.[36] In comparison to a true aneurysm, there is no myocardium between the

LV cavity and the pericardial space (Fig. 42.9). Risk factors for the development of postinfarction pseudoaneurysm are similar to those for myocardial free wall rupture.

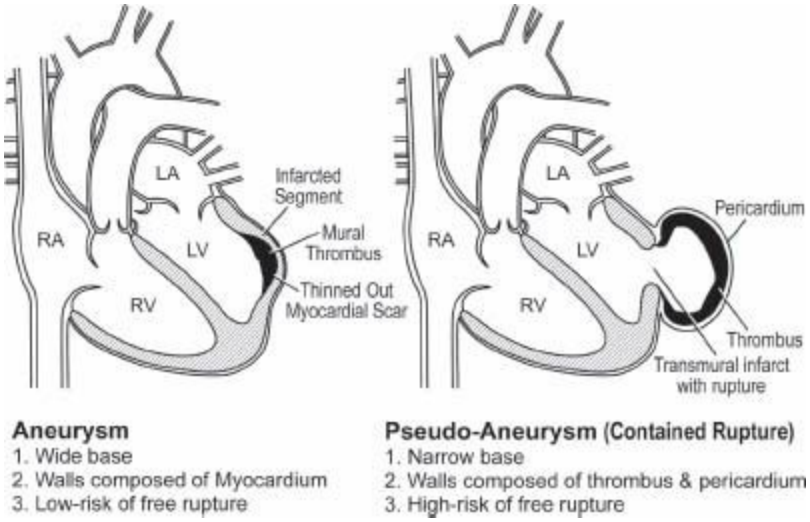

FIGURE 42.9 Pseudoaneurysm versus aneurysm. (Modified from Cercek B, Shah PK. Complicated acute myocardial infarction: heart failure, shock, mechanical complications. Cardiolo Clin. 1991;9(4):569-593.)

Symptoms and Signs

Pseudoaneurysms are often silent and are discovered on follow-up imaging or postmortem. Gradual enlargement of the aneurysmal cavity can lead to progressive heart failure symptoms, although this is rare. Some patients present with ventricular arrhythmias. Others develop arterial embolization after expulsion of thrombus from the aneurysmal cavity. The physical examination can be normal or consistent with CHF. Some patients will have a new murmur on auscultation, although 30% will have no murmur.[28] Rarely, a patient will present in CGS.

Diagnosis

The ECG may show persistent ST elevation or regional pericarditis, although it most often demonstrates nonspecific ST changes.[36] CXR can demonstrate an abnormal bulge around the site of involved myocardium but more frequently shows cardiomegaly. There are several imaging modalities available for diagnosis, including contrast ventriculography, TTE, TEE, magnetic resonance imaging (MRI), and computed tomography (CT). None of these tests has been 100% accurate, and no adequate comparisons between modalities have been made. Contrast ventriculography is the “ gold standard” and has been associated with a high degree of diagnostic accuracy. One will see a narrow orifice leading to a saccular cavity. If concomitant coronary arteriography is performed, there will be a lack of vessels at the site of the

pseudoaneurysm. Because this is an invasive modality, TTE with color Doppler is a reasonable test to perform first, although its diagnostic accuracy was found to be 26% for this condition[36] (Fig. 42.10). Although TEE and MRI have shown a higher degree of diagnostic accuracy, only small numbers have been studied and a definitive conclusion regarding superiority cannot be made. If MRI is used, cine runs will increase diagnostic sensitivity with its ability to highlight abnormal blood flow patterns and turbulence in and around the cavity of a pseudoaneurysm. In addition, it will often demonstrate loss of epicardial fat at the site of rupture.

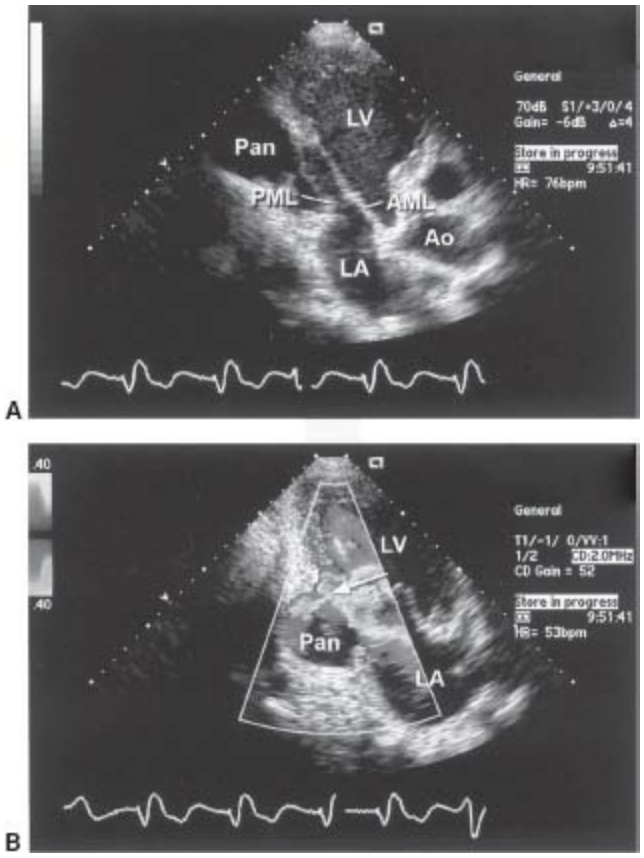

FIGURE 42.10 A: Apical long-axis view demonstrating a pseudoaneurysm of the posterior LV wall. **B:** Same view with Doppler demonstrating the rupture site (arrow) with turbulence of blood flow in and surrounding the cavity. LA, left atrium; AML, anterior mitral leaflet; PML, posterior mitral leaflet; Pan, pseudoaneurysm; Ao, aorta.

Treatment

Once a pseudoaneurysm is diagnosed, urgent surgery is indicated because of a 30% to 45% risk of rupture.[36] If the pseudoaneurysm is incidentally diagnosed or the patient is asymptomatic, the patient should be monitored until surgical evaluation has occurred. Successful percutaneous closure of pseudoaneurysms has been recently reported.

Left Ventricular Aneurysm

A true ventricular aneurysm differs anatomically from a pseudoaneurysm in that myocardium is present in its wall and there is no communication between the ventricular cavity and pericardial space (see Fig. 42.9). Its incidence following AMI has been reported as high as 38%. With the advent of reperfusion therapy, its frequency has decreased to between 8% and 15%.[26,37] Ventricular aneurysms most commonly complicate transmural anterior wall MIs and are thought to be the result of infarct expansion. In contrast to post-MI pseudoaneurysms, true ventricular aneurysms rarely rupture because the walls become fibrotic and calcified with time. True aneurysms have a wide base and are frequently associated with mural thrombus.[26]

Signs and Symptoms

Aneurysms place the entire ventricle, including the noninfarcted portion, at a mechanical disadvantage. Contractile energy is expended during passive outward expansion of the aneurysmal wall, and cardiac output decreases. This functional decline is more significant with acute aneurysms because the aneurysmal wall is more compliant and therefore expands to a greater degree during systole. Additionally, the distorted geometry can lead to misalignment of the mitral valve apparatus and result in MR.

Patients can present early or several weeks following AMI. They can be asymptomatic, or develop CHF, CGS, or recurrent ventricular arrhythmias. The index event is less often systemic embolization. The physical examination may demonstrate signs of CHF and/or CGS. In addition, patients may have a diffuse, dyskinetic apical impulse that is shifted leftward. Auscultation may reveal a murmur suggestive of MR or a third heart sound.

Diagnosis

In addition to the above physical findings, as with pseudoaneurysms, the CXR may demonstrate cardiomegaly and a bulge representing the aneurysmal area. The ECG will often show evidence of a transmural anterior MI and persistent ST-segment elevation. TTE is the diagnostic test of choice and will show thinning of the myocardium and dyskinetic wall motion at the site of infarction. Thrombus should always be excluded, as it is found in more than half of the surgical and autopsy cases that have been studied. If there is inability to exclude thrombus with a standard surface echocardiogram, contrast can be given simultaneously to improve distinction between the ventricular cavity and endocardial lining. Other imaging modalities such as cardiac MRI or CT scanning can be useful in this regard.

Treatment

Diagnosis of a ventricular aneurysm in itself does not change the treatment algorithm for a post-MI patient with comparable degrees of heart failure and/or CGS (see above). It is important to note that administration of an ACE-I within 24 hours of infarction is especially crucial in this situation, because of the drug's inhibitory effect on infarct expansion and beneficial effect on ventricular remodeling. If a patient is stable off mechanical and vasopressor support, an ACE-I should be started.

Surgery, which should include an LV aneurysmectomy and concomitant CABG, may be indicated when there are symptoms and signs related to the aneurysm.[5] However, careful evaluation and patient selection are necessary as there was no improvement in long-term outcome when aneurysmectomy was added to CABG alone in a recent RCT.[38] Patients with small or moderate-sized, asymptomatic aneurysms should not undergo surgery. They do require medical management for heart failure when it is present. Management of large, asymptomatic aneurysms remains controversial, and decisions to proceed with surgery are often individualized as above.

Anticoagulation with warfarin for at least 3 months is indicated for all post-STEMI patients who develop a mural thrombus in the acute setting. This applies to diagnoses made within 1 month of the event. Anticoagulation is indicated because systemic embolization can occur in as many as 10% with documented mural thrombi, and the risk of late thromboembolism appears to be decreased with oral anticoagulant therapy.[39,40] Although the risk of embolization decreases dramatically in the subsequent months following the infarction, therapy should be continued indefinitely for those patients who are not at an increased risk of bleeding.[5] Anticoagulation in these patients consists of the early administration of intravenous, unfractionated heparin or subcutaneous low-molecular-weight heparin, along with Coumadin therapy until the international normalized ratio is between two and three. Once this has been achieved, heparin may be discontinued. Patients who develop an LV aneurysm but no identifiable thrombus in the acute setting can similarly be anticoagulated because the incidence of thrombus in these patients, postmortem and intraoperatively, is at least 50%.[39] There is limited evidence to support long-term anticoagulation in these patients, and practice patterns often differ.

ADDITIONAL COMPLICATIONS

Right Ventricular Infarction with Hemodynamic Compromise

RV infarction rarely happens in isolation and more commonly occurs during an inferior or inferoposterior LV MI. Patients present with various degrees of RV dysfunction, but only 10% to 15% develop hemodynamically significant RV impairment. This typically occurs when there is an ostial or proximal RCA occlusion prior to takeoff of the RV marginal branches.

Symptoms and Signs

If one understands the hemodynamic relationship between the LV, RV, and pericardium, the symptoms and signs of RV infarction become clear. It is important to realize that many of the hemodynamic changes overlap with tamponade, constrictive pericarditis, and restrictive cardiomyopathy. This makes clinical context and echocardiographic examination very important.

When RV infarction occurs, the RV filling pressure becomes elevated due to systolic and diastolic dysfunction, which in turn causes elevation of right atrial filling pressures. Simultaneously, a decrease in RV output leads to a reduced LV end diastolic volume and the PCWP will be low. This is not always the case when there is concomitant LV dysfunction from a previous infarction or the current event. LV preload becomes further reduced when intrapericardial pressure is increased by abrupt dilation of the RV. Similar to tamponade, the LV and RV become interdependent. [41] This combination of events leads to the triad of hypotension, elevated neck veins, and clear lung fields.[42] Neck vein distention may not be seen if the patient is hypovolemic but may become apparent following aggressive fluid resuscitation, one of the key aspects of treatment.

Diagnosis

This diagnosis should be considered in any patient who presents with inferior ST-segment elevation on ECG. In fact, it is an ACC/AHA Class I indication to obtain a tracing of lead V_4R and a TTE to look for RV infarction in patients with inferior STEMI and hemodynamic compromise.[5] RV infarction should also be considered in patients with ST depression in leads V_1 and V_2, as this may represent acute infarction of the posterior myocardium as opposed to septal, subendocardial ischemia. Again, TTE can confirm the diagnosis by demonstrating hypokinesis and dilatation of the RV. Right heart catheterization can help confirm the diagnosis, but findings are nonspecific and may overlap with those of tamponade, constriction, and restriction. One will see elevated RV filling pressures that are equal to or greater than LV filling pressures, normal or low pulmonary arterial and PCWP, and a reduced cardiac index. Another clue to significant RV involvement in patients with inferior or posterior MI is hypotension following the administration of preload reducing agents such as diuretics and nitrates.

Treatment

Similar to patients with AMI and CGS secondary to LV dysfunction, patients with AMI complicated by severe RV dysfunction should undergo emergency diagnostic

angiography and revascularization. If CABG is indicated, it is reasonable (Class IIa ACC/AHA Recommendation) to delay it in patients with clinically significant RV dysfunction as the RV function frequently improves following several weeks of medical therapy.[5]

Patients should be monitored in the ICU with both intra-arterial blood pressure monitoring and a RHC. If shock is present, the first line of therapy is aggressive fluid resuscitation. This is done with isotonic saline until the PCWP is between 15 and 18 mm Hg. If shock remains after this is achieved, an inotropic agent should be added. Dobutamine is the preferred drug in this situation because it causes less hypotension. If vasopressors are required, a pure α-agonist should be avoided, as it will lead to pulmonary arterial vasoconstriction and further decrease forward flow into the left ventricle. If severe LV dysfunction and an elevated PCWP exist, unlike the situation of isolated LV systolic dysfunction complicating AMI, sodium nitroprusside should be avoided as a reduction in preload might cause further deterioration of hemodynamics. These patients should be considered for IABP counterpulsation. It is important to avoid factors that increase RV afterload, such as hypoxemia, α-agonists, and elevations in PCWP, which include positive end-expiratory pressure (PEEP). In addition, one should avoid agents that decrease RV preload. This includes medications such as nitrates, morphine, and diuretics; but also dysrhythmias that lead to disruption of atrioventricular (AV) synchrony, such as atrial fibrillation and high-degree AV block.

Atrial fibrillation must be dealt with emergently in the hemodynamically unstable patient following RV infarction, with immediate direct-current cardioversion (DCCV). If the patient is not hemodynamically compromised, a trial of antiarrhythmic therapy can be attempted; however, if sinus rhythm is not restored promptly, DCCV should be performed.

Bradyarrhythmias, a frequent complication of inferior myocardial infarction (IMI) with RV involvement, can be quite dangerous even when the atrium and ventricle contract synchronously. This is because the dilated right ventricle has a relatively fixed stroke volume and depends largely on heart rate to increase its output. Management of bradycardia in AMI is discussed in a subsequent section. It is important to know that if a patient with RV infarction requires temporary pacing; both atrial and ventricular leads should be placed, in order to maintain AV synchrony.

Dynamic Left Ventricular Outflow Tract Obstruction

Although development of dynamic LVOT obstruction is a rare complication of MI, it is important to recognize because many of the traditional therapies used in the treatment of AMI complicated by CGS should be avoided. These include nitrates, afterload reduction, diuretics, IABPs, and inotropic agents.

Dynamic LVOT obstruction most often occurs in the setting of an anteroapical MI with compensatory basal hyperkinesis. This combination of segmental wall motion

abnormalities causes a decrease in the cross-sectional area of the LVOT and acceleration of blood flow across this region. The acceleration of blood flow decreases pressure above the mitral valve, causing systolic anterior motion (SAM) of the anterior mitral leaflet against the interventricular septum, which worsens the LVOT obstruction.[43] These patients often have a single, significant stenosis in the LAD coronary artery, in addition to mild concentric LV hypertrophy or asymmetric septal hypertrophy.

Symptoms and Signs

Patients with dynamic LVOT obstruction usually have chest pain and evidence of an anterior or anteroapical STEMI. This complication has also been seen in non–ST-elevation myocardial infarction (NSTEMI), but much less frequently. Symptoms and signs of CHF and CGS are often present (see above). Patients can have a holosystolic murmur at the left lateral sternal border that radiates to the apex and represents MR in addition to a harsh crescendo–decrescendo systolic murmur in the left second intercostal space, representing LVOT obstruction.

Diagnosis

The possibility of LVOT obstruction should be considered in patients who have progressive hemodynamic deterioration in the setting of standard medical and mechanical therapies used to treat patients with AMI and CGS. The diagnosis is made by TTE. LVEF may be normal or depressed. Apical hypo or akinesis along with hyperkinesis of the basal segments of the heart will be seen, in addition to SAM and regurgitation of the mitral valve. The LVOT, best interrogated with continuous-wave Doppler in the apical five- and three-chamber views, will demonstrate a gradient >30 mm Hg.

Treatment

Standard revascularization and anticoagulant therapy for AMI must be instituted in these patients. What is different are the supportive measures used during the periinfarction period. This consists of beta-blockers and fluids. If shock is present, an α-agonist should be used. All of these therapies decrease the degree of LVOT obstruction. Phenylephrine, the most commonly used α-agonist, is started at 20 to 40 μg/min and titrated upward, until there is clinical improvement or the maximum dose has been reached.

Pericarditis

There are two forms of pericarditis that occur in the setting of MI. The first, typically occurring within 24 to 96 hours of transmural MI, is a form of localized inflammation in the pericardial region above the necrotic myocardium, which tends to run a benign course. The second, a form of post–cardiac injury syndrome also referred to as Dressler syndrome, can manifest 1 to 8 weeks following MI. Although the exact mechanism is unclear, it is felt to be the result of an autoimmune reaction involving myocardial antigen and antibody complexes. This form of pericarditis tends to be a more systemic inflammatory process, is often refractory to first-line therapies, and frequently recurs.

Symptoms and Signs

Patients with pericarditis often develop positional chest pain. This tends to be sharp, pleuritic, exacerbated by recumbency, and commonly radiates to the trapezius ridge. If the patient has Dressler syndrome, he or she may also complain of arthralgias and myalgias. Dressler syndrome can also be associated with pleuritis and pleural effusions. Although these effusions are typically small, they may enlarge and cause dyspnea. Patients may be febrile in both forms of pericarditis, and those with Dressler syndrome can run fevers as high as 40°C. All patients with pericarditis may have leukocytosis and elevation of inflammatory markers such as the erythrocyte sedimentation rate and C-reactive protein. Physical examination may demonstrate a pericardial friction rub.

Diagnosis

Symptoms and the presence of a pericardial friction rub are quite specific for pericarditis. ECG can be helpful but is less sensitive, especially in the acute situation, as the evolutionary changes seen following MI can mask the typical ECG features of pericarditis (Table 42.2). Although TTE is not diagnostic in situations of post-MI pericarditis, it must be obtained to rule out a significant pericardial effusion, seen more commonly in patients with Dressler syndrome. It is important to realize that the presence of an effusion is not diagnostic, as it is commonly seen following uncomplicated AMIs. Likewise, absence of a pericardial effusion does not exclude the diagnosis.

TABLE
42.2 ECG Changes in Pericarditis versus STEMI

Stage	ECG Changes Typically Associated with Pericarditis[a]
I	Diffuse, concave-up ST elevation; ST depression in aVR and V_1; PR depression in the limb leads and left chest leads; PR elevation in aVR
IIa	ST and PR segments return to baseline, while T waves remain upright
IIb	T waves begin to flatten and invert, largely in the leads that had ST elevation
III	Diffuse T-wave inversion
IV	Prepericarditis ECG, however, T-wave inversions may persist
Stage	**Evolutionary ECG Changes Typically Associated with STEMI**
I	Convex-upward ST-segment elevation and upright T waves overlying area of infarct; ST-segment depression in opposite leads; Q waves begin to develop
II	Gradual T-wave inversion followed by deep, symmetrically inverted T waves; Q waves continue to evolve
III	Resolution of ST elevation,[b] T waves begin to normalize

[a]In pericarditis, the evolution of repolarization abnormalities does not always occur simultaneously as they typically do in MI. In addition, the distribution of repolarization abnormalities in myocardial infarction remains constant, whereas in pericarditis, multiple areas on the ECG can demonstrate different repolarization patterns.

[b]If ST-segment elevation does not resolve by 6 weeks, consider the possibility of ventricular aneurysm or a large area of dyskinetic myocardium.

Treatment

There are two issues to consider and balance when treating patients with post-MI pericarditis. One is the need for antiinflammatory agents and the need to avoid anticoagulation. In terms of anti-inflammatory agents, aspirin is the first line of therapy. If patients are refractory to standard doses, as much as 650 mg every 4 to 6 hours may be used. When high doses are needed, it is advisable to place the patient on an acid-suppressive regimen. Some patients will be refractory to or unable to take high-dose aspirin therapy. In these patients, 0.6 mg of colchicine every 12 hours and/or 650 mg of acetaminophen every 4 to 6 hours can be tried. Nonsteroidal anti-inflammatory drugs (NSAIDs) other than aspirin and corticosteroids should be avoided unless used as a last resort. Corticosteroids and NSAIDs adversely affect myocardial scar formation, which can lead to thinning of the scar and, in some circumstances, infarct expansion. There are reports suggesting that both drug classes put the patient at increased risk for myocardial rupture following AMI. Per ACC/AHA, the use of NSAIDs (except for aspirin) at the time of infarction are contraindicated, and these agents should be discontinued when patients present with MI (Class I ACC/AHA recommendation).[17] There are no clear recommendations for patients who present with pericarditis after recovery from their AMI; however, given overall association of NSAIDs with progression of CAD, it is advisable not to use these agents in patients with established disease.

Clinical judgment is necessary if anticoagulation is required for a patient with post-MI pericarditis. It is an ACC/AHA Class I indication to discontinue anticoagulant therapy if an effusion develops or enlarges. This decision must be individualized and

based on the risk-to-benefit ratio. If a decision is made to continue anticoagulation, the patient must be observed diligently for effusion enlargement and impending tamponade.

ARRHYTHMIC COMPLICATIONS

Bradyarrhythmias

In the setting of AMI, management of bradyarrhythmias is complex because decisions regarding temporary and permanent pacing must be made and require multiple considerations. In the acute setting, if a patient is hemodynamically stable despite a bradyarrhythmia, a decision must be made regarding the need for prophylactic, backup pacing. This requires one to predict which patients are likely to progress to a life-threatening rhythm abnormality such as third-degree AV block. The route by which pacing is performed must involve considerations regarding patient stability, the need for AV synchrony, and the bleeding risks associated with the use of thrombolytic and postinterventional therapies.

Sinus bradycardia occurs in approximately 30% to 40% of AMIs, most commonly with inferior MI and reperfusion of the RCA.[5] Although multiple mechanisms can be responsible, the most common is hyperactivity of para-sympathetics due to stimulation of vagal afferents. This is termed the Bezold–Jarisch reflex and causes both bradycardia and hypotension. When patients become symptomatic from sinus bradycardia or from sinus pauses >3 seconds in duration, intravenous atropine is the first line of therapy.[5] This should be administered in doses of 0.5 to 1 mg every 3 minutes until the patient is no longer symptomatic or a total dose of 0.4 mg/kg has been reached. If symptomatic bradycardia persists, transcutaneous or transvenous pacing must be initiated.

The development of atrioventricular conduction block (AVB), intraventricular conduction delay (IVCD), and/or bundle branch block (BBB) in the setting of AMI is associated with an increased risk of in-hospital mortality. Decisions regarding prophylactic or therapeutic temporary pacing depend on the infarction location, the type of block and its presumed relationship to the AV node, the extent of preexisting conduction system disease, and the presence or absence of symptoms.

When dealing with any form of heart block, its relationship to the AV node is an important factor to consider. This is significant because blocks proximal to or within the AV node, often referred to as intranodal block, are generally benign, with prophylactic and eventual permanent pacing typically not required. This is in contradiction to infranodal blocks, which tend to be more dangerous, often require prophylactic and therapeutic temporary pacing, and frequently result in permanent pacemaker insertion prior to hospital discharge.[5,44] Typical intranodal blocks are first-degree and second-degree, Mobitz type I AVB. These are usually seen in inferior or inferoposterior AMIs, and the RCA is usually the culprit artery, although the LCx can be involved. If third-

degree AVB develops in the intranodal region, the QRS width is typically <0.12 seconds, the escape rate tends to be between 45 to 60 beats per minute (bpm), and asystole is uncommon. Common infranodal blocks are second-degree, Mobitz type II AVB and third-degree AVB. When infranodal blocks are present, the LAD is typically the culprit lesion. When third-degree AVB of the infranodal variety is present, the QRS width tends to be wider than 0.12 seconds, escape rates are often <30 bpm, and asystole is common. Hence, the majority of these patients require either prophylactic or therapeutic temporary pacing during the AMI setting. It is important to remember that whereas atropine is commonly the first line of treatment in patients with symptomatic, presumed intranodal AVB and sinus bradycardia, it can be dangerous in the presence of infranodal AVB. This is due to an increase in the sinus rate without an increase in the escape rate, leading to a decrease in the effective ratio of conduction and a decrease in ventricular rate.[5] Atropine is administered in intravenous doses of 0.5 to 1 mg and repeated if no response, to a total dose of 0.04 mg/kg. If the patient is hemodynamically unstable and not responsive to atropine, temporary pacing is indicated. For a summary of the Class I recommendations regarding prophylactic, temporary pacing in AMI complicated by AV and intraventricular conduction abnormalities, see Table 42.3. Third-degree AVB in the AMI setting should be treated with transvenous temporary pacing. Ventricular asystole should be treated as per the Advanced Cardiac Life Support guidelines.

TABLE
42.3 Class I Recommendations for Prophylactic, Temporary Pacing in AMI

		Atrioventricular Conduction					
		First-Degree AVB		Second-Degree AVB Type I		Second-Degree AVB Type II	
		Anterior MI	Other MI	Anterior MI	Other MI	Anterior MI	Other MI
Intraventricular Conduction	Normal	Observe	Observe	TC	TC	TC	TC
	New or old fascicular block	TC	TC (IIa)	TC	TC	TC	TC
	Old BBB	TC	TC	TC	TC	TC	TC
	New BBB	TC	TC	TC	TC	TV	TV
	Fascicular block + RBBB	TC	TC	TC	TC	TV	TV
	Alternating left and right BBB	*TV*	*TV*	*TV*	*TV*	*TV*	*TV*

The actions listed—transcutaneous (TC) pacing, transvenous (TV) pacing, or observation—are based on the patient's AV and intraventricular conduction patterns as well as the location of the MI. TC pacing refers to having pacing pads on the patient while monitoring closely. If in fact patient requires persistent TC pacing, TV pacing should be strongly considered. To determine the Class I indication, follow the row containing the patient's

intraventricular conduction pattern to the column containing the patient's AV conduction pattern and MI location. Class I recommendations are those for which there is evidence and/or general agreement that the treatment is beneficial, useful, and effective. Class IIa recommendations are those for which there is conflicting evidence and/or a divergence of opinion regarding the usefulness/effectiveness of the treatment; however, the weight of evidence or opinion is in favor of usefulness/efficacy. Class IIa is included only when a Class I recommendation does not exist. AVB, atrioventricular block; BBB, bundle branch block; RBBB, right bundle branch block.

Modified from Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary. J Am Coll Cardiol. 2004:44(3):671–719.

Tachyarrhythmias

Tachyarrhythmias are common in the setting of AMI. The most deadly, primary ventricular fibrillation (VF), occurs in 3% to 5% of patients within the first few hours of STEMI. This high frequency and early occurrence underscores the importance of early hospitalization and rapid triage to an area where continuous monitoring and rapid defibrillation can occur.

In the setting of AMI, especially when complicated by CGS, tachyarrhythmias must be dealt with emergently. They increase myocardial oxygen consumption, exacerbate ischemia, and can lead to or worsen CHF and CGS. Betablockers and calcium channel blockers must be avoided if shock or significant heart failure is present, as they can contribute to hemodynamic decompensation. Often cardioversion becomes the treatment of first choice. Heightened vigilance is appropriate when sinus tachycardia is present in the AMI setting, as this may be compensatory for a severely depressed myocardium. Although betablocker administration has been proven beneficial in the AMI setting, it can be deadly if used to treat sinus tachycardia that is compensatory for a severely depressed myocardium. Finally, accelerated idioventricular rhythm occurs in approximately 30% of AMI patients, often in those with involvement of the inferior wall and following reperfusion therapy.[41] It is characterized by a wide complex QRS with regular rates between 60 and 120 bpm, AV dissociation with the V-rate surpassing the A-rate, with fusion and capture beats. It occurs because an ectopic ventricular focus assumes the role of the predominant pacemaker. Accelerating the sinus rhythm or atrial pacing can cause suppression of this rhythm if treatment becomes necessary. Treatment is indicated only when there is hemodynamic compromise, symptoms as a result of the rhythm, or the R wave consistently falls on the T wave, predisposing to more serious ventricular arrhythmias.

SUMMARY

- Although short- and long-term mortality following AMI has improved with the use of thrombolytic therapy and early coronary reperfusion strategies, both remain high.
- The greatest fraction of deaths comes from CGS, which results from isolated LV

systolic dysfunction or mechanical disruption of the myocardium.

- It is imperative that these patients be identified early for the institution of appropriate therapeutic measures in a prompt manner. These include immediate efforts to achieve hemodynamic stability, rapid transport to the cardiac catheterization laboratory, and emergency PCI or surgical consultation when indicated.
- These patients should be monitored closely in an ICU setting, where arrhythmias and other potentially catastrophic complications can be dealt with expediently.

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QUESTIONS AND ANSWERS

Questions

1. All of the following should raise suspicion of subacute free wall rupture, except:
   a. Intermittent chest pain, hypotension, and electromechanical dissociation
   b. Agitation and apprehension
   c. Intermittent, nonspecific, ST–T-wave abnormalities
   d. Pericardial effusion and echodensities in the pericardium
   e. Nonsustained ventricular tachycardia

2. Which of the following statements regarding ventricular septal rupture complicating acute myocardial infarction (AMI) is true?
   a. It is usually seen in elderly, hypertensive patients with a history of multiple prior infarctions.
   b. It is more common in anterior than inferior infarctions.
   c. A 4/6 holosystolic murmur indicates a large defect.
   d. Either echocardiography or right heart catheterization can be used as the initial diagnostic tool.
   e. Surgery should be delayed several weeks until infarct healing occurs.

3. Which of the following statements regarding papillary muscle rupture complicating AMI is true?
   a. Papillary muscle rupture is most frequently seen in large, anterolateral infarctions.
   b. Patients should be referred for emergency catheterization and percutaneous intervention.
   c. A harsh holosystolic murmur and systolic thrill are very common.
   d. Despite pulmonary edema or shock, overall left ventricular (LV) systolic function may be normal.
   e. Right heart catheterization is the diagnostic modality of choice.

4. Case: A 75-year-old woman with a history of hypertension and hyperlipidemia presents to the emergency department (ED) with dyspnea and fatigue. Thirty-six hours prior to presentation, she experienced substernal chest pressure that was severe, sudden in onset, and persisted for " a few hours." She provides a history of exertional chest discomfort for the past 2 months.

Exam: Blood pressure 95/60, heart rate 110, respiratory rate 28, pulse oximetry 88%, room air temperature 37°C
Neck: Elevated neck veins
Lungs: Bibasilar inspiratory crackles halfway up posterior thorax
Heart: Point of maximal impact displaced laterally, palpable thrill over the left, fourth intercostal space, tachycardic, regular, S_1 and S_2 normal, 3/6 holosystolic murmur heard best at left, lateral sternal border
Extremities: Trace edema, somewhat cool, 2+ distal pulses throughout
Electrocardiogram (ECG): sinus tachycardia, Q waves and T-wave inversion in leads V_1–V_5.
Chest x-ray (CXR): Cardiomegaly, pulmonary edema
Labs: CK 500 U/L, CKMB 50 ng/mL, troponin-T 12 ng/mL, creatinine 1.5 mg/dL
In addition to ordering oxygen therapy, Lasix, aspirin, and nitroglycerin, what should be performed next?
   a. Arterial blood gas
   b. Left heart catheterization
   c. Transthoracic echocardiogram
   d. Placement of a right heart catheter
   e. Cardiac computed tomography (CT) scan

5. The above study demonstrated that the patient had an apical ventricular septal defect (VSD), an akinetic anterior wall, and right ventricular (RV) dilation. What should be the next step?
   a. Cardiothoracic surgery consultation
   b. Left heart catheterization
   c. Placement of an intra-aortic balloon pump (IABP)
   d. Placement of a right heart catheter

6. Case: A 68-year-old male with history of hypertension, hyperlipidemia, and diabetes mellitus presents to the ED with an episode of chest pain and syncope.

Exam: Blood pressure 92/50, heart rate 128, respiratory rate 28, pulse oximetry 94%, room air temperature 37°C
Neck: Elevated neck veins
Lungs: Clear to auscultation
Heart: Irregularly irregular rhythm with S_1 and S_2 normal, 3/6 holosystolic murmur heard best at left, lateral sternal border which increases with respiration
Extremities: Trace edema, somewhat cool, 1 + distal pulses throughout
ECG: Atrial fibrillation, ST elevations in II, III, and AVF (highest in lead III).
CXR: Cardiomegaly, clear lungs
Labs: CK 750 U/L, CKMB 80 ng/mL, troponin-T 12 ng/mL, creatinine 1.2 mg/dL
You have access to a catheterization laboratory in the next 90 minutes. Aside from activating the catheterization team, all of the following approaches are reasonable except:
   a. Obtaining an EKG with right-sided leads
   b. IV fluid administration
   c. Direct current cardioversion (DCCV) for treatment of atrial fibrillation
   d. IV NTG administration for relief of chest pain
   e. A-V synchronous pacing in the event of bradycardia

Answers

1. Answer E: A high index of suspicion is needed to diagnose subacute free wall rupture. Accurate and timely diagnosis provides valuable time for surgical treatment before acute rupture and pericardial tamponade lead to death. Intermittent chest pain, nausea, electromechanical dissociation, and hypotension along with dynamic ST-T-wave changes and agitation can all be present in cases of subacute rupture.

2. Answer D: In most series, the frequency of ventricular septal rupture was equal in anterior and inferior myocardial infarctions (IMIs). Although it is usually seen in elderly hypertensive patients, many times it occurs in the setting of a first myocardial infarction (MI). The intensity of the murmur is usually inversely proportional to the size of the defect. Both echocardiography and right heart catheterization can be used as initial diagnostic modalities. Surgery should be performed emergently.

3. Answer D: Many times a relatively small MI may be the culprit in papillary muscle rupture. Hyperdynamic LV function in the setting of a relatively small MI may appear puzzling in a patient with severe pulmonary edema and cardiogenic shock (CGS). Papillary muscle rupture is most frequently seen in inferior and posterior MIs because of the single blood supply of the posteromedial papillary muscle. Although coronary angiography may be needed before surgery, definitive treatment requires emergency surgery, not percutaneous intervention. In many patients a systolic murmur may be audible, but the absence of a murmur does not rule out presence of papillary muscle rupture. A systolic thrill is very uncommon in papillary muscle rupture, as opposed to ventricular septal rupture. The diagnostic modality of choice is echocardiography.

4. Answer C: The clinical picture is consistent with an anterior MI that occurred more than 24 hours ago and the patient now presents in Killip Class III heart failure. Although the congestive heart failure (CHF) may very well be secondary to a large anterior MI, her exam creates concern of a mechanical complication. In addition to oxygen therapy and initial measures to treat her pulmonary edema, she should have an emergency transthoracic echocardiography (TTE). An arterial blood gas is not essential

in this situation because the clinical picture is clear and CO_2 retention is not a concern at the moment. One can follow her oxygenation status by pulse oximetry. Although urgent left heart catheterization is indicated in patients with AMI complicated by CHF and CGS, this patient is several hours out of her acute event and the route of revascularization will be dictated by the presence or absence of a mechanical complication. A ventriculogram can diagnose a VSD as well, but there is time to obtain a transthoracic echocardiogram in the present situation. A right heart catheterization is also indicated in this situation, but this can be performed in the catheterization laboratory or the coronary intensive care unit (ICU) and does not need to be done immediately. A cardiac CT has no place in this situation.

5. Answer A: The next step should be a consultation to cardiothoracic surgery. Make the page, and while you are waiting for a response, make arrangements for the patient to go to the catheterization laboratory and subsequently the coronary ICU until surgery can be performed. In the catheterization laboratory, in addition to obtaining the coronary anatomy, an IABP and RHC can be placed. Further medical management can occur in the coronary care unit while plans for surgery are being made.

6. Answer D: The patient is presenting with IMI with RV involvement. This is suggested in a scenario of MI with clear lung fields, elevated jugular venous pressure, and suggestive EKG changes. In this scenario, EKG with rightsided leads might show ST elevations in leads V4r and V5r. These patients might present with syncope due to the preload dependence of the RV. As such, fluid administration and maintenance of sinus rhythm with AV synchrony help stabilize the hemodynamics. Administration of nitroglycerin should be avoided as this might lead to diminished preload further worsening the hemodynamic picture.

CHAPTER

Risk Stratification and Post–Myocardial Infarction Therapy

Willis M. Wu and Samir R. Kapadia

Unstable angina, non–ST-segment-elevation myocardial infarction (NSTEMI), and ST-segment-elevation myocardial infarction (STEMI) represent a spectrum of ischemic coronary disease of similar etiology—atherosclerotic plaque instability and rupture—termed acute coronary syndrome (ACS). The role of risk stratification in ACS is to identify which patients have increased risk for adverse events and are therefore more likely to benefit from the array of mechanical and pharmacologic therapies available. Risk stratification after myocardial infarction (MI) begins during the initial clinical encounter, continues throughout the index hospitalization, and remains important after discharge. Although modern advances have had a significant impact on outcomes of MI, post-ACS morbidity (and mortality) remain a challenging problem, most notably recurrent ischemia and infarction, congestive heart failure (CHF), and sudden cardiac death (SCD).

Recent data favor an early invasive approach for most patients. Early aggressive lipid-lowering therapy post-MI is clearly beneficial, with lower targets for low-density lipo-protein (LDL) levels. The importance of neurohormonal blockade has become apparent, particularly in patients with left-ventricular systolic dysfunction. Antiplatelet therapies have become essential, both during and after ACS, but in particular following percutaneous coronary intervention (PCI). The role of the implantable cardioverter–defibrillator (ICD) after MI has become clearer, with recent trials indicating no benefit to ICD early in the course post-MI, but demonstrable subsequent benefit in patients with significant left ventricular (LV) dysfunction. The recognition of the role of inflammation in ACS has led to the development of clinical assays measuring inflammatory markers such as C-reactive protein (CRP) and brain natriuretic peptide (BNP), but their role in clinical practice is not well established. Lifestyle modification and risk-factor reduction remain important, including smoking cessation, diabetes, and hypertension management.

RISK STRATIFICATION FOR ST-ELEVATION MI

Identification of high-risk characteristics early after MI is important because 25% of deaths during the first postinfarction year occur within the first 48 hours of hospitalization, and more than one-half of deaths occur within the first month after STEMI. Demographic and clinical data, electrocardiogram (ECG), serum markers, and various diagnostic tests assist in the risk assessment.

Initial Presentation

Clinical and Demographic Factors

The most important predictors of death within 30 days are age, systolic blood pressure (SBP) and heart rate at presentation, evidence of CHF on physical examination, location of infarction, and previous infarction. In the Global Utilization of Streptokinase and TPA for Occluded Arteries-I (GUSTO-1) study, these predictors accounted for >90% of the total prognostic information. Additional important prognostic factors include female gender, history of diabetes, hypertension, smoking, and vascular disease (Table 43.1).

TABLE
43.1 Predictors of Mortality in STEMI

Variable	TIMI-II (*n* = 3,339)	GISSI-2 (*n* = 10,219)	GUSTO-I (*n* = 41,021)
Age	++	++	++
Prior MI	++	++	++
Diabetes	++	+	++
Smoking	++	—	++
Hypertension	+	+	++
Female gender	++	+	+
Vascular disease	—	—	++

+ , univariate predictor; ++, multivariate predictor.

Advanced age has been recognized as an important predictor of mortality in several studies. In the NRMI (National Registry of Myocardial Infarction) registry, a community-based database with information on >350,000 patients with acute MI at U.S. hospitals, in-hospital mortality ranged from 3% for patients younger than 55 years of age to 28% for individuals more than 84 years of age. Older patients are more likely to possess a history of a prior MI, have more severe coronary disease, and consequently are more likely to develop CHF and cardiogenic shock after MI. Additionally, several reports have shown that older patients are also less likely to receive life-saving

therapies such as immediate reperfusion therapy, beta-blockers, and aspirin, which may contribute to the worsened prognosis.

In several studies, women have been shown to have higher mortality after STEMI. In the GUSTO-1 trial, women had higher 30-day mortality (11.3% vs. 5.5%), occurrence of shock (9% vs. 5%), and reinfarction (5.1% vs. 3.6%) compared to men. Part of this increased risk can be explained by the advanced age and increased prevalence of preexisting diabetes and hypertension. Additionally, women are more likely to present late during an infarction.

Paradoxically, smokers possess a lower risk for early mortality, most likely because of their younger age. Diabetes mellitus has been associated with a 1.5 to 3.0 times higher mortality after STEMI. Whether this is due to a higher atherosclerotic burden or some other characteristic induced by the diabetic state, such as silent ischemia or a larger infarct size, remains unclear. Further, the nonfatal complications are also higher in diabetic patients, including a greater incidence of postinfarction angina, reinfarction, and heart failure.

Physical Examination

The clues to right ventricular (RV) and LV dysfunction on physical examination provide the most important prognostic information. Accordingly, variables predictive of a worsened outcome include hypotension, tachycardia, jugular venous distension, an S_3 gallop, pulmonary edema, and evidence of peripheral hypoperfusion, many of which are captured by the Killip classification (Table 43.2). The physical examination can also help to identify mechanical complications of MI, such as acute mitral regurgitation, ventricular septal defect, and free wall rupture, all of which have been associated with significant mortality.

TABLE
43.2 Killip Classification and Mortality from GUSTO-I Trial

Killip Class	Features	Patients on Entry (%)	30-d Mortality (%)
I	No CHF	70	2
II	Early CHF (crackles, S_3)	20	20
III	Pulmonary edema (1/2 lung fields)	5	33
IV	Cardiogenic shock	5	66

CHF, congestive heart failure.

Electrocardiogram

The ECG provides useful information about the location and size of infarction, likelihood of tissue reperfusion after treatment, presence of ongoing ischemia, and conduction system dysfunction. The finding of ST elevation or depression has similar prognostic implications (Fig. 43.1). Mortality is greater in patients experiencing anterior wall MI compared to after inferior MI, even when corrected for infarct size. Patients with RV infarction complicating inferior infarction have a higher mortality rate than patients sustaining an inferior infarction without RV involvement. Patients with multiple leads showing ST-segment elevation and those with a high degree of ST-segment elevation have increased mortality, especially if their infarct is anterior. Patients with persistent or advanced heart block (e.g., Mobitz type II, second-degree, or third-degree AV block) or new intraventricular conduction abnormalities (bifascicular or trifascicular) in the course of an acute MI have a worse prognosis than do patients without these abnormalities. The influence of high-grade conduction block is particularly important in patients with RV infarction, for such patients have a markedly increased mortality. Other ECG findings suggesting a worse outcome are persistent horizontal or downsloping ST-segment depression, Q waves in multiple leads, evidence of RV infarction accompanying an inferior infarction, ST-segment depressions in anterior leads in patients with an inferior infarction, and atrial arrhythmias (especially atrial fibrillation).

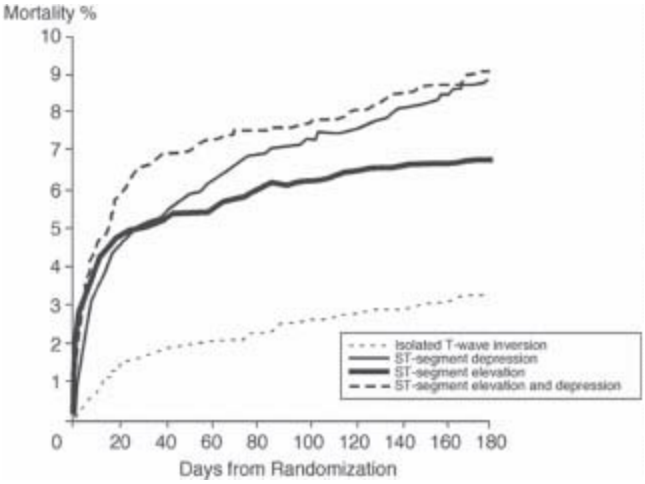

FIGURE 43.1 Mortality rate according to electrocardiographic findings on presentation with acute MI in the GUSTO IIb trial. (Adapted from Savonitto S, Ardissino D, Granger CB, et al. Prognostic Value of the Admission Electrocardiogram in Acute Coronary Syndromes.JAMA 1999;281:707–713.)

Other than these well-established predictors on ECG, ST-segment resolution has generated renewed interest in determining effectiveness of reperfusion therapy. Resolution of ST elevation predicts successful perfusion at the myocardial level, which is the most important predictor of LV function and survival. Continuous ST-segment

monitoring has been shown to yield important prognostic information after 60 minutes of observation. In the ASSENT 2 (Assessment of Safety and Efficacy of a New Thrombolytic) and ASSENT-PLUS studies, the optimal cutoff for ST-segment resolution analyses was found to be 50%, measured at 60 minutes. Patients with ST resolution (40%) by this criterion had a 30-day mortality of only 1.4%.

Biomarker Assessment

Two separate groups of biomarkers have been used to predict outcome after MI. One group includes the myocardial enzymes that predict infarct size and another group assesses the degree of systemic vascular inflammation. The prognostic value of CRP, endothelin, BNP, CD40, and CD40 ligand has recently been investigated extensively. These markers of inflammation seem to predict an active atherosclerotic disease process. Aggressive risk-factor modification may be more important when the levels of these markers are high.

More conventional markers of myocardial damage include troponin-I or -T, creatine kinase (CK), CK-MB 1 and 2 isoforms, CK-MB isoenzyme mass, and occasionally myoglobin. The presence and degree of troponin, CK, and CK-MB isoenzyme elevation on admission and thereafter have been associated with poorer outcome in the setting of both STEMI and NSTEMI. However, there is less information on troponin levels in STEMI. In the GUSTO IIa study, 30-day mortality was substantially higher among patients who were troponin-T positive. Given their more rapid return to baseline, CK and CK-MB isoenzymes are also helpful for identifying high-risk individuals by facilitating the diagnosis of reinfarction shortly after an STEMI or NSTEMI. Currently, infarct size is determined by CK-MB mass; the role of troponin-I or -T in this matter has been less well established.

Imaging

Imaging at the time of acute infarction is used to determine the amount of jeopardized myocardium. Contrast echocardiography and technetium-based imaging can be used to quantify perfusion noninvasively. Nuclear scanning is superior for quantifying perfusion, whereas echocardiography is better for assessing function. Acute imaging has been used principally in clinical trials to determine the degree of myocardial salvage, which is the percent of ischemic myocardium atpresentation that has adequate perfusion on follow-up.

During Hospitalization

Recurrent angina is an important predictor of a worsened outcome and the need for revascularization. Recurrent chest pain frequently signifies ischemic myocardium, either

in the peri-infarct territory supplied by the infarct-related artery or ischemia at a distance secondary to a non–infarct-related artery. Early revascularization is required in many patients who have postinfarct angina. Other important predictors include LV or RV dysfunction and mechanical complications of MI. Cardiogenic shock possesses a very high mortality in which medical management is not effective. Early revascularization in patients who develop cardiogenic shock within 36 hours of an MI is recommended, based on the findings of the SHOCK (Should We Emergently Revascularize Occluded Coronary Arteries for Cardiogenic Shock) trial, which showed reduced mortality with early revascularization compared to medical stabilization (33.3% vs. 51.6%). Arrhythmias, including high-grade AV block, atrial fibrillation, or ventricular tachycardia, also predict poor outcome.

Predischarge Assessment

Although significant emphasis is placed on predischarge risk stratification, many high-risk patients will declare themselves clinically during their hospital stay. The challenge for the clinician during the predischarge phase is to distinguish the few patients who remain at higher risk from the many relatively lower-risk patients. Although multiple testing technologies have been developed to aid in this process, the low event rate in these patients (1-year mortality rates of 2% to 5%) mandates that these tests must be highly sensitive and specific if they are to have clinical value. What tests should be routinely performed for predischarge risk stratification is highly debated. Risk stratification at discharge can be accomplished by determining three factors: (a) resting LV function, (b) residual potentially ischemic myocardium, and (c) susceptibility to serious ventricular arrhythmias. More sophisticated testing may provide additional data but may not be as useful in changing patient outcomes.

LV Function Assessment

Assessment of LV function is typically performed by echocardiography or by ventriculography at the time of cardiac catheterization. However, imaging of the left ventricle at rest may not distinguish between infarcted, irreversibly damaged myocardium and hibernating myocardium. Therefore, many different techniques have been used to determine viable myocardium, including dobutamine echocardiography, rest-redistribution thallium, positron emission tomography (PET) scanning, and magnetic resonance imaging (MRI). Dobutamine echocardiography can provide functional assessment along with information on viability and ischemia. However, the results are directly dependent on the expertise and experience of the interpreter. Radionucleotide imaging provides higher sensitivity to detect ischemia, but specificity can be compromised by the size of the patient, diaphragmatic or breast attenuation.

Further, regional wall motion assessment is not as precise as with echocardiography. Regardless of the imaging modality chosen, the prognosis is worse if there is significant LV dysfunction, or if there is a large amount of ischemic myocardium.

Stress Testing

Patients who do not have high-risk features after successful thrombolysis should be considered for exercise stress testing. Although the predictive accuracy of exercise stress testing has diminished in the reperfusion era as a result of the lower incidence of adverse outcomes, it is still given a Class I indication under current American College of Cardiology/American Heart Association (ACC/AHA) guidelines. In addition, although it is not known whether exercise testing can effectively risk-stratify patients who have not received acute reperfusion therapy, it is also assumed to be effective in this setting. Low-level exercise appears to be safe in patients who have been free of angina or heart failure and who possess a stable baseline ECG during the previous 2 to 3 days. Patients who are unable to exercise or who have baseline ECG abnormalities that would preclude interpretation should undergo an exercise test with imaging. Patients who cannot achieve a 3 or 4 MET workload, those who develop ischemia at a low level of exercise, or those in whom blood pressure (BP) drops during exercise should undergo coronary angiography. No further testing should be necessary in patients without these high-risk findings.

Assessment for Risk of Sudden Cardiac Death

Determination of risk for SCD after MI is important because it is highest in the first 1 to 2 years after the index event. The most important predictor for SCD is LV dysfunction. Provocative electrophysiology studies are not necessary for risk stratification. Signal-averaged ECG, heart-rate variability, QT dispersion, and baroreflex sensitivity have been investigated to select specific patients with LV dysfunction who might benefit from an ICD. The presence of a filtered QRS complex duration >120 milliseconds and abnormal late potentials recorded on a signal-averaged ECG after acute MI signifies somewhat higher risk for SCD. However, the signal-averaged ECG suffers from a high false-positive rate, which makes the test clinically less useful. Depressed heart-rate variability is an independent predictor of mortality and arrhythmic complications after acute MI. A depressed baroreflex sensitivity value (3.0 millisecond/mm Hg) is associated with about a threefold increase in the risk of mortality. These tests may provide useful prognostic information, but at present, only assessment of ejection fraction (EF) is necessary to determine eligibility for a device, where significant LV dysfunction qualifies a patient for ICD placement. Recent data indicate, however, that ICD therapy is not beneficial in the early post-MI period, and should be delayed for at

least 1 month after an infarction. ICD implantation is generally deferred for 3 months after revascularization, either surgically or percutaneously, at which time reevaluation of LV function can be performed.

Predischarge Management

In contemporary practice, most patients with MI will undergo cardiac catheterization, even after receiving thrombolytics for STEMI, based on the CARESS in AMI and TRANSFER AMI trials and the most recent guidelines. In the minority of patients who do not undergo catheterization initially, a judgment is made as to the presence of clinical variables indicative of high risk for future cardiac events. Patients with spontaneous episodes of ischemia or depressed LV function who are considered suitable candidates for revascularization based on their overall medical condition should be referred for cardiac catheterization. These patients are at increased risk of recurrent infarction (and subsequent increased mortality), and may benefit from revascularization if severe coronary artery disease (CAD) is identified at catheterization.

NON–ST-ELEVATION ACS

Many patients with ACS present without ST elevation on ECG. It is important to note that although the risk of mortality during the index hospitalization is less than in those with ST-elevation ACS, the prognosis at 1 year is similar (see Fig. 43.1). Typically, the underlying pathophysiology is a high-grade stenosis with plaque rupture, but unlike STEMI, the vessel is not totally occluded. Indeed, fibrinolysis has been shown to be of no benefit and may actually be harmful in this patient cohort. Multiple trials have investigated the role of early angiography and PCI versus conservative management in these patients, and it appears that early invasive strategy in the high-risk population provides the best outcome and may even be more cost effective than a conservative strategy.

Non–ST-Elevation MI Risk Stratification

Initial Presentation

A number of historical features predictive of a worse prognosis following non–ST-elevation ACS have been derived from existing trial data. These features are summarized in Table 43.3. The most important are older age, greater number of cardiac risk factors, known CAD, peripheral vascular or cerebrovascular disease, prior MI, previous PCI or coronary artery bypass graft surgery, history of CHF, a more severe anginal pattern, and the use of aspirin within a week of presentation.

TABLE

43.3 Predictors of a Worse Prognosis in NSTEMI

Variable	PURSUIT (*n* = 9,461)	TIMI-IIB (*n* = 1,957)	ESSENCE (*n* = 3,171)
Age	++	++	++
CAD	—	++	++
Diabetes	++	—	++
Vascular disease	++	—	—
CHF history	++	—	—
Anginal severity	++	++	++
Aspirin within 7 d	—	++	—

Other study predictors include female gender, number of risk factors, previous MI, prior PCI/CABG.

Electrocardiogram

Among patients with non–ST-elevation ACS, the presence of Q waves, ST changes associated with angina or at presentation (in particular, ST-segment depression), T-wave inversions of significant amplitude (i.e., >0.2 mV), or the absence of ECG changes during angina are important predictors of future events (see Fig. 43.1). When clinical variables are also considered, heart rate and the presence of ST depression on admission ECG are the most important multivariable predictors.

Biomarkers

The presence and degree of troponin elevation on admission and thereafter can identify patients who are at increased risk of experiencing adverse outcomes. Cardiac troponin-I and troponin-T are particularly useful in identifying high-risk patients with non–ST-elevation ACS. Other markers of inflammation, such as CRP, CD-40, CD-40 ligand, fibrinogen levels, or brain natriuretic peptide (BNP) can add to the prognostic information in ACS. Adding multiple markers to assess a patient may add important prognostic information, as illustrated in the OPUS-TIMI 16 (Oral Glycoprotein IIb/IIIa Inhibition with Orbofiban in Patients with Unstable Coronary Syndromes) trial and the TACTICS-TIMI 18 (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy) analyses (Fig. 43.2). However, at the present time, there is no clear consensus on how to incorporate these markers in patient management.

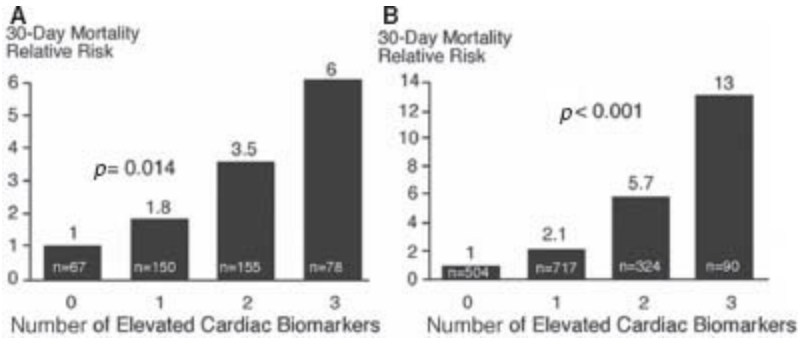

FIGURE 43.2 Relative 30-day mortality risks in OPUS-TIMI 16 **(A)** and TACTICS-TIMI 18 **(B)** in patients stratified by the number of elevated cardiac biomarkers (TnI, CRP, and BNP). (From Sabatine MS, Morrow DA, de Lemos JA, et al. Multimarker Approach to Risk Stratification in Non-ST Elevation Acute Coronary Syndromes. Circulation 2002;105:1760, with permission from Wolters Kluwer Health.)

Risk Scores

An essential element of risk stratification following an ACS is the quantification of short-term and long-term risk. Although there are many historical, physical exam, ECG, and biomarker variables that are significantly and independently associated with worse short-term outcome, the integration of these into an accurate estimation of risk is complex and has traditionally required the use of sophisticated multivariable modeling (Figs. 43.3 and 43.4). Nevertheless, simplified nomograms and risk scores incorporating the most important variables have been derived from a number of these analyses and allow for a reasonably accurate categorization of patients into low-risk, intermediate-risk, and high-risk groups. In the analysis by Boersma et al. patient age, heart rate, SBP, ST-segment deviation, signs of heart failure, and elevation of cardiac markers were the most important predictors of death or MI at 30 days. In the analysis by Antman et al. (TIMI risk score, see Fig. 43.3), age >65 years, >3 coronary risk factors, prior CAD, ST deviation, >2 angina episodes in last 24 hours, use of aspirin within 7 days, and elevated cardiac markers were important in determining death, reinfarction, or recurrent severe ischemia requiring revascularization (termed TIMI risk score).

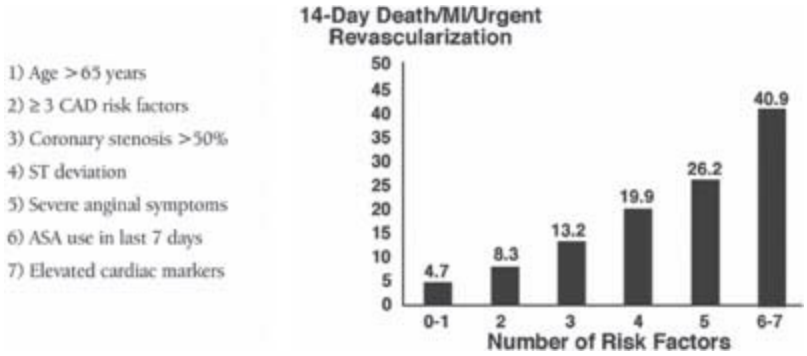

FIGURE 43.3 TIMI risk score (Adapted from Antman EM, Cohen M, Bernink PJLM, et al.The TIMI Risk Score for Unstable Angina/Non-ST Elevation MI. JAMA 2000;284:835–842.)

		Score	
		Death	Death/MI
Age (year)	50	0	8 (11)
	60	2 (3)	9 (12)
	70	4 (6)	11 (13)
	80	6 (9)	12 (14)
Gender	Female	0	0
	Male	1	1
Worst 6-wk CCS	0-2	0	0
	3-4	2	2
HR (bpm)	80	0	0
	100	1 (2)	0
	120	2 (5)	0
SBP (mmHg)	120	0	0
	100	1	0
	80	2	0
Rales	No	0	0
	Yes	3	2
Baseline ST-dep	No	0	0
	Yes	3	1

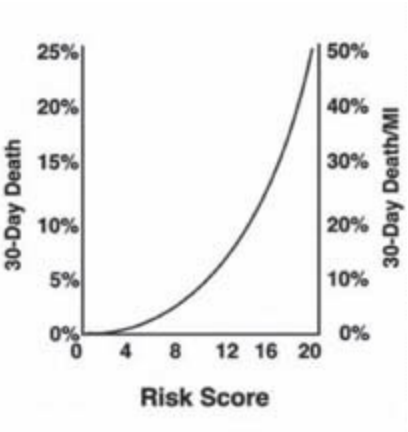

FIGURE 43.4 PURSUIT risk score 30-day outcome after non–ST-elevation ACS. (From Boersma E,Pieper KS, Steyerberg EW, et al. Predictors of Outcome in Patients With Acute Coronary Syndromes Without Persisent ST-Segment Elevation: Results From an International Trial of 9461 Patients.Circulation. 2000;101:2557–2567, with permission from Wolters Kluwer Health.)

During-Hospitalization and Predischarge Risk Stratification

According to current ACC/AHA guidelines, patients who are deemed to be high risk, including those with recurrent ischemia or reinfarction, CHF, hemodynamic compromise, or life-threatening arrhythmias, are candidates for early angiography. Additionally, the guidelines recommend angiography in those who have had prior PCI in the past 6 months, elevated cardiac biomarkers, new ST changes on EKG, high- risk score, or prior coronary artery bypass grafting (CABG).

The FRISC II (Fast Revascularization during Instability in Coronary Artery Disease) and TACTICS-TIMI 18 studies reported significant decreases in the rate of death or MI at 6 months among patients randomized to early angiography with revascularization as needed (i.e., early invasive approach.) The ISAR-COOL trial also demonstrated a decrease in death or large MI at 30-day follow-up in patients assigned to undergo angiography within 6 hours of presentation compared with 3 to 5 days. The TIMACS trial reflects contemporary medical practice by including patients treated with aspirin, clopidogrel, heparin, fondaparinux, and glycoprotein IIb/IIIa inhibitors. In this trial, the patients in the early invasive arm experienced less refractory ischemia, and patients with a higher GRACE risk score had fewer events of death, MI, and stroke.

In the absence of high-risk clinical features or post-ACS complications, patients who have not undergone coronary angiography should be considered at low or intermediate risk pending the results of further risk stratification. Noninvasive testing provides useful supplementary information beyond that available from clinically based assessments of risk in this cohort. The purpose of noninvasive testing is to identify ischemia and estimate prognosis. Accordingly, noninvasive evaluation should include an assessment of LV function and/or ischemia in order to identify patients who are at increased risk for adverse outcomes who are likely to benefit from coronary

angiography and revascularization. High-risk findings on noninvasive testing should direct patients to coronary angiography if they are eligible for revascularization (Table 43.4). It is not clear whether LV function assessment or myocardial perfusion imaging (with rest and during exercise or pharmacologic stress) is superior in assessing prognosis. The ability of most noninvasive tests to dichotomize patients into low-risk and high-risk groups appears similar (Table 43.5). Selection of the appropriate test should be based on patient characteristics, availability of the test, and institutional expertise in performance and interpretation.

TABLE
43.4 High-Risk Findings on Noninvasive Testing Leading to Coronary Angiography EKG-Abnormalities that Preclude Accurate Interpretation of an Exercise Stress Test

1. Severe resting LV dysfunction (LVEF < 0.35)
2. High-risk treadmill score (score ≤ −11)
3. Severe exercise LV dysfunction (exercise LVEF < 0.35)
4. Stress-induced large perfusion defect (particularly if anterior)
5. Stress-induced multiple perfusion defects of moderate size
6. Large, fixed perfusion defect with LV dilation or increased lung uptake (thallium-210)
7. Stress-induced moderate perfusion defect with LV dilation or increased lung uptake (thallium-201)
8. Echocardiographic wall motion abnormality (involving >2 segments) developing at a low dose of dobutamine (≤10 mg/kg/min) or at a low heart rate (<120 bpm)
9. Stress echocardiographic evidence of extensive ischemia

TABLE
43.5 Stress Test Predictors of Cardiac Death and MI

	Sensitivity		Specificity		PPV		NPV	
	CD	CD/MI	CD	CD/MI	CD	CD/MI	CD	CD/MI
Exercise ECG								
ST depression	0.42	0.44	0.75	0.70	0.04	0.16	0.98	0.91
Impaired SBP	0.44	0.23	0.79	0.87	0.11	0.21	0.96	0.88
Time of exercise	0.56	0.53	0.62	0.65	0.10	0.18	0.95	0.91
Exercise perfusion								
Reversible defect	0.89	0.80	0.38	0.48	0.07	0.16	0.98	0.95
Multiple defects	0.64	0.75	0.71	0.76	0.07	0.17	0.98	0.97
Exercise ventricular function								
Exercise RVG								
Peak EF <40%	0.63	0.60	0.77	0.75	0.27	0.31	0.94	0.91
Change in EF <5%	0.80	0.55	0.67	0.74	0.15	0.18	0.98	0.94
New wall motion defect		0.78		0.50		0.17		0.94
Exercise echocardiography								
Change in EF <5%		0.56		0.60		0.14		0.92
New wall motion defect	1.00	0.62	0.62	0.79	0.18	0.48	1.00	0.86
Pharmacologic stress myocardial perfusion								
Reversible defect	0.56	0.71	0.46	0.49	0.10	0.19	0.90	0.91
Multiple defects		0.50		0.64		0.17		0.90

PPV, positive predictive value; NPV, negative predictive value; SBP, systolic blood pressure; RVG, radionuclide ventriculography; EF, ejection fraction.

The ACC/AHA Guidelines recommend exercise ECG as the primary mode of noninvasive stress testing. Patients with baseline ECG abnormalities that preclude accurate interpretation (Table 43.6) should undergo an exercise test with imaging. Those who are unable to exercise (the cohort at highest risk of future adverse outcomes) should undergo pharmacologic stress testing with imaging. According to the ACC/AHA Guidelines, stress testing is safe in low-risk patients who have been free of ischemia or CHF for 12 to 24 hours in intermediate-risk patients (Table 43.7). Patients who do not have any high-risk findings on noninvasive evaluation require no further testing.

TABLE
43.6 EKG Abnormalities that Preclude Accurate Interpretation of an Exercise Stress Test

Left bundle branch block
Left ventricular hypertrophy
Interventricular conduction deficit
Ventricular pacing
Ventricular pre-excitation
Digoxin effect

TABLE
43.7 Noninvasive Risk Stratification Prior to Discharge in Patients Managed with a Conservative Strategy who are Low to Intermediate Risk

Type of Test	Patient Population	Timing of Test
Exercise Treadmill Test	■ Patients able to exercise ■ EKG at baseline is without • ST-segment abnormalities • Bundle branch block • Left ventricular hypertrophy • Interventricular conduction delay • Paced rhythm • Pre-excitation • Digoxin effect	■ 12–24 h after presentation if free of ischemia at rest or low-level activity and heart failure
Stress Test with Imaging modality	■ Patients able to exercise but have the above-mentioned EKG abnormalities present at baseline	■ 12–24 h after presentation if free of ischemia at rest or low-level activity and heart failure
Pharmacologic Stress Test	■ Patients with physical limitations that preclude adequate exercise testing	■ 12–24 h after presentation if free of ischemia at rest or low-level activity and heart failure
Transthoracic echocardiogram or radionuclide angiogram	■ Patients with definite ACS who are not scheduled to undergo coronary angiography and left ventriculography	■ Any time prior to discharge

POST–MYOCARDIAL INFARCTION THERAPY

After MI, secondary prevention of cardiovascular events depends on prompt institution of appropriate pharmacotherapy, lifestyle changes, and comorbid disease management. In this area, recent advances have revealed the significant benefits of antiplatelet therapy, neurohormonal blockade, and lipid-lowering therapy. The importance of diet and exercise, as well as smoking cessation, cannot be overemphasized. In addition, optimal management of diabetes and hypertension are paramount to preventing further events. Residual LV function after MI is a strong determinant of the proper approach to post-MI pharmacotherapy. This section outlines the role of these therapies as well as lifestyle changes in the post-MI patient.

Antiplatelet Therapy

A large number of randomized, controlled trials, summarized in meta-analysis by the Antiplatelet Trialists' Collaboration, have documented the benefit of daily aspirin therapy after MI. Aspirin should be taken on a daily basis indefinitely by post-MI patients who can tolerate it, based on a reduction in recurrent infarction, stroke, or vascular death.

In patients treated without stenting, a daily dose of 75 to 162 mg should be prescribed. After percutaneous intervention, a dose of 162 to 325 mg should be prescribed for at least 1 month after bare metal stent implantation, 3 months for sirolimus-eluting stent implantation, and 6 months for paclitaxel-eluting stent implantation. Thereafter, a daily dose of 75 to 162 mg should be prescribed. Although the universal application of aspirin therapy among patients without contraindications is

accepted, a subset of patients can be shown to exhibit either biochemical or clinical resistance to aspirin. Such patients may potentially benefit from dual antiplatelet therapy, with the addition of a thienopyridine. Regardless of aspirin-resistance status, clopidogrel has also been shown to be beneficial when added to aspirin among patients with UA/NSTEMI. The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study demonstrated a 20% reduction in composite endpoint of nonfatal MI, stroke, and cardiovascular death after 9 months follow-up. Clopidogrel therapy after MI is also indicated for reduction in recurrent events in the setting of coronary stent implantation, based on analysis of the CREDO (Clopidogrel for the Reduction of Events during Observation) trial. Currently, the ACC/AHA recommendation is that patients who are treated medically for MIs be treated with clopidogrel 75 mg daily for at least 1 month and ideally up to 1 year. Patients who undergo percutaneous intervention should continue thienopyridine therapy for at least a year. Based on the recent TRITON TIMI-38 trial which demonstrated superior efficacy of prasugrel over clopidogrel in decreasing ischemic events in patients with ACS, the ACC/AHA guidelines have incorporated the use of prasugrel as an alternative to clopidogrel use. In appropriate patients, a 60 mg loading dose of prasugrel should be given to patients no later than 1 hour after PCI once the coronary anatomy has been established and should be continued at a maintenance dose of 10 mg daily for at least a year. Absolute contraindications to prasugrel include prior stroke or TIA. Patients at increased risk for bleeding on prasugrel include age >75 years and weight <60 kg, and caution is needed before prescribing this medication in these subgroups. In patients with increased risk of bleeding, earlier termination of thienopyridine therapy may be considered.

Of note, ibuprofen may attenuate the beneficial effects of aspirin in patients with cardiovascular disease, and its regular use should be discouraged for patients taking aspirin after MI. In fact, the most recent ACC/AHA guidelines discourage the use of all nonsteroidal anti-inflammatory agents except aspirin during hospitalization for MI due to an increased risk of mortality, reinfarction, hypertension, heart failure, and myocardial rupture. After discharge, patients should substitute nonsteroidal anti-inflammatory drugs (NSAIDs) for an alternative medication such as acetaminophen if available.

Anticoagulation

The primary use of oral anticoagulation (warfarin) in the post-MI patient has been shown to be at least as effective as aspirin in terms of risk reduction for recurrent MI. Its use as a substitute for aspirin is only recommended among aspirin-allergic patients, however, as the difficulty of administering oral anticoagulation and risk for major bleeding makes this a less than optimal alternative. In fact, the use of a thieno-pyridine (clopidogrel) appears more practical than warfarin in aspirin-allergic patients based in part on the CAPRIE trial which demonstrated superior efficacy with clopidogrel over

aspirin in preventing vascular outcomes. Combination therapy with aspirin and low-intensity warfarin (INR < 2.0) has not been shown to be superior to aspirin alone. Moderate and high-intensity oral anticoagulation plus aspirin has been shown to reduce subsequent cardiac events over aspirin alone, with increased bleeding risk only among the high-intensity patients. The use of oral anticoagulation with dual antiplatelet therapy has not been extensively studied. Current guidelines suggest considering the use of warfarin in post-MI patients with atrial fibrillation, LV thrombus, or other indication for anticoagulation such as arterial or venous thrombosis. It may also be used for secondary prevention, in combination with aspirin, among patients with LV dysfunction, with or without CHF, and/or extensive regional wall motion abnormalities.

Neurohormonal Blockade

Renin–Angiotensin–Aldosterone System Inhibition

The finding of LV dysfunction after MI is a strong predictor of subsequent mortality. The renin–angiotensin–aldosterone system (RAAS) is pivotal in modulating the extent of post-MI remodeling and LV dysfunction. Pharmacologic agents have been developed to block this critical pathway at various levels. Many well-designed trials have indicated that angiotensin-converting enzyme inhibitor (ACE inhibitor) use can improve long-term survival and attenuate the progression of LV failure and LV dilatation among post-MI patients with LV dysfunction. This is particularly true for patients with large, anterior STEMI. Current ACC/AHA Guidelines for UA/NSTEMI extend a class I indication to their use only to patients with CHF with LV dysfunction, hypertension, or diabetes. This recommendation was initially founded on the results of the HOPE (Heart Outcomes Prevention Evaluation) trial, which evaluated the effect of long-term ACE inhibitors among high-risk patients, many of whom (52%) had a prior MI. This trial found a highly significant reduction in MI, stroke, and cardiovascular mortality among such patients. In addition, subsequent secondary analysis of the initial trials confirmed the extension of benefit to all post-MI patients. Many different ACE inhibitors have been studied, and it does appear that ACE inhibitors demonstrate a "class effect," leading to no specific recommendation on the brand of ACE inhibitor.

Similar to ACE inhibitors, positive results have been found for the use of angiotensin-receptor blockers (ARBs) in post-MI patients. This class of medications should be provided as an alternative to ACE inhibitors among patients with intolerance or allergy to ACE inhibitors when LV dysfunction or clinical heart failure is present. However, given the extensive clinical experience with ACE inhibitors, and the potential positive effects of ACE inhibitors on the vascular endothelium through the bradykinin pathway, ACE inhibitors remain the first line of therapy in patients without contraindication. The combination of ACE inhibitor (captopril) and ARB (valsartan) has been evaluated in immediately post-MI patients in the VALIANT trial (Valsartan in

Acute Myocardial Infarction Trial). In this population, combination ACE inhibitor and ARB did not show any benefit over ACE inhibitor alone or ARB alone, although the combination did have increased adverse effects. Of note, valsartan was roughly equivalent to captopril in outcomes. The CHARM trial (Candesartan in Heart Failure Assessment in Reduction of Mortality) focused on patients with chronic CHF, although 60% of the patients studied had an ischemic etiology. This trial found a small absolute risk reduction with the addition of candesartan to an ACE inhibitor. Based on the findings of these two trials, the combination of ACE inhibitor and ARB can be considered in the long-term management of STEMI patients with persistent symptomatic heart failure and left ventricular ejection fraction (LVEF) < 0.40 (CHARM), but should be avoided in the acute setting (VALIANT).

Finally, aldosterone blockade has been shown to be beneficial in post-MI patients. The RALES trial (Randomized Aldactone Evaluation Study) evaluated patients with New York Heart Association Class III or IV heart failure (55% of patients had ischemic cardiomyopathy) and found a 24% relative risk reduction in all-cause mortality with 25 to 50 mg of spironolactone daily. More recently, the EPHESUS trial (Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) evaluated the use of an aldoster-one-receptor blocker, eplerenone, in acute MI patients with LV dysfunction (EF ≤ 0.40). The patients in this trial received optimal therapy, with reperfusion, aspirin, ACE inhibitor, beta-blockers, and statins. A significant relative risk reduction for all-cause mortality of 15% was seen among patients receiving eplerenone. It is important to note that patients with severe renal impairment (serum creatinine >2.5 mg/dL) or hyperkalemia (serum potassium >5.0 mmol/L) were excluded from this trial. These findings led to the inclusion of aldosterone blocking agents for post-MI patients with an EF < 40% and symptomatic heart failure or diabetes who are already on a therapeutic dose of an ACE inhibitor into the ACC/AHA guidelines with a class I indication.

Beta-Receptor Blockade

Beta-receptor blockade (beta-blockers) has long been considered important in patients with acute MI to reduce myocardial ischemia by decreasing oxygen demand. However, long-term beta-blocker therapy in the convalescent phase of MI has also been demonstrated to be beneficial in numerous trials, as demonstrated in Figure 43.5.

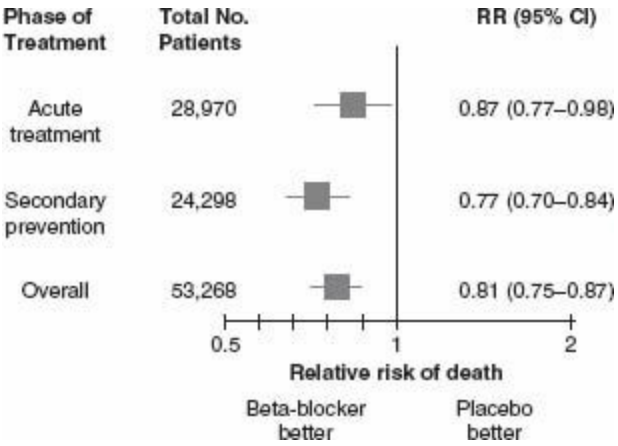

FIGURE 43.5 Summary of data from a meta-analysis of trials of beta- blockers for acute MI. (Reprinted from Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). J Am Coll Cardiol. 2004;44:E1–E211, with permission from Elsevier).

The postulated mechanism of benefit is similar to that seen with the RAAS, which is modulation of LV remodeling and LV dysfunction post-MI. After MI, the sympathetic nervous system has been found to increase infarct size, activate the RAAS, and promote myocyte injury. Oral beta- blockade should be initiated within the first 24 hours post-MI in the absence of signs of heart failure, a low output state, increased risk for cardiogenic shock (age >70, SBP < 120 mm Hg, heart rate >110 or <60 beats/min (bpm), increased time since onset of symptoms), or other relative contraindications to beta blockade (PR interval >240 milliseconds, second- or third-degree heart block, active asthma or reactive airways disease). Intravenous betablocker use is reasonable, but no longer has a class I recommendation level in the guidelines after the COMMIT trial demonstrated an increased risk of cardiogenic shock with IV betablocker use in STEMI patients, The BHAT trial (Beta-Blocker Heart Attack Trial), a prethrombolytic study, compared 180 to 240 mg of propranolol daily to placebo in post-MI patients, finding a 26% relative risk reduction for all-cause mortality, and a 28% reduction in sudden death. Although metoprolol and atenolol are frequently prescribed to post- MI patients, these agents have not been demonstrated to reduce mortality during long-term therapy. The MERIT-HF (Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure) trial evaluated the use of metoprolol in chronic CHF with EF < 40% and found a 33% reduction in mortality. This trial included 66% of patients with ischemic cardiomyopathy. The COMET (Carvedilol or Metoprolol European Trial) compared carvedilol, a nonselective beta-blocker with alpha-blocking capability, with metoprolol in patients with chronic CHF, and found a 17% reduction in the risk of death from carvedilol, relative to metoprolol. More recently, the CAPRICORN trial (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction) tested carvedilol in post-MI patients with significant LV dysfunction (EF ≤ 0.40). This trial

found similar reductions in all-cause mortality and sudden death to the BHAT trial. Current ACC/AHA Guidelines support the use of beta blockers indefinitely in all post-MI patients without contraindication, and recommend an approach that incorporates gradual titration in those patients with moderate or severe LV dysfunction.

Lipid Management

Pharmacologic lipid management after MI is crucial for secondary prevention of cardiac events. Patients should have a lipid profile checked prior to hospital discharge after MI and should have statin therapy initiated before leaving the hospital. The National Cholesterol Education Program (NCEP) published guidelines in 2001 (ATP III) for lipid-lowering therapy that encourage the use of therapeutic lifestyle changes" including weight reduction, increased physical activity, increased fiber intake, and reduced intake of saturated fats and cholesterol. The recommended drug therapy for lipid lowering includes statins, bile acid sequestrants, nicotinic acid (niacin), or fibric acids, depending on the patient's lipid profile and potential side effects.

The ATP III guidelines also established a LDL goal of <100 mg/dL among patients with known cardiovascular disease. However, since publication of that document, several trials have demonstrated that there is added benefit to additional LDL lowering in very-high-risk patients. This finding has led the ACC/AHA Guidelines writers to recommend targeting an LDL goal of "substantially <100 mg/dL" among STEMI patients. The PROVE-IT TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) study was pivotal in the change in recommendation. This trial compared moderate lipid lowering (40 mg of pravastatin) to aggressive lipid lowering (80 mg of atorvastatin) among patients with ACS. The LDL level attained with 40 mg of pravastatin was 95 mg/dL, while 80 mg of atorvastatin resulted in an LDL of 62 mg/dL, representing a 35% difference. The composite cardiovascular endpoint at 2 years was reduced by 16% with atorvastatin (Fig. 43.6).

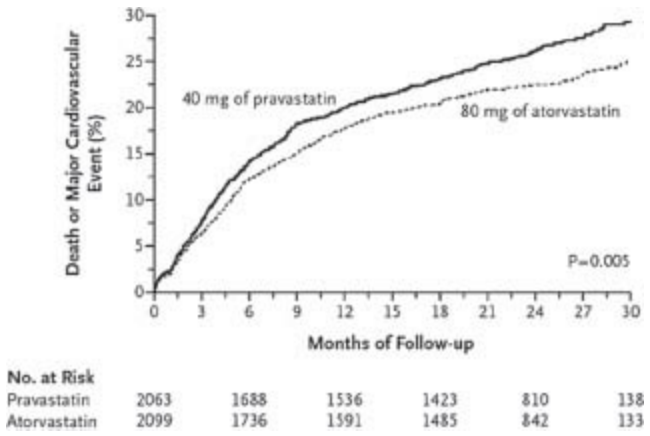

FIGURE 43.6 Kaplan–Meier estimates of the incidence of all-cause mortality in the PROVE-IT TIMI 22 study. (From Cannon C, Braunwald E, McCabe CH, et al. Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. N Engl J Med. 2004;350(15):1495–1504, with permission.)

This trial, as well as other recent trials such as MIRACL (Myocardial Ischemia Reduction with Acute Cholesterol Lowering), and Phase Z of the A to Z trial, demonstrates that more intensive LDL lowering does result in additional benefit in high-risk patients. It may be that the additional benefit to aggressive lipid lowering relates to reduction in inflammation, as evidenced by recent data from the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) trial, showing a relationship between progression of atherosclerosis and CRP levels.

Risk-Factor Management

Diabetic patients represent a high-risk subset because of macrovascular and microvascular complications including severe CAD, hypertension, peripheral vascular disease, and renal dysfunction. Prior conventional management of diabetes in the setting of ACS dictated strict management of glucose levels, but recent evidence has suggested potential harm with this strategy. The NICE-SUGAR trial enrolled patients in an ICU setting and demonstrated increased incidence of hypoglycemia and death with an intense glucose control that attempted to keep the glucose level between 81 and 108 mg/dL. Standard therapy allowed for glucose levels up to 180 mg/dL. Similarly, the ACCORD trial demonstrated increased mortality in type 2 diabetics who were assigned to the intensive therapy arm that targeted an A1c level below 6% versus those in the standard therapy group that aimed for A1c levels between 7% and 7.9%. The American Diabetes Association still recommends treating diabetic patients to achieve a target goal A1c of 7% or less, but care should be taken to avoid hypoglycemia.

Besides medical management of hyperglycemia, other clinical trials have shown that combined neurohormonal blockade with ACE inhibitors, aldosterone antagonists, and beta-blockers are essential in treatment of diabetic patients with prior MI, and these medications should be continued with this patient population. There is some concern about beta-blockers masking the symptoms of hypoglycemia in diabetic patients, but they have been shown to be beneficial and should be used with appropriate caution in this high-risk subset.

Hypertension management post-MI is important in risk reduction for subsequent MI. In addition to important lifestyle changes such as weight control, exercise, and sodium restriction, current guidelines state that treatment of BP with drug therapy post-MI should be initiated to reach a target BP of 140/80 for all patients, and 130/80 for diabetics and patients with renal insufficiency. However, it is reasonable to treat all patients post-MI to a target BP of 120/80, considering the high-risk population represented by post-MI patients. These recommendations are based on the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7). The same committee recommends the initiation of two agents if the BP is more than 20/10 mm Hg above goal. From a practical perspective, the post-MI patient should already be receiving a beta-blocker

and ACE inhibitor for reasons detailed above, especially among patients with LV dysfunction (EF < 40%). Although achieving maximal doses of these medications is essential, the optimal method of reaching target dose is a matter of conjecture. In addition to beta-blockers and ACE inhibitors, thiazide diuretics and long-acting calcium channel antagonists are excellent antihypertensive therapy choices with excellent supporting data from large, multicenter randomized trials, in particular the ALLHAT results (Antihypertensive and Lipid- Lowering Treatment to Prevent Heart Attack Trial).

Obesity is a major risk factor for coronary disease and should be carefully addressed in the post-MI patient as part of a comprehensive secondary risk-reduction strategy. In particular, body mass index and waist circumference have been shown to be important in risk assessment. The desirable body mass index range is 18.5 to 24.9 kg/m^2, and the desired waist circumference is <40 inches in men and 35 inches in women. Overweight patients should be advised regarding weight-management strategies and appropriate levels of physical activity. An initial weight loss of 10% of body weight over 6 months is the recommended target, at 1 to 2 pounds per week. Patients with an elevated waist circumference should be screened for the metabolic syndrome, a significant risk factor for coronary disease. In addition to decreasing caloric intake, patients should participate in aerobic activity, preferably individualized via an exercise prescription, for 30 to 60 minutes a day, at least five times a week. Cardiac rehabilitation has been shown to be beneficial in patients post-MI, especially for those patients with multiple modifiable risk factors and moderate-to high-risk patients that warrant a supervised exercise regimen.

Smoking cessation is a must for every post-MI patient. It is imperative that the treating physician provides adequate counseling and pharmacologic therapy to achieve this goal. Smoking has been shown to trigger coronary spasm, reduce effectiveness of beta-blockers, and increase mortality after STEMI. Patients recovering from MI should be provided with counseling and appropriate pharmacologic therapy. Of note, routine use of nicotine-replacement therapy during hospitalization with acute MI is not recommended because of the potential sympathomimetic effects of nicotine.

CONCLUSION

Risk stratification in MI is essential to determine appropriate therapy, and for allocation of limited health care resources to high-risk patients. In STEMI, the most important predictors of death include age, SBP and heart rate at presentation, CHF, and location of infarction. Early revascularization is critical to reducing the mortality rate. In NSTEMI, high-risk features, such as biomarker elevation or elevated TIMI risk score, can be used to determine which patients should be eligible for an early invasive strategy. Patients who develop evidence of recurrent ischemia or LV dysfunction after

MI have a worse prognosis, so the identification of these features is important to guiding predischarge management.

The appropriate use of pharmacotherapy after MI also depends on identification of high-risk features. Under most circumstances, post-MI therapy should include daily aspirin, a statin, a beta-blocker, and clopidogrel (especially if a stent is placed). If significant LV dysfunction is present, an ACE inhibitor and/or ARB, potentially with aldosterone blockade, are needed. Lifestyle modification remains essential to post-MI management, including smoking cessation and control of risk factors such as diabetes, hypertension, and obesity.

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QUESTIONS AND ANSWERS

Questions

1. A 52-year-old man presented to the Emergency Department with an acute anterior wall myocardial infarction (MI) and received successful lytic therapy. Physical exam findings were notable for a systolic blood pressure (SBP) of 90 mm Hg, a heart rate of 120 beats/min (bpm), and rales at both lung bases.The most important determinant of 30-day mortality in this patient is:
   a. Age
   b. Infarct location
   c. Killip class

d. SBP
e. Heart rate

2. The patient in Question 1 had an uncomplicated in-hospital course. All of the following are acceptable risk…factor stratification strategies except:
   a. Assessment of left ventricular (LV) function
   b. Predischarge cardiac catheterization
   c. Submaximal stress on days 4 to 6
   d. Symptom…limited stress on days 10 to 14
   e. Electrophysiology testing

3. The patient in Question 1 has a brief episode of chest pain (<1 minute) with transient ST depression on the morning of his scheduled submaximal stress test.The pain was relieved with one sublingual nitroglycerin tablet.You should:
   a. Proceed with submaximal stress as planned.
   b. Wait two or three additional days and proceed with stress testing if he remains asymptomatic.
   c. Order echocardiography to see if there have been any additional wall motion abnormalities.
   d. Schedule for coronary catheterization prior to discharge.

4. BF is a 48-year-old man who presents for a submaximal stress test prior to discharge after successful thrombolysis for an inferior wall MI. His baseline electrocardiogram (ECG) demonstrated a complete left bundle branch block (LBBB) but was unchanged during stress testing. He achieved 5.5 METs and the stress test was stopped because of general fatigue.You are asked to review his stress test and decide to:
   a. Discharge the patient home and schedule him for a symptom-limited stress test in 10 to 14 days.
   b. Schedule a symptom-limited stress test in 2 to 3 weeks.
   c. Perform cardiac catheterization because of the low METs achieved.
   d. Repeat the stress test with perfusion imaging secondary to baseline LBBB.

5. JT is a 65-year-old woman who presents with chest pain and her TIMI risk score is 1. She is referred for exercise stress testing. All of the following findings on EKG would preclude her except:
   a. Left ventricular hypertrophy (LVH) with strain
   b. Ventricular pre-excitation
   c. Ventricular paced rhythm
   d. Right bundle branch block

6. AH is a 79-year-old male with prior history of coronary artery disease (CAD) and prior stenting 5 years ago. He otherwise has hypertension, but no diabetes, hyperlipidemia, or other medical diagnoses. He has been having exertional chest discomfort twice a day for the last week, and is now admitted to the hospital. His daily medical regimen includes subligual nitroglycerin, metoprolol tartrate, lisinopril, and aspirin. On arrival, his EKG demonstrates ST depression in leads II, III, and F. His cardiac biomarkers are normal. Based on this information, his TIMI risk score is:
   a. 5
   b. 4
   c. 3
   d. 2
   e. 1

7. Based on this patient's TIMI risk score, the proper management strategy at this time is:
   a. Exercise treadmill stress test if no symptoms of ischemia after 24 hours
   b. Exercise stress test with nuclear imaging if no symptoms of ischemia after 24 hours
   c. Pharmacologic nuclear stress test if no symptoms of ischemia after 24 hours
   d. Dobutamine echo stress test if no symptoms of ischemia after 24 hours
   e. Coronary angiography

8. A 74-year-old female presents to the hospital with 3 days of stuttering angina which is new. Her medical history is significant for diabetes, hypertension, hyperlipidemia, chronic kidney disease stage 2, peripheral vascular disease, and a TIA 5 years ago. She is 66 inches tall and weighs 65 kg. Her blood pressure (BP) on admission is 110/70 and her HR is 99 bpm. She is referred for coronary angiography with the intention of PCI. In addition to aspirin, the best option for an oral antiplatelet agent is:
   a. Ticlopidine
   b. Clopidogrel
   c. Prasugrel
   d. Cangrelor

9. A 70-year-old patient presents with a non–ST-segment-elevation myocardial infarction (NSTEMI) and undergoes implantation of a bare-metal stent. He is prescribed aspirin, clopidogrel, metoprolol, and atorvastatin. According to the most recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines, the recommended duration for clopidogrel is:
   a. 2 weeks
   b. 4 weeks
   c. 3 months
   d. 6 months
   e. At least 12 months

10. A 65-year-old patient with hypertension, chronic kidney disease stage 3, hyperlipidemia, and obesity is discharged from the hospital after a NSTEMI. She now presents to your outpatient office. Which of the following are the most appropriate targets for her BP and lipid panel?
   a. BP < 145/90 and low-density lipoprotein (LDL) 100 mg/dL or less
   b. BP < 140/90 and LDL 100 mg/dL or less
   c. BP < 130/80 and LDL 100 mg/dL or less
   d. BP < 130/85 and LDL 130 mg/dL
   e. BP < 135/80 and LDL 130 mg/dL

Answers

1. Answer A: An analysis of 41,021 patients with acute MI enrolled in GUSTO-I, a trial of lytic therapy, found that age was the most significant predictor of 30-day mortality in a multivariable analysis. In addition, anterior infarct location, higher Killip class, elevated heart rate, and lower SBP were predictors, although they were not as significant as age.Together, these five characteristics included 90% of the prognostic information in the baseline clinical data (Lee et al., Circulation. 1995;91:1659–1668).

2. Answer E: The current ACC/AHA Guidelines for ST-segment-elevation myocardial infarction (STEMI) recommend assessment of LV function as part of a risk-stratification algorithm. It is acceptable to proceed to cardiac catheterization, particularly in patients with EF < 0.40 or with high-risk features. In patients who do not undergo cardiac catheterization, it is recommended that those with an interpretable ECG, and who can exercise, undergo exercise stress testing, either as a submaximal stress test on days 4 to 6 or a symptom-limited test on days 10 to 14. EP testing is not part of the recommended algorithm for risk stratification.

3. Answer D: Recurrent ischemia after MI is a high-risk predictor, and patients with recurrent ischemia should undergo cardiac catheterization and revascularization as indicated.

4. Answer D: LBBB precludes interpretation of a stress ECG and is a contraindication to exercise ECG testing in the absence of nuclear perfusion imaging.

5. Answer D: Baseline ECG abnormalities can preclude ECG stress test interpretation. LVH with strain,WPW, ventricular pacemaker, and baseline ST depression fall into this category. However, the ECG in right bundle branch block (RBBB) is interpretable, as ST segments are generally normal in this condition.

6. Answer A: The TIMI risk score (Entman et al. JAMA.2000; 284: 835–842) is comprised of: age >65 years old, at least three risk factors for CAD, significant coronary stenosis (prior stenosis ≥50%), aspirin

use within the last 7 days, severe angina (≥2 episodes per day during the last 24 hours), ST deviation on EKG, and positive cardiac biomarkers. This patient's score is 5, assuming his prior PCI was performed for a significant coronary stenosis.

7. Answer E: Based on the TIMI risk score, the expected rate of all-cause mortality, MI, and severe recurrent ischemia at 14 days is 26%. Patients with high-risk TIMI scores (≥3) should be referred for coronary angiography over noninvasive stress testing unless there is a contraindication.

8. Answer B: In the TRITON TIMI-38 trial (Wiviott et al. NEJM. 2007;357:2001–2015) subgroups that were at high risk for bleeding included patients older than or equal to 75 years, weight <60 kg, or prior history of TIA or stroke.Ticlopidine is not recommended over clopidogrel due to increased risk of neutropenia and agranulocytosis. Cangrelor is available only as an IV form and is not approved for clinical use.

9. Answer E: The new guidelines published by the ACC/AHA in 2011 recommends that all patients with NSTEMI continue a maintenance dose of clopidogrel 75 mg for at least 12 months unless there is a contraindication or high risk for morbidity or bleeding.

10. Answer C: According to the JNC 7 guidelines on hypertension (JAMA. 2003;289:2560–2572), patients with prior MI should have a BP goal of 140/90 for all patients and 130/80 for patients with diabetes or chronic kidney disease. According to the ATP III guidelines on lipid management (JAMA. 2001;285:2486-2497), patients with known CAD should have a LDL goal of 100 mg/dL or less.

CHAPTER

Radiation Safety in the Cardiac Catheterization Laboratory

Imran N. Ahmad, Kevin A. Wunderle, and Frederick A. Heupler, Jr.

BACKGROUND

Radiation-induced injury is a well-recognized risk associated with invasive procedures in cardiac catheterization laboratories. As the number and complexity of cases in catheterization laboratories increase and technologic advancements of fluoroscopic imaging equipment continue, so does the risk for radiation-induced injuries to patients and laboratory staff. Proper understanding of fluoroscopic imaging equipment and imaging parameters is essential to limiting these risks.

RADIATION PRODUCTION

A general understanding of fluoroscopic equipment and radiation production in the catheterization laboratory provides a foundation for appreciating radiation safety. A fluoroscope is essentially a dynamic x-ray machine capable of real-time imaging. Fluoroscopes used for cardiac catheterizations are typically in a C-arm configuration with the x-ray tube located below the patient table and the image receptor above (Fig. 44.1). There are four main components to a general x-ray imaging system: an x-ray tube, an image receptor, a generator, and an operating console.

FIGURE 44.1 Cardiac catheterization laboratory with biplane imaging capabilities. 1, Radiation dose display; 2, Bedside operation console; 3, Flat panel detector; 4, X-ray tube; 5, C-arm A-P camera; 6, C-arm lateral; 7, Wireless foot pedal; 8, Leaded skirt; 9, Moveable acrylic shield; 10, Monitors and digital flat panel screens; 11, Bedside FFR IVUS operation console.

X-Ray Tube

The x-ray tube consists of a rotating anode and generally a multifilament cathode situated inside an evacuated glass tube. The x-ray tube is immersed in oil for efficient cooling and placed inside a lead housing to limit unwanted radiation. The filament consists of a thin tungsten wire through which a high electric current is passed heating

the wire white hot. This thermal energy is sufficient to allow some electrons to overcome the electron-binding energy and provide essentially unbound electrons around the filament. This is often referred to as an electron cloud. When the system is energized, these electrons are accelerated toward and collide with the positively charged tungsten target (anode). The larger the filament, the more electrons that can be generated at one time; however, the focal spot on the anode also increases in size resulting in increased geometric blurring that degrades resolution.

All operators of radiographic equipment should understand three commonly used units displayed on all modern fluoroscopes. The milliamperes (mA) is the first unit, and it is related to the number of electrons traveling across the anode–cathode gap per second. The base unit ampere is defined as the number of coulombs per second (charge per unit time), hence a current. This is exactly what occurs when the electrons flow across the anode–cathode gap. The coulomb (C) is a unit of charge; the charge of one electron is 1.60×10^{-19} C. The next unit is related to the first but fundamentally different; it is the milliampere × seconds (mAs). The mAs is the total number of electrons traveling across the anode–cathode gap for a given exposure. The mAs is obtained by multiplying the first unit, mA, by time in seconds (s), which yields a measure of total charge (coulombs/second × seconds = coulombs). The third unit, peak kilovoltage (kVp), is equal to the applied voltage across the anode–cathode gap, which also represents the highest potential photon energy in the x-ray beam. The base units of voltage are joules/coulomb (energy per unit charge). The electrons, being charged particles, are accelerated across the gap due to the applied voltage, and therefore they gain kinetic energy. This kinetic energy is converted to electromagnetic radiation when the electrons interact with the tungsten target, primarily producing heat in the form of infrared photons, while a small fraction are converted to x-ray photons. The x-ray photons are generated isotropically, that is, with the same intensity in all directions. However, only those x-rays traveling through a small solid angle toward the x-ray tube window are used for imaging purposes. Lead shielding surrounding the x-ray tube is used to attenuate most of the unwanted x-rays; however, leakage radiation (radiation penetrating the x-ray tube housing) can be as high as 880 μGy/h (100 mR/h) at a distance of 1 m, limited by state and federal regulations, though it is commonly well below this value. In terms of affecting the output of the x-ray tube, increases in mA (or mAs) increase the radiation output linearly. As a rule of thumb, increasing kVp from kVp_1 to kVp_2 increases the output of the system by the ratio of $(kVp_2/kVp_1)^2$. Therefore, in general, increases in kVp result in a larger increase of x-ray tube output as compared to a comparable increase in mA (or mAs). Increasing kVp not only increases the radiation output of the x-ray tube but also increases the effective energy of the x-ray beam resulting in a more penetrating beam.

Image Receptor

There are two types of image receptors used in fluoroscopes: image intensifiers and digital flat panel detectors. Most state of the art fluoroscopic systems dedicated for cardiac catheterization employ digital flat panel detectors, which are required for 3-D volume imaging. Regardless of the type, the image receptor captures and converts x-rays transmitted through the patient to a signal (analog or digital) for display. It is also involved in regulating the output of the x-ray tube via a feedback loop that governs the generator and x-ray tube output.

Generator

The generator is the component responsible for supplying the electrical power to the x-ray tube. Through step-up or step-down transformers, it supplies a low current and high voltage to the anode and a high current and low voltage to the cathode, respectively. There are a variety of types of generators; however, most modern fluoroscopes use a high-frequency generator, which supplies a very stable voltage and current to the x-ray tube.

Operating Console

The operating console, in conjunction with the system software, is the interface with the fluoroscope. Commonly, there is a primary operating console that provides display and control of many of the fluoroscopic operating parameters and communicates with both the Hospital Information System (HIS) and the Picture Archiving and Communication System (PACS). There is also typically a bedside console that controls most of the fluoroscopy and acquisition functions, mechanical operations such as rotation and angulation of the C-arm, and image display properties.

RADIATION DOSE ESTIMATION AND DISPLAYS

Understanding radiation dose can be complicated. There are an inordinate number of radiation quantities, some of which are rather abstruse. Compounding this problem, there is a traditional and a System International (SI) set of radiation units. It is important to understand the fundamental radiation quantities and their units, some of which are displayed on modern fluoroscopes (Table 44.1).

TABLE
44.1 Radiation Dose Quantities

Quantity (Symbol)	SI Unit	Fundamental SI Units	Traditional Unit	Relationship	Definition/Purpose
Exposure (X or E)	Coulomb per kilogram (C/kg)	Coulomb per kilogram (C/kg), charge per unit mass	Roentgen (R)	1 R = 2.58 × 10^{-4} C/kg	Defined only in *air* for *photons* with energy below 3 MeV. It is the charge liberated (of one sign) per unit mass of air.
Kerma and air kerma (*K* and K_a)	Gray (Gy)	Joules per kilogram (J/kg), energy per unit mass	NA	NA	*Kinetic Energy Released in Material* is the kinetic energy transferred to some medium (in the case of air kerma the medium is air), during an initial interaction. Although this quantity has the same units as absorbed dose, it is different. Kerma is the energy transferred per unit mass, not all energy transferred ends up absorbed.
Absorbed dose (D)	Gray (Gy)	Joules per kilogram (J/kg), energy per unit mass	Radiation absorbed dose (rad)	1 Gy = 100 rad	Energy absorbed per unit mass of medium.
Equivalent dose (H_T)	Sievert (Sv)	Joules per kilogram (J/kg), energy per unit mass	Radiation equivalent man (rem)	1 Sv = 100 rem	Derived by multiplying the absorbed dose by a radiation weighting factor (W_r). Accounts for the fact that different types of radiation cause different degrees of biologic damage for the same energy absorbed. For photons, W_r is 1.
Effective dose (H_E, ED or EDE)	Sievert (Sv)	Joules per kilogram (J/kg), energy per unit mass	Radiation equivalent man (rem)	1 Sv = 100 rem	Derived by multiplying the equivalent dose by a tissue weighting factor for each organ exposed and then summed. Used to compare radiation doses regardless of uniformity in terms of stochastic risk.
Air kerma (at the IRP) ($K_{a,r}$)[a]	Gray (Gy)	Joules per kilogram (J/kg), energy per unit mass	NA	NA	Air kerma at the IRP, cumulative quantity for an entire procedure.
Air kerma rate (at the IRP) ($\dot{K}_{a,r}$)[a]	Gray per second (Gy/s)	Joules per kilogram (J/kg)/s, energy per unit mass per unit time	NA	NA	Air kerma rate at the IRP, instantaneous output rare. It is only displayed during x-ray generation. Generally displayed in units of Gy/min.
Air kerma area product (P_{KA})[a]	Gray times square meters (Gy × m^2)	Joules per kilogram × area (J/kg) × m^2, energy per unit mass multiplied by area	NA	NA	Air kerma multiplied by the field size. This unit is unique because it does not matter what plane is chosen the value is the same, cumulative quantity for an entire procedure. Generally displayed in units of mGy × cm^2.

[a]Quantities commonly found on modern fluoroscopes

Radiation quantities commonly displayed on modern fluoroscopes are the air kerma rate at the reference plane $\dot{K}_{a,r}$, air kerma at the reference plane $K_{a,r}$, and air kerma area product P_{KA} commonly referred to as dose-area product (DAP) (Figs. 44.2 and 44.3). The usual dose units for $\dot{K}_{a,r}$ are mGy/min, for $K_{a,r}$ are mGy, and for P_{KA} are mGy cm^2 or μGy m^2. It is important to appreciate what these quantities are and what they are not. First, none of these quantities directly represents the patient's peak skin dose $D_{skin,max}$, which is a quantity that is often sought to predict potential cutaneous injury. $\dot{K}_{a,r}$ and $K_{a,r}$ are defined in air at a reference plane, often referred to as the interventional reference

plane (IRP). The International Electrotechnical Commission (IEC) standards establish the IRP at a fixed distance 15 cm below the isocenter of the C-arm irrespective of the table height (Fig. 44.4). The assumption is that the center of the patient is at isocenter of the C-arm and that the patient is approximately 30 cm thick. Therefore, the IRP and skin entrance are both assumed to be 15 cm below isocenter. $K_{a,r}$ and P_{KA} are cumulative quantities for the entire procedure. They include radiations delivered at all projections and locations along the cranial–caudal direction (z). There are multiple reasons why $K_{a,r}$ is not a surrogate for $D_{skin,max}$:

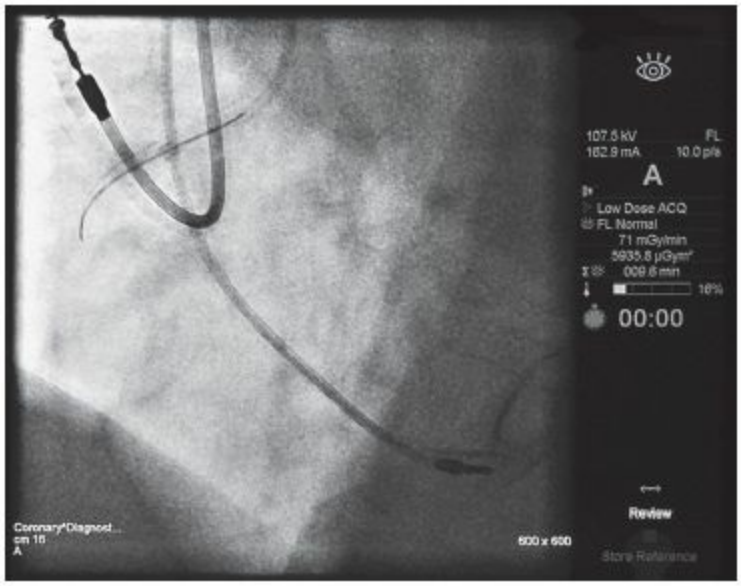

FIGURE 44.2 The displayed air kerma rate at the reference plane in this coronary cineangiogram is 71 mGy/min and the air kerma area product, commonly referred to as DAP, is 5,935.8 µGym^2.

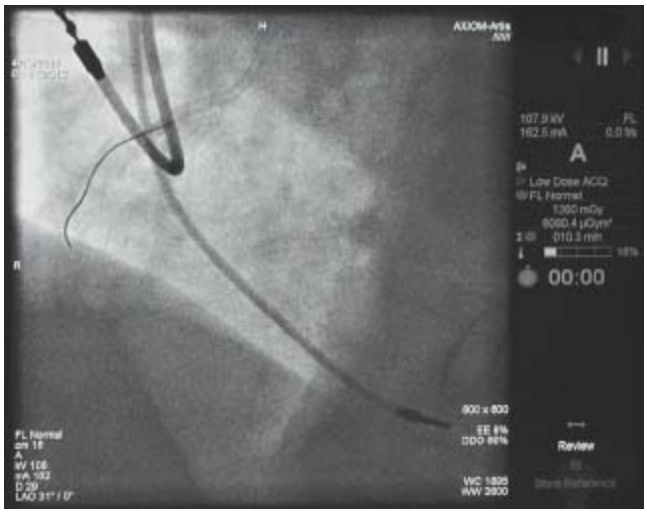

FIGURE 44.3 The air kerma at the reference plane, commonly referred to cumulative dose, is 1,260 mGy and the air kerma area product, commonly referred to as DAP, is 6,090.4 µGym^2.

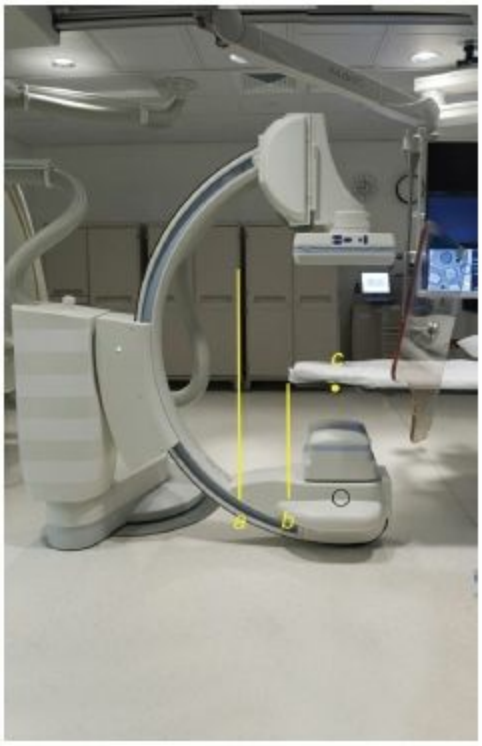

FIGURE 44.4 The x-ray focal spot is denoted on the fluoroscope by a small red dot on the x-ray tube housing (black circle). The source to image distance is the distance between the x-ray focal spot and the image receptor (**A**). The source to skin entrance distance is the distance between the x-ray focal spot and the table (**B**). The IRP is located at 15 cm below the isocenter of the C-arm, (**C**).

1. The IRP used for the $K_{a,r}$ and the plane of the skin entrance are rarely the same; they may differ, depending on the projection (AP vs. vlateral), the size of the patient, or the height of the table.
2. $K_{a,r}$ includes all radiations emitted from the x-ray tube. Many procedures use multiple projections at various locations along the z-axis that spreads the radiation delivered to the patient over a greater anatomical region generally reducing $D_{skin,max}$ (as long as the fields of view do not overlap).
3. $K_{a,r}$ by definition assumes that the medium of interaction is air. However, the absorption characteristics of skin and thereby $D_{skin,max}$ are different from air. Furthermore, $D_{skin,max}$ includes backscattered radiation as well, while air kerma does not.

The intensity of radiation follows the inverse square law that is the amount of radiation received drops by the inverse square of the distance (d) from the source, $1/d^2$. This is true for both patients and operators. Below are two clinical scenarios that exemplify limitations in air kerma as a proxy for peak skin dose.

Scenario 1

A small patient (~20 cm thick in the AP dimension) undergoes a cardiac catheterization. The physician performing the procedure is tall and performs the procedure with a source to image distance of 120 cm, source to skin entrance distance of 100 cm, and the image receptor lowered to the patient's chest. For calculation purposes, let us assume there were two discrete nonoverlapping fields that equally split a total $K_{a,r}$ of 4 Gy, the IRP is 60 cm from the x-ray tube focal spot, and that all imaging was performed in the straight AP projection (Fig. 44.5).

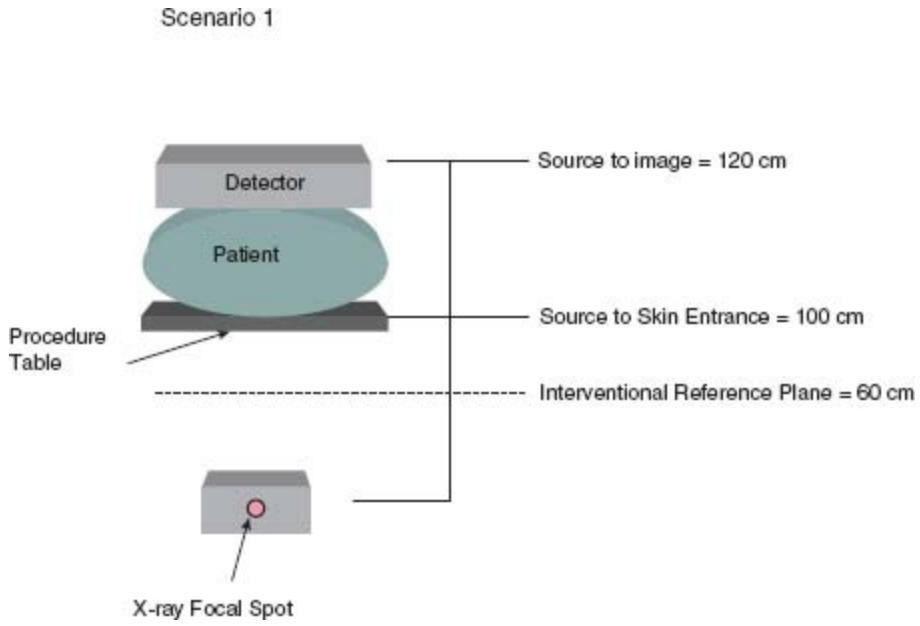

FIGURE 44.5 In Scenario 1, a relatively small patient 20 cm thick in the AP dimension undergoes catheterization. The source to image distance is 120 cm and the source to skin entrance distance is 100 cm. The IRP is approximately 60 cm above the x-ray tube. Because the radiation intensity drops as the inverse square of the distance from the x-ray source, the air kerma at the reference plane in this example grossly overestimates the air kerma at skin entrance.

Taking into account the inverse square law, the incident air kerma at skin entrance location $K_{a,i}$ is less than the displayed $K_{a,r}$ by $(60/100)^2 \times K_{a,r} = 0.36 \times K_{a,r}$. Furthermore, because the radiation was split between two discrete fields, each field actually receives only half of the total air kerma, $0.36 \times 0.5 \times K_{a,r} = 0.18 \times K_{a,r}$. In other words, the actual air kerma at the skin entrance is 18% of the displayed air kerma at the reference plane, the $K_{a,r}$ is a gross overestimation in this scenario. To obtain an estimated $D_{skin,max}$, the backscatter factor and tissue to air differences must be accounted for which will increase the $K_{a,i}$ by about 30% to 50% depending on the x-ray beam characteristics, bringing the displayed value slightly closer to $D_{skin,max}$, but still off by approximately 75%.

Scenario 2

A morbidly obese patient (~50 cm thick in lateral dimension) undergoes a cardiac catheterization. Standard size collimator covers are removed and replaced with short collimator covers allowing for a source to skin entrance distance of 30 cm. The procedure requires only one unique lateral view (Fig. 44.6).

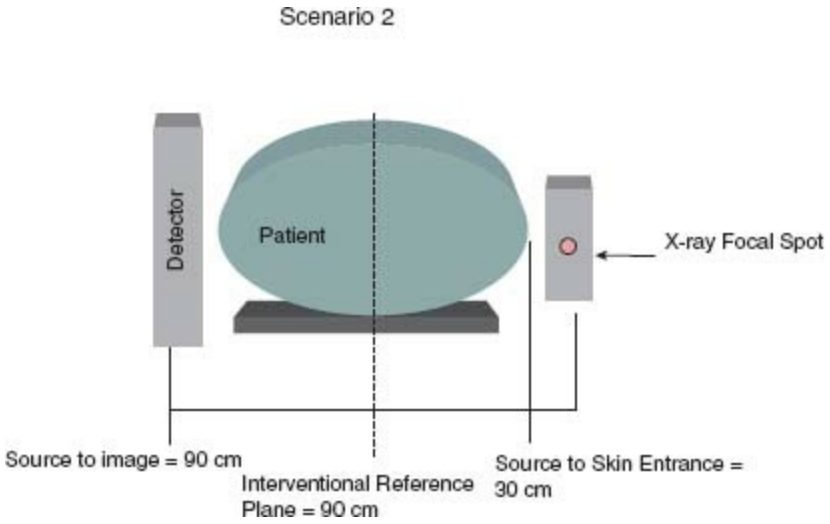

FIGURE 44.6 In Scenario 2, a relatively large patient 50 cm thick in the lateral dimension undergoes catheterization. The source to image distance is 90 cm and the source to skin entrance distance is 30 cm. The IRP is approximately 60 cm above the x-ray tube. Because the radiation intensity drops as the inverse square of the distance from the x-ray source, the air kerma at the reference plane in this example grossly underestimates the air kerma at skin entrance.

The $K_{a,r}$ and $K_{a,i}$ are different by a factor of $(60/30)^2 = 4$. In other words, the $K_{a,i}$ is four times higher than the $K_{a,r}$ displayed; the $K_{a,r}$ is a gross underestimate in this scenario. Again, accounting for backscatter and tissue versus air differences, the actual $D_{skin,max}$ is greater than the displayed value by approximately 4.5 times.

IONIZING RADIATION AND RADIATION EFFECTS

Radiation-induced detriment can be broken down into two discrete categories, deterministic (nonstochastic) and stochastic.

Deterministic Risk (Nonstochastic)

Deterministic effects are those that have a threshold, below which a given effect is not expressed and above which the severity of the expression increases with increased radiation dose beyond the threshold. Primary examples of deterministic effects are skin related erythema, epilation, and necrosis (Table 44.2).

TABLE
44.2 Skin Effects from Various Radiation Doses

Effect	Dose (Gy)	Onset
Brief erythema, hair loss	2–3	Hours to weeks
Persistent erythema, hair loss	6–7	1–3 wk
Skin fibrosis, atrophy	10–11	1–3 mo
Wet skin loss	15	1 mo
Skin necrosis	18	> 2.5 mo
Ulceration	20	> 1.5 mo

Most deterministic effects are described for acute single exposures. However, patients will often undergo repeated interventions. How the skin reacts to multiple exposures is rather complex and greatly depends on the length of time between irradiations. Although beyond the scope of this book, there are formulized models that originated with radiation therapy patients for approximating single-dose estimations from multiple irradiations within a limited span of time.

The primary radiation quantity associated with deterministic effects is the $D_{skin,max}$. However, $D_{skin,max}$ is not a quantity that is currently displayed on any fluoroscopic equipment; the closest quantity available is $K_{a,r}$, but it should be well understood that these are not the same quantity, and they can differ substantially even though they have the same unit of measure (Gy). $D_{skin,max}$ may be obtained directly by employing radiochromic films that can be calibrated to provide a dose estimate or by using smaller dosimeters such as thermoluminescent dosimeters (TLDs), placed on the patient's skin at the location where $D_{skin,max}$ is most likely to occur. Based on $K_{a,r}$ though, patient education material should be made available to patients about the potential skin effects of radiation.

Generally speaking, there are no limits on the amount of radiation a patient can receive for diagnostic or interventional fluoroscopically guided procedures. It is assumed that any use of radiation is offset by the potential benefit to the patient otherwise the procedure would not be performed. The one exception is a quasi-threshold established by the Joint Commission (JC) that defines a sentinel event for >15 Gy of cumulative skin entrance dose to a single field. Our catheterization laboratory has a specific protocol to deal with escalating doses of patient radiation dose (Fig. 44.7). There is a great deal of ambiguity surrounding this sentinel event, not the least of which is what constitutes "cumulative." The JC itself has suggested using 6 to 12 months as a period of time to include in the cumulative dose; however, they have not declared an official time period. If a patient has had multiple prolonged fluoroscopically guided procedures within a time period of 6 months or less, it is best to consult with a medical physicist regarding the likelihood of skin injury with a subsequent fluoroscopic

procedure and determination of a combined dose for determining the classification of a sentinel event.

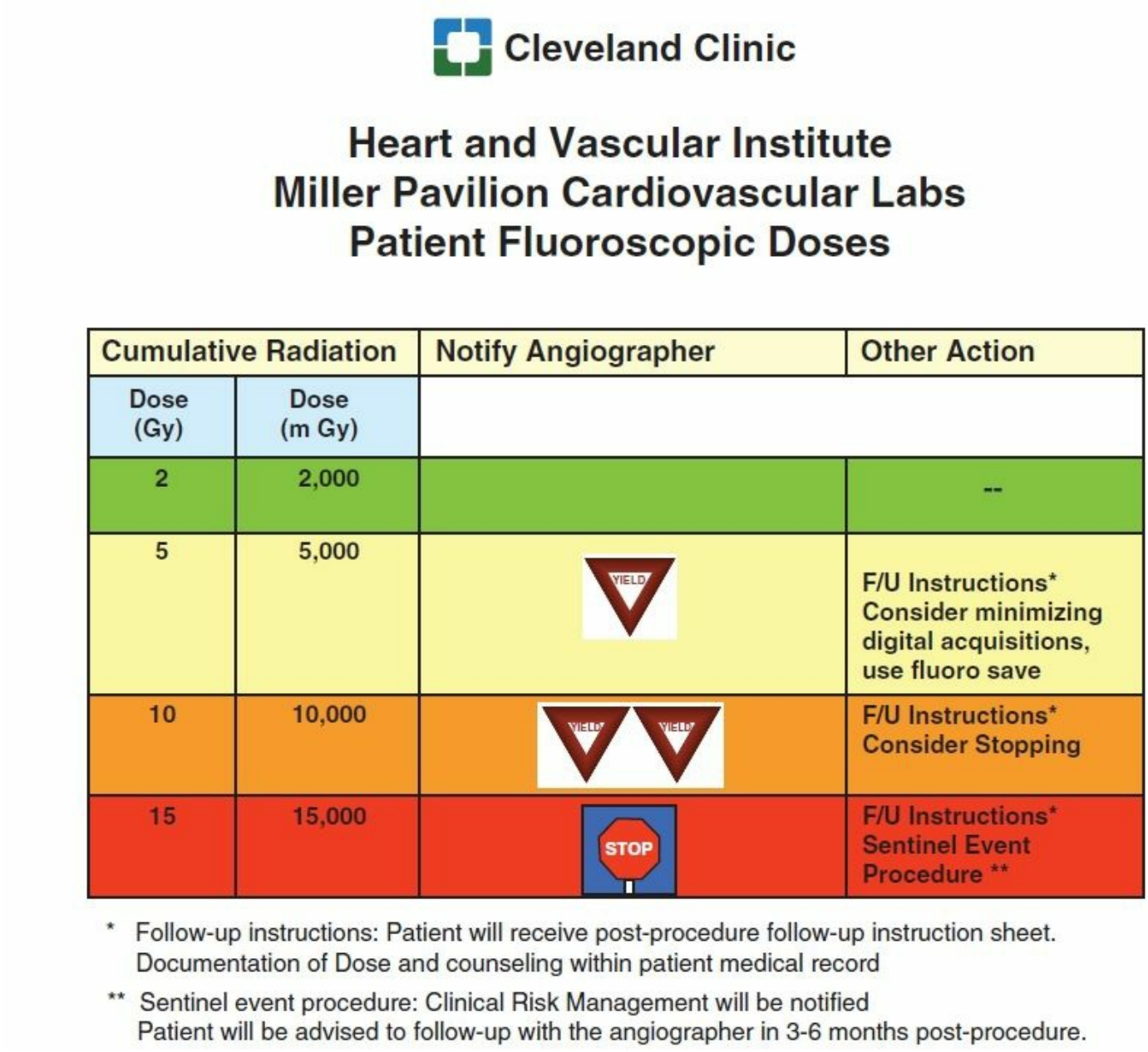

FIGURE 44.7 Protocol for increasing doses of cumulative radiation in the cardiac catheterization laboratory. (Courtesy Cleveland Clinic.)

Stochastic Risk

Stochastic effects are characterized by the absence of a threshold for expression. They are primarily governed by a statistical risk with the probability of onset increasing with increased radiation dose. There is an all or nothing expression of the effect. Although the likelihood increases with increased dose, the severity of the effect is unrelated to dose.

The primary radiation quantity associated with stochastic effects is the effective dose (ED), commonly expressed in millisieverts (mSv). Table 44.3 outlines typical EDs associated with various procedures that utilize ionizing radiation. There is no fluoroscopic equipment currently available that displays an ED. The closest related quantity is the P_{KA}. Again, P_{KA} is not the ED and other factors must be taken into account to obtain the ED. For some specific procedure types, there are conversion factors that have been derived to convert P_{KA} to an estimated ED.

TABLE
44.3 Typical ED Estimates for Various Procedures that Utilize Ionizing Radiation

Procedure	ED Estimate (mSv)
Chest x-ray	0.04
Chest CT (standard)	7.0
Chest CT (cardiac)	16
Diagnostic coronary angiogram	7.0
Percutaneous coronary intervention	15.0
Radiofrequency ablation	15.0
TIPS	70.0
ERCP	4.0
Tc-99 m cardiac perfusion	11.4
Thallium cardiac perfusion	16.9

The primary example of a stochastic effect is carcinogenesis. Although there is much debate surrounding exposure to low levels of ionizing radiation, the currently accepted model is the linear no-threshold (LNT) model of carcinogenesis. According to the most recent reports available, there is approximately a 10% increased risk of cancer incidence and approximately a 5% increase in cancer death per 1,000 mSv of ED above natural occurrence for adults. Pediatric lifetime risk is elevated by as high as a factor of 3 or 4 compared with adults depending on various factors. Pediatric risk is higher because on average children will live longer providing a longer potential period to clinically express any radiation-induced effects.

RADIATION MANAGEMENT

The ALARA principle states that radiation exposure to the patient and operator should be kept as low as reasonably achievable to minimize both the deterministic and stochastic effects, essentially limiting the amount of radiation used to that which is absolutely necessary under reasonable conditions. In terms of operator and staff, the

major contributor of exposure is scattered radiation from the patient and other objects in the path of the x-ray beam. Table 44.4 outlines some of the key components to a procedure that minimize patient radiation exposure.

TABLE
44.4 Minimizing Patient Radiation Exposure in the Cardiac Catheterization Laboratory

Ways to Minimize Patient Radiation Exposure
■ Limit foot pedal on-time
■ Lower frame rate to 10 frames/s
■ Limit number and duration of cine runs
■ Substitute standard cine runs with low-dose acquisition
■ Limit fluoroscopy time
■ Work in shallow angulations when possible to avoid higher radiation doses
■ Avoid lowering the table from isocenter
■ Lower image detector as close to the patient as possible
■ Use magnified views only when necessary
■ Collimation

Patient Radiation Management

Of the many specific parameters that affect patient dose, seven deserve special attention:

1. Patient distance to the radiation source and distance to image receptor
2. Path length and approach of the x-ray beam
3. Dose and frame rate settings
4. Fluoroscopy time and the number of acquisitions
5. Use of magnification
6. Collimation
7. Grid use

Patient Distance to the Radiation Source and Distance to the Image Receptor

One of the easiest ways to reduce patient dose is to keep the image receptor as close to the patient as possible. Because of the inverse square law even a 10 cm gap can mean a 40% or greater difference in the dose to the patient. Ideally, the patient should be as far away from the x-ray source as possible; however, once we reach the surface of the

image receptor, it does not serve much purpose to increase both the patient and image receptor distances from the source.

Path Length and Approach of the X-Ray Beam

Lateral, oblique, or other projections that extend the x-ray path length through the patient increase the dose in two ways (as compared to a PA projection). First, the more tissue in the path length, the more attenuation of the x-ray beam, which results in increased radiation output by the fluoroscopic system. As a general rule, approximately 25% of the x-ray beam is attenuated for each 1 cm of soft tissue traversed. This does not mean that after 4 cm of soft tissue, there are zero photons left because entering the second centimeter of tissue was only 75% of the original beam. Therefore, after 4 cm of soft tissue, there is approximately $(0.75)^4 = 0.32$ of the original beam. Likewise, if we increase the path length through the patient by 4 cm, the system needs to increase its output by approximately 68% to compensate. Second, the longer the path length, the closer the skin entrance is to the x-ray source, which increases the radiation dose by the inverse square law.

Dose and Frame Rate Settings

The machine settings make a significant difference in the dose/dose rate delivered to the patient. Pulsed fluoroscopy can provide dose rates 25% to 50% lower than continuous fluoroscopy. Generally, 7.5 to 10 pulses per second fluoroscopy is recommended for coronary angiographic procedures. If the pulse rate is slower, temporal lag produces a stuttering effect in the image, whereas a higher pulse rate results in unnecessarily high dose rates. The same concept applies to acquisition frame rates, the lower the frame rate, the lower the dose rate however the greater the temporal lag. Almost all fluoroscopic systems have the ability to choose between two or three different dose delivery modes. The dose rate mode can change the dose rate by 30% to 60%. The operator should choose the lowest dose mode available to start any procedure and then increase to a higher dose mode if there is too much noise in the image. Remember, the goal is to be able to perform the task at hand with the worst image quality that will allow you to successfully complete the task. Better image quality almost always results from higher radiation dose.

Fluoroscopy Time and Number of Acquisitions

Although it should be obvious, reducing the fluoroscopy time and the length and quantity of acquisitions will limit the amount of radiation delivered to the patient. Many systems now have the capability of recording fluoroscopic imaging sequences, which may allow for a reduction in acquisitions, thereby reducing patient dose. All modern fluoroscopic systems provide a last image hold feature allowing for the operator to stop x-ray

production but still see the last image acquired. This feature can drastically reduce radiation doses if well utilized.

Use of Magnification

Magnification modes significantly increase the radiation dose; the greater the magnification, the greater the dose. The difference in dose rate between a 7 inches (~22 cm diagonal) field of view and a 5 inches (~16 cm diagonal) field of view can be as high as a factor of 2. The operator should always use the largest field of view possible while still being able to visualize the necessary anatomy and instrumentation.

Collimation

Although collimation does not generally affect the region of skin remaining in the field of view, it does reduce the overall amount of radiation absorbed by reducing the total quantity of tissue irradiated. Collimation reduces the P_{KA}, which is the product of the $K_{a,r}$ and the area of the field. The P_{KA} is the closest related machine generated parameter to the ED. Therefore, collimation does not significantly affect deterministic effects; however, it does affect stochastic effects.

Grid Use

All fluoroscopic systems are provided with a grid on the face of the image receptor. The purpose of a grid is to remove scatter radiation, increase the contrast, and improve image quality. However, the down side of a grid is that it may absorb both scatter radiation and some primary radiation, which requires an increased output of the x-ray tube, thus increasing the patient dose. For petite patients and especially pediatric patients, it may be feasible to remove the grid, which will decrease the radiation dose to the patient; however, image contrast will suffer.

Operator Radiation Management

It is vitally important to first understand that the radiation dose to the operator is directly proportional to the radiation dose of the patient. In fact, the patient is the primary source of radiation exposure to the personnel in the lab. As a rule of thumb, the air kerma rate at 1 m from the patient is equal to 1/1,000th of the air kerma rate at the patient's skin entrance. Therefore, all the methods used to decrease the radiation exposure to the patient will in effect also reduce the exposure to the operator.

In addition, there are ways an operator can further reduce his or her exposure. The cardinal principles of radiation protection are time, distance, acquisition mode, and shielding (Table 44.5). Scatter radiation to the operator is maximized in the LAO views and minimized in the RAO views when the operator is standing on the right side of a supine patient. By the inverse square law, the intensity of radiation decreases by the

square of the distance from the source. Therefore, if we increase our distance from 1 m from the patient to 2 m from the patient, the air kerma rate will be approximately 1/4,000th that of the patient's entrance exposure (it will decrease by a factor of 4). An operator can move farther away from the x-ray tube and patient by taking advantage of the catheter length, particularly during extremity cases and power injections.

TABLE
44.5 Minimizing Operator Radiation Exposure in the Cardiac Catheterization Laboratory

Ways to Minimize Operator Radiation Exposure
Time
■ Reduce unnecessary fluoroscopy time
Distance
■ Step back from the x-ray source and patient
Angulation
■ Minimize LAO views
■ Minimize steep angulations
Shielding
■ Leaded glasses
■ Leaded apron with leaded thyroid collar
■ Table skirt and moveable shields
Acquisition mode
■ Substitute fluoroscopy recordings or low dose cine for standard cine

In general, shielding is a must in the catheterization laboratory. This includes a moveable acrylic shield, table skirt, leaded apron, thyroid collar, and leaded glasses. Lead aprons and thyroid collars are very effective at reducing radiation exposure. Generally speaking, the operator is protected from 95% or more of the incident scattered radiation by the lead protective apparel. In addition, floor-standing shields are particularly useful in cases that utilize biplane angiography to cover radiation scatter from the lateral x-ray tube. The operator must carefully avoid inserting his hands in the direct beam of the x-ray tube. Leaded gloves may increase the dose to the patient and operator if they are introduced into the direct x-ray beam. It is also of utmost importance that all staff present during fluoroscopically guided procedures wear dosimeters. Dosimeters are the only way that radiation management has to monitor the radiation doses to operators and staff.

REGULATORY RECOMMENDATIONS

As stated earlier, ED (mSv) reflects stochastic risk in wholebody equivalents by

summing the weighted doses to each organ or tissue irradiated. The whole-body dose limits for radiation workers recommended by the National Council on Radiation Protection and Measurements (NCRP) are 50 mSv annually and the cumulative ED limit is 10 mSv times the operator's age in years (Table 44.6). These recommendations have been adopted by the Nuclear Regulatory Commission and all US states as annual occupational exposure limits. The NCRP in part bases its recommendations on scientific data from United Nations Commission on the Effects of Ionizing Radiation (UNCEIR) and the National Academy of Sciences in the Biological Effects of Ionizing Radiation (BIER). Many of the US regulations are derived from NCRP reports and the recommended dose limits have been adopted into law. These recommendations are meant to ensure the cancer risk in radiation workers is that of workers in "safe" industries.

TABLE
44.6 Dose Limits Recommended by the NCRP

Recommended Dose Limits	
Occupational exposures	
■ ED	Annual: 50 mSv Cumulative: 10 mSv × age
■ Equivalent annual dose for tissues and organs	
a. Eye	150 mSv
b. Thyroid, skin, hands, and feet	500 mSv
Embryo-fetus exposures	
■ Total equivalent doses	5 mSv
■ Equivalent dose in 1 mo	0.5 mSv
Public exposure	1 mSv
Annual background radiation (average)	3.6 mSv

Personal dosimeters are used to monitor the ED with either one or two badges. Recommendations on how to wear radiation badges have been published by the Society for Cardiovascular Angiography and Interventions. The badges most commonly used are either TLDs or optical stimulated luminescence (OSL) dosimeters. Lithium fluoride crystals in the TLDs when heated emit light in direct proportion to the amount of radiation absorbed. Aluminum oxide crystals in the OSL dosimeters emit light after being stimulated by laser in direct proportion to the radiation absorbed.

The natural background radiation from cosmic rays, rocks and soil, radon gas, and ingested food is on average 3.6 mSv per year in the United States. Given that the

average chest x-ray results in 0.04 mSv, background radiation produces an ED that is equivalent to 90 chest x-rays per year. The average coronary interventional procedure can produce anywhere from 7 to 20 mSv.

Skin injury risk is predictable and patient radiation exposure is monitored. If patient radiation doses approach concerning levels, the responsible physician must weigh the risks and benefits and continue only in cases when the potential benefit outweighs the potential risk.

CONCLUSION

Basic rules of radiation safety require the operator to minimize radiation exposure to the patient, him or herself, and to other personnel in the x-ray suite while obtaining adequate images for patient carIt is obviously important for the operator to understand the main principles of radiation production, protection, and radiation-induced injury.

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QUESTIONS AND ANSWERS

Questions

1. Which of these statements is TRUE regarding radiation dose terminology?
   a. Dose-area product (DAP) reflects the total radiation delivered to the patient.
   b. Skin dose is measured in units of Sieverts (Sv).
   c. Kerma reflects the biologic impact of different radiation types.
   d. Fluoroscopy time is a good measure of radiation dose.
2. What is the greatest source of radiation exposure to the operator?
   a. Flat-panel detector close to the operator
   b. Tube leakage
   c. Scattered radiation from the patient
   d. RAO camera angles
3. Which one of the following reduces air kerma radiation dose at the reference plane?
   a. Collimation
   b. Increasing the source to image distance
   c. Changing the field of view from 22 to 16 cm
   d. Lowering the flat-panel detector to the patient
4. Which of the following reduces DAP?
   a. Collimation
   b. Lowering the table height
   c. Changing x-ray orientation from PA to AP
   d. Increasing the table height
5. Which of the following statements regarding stochastic and deterministic risks is TRUE?
   a. Deterministic risk is the major radiation hazard posed to operators.
   b. For the same amount of radiation exposure, the stochastic risk is higher in older operators than younger operators.
   c. A stochastic effect such as cancer cannot be predicted from a threshold level of radiation exposure.
   d. A deterministic effect such as skin injury cannot be predicted from a threshold level of radiation exposure.
6. What is the maximal recommended ED per year for an operator in the cardiac catheterization laboratory?
   a. 5 mSv
   b. 10 mSv
   c. 50 mSv
   d. 100 mSv

7. Which one of the following is TRUE regarding SCAI recommendations regarding personal dosimeter badges in the cardiac catheterization laboratory?
   a. Wear one badge inside the thyroid collar and one badge at the waist outside the apron.
   b. Wear one badge outside the thyroid collar and one badge at the waist outside the apron.
   c. Wear another operator's badge if you forget your own.
   d. Wear one badge outside the thyroid collar.

8. Which of the following statements is FALSE regarding radiation-induced skin injury?
   a. Peak skin dose is difficult to estimate because of varying distance between the x-ray tube and the patient's back during a procedure.
   b. Radiation skin injury can manifest weeks to months after a procedure.
   c. By the inverse square law, lowering the table height will decrease the skin dose (Gyt).
   d. There are multiple ways to estimate skin dose including the use of radiochromic films.

9. X-rays are generated at the:
   a. Generator
   b. Cathode
   c. Anode
   d. Collimator

10. Which statement below is TRUE?
   a. K_{ar} is equal to the patient's skin dose.
   b. $D_{skinmax}$ is displayed on the monitors in the catheterization laboratory.
   c. Of the displayed radiation quantities, $K_{a,r}$ is closest related to deterministic effects.
   d. Of the displayed radiation quantities, P_{KA} is closest related to stochastic effects.
   e. Both C and D

Answers

1. Answer A: Skin dose is estimated in units of Gray (Gy). Radiation from different sources can cause different degrees of biologic damage for the same amount of energy absorbed and this is accounted for by the equivalent dose. The ED is the sum of equivalent doses to each organ exposed to radiation and reflects stochastic risk. Fluoros-copy time is not a good measure of radiation dose.

2. Answer C: The greatest source of radiation exposure to the operator is scattered radiation from the patient. The lead housing around the x-ray tube is meant to prevent radiation leakage. With respect to camera angles, LAO views with the x-ray tube close to the operator on the right side of the patient are associated with higher operator exposure than RAO views due to the inverse square law, which states that radiation dose decreases the inverse square of the distance from the source.

3. Answer D: Collimation reduces scatter radiation and improves image quality. It does not reduce air kerma radiation dose. Increasing the source to image receptor distance and magnification of the field of view both increase air kerma dose. Lowering the flat-panel detector does decrease the air kerma dose.

4. Answer A: Collimation reduces the area of tissue irradiated without a change in the radiation beam intensity and therefore reduces DAP. DAP remains the same irrespective of table height or x-ray orientation and camera angle.

5. Answer C: Deterministic risk is the major hazard posed to patients from radiation-induced skin injury and can be directly correlated with peak skin dose measurements. Younger operators theoretically have a higher stochastic risk for the same amount of radiation due to the longer potential to express that risk. There is no threshold level of radiation exposure with which a stochastic effect is guaranteed to occur, although the probability increases with higher levels of exposure.

6. Answer C: The whole-body dose limit for radiation workers is 50 mSv annually.

7. Answer D: The recommendations are if two badges are worn, one should be outside the thyroid

collar and the second at waist level under the apron. If one badge is worn, it should be outside the thyroid collar. You should never wear another operator's badge.

8. Answer C: Lowering the table height will increase the skin dose as the radiation source is closer to the skin.

9. Answer C: The cathode is made up of tungsten filaments that become white hot from the current. The electrons travel from the filaments and strike the rotating anode, releasing the x-rays used for imaging.

10. Answer E: There is no fluoroscope available that displays peak skin dose measurements and air kerma is just an estimate.

CHAPTER

Hemodynamic Measurements

James E. Harvey and Frederick A. Heupler, Jr.

PHYSICS OF PRESSURE MEASUREMENT

The most common method of measuring pressures in the cardiac catheterization laboratory is to use fluid-filled catheter systems that convey the pressure wave from the site of interest through a catheter, manifold, and a pressure transducer that converts the pressure waveform to an electrical signal. A catheter with a pressure transducer at the tip provides a more accurate pressure recording, but these catheters are too expensive for routine clinical use.

Fluid-filled catheters commonly produce several types of artifacts in recorded waveforms:

1. Low-frequency response
2. Overshoot
3. Zero level

Low-frequency response and overshoot are common to all types of fluid-filled pressure-transmitting devices. The natural resonant frequency of a catheter–manometer system is the frequency at which the system oscillates when stimulated. The desirable frequency response for measuring intracardiac pressures in an adult with a fluid filled catheter system is about 20 Hz or more. When the natural resonant frequency response of a catheter system is below about 12 Hz, low-frequency catheter oscillation waves will obscure high-frequency cardiac waveforms. The operator should try to minimize the following factors that lower the frequency response of a catheter–manometer system:

1. Air bubbles in the catheter system
2. High-viscosity fluid in the catheter (e.g., contrast material instead of saline)
3. Long fluid-filled tubing between the catheter and the pressure transducer
4. A long catheter

5. A narrow-bore catheter
6. A catheter made of soft, compliant material

Overshoot is produced by reflected waves within the catheter–manometer system. The magnitude of overshoot can be reduced by mechanical or electrical damping. Overdamping eliminates overshoot, but it reduces frequency response. Optimal damping reduces overshoot without producing a major drop in frequency response (Fig. 45.1).

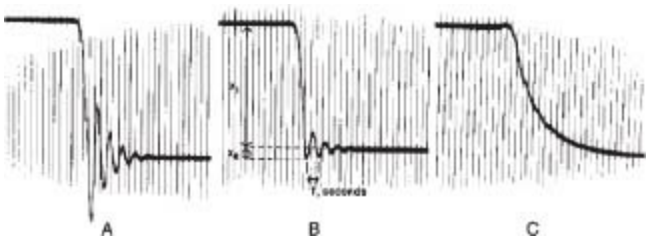

FIGURE 45.1 **A:**Underdamped. **B:** Optimally damped. **C:** Overdamped.

The pressure transducer in a fluid-filled catheter system must be placed in a position equal to the mid-height atrial level to achieve the "zero level." This is approximately one-half the distance between the front and the back of the chest in a supine patient. If the transducer is placed at the level of the anterior chest surface of a supine patient, the recorded pressures will be falsely low.

Respiration produces cyclical changes in the absolute pressure of all intrathoracic cardiovascular structures. Pressure measurement should be measured during end expiration. The ultimate goal of setting up a fluid-filled catheter pressure measurement system is to achieve the highest frequency response possible, optimally damp the system to eliminate overshoot, and locate the pressure transducer at the zero level.

BASIC INTRACARDIAC WAVEFORMS

The basic configuration of normal waveforms is similar for the right and left atria. The V-wave amplitude is generally greater than the A wave in the left atrium, whereas the A wave predominates in the right atrium (RA). Electromechanical delay is about 40 to 80 milliseconds. The basic intra-atrial waveforms and the events to which they correspond are as follows:

A: atrial contraction

C: ventricular contraction

V: rising atrial pressures during ventricular systole; occurs during the T wave

C-V, or systolic: rapidly rising atrial pressure due to severe atrioventricular valve regurgitation

X descent: atrial relaxation; occurs after the A-wave peak, before the C wave

X′ descent: atrial relaxation; occurs after the C wave and before the V wave

Y descent: opening of the atrioventricular valve; occurs after the peak of the V wave (Fig. 45.2).

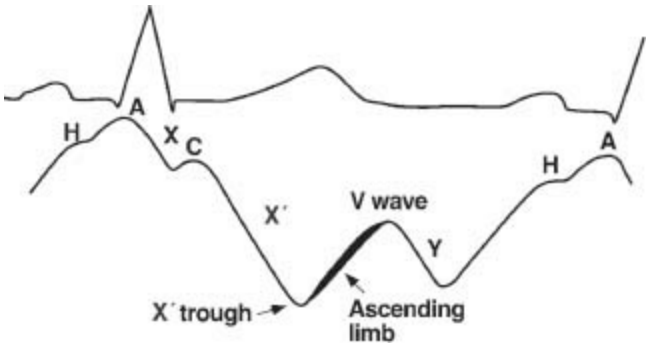

FIGURE 45.2 Timing of the interatrial waveform with the electrocardiogram.

Arrhythmias may produce a variety of changes in intracardiac pressures:

1. Atrial fibrillation will eliminate A waves.
2. Junctional rhythm will displace A waves closer to the C wave.
3. Premature ventricular contractions (PVCs) and ventricular pacemaker rhythm may produce cannon A waves in the atrium as a result of atrial contraction against a closed atrioventricular valve.

Normal values for intracardiac pressures are listed in Table 45.1.

TABLE
45.1 Normal Values for Intracardiac Pressure

Chamber	Normal Pressure (mm Hg)
RA	5 (±2)
RV	25 (±5)/5 (±2)
Pulmonary artery	25 (±5)/10 (±2)
Left atrium	10

Pulmonary Capillary Wedge Pressure Waveforms

Pulmonary capillary wedge (PCW) pressures indirectly reflect left atrial pressures. PCW waveforms demonstrate a mechanical time delay, decreased amplitude, and decreased frequency response compared to simultaneously recorded left atrial waveforms (Fig. 45.3). The reason for these changes is the retrograde transmission of pressure waves from the left atrium through the pulmonary veins, capillaries, and

arterioles to the wedged catheter in the pulmonary artery. The mechanical time delay is determined by the location of the wedged catheter in the pulmonary arterial circuit and by the volume and compliance of the pulmonary venous circuit and left atrium. A stiff 7 French end-hole catheter (e.g., Cournand) will wedge more distally in the pulmonary artery, with a mechanical time delay of about 70 to 80 milliseconds. A balloon-tipped catheter will wedge more proximally in the pulmonary artery branches, with a mechanical time delay up to 150 to 160 milliseconds. Proper wedging of the right heart catheter can be demonstrated by:

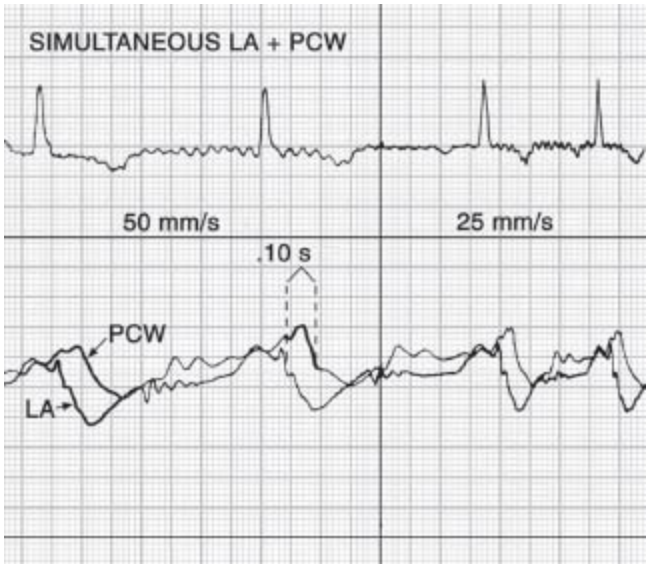

FIGURE 45.3 Electromechanical delay between left atrial waveform and pulmonary capillary wedge pressure waveform.

1. A mean PCW pressure about 10 mm Hg lower than mean PA pressure
2. Blood withdrawn from the wedged catheter has an oxygen saturation at least equal to arterial saturation.

For the PCW to accurately reflect left atrial pressure, the pulmonary artery catheter must be positioned in an area of the lung where the mean pulmonary capillary pressure (P_c) exceeds the mean alveolar pressure (P_A). The lungs can be divided into three physiologic zones of blood flow. These zones are based upon the relative differences in alveolar pressure, mean pulmonary artery pressure, and pulmonary capillary pressure:

- Zone 1 (highest in elevation): This is the part of the lung that is above the level where the alveolar pressure (P_A) is equal to the pulmonary artery pressure (P_a), such that $P_A > P_a > P_c$ throughout this zone. There is minimal to no blood flow in this zone because the pressure exerted on the pulmonary artery by the alveoli prevents blood flow to the capillaries.

- Zone 2 (middle elevation): This region of the lung lies between where the pulmonary artery pressure equals the alveolar pressure and where the alveolar pressure equals the pulmonary capillary pressure; such that $P_a > P_A > P_c$.
- Zone 3 (lowest in elevation): This is the region of the lung that lies below the level where the alveolar pressure equals the pulmonary capillary pressure, such that $P_a > P_c > P_A$.

If the pulmonary catheter is in an area where the alveolar pressure is greater than the pulmonary capillary pressure, then the PCW waveform will be falsely elevated. Thus, the PCW pressure accurately reflects left atrial pressure only when the catheter is in zone 3 of the lung. In the catheterization laboratory, a newly placed pulmonary artery catheter selectively advances to zone 3, thereby assuring valid PCW measurement. However, when in the intensive care unit, the patient can be repositioned or significant fluid changes can occur thereby changing the intrapulmonary hemodynamics. Thus it is often necessary to verify that the location of the catheter tip still exhibits zone 3 physiology. Marked respiratory variation in the PAWP tracing and a loss of the normal atrial pressure waveform suggest that the catheter is in a zone other than zone 3. When using a balloon-tipped pulmonary artery catheter, withdrawing the catheter back to the right ventricle (RV) and then readvancing the catheter with the balloon tip inflated will usually reposition the catheter into zone 3.

Accurate PCW pressures may be difficult to obtain in patients with near systemic levels of pulmonary hypertension. Characteristically, the PCW pressures may appear falsely elevated, which may lead to a false impression of postcapillary pulmonary hypertension. In these cases, direct left ventricular and/or left atrial pressure measurement may be required to determine if the left heart pressures are truly elevated.

Pressure Wave Artifacts

In addition to the artifacts that may be produced by low-frequency response and overshoot, catheter structure or placement may introduce artifacts in pressure recordings.

End-hole artifacts may occur when the tip of an end-hole catheter becomes occluded during contraction of an atrial or ventricular wall. If this occurs during atrial systole with a catheter in the atrium, the A wave will appear greatly magnified (Fig. 45.4). If end-hole occlusion occurs with a catheter in a pulmonary artery, the PCWP will appear falsely low and flat.

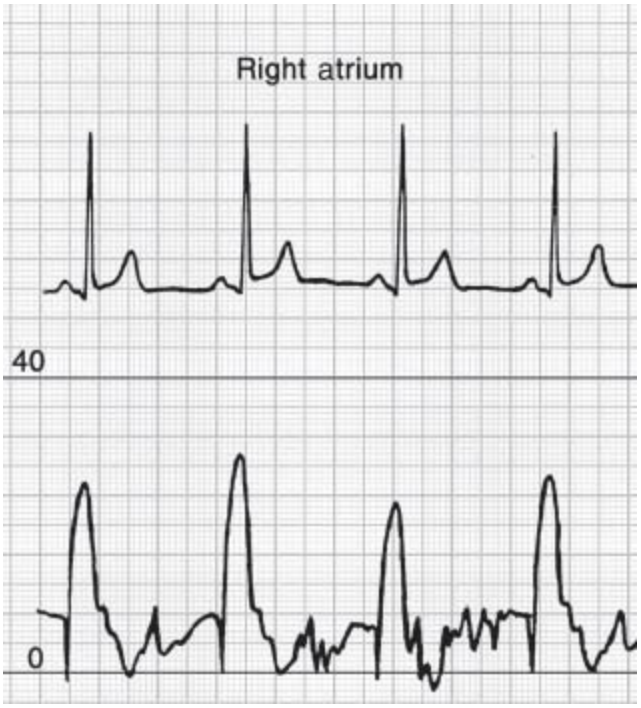

FIGURE 45.4 Falsely elevated A wave recorded from an endhole catheter in the right atrium.

Simultaneous recording of ventricular and aortic pressures may occur when the tip of a pigtail catheter is located in the ventricle and the side port in the aorta. This may produce a bizarre-looking pressure wave with an apparently elevated diastolic left ventricular pressure (Fig. 45.5).

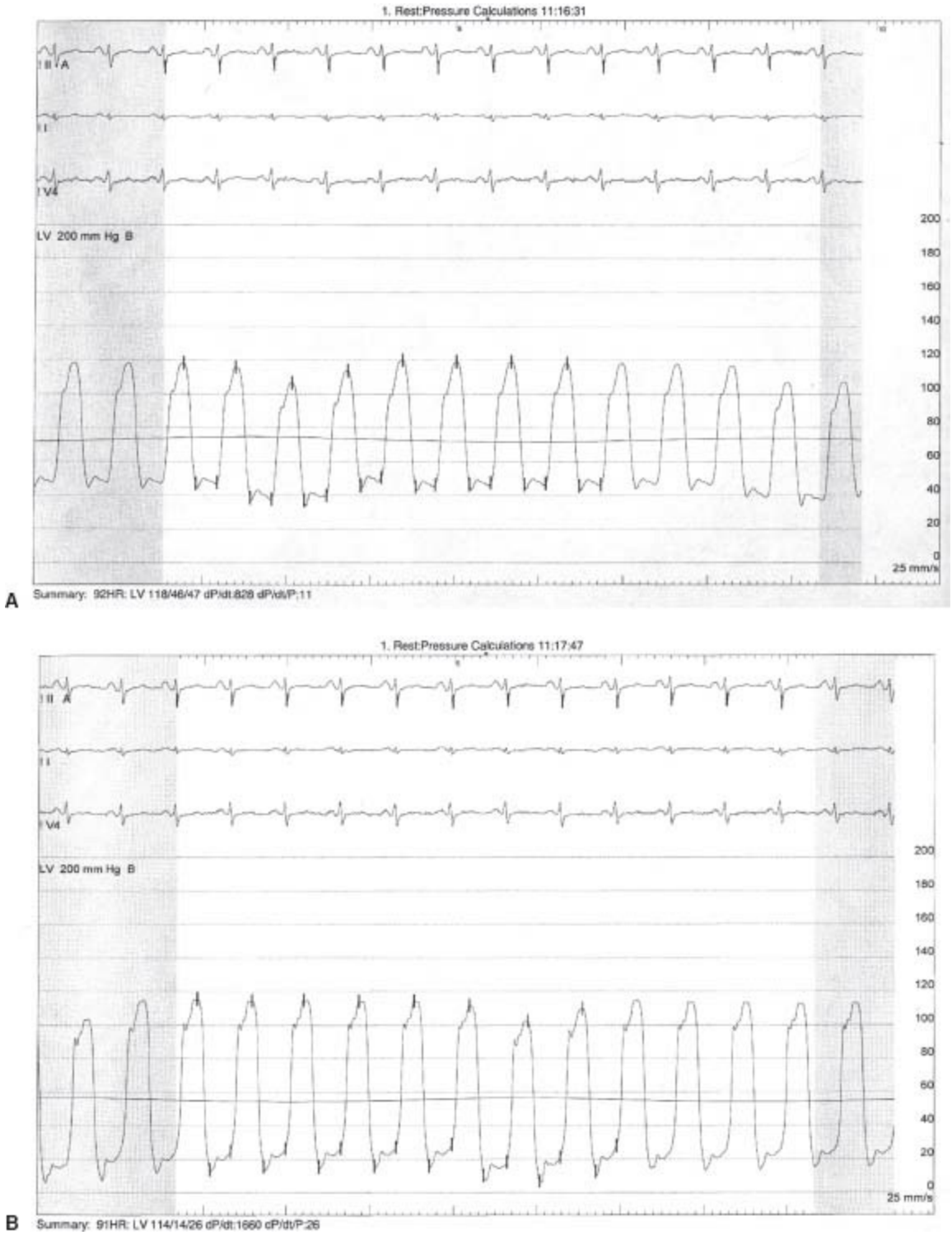

FIGURE 45.5 A: Pressure recording from pigtail catheter with endhole in the left ventricle and side-holes in the aorta revealing a falsely elevated LVEDP. **B:** Pressure recording in same patient with pigtail catheter completely in left ventricle demonstrating the accurate LVEDP.

Catheter-whip artifact is a high-frequency oscillation that results from rapid movement of the catheter by blood flow. This is particularly likely to occur in the pulmonary artery and above a stenotic aortic valve.

Cardiac Output Measurement

The fundamental function of the heart is to deliver enough blood to the systemic circulation to meet the oxygen demands of tissues. The normal cardiac output (CO) increases with body size and exercise and decreases with age. Numerous other factors may affect resting CO. In order to account for body size, the CO is normalized to body surface area (BSA) in square meters (m^2), and the result is the cardiac index. BSA may be obtained from a nomogram or calculated by the following formula:

$$\text{BSA } (m)^2 = \sqrt{\frac{\text{Ht (cm)} \times \text{Wt (kg)}}{3{,}600}}$$

The normal resting cardiac index falls from about 4.5 L/min/m^2 at age 7 years to 3 L/min/m^2 in middle age, and to 2.5 L/min/m^2 at age 70.

The two major methods for measurement of CO in the cardiac catheterization lab are the Fick oxygen technique and the indicator dilution technique.

The Fick Technique

The Fick principle states that the total uptake or release of any substance (such as oxygen) by an organ (such as the lungs) is the product of blood flow to the organ and the arteriovenous (A-V) concentration difference of the substance. If pulmonary blood flow equals systemic blood flow, then

$$\text{CO} = \frac{\text{O}_2 \text{ consumption}}{\text{A} - \text{V O}_2 \text{ difference}}$$

Oxygen consumption can be estimated by measuring the oxygen uptake from room air by use of a Douglas bag or metabolic hood. In order to conserve time and expense, many laboratories use an assumed oxygen consumption based on the formula 125 mL/min/m^2 for younger patients (110 mL/min/m^2 for older patients) or 3 mL/min/kg. However, assumed oxygen consumption values may produce discrepancies of ±10% to 25% in about half of patients.

A-V oxygen difference is obtained by subtracting the oxygen content of pulmonary venous (or systemic arterial) from pulmonary arterial (or "mixed venous") blood. Oxygen content may be calculated using the formula

$$\begin{aligned}\text{O}_2 \text{ content} = {} & \text{O}_2 \text{ saturation} \\ & \times 1.36 \text{ (mL O}_2\text{/g Hb)} \\ & \times \text{ (g Hb/100 mL blood)}\end{aligned}$$

where Hb is hemoglobin.

The final formula for calculation of CO then becomes

$$\text{CO} = \frac{\text{O}_2 \text{ consumption (mL/min)}}{(\text{systemic arterial O}_2 - \text{mixed venous O}_2 \text{ saturation}) \times 1.36 \text{ Hb} \times 10}$$

Estimation of pulmonary arterial oxygen content by using "mixed venous" blood from

the venae cavae is less accurate. Mixed venous blood oxygen saturation is an estimation of what the pulmonary artery blood oxygen saturation would be if no shunt were present. This can be approximated by the following formula:

$$\text{Mixed venous blood} = \frac{\text{SVC} + 2\text{IVC}}{3} \text{ (while exercising)}$$

and

$$\text{Mixed venous blood} = \frac{\text{SVC} + 2\text{IVC}}{3} \text{ (while exercising)}$$

where superior vena cava (SVC) and inferior vena cava (IVC) are the respective O_2 saturations.

Use of arterial blood to estimate pulmonary venous blood oxygen content is acceptable, because, in the absence of shunts, only a small amount of venous blood enters the arterial circuit within the heart via the Thebesian veins. Narrow A-V oxygen differences (as seen with high CO) are more likely to introduce error than wide differences (as seen with low CO). Thus, the Fick method is most accurate in patients with low CO.

Assume that a patient has the following measured values:
Oxygen consumption = 250 mL/min
Femoral artery oxygen saturation = 97%
SVC oxygen saturation = 70%
IVC oxygen saturation = 78%
Hb concentration = 14.0 g%
The mixed venous blood saturation will be

$$\frac{3\,(0.7) + (0.78)}{4} = 0.72$$

In this case, the CO can be calculated as

$$\text{CO} = \frac{250 \text{ mL/min}}{(0.97 - 0.72) \times 1.36 \times 14 \times 10} = 5.25 \text{ L/min/m}^2$$

Indicator Dilution Methods

The most commonly used indicator dilution method today is the thermodilution technique. This method utilizes a bolus injection of saline, followed by continuous measurement of the temperature of the blood by a thermistor in the pulmonary artery. The resulting curve is analyzed by computer to derive the CO using the basic indicator dilution equation. With this method, the temperature of the injectate (measured in the injectate fluid container before injection) is assumed to increase by a predictable amount during injection.

Accurate measurement of both blood and injectate temperatures immediately before injection is important for measuring thermodilution COs. According to the formula for

calculating thermodilution CO, the temperature difference between blood and injectate (typically 16°C when room-temperature injectate is used) is directly proportional to CO. Small errors in either of these measurements can produce errors in calculated CO.

Thermodilution CO will be overestimated if the injectate temperature is inappropriately increased by permitting the injectate to remain in the syringe or by holding the syringe in the hand before and during injection. Use of cooled injectate, as opposed to room-temperature injectate, may produce an even greater mean error, probably because warming of the cooled injectate in the tubing and syringe produces an even greater increase in temperature than use of room-temperature injectate. Even though there is a theoretical advantage to iced injectate because of its greater signal-to-noise ratio, most studies have shown no advantage to iced over room-temperature injectate. A dual-thermistor catheter appears to minimize these problems with injectate temperature, resulting in more consistent and accurate CO measurements, but at increased expense.

The thermodilution technique will overestimate CO in low-flow states because of warming of blood by the cardiac chambers. The thermodilution method is most accurate in high-flow states. It is unreliable in the presence of significant tricuspid regurgitation because the injectate is warmed during its prolonged stay within the RA and R V. Overall, the thermodilution method should have an error of no more than 5% to 10% when performed correctly.

Shunt Calculation

An intracardiac shunt is an abnormal communication between the left and right heart chambers. A left-to-right intracardiac shunt increases pulmonary blood flow in relation to systemic flo w, and a right-to-left shunt does the opposite.

Oximetry is the most common method for calculating intracardiac shunts in the catheterization laboratory, although dye dilution curves and angiography may also be used. Oximetry is not as sensitive as dye dilution curves for detecting small shunts, but it should be capable of detecting any shunt that is large enough to merit surgical correction. Detailed oximetric analysis requires sampling in the RA (three sites), SVC (high and low), IVC (at renal artery level and below the diaphragm), RV (three sites), pulmonary artery, and aorta.

When a left-to-right shunt exists at the atrial level, it is necessary to use the SVC and IVC oxygen saturations to calculate the mixed venous blood saturation, as described above. The same principle applies when a left-to-right shunt exists at the right ventricular level, especially when tricuspid regurgitation is present. A significant increase in oxygen saturation in the right side of the heart is considered to exist when there is >7% increase from the SVC/IVC to the RA, >5% from the RA to the RV, and >5% from the RV to the PA.

Left-to-right shunts are commonly expressed as Q_p/Q_s. Q_p, or pulmonary flow, and

Q_s, or systemic flow, are calculated using the formula given above for calculating CO. The A-V O_2 difference for Q_p requires pulmonary arterial and pulmonary venous samples (or assumption of a pulmonary venous saturation of 95%). The A-V O_2 difference for Q_s requires arterial and mixed venous samples. A Q_p/Q_s <1.5 signifies a small left-to-right shunt, 1.5 to 2.0 an intermediate size, and >2.0 a large shunt. A Q_p/Q_s <1.0 indicates a net right-to-left shunt.

When Q_p/Q_s is calculated, all the components of the CO formula factor out, leaving only the oxygen saturations. Therefore, Q_p/Q_s can be calculated by the following formula:

$$\frac{Q_p/Q_s = \text{systemic arterial oxygen saturation} - \text{mixed venous oxygen saturation}}{\text{pulmonary venous oxygen saturation} - \text{pulmonary artery oxygen saturation}}$$

Assume that a patient with an ostium secundum interatrial septal defect has the following measured values:
LV oxygen saturation = 96%
SVC oxygen saturation = 67.5%
IVC oxygen saturation = 73%
PA oxygen saturation = 80%
The mixed venous blood saturation is

$$\frac{3(0.675)+(0.73)}{4} = 0.69$$

In this case, Q_p/Q_S is calculated as follows:

$$Q_P/Q_s = \frac{0.96-0.69}{0.96-0.80} = 1.69$$

Vascular Resistance

Vascular resistance is defined by the ratio of pressure gradient across a vascular circuit divided by the flow. In a rigid tube with steady laminar flow of a homogeneous fluid, the relationship between pressure and flow is described by Poiseuille's law, which states that the pressure drop across a circuit with fluid flowing at a constant rate (and therefore its resistance) is directly proportional to the length of the tube and the viscosity of the fluid and indirectly proportional to the fourth power of the radius of the tube. Within the bloodstream, Poiseuille's law is inaccurate because blood flow is pulsatile and nonlaminar, blood is not homogeneous, and blood vessels are nonlinear and elastic. However, the basic principles of this law still apply in clinical measurements of resistance.

For clinical purposes, two important vascular resistance concepts are commonly derived from pressure and flow data:

$$\text{Systemic vascular resistance (SVR)} = \frac{\overline{Ao} - \overline{RA}}{Q_S}$$

$$\text{Pulmonary vascular resistance (PVR)} = \frac{\overline{PA} - \overline{LA}}{Q_P}$$

where $\overline{Ao}$ is the mean systemic arterial pressure, $\overline{RA}$ the mean right atrial pressure, $\overline{PA}$ the mean pulmonary arterial pressure, $\overline{LA}$ the mean left atrial pressure, Q_S the systemic blood flow, and Q_P the pulmonary blood flow. The mean PCW pressure is often used as an approximation of the left atrial pressure.

These calculations yield vascular resistance in Wood units, named after Dr. Paul Wood. To convert to metric resistance units, expressed in dynes-sec-cm^{-5}, multiply vascular resistance by 80. Vascular resistance index (VRI) is obtained by multiplying vascular resistance by body surface area.

Normal values for vascular resistance (in dynes-sec-cm^{-5}) are:
SVR: 1,150 ± 300
SVRI: 2,100 ± 500
PVR: 70 ± 40
PVRI: 125 ± 70
Clinically, SVR calculations are commonly used to diagnose and treat patients with hypotension or heart failure, and PVR to evaluate pulmonary arterial hypertension and the suitability of patients with congenital heart disease for cardiac surgery. PVR calculations are also frequently used to determine the severity of PVR in patients with end-stage heart failure being evaluated for heart transplantation and in patients with end-stage liver failure being evaluated for liver transplantation. Because the length of the vascular bed is likely to be constant in any adult patient, changes in SVR and PVR reflect either altered viscosity of blood or a change in the cross-sectional area of the vascular bed. Severe chronic anemia lowers the values for measured vascular resistance. If the hematocrit remains stable, changes in SVR are produced primarily by altered arteriolar tone. Thus, measurement of SVR becomes the basis for hemodynamic evaluation of shock.

Vasodilatory shock, such as in sepsis or adrenal insufficiency, is associated with markedly decreased SVR and normal or increased CO. Cardiogenic and hypovolemic shock usually produce a decreased CO and markedly increased SVR due to intense peripheral vasoconstriction.

In congenital heart disease, the ratio of PVR to SVR is commonly used as a criterion for operability. Normal is <0.25. Moderate pulmonary vascular disease is 0.25 to 0.75, severe is 0.75 to 1.0, and ≥1.0 is generally considered inoperable. Administration of oxygen or vasodilator drugs, such as nitric oxide, helps to differentiate reversible pulmonary vasoconstriction versus permanent obliterative changes in the pulmonary vasculature.

CALCULATION OF VALVE ORIFICE AREA

Proper calculation of stenotic valve orifice area (VOA) is critically important for proper timing of valve surgery and valvuloplasty. The "gold standard" for calculating VOA is the Gorlin formula, which was developed by Dr. Richard Gorlin.

Gorlin Formula

The Gorlin formula relies on measurement of three variables:

1. CO
2. mean pressure gradient
3. flow period (the portion of the cardiac cycle during which pulsatile flow actually occurs)

The diastolic filling period (DFP) is used for the mitral and tricuspid valves, because flow occurs through these valves only during diastole; the systolic ejection period (SEP) is used for the aortic and pulmonic valves. The final formula for the calculation of VOA is

$$\text{VOA} = \frac{\text{CO} / (\text{HR})(\text{DFP or SEP})}{44.3C\sqrt{\Delta P}}$$

where VOA is the valve orifice area in cm^2, CO the cardiac output (mL/min), DFP the diastolic filling period (s/beat), SEP the systolic ejection period (s/beat), HR the heart rate (beats/min [bpm]), C the empiric constant, and ΔP the pressure gradient. An empiric constant of 0.85 is used for mitral valve calculations, and 1.0 for all other valves.

Hakki Formula

A simplified formula for calculating VOA introduced by Hakki is

$$\text{VOA} = \frac{\text{CO (L/min)}}{\sqrt{\Delta P}}$$

This simplification is based on the fact that, at normal heart rates, the product of heart rate, SEP or DFP, and the Gorlin constant is approximately 1.0 for all patients.[1]

However, in the presence of tachycardia, the simplified formula may be less useful because the percentage of time/minute spent in systole or diastole changes markedly at higher heart rates. Therefore, Angel introduced a correction for heart rate: the Hakki equation should be divided by 1.35 when the heart rate is <75 bpm with mitral stenosis and >90 bpm with aortic stenosis (AS).[2]

Aortic Valve Resistance

Aortic valve resistance (AVR) is another method of estimating severity of AS. The simplified method of AVR calculation is

$$AVR = \frac{(LV - Ao) \times 80}{CO \times 2.5}$$

where (LV-Ao) is the mean aortic valve gradient, 80 the conversion factor to dynes-s-cm^{-5}, CO the cardiac output, and 2.5 assumes that the systolic ejection period comprises 40% of the R-R cycle. Severe AS (aortic VOA <0.7 cm^2) corresponds to AVR ≥300 dynes-s-cm^{-5}.

SPECIFIC HEMODYNAMIC EXAMPLES

Mitral Regurgitation

The characteristic atrial pressure waveform in mitral or tricuspid regurgitation consists of an earlier V-wave upstroke, increased amplitude, and a steep Y descent. In severe mitral regurgitation, the V wave may fuse with the C wave, producing a systolic wave (Fig. 45.6). The amplitude of the systolic wave in mitral regurgitation is determined by the severity and acuity of the regurgitation and the size of the atrium. Acute severe mitral regurgitation is often associated with normal atrial size, in which case the atrium is noncompliant and the systolic wave is very high. When the atrium is quite dilated and compliant, as with chronic rheumatic mitral regurgitation, the systolic wave is likely to be much lower in amplitude.

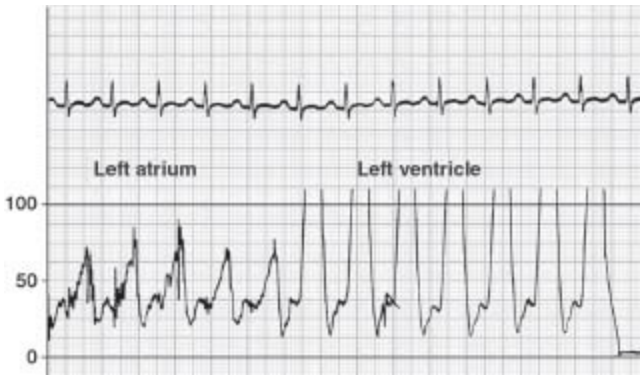

FIGURE 45.6

Mitral Stenosis

Doppler echocardiography of the mitral valve from the transapical position usually provides adequate information to accurately determine the VOA in mitral stenosis. Thus, invasive hemodynamic assessment is rarely needed to quantify the severity of mitral stenosis. However, when accurate echocardiographic imaging and Doppler assessment are unable to be obtained, invasive hemodynamic assessment is usually necessary. Also, catheterization for hemodynamic assessment is indicated when there is a discrepancy between the Doppler-derived gradient and the valve area. Left ventriculography is generally included to evaluate the severity of concomitant mitral

regurgitation. The American College of Cardiology/American Heart Association (ACC/AHA) recommendations for catheterization and invasive hemodynamic evaluation in the assessment of mitral stenosis are listed in Table 45.2.

TABLE
45.2 ACC/AHA Indications for Invasive Hemodynamic Assessment in the Evaluation of Mitral Stenosis

Class I

1. Cardiac catheterization for hemodynamic evaluation should be performed for assessment of severity of MS when noninvasive tests are inconclusive or when there is discrepancy between noninvasive tests and clinical findings regarding severity of MS. *(Level of Evidence: C)*
2. Catheterization for hemodynamic evaluation including left ventriculography (to evaluate severity of MR) for patients with MS is indicated when there is a discrepancy between the Doppler-derived mean gradient and valve area. *(Level of Evidence: C)*

Class IIa

1. Cardiac catheterization is reasonable to assess the hemodynamic response of pulmonary artery and left atrial pressures to exercise when clinical symptoms and resting hemodynamics are discordant. *(Level of Evidence: C)*
2. Cardiac catheterization is reasonable in patients with MS to assess the cause of severe pulmonary arterial hypertension when out of proportion to severity of MS as determined by noninvasive testing. *(Level of Evidence: C)*

Class III

1. Diagnostic cardiac catheterization is not recommended to assess the MV hemodynamics when 2D and Doppler echocardiographic data are concordant with clinical findings. *(Level of Evidence: C)*

From Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA Practice Guidelines. ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease. Circulation 2006;114:e84–e231, with permission.

The typical atrial waveform configuration of mitral or tricuspid stenosis depends on its severity and the pliability of the valve. The characteristic features are elevation of the mean pressure, a diastolic gradient that is higher in early diastole, and a slow Y descent (Fig. 45.7). The A and C waves are increased in amplitude when the valve is pliable.

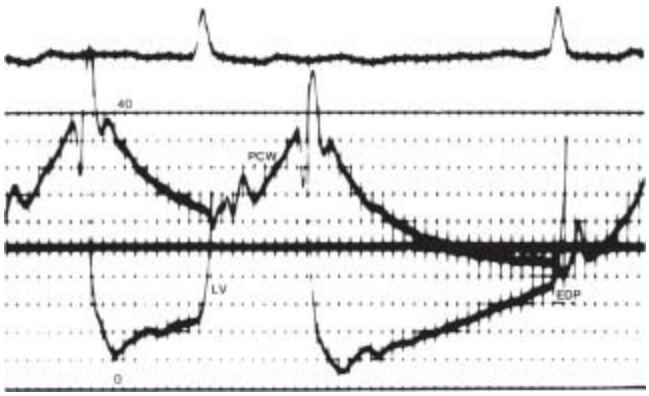

FIGURE 45.7

The normal mitral valve area is 4.0 to 5.0 cm^2. A normal CO of about 5 L/min can be maintained across a mitral valve with only a minimal diastolic gradient until the valve area falls to about 2.0 cm^2. When the valve area falls to about 1.0 cm^2, the resting gradient increases to about 10 mm Hg with this CO, and substantial increases in the diastolic gradient, and therefore in left atrial and PCW pressures, will occur as the pulse rate rises. Therefore, a mitral valve area of 1.0 cm^2 is generally the "critical" area at which intervention may be required. For a large patient, an area of 1.2 may be critical.

Several factors may interfere with accurate determination of mitral valve area, including CO measurements, presence of mitral regurgitation, and the phase delays and amplitude of PCW pressures compared to left atrial pressures.

CO measurements should ideally be made simultaneously with the measurement of pressure gradients. When mitral regurgitation coexists with mitral stenosis, calculations of valve area using only net forward flow will underestimate the actual VOA because they fail to take into account the additional diastolic flow across the valve due to the regurgitation.

PCW pressure is commonly used as a substitute for left atrial pressures to calculate mitral VOA. Some authors suggest that, especially in prosthetic mitral valve stenosis, use of the PCW results in overestimation of transvalvular gradients. Others claim that the PCW pressure is adequate for this purpose, as long as the right heart catheter is properly wedged. To be certain that the transvalvular mitral gradient is not falsely elevated, an atrial transseptal puncture can be performed with insertion of a catheter into the left atrium for direct pressure measurement. For purposes of the Cardiovascular Board Examination, echocardiographic Doppler assessment of the mitral valve is considered the gold standard for valve area assessment when adequate transapical images can be obtained.

The following is an example of measurements made in a patient with mitral stenosis:
CO = 4,700 mL/min
Heart rate = 80 bpm

Diastolic filling period = 0.4 s/beat
Mean mitral diastolic gradient = 20 mm Hg
From these values, the mitral VOA can be calculated by the Gorlin formula as follows:

$$= \frac{(4{,}700 \text{ mL/min})/(80 \text{ beats/min})\,(0.4 \text{ s/beat})}{(44.3)\,(0.85)\,(\sqrt{20 \text{ mm Hg}})}$$
$$= 0.9 \text{ cm}^2$$

The mitral VOA can be calculated by the Hakki formula as follows:

$$\text{Mitral orifice area} = \frac{4.7 \text{ L/min}}{\sqrt{20 \text{ mm Hg}}} = 1.0 \text{ cm}^2$$

Aortic Regurgitation

The aortic waveform in chronic severe aortic regurgitation is characterized by a wide pulse pressure, commonly >100 mm Hg, and a low diastolic pressure, often <50 mm Hg. When the pulse is fast, the aortic diastolic pressure tends to be higher and the left ventricular diastolic pressure lower. When the pulse rate is slow, the aortic diastolic pressure falls, and it may become equal to the left ventricular diastolic pressure. Patients with severe aortic insufficiency tolerate bradycardia poorly because of the resulting increase in LV end-diastolic pressure (LVEDP).

Aortic Stenosis

Doppler echocardiography is the most commonly used modality to measure the transvalvular aortic pressure gradient, and it is usually adequate to determine the severity of AS. However, invasive hemodynamic measurement of AS is still the gold standard and it is often necessary. This is particularly true in cases when the clinical symptoms and echocardiography data are discordant. The ACC/AHA guideline recommendations for the use of cardiac catheterization for the assessment of AS are listed in Table 45.3.

TABLE
45.3 ACC/AHA Indications for Invasive Hemodynamic Assessment in the [Evaluation of Aortic Stenosis

Class I

1. Coronary angiography is recommended before AVR in patients with AS at risk for CAD (see Section 10.2). *(Level of Evidence: B)*
2. Cardiac catheterization for hemodynamic measurements is recommended for assessment of severity of AS in symptomatic patients when noninvasive tests are inconclusive or when there is a discrepancy between noninvasive tests and clinical findings regarding severity of AS. *(Level of Evidence: C)*
3. Coronary angiography is recommended before AVR in patients with AS for whom a pulmonary autograft (Ross procedure) is contemplated and if the origin of the coronary arteries was not identified by noninvasive technique. *(Level of Evidence: C)*

Class III

1. Cardiac catheterization for hemodynamic measurements is not recommended for the assessment of severity of AS before AVR when noninvasive tests are adequate and concordant with clinical findings. *(Level of Evidence: C)*
2. Cardiac catheterization for hemodynamic measurements is not recommended for the assessment of LV function and severity of AS in asymptomatic patients. *(Level of Evidence: C)*

From Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA Practice Guidelines. ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease. Circulation 2006;114:e84–e231, with permission.

The aortic waveform in AS is generally characterized by a slow upstroke, but the upstroke may be brisk in elderly patients with stiff, noncompliant vessels. The aortic transval-vular gradient may be expressed as:

1. Peak-to-peak gradient, which uses the maximum left ventricular and maximum aortic pressures. This measurement has no physiologic meaning because the two peaks occur at different times. This gradient approximates the mean gradient in severe AS.
2. Peak instantaneous gradient, which is usually derived from Doppler flow velocity
3. Mean gradient, which represents the planimetered area under the simultaneous aortic–left ventricular curves

Normal aortic valve area is about 3.0 to 4.0 cm^2. AS is generally considered severe enough to produce symptoms when the aortic VOA is reduced to <0.8 cm^2. In a very large person, for example, someone with a body surface area of >2.2 m^2, an orifice area of 0.9 to 1.0 cm^2 may be considered severe. Unlike mitral stenosis, in which the transvalvular gradient increases with increasing heart rate, the gradient in AS increases with decreasing heart rate.

Several factors may interfere with accurate determination of aortic VOA, including use of simultaneous left ventricular and peripheral arterial pressures, catheter position

in the left ventricular outflow tract, low-flow states, and pullback pressures, especially in the presence of arrhythmias. In addition, aortic VOA calculations in patients with associated severe aortic regurgitation will underestimate the aortic flo w, and therefore the VOA.

Ideally, the aortic valve gradient should be measured simultaneously in the left ventricle and ascending aorta, either with a double-lumen catheter or with separate catheters. Compared to the ascending aorta pressure, the femoral artery pressure wave is delayed and widened, and the peak systolic pressure is amplified. If the femoral artery and ventricular waveforms are aligned, the mean gradient is overestimated by nearly 10 mm Hg. With alignment, the gradient is underestimated by about 10 mm Hg. These errors are of particular significance when the gradient is <50 mm Hg.

Patients with AS who have low CO and a small gradient present a special problem. For instance, a 0.7-cm^2 aortic VOA combined with a CO of 3 L/min will produce a gradient of only 20 mm Hg. The Gorlin formula becomes very flow-dependent at COs of <3 to 4 L/min. Maneuvers such as exercise or infusion of an inotropic agent or sodium nitro-prusside may produce a higher CO, which allows calculation of a more reliable VOA. In mild aortic valve disease, the calculated valve area increases, indicating that surgery may not be necessary. In severe AS, the valve area remains small.

Pullback pressures across the aortic valve may introduce errors in calculation of the VOA as a result of respiratory variation or due to transient changes that occur in the systolic pressure during sinus beats that follow a PVC during pullback. In addition, when the VOA is <0.6 cm^2, a 7 or 8 French catheter may occupy a significant amount of the remaining VOA, in which case the catheter temporarily increases the severity of the stenosis.

The following is an example of measurements obtained in a patient with AS:
CO = 4,500 mL/min
Heart rate = 72 bpm
Systolic ejection period = 0.33 s/beat
Mean aortic systolic gradient = 50 mm Hg
From these values, the aortic VOA can be calculated as follows:
Aortic orifice area

$$= \frac{(4{,}500 \text{ mL/min})/(72 \text{ beats/min})\,(0.33 \text{ s/beat})}{(44.3)\sqrt{50 \text{ mm Hg}}}$$
$$= 0.6 \text{ cm}^2$$

The aortic VOA can be calculated by the Hakki formula as follows:

$$\text{Aortic orifice area} = \frac{4.5 \text{ L/min}}{\sqrt{50 \text{ mm Hg}}} = 0.6 \text{ cm}^2$$

The AVR in this patient can be calculated by the following formula:

$$AVR = \frac{50\ mm\ Hg \times 80}{4.5\ L/min \times 2.5} = 356\ dynes \cdot s \cdot cm^{-5}$$

For purposes of the cardiovascular board examination, the Hakki formula should be the only equation necessary to calculate the area of a stenotic aortic valve.

Hypertrophic Obstructive Cardiomyopathy

Hypertrophic obstructive cardiomyopathy (HOCM) produces characteristic hemodynamic changes that may vary greatly with physiologic maneuvers. It is important to understand the underlying physiology of HOCM because there may be no intraventricular gradient at rest, and therefore it is necessary to provoke the gradient during the catheterization procedure. The three principal mechanisms that may provoke an intraventricular gradient in HOCM are:

1. Decreased LV end-diastolic volume (e.g., Valsalva maneuver, nitroglycerin, dehydration, upward tilt, phlebotomy)
2. Increased force or duration of ventricular contraction (e.g., following a PVC, intravenous isoproterenol infusion)
3. Decreased aortic outflow resistance (e.g., amyl nitrite inhalation)

PVCs produce characteristic changes in LV pressure and gradient in HOCM (Fig. 45.8). The peak LV systolic pressure of the sinus beat that follows a PVC is:

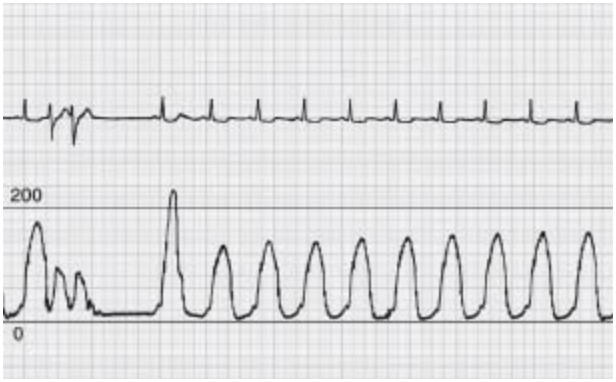

FIGURE 45.8 Post-PVC potentiation of LV pressure in a patient with HOCM.

- Lower in the normal heart
- Higher with left ventricular outflow tract obstruction (HOCM, valvular AS), severe mitral stenosis, and severe dilated cardiomyopathy

A characteristic feature of HOCM that differentiates it from valvular AS is the Brockenbrough sign: with HOCM, the arterial pulse pressure of the sinus beat that follows a PVC is lower than the sinus beat that precedes the PVC (Fig. 45.9); with valvular AS, it is higher. In addition, both the Valsalva maneuver and nitroglycerin increase the gradient in HOCM, but decrease the gradient in valvular AS.

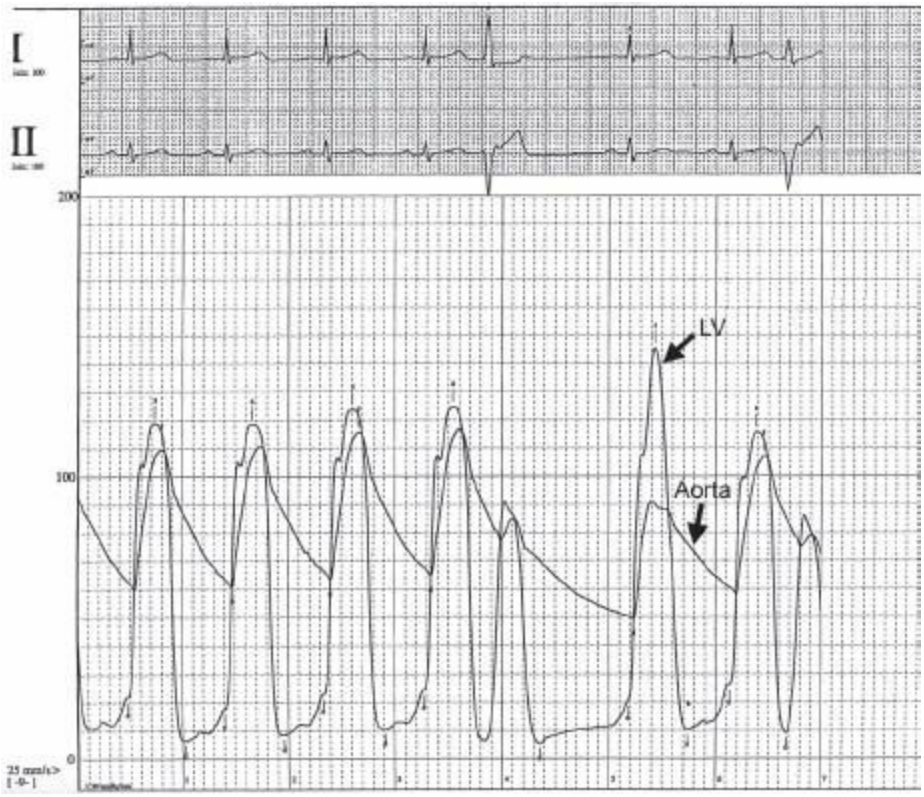

FIGURE 45.9 Brockenbrough sign: Potentiation of LV pressure and decrease in aortic pressure seen after a PVC in patients with HOCM.

Constrictive Physiology

Pericardial tamponade and chronic constrictive pericarditis are the two classic syndromes of constrictive physiology. A third syndrome, effusive-constrictive pericarditis, has intermediate hemodynamic features. All three are characterized by diastolic dysfunction, with impaired atrial and ventricular filling patterns. Clinically, the differentiation of pericardial tamponade and constrictive pericarditis is simple. However, the differentiation of constrictive pericarditis and restrictive cardiomyopathy may be much more difficult, even with the use of modern diagnostic tools.

Pericardial Tamponade

The classic features of pericardial tamponade include:

- Elevation and equalization of right and left ventricular diastolic pressures and right and left atrial pressures (Fig. 45.10)
- Pulsus paradoxus, that is, exaggerated (>10 mm Hg) inspiratory fall in arterial pressures
- Prominent X descent with blunted Y descent
- Arterial hypotension, as a late event

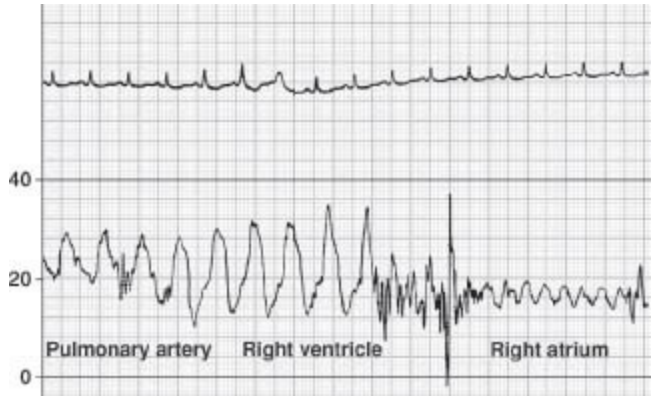

FIGURE 45.10 Pressure tracing pullback from the pulmonary artery to the right atrium demonstrating equalization of diastolic pressure seen in pericardial tamponade.

Pulsus paradoxus is a characteristic finding in pericardial tamponade, but it may be found in chronic obstructive pulmonary disease and rarely in pulmonary embolus and in constrictive pericarditis. Pulsus paradoxus in tamponade is associated with narrowing of the pulse pressure during inspiration, but the pulse pressure is normal in chronic pulmonary disease (Fig. 45.11). Pulsus paradoxus may be impossible to detect in a patient with an irregular rhythm such as atrial fibrillation.

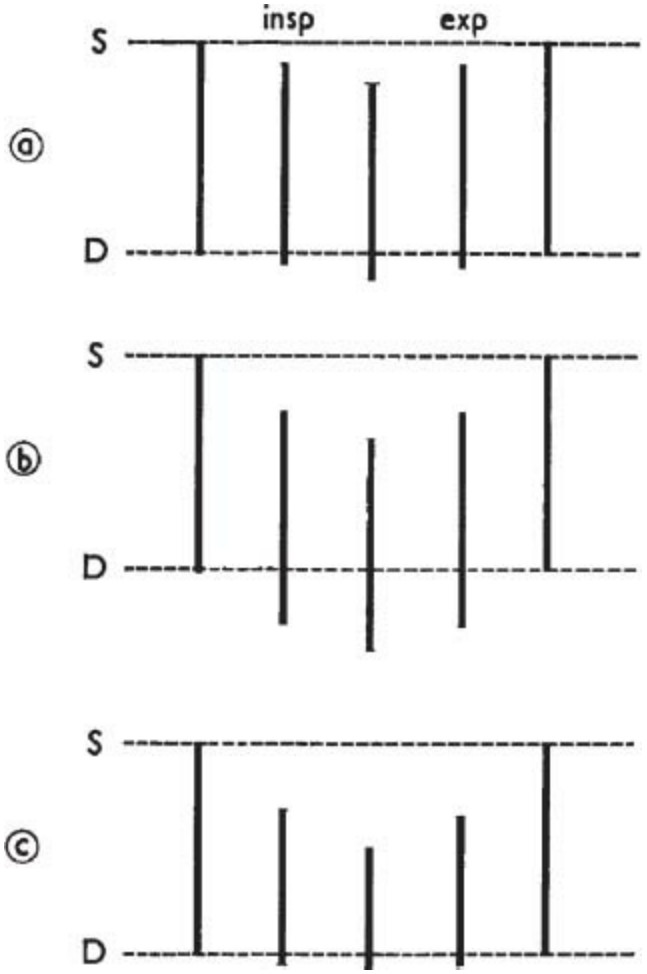

FIGURE 45.11

Three phases of cardiac tamponade have been described:

Phase 1. Only intrapericardial and right atrial pressures are elevated.

Phase 2. Elevated intrapericardial pressure produces equilibration of right atrial and right ventricular diastolic pressures, but not PCW (or left ventricular filling) pressure. It is also associated with pulsus paradoxus and a modest decrease in CO.

Phase 3. Elevated intrapericardial pressure results in equilibration of right and left ventricular filling pressures, marked pulsus paradoxus, decreased CO, and hypotension.

Echocardiography is fairly sensitive for the detection of phases 2 and 3 of cardiac tamponade, characterized by right heart chamber collapse during diastole in the presence of pericardial effusion. However, the echocardiogram may fail to detect pericardial tamponade even in patients with phase 3 tamponade, in which the clinical findings are obvious on physical examination.

Constrictive Pericarditis and Restrictive Cardiomyopathy

The classic features of constrictive pericarditis include:

- Elevation and equalization of diastolic pressures in all four cardiac chambers
- Deep, rapid Y descent (corresponding clinically to Friedreich sign—the abrupt collapse of the jugular vein during diastole)
- Attenuation of the X descent, which, in conjunction with the deep Y descent, produces an M or W configuration in the atrial tracing
- Elevation of the right atrial mean pressure during inspiration (corresponding clinically to Kussmaul sign—the elevation of jugular venous pressure with inspiration)
- "Dip and plateau" pattern in right and left ventricular pressures
- RVEDP > one-third the right ventricular systolic pressure (RVSP)
- PA systolic pressure <55 mm Hg
- Pulsus paradoxus when pericardial pressures are equilibrated with right, but not left, ventricular filling pressures (Fig. 45.12)

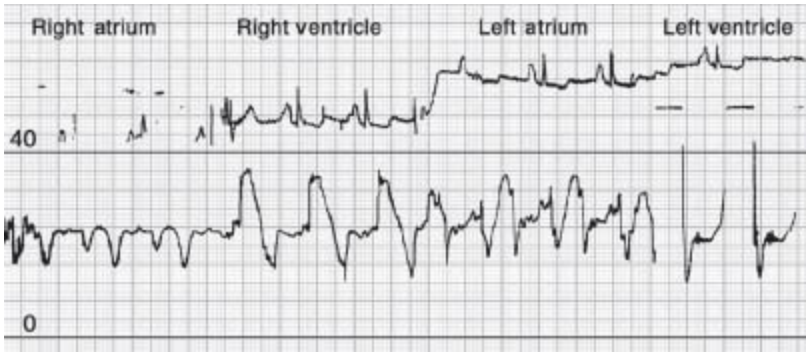

FIGURE 45.12

None of these features is diagnostic of constrictive pericarditis. Pulsus paradoxus without a Kussmaul sign is characteristic of cardiac tamponade, whereas Kussmaul sign without pulsus paradoxus is characteristic of pericardial constriction. However, Kussmaul sign and a rapid Y descent in the right atrial pressure tracing may be seen in right ventricular dysfunction of any cause, such as right ventricular infarction and restrictive cardiomyopathy. Kussmaul sign may also occur in respiratory failure, when the systolic and diastolic pressures fall equally with no change in pulse pressure, whereas tamponade produces a fall in systolic pressure and pulse pressure. A dip-and-plateau pattern is not diagnostic of constrictive pericarditis, and it may be absent in constrictive pericarditis if the pulse rate is rapid.

Hemodynamic Criteria

Three hemodynamic criteria, based on respiratory dynamics, have been introduced recently, and they improve accuracy in differentiating constrictive pericarditis from restrictive cardiomyopathy. They are:

- Respiratory discordance in early diastolic PCW–LV pressure gradient
- Respiratory discordance in left ventricular systolic pressure (LVSP) and RVSP
- Systolic Area Index (SAI)

In the normal heart and in restrictive cardiomyopathy, the drop in intrathoracic pressure that occurs with inspiration is transmitted to both the pericardial sac (and therefore the heart) and the pulmonary veins. The effective filling gradient (EFG) between the PCW pressure and the left ventricular diastolic pressure remains nearly constant.

However, in cardiac tamponade and constrictive pericarditis, inspiration decreases both the intrathoracic pressure and the pulmonary venous pressure (and PCW pressure), but does not affect the pressures in the pericardial sac or left ventricular diastolic pressure. This produces a discordance in the EFG: with inspiration, the PCW falls but the LV diastolic pressure does not, resulting in a marked decrease in EFG, which corresponds to the decrease in diastolic flow across the mitral valve seen on the

echocardiogram. With expiration, the PCW and the EFG rise and the diastolic flow across the mitral valve increases.

Discordance in the RVSP and LVSP with inspiration may occur because the relatively fixed intracardiac volume imposed by constrictive pericarditis produces ventricular "interdependence" (Fig. 45.13). Because the ventricles in constrictive pericarditis cannot fill independently of one another, the filling of one ventricle impairs the filling of the other. Inspiration augments the diastolic filling of the RV at the expense of the left ventricle, with a shift of the interventricular septum to the left. During inspiration, the RVSP increases due to the increased RV volume, whereas the LVSP decreases.

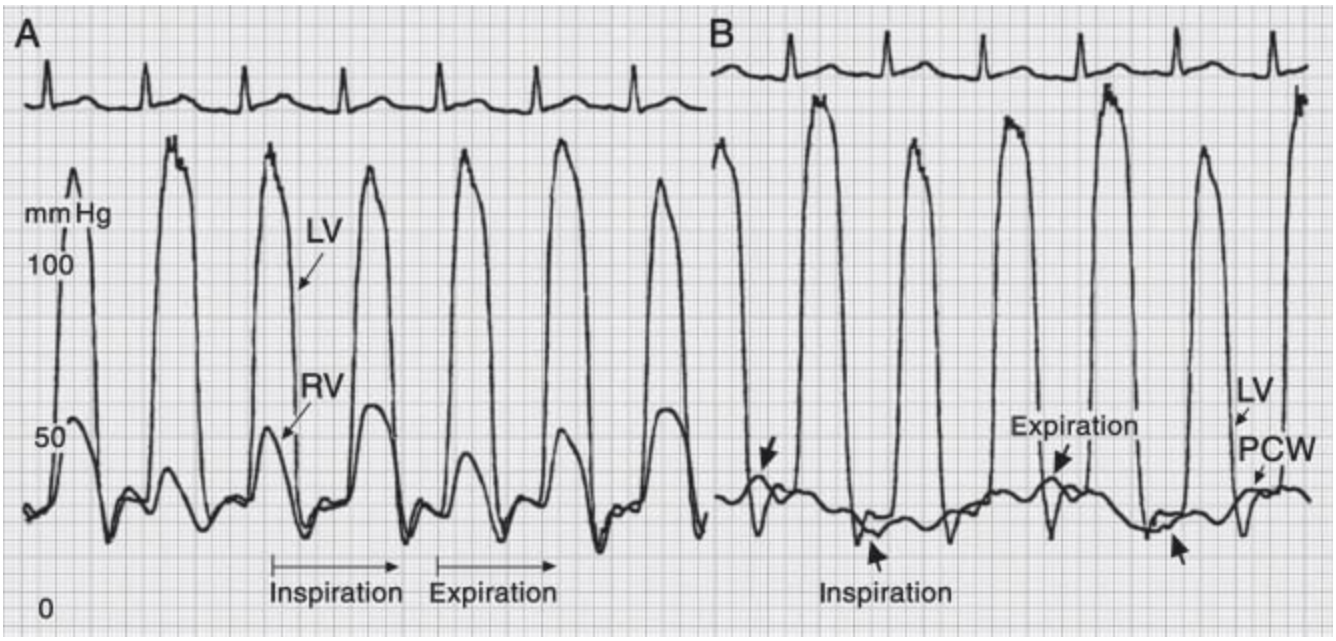

FIGURE 45.13

The SAI is a quantitative measurement of the difference between the right ventricular systolic area (mm Hg × s) and the left ventricular systolic area (mm Hg × s) with respiration during systole. The SAI is defined as the ratio of the RV systolic area to the LV systolic area in inspiration versus expiration. This is calculated by measuring the RV and LVSP –time integrals at the peak inspiratory beat (defined as the systolic impulse that was preceded by the lowest early diastolic nadir of the LV pressure) and at the peak expiratory beat (defined as the systolic impulse that was preceded by the highest early diastolic nadir of the LV pressure) (Fig. 45.14). When using a threshold of >1.1, the SAI has been found to be 97% sensitive and 100% specific for the diagnosis of constrictive pericarditis.

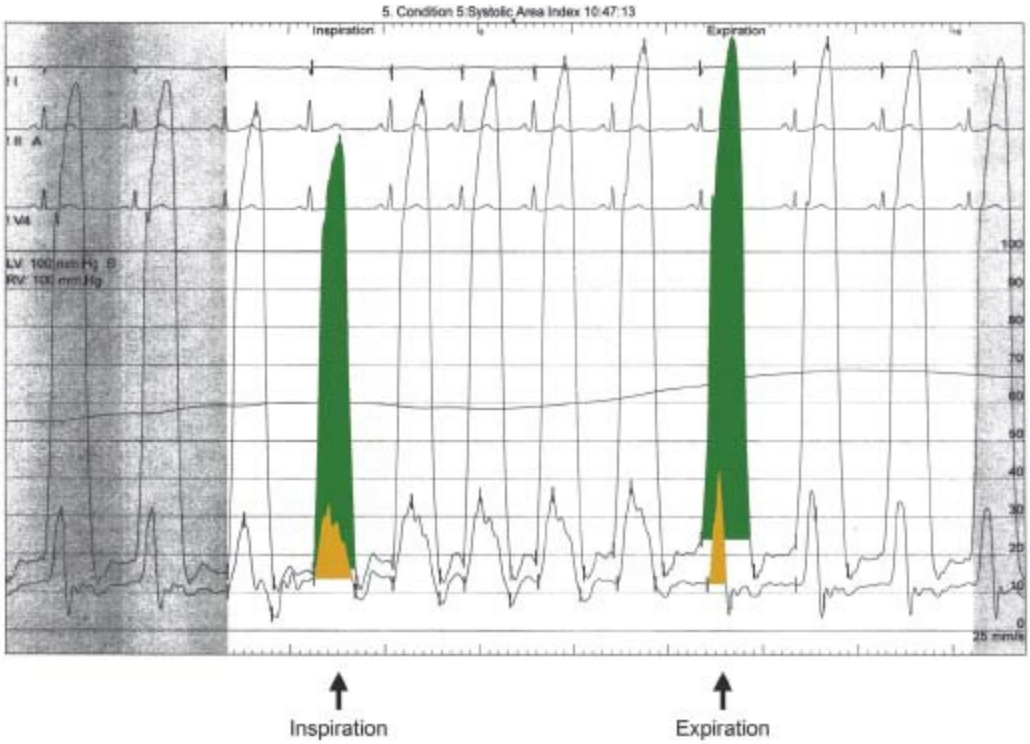

FIGURE 45.14 Graphic measurement of the systolic pressure-time integrals of the left ventricle (green areas) and right ventricle (yellow areas) at the peak inspiratory beat and the peak expiratory beat. These integrals are used to calculate the systolic area index.

The presence of an irregular rhythm, especially atrial fibrillation, may obscure the respiratory variations that occur in the hemodynamics of constrictive pericarditis. In this case, the varying R-R intervals may be regularized with a temporary pacemaker.

Diagnosis of constrictive pericarditis may also be problematic in a variety of other circumstances:

- Severe lung disease with marked respiratory changes
- Right ventricular infarction
- Severe tricuspid regurgitation
- Low filling pressures, for example, due to diuresis. If the filling pressure is <15 mm Hg, constrictive pericarditis can be "unmasked" by rapid infusion of 500 to 1,000 mL of saline resulting in abnormalities in the above parameters.

SUMMARY POINTS FOR THE BOARDS

- Optimal intravascular pressure recording requires high-frequency response, proper damping to eliminate overshoot, and accurate zero level.
- The Fick CO equals the O_2 consumption/A-V Oxygen difference. This method is most accurate when CO is low.

- The thermodilution method of CO calculation is most accurate when the CO is high.
- The pulmonary to systemic flow ratio in a left-to-right shunt (Q_p /Q_s) may be estimated by

$$\frac{Q_p/Q_s = \text{systemic arterial oxygen saturation} - \text{mixed venous oxygen saturation}}{\text{pulmonary venous oxygen saturation} - \text{pulmonary artery oxygen saturation}}$$

- Vascular resistance is the ratio of the pressure gradient across a vascular structure (e.g., the pulmonary vasculature) divided by the flow through the structure.
- The Hakki formula for calculation of stenotic VOA is

$$\text{VOA} = \frac{\text{CO (L/min)}}{\sqrt{\Delta P}}$$

While this simplified formula tends to be inaccurate when the heart rate is too slow or too fast, it is generally sufficient for accurate calculation of stenotic VOA for purposes of the Cardiovascular Medicine Board Examination.

- The measurements of CO should be made at the same time as measurement of the valve gradients in order for the estimation of stenotic VOA to be accurate.
- In the presence of concomitant valvular regurgitation, calculations of stenotic aortic and mitral VOA using only net forward flow will underestimate the actual VOA.
- Optimal measurement of the stenotic aortic valve gradient requires simultaneous sampling in the LV apex or inflow tract and in the ascending aorta. Pullback pressures and peripheral arterial sampling sites may produce inaccurate results, especially in moderate AS.
- Maneuvers that provoke an intraventricular gradient in HOCM include:
    1. Decreasing LV end-diastolic volume (e.g., Valsalva maneuver)
    2. Increasing the force or duration of contraction (e.g., post-PVC or administering dobutamine)
    3. Decreasing aortic outflow resistance (e.g., administering amyl nitrate)
- An increase in the LVSP of the sinus beat that follows a PVC is characteristic of HOCM, valvular AS, mitral stenosis, and dilated cardiomyopathy; it is not usually seen in the normal heart.
- Pulsus paradoxus is characteristic of phases 2 and 3 of pericardial tamponade.
- The SAI is the most sensitive and specific method to diagnose constrictive pericarditis by hemodynamic measurements.

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QUESTIONS AND ANSWERS

Questions

1. A 42-year-old woman with exertional dyspnea is found to have a ventricular septal defect with left-to-right shunt and a dilated right ventricle (RV) with severe systolic dysfunction by surface echocardiography. Right heart catheterization is performed and reveals:

Arterial oxygen saturation = 95%
Superior vena cava (SVC) oxygen saturation = 48%
Inferior vena cava (IVC) oxygen saturation = 52%
RA oxygen saturation = 61%
RV oxygen saturation = 78%
PA oxygen saturation = 77%
RA = 12 mm Hg
RV = 62/12 mm Hg
PA = 63/39 (mean 47) mm Hg
PCWP = 14 mm Hg

What is this patient's pulmonary-to-systemic shunt fraction?

a. 1.8
b. 2.2
c. 2.6

d. 3.0

2. If the patient's pulmonary flow (Q_p) is 11 L/s, what is this patient's pulmonary vascular resistance (PVR)?
   a. 3 dynes-sec-cm^{-5}
   b. 30 dynes-sec-cm^{-5}
   c. 80 dynes-sec-cm^{-5}
   d. 240 dynes-sec-cm^{-5}

3. A patient referred to you for invasive hemodynam-ic evaluation of his aortic valve has the following:
Cardiac output (CO) = 4.5 L/min
Heart rate = 72
SEP = 0.33
Mean aortic gradient = 56 mm Hg
What is the aortic valve area?
   a. 0.4 cm^2
   b. 0.6 cm^2
   c. 0.8 cm^2
   d. 1.0 cm^2

4. The peak left ventricular systolic pressure of a sinus beat following a PVC is higher than the preceding beat with:
   a. Severe dilated cardiomyopathy
   b. HOCM
   c. Normal heart
   d. Severe aortic stenosis (AS)
   e. Severe dilated cardiomyopathy, HOCM, and severe AS

5. Which is (are) characteristic of constrictive pericarditis?
   a. Right ventricular systolic pressure (RVSP) = 80/10
   b. Respiratory discordance in RVSP and left ventricular systolic pressure (LVSP)
   c. X-descent deeper than Y-descent in RA
   d. All of the choices

6. A patient with exertional dyspnea is referred to you for evaluation. Transthoracic echocardiography reveals no significant valvular abnormalities. Invasive hemodynamic evaluation reveals the following measurements:
Mean RA pressure: 16 mm Hg
RV pressure: 78/16 mm Hg
PA pressure: 78/32 mm Hg
Mean PCWP: 26 mm Hg
LV end-diastolic pressure (LVEDP): 23 mm Hg
LVEF: 65%
CO: 2.9 L/min
   Which of the following therapies would most likely benefit this patient?
   a. Dobutamine and furosemide
   b. Candesartan and furosemide
   c. Sildenafil

7. A patient with exertional dyspnea is referred to you for evaluation. Transthoracic echocardiography reveals no significant valvular abnormalities. Invasive hemodynamic evaluation reveals the following measurements:

Mean RA pressure: 16 mm Hg RV pressure: 78/16 mm Hg PA pressure: 78/32 mm Hg Mean PCWP: 9 mm Hg LVEDP: 8 mm Hg LVEF: 65% CO: 2.9 L/min

Which of the following therapies would most likely benefit this patient?

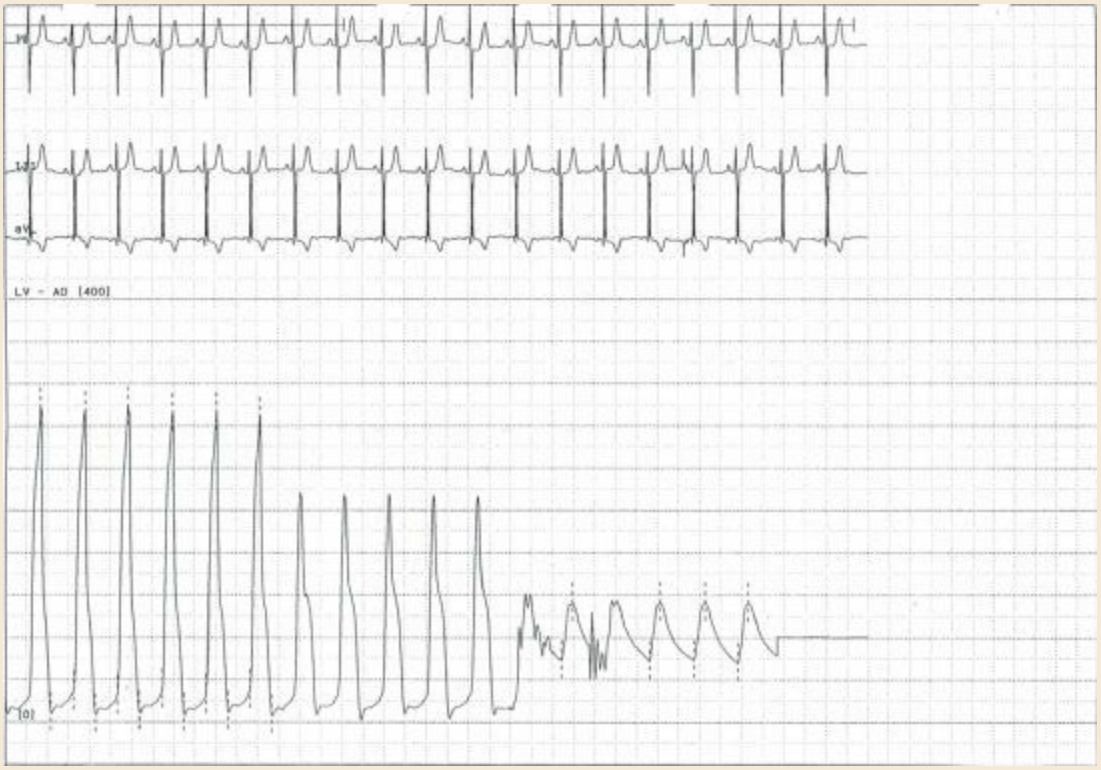
a. Dobutamine and furosemide
b. Candesartan and furosemide
c. Sildenafil

8. A 72-year-old man is referred to you for evaluation of AS. He describes a 1-year history of worsening shortness of breath to the extent that he can no longer climb one flight of stairs without significant dyspnea. Physical examination reveals a blood pressure of 150/96 mm Hg, a diminished carotid upstroke, a late peaking 3/6 systolic murmur at the left superior sternal border, and a soft second heart sound. Transthoracic echocardiogram reveals a calcified aortic valve with a mean pressure gradient of 24 mm Hg; the calculated aortic valve area is 1.2 cm^2. What would you recommend?

a. Surgical aortic valve replacement
b. Coronary angiography and aortic valve replacement ± coronary artery bypass grafting
c. Medical treatment of hypertension
d. Invasive hemodynamic study
e. Repeat transthoracic echocardiogram in 6 to 12 months

9. A multipurpose A catheter is slowly withdrawn from the left ventricular apex to the ascending aorta and reveals the waveform (see figure).

These findings are most consistent with which diagnosis?



a. Severe AS
b. Hypertrophic obstructive cardiomyopathy (HOCM)
c. Severe AS with concomitant HOCM
d. Dilated cardiomyopathy

10. A 58-year-old woman with history of moderate mitral stenosis is referred to you for consultation. She has no dyspnea at rest but describes a 2-year history of worsening exertional dyspnea that occurs with minimal house work such as cleaning the dishes. Transthoracic echocardiogram reveals a mildly thickened and calcified mitral valve with a mean pressure gradient of 9 mm Hg and a splittability index

of 7; the calculated mitral valve area is 1.2 cm^2. What would you recommend?

a. Balloon mitral valvuloplasty
b. Exercise echocardiography
c. Invasive hemodynamic study
d. Repeat transthoracic echocardiogram in 6 to 12 months

Answers

1. Answer C: Pulmonary to systemic shunt fraction (Q_P/Q_S) is determined by:

$$Q_P/Q_S = \frac{\text{systemic arterial oxygen saturation} - \text{mixed venous oxygen saturation}}{\text{pulmonary venous oxygen saturation} - \text{pulmonary artery oxygen saturation}}$$

Because a left-to-right shunt exists, the mixed venous oxygen saturation can be calculated by:

$$\text{Mixed venous oxygen saturation (MVO2)} = \frac{3\,\text{SVC} + \text{IVC}}{4} = \frac{3(0.48)+0.52}{4} = 0.49$$

and the pulmonary venous oxygen can be approximated using the arterial saturation such that:

$$Q_P/Q_S = \frac{0.95-0.49}{0.95-0.77} = 2.6$$

2. Answer D:

$$\text{Pulmonary vascular resistance (Woods units)} = \frac{\overline{PA} - \overline{LA}}{Q_P} = \frac{47-14}{11} = 3 \text{ Woods units}$$

$$3 \text{ Woods units} \times \frac{80 \text{ dynes-sec-cm}^{-5}}{\text{Woods unit}} = 240 \text{ dynes-sec-cm}^{-5}$$

3. Answer B: Valve orifice area can be calculated by

$$\text{the Hakki formula: VOA} = \frac{\text{CO (L/min)}}{\sqrt{\Delta P}}$$

$$\text{Thus, VOA} = \frac{4.5\,(\text{L/min})}{\sqrt{56\,\text{mmHg}}} = 0.6\ \text{cm}^2$$

4. Answer E: This statement is not true for a normal heart.

5. Answer B: The classic features of constrictive pericarditis include an RSVP <55 mm Hg, respiratory discordance in RVSP and LVSP, and a Y-descent deeper than X-descent in the RA. Thus, only respiratory discordance in RVSP and LVSP is correct.

6. Answer B: This patient has findings consistent with congestive heart failure with preserve systolic function. Candesartan has been shown to improve outcomes in these patients. In addition, the patient's LVEDP is elevated, thus diuresis with furosemide should improve the patient's symptoms.

7. Answer C: This patient's markedly elevated pulmonary pressures with normal LVEDP and PCWP is consistent with true pulmonary arterial hypertension. This patient would most likely benefit from sildenafil therapy.

8. Answer D: This patient has symptoms and physical exam findings consistent with severe AS; however, the echocardiographic findings suggest only moderate AS. An invasive hemodynamic study is the "gold standard" for the assessment of AS. Thus, when AS is suspected and the symptoms, physical exam findings, and echocardiographic findings do not agree, then an invasive hemodynamic study is

indicated.

9. Answer B: Slow pull back with an “end-hole” catheter from the left ventricular apex to the ascending aorta reveals two distinct areas with a significant pressure gradient. This is consistent with both true aortic valve stenosis and an HOCM. Of note, performing this test with a pigtail catheter or other “side-hole” catheter could produce erroneous results.

10. Answer B: This patient describes exertion dyspnea suggestive of severe mitral stenosis; however, her echocardiographic findings suggest only moderate mitral stenosis. Because mitral valve gradients are significantly affected by heart rate, it is appropriate to exercise this patient and reassess her mitral valve gradients at peak exercise. Echocardiography is the “gold standard” for the assessment of mitral stenosis, thus, an invasive hemodynamic study is not indicated.

CHAPTER

Catheterization Laboratory Imaging and Functional Assessment

Sachin S. Goel and Samir R. Kapadia

Over the last two decades, interventional cardiology has rapidly expanded in the field of coronary and noncoronary structural interventions such as valve repair, transcatheter valve replacement, septal defect closure, etc. Coronary angiography is the gold standard for assessing coronary anatomy; however, sometimes it does not provide information about the physiologic or functional significance of a stenotic lesion, and neither does it adequately assess the severity and extent of atherosclerotic plaque in the vessel wall. Fractional flow reserve (FFR) has emerged as an excellent tool for assessing the physiologic impact of a lesion, and intracoronary imaging with intravascular ultrasound (IVUS) and optical coherence tomography (OCT) have shown promise in assessing the atherosclerotic plaque and the response of the coronary vessel wall to percutaneous coronary intervention (PCI). Integration of information from various imaging modalities such as fluoroscopy, cineangiography, echocardiography, and computed tomography (CT) is critical for safety and success of structural cardiac interventions. In this chapter, we first highlight the role of functional imaging in the catheterization laboratory by means of FFR and the role of intracoronary imaging with IVUS and OCT and then discuss structural cardiac anatomy using various imaging techniques and their utility in guiding different structural interventions.

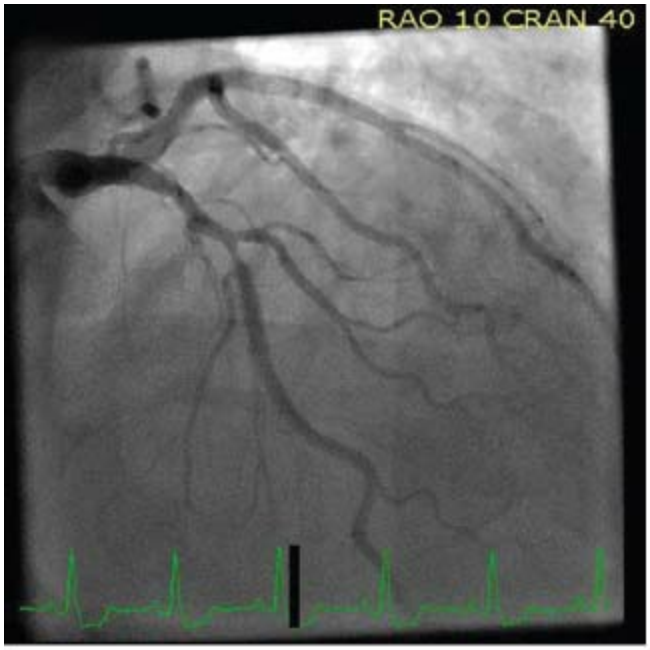
PHYSIOLOGIC ASSESSMENT OF CORONARY ARTERY DISEASE IN THE CATHETERIZATION LABORATORY

The goals of treatment in patients with coronary artery disease (CAD) are reduction in symptoms and risk of myocardial infarction (MI) and improvement in survival. The randomized prospective COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial showed that revascularization with PCI does not

reduce the risk of MI or improve survival in patients with stable CAD when added to optimal medical therapy (OMT).[1] Presence of myocardial ischemia is a risk factor for adverse clinical outcome in patients with CAD, and concurrently, PCI was shown to reduce major adverse events in the subset of COURAGE population with significant ischemia on stress testing.[2] The observed lack of benefit of PCI in all comers with stable CAD is likely due to the lack of correlation of severity of coronary stenosis, as assessed by coronary angiography, with the degree of ischemia or hemodynamic significance of coronary stenosis.[3] In addition, PCI has occasional complications, which can affect long-term outcomes. Coronary angiography provides a two-dimensional (2-D) image of the three-dimensional (3-D) vessel lumen, which coupled with vessel overlap, tortuosity and eccentricity of lesions, often makes it very difficult for the angiographer to assess the functional or physiologic impact of a lesion despite multiple views. This can be assessed most accurately by means of a noninvasive stress test or an invasive physiologic test that can be performed in the catheterization laboratory, namely FFR.

Fractional Flow Reserve

FFR is defined as the ratio of maximal blood flow in a stenotic artery to normal maximal flow.[4] It can be measured during coronary angiography by passing a 0.014-inch pressure sensor angioplasty wire through a guiding catheter into the coronary artery. The wire's pressure signal is first matched with the aortic pressure (P_a) and then the lesion in question is crossed with the wire. Coronary hyperemia is then induced, usually with intravenous adenosine. The pressure in the coronary artery distal to the stenotic lesion (P_d) and P_a are continuously recorded, and FFR is calculated as the ratio P_d/P_a at maximal hyperemia (Fig. 46.1).



A

B

FIGURE 46.1 A: Coronary angiogram demonstrating intermediate severity lesion (50% to 60% stenosis) in the mid-LAD. **B:** FFR demonstrating a value of 0.88 indicating hemodynamically insignificant stenosis.

- FFR in a normal coronary artery equals 1.0. An FFR value of 0.80 or less indicates hemodynamically significant coronary stenosis with an accuracy of >90%.[5]

In contrast to noninvasive myocardial perfusion imaging studies, FFR is a vessel-specific index of ischemia and hence more specific and has better spatial resolution. In the DEFER study, 325 patients underwent FFR of an intermediate coronary lesion prior to planned PCI. Patients with FFR $\geq$ 0.75 were randomized to deferral of PCI (Defer group, n = 91) or performance of PCI (Perform group, n = 90).[6] If FFR was $\leq$0.75, patients PCI was performed as planned (Reference group; n = 144). At 5 years of followup, the event-free survival was similar in the Defer and Perform groups (80% vs. 73%, p = 0.52). In addition, the composite rate of death and MI was not different in the Defer and Perform groups (3.3% vs. 7.9%, p = 0.21).[6] Similarly, in patients with multivessel CAD, nonrandomized studies have shown that FFR-guided PCI is associated with favorable outcomes and lower cost when compared to angiographically guided PCI without a physiologic assessment by FFR.[7,8]

These studies led to the large, prospective, multicenter, randomized FAME trial (FFR versus Angiography in Multivessel Evaluation), to compare FFR-guided PCI compared to conventional angiographically guided PCI in patients with multivessel CAD.[9]

- In the FAME study, 1,005 patients with multivessel CAD were randomly assigned to undergo PCI with drug-eluting stent (DES), guided by angiography alone or PCI guided by an abnormal FFR $\leq$ 0.80. The mean SYNTAX score was 14.5 in each group, indicating low-intermediate risk patients.
- The 1-year combined primary endpoint of death, MI, and repeat revascularization was lower at 13.2% in the FFR-guided PCI group compared to 18.3% in the angiography-guided PCI group (p = 0.02). In addition, the FFR-guided PCI group had less death or MI (7.3% vs. 11.1%, p = 0.04), fewer stents used per patient (1.9 $\pm$ 1.3 vs. 2.7 $\pm$ 1.2, p < 0.001), less use of contrast (272 mL vs. 302 mL, p < 0.001) and lower procedural cost ($5,332 vs. $6,007, p < 0.001).

The exact mechanism of benefit in the FFR-guided PCI arm of the FAME trial is not known; however, it appears to support the well-recognized fact that the most important prognostic indicator for adverse outcome in patients with CAD is the presence and extent of ischemia.[10] It is possible that FFR-guided PCI results in a net clinical benefit as the reduction in ischemia by PCI outweighs the risks of PCI (stent thrombosis, restenosis) due to fewer implanted stents. The beneficial effects of FFR-guided PCI were maintained out to 2 years on follow-up in the FAME study.[11] The purpose of the randomized FAME II trial is to compare outcomes of FFR-guided PCI plus OMT versus OMT alone in patients with stable CAD.

CORONARY INTRAVASCULAR IMAGING

Coronary angiography, which provides a luminogram, does not provide information about the atherosclerotic plaque in the vessel wall and often underestimates the severity and extent of atherosclerosis. Over the last two decades, IVUS has evolved as adjunct to coronary angiography and provides valuable information about the vessel wall with several research and clinical applications. Recently, infrared light-based imaging technology such as OCT has emerged, which provides significantly improved image resolution compared to IVUS.

Intravascular Ultrasound

The IVUS equipment consists of a special transducer mounted catheter and a console to reconstruct and display the image. Current IVUS catheters range from 2.6 to 3.5 French (Fr) in size and can be advanced through a conventional 6-Fr guide catheter over a 0.014-inch angioplasty guidewire. There are two types of IVUS catheters, phased array and rotating transducer. High ultrasound frequencies (20 to 40 MHz) are employed resulting in excellent axial and lateral resolution. Intravenous heparin and intracoronary nitroglycerin are routinely administered before performing IVUS. Subsequently, the angiographer retracts the transducer manually or with a motorized pullback device. Images are obtained and recorded digitally for analysis during pullback, using side branches visualized with both angiography and ultrasound, as landmarks to facilitate interpretation. IVUS is a safe procedure with few documented complications. Coronary spasm is the most frequent complication (1% to 3%) and this responds well to intracoronary nitroglycerin. Major complications including dissection or vessel occlusion are rare (<0.5%).

Normal Coronary Anatomy by IVUS

In normal coronaries, a standard IVUS image usually shows the vessel wall as a trilaminar structure, consisting of the intima, media, and adventitia (Fig. 46.2), due to visualization of two strong acoustic interfaces by ultrasound, the leading edge of the intima (at the interface between the blood-filled lumen and the endothelium) and the external elastic membrane (EEM, located at the media–adventitia interface). The lumen shows swirling echoes from circulating blood elements and this “blood speckle” helps identify dissection planes.

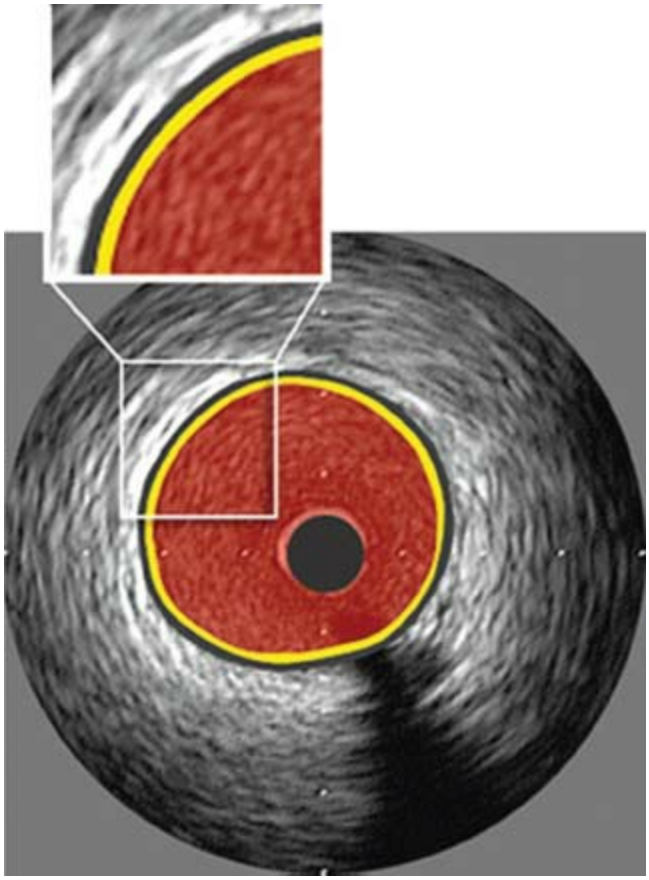


FIGURE 46.2 Normal coronary artery anatomy by IVUS. Yellow color represents intima; black color represents media; red color represents blood-filled lumen. (Reproduced from Tuzcu EM, Bayturan O, Kapadia S. Invasive imaging: Coronary intravascular ultrasound: a closer view. Heart. 2010;96:1318–1324, with permission from BMJ Publishing Group Ltd.)

Characterization of Atherosclerosis by IVUS

IVUS studies have shown that atherosclerosis is much more extensive and severe than what is apparent on coronary angiography. Atherosclerotic plaques can range in appearance from soft or hypoechoic plaques that have high lipid content to bright echogenic plaques that have more fibrous and calcified components. A more detailed analysis of plaque composition is possible using IVUS-derived virtual histology (IVUS-VH), which has good histopathologic validation and is based on spectral analysis of radiofrequency signals. Using IVUS-VH, atherosclerotic plaque is color coded into different types based on lipid, fibrous, and calcium content. Studies have shown a greater proportion of lipid and necrotic core with a thin fibrous cap in patients presenting with acute coronary syndrome.[12] Another interesting concept revealed by IVUS studies is arterial remodeling (positive or negative), which refers to changes in arterial dimensions associated with the development of atherosclerosis. Positive or expansive remodeling refers to increase in the lumen area in the initial stages of atherosclerosis due to expansion of the EEM area with plaque deposition.[13] This may explain the discrepancy between IVUS findings of significant plaque and normal or

mildly abnormal coronary "luminogram" by angiography. It has been shown that lesions associated with expansive remodeling are prone to rupture and lead to acute coronary syndromes.[14] IVUS studies have also demonstrated the other kind of remodeling, referred to as negative remodeling or arterial shrinkage, which is more common in stable CAD.[15] It has been implicated in restenosis following balloon angioplasty. Precise quantitation of the extent of atheroma at different time points using IVUS has been instrumental in understanding the natural history of atherosclerosis as well as the impact of cholesterol-lowering drugs in reducing the progression of atherosclerosis[16] and even its regression.[17]

- The first large prospective, randomized multicenter IVUS trial of statins, the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) study, randomly assigned patients to receive a moderate lipid-lowering regimen consisting of 40 mg of pravastatin or an intensive lipid-lowering regimen consisting of 80 mg of atorvastatin.[16] With significantly greater reductions in LDL and CRP levels, the intensive lipid-lowering regimen halted the progression of coronary atherosclerosis as assessed by IVUS, compared to the moderate lipid-lowering regimen.
- The prospective ASTEROID study (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) evaluated coronary atherosclerosis by IVUS before and after 24 months of intensive lipid-lowering therapy with 40 mg/d of rosuvastatin.[17] With a lowering in mean LDL-C to 61 mg/dL and an elevation in HDL-C by 14.7%, significant reduction in atheroma burden was observed by IVUS, consistent with regression of coronary atherosclerotic plaque.

Applications of IVUS in the Catheterization Laboratory

It is common to encounter lesions on angiography that are of uncertain significance such as angiographically moderate stenosis (50% to 70%), difficult to assess sites such as ostial or bifurcation lesions, left main trunk disease, intraluminal filling defects, and hazy lesions. Unlike FFR, specific threshold criteria for intervention by IVUS have not been prospectively validated.

- A minimal luminal area of 3 to 4 mm^2 by IVUS correlates with a significant reduction in FFR for a native coronary artery[18] and a minimal luminal area of <6 to 7.5 mm^2 usually indicates a significant lesion in the left main trunk.[19,20]

Cardiac allograft vasculopathy is known to be associated with a poor outcome in heart transplant patients. IVUS allows assessment of early plaque accumulation before luminal stenosis develops, thus recognizing silent vasculopathy, which has been

identified as a powerful predictor of subsequent adverse outcomes in transplant recipients.[21] IVUS has several important applications before, during, and after PCI.

- Pre-PCI IVUS allows assessment of plaque distribution, especially whether the lesion involves or spares the ostium of the vessel that may help with optimal balloon and stent positioning. The presence and distribution of calcification can be assessed with IVUS.
- Stent undersizing is a well-known predictor of stent thrombosis,[22] and IVUS can help with selecting the optimal stent size based on vessel and lumen size.

IVUS has provided pivotal insights into the effect of various interventional techniques on the arterial wall. It was first shown by Colombo et al.[23] that high pressure stent deployment by IVUS guidance resulted in better stent expansion, complete apposition, and prevention of subacute thrombosis. With bare metal stents (BMS), IVUS studies have shown that larger in-stent lumen area was associated with lower restenosis and target vessel revascularization rates.[24] Although the rates of instent restenosis are much lower in the DES era, IVUS studies have clearly demonstrated that underexpansion of DES (Fig. 46.3) is the predominant mechanism leading to DES restenosis.[25] A postdeployment minimal stent area of 5 mm^2 has been shown to decrease the likelihood of angiographic restenosis.[25]

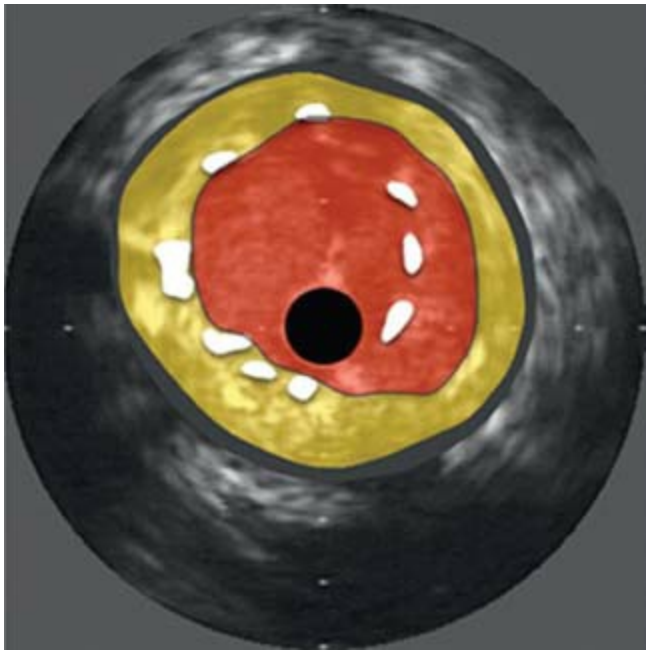


FIGURE 46.3 IVUS demonstrating unopposed coronary stent struts. (Reproduced from Tuzcu EM, Bayturan O, Kapadia S. Invasive imaging: Coronary intravascular ultrasound: a closer view. Heart. 2010;96:1318–1324, with permission from BMJ Publishing Group Ltd.)

Even though cessation of dual antiplatelet therapy is the most important mechanism

in DES thrombosis, incomplete stent expansion remains a risk factor and IVUS can be used poststent deployment to assess adequacy of deployment and apposition. In addition, late stent malapposition, in which stent struts are no longer adjacent to the vessel wall late following stent implantation, was shown to be four times higher in DES compared to BMS in a recent meta-analysis.[26] This was found to be associated with late and very late stent thrombosis. IVUS can also be very useful in identifying and guiding the management of complications following stent placement such as dissection, which has been shown to increase the rate of restenosis.

IVUS has played a pivotal role in clinical trials studying progression and regression of coronary atherosclerosis. Adverse events following PCI such as instent restenosis and stent thrombosis correlate with IVUS findings.

Optical Coherence Tomography

OCT is an emerging intracoronary imaging modality that uses backscattering of infrared light to obtain high-resolution tissue images. It is similar in principle to IVUS but uses light rather than acoustic waves. Current OCT systems consist of an optical fiber, a proximal low pressure occlusion balloon catheter, and an OCT imaging system console. Important differences compared to IVUS are that an occlusion balloon is needed proximal to the area of interest that is being imaged, in addition to continuous infusion of Ringer lactate or iodinated contrast media when using nonocclusion technique, to remove blood from the imaging field. An OCT image at the site of a previously placed stent is shown in Figure 46.4.

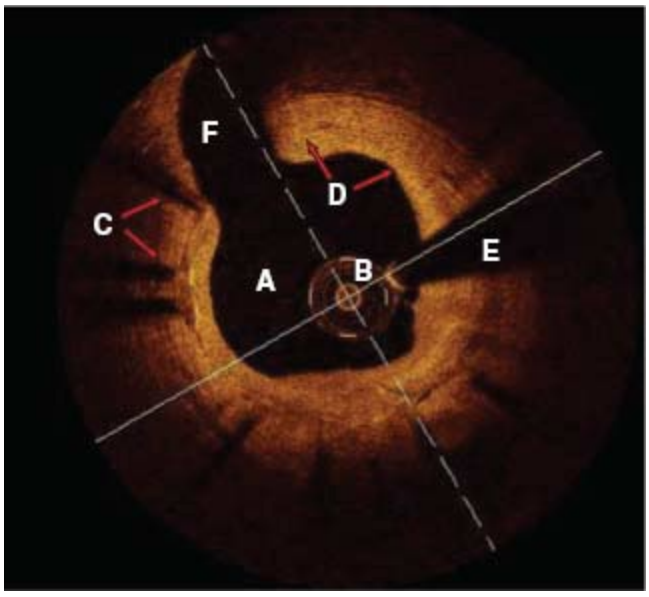


FIGURE 46.4 OCT at a site of previously placed coronary stent demonstrating **(A)** blood-filled coronary lumen, **(B)** catheter, **(C)** stent struts, **(D)** intimal thickening, **(E)** ring artifact, **(F)** a branch vessel.

Applications of OCT

As noted above, atheromas with a thin fibrous cap are thought to be more vulnerable to plaque rupture, leading to acute coronary syndromes. Ex vivo and in vivo studies have shown OCT to be a potentially complimentary technique to IVUS in characterization of atherosclerotic plaques,[27,28] providing the potential for fibrous cap plaque measurement and identification of vulnerable plaque. Late stent thrombosis in patients with DES has been shown to be associated with delayed healing and poor endothelialization with incomplete stent strut coverage and apposition.[26,29] OCT has shown higher sensitivity compared to IVUS in assessment of incomplete stent apposition and stent coverage.[30] Studies are ongoing to assess the impact of information gauged by these newer intravascular imaging techniques on patient outcomes.

IMAGING FOR STRUCTURAL CARDIAC INTERVENTIONS

Fluoroscopy

Left Ventriculogram

A left ventriculogram is often performed to assess for presence of left ventricle (LV) wall motion abnormalities, degree of mitral regurgitation, presence of ventricular septal defect, and LV thrombus. It is typically performed with a pigtail catheter, in the 30-degree right anterior oblique (RAO) projection. Anterior and inferior walls of the LV and the apex are seen in this view (Fig. 46.5A). Anterior and posterior mitral valve leaflets are seen from the side in a longitudinal plane along with the inflow portion of the ventricle. This relationship is critical to recognize when performing mitral valve intervention when devices have to be advanced coaxially in the inflow (e.g., Inoue balloon). Adding steeper RAO angulation (45 degrees) moves the left atrium away from the spine and enables assessment of severity of mitral regurgitation. The lateral wall and septum are best assessed in a 60-degree LAO projection (Fig. 46.5B). Various segments of the mitral valve leaflets (A1, A2, A3 and P1, P2, P3) can be assessed in this view. The orientation of the aortic valve cusps (right, left, and noncoronary) can be assessed in the RAO and LAO projections as shown in Figure 46.5A,B.

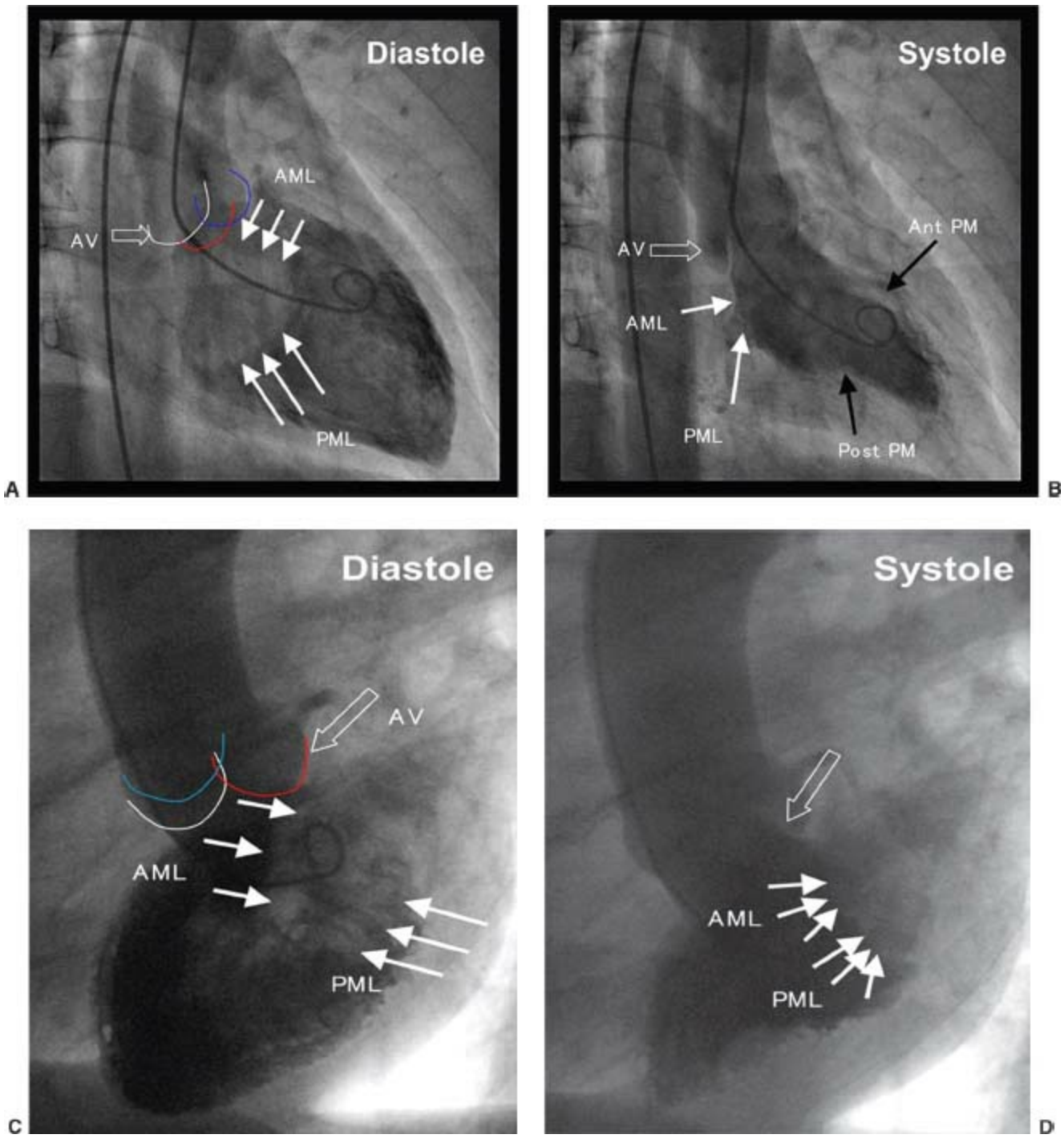


FIGURE 46.5 Left ventriculogram. **(Top panels).** RAO 30-degree view of the LV in diastole and systole. The aortic valve (open arrow) with three leaflets (RCC blue, NCC white, and LCC with red lines), mitral valve (solid white arrow), and the papillary muscles (solid black arrows) are shown. In diastole **(A),** the mitral valve is open and there is clearance of contrast as the blood enters the LV from left atrium. Anterior and posterior leaflets are seen separate in diastole **(left panel).** In systole **(B),** the mitral valve is closed and the aortic valve is open **(right panel).** In this view, anterior, apex, and the inferior walls can be assessed. Left ventriculogram **(Bottom panels).** LAO 60-degree view of the LV in diastole **(C)** and systole **(D).** Open arrow shows the aortic valve with three leaflets (RCC blue, NNC white, and LCC with red lines) and solid white arrow shows the mitral valve. In diastole, the mitral valve is open and there is clearance of contrast as the blood without contrast enters the LV from left atrium. Anterior and posterior leaflets are seen separate in diastole. In this view, the lateral and the septal walls of the LV can be assessed. AV, aortic valve; AML, anterior mitral leaflet; LCC, left coronary cusp; NCC, noncoronary cusp; PML, posterior mitral leaflet; Ant PM,

anterolateral papillary muscle; Post PM, posterolateral papillary muscle; RAO, right anterior oblique; RCC, right coronary cusp. (Reprinted from Shishehbor M, Kapadia SR. Imaging for intracardiac intervention. In: Topol EJ, ed. Textbook of Interventional Cardiology, 5th ed. Philadelphia: Saunders Elsevier; 2008, with permission.)

Right Ventriculogram

The inflow and outflow tracts of the right ventricle (RV) are at right angles to each other. Right ventriculogram is typically performed in anteroposterior and lateral projection with the catheter (pigtail or National Institutes of Health [NIH]) positioned in the mid cavity with a high rate of injection (>25 mL/s). Right ventriculogram can be used to assess the pulmonary valve, the tricuspid valve, and right ventricular outflow tract obstruction (Fig. 46.6).

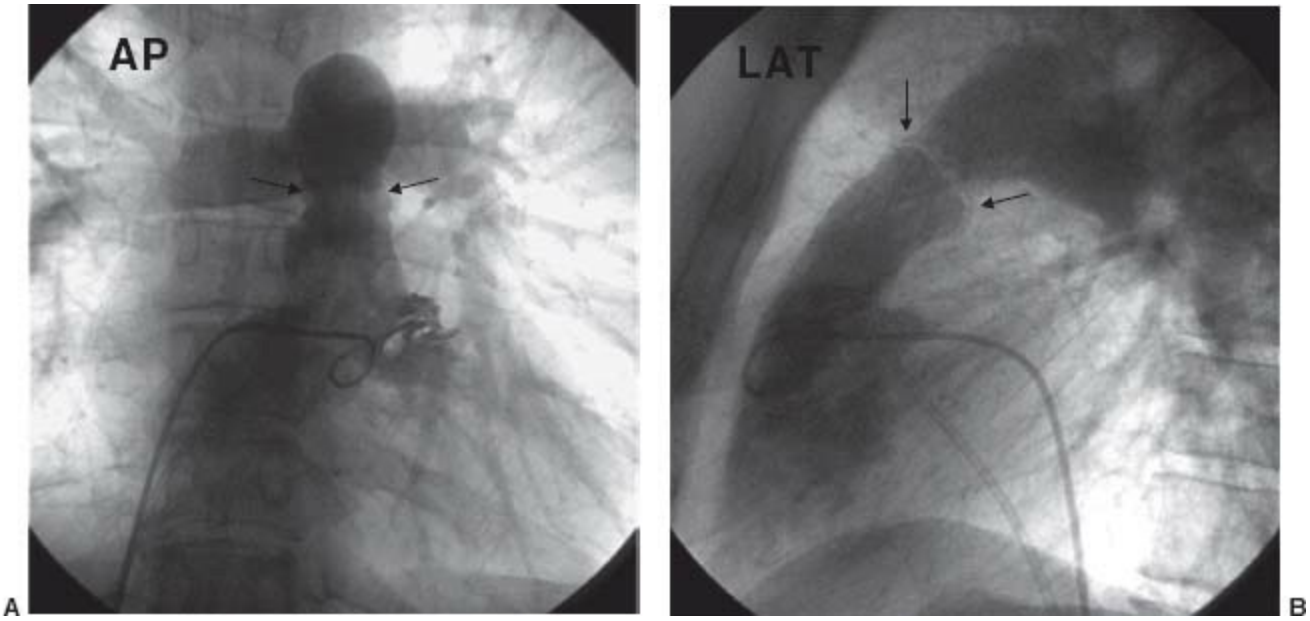


FIGURE 46.6 Anteroposterior and lateral view of the RV with the pigtail catheter in the right ventricular outflow tract. Note doming of the pulmonic valve as shown by the black arrows. (Reprinted with permission from Shishehbor M, Kapadia SR. Imaging for intracardiac intervention. In: Topol EJ, ed. Textbook of Interventional Cardiology. 5th ed. Philadelphia: Saunders Elsevier; 2008).

Right Atrial Angiogram

Right atrial angiogram, typically performed with a pigtail or NIH catheter and a rapid injection, is used to evaluate the interatrial septum (IAS) and the structures seen are shown in Figure 46.7. This procedure can be useful during transseptal puncture and transcatheter patent foramen ovale (PFO) or atrial septal defect (ASD) closure.

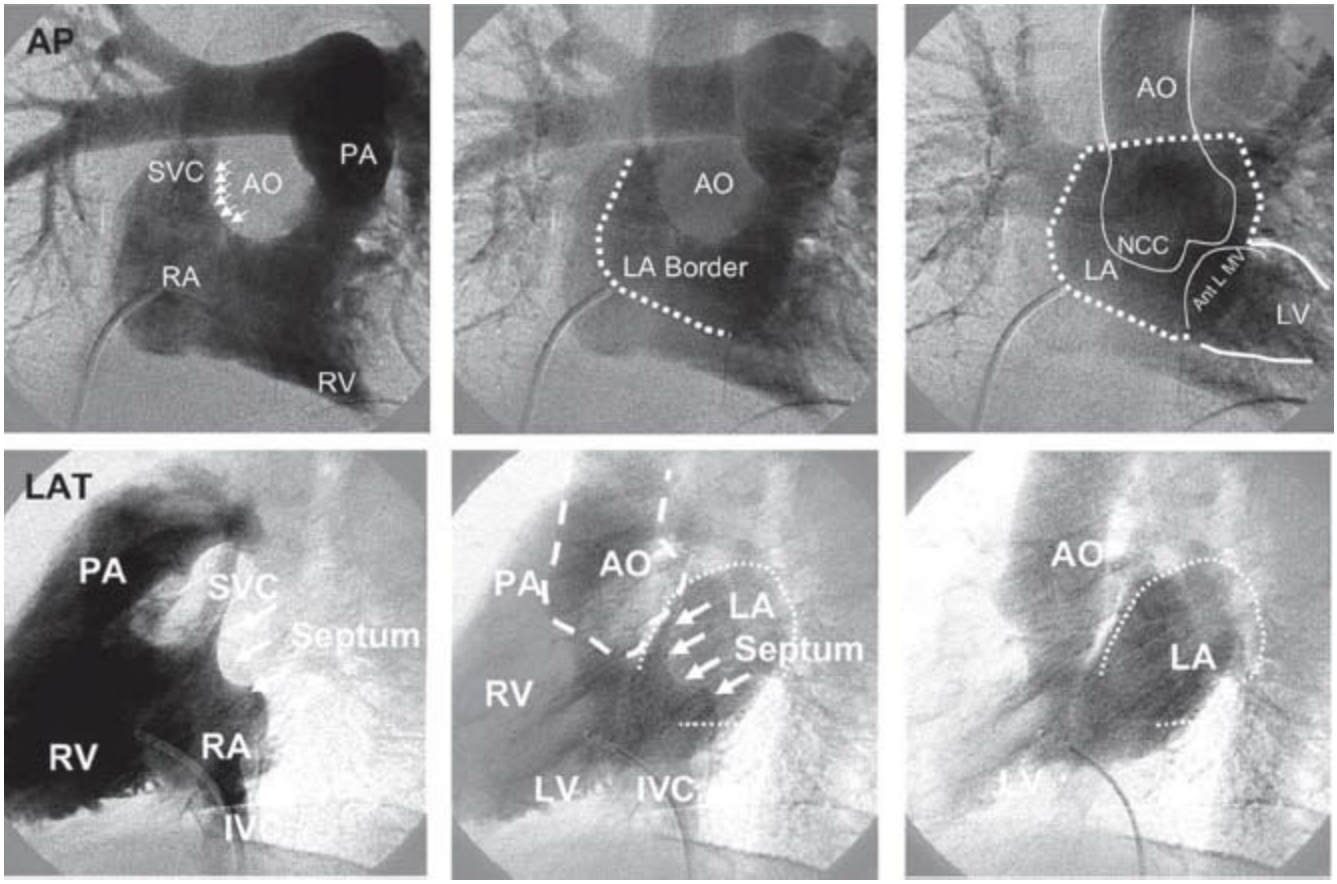


FIGURE 46.7 Anteroposterior **(top panel)** and lateral **(bottom panel)** view of a right atrial angiogram. **Left panel** is dextro phase, right panel is levo phase, and the mid panel is these two phases superimposed on each other. SVC, superior vena cava; IVC, inferior vena cava; RA, right atrium; LA, left atrium; AO, aorta; RV, right ventricle; PA, pulmonary artery; NCC, non-coronary cusp; antL MV, anterior leaflet of the mitral valve. (Reprinted from Shishehbor M, Kapadia SR. Imaging for intracardiac intervention. In: Topol EJ, ed. Textbook of Interventional Cardiology, 5th ed. Philadelphia: Saunders Elsevier; 2008, with permission.)

Pulmonary Angiogram

Pulmonary angiography is the gold standard imaging modality for diagnosing pulmonary embolism. In addition, it is used to assess a variety of other conditions such as pulmonary valve stenosis, pulmonary artery stenosis, anomalous pulmonary venous return, and pulmonary arteriovenous malformations. Most commonly, multi–side hole pigtail or NIH catheter is used with high injection rate (40 mL/s; Fig. 46.8).

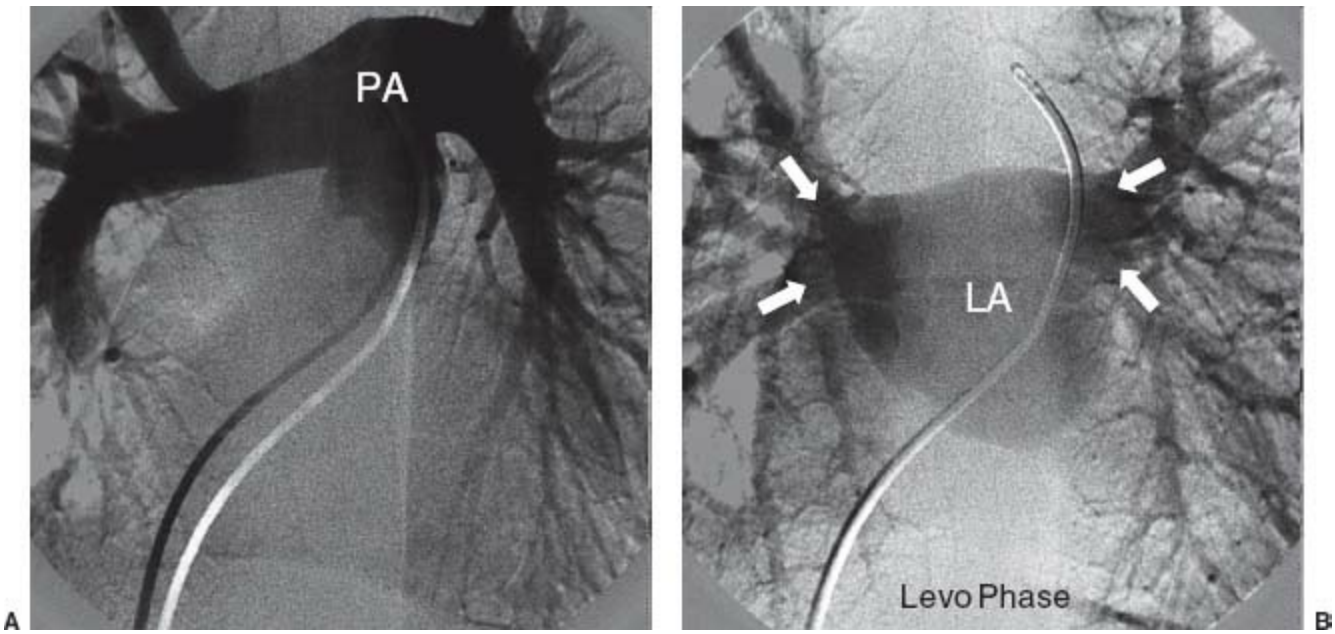


FIGURE 46.8 Normal pulmonary angiogram in the anteroposterior view. **A:** Shows the pulmonary artery trunk and the left and right pulmonary arteries and their branches. **B:** Shows opacification of the left atrium in levo phase. Digital subtraction is used to visualize the pulmonary veins (solid white arrows). PA, pulmonary artery; LA, left atrium. (Reprinted with permission from Shishehbor M, Kapadia SR. Imaging for intracardiac intervention. In: Topol EJ, ed. Textbook of Interventional Cardiology, 5th ed. Philadelphia: Saunders Elsevier; 2008, with permission.)

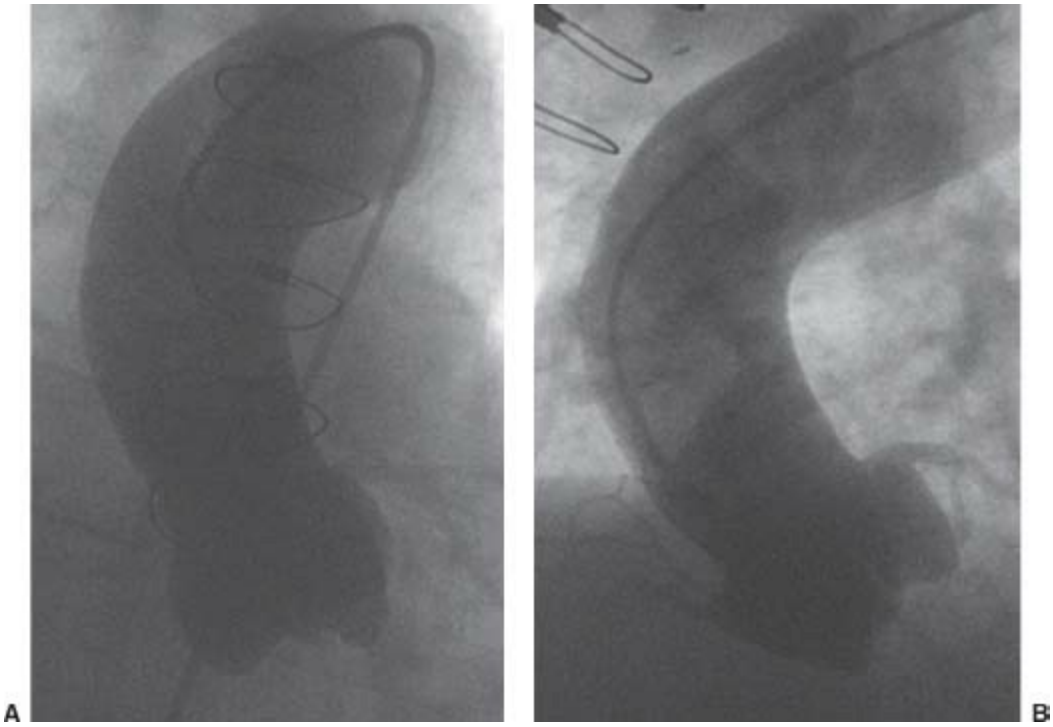
Left Atrial Angiogram

Left atrial angiogram is rarely performed by direct injection, but LA is frequently seen on the levo phase of the right-sided angiogram or pulmonary angiogram. Pulmonary artery angiogram performed in the anteroposterior (AP) and lateral views can be useful to visualize the LA and assess pulmonary vein drainage prior to ASD closure (see Fig. 46.8, right panel). Direct injection in the left atrial appendage (LAA) can be performed to evaluate the anatomy prior to percutaneous closure.

Aortography

Ascending aortography is performed to evaluate aortic valve disease and the ascending aorta. It has become particularly important with the advent of transcatheter aortic valve replacement (TAVR). Aortogram is performed in the RAO (30 degrees) and LAO (40 degrees) projections with a multi–side hole pigtail catheter positioned just 2 to 3 cm above the sinuses of Valsalva and a high rate of injection (20 mL/s for 2 to 3 seconds). Various anatomical relationships are important to recognize on fluoroscopy. Visualization of the aortic valve plane is critical for optimal valve positioning during TAVR (Fig. 46.9). In the RAO projection, the right coronary cusp (RCC) is the most anterior located cusp and the noncoronary cusp (NCC) is the most posterior located cusp with the left coronary cusp (LCC) in between the RCC and NCC (see Fig. 46.9). In the LAO projection, the LCC is well visualized (closest to the lateral wall of the

ventricle), whereas the NCC and RCC are superimposed on one another with NCC lying slightly below RCC (see Fig. 46.9). In order to achieve alignment of the aortic valve cusps during TAVR, a slight caudal angulation is needed in the RAO projection, and cranial angulation is needed in the LAO projection. Preprocedural CT imaging of the aortic root also helps define accurate angiographic planes for valve implantation during TAVR. [31] Fluoroscopy is also important in recognizing other important anatomic features such as the relation of the NCC with the IAS for transseptal puncture, superior vena cava for intracardiac echocardiography (ICE) imaging, and anterior leaflet of the mitral valve for antegrade interventions, which are shown in the PA view on RA angiogram (see Fig. 46.7).



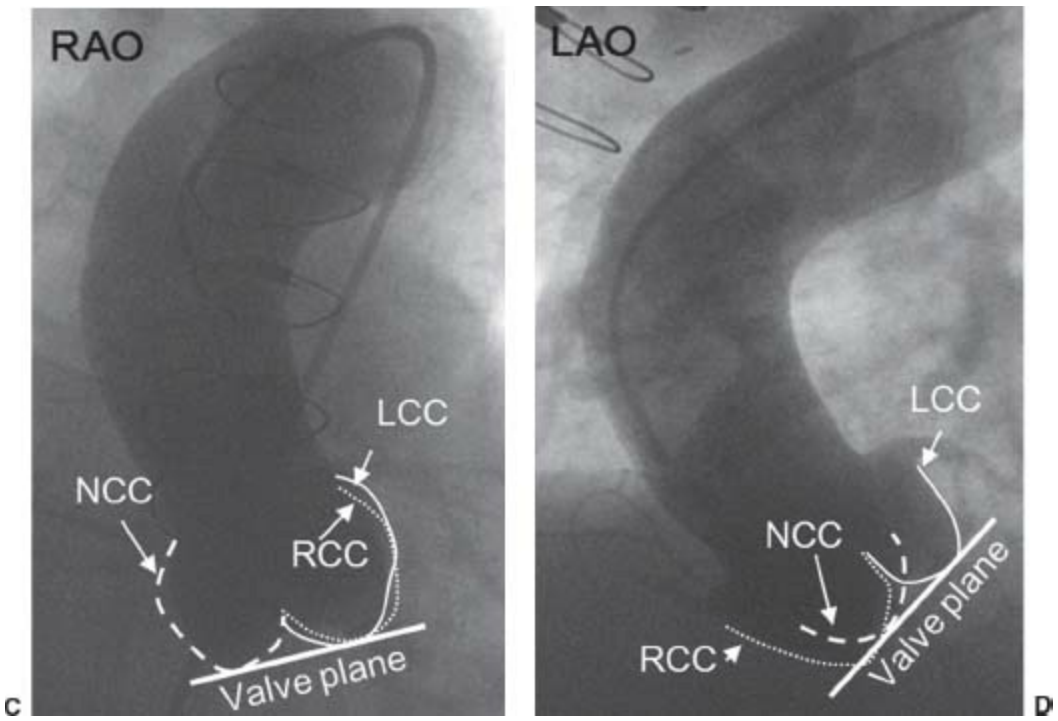


FIGURE 46.9 Aortic root angiography and alignment of the aortic valve plane for transcatheter aortic valve implantation. Views are LAO 40 degrees with 20 degrees caudal and RAO 20 degrees with 20 degrees caudal. NCC, noncoronary cusp; LCC, left coronary cusp; LAO, left anterior oblique; RAO, right anterior oblique; RCC, right coronary cusp. (Reprinted with permission from Shishehbor M, Kapadia SR. Imaging for intracardiac intervention. In: Topol EJ, ed. Textbook of Interventional Cardiology, 5th ed. Philadelphia: Saunders Elsevier; 2008, with permission.)

Transesophageal Echocardiography

Transesophageal echocardiography (TEE) provides high-resolution images and has become an integral part of structural cardiac interventional procedures including balloon mitral valvuloplasty, TAVR, transcatheter mitral valve repair, and occasionally, closure of interatrial communications. TEE can be performed relatively safely in the catheterization laboratory in supine position with judicious use of short-acting sedatives and posterior pharyngeal suction, without general anesthesia. The common positions for the TEE transducer are the upper mid esophagus, mid esophagus, and transgastric positions. The common views include the 0, 40 to 60, 90, and 120 degrees.

Intracardiac Echocardiography

ICE provides excellent images without the associated patient discomfort and airway issues, as may occur with TEE. In some situations, ICE can produce better images compared to TEE, for example, the posterior and inferior part of the IAS where TEE probe is too close to that area and the pulmonary valve and apical portion of the interventricular septum due to their anterior position. In addition, using ICE obviates the need for an imaging cardiologist in the catheterization laboratory. In our catheterization laboratory, we use the 8 F or 11 F probes with phased array system, which is capable

of color Doppler imaging and allows imaging comparable to TEE, to guide our structural heart interventions. ICE is mainly used to assess the IAS and pulmonary veins during transcatheter PFO or ASD repairs, transseptal puncture, and for aortic and mitral valve interventions in some cases.[32] In the electrophysiology laboratory, ICE is very useful during catheter ablation procedures for arrhythmias.

Multidetector Computed Tomography

Multidetector computed tomography (MDCT) is playing an increasingly important role in screening patients for structural cardiac interventions, particularly TAVR. [33] It is useful in assessing several characteristics of the aortic valve and its surrounding anatomy such as (a) severity and location of calcification, (b) aortic annulus dimensions, (c) plane of the aortic annulus, (d) assessment of sinotubular junction, (e) distance of the coronary ostia from the aortic cusp margin and the length of the leaflets, and (f) aortic and iliofemoral anatomy. In addition, fusion of preprocedural MDCT with intraprocedural 3-D CT and routine fluoroscopic images in the catheterization laboratory has been shown to be feasible, allowing for improved guidance and manipulation of catheters and devices, with potential for increased safety and efficacy.[34]

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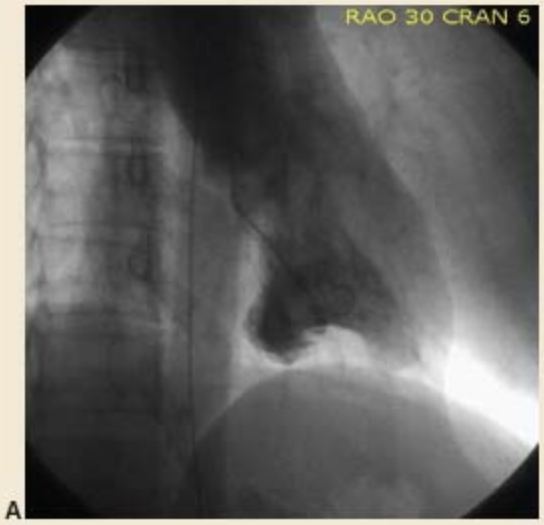
QUESTIONS AND ANSWERS

Questions

1. A 68-year-old woman with history of hypertension, hyperlipidemia, and diabetes mellitus presents with symptoms of intermittent exertional chest discomfort for the last 3 weeks. Coronary angiogram reveals 70% to 80% stenosis in the mid left anterior descending (LAD) and a 50% to 60% stenosis in the proximal right coronary artery (RCA). What is the most appropriate next best step?



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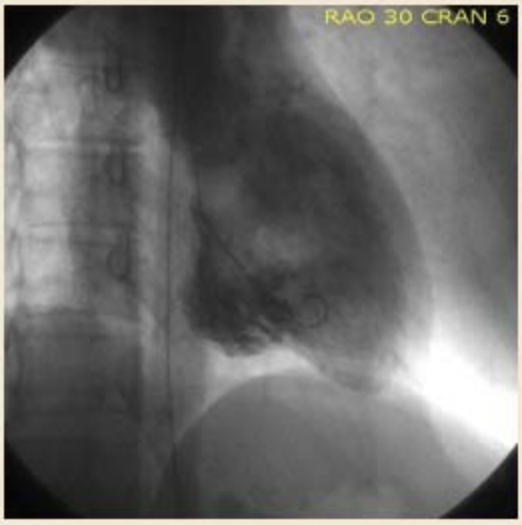


B

a. Proceed with percutaneous coronary intervention (PCI) on the mid-LAD and proximal RCA.
b. Perform fractional flow reserve (FFR).
c. Stop the procedure and perform exercise stress test.

d. Refer the patient for coronary artery bypass grafting to the LAD and RCA.

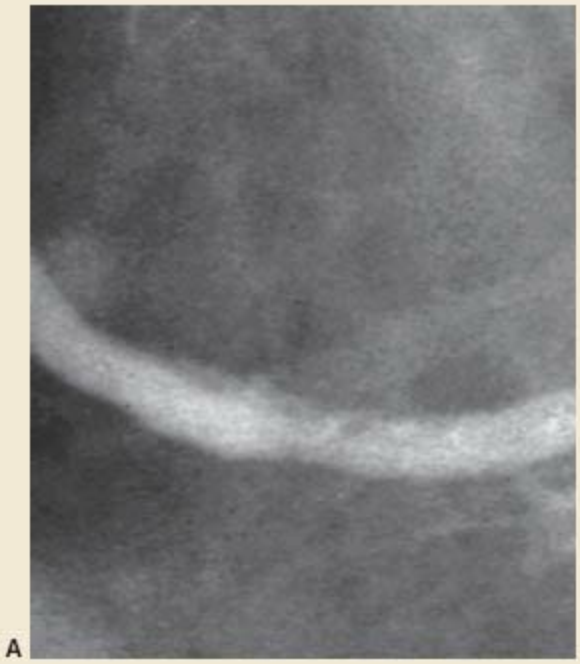
2. The above patient had FFR of 0.88 across the proximal RCA lesion and 0.72 across the mid-LAD lesion. What is the most appropriate next step?
   a. PCI on the LAD and RCA
   b. PCI on the RCA only
   c. PCI on the LAD only
   d. Medical management

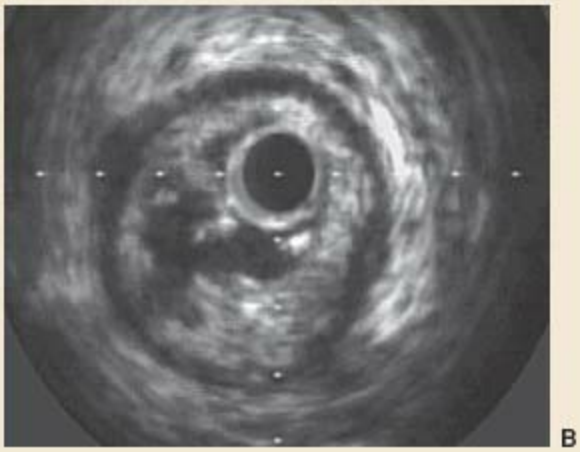
3. In patients being referred for transcatheter aortic valve replacement (TAVR), multidetector computed tomography (MDCT) is useful in assessing which of the following?
   a. Dimensions of the aortic root
   b. To determine coaxial angles for optimization of valve implantation
   c. Distance of the coronary ostia from the aortic cusp margin and the length of the aortic valve leaflets
   d. Aortic and iliofemoral anatomy
   e. All of the above

4. Which of the following is NOT true regarding coronary intravascular ultrasound (IVUS)?
   a. Coronary spasm is the most frequent complication of IVUS, and this responds well to intracoronary nitroglycerin.
   b. In the drug-eluting stent (DES) era, a postdeployment minimal stent area of >5 mm^2 by IVUS has been shown to decrease the likelihood of angiographic restenosis.
   c. Stent undersizing is a well-known predictor of stent thrombosis, and IVUS can help with choosing the optimal stent size based on vessel and lumen size.
   d. IVUS has played a very important role in understanding the natural history of atherosclerosis and the impact of cholesterol-lowering drugs in reducing the progression of atherosclerosis and even its regression.
   e. A minimal luminal area of <8 mm^2 by IVUS correlates with a significant reduction in FFR for a native coronary artery.

5. The left ventriculogram shown above (Top—systole, Bottom—diastole) depicts which of the following?
   a. Severe mitral regurgitation
   b. Ventricular septal rupture
   c. Inferobasal left ventricular aneurysm
   d. Left ventricular thrombus
   e. Left ventricular free wall rupture

6. A 65-year-old man with history of hypertension, hyperlipidemia, and diabetes mellitus, presenting with severe substernal crushing chest pain, undergoes coronary angiography that reveals a hazy lesion in the RCA as shown below. IVUS is performed to investigate the cause of haziness. The IVUS image on the right (B) demonstrates which of the following?





a. Ulcerated plaque
b. Severe calcification
c. Coronary dissection
d. Coronary arterial remodeling
e. Air embolism

Answers

1. Answer B: This patient has a severe lesion in the mid-LAD and an intermediate lesion in the RCA. Based on the FAME trial, a strategy of measuring FFR in patients with multivessel coronary disease undergoing PCI and stenting lesions only with FFR ≤ 0.80 was found to reduce the rate of death, nonfatal myocardial infarction (MI), and repeat revascularization on follow-up. The functional significance of the RCA lesion must first be determined and this can be easily performed while in the catheterization laboratory using FFR, and there is no need to stop the procedure and perform an exercise stress test.

2. Answer C: Deferring PCI in patients with stable angina and normal FFR yields excellent event-free survival, and the risk of cardiac death or MI related to that lesion is <1% per year and not decreased with stenting (DEFER trial). Treating only the clearly ischemic lesion, that is, the LAD, is the best strategy in this case.

3. Answer E: MDCT is very useful in assessing all of the above.[35]

4. Answer E: A minimal luminal area of 3 to 4 mm^2 by IVUS correlates with a significant reduction in FFR for a native coronary artery. A minimal luminal area of <6 to 7.5 mm^2 usually indicates a significant lesion in the left main trunk. All other statements are true.

5. Answer C: The left ventriculogram clearly demonstrates an aneursym of the inferobasal left ventricular wall.

6. Answer A: The IVUS image demonstrates an ulcerated plaque, which is responsible for the haziness in the distal RCA.

CHAPTER

Percutaneous Coronary Intervention

Matthew Cavender and Stephen G. Ellis

Despite tremendous advances in the care of patients with heart disease seen over the past 30 years, coronary artery disease remains the leading cause of mortality and morbidity in the world.[1] With an international population that is increasingly affected by hypertension, diabetes, and obesity, the incidence of coronary artery disease will continue to affect large proportions of the world's population.[2] Advances in the medical treatment of patients with coronary artery disease have improved outcomes over this period of time; however, the use of revascularization to prevent mortality, improve anginal symptoms, and increase exercise capacity remains a fundamental component in management in patients with ischemic heart disease.[3-5]

Revascularization strategies were initially limited to surgical procedures such as coronary artery bypass grafting (CABG). This paradigm began to shift in 1977 when Andreas Gruentzig performed the first percutaneous transluminal coronary angioplasty (PTCA) that successfully increased coronary blood flow previously limited by coronary atherosclerosis. Initial attempts at percutaneous revascularization were hindered by high rates of acute closure and restenosis of the treated lesions.[6] With the development of more potent antiplatelet agents such as thienopyridines and the increased use of coronary stents (percutaneous coronary intervention [PCI]), these limitations have been reduced such that PCI is now the predominant form of coronary revascularization in the United States.[7]

As such, PCI has been the focus of some of the most important clinical trials in cardiology that have shaped clinical practice and defined the algorithms established in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines.[3-5] The current format of the cardiovascular board exam focuses approximately 25% of the content on the management of patients with coronary artery disease and acute myocardial infarction (MI). Revascularization strategies are an important component in the management of these problems. The constant evolution in

both the management of patients with ischemic heart disease and the use of PCI makes it challenging to present from the perspective of the Cardiology Board exam, which is based mostly on the most current ACC/AHA guidelines, and thus lags current practice by a few years. In this chapter, we focus briefly on the techniques and complications of PCI while devoting increased attention to the ACC/AHA guidelines and major clinical trials evaluating the role of PCI in the management of patients with ischemic heart disease.

INDICATIONS AND APPROPRIATENESS OF PCI

ST-Elevation Myocardial Infarction

It is now well established that ST-elevation myocardial infarction (STEMI) occurs when an atherosclerotic plaque ruptures or erodes leading to thrombosis in an epicardial coronary artery. Initial attempts at restoring coronary flow utilized medications with fibrinolytic capabilities designed to breakdown the coronary thrombosis. These therapies, tested in numerous clinical trials (GUSTO, GISSI, ISIS-2, FTT), clearly showed that patients treated with reperfusion therapy had improved survival as compared to those patients treated with conservative management.[8-11] Fibrinolytic therapy was hindered by its relatively high rates of intracranial hemorrhage leading to the search for improved revascularization techniques.[12]

Initial attempts to treat STEMI with percutaneous therapies were limited to balloon angioplasty (PTCA). Studies comparing primary PTCA to fibrinolytic therapy demonstrated less recurrent ischemia, reinfarction, reocclusion, and strokes in patients treated with primary PTCA. While the long-term mortality benefit of primary PTCA was not consistent in the various studies (GUSTO-2B, PAMI), a metaanalysis by Keeley et al. showed a 23% relative reduction in mortality (7% in PTCA vs. 9% in fibrinolytic; $p = 0.0002$) for PTCA compared to thrombolysis.[13,14] Since these trials were conducted, additional therapies such as coronary stenting (which prevents acute vessel closure) and aspiration thrombectomy (removes clot from the coronary artery) have been developed and found to be beneficial in patients with STEMI.[15] Studies have shown that the use of coronary stents in STEMI is more effective than PTCA alone in increasing postintervention lumen size and decreasing the risk of acute vessel closure, subsequent ischemic events, and repeat target vessels revascularization (GRAMI, FRESCO, stent-PAMI).[16-18] There have been no studies demonstrating a survival benefit for stents compared to PTCA alone.

The superiority of PCI as compared to fibrinolytic therapy is reflected in the current ACC/AHA guidelines that support the use of primary PCI in patients with STEMI or chest pain and a new left bundle branch block in situations where it can be performed in a timely manner (door to balloon time of <90 minutes). The timing of symptom onset is

an important component of the decision to pursue percutaneous revascularization. For patients with symptom onset within 12 hours of presentation, primary PCI is given a Class I indication. Patients with the onset of symptoms within 12 to 24 hours who have severe congestive heart failure, hemodynamic/electrical instability, or evidence of persistent ischemia (i.e., continued chest pain) are also candidates for percutaneous revascularization (Class IIa recommendation). Asymptomatic patients who present more than 12 hours after the onset of symptoms should not be treated with percutaneous revascularization (Class III recommendation) (Table 47.1).

TABLE
47.1 Recommendations for the Use of PCI in Patients with STEMI

Class I Recommendations

1. If immediately available, primary PCI should be performed in patients with STEMI (including true posterior MI) or MI with new or presumably new left bundle branch block who can undergo PCI of the infarct artery *within 12 h of symptom onset*, if performed in a timely fashion (*balloon inflation goal within 90 min of presentation*). (Level of Evidence: A)
2. Primary PCI should be performed as quickly as possible, with a goal of a medical contact-to-balloon or door-to-balloon time within 90 min. (Level of Evidence: B)
3. Primary PCI should be performed in fibrinolytic-ineligible patients who present with STEMI within 12 h of symptom onset. (Level of Evidence: C)
4. Aspiration thrombectomy is reasonable for patients undergoing primary PCI. (Level of Evidence: B)

Class IIa Recommendations

1. It is reasonable to perform primary PCI for patients (even if fibrinolytic ineligible) with onset of symptoms within the prior 12–24 h and one or more of the following:
   a. Severe congestive heart failure (Level of Evidence: C)
   b. Hemodynamic or electrical instability (Level of Evidence: C)
   c. Evidence of persistent ischemia (Level of Evidence: C)

Class III Recommendations

1. Elective PCI should not be performed in a *non–infarct-related artery* at the time of primary PCI of the infarct-related artery in patients without hemodynamic compromise. (Level of Evidence: C)
2. Primary PCI should not be performed in *asymptomatic patients more than 12 h after onset of STEMI* who are hemodynamically and electrically stable. (Level of Evidence: C)

Modified from the ACC/AHA guidelines: King SB III, Smith SC Jr, Hirshfeld JW Jr, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. J Am Coll Cardiol. 2008;51:172–209; Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). Circulation. 2006;113:156–175; Kushner FG, Hand M, Smith SC Jr, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused

update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2009;54:2205–2241.

PCI in Cardiogenic Shock

Approximately 5% of patients with STEMI have a significant decrease in cardiac output resulting in end-organ malperfusion. This condition, known as cardiogenic shock, is defined clinically by the presence of a systolic blood pressure <90 mm Hg lasting for more than 30 minutes (in the absence of hypovolemia) or vasopressors required to achieve a systolic blood pressure ≥90 mm Hg combined with a reduced cardiac index (1.8 L/min/m^2) and evidence of an elevated left ventricular filling pressure (i.e., pulmonary capillary wedge pressure >18 mm Hg).[19] Patients who develop cardiogenic shock are at increased risk of death with mortality rates ranging from 30% to 50%.[20] The SHOCK trial was a landmark trial that serves as the basis for the current ACC/AHA recommendations for the treatment of patients in cardiogenic shock. This trial showed that revascularization performed within 36 hours from symptom onset was superior to initial medical stabilization with a lower mortality rates at 6 months (50% with PTCA vs. 63% with initial medical therapy, p = 0.027).[21]

Subset analysis from the SHOCK trial showed that patients ≥75 years old did not have the same benefit from revascularization raising questions as to whether patient revascularization should be pursued in the elderly. While subsequent observational and post hoc analysis have provided support for the use of revascularization in the elderly, this ambivalence is reflected in the current ACC/AHA guidelines (Table 47.2).[22]

TABLE
47.2 Recommendations for the Use of PCI in Patients with Cardiogenic Shock

Class I Recommendations

1. Primary PCI should be performed for patients <75 y *old* with ST elevation or presumably new left bundle branch block *who develop shock within 36 h of MI* and are suitable for *revascularization that can be performed within 18 h of shock*, unless further support is futile because of the patient's wishes or contraindications/unsuitability for further invasive care. (Level of Evidence: A)
2. Primary PCI should be performed in patients with severe congestive heart failure and/or pulmonary edema (Killip class 3) and onset of symptoms within 12 h. The medical contact-to-balloon or door-to-balloon time should be as short as possible (i.e., goal within 90 min). (Level of Evidence: B)

Class IIa Recommendations

1. Primary PCI is reasonable for selected patients *75 y or older* with ST elevation or left bundle branch block or who develop shock within 36 h of MI and are suitable for revascularization that can be performed within 18 h of shock. Patients with good prior functional status who are suitable for revascularization and agree to invasive care may be selected for such an invasive strategy. (Level of Evidence: B)

Modified from the ACC/AHA guidelines: King SB III, Smith SC Jr, Hirshfeld JW Jr, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. J Am Coll Cardiol. 2008;51:172–209; Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). Circulation. 2006;113:156–175; Kushner FG, Hand M, Smith SC Jr, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2009;54:2205–2241.

Role of PCI in Patients Treated with Fibrinolytics

Not all hospitals are equipped with catheterization laboratories capable of performing emergent PCI in the setting of STEMI. As a result, some patients with STEMI may be treated with fibrinolytic therapy if transfer to a PCI hospital cannot be performed in a timely manner. Attempts to combine lower dose fibrinolytic therapies with PCI have largely been unsuccessful in improving outcomes. The FINESSE trial (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) randomized patients with STEMI to facilitated PCI (half-dose fibrinolytics + abciximab), abciximab-facilitated PCI, or primary PCI.[23] At 90 days, there was no difference in the primary endpoint (composite of death from all causes, ventricular fibrillation occurring more than 48 hours after randomization, cardiogenic shock, and congestive heart failure during the first 90 days after randomization). Based on this study, facilitated PCI (fibrinolytics as an intentional prelude to primary PCI) should not be performed.

The lack of benefit for facilitated PCI does not imply that PCI does not have a role

in the management of patients treated with fibrinolytic therapy. Up to 25% of patients treated with fibrinolytics will not achieve coronary reperfusion.[24] Identifying this subset is important since patients with a patent infarct–related artery have improved clinical outcomes as compared to patients in which reperfusion is not successful. Continued chest pain and persistent ST elevations are typically considered markers of failed reperfusion; however, prior studies have found that approximately half of patients with persistent chest pain and ST elevations will actually have a patent infarct artery.[24] Despite this limitation, persistent ST elevation of >50% remains an indication for rescue PCI (PCI performed after failed fibrinolysis) due to the large benefit of rescue PCI shown in the REACT trial. The REACT trial randomized patients who did not have a >50% reduction in ST elevation to conservative therapy, repeat thrombolysis, or rescue PCI. At 6 months, patients treated with rescue PCI were significantly more likely to be free from death, reinfarction, stroke, or severe heart failure (adjusted hazard ratios of 0.43; $p = 0.001$ for rescue PCI vs. repeated thrombolysis).[25] In addition to the ECG requirement, ACC/AHA guidelines also support immediate PCI following the administration of fibrinolytic therapy for patients with recurrent MI (Class I indication), moderate or severe ischemia (Class I indication), cardiogenic shock/hemodynamic instability (Class I indication), LVEF <40% (Class IIa indication), and serious ventricular arrhythmias (Class IIa indication) (Table 47.3).

TABLE
47.3 Recommendations for PCI After Failed Fibrinolysis (Rescue PCI)

Class I Indications

1. A strategy of coronary angiography with intent to perform PCI (or emergency CABG) is recommended for patients who have received fibrinolytic therapy and have any of the following:
   a. Cardiogenic shock in patients <75 y who are suitable candidates for revascularization (Level of Evidence: B)
   b. Severe congestive heart failure and/or pulmonary edema (Killip class III) (Level of Evidence: B)
   c. Hemodynamically compromising ventricular arrhythmias (Level of Evidence: C)

Class IIa

1. A strategy of coronary angiography with intent to perform PCI (or emergency CABG) is reasonable in patients 75 y of age or older who have received fibrinolytic therapy and are in cardiogenic shock, provided that they are suitable candidates for revascularization. (Level of Evidence: B)
2. It is reasonable to perform rescue PCI for patients with one or more of the following:
   a. Hemodynamic or electrical instability (Level of Evidence: C)
   b. Persistent ischemic symptoms (Level of Evidence: C)
3. A strategy of coronary angiography with intent to perform rescue PCI is reasonable for patients in whom fibrinolytic therapy has failed (ST-segment elevation <50% resolved after 90 min following initiation of fibrinolytic therapy in the lead showing the worst initial elevation) and a moderate or large area of myocardium is at risk (anterior MI, inferior MI with right ventricular involvement, or precordial ST-segment depression). (Level of Evidence: B)

Class III

1. A planned reperfusion strategy using full-dose fibrinolytic therapy followed by immediate PCI may be harmful. (Level of Evidence: B)

Modified from the ACC/AHA guidelines: King SB III, Smith SC Jr, Hirshfeld JW Jr, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. J Am Coll Cardiol. 2008;51:172–209; Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). Circulation. 2006;113:156–175; Kushner FG, Hand M, Smith SC Jr, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2009;54:2205–2241.

Patients should be transferred to a hospital with PCI capabilities after the administration of fibrinolytics due to the numerous potential indications for PCI. In patients with successful fibrinolysis who are asymptomatic, earlier trials that predated the routine use of clopidogrel and GP IIb/IIIa inhibitors showed no evidence that immediate PCI of the infarct-related artery provided any further reduction in death, reinfarction, or myocardial salvage (SWIFT and TIMI II). Other trials such as SIAM III, GARCIA-1, and CAPITAL-AMI showed significant reduction in mortality and ischemic

events in those who underwent immediate PCI after successful fibrinolysis. A larger, definitive trial has also provided evidence of benefit. The TRANSFER-AMI study randomized patients to either standard treatment (including rescue PCI) or immediate transfer to another hospital for PCI within 6 hours after fibrinolysis.[26] At 30 days, there was a significant decrease in the number of patients with death, reinfarction, recurrent ischemia, new or worsening congestive heart tailure, or cardiogenic shock (relative risk with early PCI, 0.64; p = 0.004).This has been further clarified with results of a meta-analysis by D'Souza et al., which showed that an early invasive PCI strategy following administration of fibrinolytic therapy results in a 53% reduction (odds ratio 0.47 [95% confidence interval (CI), 0.32-0.68, p <0.0001]) in a combined endpoint of 30-day mortality, reinfarction, and ischemia. The majority of the difference was in a significant reduction in both reinfarction and recurrent ischemia that 30-day mortality and major bleeding rates between strategies were not significantly different.[27] While not yet reflected in the ACC/AHA guidelines, many providers now advocate routine angiography following the administration of fibrinolytic therapy; however, the optimal timing of PCI following the administration of fibrinolytic therapy remains unknown (Table 47.4).

TABLE
47.4 Recommendations for PCI After Successful Fibrinolysis or for Patients Not Undergoing Primary Reperfusion

Class I

1. In patients whose anatomy is suitable, PCI should be performed when there is objective evidence of recurrent MI. (Level of Evidence: C)
2. In patients whose anatomy is suitable, PCI should be performed for moderate or severe spontaneous or provocable myocardial ischemia during recovery from STEMI. (Level of Evidence: B)
3. In patients whose anatomy is suitable, PCI should be performed for cardiogenic shock or hemodynamic instability. (Level of Evidence: B)

Class IIa

1. It is reasonable to perform routine PCI in patients with LV ejection fraction ≤0.40, heart failure, or serious ventricular arrhythmias. (Level of Evidence: C)
2. It is reasonable to perform PCI when there is documented clinical heart failure during the acute episode, even though subsequent evaluation shows preserved LV function (LV ejection fraction >0.40). (Level of Evidence: C)
3. It is reasonable for high-risk patients who receive fibrinolytic therapy as primary reperfusion therapy at a non–PCI-capable facility to be transferred as soon as possible to a PCI-capable facility where PCI can be performed either when needed or as a pharmacoinvasive strategy. Consideration should be given to initiating a preparatory antithrombotic (anticoagulant plus antiplatelet) regimen before and during patient transfer to the catheterization laboratory.[14,15]. (Level of Evidence: B)

Class IIb

1. PCI of a hemodynamically significant stenosis in a patent infarct artery >24 hours after STEMI may be considered as part of an invasive strategy. (Level of Evidence: B)
2. Patients who are not at high risk who receive fibrinolytic therapy as primary reperfusion therapy at a non–PCI-capable facility may be considered for transfer as soon as possible to a PCI-capable facility where PCI can be performed either when needed or as a pharmacoinvasive strategy. Consideration should be given to initiating a preparatory antithrombotic (anticoagulant plus antiplatelet) regimen before and during patient transfer to the catheterization laboratory. (Level of Evidence: C)

Class III

1. PCI of a totally occluded infarct artery >24 hours after STEMI is not recommended in asymptomatic patients with 1- or 2-vessel disease if they are hemodynamically and electrically stable and do not have evidence of severe ischemia. (Level of Evidence: B)

Modified from the ACC/AHA guidelines: King SB III, Smith SC Jr, Hirshfeld JW Jr, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. J Am Coll Cardiol. 2008;51:172–209; Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). Circulation. 2006;113:156–175; Kushner FG, Hand M, Smith SC Jr, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2009;54:2205–2241.

Unstable Angina/Non–ST-Elevation Myocardial Infarction

The proportion of patients with high-risk unstable angina or non–ST-elevation acute coronary syndrome (NSTEMI) is increasing in the United States.[28] Current ACC/AHA guidelines assume that patients with UA/NSTEMI are already on intensive medical therapy including aspirin, thienopyridine, antithrombotic (heparin, bivalirudin, etc.) beta-blockers, and statins. The role of revascularization in this population has been the focus of much attention and numerous clinical trials, including TIMI-IIIB, VANQWISH, FRISC II, TACTICS TIMI-18, RITA-3, and ICTUS. While there has been differences in the conclusions drawn from these studies, the bulk of the trials and a large meta-analysis support the use of an early invasive revascularization strategy (performance of diagnostic angiography with intent to perform revascularization within 48 hours of presentation).[29] In patients with refractory angina or hemodynamic/electrical instability, revascularization should be performed in a semiemergent manner.[30]

While the early invasive strategy is preferred for patients who are suitable candidates for revascularization, the largest benefit comes from revascularization in patients considered to be high risk. Numerous risk prediction models, including the GRACE and PURSUIT risk scores, have been developed in order to guide the decision to refer to revascularization. The most well validated and widely used of these risk scores is the TIMI Risk Score that assigns patients one point for each of the following risk factors: age >65, known coronary artery disease (lesion >50%), three of more risk factors of coronary artery disease (tobacco abuse, family history, diabetes, hypertension, hyperlipidemia), aspirin use within 7 days, positive cardiac biomarkers, ST changes of >1 mm, and two or more episodes of chest pain within the past 24 hours. Patients with greater than two risk factors derive benefit from an early invasive strategy[31] (Table 47.5).

TABLE
47.5 Risk Stratification in UA/NSTEMI

TIMI Risk Score
■ Age >65 ■ Known coronary artery disease (lesion >50%) ■ Three or more risk factors of coronary artery disease (tobacco abuse, family history, diabetes, hypertension, hyperlipidemia) ■ Aspirin use within 7 days ■ Positive cardiac biomarkers ■ ST changes of >1 mm ■ Two or more episodes of chest pain within the past 24 hours

Adapted from Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA. 2000;284:835–842.

In patients who are stable, an initial conservative strategy may be considered even in high-risk patients if preferred by either patients or their physicians. While the guidelines support early catheterization for patients, this does not imply that all patients with UA/NSTEMI warrant revascularization. Revascularization is not indicated in patients with—one- to two-vessel CAD with either no symptoms or symptoms that are unlikely to be due to myocardial ischemia. In addition, revascularization is contraindicated in patients without high risk features who have only a small area of at-risk myocardium, lesions that have a low likelihood of revascularization, high risk of procedure-related morbidity/mortality, and stenosis of <50% or patients with left main CAD who are candidates for CABG (Table 47.6).

TABLE
47.6 Recommendations for PCI in Patients with UA/NSTEMI

Class I

1. An early invasive PCI strategy is indicated for patients with UA/NSTEMI who have no serious comorbidities. (Level of Evidence: A)
2. PCI (or CABG) is recommended for UA/NSTEMI patients with 1- or 2-vessel CAD with or without significant proximal LAD CAD but with a large area of viable myocardium and high-risk criteria on noninvasive testing. (Level of Evidence: B)
3. PCI (or CABG) is recommended for UA/NSTEMI patients with multivessel coronary disease with suitable coronary anatomy, with normal LV function, and without diabetes mellitus. (Level of Evidence: A)
4. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is indicated in UA/NSTEMI patients who have refractory angina or hemodynamic or electrical instability (without serious comorbidities or contraindications to such procedures). (Level of Evidence: B)
6. Patients with definite or likely UA/NSTEMI selected for an invasive approach should receive dual-antiplatelet therapy. (Level of Evidence: A) Aspirin should be initiated on presentation. (Level of Evidence: A) Clopidogrel (before or at the time of PCI) (Level of Evidence: A) or prasugrel (at the time of PCI) (Level of Evidence: B) is recommended as a second antiplatelet agent.

Class III

1. PCI (or CABG) is not recommended for patients with 1- or 2-vessel CAD without significant proximal LAD CAD with no current symptoms or symptoms that are unlikely to be due to myocardial ischemia and who have no ischemia on noninvasive testing. (Level of Evidence: C)
2. In the absence of high-risk features associated with UA/NSTEMI, PCI is not recommended for patients with UA/NSTEMI who have single-vessel or multivessel CAD and no trial of medical therapy, or who have one or more of the following:
   a. Only a small area of myocardium at risk (Level of Evidence: C)
   b. All lesions or the culprit lesion to be dilated with morphology that conveys a low likelihood of success (Level of Evidence: C)
   c. A high risk of procedure-related morbidity or mortality (Level of Evidence: C)
   d. Insignificant disease (<50% coronary stenosis) (Level of Evidence: C)
   e. Significant left main CAD and candidacy for CABG (Level of Evidence: B)
3. A PCI strategy in stable patients with persistently occluded infarct-related coronary arteries after STEMI/ NSTEMI is not indicated. (Level of Evidence: B)

Modified from the ACC/AHA guidelines: King SB III, Smith SC Jr, Hirshfeld JW Jr, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. J Am Coll Cardiol. 2008;51:172–209; Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). Circulation. 2006;113:156–175; Kushner FG, Hand M, Smith SC Jr, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2009;54:2205–2241.

Stable Angina

Percutaneous revascularization was first utilized in patients with severe, chronic angina. In the current era, symptom relief from chronic stable angina remains the most frequent indication for revascularization. The decision to pursue medical therapy or revascularization is a highly individualized decision based on patient characteristics, symptoms, lifestyle, and preferences. The severity of angina is typically classified on the Canadian Cardiovascular Society Functional Classification of Angina Pectoris scale[32] (Table 47.7).

TABLE
47.7 Canadian Cardiovascular Society Angina Pectoris Scale

I	No limitations on activity—no angina with normal physical activity, strenuous exertion may produce symptoms.
II	Some limitations on activity—moderate exertion results in symptoms (climbing more than one flight of stairs).
III	Significant limitations due to angina—Angina occurs with limits on normal activity of daily living (climbing one flight of stairs).
IV	Unable to perform any activity with angina, may have angina at rest

From Campeau L. Letter: grading of angina pectoris. Circulation. 1976;54:522–523, with permission from Wolters Kluwer Health.

There is a significant amount of clinical trial data comparing outcomes in patients treated with medical therapy versus revascularization. Numerous clinical trials and observational studies have been conducted in an attempt to understand the patient populations most likely to benefit from PCI. The RITA-II trial (Second Randomized Intervention Treatment of Angina) randomized 1,018 patients with angina to either PTCA (only 8% received stents) or medical therapy.[33] After 2.7 years, death or definite MI occurred in 6.3% of patients treated with PCI, whereas these endpoints occurred in 3.3% of patients with medical care ($p = 0.02$). The difference between the two groups was primarily due to seven periprocedural nonfatal MIs in the revascularization group (which are of questionable significance). Revascularization did result in significant improvement in angina. There was a 16.5% absolute excess of moderate/severe angina in the patients treated with medical therapy. In addition, patients treated with revascularization have longer exercise times on the Bruce protocol. By 7 years, the incidence of death or MI was comparable in both groups.[34]

The ACIP trial (Asymptomatic Cardiac Ischemia Pilot) evaluated a slightly different

population.[35] Five hundred and fifty-eight patients with evidence of ischemia who underwent angiography and were found to have coronary artery disease amenable to revascularization were randomized with angina-guided medical therapy, ischemia-guided medical therapy, or revascularization with CABG or PTCA. After 2 years, the total mortality was 6.6% in the angina-guided group, 4.4% in the ischemia-guided group, and 1.1% in those receiving revascularization. These data suggested a benefit from initial revascularization compared to medical therapy in patients with demonstrable ischemia.

The most recent trial of medical therapy versus revascularization trial in patients with stable coronary artery disease was the COURAGE study (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation).[36] This trial randomized 2,287 patients with coronary artery disease and evidence of ischemia to either PCI with optimal medical therapy (PCI group) or initial optimal medical therapy. Approximately one out of every three patients initially treated with medical therapy had a revascularization at some point during the follow-up period. After a median follow-up of 4.6 years, there was no difference in either all-cause mortality or nonfatal MI between the two groups. Relief from angina was significantly improved in patients treated with revascularization plus optimal medical therapy. This difference was attenuated over time possibly due to the significant number of patients in the initial medical therapy arm who eventually underwent revascularization. On the basis of this study, patients with stable angina can be treated initially with a trial of medical therapy with revascularization reserved for those patients with persistent angina.

It is possible that the use of functional assessment of coronary artery stenosis using either fractional flow reserve or stress imaging may provide an appropriate way of risk stratifying those patients most likely to benefit from revascularization instead of initial medical management. For example, a substudy of the COURAGE trial showed that patients with a >5% reduction in the amount of ischemia had improved outcomes, and PCI was more effective than medical therapy in reducing myocardial ischemia.[37] This provides support for the use of ischemia-guided PCI; however, it remains unclear whether reduction of ischemia with PCI will improve clinical outcomes in patients with stable coronary artery disease.

The continuing improvements in outcomes with revascularization and the individuality of each patient's symptoms and coronary anatomy make definitive conclusions about generalized patient populations challenging. It is apparent that patients with chronic stable angina have more effective relief of angina with percutaneous revascularization; however, it is likely that there is no difference between the two strategies in regard to the risk of MI, death, or need for future PCI and/or CABG. Patients with more severe angina and demonstrable ischemia on stress testing have a greater benefit in regard to relief of angina, while the effect on mortality remains debatable. As a result, a strategy of initial medical management in this population is

both safe and effective.

Appropriateness criteria have been developed by the ACC/AHA to help guide the decision on which patients are likely to have the greatest benefit from revascularization.[38] These criteria were developed largely from expert opinions based on the limited data available and the clinical experience of those involved in formulating the guidelines. For the purposes of the boards, these criteria do not need to be committed to memory but are a useful reference for making decisions regarding the decision to pursue revascularization. Factors considered in the development of the appropriateness criteria for revascularization include the location and extent of the coronary disease, severity of symptoms, extent of ischemia on stress testing, and use of medical therapy. Those patients with increased severity of coronary artery disease, larger area of ischemia, and more severe symptoms are those patients most likely to benefit from revascularization therapy. In contrast, those patients with minimal symptoms, small areas of ischemia, and less extensive coronary artery disease are those who are most likely to benefit from medical therapy with aspirin, antianginal medication (nitrates, beta-blockers, calcium channel blockers), and statins. Revascularization is also often considered in patients with ischemic heart disease prior to planned surgery. There is no evidence that prophylactic revascularization improves outcomes as compared to medical therapy with aspirin, beta-blockers, and statins. As a result, revascularization should only be considered for patients if they meet an indication for revascularization irrespective of their planned surgery.[39]

The revascularization options for patients with stable angina include both CABG and PCI. The landmark BARI (Bypass Angioplasty Revascularization Investigation) trial randomized 1,829 patients with multivessel coronary artery disease (patients with left main disease were excluded) to either PTCA (prior to the use of stents) or CABG. There was no difference in survival between the two groups at 5 years; however, post hoc analysis showed that patients with diabetes had a 15% absolute reduction in mortality when undergoing CABG.[40] Based on the results of BARI, surgical therapy has historically been the preferred method of revascularization in patients with diabetes or three-vessel coronary artery disease.

The SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial was designed to provide contemporary data to guide the type of revascularization for patients with severe coronary artery disease.[41] This contemporary trial differed from the BARI trial by including patients with left main disease and/or three-vessel coronary artery disease and randomizing them to either CABG or complete revascularization with drug-eluting stents. In addition, the SYNTAX trial utilized a team approach that included both an interventional cardiologist and a cardiac surgeon to determine whether patients were a candidate for both percutaneous revascularization and CABG. This team calculated a SYNTAX score which takes into

account calcification, tortuosity, and length for every stenosis >50% found in vessels more than 1.5 mm in diameter. The SYNTAX score, if used by trained personnel, can be a reproducible score that allows for direct comparison of the severity of coronary artery disease between patients (SYNTAX score <22 = low risk, 23 to 32 = intermediate risk, ≥33 = high risk). In the 4,337 patients randomized, there was no difference in all-cause mortality, stroke, or MI at 1 year between the two groups (PCI 7.7% vs. CABG 7.6%, p = 0.99); however, the primary endpoint that added repeat revascularization to the three other endpoints occurred more frequently in the patients treated with PCI (17.8% vs. 12.4%, p = 0.002). Post hoc analysis at 4 years showed that patients treated with CABG had lower cardiovascular mortality when compared to patients treated with PCI (4.3% vs. 7.6%, p = 0.004) although the validity of this finding is uncertain given the difference in the numbers of patients lost to follow-up seen between the two arms (CABG arm had more patients lost to follow-up). These results largely coincided with smaller randomized clinical trials that evaluated PCI with bare metal stents to CABG which suggested that there is no mortality benefit provided by PCI over CABG [ARTS-I (Arterial Revascularization Therapies Study Part I), MASS-II (Medicine, Angioplasty, or Surgery Study for Multivessel Coronary Artery Disease), ERACI-II (Argentine Randomized Study of Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in Patients with Multiple Vessel Disease), and AWESOME (Angina with Extremely Serious Operative Mortality Evaluation)]. Patients with more severe coronary artery disease are likely to see lower rates of repeat revascularization after CABG; however, those patients with isolated left main disease and/or low SYNTAX score have improved outcomes with percutaneous revascularization.

In summary, CABG has previously been the preferred method of revascularization for patients with three-vessel coronary artery disease and LV dysfunction, left main disease, or diabetes and multivessel disease. With the potential exception of patients with diabetes, there has been no definitive mortality difference between the two types of revascularization. Patients undergoing CABG are at increased risk of perioperative stroke, while patients undergoing PCI are at increased risk of restenosis and the need for repeat revascularization. Drug-eluting stents have been successful in decreasing the rates of restenosis allowing for the percutaneous revascularization of the left main artery and patients with three-vessel coronary artery disease; however, the use of drug-eluting stents remains associated with higher rates of repeat revascularization. CABG provides the most enduring revascularization for patients with the most extensive coronary artery disease (SYNTAX > 22) (Table 47.8).

TABLE
47.8 ACC/AHA Appropriateness Criteria for the Selection Of PCI or CABG in Patients with Severe Coronary Artery Disease

	No Diabetes, Normal LVEF		Diabetes		Depressed LVEF	
	PCI	CABG	PCI	CABG	PCI	CABG
2-Vessel CAD with proximal LAD stenosis	A	A	A	A	A	A
3-Vessel CAD	U	A	U	A	U	A
Isolated left main	I	A	I	A	I	A
Left main disease + CAD	I	A	I	A	I	A

A, Appropriate; U, Appropriateness uncertain; I, Inappropriate.

Modified from Patel MR, Dehmer GJ, Hirshfeld JW, et al. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol. 2009;53:530–553..

Patients Who Are Undergoing PCI Post-CABG

Patients who undergo CABG are still at risk of ischemia due to either graft occlusion or the progression of disease in the native vessels. Considering that repeat CABG carries a higher risk (approximately two times the risk of mortality in an otherwise low-risk patient), a post-CABG patient with recurrent ischemia may require PCI procedures to the grafts or the native vessels. The timing of ischemia following CABG offers insight into the etiology of the ischemia and the appropriateness for PCI in the management of this population. Ischemia within 30 days (very early ischemia) is usually secondary to graft failure from thrombosis or native vessel disease that was not supplied by the coronary bypass grafts. Ischemia occurring 30 days to 1 year following CABG is usually secondary to perianastomotic graft stenosis (early ischemia). Ischemia occurring >1 year after CABG (late ischemia) is usually secondary to disease progression in the grafts and/or native coronary vessels. PCI may be used to recanalize thrombosed vessels, dilate anastomotic points, or balloon or stent native vessels or grafts. It is important to keep in mind that the choice of PCI versus redo CABG in patients with recurrent ischemia depends on multiple factors including the potential graft conduits (arterial vs. venous), the number of grafts required and how many are occluded, the location of recurrent disease (in native vessels vs. grafts), LV function, and associated comorbidities.

ADJUNCT THERAPY FOR PCI

Antiplatelet Therapies

Aspirin/Thienopyridines

Early efforts at coronary stenting were hindered by high rates of stent thrombosis following PCI. Aspirin and thienopyridine have become the standard antiplatelet regimen used after PCI to prevent stent thrombosis after the conclusion of the STARS trial (Stent Anticoagulation Restonosis Study).[42] The STARS trial randomized 1,653 patients with recent stent implantation to aspirin only, aspirin plus ticlopidine, or aspirin plus warfarin. At 30 days, only 0.5% of patients treated with aspirin and ticlopidine had the primary endpoint (death, MI, revascularization of the target lesion, and angiographically evident stent thrombosis) that was significantly less than both aspirin alone (3.6%) and aspirin plus warfarin (2.6%). The use of ticlopidine in clinical care was hindered by its side effect profile that included both neutropenia and thrombotic thrombocytopenic purpura. As a result, clopidogrel, which has a lower incidence of these side effects, has become the most used thienopyridine.[43] The efficacy of clopidogrel in patients treated with PCI has been tested and shown to be effective in multiple studies. The CREDO (Clopidogrel for the Reduction of Events during Observation) trial randomized 2,116 patients undergoing PCI with bare metal stenting to either clopidogrel load with continued therapy for 1 year or clopidogrel after PCI with continued therapy for 28 days. Those patients treated with long-term clopidogrel had a 27% relative risk reduction in death, MI, or stroke at 1 year.[44]

Prasugrel is a new thienopyridine that has a faster onset and more potent antiplatelet effects than clopidogrel.[45] It was approved for use in patients with acute coronary syndrome based on the results of the TRITON TIMI-38 trial.[46] TRITON randomized 13,608 patients with acute coronary syndrome undergoing PCI to standard therapy with clopidogrel (300-mg loading dose and long-term treatment with 75 mg/d) or prasugrel (60-mg loading dose and long-term treatment with 10 mg/d). After a follow-up that ranged between 6 and 15 months, cardiovascular mortality, nonfatal MI, and nonfatal stroke were significantly lower in the group treated with prasugrel (hazard ratio for prasugrel vs. clopidogrel, 0.81; $p < 0.001$). There were some significant safety concerns that have limited the widespread adoption of this agent. Patients treated with prasugrel had a significant increase in bleeding (hazard ratio, 1.32; 95% CI, 1.03 to 1.68; $p = 0.03$) and patients with prior transient ischemic attack/cerebral vascular accident (TIA/CVA) had worse outcomes when treated with prasugrel. Also, patients older than 75 years and <60 kg did not appear to benefit from increased platelet inhibition. Based on this subgroup analysis, prasugrel is contraindicated in patients with prior TIA/CVA, age >75 years old, or <60 kg due to the increased bleeding risk.

Ticagrelor is a newly approved antiplatelet agent that is a direct and reversible inhibitor of the P_2Y_{12} receptor. The half-life of the drug is 12 hours and as a result is given twice daily. The largest study of ticagrelor is the Study of Platelet Inhibition and Patient Outcomes (PLATO).[47] The PLATO study randomized 18,624 patients with ACS

to either ticagrelor (180-mg loading dose and then 90 mg twice daily) or clopidogrel (300- to 600-mg loading dose and then 75 mg daily). After 12 months, death from vascular causes, MI, or stroke was less common in the patients treated with ticagrelor (HR 0.84, $p < 0.001$).[48] While the overall outcomes favored ticagrelor, there are some safety concerns. Among patients not undergoing CABG, bleeding rates were higher in patients treated with ticagrelor (4.5% vs. 3.8%, $p = 0.03$). In addition, a post hoc analysis demonstrated that patients randomized from the United States had worse outcomes with ticagrelor.[49] It is unclear whether this is due to statistical chance or that patients in the United States were more likely to be on higher doses of aspirin. In summary, ticagrelor is an agent with antiplatelet effects that are reversible and have a short half-life. Given the potential interaction between high-dose aspirin and outcomes, ticagrelor should only be used in conjunction with low doses of aspirin.

The dosing and duration of dual antiplatelet therapy (DAPT) have changed over time. Current guidelines recommend that patients not already taking daily chronic aspirin therapy should be given 300 to 325 mg of aspirin before the PCI with long-term therapy at a dose between 75 mg and 325 mg/d. Further insight into the most appropriated aspirin dose has been provided with the CURRENT OASIS-7 trial. This trial randomized patients with ACS treated with an early invasive strategy in a two-by-two factorial design to low- versus high-dose aspirin and low- versus high-dose clopidgrel.[50] At 30 days, there was no difference in the primary endpoint of cardiovascular death, MI, or stroke. Given the higher bleeding rates seen with higher doses of aspirin, it is reasonable to treat patients with the lowest available aspirin dose.[51] Current ACC/AHA guidelines do not yet reflect the results of this trial. Despite concurrent thienopyridine, aspirin remains necessary for patients treated with PCI. Among patients with aspirin sensitivity, desensitization can be considered; however, thienopyridines alone are more frequently utilized.

The duration of clopidogrel treatment after PCI is also subject to some debate. Originally, it was recommended that patients treated with bare metal stent be treated for at least 4 weeks, while patients treated with drug-eluting stents be treated for 3 to 6 months depending on the type of stent. Over time, it became apparent that there was a small but significant incidence of late stent thrombosis in patients treated with drug-eluting stents.[52] This was attributed to the lack of endothelialization caused by the medications on the stent designed to inhibit restenosis. Current guidelines support the use of DAPT for at least 12 months; however, there will be no definitive answer regarding the optimal duration of DAPT therapy until the completion of the ongoing DAPT Study (Dual Antiplatelet Therapy Study).[53] This trial is enrolling patients treated with drug-eluting stents who will then be treated for 12 months with DAPT. After 12 months, patients will be randomized to either placebo (thereby completing DAPT) or an additional 18 months of DAPT (long- term DAPT). Scheduled for completion in

December 2013, this trial will provide evidence that will be helpful in determining whether long-term DAPT past 1 year is necessary (Table 47.9).

TABLE
47.9 Recommendations for Adjunctive Antiplatelet Therapies in PCI

Class I

1. Patients already taking daily chronic aspirin therapy should take 75–325 mg of aspirin before the PCI procedure is performed. (Level of Evidence: A)
2. Patients not already taking daily chronic aspirin therapy should be given 300–325 mg of aspirin at least 2 h and preferably 24 h before the PCI procedure is performed. (Level of Evidence: C)
3. After PCI, in patients without allergy or increased risk of bleeding, aspirin 162–325 mg daily should be given for at least 1 mo after BMS implantation, 3 mo after sirolimus-eluting stent implantation, and 6 mo after paclitaxel-eluting stent implantation, after which daily long-term aspirin use should be continued indefinitely at a dose of 75–162 mg. (Level of Evidence: B)
4. A loading dose of thienopyridine is recommended for STEMI patients for whom PCI is planned. Regimens should be one of the following:
   a. At least 300–600 mg of clopidogrel should be given as early as possible before or at the time of primary or nonprimary PCI. (Level of Evidence: C)
   b. Prasugrel 60 mg should be given as soon as possible for primary PCI. (Level of Evidence: B)
   c. For STEMI patients undergoing nonprimary PCI, the following regimens are recommended:
      (i) If the patient has received fibrinolytic therapy and has been given clopidogrel, clopidogrel should be continued as the thienopyridine of choice. (Level of Evidence: C)
      (ii) If the patient has received fibrinolytic therapy without a thienopyridine, a loading dose of 300 to 600 mg of clopidogrel should be given as the thienopyridine of choice. (Level of Evidence: C)
      (iii) If the patient did not receive fibrinolytic therapy, either a loading dose of 300 to 600 mg of clopidogrel should be given or, once the coronary anatomy is known and PCI is planned, a loading dose of 60 mg of prasugrel should be given promptly and no later than 1 h after the PCI. (Level of Evidence: B)
5. The duration of thienopyridine therapy should be as follows:
   a. In patients receiving a stent (BMS or DES) during PCI for ACS, clopidogrel 75 mg daily (Level of Evidence: B) or prasugrel 10 mg daily (Level of Evidence: B) should be given for at least 12 mo.
   b. If the risk of morbidity because of bleeding outweighs the anticipated benefit afforded by thienopyridine therapy, earlier discontinuation should be considered. (Level of Evidence: C)
6. Managing warfarin to an INR = 2.0–3.0 for paroxysmal or chronic atrial fibrillation or flutter is recommended, and in post-MI patients when clinically indicated (e.g., atrial fibrillation, left ventricular thrombus). (Level of Evidence: A)
7. Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. (Level of Evidence: B)
8. In patients requiring warfarin, clopidogrel, and aspirin therapy after PCI, an INR of 2.0–2.5 is recommended with low-dose aspirin (75–81 mg) and a 75-mg dose of clopidogrel. (Level of Evidence: C)
9. In patients taking a thienopyridine in whom CABG is planned and can be delayed, it is recommended that the drug be discontinued to allow for dissipation of the antiplatelet effect. (Level of Evidence: C) The period of withdrawal should be at least 5 d in patients receiving clopidogrel (Level of Evidence: B) and at least 7 d in patients receiving prasugrel (Level of Evidence: C), unless the need for revascularization and/or the net benefit of the thienopyridine outweighs the potential risks of excess bleeding. (Level of Evidence: C)

Class III

1. In STEMI patients with a prior history of stroke and TIA for whom primary PCI is planned, prasugrel is not recommended as part of a dual-antiplatelet therapy regimen. (Level of Evidence: C)

Adapted from the ACC/AHA guidelines: King SB III, Smith SC Jr, Hirshfeld JW Jr, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. J Am Coll Cardiol. 2008;51:172–209; Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 Guideline Update

for Percutaneous Coronary Intervention—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). Circulation. 2006;113:156–175; Kushner FG, Hand M, Smith SC Jr, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2009;54:2205–2241.

Glycoprotein IIb/IIIa Inhibitors

Thrombosis of the coronary artery is mediated by platelet aggregation and linkage via glycoprotein IIb/IIIa (GP IIb/IIIa) receptors. Commercially available GP IIb/IIIa inhibitors (abciximab, eptifibatide, and tirofiban) prevent platelet aggregation by blocking fibrinogen from binding to these receptors.[54] Abciximab is a chimeric monoclonal antibody that binds nonspecifically to the GP IIb/IIIa receptor causing an irreversible inhibition. Eptifibatide is a cyclic heptapeptide with a lysine–glycine–aspartic acid (KGD) sequence that binds selectively to the GP IIb/IIIa receptor. Tirofiban hydrochloride is a nonpeptide derivative of tyrosine that binds selectively to the GP IIb/IIIa receptor. While these agents have similar actions, they differ in their modes of action, costs, and indications for use.

The majority of evidence for the efficacy of GP IIb/IIIa inhibitors was derived in anera that predated the routine use of DAPT. As a result, there are little data from the modern era in which GP IIb/IIIa inhibitors have been found to be effective. The EARLY-ACS (Early GP IIb/IIIa Inhibition in Non–ST-Segment Elevation Acute Coronary Syndrome) study randomized 9,492 patients with high-risk NSTEMI (had two or more of the following features: ischemic changes on electrocardiography, elevated cardiac biomarkers, and age >60 years) to either early, routine administration of eptifibatide or early administration of placebo with delayed, provisional administration of eptifibatide.[55] Only 39% of the patients in the delayed/provisional arm received eptifibatide, yet there was no difference in the primary endpoint of all-cause mortality, MI, recurrent ischemia requiring urgent revascularization, or thrombotic bailout at 96 hours (9.3% in early treatment group versus 10% in delayed treatment group; odds ratio 0.92; 95% CI 0.80 to 1.06; p = 0.23). These data correspond with recent contemporary clinical trials such as ON-TIME2 (no significant difference in death, recurrent MI, or urgent target vessel revascularization at 30 days in highdose tirofiban group), HORIZONS-AMI (major bleeding and adverse events were higher in the group randomized to GP IIb/IIIa as compared to bivalirudin), FINESSE (no benefit with prehospital abciximab before primary PCI, either by itself or in combination with fibrinolytic therapy), and a meta-analysis (22 trials in patients undergoing elective PCI with DAPT who received GP IIb/IIIa inhibitors) that showed no effect of GP IIb/IIIa inhibitors in mortality.[23,56–58] Based on these results, ACC/AHA guidelines conclude

that the use of GP IIb/IIIa inhibitors before primary PCI is of uncertain benefit. Therefore, the use of GP IIb/IIIa inhibitors can be considered in selective cases such as in patients with significant thrombus or those in whom DAPT has not been initiated; however, the routine use of GP IIb/IIIa inhibitors is not recommended (Table 47.10).

TABLE
47.10 Recommendations for the Use of GP IIb/IIIa

Class I

1. In patients with UA/NSTEMI undergoing PCI without clopidogrel administration, a GP IIb/IIIa inhibitor (abciximab, eptifibatide, or tirofiban) should be administered. (Level of Evidence: A)

Class IIa

1. In patients with UA/NSTEMI undergoing PCI with clopidogrel administration, it is reasonable to administer a GP IIb/IIIa inhibitor (abciximab, eptifibatide, or tirofiban). (Level of Evidence: B)
2. It is reasonable to start treatment with GP IIb/IIIa receptor antagonists (abciximab, Level of Evidence: A; tirofiban, Level of Evidence: B; or eptifibatide, Level of Evidence: B) at the time of primary PCI (with or without stenting) in selected patients with STEMI.
3. In patients undergoing elective PCI with stent placement, it is reasonable to administer a GP IIb/IIIa inhibitor (abciximab, eptifibatide, or tirofiban). (Level of Evidence: B)

Class IIb

1. The usefulness of GP IIb/IIIa receptor antagonists (as part of a preparatory pharmacologic strategy for patients with STEMI before their arrival in the cardiac catheterization laboratory for angiography and PCI) is uncertain. (Level of Evidence: B)

Adapted from the ACC/AHA guidelines: King SB III, Smith SC Jr, Hirshfeld JW Jr, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guidel0069ne update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. J Am Coll Cardiol. 2008;51:172–209; Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). Circulation. 2006;113:156–175; Kushner FG, Hand M, Smith SC Jr, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2009;54:2205–2241.

Antithrombin Therapies

Heparin Agents

Antithrombotic agents block the coagulation cascade and are necessary when performing coronary interventions in order to prevent coronary artery thrombosis.

Unfractionated heparin (UFH) was the first agent utilized for this purpose. High doses of heparin with intravenous boluses of 100 IU/kg to maintain an activated clotting time (ACT) of 250 to 350 seconds have been used in the past. With improved interventional technology and accumulation of clinical experience, it has been possible to reduce the dose of intravenous UFH to 60 IU/kg plus an infusion of 12 IU/kg/h with a goal PTT of 50 to 70 (ACT of 200 to 250 seconds) in an attempt to reduce bleeding complications.[59] It is necessary to monitor the degree of anticoagulation because heparin binds strongly to plasma proteins resulting in unpredictable levels of antithrombotic effects.

Enoxaparin is a low-molecular-weight heparin that inhibits factor Xa. Administration of enoxaparin gives more consistent plasma levels resulting in a more predictable degree on anticoagulation and does not require routine monitoring. The lack of routine monitoring caused some concern among interventionalists leading to low utilization rates while performing PCI. Due to the evidence of its effectiveness in patients with acute coronary syndromes, it is increasingly utilized in clinical practice (especially for patients with NSTEMI).[60] For patients undergoing PCI, 1 mg of enoxaparin per kilogram should be administered subcutaneously twice a day before angiography. If the most recent subcutaneous dose has been given more than 8 hours earlier, an intravenous bolus of an additional 0.3 mg/kg should be given. An additional intravenous bolus of 0.75 mg/kg should be administered before PCI if the most recent subcutaneous dose has been >16 hours prior. Both approaches appear to be safe and efficacious in patients with ACS, although a concern remains about increased bleeding rates with LMWH use. Additionally, UFH is effectively reversed with protamine, whereas LMWH is only partially reversed. Currently there is no evidence to support a preference for LMWH over UFH.

Bivalirudin

Bivalirudin is a direct thrombin inhibitor and has been suggested as a replacement for UFH because it causes significantly less bleeding when compared with heparin alone in stable patients undergoing PCI, NSTEMI, and STEMI. The ACUITY trial randomized 13,819 patients to UFH or enoxaparin plus a GP IIb/IIIa inhibitor, bivalirudin plus a GP IIb/IIIa inhibitor, or bivalirudin alone.[59] There was no difference in a composite endpoint of death, MI, and unplanned revascularization for ischemia between patients treated with bivalirudin and UFH or enoxaparin plus a GP IIb/IIIa inhibitor (7.8% and 7.3%, respectively; $p = 0.32$). Patients treated with bivalirudin had significantly lower rates of major bleeding (3.0% vs. 5.7%; $p < 0.001$). Similar results in patients with STEMI undergoing PCI were shown in the HORIZONS-AMI trial.[57] The reduction in hemorrhagic complications, cost savings, and ease of administration have established bivalirudin plus provisional GP IIb/IIIa inhibition as an attractive antithrombotic strategy for patients undergoing elective or urgent PCI.

COMPLICATIONS

Improved equipment and increased operator experience have improved PCI outcomes and decreased the risk of complications. In the early days of interventional cardiology, cardiac surgery backup was required given the high rates of acute vessel closure; however, PCI is now routinely performed without cardiac surgery backup. Despite these improvements, complications including cath lab deaths are still seen. The latest statistics from a national quality improvement database report an overall unadjusted mortality rate for PCI of 1.3%.[61] The risk of mortality varies depending on the characteristics of the patients: older patients, women, and patients with diabetes having increased risk associated with PCI.[62] The mortality rate also varies depending on the indication with the mortality rate of elective PCI being 0.4% to 0.7% while the mortality rate of ST-elevation MI is 4.8%. In order to better quantify risk, PCI risk scores have been developed by investigators from the NCDR CathPCI database and Mayo Clinic that are able to provide some idea of preprocedural risk[61,63] (Table 47.11).

TABLE
47.11 Predictors of Mortality in Patients Undergoing PCI Used in Risk Prediction Models

NCDR Risk Score	Mayo Risk Score
Age	Age
Cardiogenic shock	Preprocedural shock
Prior CHF	Left ventricular ejection fraction <60%
Peripheral vascular disease	Peripheral artery disease
Chronic lung disease	
GFR	Serum creatinine level
NYHA functional class IV	Congestive heart failure
STEMI	MI within 24 h
PCI status (elective, urgent, emergent, salvage)	

Adapted from Peterson ED, Dai D, DeLong ER, et al. Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588,398 procedures in the National Cardiovascular Data Registry. J Am Coll Cardiol. 2010;55:1923–1932; Singh M, Rihal CS, Lennon RJ, et al. Bedside estimation of risk from percutaneous coronary intervention: the new Mayo Clinic risk scores. Mayo Clin Proc. 2007;82:701–708.

Renal Failure

Invasive procedures utilizing contrast dye are associated with the development of renal

dysfunction, known as contrast-induced nephropathy (CIN). CIN is most commonly defined as a rise in creatinine by >0.5 mg/dL or a 25% increase from the baseline creatinine. CIN is typically classically described as nonoliguric renal dysfunction; however, oliguria can occur in patients with CIN. The pathophysiology of CIN is not well understood but vasoconstriction and injury to the renal tubules have been proposed as possible explanations.

The incidence of CIN is variable but averages around 12%.[64] This risk is dependent upon both patient and procedural characteristics (Table 47.12). Advanced age, large volumes of contrast dye, cardiogenic shock, and advanced chronic kidney disease have been found to be some of the strongest predictors.[65] The increase in creatinine seen with CIN typically is not seen until 48 hours after angiography, peaks at 5 days postcatheterization, and returns to h1 by days 7 to 10. Patients with CIN typically do not require hemodialysis (incidence is <1%), although the risk of hemodialysis is increased among patients who are at highest risk of developing CIN and receive large amounts of contrast dye.

TABLE
47.12 Risk Factors for the Development of CIN

Patient Characteristics
Chronic kidney disease
Diabetes mellitus
Intra-aortic balloon pump
Congestive heart failure/cardiogenic shock
Increased age
Hypertension
Anemia
Procedural Characteristics
Type of contrast (ionic, high osmolar)
Contrast volume

Modified from Pannu N, Wiebe N, Tonelli M. Prophylaxis strategies for contrast-induced nephropathy. JAMA. 2006;295:2765–2779.

The development of CIN is associated with increased hospital length of stay and is a predictor of long-term mortality in patients undergoing primary PCI. As such, there has been considerable effort placed in exploring strategies to reduce the incidence of CIN. To date, hydration prior to catheterization is the only therapy with convincing evidence of efficacy. There has been some indication that N-acetylcysteine (Muco-myst) may provide benefit; however, the studies examining its use have provided contradictory results. In addition, the majority of these studies have been limited with one or more significant limitations such as small sample size, inadequate controls, etc.65 The ACT trial (Acetylcysteine for Contrast-Induced Nephropathy Trial) provides strong evidence

against its efficacy. In this study, 2,308 patients were randomized to N-acetylcysteine or placebo and there were no differences in the incidence of CIN or serum creatinine elevation seen between the two groups.[66] As such, N-acetylcysteine is not recommended for routine use in the prevention of CIN. In patients at high risk of developing CIN, attempts should be made to provide adequate hydration prior to catheterization and minimize the amount of contrast dye used during the procedures. There is some evidence that selection of contrast material may alter the rate of CIN (see below).

Bleeding

Bleeding is a common complication from PCI that is associated with increased patient discomfort, length of stay, cost, and risk of mortality (both short and long term).[67] While the mechanism linking bleeding with an increased risk of mortality is not well understood, it has been identified in multiple studies.[68,69] The mechanisms for the association of bleeding complications with mortality are likely multifactorial and include the physiology effects of hemorrhage, decreased medication use/adherence after bleeding events, deleterious effects of anemia/red blood cell transfusions, and the increased comorbidities seen in patients who develop bleeding complications.[70–72] Regardless of the etiology, the OASIS-5 and HORIZONS-AMI trials evaluating therapies for the treatment of acute coronary syndrome found that mortality could be decreased through a reduction in the incidence of bleeding. As such, the development of strategies that reduce the incidence of bleeding may improve the outcomes of patients undergoing PCI. The increased emphasis on comparing bleeding risk among PCI strategies and techniques has also led to the development of a standardized bleeding definition that should improve the ability to perform comparative effectiveness research.[73,74]

The incidence of bleeding varies depending on the patient population being studied and the definition used for bleeding. Registries following patients with NSTEMI have found bleeding rates as high as 9% to 12%, while patients undergoing elective PCI have considerably lower risk of bleeding. This illustrates that the characteristics of both the patient and the procedural determine the risk of bleeding. Female sex, baseline anemia, renal dysfunction, diabetes, and the use of GP IIb/IIIa inhibitors, large sheaths, femoral access and intra-aortic balloon pumps have been consistently identified as risk factors associated with increased bleeding complications (Table 47.13).

TABLE
47.13 Factors Associated with Bleeding in Selected Non–St-Elevation ACS

Study	% Invasive	Study Enrollment	Factors Associated with Bleeding[a]	
CURE OASIS-5[69]	28%	34,419	GP **IIb/IIIa inhibitor** Coronary angiogram CABG Intra-aortic balloon pump	**Increasing age** **Increased creatinine** Prior stroke Antithrombotic medication
CRUSADE[85]	Not Reported	74,271	Transient ST-segment elevation BMI Medicaid No family history of CAD HTN Absence of hyperlipidemia Nonwhite vs. white Previous stroke ST-segment depression	**Renal insufficiency** Systolic BP (per 10 mm Hg drop) **Female gender** Diabetes mellitus **Older age** Signs of CHF Heart rate (per 10 beats/min increase) Positive cardiac markers
REPLACE-2[86]	100%	6,002	Intra-aortic balloon pump GP **IIb/IIIa inhibitor** **Age (per 10 y)** **Female gender**	**Decreased GFR** Anemia Low-molecular-weight heparin
ACUITY[87]	100%	13,819	**Age > 75 y** **Female gender** Hypertension Diabetes No prior PCI	Anemia **Renal insufficiency (CrCl < 60 mL/min)** Baseline ST-segment elevation ≥ 1 mm Baseline biomarker elevation **Heparin + GP IIa/IIIb** PCI
PRISM-Plus[88]	90%	1,570	**Female age**	**Decreased creatinine clearance**
GRACE[89]	Not Reported	7,440	**Age (per 10 y increase)** **Female sex** **History of renal insufficiency** History of bleeding Mean arterial pressure (per 20 mm Hg decrease) Diuretic use	Antithrombotic use **GP IIb/IIIa inhibitor** IV inotropic medications Right heart catheterization
Kinnaird et al.[90]	100%	10,974	Intra-aortic balloon pump Procedural hypotension **Age > 70 y**	**GP IIb/IIIa** **Chronic renal insufficiency**

[a]Patient characteristics in **bold** are those found consistently through the majority of studies.

Modified from Cavender MA, Rao SV Ohman EM. Major bleeding: management and risk reduction in acute coronary syndromes. Exp Opin Pharmacother. 2008;9:1869–1883.

The majority of early bleeding events are related to vascular access and hemostasis. Over time, the risk of vascular access complications decrease and gastrointestinal bleeding in the setting of chronic antithrombotic therapy becomes the predominant

etiology of blood loss.[45] Strategies for reducing bleeding, termed by some as bleeding avoidance strategies, thus far have been predominately focused on reducing early bleeding through optimization of procedural pharmacology and procedural techniques. For example, bivalirudin has been found both in the ACUITY trial (NSTEMI) and HORIZONS-AMI to reduce bleeding rates of bleeding.[57, 59]HORIZONS-AMI compared three pharmacologic strategies in patients with ST-elevation ACS: heparin plus GP IIb/IIIa inhibitor, bivalirudin plus GP IIb/IIIa inhibitor, and bivalirudin alone. Patients treated with bivalirudin alone had a 24% lower incidence of major bleeding and combined adverse clinical events (combination of major bleeding or major adverse cardiovascular events—death, reinfarction, target-vessel revascularization for ischemia, and stroke) at 30 days.[57] Further pharmacologic modifications such as utilization of lower levels of anticoagulation with heparin, decreasing the utilization and/or duration of therapy with GP IIb/IIIa inhibitors, and long-term maintenance on low-dose aspirin instead of full strength may be useful in decreasing bleeding complications.[67] Finally, utilizing procedural techniques such as radial artery access and smaller sheath sizes that are associated with lower rates of bleeding provide additional benefit.

PERIPROCEDURAL MYOCARDIAL INFARCTION

There is no standard, universally accepted definition of a periprocedural MI used in clinical studies. The definition has varied over time but most studies now define it as a rise in CK-MB and/or troponin >3x the upper limit h1.[75,76] This definition is widely used despite the fact that there is a poor correlation between troponin elevations and adverse clinical outcomes. This is likely due to the fact that troponin elevations are more sensitive for myocardial damage allowing the detection of myocyte death that is not even detectable on cardiac MRI.[77] Patients who develop a rise in cardiobiomarkers that does not meet the definition for periprocedural MI (1 to 3 x the upper limit of h1 [ULN]) are considered to have periprocedural myonecrosis that has not been closely correlated with adverse outcomes. No criteria have been developed for periprocedural MI in the setting of cardiac biomarkers that were increasing prior to the start of the procedure. Patients with biomarkers that are already elevated (but are stable or declining) prior to the start of the procedure are considered to have a periprocedural MI when the biomarkers increase by >20% from the preprocedural level.

Chest pain following PCI is common and occurs in up to 40% of all patients. The majority of these patients do not develop evidence of periprocedural MI. Observational studies of post-PCI patients have found that the development of Q waves or CK-MB >3 x ULN increases the risk of adverse outcomes and serious PCI-related complications (distal embolization, dissection, side branch occlusion, stent thrombosis). As a result,

some have suggested that periprocedural MIs are simply a reflection of patient comorbidities such as atherosclerotic burden and the complexity of the PCI. This has been illustrated by intravascular ultrasound studies that correlated the degree of atherosclerosis with the development of periprocedural MI. As such, efforts including the use of embolic protection devices when performing PCI in saphenous vein grafts (that frequently have significant atherosclerotic/thrombotic burden) have shown the ability to reduce the incidence of periprocedural MI.

In practice, the debate over the prognostic implications of periprocedural MI and its impact on therapy have kept many providers from routinely checking biomarkers following PCI. Patients who have chest pain following PCI should have cardiac biomarkers checked as significant increases in combination with persistent pain and/or ECG changes may require repeat angiography or treatment with GP IIb/IIIa inhibitors.

TECHNICAL ASPECTS OF ANGIOGRAPHY AND PCI

Covering all the technical aspects of angiography and PCI in detail is beyond the scope of this book and the boards. The following sections attempt to cover the topics that may be seen on the general cardiology board exam.

Access

Catheterization originally was performed through a method known as the Sones technique that involved a cut-down of the brachial artery. As the indications for catheterization grew, accessing the vasculature through the femoral artery was found to be less invasive and associated with lower risks to the patient. Femoral access replaced the Sones technique as the predominant method of catheterization over the past 20 years.[78] Advances in catheter design and improvements in technique have made the routine use of catheterization via the radial artery feasible in routine clinical practice. Data from the NCDR CathPCI database have shown that radial artery catheterization is associated with lower odds of bleeding complications at the expense of increased radiation exposure. While there is a learning curve associated with the adoption of catheterization from the radial artery, increased patient satisfaction and lower rates of vascular complications such as bleeding have increased its acceptance into clinical practice.

Catheters

Catheters commonly used to enter the left coronary circulation are Judkins left (JL) catheters and Amplatz left (AL) catheters. The JL catheter has a double curve with the length of the segment (in centimeters) between the first and second curves that determines the size of the catheter (JL 3.5, 4, 5, or 6 cm). The AL catheter has a preshaped half-circle with a tip extending out of the curve and perpendicular to it, giving the catheter three curves. AL catheters come in three sizes (0.5, 0.75, and 1 cm)

based on the diameter of the half-circle/secondary curve. The increasing use of radial artery catheterization has resulted in the development of new catheters, such as the Jacky and Tiger catheters, specifically designed for accessing the coronary arteries through the arm. These catheters have a double bend similar to the AL catheters but differ in the design of the tip. The Jacky (tip which points slightly outward) and Tiger catheter (straight tip) are able to engage both the left and right coronary artery by advancing the catheter into the aortic root and then manipulating the catheter into the different coronary ostia.

During catheterization from the femoral artery, the JL4 is typically used as a starting catheter as it will be successful in engaging the left coronary artery in the majority of patients. Patients with a large aortic root, tortuous aorta, or large body habitus may require a larger catheter (JL5, JL6). Coronary artery anomalies may require the use of different catheters. For example, when the left main artery is located superiorly, a smaller JL catheter (JL3.5) or AL catheter is frequently used. Inferior origins of the left main may require a multipurpose catheter that has a downward tip. Short left main arteries or separate ostia for the left anterior descending (LAD) and left circumflex are more easily accessed using AL catheters. The LAD artery can be cannu- lated in these circumstances by clocking and advancing the catheter while the left circumflex artery can be accessed by counterclocking the catheter. The most common catheters used to enter the right coronary artery are the Judkins right (JR) catheters, 3DRC, and Amplatz right (AR). These catheters can also be used to access saphenous vein grafts and the subclavian artery.

Contrast Material

Coronary angiography utilizes contrast agents that allow for the visualization of the coronary vasculature. Currently available contrast agents contain iodine that more readily absorbs x-rays as compared to the surrounding tissue. This differential absorption of radiation results in the ability of the contrast agents to provide contrast and visualization of the coronary arteries. Contrast agents are divided based on osmolality (high, low, isosmolar) (Table 47.14). The majority of contrast agents used in current practice are low osmolar or isosmolar because high-osmolar agents have been found to have more hypotension, myocardial depression, heart failure, and electrical abh1ities (bradycardia, QRS and QT-interval prolongation, ventricular fibrillation).

TABLE
47.14 Summary of the Various Types of Contrast Agents Used in Coronary Angiography

Class	Trade Name	Generic Name	Iodine (mg/mL)	Osmolality (mOsm/kg)[a]	Sodium (mEq/L)
Ionic					
High osmolar	MD 76 R	Sodium diatrizoate	370	2,140	190
	Angiovist 370	Sodium diatrizoate	370	2,076	150
	Hypaque	Sodium diatrizoate	370	2,076	160
Low osmolar	Hexabrix	Ioxaglate	320	600	157
Nonionic					
Low osmolar	Omnipaque	Iohexol	350	844	Trace
	Optiray 320	Ioversol	320	702	Trace
	Oxilan 350	Ioxilan	350	695	Trace
	Isovue 200	Iopamidol	200	413	Trace
Isosmolar	Visipaque 320	Iodixanol	320	290	Trace

[a]Blood osmolality is 275 mOsmol/L.

Adapted from Askari AT, et al., eds. Introductory guide to cardiac catheterization. Philadelphia, PA: Lippincott Williams & Wilkins.

Prior ACC/AHA guidelines recommended the use of isosmolar contrast agents (i.e., iodixanol) in patients with chronic kidney disease. This was based upon the RECOVER trial that randomized 300 patients with a creatinine clearance <60 mL/min to either a low osmolar contrast agent (ioxaglate) or an isosmolar agent (iodixanol). The primary endpoint was CIN, defined as an increase in serum creatinine by 25% or >0.5 mg/dL. Patients treated with iodixanol had significantly lower rates of CIN (7.9%) than patients treated with ioxaglate (17.0%; p = 0.021).[79] These recommendations have since been modified after the publication of the CARE study. This study randomized 482 patients with a creatinine clearance between 20 and 59 mL/min to iopamidol and iodixanol. Rates of CIN (defined as increase in serum creatinine ≥0.5) were similar in the two groups (4.4% after iopamidol and 6.7% after iodixanol) suggesting no difference between the agents.[80] The lack of benefit with low osmolar agents was further supported with a subsequent meta-analysis.[81] This analysis included 16 randomized controlled trials and 2,763 patients and did not find isosmolar agents to be protective against CIN when compared to all low osmolar agents except ioxaglate and iohexol. As such, current ACC/AHA guidelines have been modified to state that patients with chronic kidney disease can be treated with either an isosmolar contrast agent or a low osmolar contrast agent other than ioxaglate or iohexol.

Stents

Initial attempts at percutaneous revascularization with angioplasty were hindered by a high-rate acute vessel closure requiring cardiac surgery (often due to dissection). In 1993, the FDA approved the Gianturco–Roubin stent, making it the first coronary stents approved for routine clinical use.[6]Since that time, coronary artery stenting has undergone many advances and now serves as the predominant form of coronary

revascularization. Initial stents were hindered by the proliferation of smooth muscle at the site of injury (known as restenosis). In response to this restenosis, stents coated with antiproliferative agents such as sirolimus, paclitaxel, everolimus, and zotarolimus were developed. As compared to bare metal stents, drug-eluting stents (DESs) greatly reduce the risk of in-stent restenosis and target lesion revascularization.

Some observational studies have suggested that drug-eluting stents have a mortality benefit.[82] A mortality benefit has not been demonstrated in randomized data and is likely due to unmeasured differences in the two groups.[83] Given the concern over stent thrombosis and the requirement that patients who receive DES be treated with DAPT for up to a year, it is important to understand the patient populations who benefit most from drug-eluting stent implantation. Patients with diabetes, small vessel diameter (<3.0 mm), and long lesion length (>30 mm) are those patients who have consistently been shown to have the highest rate of restenosis and derive the most benefit from treatment with drug-eluting stents.[84]

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QUESTIONS AND ANSWERS

Questions

1. A 73-year-old man underwent percutaneous coronary intervention (PCI) after a non–ST-elevation myocardial infarction (NSTEMI). He was pretreated with 325 mg of aspirin and 600 mg of clopidogrel, plus bivalirudin during the intervention. A DES is deployed into the mid-left anterior descending (LAD). Following the procedure, which of the following antiplatelet regimens is most appropriate?
   a. Continue 325 mg aspirin and 75 mg clopidogrel for 12 months.
   b. Continue 81 mg aspirin for life and clopidogrel 75 mg for 6 months.
   c. Continue 81 mg aspirin for life and clopidogrel for at least 12 months.
   d. Continue 81 mg aspirin for 12 months and clopidogrel 75 mg for 6 months.

2. A 62-year-old woman with stable angina has presented for elective PCI to a known focal stenosis in a moderate-sized first diagonal branch. She is not taking medications and has a severe allergy to shellfish (hives), and she also reports an allergy to aspirin although she cannot specify the reaction. Which of the following statements regarding patient management is correct?
   a. Administer 100 mg hydrocortisone IV, 50 mg diphenhydramine (Benadryl) IV, and 600 mg clopidogrel orally before the procedure, and then proceed with the scheduled intervention.
   b. Administer 40 mg methylprednisolone IV, 50 mg diphenhydramine (Benadryl) IV, 600 mg clopidogrel orally, and proceed with the scheduled intervention.
   c. Administer 100 mg hydrocortisone IV, 50 mg diphenhydramine (Benadryl) IV, 325 mg aspirin, and 300 mg clopidogrel orally before the procedure, and then proceed with the scheduled intervention.
   d. Consult an allergy specialist and postpone the intervention.

3. A 50-year-old man presents to the emergency room (ER) about 100 minutes after the onset of chest pain. The pain is substernal, radiates to the left arm, and is associated with vomiting and diaphoresis. On examination, the patient is tachycardic with a heart rate of 104 and hypertensive with blood pressure of 150/88. An electrocardiogram showed 3 mm ST elevation in the anterior and lateral leads. Symptoms were not relieved with sublingual nitroglycerin or beta-blocker therapy. An IV nitroglycerin drip was titrated to control the patient's symptoms. The closest interventional cardiology center is 120 minutes away. The patient has asked about the therapeutic options at this point. What can you tell him about the various therapeutic modalities?
   a. Primary PCI is recommended over thrombolytics because PCI has short-term mortality benefit, reduced reinfarction risk, and reduced risk of stroke, regardless of duration of symptoms and time required to PTCA.
   b. Thrombolysis followed by transfer to center with PCI capabilities
   c. Half-dose thrombolysis should be recommended; then the patient should be transferred for PCI.
   d. Thrombolysis. Transfer to center with PCI capabilities if chest pain and ECG changes do not resolve within 3 hours.

4. A 62-year-old woman, with ongoing tobacco abuse, diabetes, hypertension, and hyperlipidemia,

presents to the ER with a 2-day history of intermittent chest pain. On examination, she is tachycardic with a heart rate of 101 beats/min (bpm) and hypertensive with a blood pressure of 160/100 mm Hg. The patient does not have any signs of heart failure. An electrocardiogram showed 2-mm depression in V_2–V_6. The patient is started on heparin and given IV metoprolol and nitroglycerin. In addition, she was started on an eptifibatide infusion. The patient remained asymptomatic until her coronary angiogram. The left heart catheterization showed 90% stenosis in the proximal third of the LAD and 80% stenosis in the proximal RCA, with 70% disease in the middle circumflex artery. The best plan of treatment for this patient is:

a. Complete revascularization with multivessel PCI
b. Referral for three-vessel CABG
c. PCI to the LAD with staged intervention to the RCA and LCx
d. Medical management with no PCI or CABG

5. A previously healthy 78-year-old male presents to the emergency department (ED) complaining of chest pain and shortness of breath. His initial blood pressure is 79/40 and his heart rate is 117 bpm. His initial ECG shows 3 mm ST elevations in V_1–V_4 and his chest x-ray is notable for pulmonary edema. What is the next best treatment option?
   a. Medically stabilize with IV diuretics and antithrombotic agents. Consider revascularization once medically stabilized.
   b. Fibrinolytic therapy
   c. Urgent angiography with goal to provide revascularization therapy
   d. Intubate and place Swan Ganz catheter to help determine etiology of illness. Place intra-aortic balloon pump if the patient appears to have cardiogenic shock with low cardiac index and elevated pulmonary capillary wedge pressure.

6. A 56-year-old female with hypertension, obesity, obstructive sleep apnea, and fibromyalgia is undergoing angiography for chest pain. She describes her chest pain as stabbing in nature. It occurs mostly when performing housework or in periods of increased stress. It is not associated with shortness of breath. Her primary care physician evaluated her with a nuclear stress test that showed no evidence of ischemia; however, she continued to have this discomfort. The patient was scheduled for angiography to provide a definitive workup for her persistent chest pain. Angiography was notable for a 60% stenosis in the left circumflex artery and mild diffuse coronary artery disease in the LAD artery and right coronary artery. The most appropriate management is:
   a. Medical therapy with aspirin and statin as there is no indication for revascularization.
   b. Begin secondary prevention medications and schedule repeat stress test in 1 year.
   c. PCI to the left circumflex
   d. Perform FFR of the left circumflex.

7. An 85-year-old female with a creatinine of 1.6 is undergoing angiography after a positive stress test. Which of the following interventions reduces her risk of contrast-induced nephropathy (CIN)?
   a. Admission the night before catheterization for N-acetylcysteine and sodium bicarbonate infusion
   b. Biplane angiography and iodixanol contrast
   c. Hydration with h1 saline prior to the catheterization
   d. Discontinuation of lisinopril 1 week prior to angiography

8. A 67-year-old male with diabetes and hypertension presents with three episodes of chest pain at rest over the past 24 hours. He is currently chest pain–free. His home medications include aspirin, lisinopril, and simvastatin. He continues to abuse tobacco. His first set of cardiac biomarkers is notable for a troponin of 0.94 and a CK-MB of 54. The next step in the management of this patient is:
   a. Give 325 mg of aspirin and 600 mg of clopidogrel and begin infusion of eptifibatide and heparin. Schedule angiography as soon as possible (urgent, not emergent).
   b. Give 325 mg of aspirin and 600 mg of clopidogrel and begin infusion of heparin. Schedule stress test once cardiac enzymes begin to decline.
   c. Give 325 mg of aspirin and 600 mg of clopidogrel and begin infusion of heparin. Schedule

angiography as soon as possible (urgent, not emergent).
d. Give 325 mg of aspirin and 600 mg of clopidogrel and begin infusion of eptifibatide and heparin. Schedule stress test once cardiac enzymes begin to decline.

9. Which of following is not a relative contraindication for the use of prasugrel in patients with acute coronary syndrome undergoing PCI?
   a. Weight <60 kg
   b. Previous TIA/CVA
   c. Creatinine clearance <30
   d. Age ≥75

10. Which is following statements is false regarding the indications for routine PCI immediately following administration of fibrinolytic therapy for patients with ST-elevation myocardial infarction (STEMI)?
   a. Patients with hemodynamic instability following fibrinolytic therapy should undergo rescue PCI.
   b. Patients with sustained, unstable ventricular tachycardia following fibrinolytic therapy should undergo rescue PCI.
   c. Patients with <50% resolution of ST-segment elevation 30 minutes after fibrinolytic therapy should undergo rescue PCI.
   d. Patients with <50% resolution of ST-segment elevation 90 minutes after fibrinolytic therapy should undergo rescue PCI.

Answers

1. Answer C: There is no indication for high-dose aspirin therapy following PCI based on the CURRENT OASIS-7 trial. Patients with prior PCI should continue on low-dose aspirin for the remainder of their lifetime. The length of time in which clopidogrel is necessary is currently unknown. Prior recommendations suggested that 3 to 6 months (depending on the type of stent) of thienopyridine therapy was sufficient; however, there was a small but potentially devastating risk of late-stent thrombosis. Given this risk of stent thrombosis, thienopyridines are recommended for at least 1 year. Patients at low risk of bleeding can continue therapy past 1 year, but the optimal length of therapy will not be known until the completion of the ongoing DAPT trial.
2. Answer D: Consult an allergy specialist and postpone the intervention. Manifestations of aspirin sensitivity such as exacerbations of respiratory tract disease and urticaria can occur in up to 10% and 0.2% of the general population, respectively. An urgent intervention could be undertaken with the pharmacologic therapy described in the second option. However, an elective intervention should be postponed, awaiting appropriate workup and desensitization. There is little or no experience with aspirin desensitization in patients with aspirin-induced anaphylaxis. Potent platelet inhibitors, such as prasugrel and clopidogrel, can be used in patients with aspirin allergy.
3. Answer B: Current American College of Cardiology/American Heart Association (ACC/AHA) guidelines for management of patients with STEMI are dependent on the duration of symptoms, mortality risk of the STEMI, the risk of bleeding, and the difference between time to PCI and time to thrombolytics. PCI is recommended over thrombolysis when experienced operators restore blood flow in <90 minutes. The patient in this question is relatively young, with a large STEMI that has a high mortality risk. He has been having symptoms for 80 minutes and requires 120 minutes or more to have perfusion established with PCI. He is hemodynamically stable. Delayed treatment affects outcome negatively, whether treatment is PCI or thrombolytics. Thrombolysis is highly effective in restoring coronary flow in STEMI, particularly when the patient has presented within 3 hours of symptoms. Data from the National Registry of MI showed increased mortality when PCI is delayed beyond 2 hours. Hence, this patient will likely have better outcome if he receives thrombolysis. Following thrombolysis, he should be transferred to a center with PCI capabilities for angiography.
4. Answer B: The patient is diabetic with multivessel coronary artery disease. CABG has been shown to provide a survival benefit over PTCA according to the BARI trial. However, in the PCI era, one could recommend PCI with stenting in patients with low/immediate SYNTAX score because there was no survival benefit of CABG over PCI shown in the SYNTAX trial. Patients treated with PCI are more likely to require further revascularization and more antianginal medications; hence, the current appropriateness

criteria for PCI give CABG an appropriate rating, while PCI is given an indeterminate rating.

5. Answer C: The patient is clearly in cardiogenic shock due to a large anterior myocardial infarction (MI). Placement of a Swan Ganz catheter would only delay definitive therapy with revascularization. The SHOCK trial showed that patients with cardiogenic shock benefit from emergent revascularization when compared to initial medical stabilization and therapy. While the SHOCK trial did not show definite benefit for patients older than 75 years, there is no reason to suggest that a previously well 78-year-old patient would not derive similar benefit. Observational studies of elderly patients undergoing revascularization for cardiogenic shock have suggested no increased harm in this population.

6. Answer D: The patient has a moderately severe stenosis in the left circumflex. While her symptoms are somewhat atypical, women are less likely to have classic stable angina. The normal stress test is reassuring; however, direct measurement of the physiologic significance of the stenosis is a useful tool. The FAME trial showed that deferring intervention in patients with an FFR of >0.80 is safe and reduces the utilization of PCI. The use of FFR-guided PCI in patients such as this reduces the use of unnecessary PCI while utilizing PCI in those patients with lesions resulting in limitation of coronary perfusion. Based on the results of the COURAGE trial, it is not unreasonable to pursue medical therapy (Choice A); however, the patient should be started on an antianginal therapy such as calcium channel blocker, nitrate, etc. PCI to the left circumflex is not indicated given her atypical symptoms without some evidence of physiologic significance (i.e., stress test, FFR, IVUS).

7. Answer C: The only strategy proven to reduce CIN is adequate hydration prior to angiography. Iodixanol, an isosmolar/nonionic contrast dye, has some evidence that it reduces CIN; however, when compared to iopamidol, a low osmolar/nonionic contrast dye, there was no difference in CIN. W-acetylcysteine has not been shown in large studies to reduce CIN when compared to simple hydration. While angiotensin-converting enzyme inhibitors should be discontinued if CIN develops, there is no evidence that discontinuing these medications will prevent CIN.

8. Answer D: His TIMI risk score is 5 (age >65, three or more risk factors for CAD, two or more episodes of chest pain, aspirin use within 7 days, and positive cardiac bio-markers). Patients with TIMI risk score >2 benefit from an early invasive revascularization strategy. Based on the EARLY-ACS trial, there is no indication for glycoprotein IIb/IIIa inhibitors (GP IIb/IIIa inhibitors) at this time. GP IIb/IIIa inhibitors can be safely reserved for provisional use in the cath lab if necessary or in patients who have not had thienopyridine pretreatment.

9. Answer C: The TRITON TIMI-38 trial showed that patients with ACS undergoing PCI who were randomized to prasugrel had a 19% reduction in death, nonfatal MI, or nonfatal stroke when compared to patients randomized to clopidogrel. However, patients with age ≥75 years, weight <60 kg, or a previous TIA/CVA had less efficacy and more bleeding events. As a result, prasugrel is contraindicated in these patient populations.

10. Answer C: ST-segment resolution is a frequently used but relatively poor marker of the success of fibrinolytic therapy. Patients who are otherwise stable but have persistent ST-segment elevations on electrocardiograms taken immediately after the administration of fibrinolytics should be monitored and not proceed with rescue PCI as long as they do not develop hemodynamic or electrical instability. If ST segments have seen >50% resolution after 90 minutes, rescue PCI should be performed.

SECTION VIII ■ AORTA/PERIPHERAL VASCULAR DISEASE

CHAPTER

Diseases of the Aorta

Gian M. Novaro

Diseases of the aorta account for significant cardio-vascular morbidity and mortality. The incidence of these diseases is expected to rise with the increasing age of the population. Diagnostic evaluation of aortic disorders has vastly improved over the last two decades, allowing for earlier diagnosis and therapeutic intervention. This chapter summarizes the major disease entities affecting the aorta.

ANATOMY OF THE AORTA

The aorta is the main conduit and reservoir of blood in the body. It is an elastic artery composed of three layers:

1. The intima, which includes the single-layered endothelium
2. The media, which is the thickest layer of the aortic wall. It is composed of sheets of elastic tissue and collagen, which provide the aorta its tensile strength and distensibility. Smooth muscle cells and ground substance are also present. The components of the media are organized into functional units known as lamellae.
3. The adventitia, which is composed of loose connective tissue and contains nerves and the vasa vasorum, which provides the main blood supply to the aortic wall. Elastin, collagen, and fibroblasts are also present.

Anatomically, the aorta is divided into two main subcomponents:

1. The thoracic aorta consists of the aortic root (from the aortic annulus, including the sinuses of Valsalva, up to the level just above the sinotubular junction), the ascending aorta (average diameter 3 cm), the arch, and the descending thoracic aorta

(average diameter 2.5 cm—begins after the origin of the left subclavian artery).

2. The abdominal aorta, which is the part of the descending aorta after it passes through the diaphragm. The abdominal aorta (average diameter 2.0 cm) is further classified as either suprarenal or infrarenal.

PATHOLOGIC PROCESSES

Cystic Medial Degeneration

Cystic medial degeneration is an important predisposing factor to diseases of the aorta, particularly the ascending aorta. It is characterized by smooth muscle cell loss and apoptosis plus fragmentation of elastic fibers within the media of the aortic wall. Basophilic ground substance occupies these areas of structural defects, which are incorrectly termed cysts. This degenerative process also extends to the elastic components of the adventitial layer. The weakened aortic wall is prone to aneurysm formation and dissection. This degenerative process, which may be determined genetically, is seen classically in connective tissue diseases such as Marfan, Loeys-Dietz, and Ehlers–Danlos syndrome. However, various degrees of degeneration can be seen in patients without these disorders, occurring as an idiopathic variant, in familial syndromes, or as an acquired form. Hypertension and advancing age are associated with the latter. Varying degrees of cystic medial degeneration can also be seen in genetically predisposed aortas in association with congenital abnormalities including bicuspid or unicuspid aortic valve, aortic coarctation, Turner syndrome, and Noonan syndrome.

Atherosclerosis

Atherosclerosis appears to play a significant role in diseases of the aortic arch, descending thoracic and abdominal aorta. Atherosclerosis can result in weakening of the aortic wall, making it prone to aneurysm formation or dissection.

The development of aortic atherosclerosis is associated with the traditional cardiac risk factors of smoking, hypertension, hyperglycemia, and atherogenic lipoproteins. Atherosclerosis can also result in formation of complex atheromatous plaques, which are prone to embolization, resulting in cerebral and peripheral arterial events.

Inflammatory Disorders

Inflammatory disorders represent a third broad category in the etiology of aortic diseases. These can occur in isolation or in the context of systemic disorders.

Trauma

Aortic injury from trauma usually occurs as a result of deceleration injuries. It frequently occurs at the level of the left subclavian artery near the aortic isthmus or near the diaphragm, both points of attachment. If the patient survives, injury can progress to form a chronic pseudoaneurysm.

AORTIC DISSECTION

Aortic dissection comprises one of the more ominous acute aortic syndromes (also known as acute thoracic pain syndromes), which include the dissection variants of penetrating aortic ulcers, intramural hematomas, and symptomatic aneurysms. It involves cleaving of the aortic wall, resulting in the formation of an aortic false lumen, which courses along with a true lumen.

The hallmark of aortic dissection is an intimal tear that permits access of pulsatile high-pressure blood into the aortic media, separating it from the basal layers (Fig. 48.1). Typically, the so-called intimal flap is usually an intimal–medial flap.

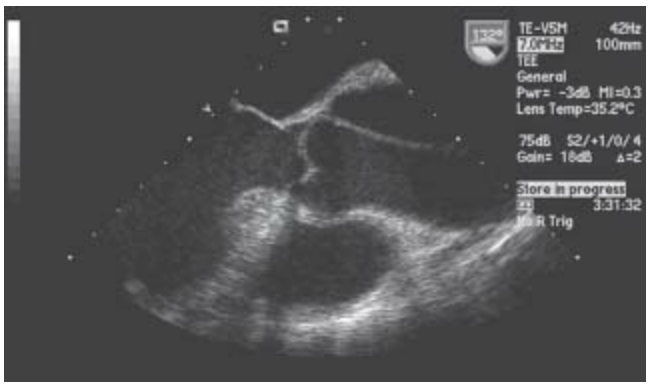

FIGURE 48.1 TEE in a long-axis view that shows a large dissection flap in the ascending aorta extending from the level of the aortic sinuses.

The initiating event of dissection may be a tear in the intima. Alternatively, primary rupture of the vasa vasorum may result in an intramural hematoma that leads secondarily to an intimal tear as blood vents from the intramural space (Fig. 48.2). Regardless of the initiating event, the force of blood flow propagates the dissection antegrade (and less commonly retrograde), a variable extent along the vessel, cleaving the aortic wall usually along the outer one-third of the medial layer.

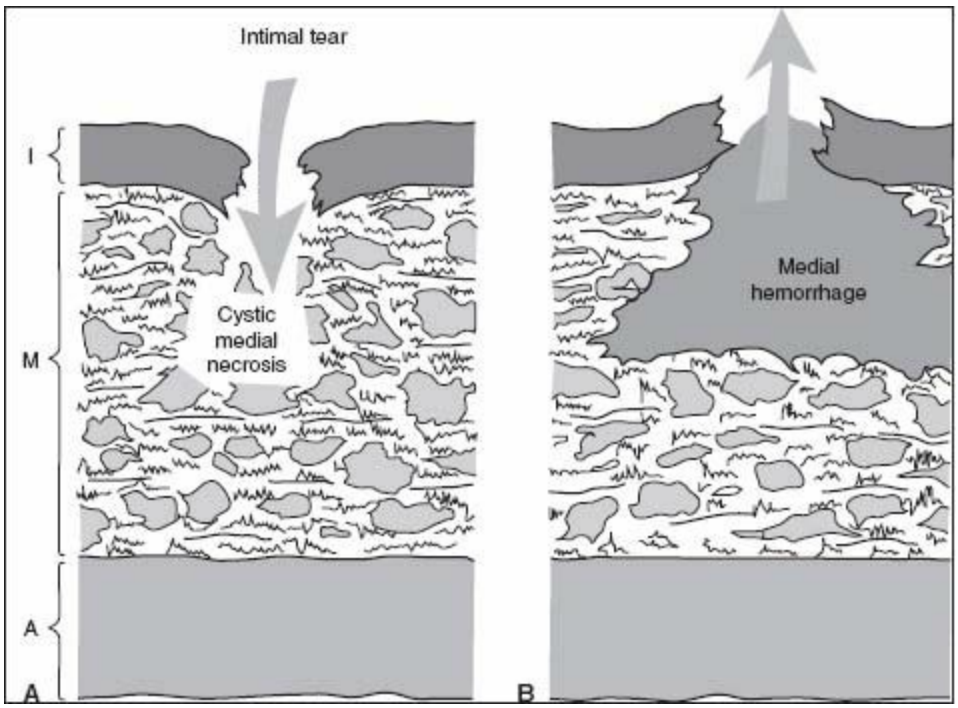

FIGURE 48.2 Schematic representing the initiating event of aortic dissection. Panel **(A)** shows a tear in the intima. Panel **(B)** shows primary rupture of the vasa vasorum, secondarily leading to an intimal tear as blood vents from the intramural space.

Classification

Dissections are classified by their location of origin and how far along they extend in the aorta. There are two important classification systems: the DeBakey system and the Stanford system (Table 48.1; Fig. 48.3). Dissections are also classified by their duration. Acute dissections are those of <2 weeks' duration after symptom onset; chronic are those that have been present for more than 2 weeks.

TABLE
48.1 Classification of Aortic Dissections

Classification System	Extent of Aortic Involvement
DeBakey	
Type I	Originates in ascending aorta, propagates to involve the descending aorta
Type II	Confined to ascending aorta
Type IIIa	Confined to descending thoracic aorta
Type IIIb	Involves the descending aorta, extending to abdominal aorta
Stanford	
Type A	Involves the ascending aorta
Type B	Restricted to the descending aorta

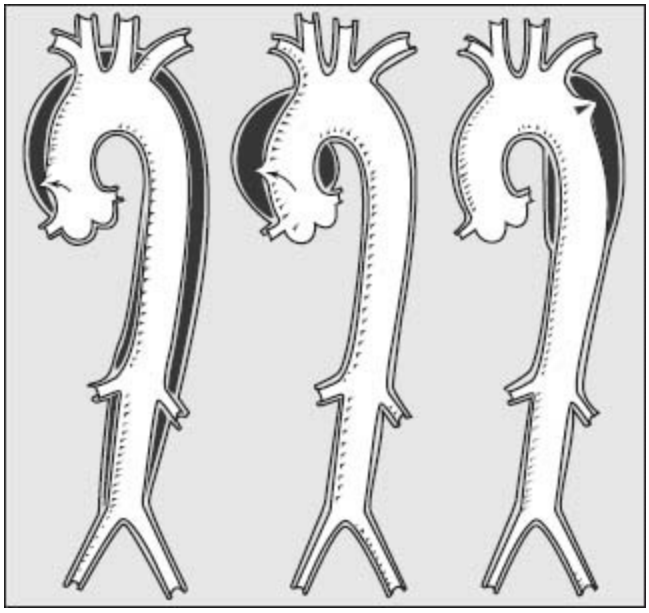

FIGURE 48.3 Diagram showing the types of aortic dissection by the DeBakey classification. Shown are types I, II, and IIIa, from left to right.

Clinical Presentation

Dissections typically present between the fifth and seventh decades of life, with a male preponderance. Patients typically present with the acute onset of pain, present in up to 95% of cases. Pain is often most severe at its onset and described as a " tearing," " ripping," or " stabbing" sensation. Often the pain is migratory, a crucial component of the history, reflecting propagation of the dissection. Involvement of the ascending aorta results in anterior chest or neck pain, with intra-/subscapular pain with involvement of the descending thoracic aorta, and lower back and left flank pain with the thoracoabdominal aorta.

Hypertension upon presentation is common, more so in distal dissection, although hypotension can be seen if complications have developed, particularly in proximal dissections. The dissection may compromise flow to the great vessels, and pulse deficits (these can be transient, as the dissection flap can oscillate) may be present. Actual blood pressure may not be appreciated if the arm utilized has compromise of the brachial vasculature (pseudohypotension).

If the dissection involves the aortic root, commissural involvement of the aortic valve can lead to aortic insufficiency. Dilatation of the root and aortic annulus, without leaflet involvement, can also lead to aortic valve insufficiency. A diastolic murmur will be evident in these cases.

Dissections can involve the ostia of the coronary arteries, resulting in acute myocardial ischemia and infarction (present in 2% to 3% of cases). The right coronary artery ostium is more commonly affected than the left main. The dissection can extend proximally into the pericardial space, resulting in pericardial effusion and tamponade, a

common mechanism of syncope and hypotension in dissection. A pericardial friction rub can be a clue to the presence of hemopericardium. Rupture into the pericardial space represents the most common mode of death in patients with aortic dissection. Acute lower-extremity, renal, or mesenteric ischemia can be seen in descending aortic dissections. Focal neurologic deficits can occur with involvement of the great vessels. Compromise of spinal artery perfusion may result in paraparesis.

Although chest pain and pulse deficits are classically described, it is important to recognize that <20% of patients present with these findings. Therefore, a high clinical suspicion for dissection is paramount.

Diagnostic Testing

The chest x-ray can be normal in cases of dissection. A well-recognized finding is mediastinal widening, present in about 60% of cases. Rupture into the pleural or pericardial space manifests as pleural effusions or an enlarged cardiac silhouette (the latter may also be present, as a result of chronic aortic insufficiency). The electrocardiogram may be normal, but it often shows nonspecific ST–T-wave changes. Involvement of the coronary artery ostia may result in ST-segment elevation, representing an acute myocardial injury pattern. Transthoracic echocardiography can on occasion identify a proximal or even distal dissection flap. Even if a flap is not seen, the presence of aortic dilatation, aortic insufficiency, and/or an unexplained pericardial effusion can be important clues in the diagnostic consideration of a patient with chest pain.

More definitive diagnostic modalities include transesophageal echocardiography (TEE), computed tomography (CT), and magnetic resonance angiography (MRA). Each has relative advantages and disadvantages, but all have excellent sensitivity and specificity (Table 48.2).

TABLE
48.2 Comparison of Imaging Modalities for Aortic Dissection

Modality	Advantages	Disadvantages
TEE	Portability Assess valvular function Assess ventricular function No contrast agent	"Blind spot": ascending aorta at level bronchi crosses esophagus Difficulty in assessing the great vessels Difficulty in diagnosing intramural hematoma Invasive procedure
CT	Assess great vessels and branch vessels	Lack of valvular and ventricular function assessment Lack of portability IV contrast agent required
MRA	Detailed resolution of aorta (i.e., intramural hematoma) in addition to assessing branch vessels Contrast agent without nephrotoxicity	Lack of portability Access to scanners Cost
Angiography	Assess coronary anatomy (controversial whether this should be done prior to surgery for dissection)	Invasive Risk and difficulty in accessing true lumen Contrast agent required

TEE, transesophageal echocardiography; CT, computed tomography; MRA, magnetic resonance angiography.

Angiography is less commonly utilized for the primary diagnosis of aortic dissection. The test of choice is often dependent on expedited availability and expertise at the center where the patient is evaluated. An important caveat is that in most patients, more than one test may be required. If the clinical suspicion is high enough and the initial test is negative or equivocal, then consideration should be given to performing another confirmatory test.

Management

Anti-impulse medical therapy should be initiated as soon as the diagnosis of dissection is considered, even while waiting confirmatory diagnostic testing. In patients who are hypertensive, intravenous beta-blockade followed by sodium nitroprusside is the treatment of choice. Beta-blockade should be initiated prior to sodium nitroprusside to avoid a rise in cardiac contractility and dp/dt associated with the isolated use of vasodilators. In the absence of hypertension, beta-blockers can be used alone. For patients with ascending aortic dissections, these are temporizing agents while preparing for definitive surgical therapy. For patients with descending dissections, these agents are first-line therapy, before longer-acting oral agents are initiated. Intravenous nondihydropyridine calcium antagonists such as verapamil and diltiazem are alternatives for those who cannot tolerate beta-blockers.

Dissections that involve the ascending aorta (proximal, type A) require urgent surgical therapy, as there is a very high early mortality rate (approaching 1% to 2% per hour for the first 24 to 48 hours). Even with timely surgical intervention, the mortality rate of proximal aortic dissection approaches 25%.

An important management point arises with patients who have pericardial effusion or tamponade in association with a proximal dissection. These patients should not

undergo percutaneous pericardiocentesis, unless they are in absolute extremis. The evacuation of pericardial blood by such a route has been associated with aortic rupture and increased mortality, perhaps secondary to dissection extension and/or aortic rupture as blood pressure and dp/dt increase after tamponade resolution. Pericardial access should be obtained in the operating room, with the institution of cardiopulmonary bypass.

Dissections that involve the descending aorta (distal, type B) should be initially treated medically. Data suggest that medical therapy is the preferred initial treatment, with surgery guided by a complication-specific approach. This is because acute aortic surgery is associated with a high mortality and paraplegia rate (inadequate protection of the spinal arteries). Surgery should be considered for the following indications: evidence of malperfusion syndromes (organ ischemia secondary to compromise of the branch vessels); persistent pain; aneurysm formation, particularly if saccular; and retrograde dissection to a proximal extent. Alternatively, aortic fenestration, surgical or percutaneous, can also be considered for organ or limb malperfusion in carefully selected patients.

Distal (type B) dissections in Marfan syndrome patients carry a poor prognosis and have thus led to recommendations of early aortic surgery.

Aortic Dissection in the Young

Dissections occurring in younger patients (<40 years old) typically occur in the context of connective tissue disorders such as Loeys-Dietz, Marfan, or Ehlers–Danlos syndrome. Other conditions involving younger patients and dissection include congenital bicuspid aortic valve, patients with prior aortic surgery, or women in the peripartum period. During late pregnancy, it is thought that hormonal changes and a loosening in the ground substance of connective tissue can predispose to a heightened risk of dissection.

Chronic Aortic Dissection

Chronic dissection patients (present for >2 weeks) have survived the period of increased mortality. They can often be managed medically, even in the presence of a proximal dissection. However, their aortas often dilate and are at higher risk for aneurysm formation because of the thinned aortic wall as a result of dissection.

A complication-specific approach can be used for chronic dissection patients to guide elective surgical therapy: recurrent pain; aneurysm formation, particularly if saccular; and retrograde dissection extension to a proximal extent. Serial follow-up imaging (usually with CT or MRA), initially at shorter intervals, is vital in these patients because of their weakened aortic walls.

Iatrogenic Aortic Dissection

Special mention should be afforded to iatrogenic dissections. Angiographic catheters

and guidewires can disrupt the intima and result in dissections anywhere along the aorta's course. These typically result in retrograde dissections, and the false lumens may thrombose spontaneously if dissections are limited. Catheter-related dissections are most often distal, Type B injuries and can often be managed medically unless the dissection is extensive (Fig. 48.4).

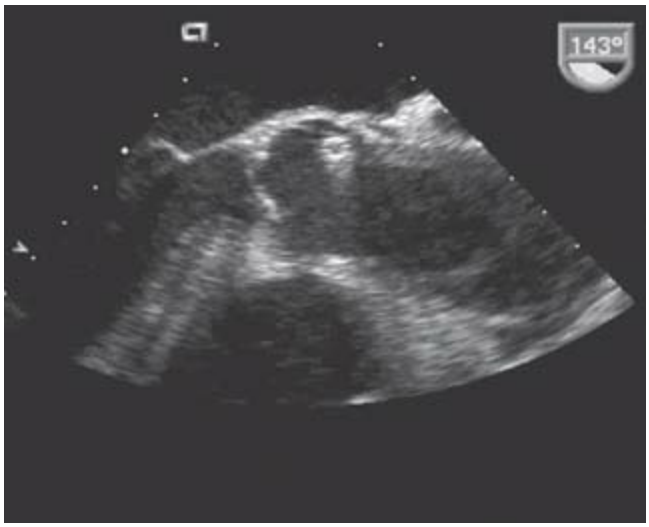

FIGURE 48.4 TEE in a long-axis view demonstrating a case of iatrogenic dissection. A bare metal stent is entrapped in the left main trunk and has caused a retrograde dissection to the aortic sinuses with antegrade propagation distally to the descending thoracic aorta (not shown).

Dissections can also occur during aortic cross clamping, cannulation, or manipulation during cardiac surgery. Such dissections are often proximal, Type A dissections, and are diagnosed and treated urgently and successfully at the time of surgery.

INTRAMURAL HEMATOMA AND PENETRATING AORTIC ULCER

Intramural hematoma and penetrating aortic ulcer are two aortic dissection variants that vary from classic dissection by the absence of a classic intimal flap. Recent advances in diagnostic imaging modalities have led to an increased awareness and better understanding of these entities.

Intramural Hematoma

Intramural hematoma consists of a noncommunicating blood collection in the aortic wall. Unlike a true dissection, there is no loss of intimal continuity, no entry tear, and thus no intimal flap. The pathophysiology may be related to rupture of the aortic vasa vasorum.

By TEE, intramural hematoma is characterized by absence of a dissection flap, a

regional crescent-shaped thickening of the aortic wall usually >0.7 cm, and central displacement of intimal calcium (Fig. 48.5). At times, intramural echolucencies representing noncommunicating pockets of fresh blood can be seen. Distinguishing intramural hematoma from severe atheroma, a thrombosed false lumen, or aneurysm with mural thrombus can be difficult. Angiography is of limited diagnostic accuracy in the evaluation of hematomas, as it fails to image the aortic wall. If the clinical history is concerning, a negative TEE should not represent the final diagnostic evaluation. CT and MRA represent highly accurate imaging modalities that are frequently used as an initial or complementary study in the evaluation of hematomas.

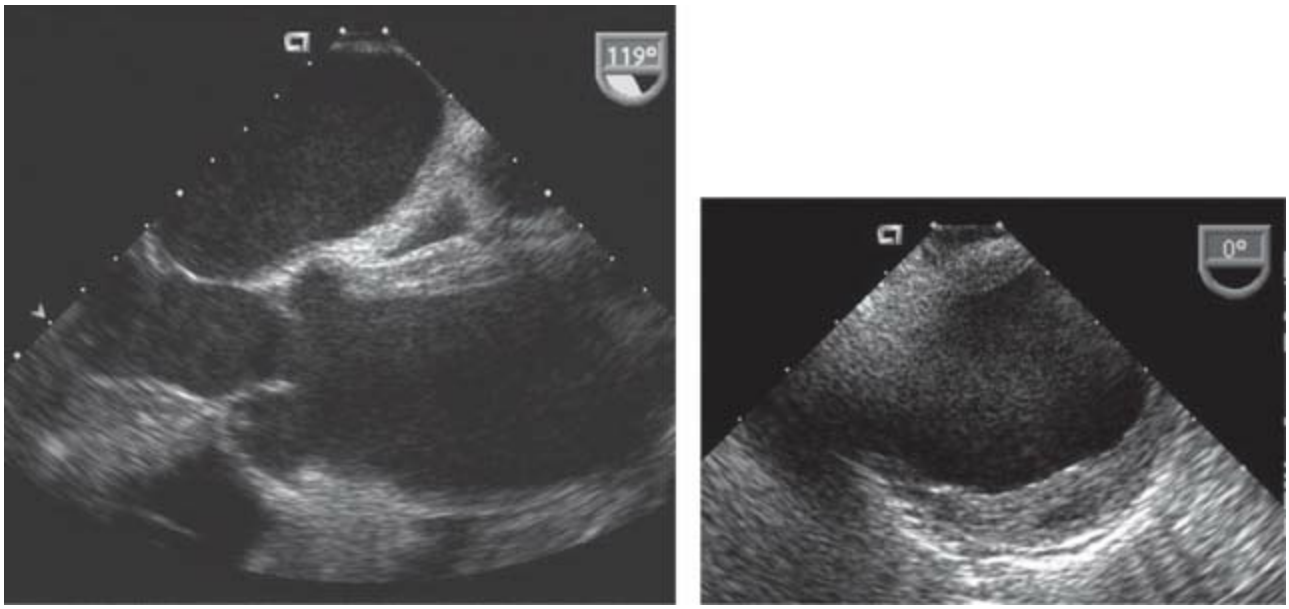

FIGURE 48.5 TEE in both long- and short-axis views showing an intramural hematoma, characterized by no dissection flap, a crescent-shaped thickening of the aortic wall, central displacement of intimal calcium, and echolucent intramural pockets representing intramural blood.

Intramural hematomas can communicate with the adventitial space, lead to rupture, or progress to overt dissection with an intimal tear. However, they may also have a more benign course and gradually resolve with medical therapy and blood pressure control.

Penetrating Aortic Ulcer

Penetrating aortic ulcer exists when an atheromatous plaque erodes inward into the aortic media. The advanced atherosclerotic disease burden prevents the erosion from extending longitudinally along the vessel as in classic dissection. The ulcer is apparent on imaging modalities as an ulcer crater or contrast-filled outpouching. Depending on how far into the aortic wall the plaque erosion occurs, there may be formation of an intramural hematoma, saccular aneurysm, pseudoaneurysm, or even complete aortic rupture (Fig. 48.6).

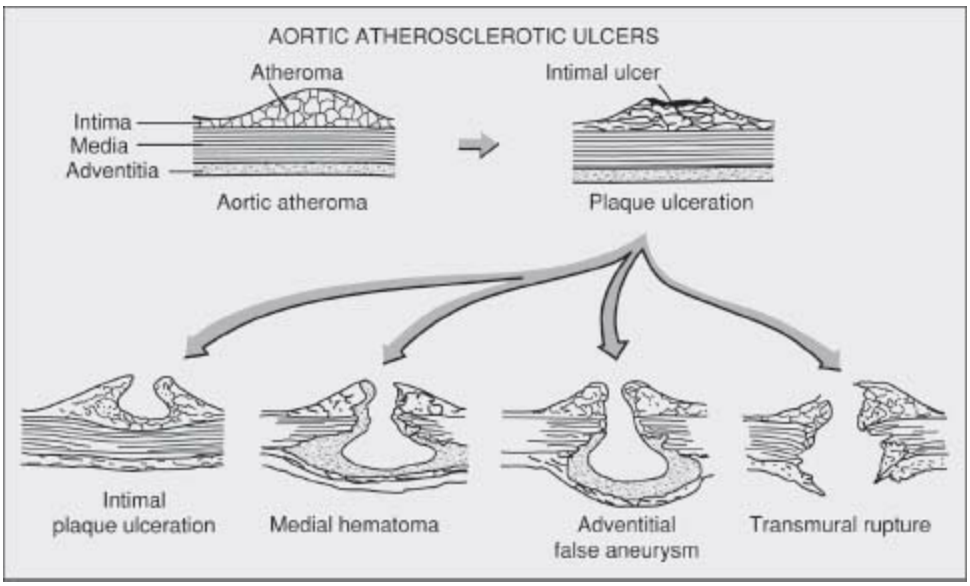

FIGURE 48.6 Schematic of a penetrating aortic ulcer and the progression to the various aortic wall complications.

Clinical Presentation

Patients with these acute aortic syndromes often present with the same chest and/or back pain as do patients with classic dissection. They may be associated with a higher incidence of rupture than seen for classic dissections. Compared to intramural hematomas, patients with penetrating ulcers are usually older and tend to have more atherosclerotic burden. Isolated intramural hematomas can occur in both the ascending and descending aorta, whereas intramural hematomas associated with penetrating aortic ulcers are more commonly located in the descending aorta, where the atherosclerotic process is more common.

Management

As in aortic dissection, anti-impulse medical therapy should be initiated as soon as the diagnosis of a dissection variant is considered. Intravenous beta-blockade initially and, if needed for blood pressure control, sodium nitroprusside are the treatment agents of choice.

For the dissection variants involving the ascending aorta, prompt surgical intervention is considered the treatment of choice. However, some data suggest that select patients with intramural hematomas in the ascending aorta, particularly if small (<11 mm) and with nondilated aortas, can be managed medically. Recent data suggest that penetrating ulcer-like findings in an area of intramural hematoma can identify high-risk individuals. Symptoms of sustained or recurrent pain or findings of an increasing pleural effusion are suggestive of disease progression and favor surgical intervention. Guidelines and management strategies for this patient population are still evolving.

For the dissection variants that involve the descending aorta, especially intramural hematoma without penetrating ulcers, medical therapy is the preferred initial treatment.

However, some have argued that there should be a lower threshold for surgical intervention than for classic distal dissection, particularly when clinical signs of instability are present. The presence of a severely bulging hematoma or a deeply penetrating ulcer may warrant surgical repair. The development of a saccular aneurysm or pseudoaneurysm should merit consideration for surgical repair. For those treated medically, serial imaging studies are warranted to assess for progression or increase in aortic diameter, in which case surgical repair or stent-graft placement may be considered.

AORTIC ANEURYSM

An aortic aneurysm is present when there is dilatation of the aorta, typically at least 1.5 times its normal reference dimension for an adjacent segment. This dilatation may involve the entire circumference of the aortic wall (fusiform) or a localized protrusion of one of the walls (saccular). Ectasia is characterized by dilatation <1.5 times the normal reference dimension.

Thoracic Aortic Aneurysm

The incidence of thoracic aortic aneurysm (TAA) is estimated at 5.9 cases per 100,000 patient years. Leading etiologies include congenital bicuspid aortic valve, Marfan syndrome (Fig. 48.7), idiopathic annuloaortic ectasia, familial TAA syndrome, inflammatory aortitis, acquired due to increased age and hypertension, syphilis, and trauma.

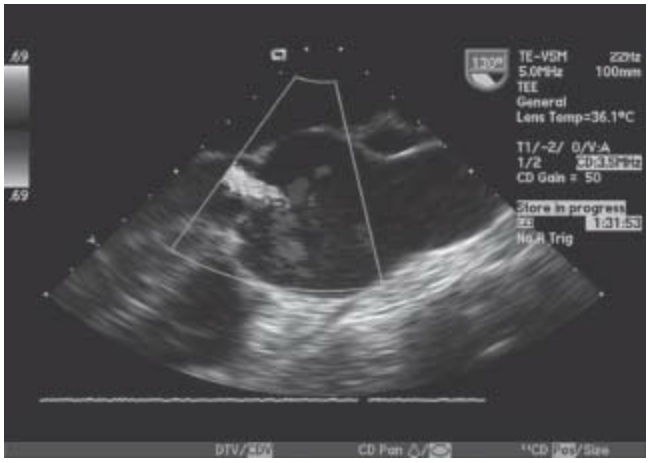

FIGURE 48.7 TEE in a long-axis view illustrating an ascending TAA, with predominant dilatation at the level of the sinuses, in a patient with Marfan syndrome.

Descending TAA may extend distally and involve the abdominal aorta creating a thoracoabdominal aneurysm. Patients are often asymptomatic at the time of presentation, and the TAA may be diagnosed by an imaging modality ordered for other clinical

indications. Physical findings may likewise be absent. When signs and symptoms do manifest, they are often the result of mass effect. The enlarging aorta may compress nearby structures such as the superior vena cava, the trachea, esophagus, and recurrent laryngeal nerve. This may result in superior vena cava syndrome, stridor, dysphagia, and hoarseness, respectively.

Progressive dilatation of the aortic root can lead to aortic insufficiency, which can produce symptoms of congestive heart failure. Enlargement of the aortic sinuses can lead to narrowing of the coronary artery ostia, which can lead to myocardial ischemia and even infarction.

Blood flow can be static in large aneurysms, predisposing to thrombus formation and distal embolization, a process which can be seen in descending thoracic and thoracoabdominal aneurysms.

Noninvasive Imaging

- TAA are often noted incidentally on chest x-ray as mediastinal widening or a prominent aortic knob.
- Transthoracic echocardiography is the most common modality to initially diagnose and monitor dilatation of the aortic root.
- CT scanning and MRA are the preferred techniques to accurately define the entire thoracic aorta and its branch vessels and precisely measure TAA.

Because the thoracic aorta may be tortuous, care must be given to not measure off-axis axial cuts, as these can
overestimate the true cross section as compared to the actual orthogonal diameter. As suggested in the guidelines, measurements of aortic diameter should be made using the internal diameter when taken by echocardiography and the external diameter when taken by CT imaging or MRA.

Medical Treatment

There are data that beta-adrenergic blockade can slow the rate of thoracic aneurysm expansion in patients with Marfan syndrome, resulting in improved survival. Although the data are extrapolated to those without Marfan syndrome, it seems reasonable to recommend such therapy while TAA patients are being followed medically. More recent studies have suggested that angiotensin II receptor blockers may slow the rate of aortic dilation in Marfan patients; prospective investigation using these agents is underway.

Recognizing that patients treated with beta-adrenergic blockade can still manifest aortic dilatation is important, as serial evaluation and imaging is required.

Marfan Syndrome, Thoracic Aortic Aneurysms, and Pregnancy

- Women with Marfan syndrome have an increased risk of aortic dissection during pregnancy, particularly during the third trimester.
- The risk of dissection greatly increases if the aortic root diameter is >4.0 cm or if there is evidence of rapid aortic root dilatation during pregnancy.
- If elective surgical repair is not performed prepartum, betaadrenergic blockade should be used during pregnancy, particularly during the third trimester and peripartum.
- Close echocardiographic follow-up and cesarean delivery should be considered if the aortic root size exceeds 4.0 cm or rapid aortic dilatation is evident.

Indications for Surgical Treatment

Dissection and rupture are the feared complications of TAA, and prevention of these conditions is the purpose for elective surgical aortic repair. Size is a clear risk factor and principal harbinger for dissection and rupture. In one series, the annual rate of dissection or rupture was 2% for TAAs < 5 cm, 3% for TAAs between 5.0 and 5.9 cm, and 7% for TAAs > 6 cm. Therefore, prophylactic surgical intervention should be considered before a TAA reaches a size that predisposes to aortic instability.

Although the optimal timing of prophylactic surgery remains uncertain, recommendations for surgical repair are >5.0 to 5.5 cm for an ascending TAA and >6.0 to 6.5 cm for a descending TAA. Patients with Marfan syndrome, Loeys-Dietz syndrome, bicuspid aortic valve, or family history of premature aortic instability should be considered for earlier repair (perhaps at 4.5 to 5.0 cm and 5.5 to 6.0 cm for ascending and descending TAAs, respectively). For patients undergoing aortic valve surgery, concomitant ascending aortic repair should be considered for a TAA > 4.5 cm.

Rapid enlargement of the aorta (>0.5 to 0.75 cm/year) or symptom development has also been advocated as indications for surgery. The decision for operative repair must of course take into account the patient's medical comorbidities, and a risk/benefit ratio must be individualized for each patient. Patients who are otherwise low medical risk may be considered for intervention at smaller aortic sizes.

Abdominal Aortic Aneurysm

- The incidence of abdominal aortic aneurysm (AAA) is estimated at 36.5 per 100,000 person years.
- AAA represents the most common form of arterial aneurysm.
- The majority of AAAs are infrarenal in location (75%).
- Atherosclerosis is the dominant risk factor in the development of an AAA.

Additional risk factors associated with AAAs are male gender (AAA is four to five times more common in men), increasing age, smoking, and hypertension.

- There is a clear familial predisposition to AAA, with relatives of affected patients having up to 25% increased risk for the development of an AAA.

Asymptomatic AAA is often diagnosed on physical examination by abdominal palpation. The most common symptom is pain, and is usually steady. The pain may be localized abdominal pain, or may radiate to the back, flank, or groin. Sudden onset of severe abdominal and back pain suggests rupture, representing a surgical emergency. Up to only a third of patients with rupture will present with the classic triad of pain, pulsatile abdominal mass, and hypotension. Atheroemboli may be the first manifestation of an AAA.

Noninvasive Imaging

Ultrasonography, CT scanning, aortography, and MRA have all been used in the initial diagnosis, sizing, and monitoring of AAA. Ultrasonography represents the most practical method of screening and serial monitoring, while CT scanning and MRA remain superior in accurately detailing the morphology and extent of the AAA.

At initial diagnosis, the rate of dilatation cannot be determined and thus the next serial study should be performed in 6 months. In general, for AAAs <4.0 cm, yearly surveillance imaging is recommended; for AAAs 4.0 to 5.0 cm, imaging every 6 to 12 months; and for AAAs >5.0 cm, imaging every 3 to 6 months.

Baseline AAA size is the best predictor of rate of dilatation. Larger aneurysms expand at higher rates than smaller ones.

Medical Treatment

Beta-adrenergic blockade with careful control of hypertension appears to have impact on delaying the rate of AAA expansion.

Smoking should be discontinued, as rupture risk is greater among active smokers.

Indications for Surgical Treatment

Mortality from an AAA is primarily related to rupture. As with thoracic aneurysms, increasing size is the harbinger of rupture risk. Aneurysms <4 cm in size have a 0% to 2% risk of rupture over 2 years, whereas those that are >5 cm in size have a 22% risk of rupture over 2 years, with those >6 cm showing the sharpest rise in risk. As such, an aortic diameter of 5.0 to 5.5 cm is recommended as an indication for prophylactic surgery in asymptomatic AAA patients. Although AAAs are less common in women,

when they are present they are at greater risk of rupture and at smaller aortic diameters than in men. Thus, it is recommended that women undergo prophylactic AAA repair at 4.5 to 5.0 cm.

Aneurysms that expand rapidly (>0.5 to 1.0 cm/year) are also associated with an increased risk of rupture, and are thus considered for elective surgical repair.

Inflammatory AAA is present in up to 10% of cases. There appears to be a familial tendency for these, and they often occur in the context of smoking. Patients will present with constitutional symptoms and have an elevated sedimentation rate in addition to the classic symptoms of pain. CT scanning or MRA can identify the inflammatory component. Treatment is aortic surgery.

Endovascular Stent-Graft Repair

A relatively recent therapeutic option for AAA repair is the percutaneous placement of an endovascular stent graft. The endovascular stent graft is placed within the aneurysmal segment of the aorta, bridging the normal segments and excluding the aneurysm. However, just over half of all AAA possess anatomy favorable for stentgraft placement.

Data are still forthcoming on the long-term success of endovascular stent grafting. In randomized trials thus far, it appears that endovascular repair incurs a lower operative mortality compared to open AAA surgery, but no benefit in total mortality in the long term has been demonstrated. Nonetheless, the procedure remains an attractive alternative to conventional surgical repair, but is usually limited to patients with significant comorbid medical conditions who are at high surgical risk.

ATHEROMATOUS AORTIC DISEASE

- Atherosclerotic plaques in the aorta can give rise to cerebral and peripheral embolic events (Fig. 48.8).
- TEE, in particular, has been a valuable imaging modality in assessing the presence, composition, and extent of these plaques.
- Plaques >4 mm in thickness, or those with mobile or ulcerated components, appear to be strongly associated with subsequent embolic events.

Treatment strategies for patients with such plaques have not been evaluated in sufficient numbers in a prospective randomized fashion. However, there is evidence that lipidlowering therapy with a statin is a reasonable treatment option, and anticoagulation with warfarin or antiplatelet therapy may benefit some patients.

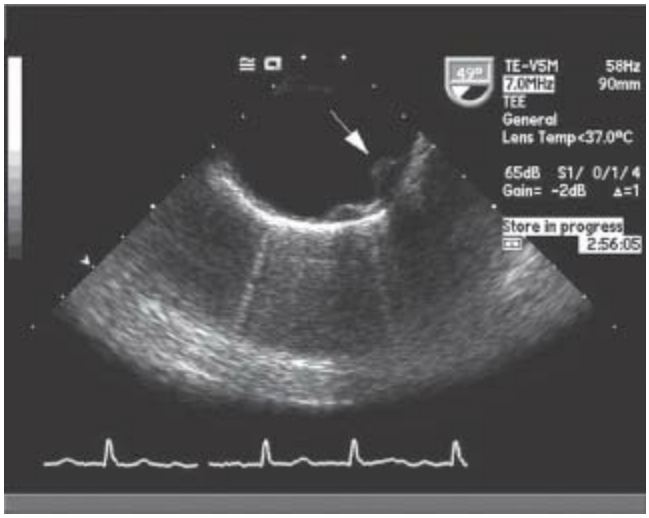

FIGURE 48.8 TEE in a short-axis view identifying a protruding thick (>4-mm) atheroma in the descending thoracic aorta.

Earlier reports of a potential association between warfarin and the cholesterol embolization syndrome have produced some reluctance to use such anticoagulant therapy in these patients, and further study is thus needed. The potential role of aortic replacement or removal of atheroma remains to be defined.

It has become increasingly common for cardiac surgeons to assess the aorta before the institution of cardiopulmonary bypass. The presence of significant plaque may alter the cross-clamp site or may even lead to endarterectomy or aortic replacement at the time of surgery.

Cholesterol Embolization Syndrome

The cholesterol embolization syndrome can be seen in patients undergoing diagnostic angiography, but can also occur spontaneously. There is a reported association between warfarin anticoagulation and these events.

The syndrome represents a showering of emboli, typically from the descending aorta. Patients most often present with the skin findings of livedo reticularis and blue toes, in the presence of palpable pulses. Renal insufficiency may occur, and may not be reversible. Transient eosinophilia is often present, and treatment is supportive.

If the atheroma arose from an AAA, then surgical intervention can help prevent future events.

INFLAMMATORY AORTITIS

Giant Cell Arteritis

Giant cell arteritis is an inflammatory disease that affects the temporal arteries, producing local tenderness and headaches. Patients affected are typically over the age of 55 years, and women are affected twice as frequently as men.

The most devastating consequence is blindness. Although temporal arteritis is the hallmark of this disorder, there may be involvement of the thoracic aorta and the great vessels. This can lead to branch vessel occlusion, aneurysm formation, or even dissection.

Corticosteroid treatment is the mainstay of therapy. With the development of advanced aortic involvement, surgical treatment may be required.

Takayasu Arteritis

Takayasu arteritis is an inflammatory disorder of the aorta that typically affects women under age 40 years. Its prevalence is greater in Asian and African populations than in those of European or North American descent.

A subacute inflammatory illness phase is manifested by constitutional symptoms. Later, there is occlusive inflammation of the aorta and branch vessels, with segmental narrowing apparent. Symptoms of arterial insufficiency will be present, depending on the vessels involved. Acquired coarctation can occur, leading to hypertension, as can aneurysm formation.

Treatment is corticosteroids. For occlusive lesions that do not respond to steroids, surgical bypass may be warranted.

Syphilitic Aortitis

Syphilitic aortitis represents a manifestation of tertiary syphilis, which may occur 10 to 30 years after the initial infection. This inflammation results in a weakening of the vessel wall and can lead to aneurysm formation, usually saccular.

Syphilitic aortitis most commonly affects the ascending aorta, and hence can result in aortic insufficiency. The arch may also be affected. Involvement of the descending aorta occurs less often.

Other Inflammatory Aortitis

Aortitis can also be seen in other systemic inflammatory diseases such as reactive arthritis, ankylosing spondylitis, rheumatoid arthritis, Wegener granulomatosis, and enteropathic arthropathies.

A common genetic underpinning of these conditions is the HLA-B27 genotype, which should be considered in cases of lone aortic regurgitation, ascending aortic dilatation, and conduction system disease.

Treatment involves addressing the underlying disorder, with surgery as needed for aneurysmal or aortic valvular complications.

Mycotic Aneurysms

Bacteremia (from endocarditis, trauma, intravenous drug abuse) can result in infection within the weakened aneurysmal arterial wall. Persistent fevers after treatment of the inciting event should raise concern for an infected aneurysm.

Mycotic aneurysms more commonly involve the abdominal aorta. Atheromatous

plaques can also become infected (bacterial aortitis), serving as a nidus for infection requiring prolonged antibiotic therapy.

ESSENTIAL FACTS

Aortic Dissection

- The hallmark of aortic dissection is an intimal flap.
- Increasing aortic size and aneurysm formation is a harbinger of aortic dissection.
- Proximal (ascending) aortic dissections are treated with surgery.
- In cases of cardiac tamponade, evacuation of hematoma should be performed in the operating room under cardiopulmonary bypass support.
- Distal (descending) aortic dissections are treated medically, with surgery guided by a complication-specific approach.
- Congenital bicuspid aortic valve, Marfan syndrome, Loeys-Dietz syndrome, prior aortic surgery, and the peripartum period represent risk factors for aortic dissection in the young.
- A negative surface echocardiogram, absence of pulse deficits, or a normal mediastinum on chest x-ray does not exclude the presence of aortic dissection.
- Anti-impulse medical therapy with intravenous beta-blockade followed by sodium nitroprusside is the mainstay of medical treatment.

Intramural Hematoma and Penetrating Aortic Ulcer

- Penetrating aortic ulcers arise more commonly in areas of atheromatous disease such as the thoracoabdominal aorta.
- Penetrating aortic ulcers that involve the ascending aorta are treated surgically.
- Intramural hematomas that involve the ascending aorta are generally treated surgically, although recent publications have raised some controversy and suggest that medical management may be an option in some populations.
- Neither of the aortic dissection variants involves an intimal dissection flap.

Aortic Aneurysm

- Indications for surgery:
  1. Symptoms
  2. Inflammatory or infectious
  3. Rapidly expanding 0.5 cm/year, even if asymptomatic
  4. >5.0 to 5.5 cm diameter for ascending thoracic
  5. >6.0 to 6.5 cm diameter for descending thoracic

6. >5.0 to 5.5 cm diameter for abdominal

- Earlier surgical intervention (>4.5 to 5.0 cm) is recommended in Marfan syndrome, Loeys-Dietz syndrome, and bicuspid aortic valve patients.
- Beta-adrenergic blockade may slow the progression of aortic dilatation.

Atheromatous Aortic Disease

- Mobile, ulcerated, or thick atheromatous plaques (>4 mm) identified by TEE are associated with embolic events.

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QUESTIONS AND ANSWERS

Questions

1. A 70-year-old man presents with the sudden onset of tearing chest pain. On presentation, he has a heart rate of 130 beats/min (bpm) with a systolic blood pressure of 80 mm Hg. A bedside transesophageal echocardiography (TEE) demonstrates the presence of a proximal aortic dissection. A pericardial effusion with partial diastolic collapse of the right ventricle is also present. Significant respiratory variation is noted across mitral and tricuspid Doppler inflows. Appropriate treatment is:
   a. Immediate percutaneous pericardiocentesis to relieve the tamponade, followed by surgery to replace the ascending aorta
   b. To proceed immediately to the operating room
   c. Emergency angiography to define coronary anatomy, followed by surgery
   d. Intra-aortic balloon pump to stabilize the hemodynamics, followed by surgery
2. A 60-year-old hypertensive man presents with tearing back pain. MRI confirms the presence of a descending thoracic dissection originating beyond the left subclavian artery. Appropriate initial treatment includes:
   a. Immediate surgery to replace the descending aorta
   b. Intravenous nitroprusside followed by immediate surgery
   d. Intravenous nitroprusside alone; surgery for persistent pain, or for involvement of renal or mesenteric arteries
   e. Intravenous beta-blockade and nitroprusside; surgery for persistent pain, or for involvement of renal or mesenteric arteries
3. A 56-year-old man presents for screening physical examination. He is asymptomatic. Vital signs reveal a heart rate of 80 bpm with a blood pressure of 160/90 mm Hg. His exam is remarkable only for a pulsatile mass in the abdomen. Ultrasound reveals the presence of a 3.9-cm abdominal aortic aneurysm (AAA). Appropriate management includes
   a. Immediate referral for surgery:
   b. Start a beta-blocker and repeat ultrasound in 6 months
   c. Refer for stenting of the AAA
4. A 76-year-old woman with hypertension presents with severe chest pain. Her blood pressure is 200/110 mm Hg. Electrocardiogram reveals nonspecific ST–T changes. Chest x-ray is unremarkable. CT scan demonstrates the presence of a penetrating ulcer in the ascending aorta. No dissection flap is seen. Appropriate management includes:
   a. Start intravenous beta-blocker and nitroprusside while plans are being made for surgery
   b. Intravenous beta-blocker and nitroprusside, with surgery only if complications develop
   c. Intravenous nitroprusside alone, with surgery only if complications develop
5. A 23-year-old patient with Marfan syndrome presents for routine evaluation. He is asymptomatic. Workup includes a CT scan that reveals the presence of a 4.2-cm ascending aorta. Appropriate management includes:
   a. Refer for surgery
   b. Start on beta-blocker and reimage in 6 to 12 months
   c. Reimage in 6 to 12 months
6. The same patient returns for follow-up in 12 months. The aorta now measures 5.0 cm in size. He remains asymptomatic. Appropriate management includes:
   a. Refer for surgery
   b. Continue beta-blocker, reassess in 6 months
   c. Reassess in 3 months

7. Which of the following disorders is associated with involvement of the aorta?
   a. Marfan syndrome
   b. Giant cell arteritis
   c. Ankylosing spondylitis
   d. Syphilis
   e. All of these disorders can have aortic involvement.

8. Which of the following statements regarding transesophageal findings of aortic atheroma is not true?
   a. Plaques >2 mm in the ascending aorta are associated with increased risk of stroke.
   b. Plaques >4 mm in the ascending aorta are associated with increased risk of stroke.
   c. Mobile components are associated with an increased risk of stroke.
   d. Limited data suggest that these patients may benefit from anticoagulation therapy with warfarin.

Answers

1. Answer B: This patient should be taken to the operating room immediately. Percutaneous drainage has been associated with increased mortality in this setting. Given the hemodynamic status, there is no time to proceed with angiography first. Balloon pumps are contraindicated with aortic dissection.

2. Answer D: Initial therapy for descending aortic dissection is medical, with surgery reserved for special circumstances. The goal of treatment is reduction in blood pressure, as well as reduction in dp/dt. Both beta-blockade, started immediately, and nitroprusside should be used.

3. Answer B: Asymptomatic aneurysms of 3.9 cm have a very small risk of rupture. The patient should be followed by serial examination to assess size and rate of expansion. Control of his hypertension with beta-blockers may delay the growth of the aneurysm. There are no data as of yet that endovascular stent grafts will lower the threshold for intervention for these aneurysms.

4. Answer A: Penetrating aortic ulcers involving the ascending aorta are generally treated like dissections, with prompt referral for surgery.

5. Answer B: The patient's aorta has not yet reached a size that would be considered for surgery in the absence of symptoms. There are data that beta-blockers can slow the rate of expansion of these aneurysms and improve survival.

6. Answer A: There has been rapid growth in the size of the aneurysm (0.8 cm in 1 year). The patient should be referred for surgery.

7. Answer E: All of the disorders listed can include involvement of the aorta.

8. Answer A: Plaques >4 mm have been associated with cerebral embolic events. The role of anticoagulation needs to be more clearly defined, but there are some data to support its use.

CHAPTER

Venous Thromboembolism

Firas Al Solaiman and John R. Bartholomew

Venous thromboembolism (VTE) is a common disease that includes both pulmonary embolism (PE) and deep vein thrombosis (DVT). It is the third most frequently occurring cardiovascular condition after ischemic heart disease and cerebrovascular accidents in the United States. Approximately 1 million people develop DVT and 600,000 develop PE each year, and death from VTE has been estimated to occur in as many as 60,000 to 200,000 Americans annually.[1]

ESSENTIAL FACTS ABOUT VTE

It is important to recognize the natural history of VTE to more fully appreciate its short-term mortality and long-term morbidity.

- VTE is a recurrent disease with a risk of recurrence up to 30% at 10 years for unprovoked events.[2]
- PE is the third most common cause of hospital-related death and is the most common preventable cause of hospital death.[3,4]
- The mortality rate for PE without treatment is approximately 30%.[5]
- Patients with an acute PE who have right ventricular (RV) dysfunction documented by a transthoracic echocardiogram (TTE) have a higher in-hospital mortality (14%) and short-term mortality (20%) rate at 3 months.[6]
- Chronic thromboembolic pulmonary hypertension (CTPH) develops in as many as 3.8% of all PE patients by 2 years after their initial event.[7]
- Approximately 40% to 50% of all patients with an acute symptomatic DVT (proximal to the popliteal vein), who are asymptomatic for PE, will have a high-probability ventilation/perfusion scan.
- The most common long-term complication of DVT is the postthrombotic syndrome

(PTS), characterized by chronic leg swelling, pain, and nonhealing venous stasis ulcers, which occurs in as many as 30% of all patients within 10 years after a documented DVT.[8,9]

RISK FACTORS FOR VENOUS THROMBOEMBOLISM

Venous thrombosis results from the combination of acquired and hereditary causes. The most common acquired and hereditary risk factors (referred to as hypercoagulable states or thrombophilia) are shown in Tables 49.1 and 49.2.

TABLE
49.1 Acquired Risk Factors For VTE

Older age
MI, CHF, stroke, pneumonia
Prolonged immobilization
Long-distance travel (airplane or automobile trips)
Surgery or trauma
Smoking
Obesity
Malignancy
Pregnancy, oral contraceptives, or hormone replacement therapy
Previous VTE
Pacemaker wires, CVP catheters
Varicose veins
Antiphospholipid antibody syndrome
HIT
Nephrotic syndrome, inflammatory bowel disease, myeloproliferative disorders

TABLE
49.2 Hereditary Risk Factors for VTE

Activated protein C resistance due to factor V Leiden mutation
Prothrombin gene mutation (G20210A)
Antithrombin deficiency
Protein C and S deficiencies
Elevated factor VIII levels
Increased levels of homocysteine

As many as 20% of white patients presenting with an idiopathic or unprovoked DVT are heterozygous for the factor V Leiden mutation, while 6% are heterozygous for the

prothrombin G20210A mutation[10] Both of these disorders are rare in the African and Asian populations.[11,12] Other, less common hereditary hypercoagulable states include protein C and S and antithrombin deficiencies, hyperhomocystinemia, elevated levels of factor VIII, and dysfibrinogenemia.

DEEP VEIN THROMBOSIS: CLINICAL PRESENTATION AND DIAGNOSIS

Although VTE is considered to be one disease entity, the clinical presentation and diagnosis for DVT and PE are different. The characteristic symptoms for an acute DVT include leg or arm pain, swelling, increased skin temperature, and discoloration (erythrocyanosis), although these findings may be absent. Unfortunately, the clinical examination is often unreliable and the diagnosis is only confirmed in 20% to 40% of patients presenting with typical signs and symptoms.[13] This is due in part to the varied differential diagnosis for DVT, which includes:

- Cellulitis
- Arthritis, synovitis, myositis
- Lymphedema
- Arterial insufficiency
- Muscle ache or tear
- Baker cyst
- Chronic venous insufficiency
- Systemic causes of edema (congestive heart failure [CHF], nephrotic syndrome, liver dysfunction, hypoalbuminemia)

Clinical models have been developed to help diagnose an acute DVT. Wells et al. stratified outpatients presenting with a suspected DVT into low, intermediate, or high pretest probability categories based on a number of clinical "points."[14] According to their model, 3% of low, 17% of moderate, and 75% of high pretest probability patients were diagnosed with a DVT. Although it is not widely used, this model may be a helpful objective assessment tool for clinicians (Table 49.3).

TABLE
49.3 Clinical Feature Score According to Wells et al. Criteria

	Points
Active cancer	1
Paralysis, paresis, or recent cast	1
Recent immobilization for >3 d or major surgery <4 wk	1
Local tenderness along the deep veins	1
Swelling of the entire leg	1
Calf swelling by >3 cm when compared with the asymptomatic leg	1
Pitting edema	1
Collateral veins	1
Alternative diagnosis likely	−2

Risk score: low, <0 points; moderate, 1–2 points; high, >3 points. Adapted from Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet. 1997; 350:1795–1878.

OBJECTIVE TESTING FOR DEEP VEIN THROMBOSIS

DVT can be confirmed using invasive and noninvasive studies as well as laboratory tests. These tests include:

- D-Dimer assay
- Duplex ultrasonography
- Venography
- Computed tomography venography (CTV)
- Magnetic resonance venography (MRV)
- Impedance plethysmography (IPG)

The more commonly used diagnostic tests include a D-dimer assay and duplex ultrasonography.

D-Dimer

D-Dimer is a specific fragment of a fibrin clot whose presence indicates degradation of fibrin and serves as an indirect indicator for thrombotic activity. D-Dimer assay has been utilized to a great extent in the outpatient setting and emergency departments to rule out VTE, because of its high sensitivity and negative predictive value. An elevated D-dimer level, however, is not specific for VTE and can be seen in a variety of conditions, including pregnancy, infection, disseminated intravascular coagulation (DIC), hemorrhage, malignancy, liver disease, surgery, trauma, cardiac or renal failure, acute coronary syndrome (ACS), and acute nonlacunar stroke. It is important to

remember that not all D-dimer assays are alike and that it can be measured using a number of different methods. A recent analysis found that the Enzyme-linked immunosorbent assay (ELISA) and quantitative rapid ELISA tests were superior to other methods.[15]

Most physicians feel that anticoagulation can be withheld from patients suspected of acute VTE in the outpatient setting if the D-dimer assay is negative. It is extremely important, however, for clinicians to know the sensitivity and specificity of their hospital's D-dimer assay before making such a decision. If the clinician's suspicion of VTE remains high despite a negative D-dimer assay, further imaging studies are recommended.

Duplex Ultrasonography

Duplex ultrasonography is a readily available, noninvasive modality that can be performed routinely in the hospital or outpatient setting or at bedside for a critically ill patient. It has replaced venography as the diagnostic method of choice for acute DVT and is the most accurate noninvasive test currently available. Duplex ultrasonography allows for direct visualization of the venous system. An inability to compress the vein with the ultrasound transducer is considered diagnostic for DVT. The other ultrasound findings that may help in the diagnosis of acute DVT are listed in Table 49.4.

TABLE
49.4 Ultrasound Characteristics of Acute DVT

Inability to compress the vein
Low echogenicity (of thrombus)
Dilated veins
Free floater
Absence of collateral vessels
Filling defects found on color Doppler
Absence of Doppler flow

Physicians must recognize that duplex ultrasonography is very operator dependent. Its sensitivity is approximately 95% and its specificity 96% in symptomatic patients with a proximal DVT, but it is less reliable in asymptomatic patients, those with thrombus above the inguinal ligament, or those with calf vein thrombosis. The sensitivity and specificity for isolated calf vein thrombosis approaches 60% to 70%.[16]

In a study involving 375 patients, the validity of withholding anticoagulation in patients with a negative ultrasound and a low clinical suspicion for DVT was examined.[17] Only three patients who had anticoagulation withheld developed a new VTE event. Two patients developed an isolated calf vein DVT and one patient a

proximal DVT (total of 0.8%). No patient developed a PE at the 3-month follow-up.

Duplex ultrasonography may also be useful in patients suspected of an acute PE. If the arms or legs are positive for an acute DVT, further confirmatory studies may be unnecessary in most patients, assuming that would not change the management of the patient.

Venography

The venogram is an invasive procedure now replaced for the diagnosis of DVT by duplex ultrasonography. An intraluminal-filling defect must be seen in at least two different projections for confirmation. A venogram should be considered in the appropriate clinical setting or when other tests are nondiagnostic. Despite its clinical utility, complications such as contrast allergy and postprocedural acute DVT should not be overlooked. The latter complication has been reported to occur in approximately 1% to 2% of all patients.

Other Diagnostic Testing Options

CTV of the legs can be performed in conjunction with a computed tomographic pulmonary angiogram (CTPA) of the chest used to rule out PE. Although more radiation is required, no additional contrast is needed and imaging of the more proximal leg veins (iliacs), pelvic veins, and the inferior vena cava (IVC) is possible. However, recent studies showed that routine CTV of the pelvis during CTPA does not significantly improve the detection of VTE and therefore should not be performed routinely in all patients being evaluated for PE.[18,19]

MRV imaging can also be utilized to diagnose DVT. Its sensitivity and specificity has been reported to be >95% when compared to standard venography for the diagnosis of a proximal DVT, although outcome data are lacking. It has several advantages, including (a) detecting pelvic, iliac, and IVC thrombosis and (b) no need for ionizing radiation. Potential drawbacks include lack of availability, high cost, reader expertise, difficulty with morbidly obese patients, and the presence of metallic objects (stents or other hardware) in the area of interest. The MRV modality may be beneficial in pregnancy when there is a high clinical suspicion for an IVC, pelvic, or iliac vein DVT that is not detectable with duplex ultrasonography, or for patients with an allergy to contrast dye. However, this imaging technique should not be used in patients with acute or chronic renal insufficiency to prevent the adverse effect of nephrogenic systemic fibrosis (NSF).[20]

IPG has largely been replaced by duplex ultrasonography at hospitals in the United States.

PULMONARY EMBOLISM: CLINICAL PRESENTATION AND

DIAGNOSIS

Autopsy studies continue to demonstrate that most fatal cases of PE are unrecognized or not diagnosed.[21] Patients presenting with PE often have nonspecific signs and symptoms, making the diagnosis more difficult and frequently overlooked. In a review of the most common signs and symptoms of patients presenting with an acute PE without underlying cardiopulmonary disease, dyspnea was most common, followed by pleuritic chest pain. These manifestations are valuable clues to the diagnosis in this patient population. However, in the individual with heart or lung disease, they may be mistaken for symptoms of the underlying disease process. Other signs and symptoms of an acute PE include cough, leg swelling, thrombophlebitis, hemoptysis, palpitations, wheezing, angina-like pain, apprehension, and fever.[22].

Patients may present with a massive or submassive PE, or they may be entirely asymptomatic. Patients who have a massive PE (systolic arterial pressure <90 mm Hg) present with circulatory collapse and shock or syncope. Fortunately, this is not a common manifestation, representing only in about 8% of all patients.[23] Acute shortness of breath, with tachycardia, chest pain, tachypnea, and cyanosis, may be the result of a submassive PE (pulmonary hypertension or RV dysfunction without arterial hypotension or shock). Patients with acute PE may also be entirely asymptomatic, especially in the postoperative period. Because of the wide variety of clinical presentations, both noninvasive and invasive diagnostic methods may be necessary to confirm the diagnosis. The differential diagnosis of PE includes:

- Unstable angina, myocardial infarction (MI)
- Pneumonia
- Chronic obstructive pulmonary disease (COPD), bronchitis
- CHF
- Pericarditis
- Pneumothorax
- Costochondritis

The diagnosis of PE should start with establishing the clinical probability. Wells et al. stratified the clinical features of PE into "points" (similar to their DVT criteria), and their model is useful as an objective tool to assess the pretest probability of an acute PE (Table 49.5).[24] In their model, the probability of an acute PE with >6 points (high risk) was 78.4%, while that for 2 to 6 points (moderate risk) was 27.8% and for <2 points (low risk), it was 3.4%. The combination of a negative D-dimer and low to moderate pretest probability has a very high negative predictive value (~99%). In validation study using Wells criteria in combination with negative D-dimer, only 0.5% of patients with low to moderate pretest probability for PE later developed nonfatal VTE.[25] D-

Dimer has limited value in patients with a high clinical suspicion for PE,[26] and the clinician should proceed directly with multidetector CTPA scan.

TABLE
49.5 Wells et al. Clinical Prediction for PE

	Points
Major criteria	
Clinical symptoms of DVT	3
Other diagnosis less likely than PE	3
Minor criteria	
Heart rate > 100 bpm	1.5
Immobilization or surgery within past 4 wk	1.5
Previous DVT or PE	1.5
Hemoptysis	1.5
Malignancy	1

Risk score: low probability < 2, moderate probability 2–6, high probability > 6. Adapted from Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost. 2000;83:416–420

OBJECTIVE TESTING FOR PULMONARY EMBOLISM

Traditional tests used to assist a physician faced with the presumptive diagnosis of an acute PE include a chest x-ray, electrocardiogram (ECG), and an arterial blood gas.

The chest x-ray may be more helpful to rule out pneumonia, a pneumothorax, or a malignancy. The most common x-ray features of acute PE are consolidation, a pleural effusion, atelectasis, Hampton hump (wedge-shaped opacity along the pleural surface), Westermark sign (oligemia), and Palla sign (an enlarged right descending pulmonary artery).[27] These latter three classic radiographic findings are rarely seen, however.

An ECG may exclude cardiac causes that mimic PE, such as an MI or a pericarditis. ECG findings suggestive of a PE include sinus tachycardia, new-onset atrial fibrillation or flutter, right bundle branch block, right-axis deviation, and nonspecific ST–T-wave changes. The classic finding of $S_1Q_3T_3$ indicates acute cor pulmonale but is seen in <10% of all patients.[27] Evidence of acute RV myocardial injury may also be seen, manifest as ST-segment elevation isolated to lead V_1 and, at times, extending to lead V_2.

PE must not be excluded based on either a normal arterial blood gas or a normal alveolar–arterial gradient (A-a gradient). In several studies, up to 20% of patients had normal oxygen levels and A-a gradients despite angiographically proven PE.[28]

Computed Tomography Pulmonary Angiography

CTPA not only allows direct visualization of the thrombus but also has great value in excluding other diseases, including an aortic dissection, pneumonia, or malignancy.

Over the last decade, multidetector spiral computed tomography (CT) has become the standard imaging technique for diagnosis of PE. Earlier reports suggested that a single row detector CTPA is both highly sensitive and specific for the diagnosis of a central PE (main, lobar, or segmental pulmonary arteries) but insensitive to the diagnosis of a subsegmental event, with a potential to miss smaller emboli. However, the use of multidetector CTPA has greatly increased its sensitivity and specificity for diagnosis of small peripheral or subsegmental PEs. A recent study suggested that CTPA is more sensitive than a ventilation/perfusion (V/Q) scan for the diagnosis of PE.[29] In a meta-analysis of 23 studies involving 4,657 patients with a negative multidetector CT who did not receive anticoagulation therapy, the incidence of VTE was only 1.4%.[30]

CTPA can also assist in risk-stratifying patients with acute PE by identifying patients with an enlarged RV. RV enlargement on multidetector CT (defined by RV/left ventricular [LV] diameter ratio > 0.9) has been shown to predict doubling of mortality in the 30 days following diagnosis.[31]The major disadvantage of CTPA is the risk of contrast-induced nephropathy and radiation exposure.

Ventilation/Perfusion Scan

The V/Q scan was long considered one of the most useful aids to diagnose acute PE. The PIOPED trial (prospective investigation of pulmonary embolism diagnosis) combined low, intermediate, or high preclinical suspicion with a normal-, low-, intermediate-, or high-probability V/Q scan.[32]A normal V/Q scan effectively excluded the diagnosis of an acute PE, whereas if the clinical suspicion and the perfusion scan showed high probabilities, the diagnosis was very likely. Ventilation/perfusion scans interpreted as low or intermediate probability were considered nondiagnostic and required further testing to confirm or exclude an acute PE.

In the PIOPED trial, 88% of patients with a high clinical suspicion and high-probability V/Q scan had acute PE confirmed by pulmonary angiography. Among patients with a low-probability V/Q scan, angiographically proven PE was identified in 40% and 4% of patients with a high and low preclinical suspicion, respectively.

Unfortunately, in as many as 75% to 80% of all PIOPED patients, no definitive diagnosis could be made because studies were interpreted either as low or intermediate probability.

Ventilation/perfusion scanning has been replaced by multidetector CTPA and currently is considered a second-line modality in the diagnosis of PE. However, V/Q scan remains a valuable tool in the diagnosis of acute PE in patients with a normal chest x-ray or patients who cannot undergo CTPA (contrast allergy, renal insufficiency, or

pregnancy)

Pulmonary Angiography

Pulmonary angiography remains the reference standard for which most studies are compared in the diagnosis of PE, despite the fact that it is not universally available, is invasive, and is costly. The definitive diagnosis of acute PE requires the presence of an intraluminal-filling defect in at least two views or demonstration of an occluded pulmonary artery. It is not without complications, and morbidity of 5% and mortality of 0.5% were reported in the PIOPED trial.[32]

Echocardiography (Transthoracic and Transesophageal)

Abnormal TTE findings in acute PE include RV dilatation, RV hypokinesis, interventricular septal flattening or paradoxical motion, decreased inspiratory collapse of IVC, pulmonary artery hypertension and pulmonary artery dilatation, tricuspid regurgitation, patent foramen ovale (PFO) and rarely direct visualization of thrombus. The finding of akinesia of the mid-free RV wall with relative sparing of apex is referred to as McConnell sign. This sign was found in one study to have 94% specificity and 71% positive predictive value for the diagnosis of acute PE.[33]

Hemodynamically unstable patients generally suffer severe RV dysfunction; however, RV hypokinesis presents in only 40% of patients with normal systemic pressure. A TTE alone cannot be used to diagnose PE but is a useful tool for risk stratification and identifying patients with acute PE who may have a poor prognosis. RV dysfunction on TTE has been associated with increased mortality among patients with acute PE. In a retrospective study, patients with an RV/LV ratio ≥ 0.9 were 2.6 times more likely to die during hospitalization independently of other risk factors.[34]

Transesophageal echocardiogram (TEE) can be used as a rapid bedside test to allow direct visualization of the main pulmonary arteries and should be considered in the hemodynamically unstable patients who cannot be moved to undergo a CTPA scan or pulmonary angiogram.[35]

In PIOPED III, magnetic resonance angiography (MRA) had insufficient sensitivity and a high rate of technically inadequate images. Addition of MRV to MRA improves sensitivity; however, 52% of patients in the study had a technically inadequate study. At the current time, an MRA/MRV should be considered only at those centers with experience with this modality and only for patients for whom standard tests are contraindicated.[36]

Cardiospecific Biomarkers in Pulmonary Embolism

Cardiospecific biomarkers, including cardiac troponin and brain natriuretic peptide (BNP), have become useful in the risk stratification strategy of patients with an acute

PE. Elevation in troponin levels and BNP correlate with the presence of RV dysfunction and appear to be independent risk factors for poor or fatal outcome. In a meta-analysis of 1985 acute PE patients, any elevation in troponin was found to confer a fivefold increase in short-term mortality.[37] A troponin level is considered the single most useful blood test for the risk stratification of patients with acute PE, while a normal BNP has a negative predictive value of 97% to 100%.[38,39]

KEY POINTS IN DIAGNOSIS OF VTE

- Clinical prediction rules should be used to estimate the pretest probability for DVT and PE.
- In patients with a low to moderate pretest probability for DVT or PE, a negative high sensitivity D-dimer has a very high negative predictive value (indicating a very low likelihood of VTE).
- Patients with a high pretest probability of VTE require additional diagnostic imaging studies.
- Duplex ultrasonography is accepted as the first-line diagnostic imaging study for DVT.
- Begin anticoagulation once suspect DVT (unless there is a contraindication for its use).
- Patients with a high pretest probability of PE require additional diagnostic imaging studies such CTPA.
- Multidetector CTPA is accepted as the first-line diagnostic imaging study for acute PE.
- A V/Q scan is helpful if the chest x-ray is normal and a CTPA scan not possible or if the patient has renal insufficiency.
- Two D-echo or TEE is useful for the critically ill patient as a bedside test to help diagnose PE.
- The presence of DVT on duplex ultrasonography is generally adequate for treatment of a PE.
- Pulmonary angiogram remains the gold standard diagnostic imaging for PE if diagnosis uncertain.
- Troponins, BNP, and RV enlargement on echo or CT help predict outcome and are useful for risk stratification.
- Begin anticoagulation once suspect PE (unless there is a contraindication for its use) using risk stratification tools including echocardiography and troponins or BNP.

TREATMENT OF VENOUS THROMBOEMBOLISM

The goals of treatment for VTE are to prevent extension, propagation, or embolization and recurrence of thrombosis. Treatment is also aimed at preserving valve function and preventing the PTS in patients with DVT and to prevent CTPH and RV dysfunction in individuals with PE. Initial inpatient management should begin with weight-adjusted unfractionated heparin (UFH), a weight-based low-molecular-weight heparin (LMWH) preparation, or the anti-Xa inhibitor fondaparinux. A vitamin K antagonist (VKA) should be started as soon as possible, overlapping for a minimum of 5 days with one of the above-listed anticoagulants until the international normalized ratio (INR) is stable and ≥2.0 for at least 24 hours.

Unfractionated Heparin

UFH is generally administered intravenously, although it can also be effective when given subcutaneously. Dosing is generally determined from a weight-based nomogram, and a bolus of 80 U/kg followed by 18 U/kg/h is commonly recommended for most adult patients. Subsequent dose adjustments are made based on the results of either an activated partial thromboplastin time (aPTT) or an anti-Xa assay using an amidolytic assay.

Heparin has a number of drawbacks. It has a variable anticoagulant response among patients, a relatively short half-life, and adverse effects of bleeding, osteoporosis, and heparin-induced thrombocytopenia (HIT). HIT (an immune-mediated disorder that typically occurs 4 to 11 days after exposure to heparin products) is reported to occur in as many as 3% to 5% of all patients receiving UFH but occurs much less frequently in patients receiving any of the LMWH preparations. It can result in significant morbidity and mortality, with life- and limb-threatening thrombotic complications including the loss of a limb, stroke, MI, DVT, or PE. Treatment revolves around immediate cessation of UFH or LMWH and replacement with an alternative antithrombotic agent (direct thrombin inhibitor [DTI]). Currently, two DTIs are approved by the U.S. Food and Drug Administration (FDA) for the treatment of HIT: argatroban, a small synthetic molecule, and a hirudin derivative (lepirudin).

Low-Molecular-Weight Heparin

Depolymerization of UFH by chemical or enzymatic cleavage of its polysaccharide chains yields a mixture of heparin fragments known as LMWH that have a mean molecular weight of approximately 5,000 Da. This reduction in molecular weight leads to more predictable pharmacokinetics and a greater bioavailability than with UFH. A subcutaneous administered LMWH is the preferred anticoagulant for most hemodynamically stable patients. Advantages of the LMWHs include:

- Once or twice-daily subcutaneous injections
- Easy administration
- Dose by a weight-base adjusted regimen
- No monitoring necessary for most patients (see below)
- Outpatient administration
- Lower incidence of HIT
- Less osteoclast activation and lower incidence of osteoporosis

Although laboratory monitoring is generally not necessary, it is recommended in patients who are morbidly obese or who have significant renal disease, and in pediatric or pregnant patients. In these individuals, a 4-hour postinjection anti-Xa level using LMWH as the standard is recommended. Therapeutic levels are 0.6 to 1.0 IU/mL for twice-daily injections and 1.0 to 2.0 IU/mL for once-a-day administration.[40] LMWH preparations require dose adjustment for patients with a creatinine clearance ≤30 mL/min and are contraindicated in patients on hemodialysis.

The introduction of LMWH has dramatically altered the management of DVT in the United States. Two landmark clinical trials and a meta-analysis have demonstrated that subcutaneous injection of LMWH is as safe and effective in the outpatient treatment of acute DVT as UFH given in a hospital setting.[41] Meta-analyses comparing LMWH to UFH found similar rates of major bleeding and recurrent VTE.[42]

Although the LMWHs are not approved in the United States for outpatient treatment of acute PE, several clinical trials have demonstrated their safety. A meta-analysis comparing UFH with LMWH in the inpatient treatment of hemodynamically stable PE patients demonstrated similar incidences of recurrent VTE, bleeding, and death.[43] Heparin should still be first line of therapy in the following cases:

- Persistent hypotension due to PE (massive PE)
- Increased risk of bleeding
- Concern about subcutaneous absorption (morbid obesity, anasarca)
- When thrombolysis is being considered
- Patients with end-stage renal disease

Fondaparinux

Fondaparinux (Arixtra) is the only synthetic pentasaccharide that has been approved by the FDA for the treatment of acute DVT and PE. It is administered subcutaneously once daily and is almost 100% bioavailable. Dosing is weight based; 5 mg is recommended for individuals weighing <50 kg, 7.5 mg for those who weigh 50 to 100 kg, and 10 mg for individuals who weigh >100 kg. Fondaparinux does not require dose adjustment or

monitoring, but caution should be exercised while using this drug because of its long half-life and the lack of an antidote. Warfarin should be started concurrently and continued for at least 5 days, until a therapeutic INR is attained. Fondaparinux is contraindicated in patients with renal insufficiency defined as a creatinine clearance <30 mL/min and in patients on hemodialysis.

Vitamin K Antagonists

Warfarin is the only VKA available for long-term management of VTE in the United States and currently remains the mainstay therapy for long-term treatment of VTE. Despite its use for many decades, two areas often remain confusing and controversial to physicians. One is the optimal dose for initiating therapy; the other revolves around duration of anticoagulation. Two trials compared different initiating doses of warfarin (5 vs. 10 mg). Both studies reported that 5 mg reduced the likelihood of excessive early anticoagulation, avoided rapid drops in the level of protein C, and did not appear to prolong the time required to achieve a therapeutic INR.[44,45] In contrast, a more recent study performed in the outpatient setting demonstrated that higher initial doses (10 mg) of warfarin were superior to lower doses (5 mg).[46] In this study, patients reached a target INR on average 1.4 days earlier, without an increase in recurrent events or major bleeding. In general, the dose should be tailored to each individual patient. Lower doses are often recommended for elderly patients and for those who have comorbid conditions such as recent surgery, hypertension, stroke, CHF, renal or liver disease, anemia, diabetes, cancer, or a history of bleeding. Genotype-based dosing is a tool that has gained much attention in managing warfarin. The FDA has approved labeling changes for warfarin recommending lower initiation doses for patients with genetic variations in VKORC1 and CYP2C9 enzymes. However, clinical evidence for the clinical utility and cost-effectiveness of this approach is lacking.[47]

There is controversy about the optimal length of treatment. Most patients require 3 months of therapy if an underlying precipitating event (surgery, trauma, medical condition) has been identified and resolved, whereas longer therapy is recommended if no underlying cause can be found (idiopathic or unprovoked) or if the precipitating factor cannot be rectified.

Two studies have demonstrated the benefits of longterm anticoagulation in patients with an idiopathic DVT. The prevention of recurrent venous thromboembolism (PREVENT) trial compared patients treated with low-intensity warfarin (INR of 1.5 to 2.0) to placebo following 6 months of standard VKA therapy. This trial showed a 64% reduction in recurrent VTE in the low-intensity warfarin group when compared to those on the placebo group. Patients were followed on average for 4.3 years, and there was no significant difference in bleeding between the two groups.[48]

The second trial, Extended Low-Intensity Anticoagulation for Thromboembolism

(ELATE) trial, compared long-term low-intensity warfarin (INR 1.5 to 1.9) to the conventional dose maintaining an INR between 2.0 to 3.0. These authors found conventional-dose warfarin better than low-intensity warfarin in preventing recurrences of VTE, without a significant increase in the risk of bleeding.[49]

The latest American College of Chest Physicians (ACCP) guidelines recommend at least 3 months of therapy for patients with an idiopathic or unprovoked VTE and suggest that indefinite therapy is considered if the patient is at low risk for bleeding.[50]

Patients with the antiphospholipid antibody syndrome, individuals who are homozygous for factor V Leiden, deficient in antithrombin or individuals with two or more hereditary thrombophilia conditions should also be considered for long-term anticoagulation although no specific recommendations were addressed for these conditions in the latest ACCP guidelines.[50] For patients with VTE and cancer, LMWH is recommended for the first 3 to 6 months of treatment. This patient population should receive indefinite anticoagulation or until the cancer is deemed cured.[50]

New Oral Anticoagulants

Until recently, warfarin was the only available oral anticoagulant for the treatment of VTE. Multiple new oral agents, with different mechanisms of action, have been evaluated in phase III clinical trials and have become available in the markets outside the United States. These new anticoagulants are poised to replace warfarin and potentially change completely the way patients with VTE are being managed. The agents that are most advanced in their development are the oral DTI (dabigatran etexilate) and oral direct factor Xa inhibitors (such apixaban and rivaroxaban). In contrast to warfarin, these new oral anticoagulants in general have a more rapid onset of action that may obviate the need for parenteral anticoagulation in the initial treatment of VTE. Also because these agents have stable pharmacodynamics, unlike warfarin, routine monitoring is not required, which make them more ideal agents for long-term anticoagulation. Currently there are no antidotes for these agents.

Oral Direct Thrombin Inhibitors

Ximelagatran was the first oral DTI to complete phase III clinical trials; however, because of the high incidence of hepatotoxicity, the sponsoring company withdrew it from the market.

Dabigatran etexilate—a prodrug—has been shown to be not inferior to subcutaneous enoxaparin in the prevention of VTE after total knee or total hip arthroplasty with similar bleeding risks.[51–53] In a randomized, double-blind, noninferiority trial involving 2,539 patients with acute VTE (RE-COVER), a fixed dose of dabigatran without requiring laboratory monitoring was shown to be as effective as warfarin for the treatment of acute VTE, with a similar safety profile.[54] Dabigatran is not approved yet

by the FDA for prevention and treatment of VTE. However, it has been approved recently for **the** prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation based on the data from the RE-LY trial.[55] It requires dose adjustments for patients with a creatinine clearance of 15 to 30 mL/min and is not recommended if the creatinine clearance is ≤15 mL/min.

Oral Direct Factor Xa Inhibitors

Rivaroxaban is an oral direct factor Xa inhibitor with a relatively short half-life of 5 to 9 hours and rapid onset of action of 2.5 to 4 hours. In the EINSTEIN trial,[56] oral rivaroxaban given alone (twice daily for 3 weeks followed by once daily thereafter) was not inferior to subcutaneous enoxaparin followed by a VKA antagonist for treatment of acute symptomatic DVT with a similar safety profile.

In the RECORD trials[57–60]—four phase III doubleblinded randomized trials—rivaroxaban has been shown to be superior to enoxaparin for the prevention of VTE following knee and hip arthroplasty with a similar safety profile. Rivaroxaban was recently approved in USA for the prevention of VTE in adults following hip and knee arthroplasty.

Rivaroxaban should not be used in patients with severe renal insufficiency or significant hepatic impairment.

Apixaban is another oral direct factor Xa inhibitor with promising data. Apixiban was found to be comparable to warfarin in a small phase II trial for the treatment of DVT.[61] In two phase III trials,[62,63] apixaban was superior to enoxaparin when given using the European regimen (40 mg daily starting on the evening before surgery) in preventing VTE after knee and hip arthroplasty. However, in another study,[64] apixaban failed to meet the noninferiority standards for the prevention of VTE after knee arthroplasty when compared to enoxaparin (given in the North American regimen of 30 mg every 12 hours starting 12 to 24 hours after surgery). Other direct factor Xa inhibitors in development include betrixaban, razaxaban, and otamixaban.

Thrombolytic Therapy for Venous Thromboembolism

Thrombolytic therapy for the initial treatment of VTE has been used for well over a quarter of a century. It has been promoted for the treatment of both DVT and PE. Currently, there are three agents available in the United States: rt-PA, reteplase, and tenecteplase.

The goal of thrombolytic therapy for an acute DVT is to produce rapid clot lysis, with the intent of preserving valvular function and preventing the PTS. Earlier data pooled from six randomized DVT trials comparing streptokinase to heparin demonstrated that thrombus resolution was achieved 3.7 times more often among individuals treated with streptokinase. These studies also showed that major bleeding

was approximately three times more frequent in the streptokinase groups.[65] More recent reports utilizing urokinase and recombinant tissue-type plasminogen activator (t-PA) have reported similar findings.[66]

Thrombolytic therapy for DVT is best performed using a catheter-directed infusion. It should be initiated within the first 2 weeks of an acute event and should be reserved for individuals at low risk for bleeding and good functional status with an acute extensive proximal DVT or in patients with a limb-threatening circulatory compromise as in phlegmasia cerulea dolens, or individuals with effort vein thrombosis of the upper extremity (Paget–von Schroetter syndrome). It may also be beneficial in patients with an occluded central venous catheter, in hopes of preserving the function of the catheter and avoiding its removal.

One of the more controversial areas is the use of thrombolytic therapy for acute PE. Most clinicians favor the use of these agents over pulmonary embolectomy for patients with a massive PE defined as a systolic blood pressure (BP) under 90 mm Hg. Thrombolysis accelerates resolution of emboli, improving RV function, pulmonary perfusion, and the hemodynamic status of the patient.

In a meta-analysis of nine trials using thrombolytic therapy for acute PE, Anderson et al. found more rapid resolution of the radiographic appearance and hemodynamic abnormalities when compared to heparin. There was no difference, in the clinically relevant outcomes of death or the rate of resolution of symptoms in the two groups, but there was a 1% to 2% increased risk of intracranial hemorrhage in the thrombolysis group.[50]

Thrombolytic therapy has also been recommended for a carefully selected subgroup of patients who are hemodynamically stable but have high risk features (echocardiographic evidence for RV dysfunction and positive biomarkers) and judged to have a low risk of bleeding. In this setting, the goal of therapy is rapid reversal of right-sided heart dysfunction, to reduce the potential for CTPH, death, and recurrent pulmonary emboli.[50]

Thrombolytic therapy should be reserved for those individuals with a massive PE and hemodynamic instability. Although the risk for major bleeding has improved with physician experience, and the intracranial bleeding rate is small, the current ACCP guidelines do not recommend thrombolytic therapy for patients with smaller emboli or routine use in the majority of individuals with PE-associated RV dysfunction.[50]

To date, most studies demonstrate a favorable outcome for patients who are hemodynamically stable and who are promptly diagnosed and treated for acute PE with UFH, LMWH, or fondaparinux.

MECHANICAL AND SURGICAL APPROACHES TO TREATING VTE

Other therapeutic options for the management of acute VTE have been tried, including mechanical and surgical approaches. Open surgical thrombectomy had previously fallen out of favor; however, with newer surgical techniques, it has regained a role in the management of DVT. Percutaneous mechanical thrombectomy using rotational or hydrodynamic (rheolytic) devices may provide another option for patients with DVT. These devices may be beneficial in individuals who are not candidates for thrombolytic therapy or in patients who may not tolerate traditional doses of thrombolytic therapy but who have considerable clot burden. Angioplasty and stenting have also been used and may be of help in treating individuals with a left common iliac vein stenosis, known as the May–Thurner syndrome. For most of these devices, only small case studies have been reported; therefore, the experience has been insufficient to recommend their routine use.

Percutaneous embolectomy and pulmonary embolectomy are other available options for a patient with PE who is not a candidate for thrombolytic therapy. The percutaneous devices remove, fragment, or aspirate emboli, offering rapid relief of central thrombus. Pulmonary embolectomy, generally considered for select patients who are not candidates for thrombolysis, may be lifesaving for a patient presenting with hemodynamic instability. Pulmonary thromboendarterectomy is considered the treatment of choice for patients with CTPH when their disease is accessible surgically.

Inferior Vena Cava Interruption (IVC Filters)

Absolute indications for IVC filter placement are (a) a contradiction to anticoagulation, (b) recurrent thromboembolic disease despite adequate anticoagulation therapy, (c) complication of anticoagulation therapy, and (d) for patients who require pulmonary embolectomy or a thromboendarterectomy.

There are a number of relative indications for IVC filter placement, including free-floating thrombus, PE in the setting of cor pulmonale, ataxia, or patients with a recent VTE who require urgent surgery.

Recurrent clinically symptomatic PE after IVC filter placement has been reported in approximately 2% to 5% of cases.[67] The source of PE could be de novo thrombus forming within the filter, or propagation of a preexisting thrombus through the filter, or thrombus that originates from the arm or neck veins. Current recommendations advise that patients with IVC filters receive full-dose anticoagulation once it becomes safe to do so. In one study of 400 patients who received either an IVC filter or standard anticoagulation for treatment of VTE, a statistically higher DVT recurrence rate was identified in the filter population.[68]

In addition to the increased risk for recurrent VTE, IVC filters can lead to thrombosis at the venous access site, filter migration, or penetration and obstruction of the vena cava. Therefore, it is prudent to adhere strictly to the appropriate criteria when evaluating patients for IVC filter placement.

Although they are not yet FDA approved as "optional devices," retrievable IVC filters are approved as permanent filters. Indications for their use should follow the same guidelines as used for the placement of permanent filters.[69]

THROMBOPROPHYLAXIS

Although thromboprophylaxis should be provided to all hospitalized patients, unfortunately all physicians do not universally practice this policy, largely because it is either overlooked or not even considered. Individuals who are considered at greatest risk for VTE are those over 40 years of age, patients who are immobilized, or patients who have an underlying medical condition (MI, stroke, CHF, pneumonia), have a trauma, or underwent a recent surgical procedure (especially hip fracture, total knee or hip replacement, or neurosurgical procedures).

There are two major forms of prophylaxis, mechanical and pharmacologic. Those who cannot receive prophylactic anticoagulation should be prescribed mechanical modalities such as graduated compression stockings or intermittent pneumatic compression devices. Pharmacologic prophylaxis can be achieved by a number of agents, including UFH, LMWH, fondaparinux, the DTI desirudin (only approved for hip replacement surgery), or a VKA. In high-risk populations such as those with hip fracture, or hip or knee replacement, a combination of mechanical and pharmacologic therapies should be considered. A new oral anticoagulant, Rivaroxaban, was recently approved in USA for the prevention of VTE in adults following hip and knee arthroplasty. Other oral anticoagulant agents (dabigatran and apixaban) are available outside the United States for prophylaxis and will likely be available sometime in the near future in the United States.

More specific indications for certain high-risk clinical situations are listed below. These recommendations are based on the most recent ACCP guidelines.[70]

- Hip fracture surgery—Fondaparinux
- Total hip/knee arthroplasty—LMWH, Fondaparinux, Rivaroxaban or warfarin with an INR target of 2.0 to 3.0
- Neurosurgery—Intermittent pneumatic compression devices with or without graduated compression stockings, postoperative use of UFH, or LMWH when acceptable bleeding risk
- Medical conditions—LMWH or UFH
- High-risk general surgery/gynecologic surgery—LMWH, fondaparinux, or UFH and intermittent pneumatic compression ± graduated compression stockings

Prophylaxis should continue until the patient starts ambulating and/or the physician is comfortable that the individual is no longer at risk to develop a VTE. In select surgical

procedures, extended prophylaxis is recommended. For example, extended prophylaxis for up to 28 to 35 days is recommended for patients who have had a hip fracture or who undergo total hip replacement surgery.[70] Patients undergoing high-risk general surgery or gynecologic surgery (especially cancer surgery) should also receive extended prophylaxis (up to 28 days is recommended).[70]

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QUESTIONS AND ANSWERS

Questions

1. A 57-year-old male is brought to the emergency room by emergency medical services (EMS) after suffering from a syncopal episode. He has noticed dyspnea on exertion for the last 2 days and suddenly lost consciousness while sitting on his couch. His wife witnessed the event. He did not have jerky movements, and he regained consciousness spontaneously after 2 minutes. EMS found him hypoxic with O_2 saturation of 84% on room air.He denied chest pain or dizziness preceding the syncopal event and denied fever or chills. In the ED, his blood pressure (BP) was 110/70, heart rate 110, and sat 94% on 2 L of O_2. On exam, he had no jugular venous distension (JVD), normal heart sounds with no murmurs, and clear lungs without crackles or rales. There was 1+ LE edema. EKG showed sinus tachycardia and nonspecific T-wave changes in the inferior leads. Bedside troponin is positive. CK and full metabolic profile are negative. He smokes one pack of cigarettes a day. He denies HTN or hyperlipidemia. His father had coronary artery bypass graft (CABG) at age 75. He just returned 2 weeks ago from a short business trip to China where he was treated for traveler diarrhea. In managing this patient, what is your first diagnostic test?
   a. Transthoracic echo (TTE)
   b. Left heart catheterization
   c. Spiral computed tomography (CT) of the chest
   d. Transesophageal echocardiogram (TEE)
   e. Pharmacologic nuclear stress test
2. A 50-year-old male is brought to the emergency room by EMS after suffering from a syncopal episode. He has noticed dyspnea on exertion for the last 2 days and suddenly lost consciousness while sitting on his couch. His wife witnessed the event. He did not have jerky movements, and he regained consciousness spontaneously after 2 minutes. EMS found him hypoxic with O_2 saturation of 84% on room air. He denied chest pain or dizziness preceding the syncopal event and denied fever or chills. In the ED, his BP was 110/70, heart rate 101, and sat 94% on 2 L of O_2. On exam, he had no JVD, normal heart sounds with no murmurs, and clear lungs without crackles or rales. There was 1 + LE edema. EKG showed sinus tachycardia and nonspecific T-wave changes in the inferior leads.

Bedside troponin is negative. CK and full metabolic profile are negative. He smokes one pack of cigarettes a day. He denies HTN or hyperlipidemia. His father had CABG at age 75. He just returned 2 weeks ago from a short business trip to China where he was treated for traveler diarrhea.

CT scan of the chest is done and showed saddle pulmonary embolism (PE). What is the most appropriate treatment?

a. TPA + IV heparin
b. IV heparin bolus followed by continuous drip
c. Inferior vena cava (IVC) filter placement
d. Surgical embolectomy

3. A 68-year-old woman who is currently undergoing chemotherapy for a recent diagnosis of breast cancer presents to the emergency room with 2 days of right leg swelling. She denies chest pain, shortness of breath, dizziness, or syncope. She has a history of HTN and hyperlipidemia. She has no previous cardiac history. She is active and walks 1 to 2 miles daily. On physical exam, she has 2+ pitting edema of her right leg with mild calf tenderness. Pedal pulses are normal. Skin is warm with normal capillary refill. Lower extremity ultrasound showed right common femoral and distal iliac arteries to be dilated and not compressible.

Her platelet count is 110K and hemoglobin 10.7. Blood count and metabolic profile otherwise are normal. What is the most appropriate treatment?

a. IVC filter insertion
b. Enoxaparin with bridge to coumadin until INR is therapeutic
c. Low-molecular-weight heparin (LMWH) as monotherapy
d. LMWH and placement of IVC filter
e. Catheter-directed thrombolysis

4. A 45-year-old obese female with a history of hypertension, hyperlipidemia, and rheumatoid arthritis is hospitalized for elective cholecystectomy. On postoperative day 1 after uncomplicated surgery, she develops sudden onset of chest pain and shortness of breath. On exam, she has a heart rate of 124 bpm, her BP is 78/50, and O_2 sat 86% on room air and 95% on 4 L of O_2. Heart sounds are normal with no murmur. Lungs are clear to auscultation. Lower extremities show bilateral mild pitting edema. Her metabolic panel and blood count are normal. Troponin T is 0.12 (slightly elevated). Bedside stat echo shows moderate right ventricular (RV) dysfunction. Spiral CT of the chest shows large thrombus in the main pulmonary artery extending into left and right pulmonary arteries. The best treatment is:

a. IV heparin bolus followed by heparin drip
b. TPA followed by IV heparin
c. Insertion of IVC filter
d. Call cardiothoracic surgery for emergent surgical pulmonary artery thrombectomy

5. A 28-year-old female para 0 gravida 1, who is 12 weeks pregnant, presented to the emergency room with right leg swelling, redness, and pain. The pain started 2 days ago and has gotten worse since. She denies leg trauma, recent surgery, or immobilization. She has no chest pain, shortness of breath, dizziness, or syncope. Her heart rate is 89, BP 125/80, and sat 97% on RA. D-Dimer test was positive. Ultrasound of her lower extremities showed dilated and noncompressible right femoral and popliteal veins. She is healthy and has no previous medical history. Her mother had PE after delivery of her second child. She smoked for 5 years and quit recently when she learned that she was pregnant. The best treatment option is:

a. IV heparin with bridge to coumadin
b. Therapeutic dose subcutaneous enoxaparin with bridge to coumadin
c. Therapeutic dose subcutaneous enoxaparin as monotherapy
d. Coumadin alone; no need for bridging
e. IVC filter

6. Duration of anticoagulation for the patient in Question 5 should be:

a. 3 months

b. 6 months
c. Throughout her pregnancy
d. Throughout her pregnancy, hold around delivery and resume for 6 more weeks postpartum
e. Lifelong

7. A 69-year-old obese female was recently diagnosed with nonresectable lung cancer is in the process of initiating chemo therapy and radiation therapy. She presented to the emergency room with sudden onset of shortness of breath. She has hypertension and hyperlipidemia. She has no known cardiac disease. She denies chest pain, cough, fever, or chills. Physical exam reveals heart rate of 95 bpm, BP 120/78, and sat 91% on RA. She has normal heart sounds and decreased breath sounds over the right lower lobe. She has right leg swelling. EKG shows sinus tachycardia with nonspecific T-wave changes. Chest x-ray shows a right lower lobe nodule and moderate left pleural effusion. Her metabolic panel is normal, D-dimer is 750 ng/ml {500 upper normal limit), and troponin is negative. Lower extremity venous ultrasound is negative for DVT. Spiral CT of the chest is not diagnostic due to tachycardia and motion artifact. The best next step in confirming your diagnosis is:
   a. Repeat spiral CT of the chest
   b. Ventilation/perfusion {V/Q) scan
   c. Magnetic resonance imaging (MRI) of the chest
   d. Pulmonary artery angiogram
   e. Transthoracic Echocardiogram
   f. Transesophageal echocardiogram (TEE)

8. Pulmonary angiogram was done and showed left and right lower lobe segmental and subsegmental filling defect consistent with acute PE. Best treatment option and duration of therapy is:
   a. LMWH bridge to coumadin for 6 months.
   b. Heparin bridge to coumadin for 6 months
   c. LMWH as monotherapy for 6 months
   d. LMWH as monotherapy for 6 months, followed by transition to coumadin indefinitely
   e. Fondaparinux as monotherapy for 6 months
   f. Dabigatran indefinitely

Answers

1. Answer C: The patient is at risk for PE with a recent long-distance trip. Syncope is not an uncommon presentation for acute PE and should not be overlooked. Positive troponin here reflects RV strain and not acute coronary syndrome (ACS).

2. Answer A: The patient is hemodynamically stable. Treatment of choice is full-dose anticoagulation with unfractionated intravenous heparin or subcutaneous therapeutic dose LMWH. There is no indication for thrombolysis or surgical embolectomy in the absence of hemodynamic instability. IVC filter is not indicated unless the patient has contraindication for full-dose anticoagulation.

3. Answer C: The patient has an unprovoked thromboembolic event in the setting of an active malignancy. The current guidelines recommend use of LMWH as monotherapy for 3 to 6 months before considering transition to coumadin. Catheter-directed thrombolysis would be indicated if the limb was threatened due to extensive thrombosis. IVC filter is not indicated unless the patient has contraindication for full-dose anticoagulation.

4. Answer D: The patient is hemodynamically unstable, and treatment with heparin only carries a mortality as high as 50%. T-PA is contraindicated few hours after surgery. Emergent thrombectomy should be considered in cases of hemodynamic instability when thrombolytic therapy is contraindicated.

5. Answer C: Coumadin is teratogenic and should not be used during pregnancy. Therapeutic dose of enoxaparin would be the best option for this patient. Treatment options for this patient include LMWH or full dose subcutaneous unfractionated heparin that is associated with a high risk of osteoporosis when taken for a long time.

6. Answer D: During the postpartum period, this patient continues to be hypercoagulable and should be

kept anticoagulated for at least 6 weeks. The patient can be transitioned to coumadin after delivery.

7. Answer D: Pulmonary artery angiogram is still considered the gold standard for diagnosing PE and should be considered when a high clinical suspicion cannot be confirmed by other modalities. Because of her abnormal chest x-ray, a V/Q scan is unlikely to be helpful in confirming the diagnosis. Transthoracic Echocardiogram is used to risk stratify patients with confirmed acute PE; however, it cannot be used to establish the diagnosis. Even though a central PE can be visualized by TEE, segmental or subsegmental PE would be missed.

8. Answer D: Patients with unprovoked venous thromboembolism (VTE) in the setting of an active malignancy should be treated indefinitely in the absence of contraindications, as long as their malignancy is active. LMWH is the treatment of choice in the first 3 to 6 months in patients with active malignancy. Dabigatran is not approved for treatment of venous thrombosis at this time.

CHAPTER

Peripheral Artery Disease

Siddharth A. Wartak and Heather L. Gornik

Lower extremity peripheral artery disease (PAD) is a marker of systemic atherosclerosis and has been estimated to affect approximately 8 to 12 million Americans.[1] PAD is associated with functional and quality of life (QOL) impairment, increased risk of progressive limb ischemia, and increased risk of cardiovascular ischemic events (i.e., myocardial infarction [MI] and stroke) and mortality. Although screening for PAD is simple, easy, and inexpensive using the ankle–brachial index (ABI), PAD remains an underdiagnosed and undertreated health condition. Treatment of the PAD patient requires attention to leg symptoms and functional capacity as well as aggressive cardiovascular risk reduction therapies.

DEFINITION

Atherosclerotic peripheral vascular disease includes a diverse group of disorders that lead to progressive stenosis, occlusion, or aneurysmal dilation of the aorta and its noncoronary branch arteries, including the carotid and vertebral, upper extremity, visceral, and lower extremity arterial branches. According to the American Heart Association, PAD is the preferred clinical term used to describe disease of the arteries of the arms and legs. This chapter focuses on lower extremity PAD, although it is recognized that upper extremity PAD, especially subclavian artery stenosis, can be an important clinical disorder that may lead to discrepant blood pressures in the arms, arm claudication, or vertebral–subclavian or coronary–subclavian steal phenomena. In addition, while lower extremity PAD may uncommonly be caused by nonatherosclerotic disease (e.g., large vessel vasculitis, arterial entrapment syndromes, fibromuscular dysplasia), this chapter focuses on lower extremity PAD due to atherosclerotic vascular disease, the most common cause.

EPIDEMIOLOGY AND RISK FACTORS

The prevalence of PAD increases with age, and the disease affects men and women nearly equally, up to 29% of the elderly population in a general medical practice.[2,3] Risk factors for PAD are similar to those of coronary artery disease. They can be categorized as hereditary or acquired. The most important risk factors for PAD are advanced age, diabetes mellitus, and tobacco use. Additional risk factors for PAD are shown in Table 50.1.

TABLE
50.1 Risk Factors for Lower Extremity PAD

Traditional Atherosclerotic Risk Factors
Advanced age
Tobacco smoking
Diabetes mellitus
Hypertension
Hypercholesterolemia
Additional Risk Factors
Hyperhomocystinemia
African American race (twofold increased risk for PAD)[48]
Chronic renal insufficiency
Inflammation (e.g., elevated C-reactive protein)
Elevated lipoprotein (a)

PAD IS A MARKER OF INCREASED CARDIOVASCULAR RISK

PAD is a marker for extensive systemic atherosclerosis and high cardiovascular risk. It has been estimated that among patients with symptomatic PAD (claudication) the 5-year mortality is as high as 30% with an additional 20% suffering a nonfatal MI or stroke.[4] In published case series of PAD patients, 60% to 80% have significant coronary artery disease in at least one vessel on angiography[5,6] and up to 25% of patients will have significant internal carotid artery stenosis [7,8] In the recent REACH registry, 21% of patients with PAD suffered an MI, a stroke, cardiovascular death, or hospitalization within 1 year of follow-up as compared to 15% of patients with established coronary artery disease.[9]

A low ABI has been shown in multiple studies to be an independent predictor of mortality.[10,11] Patients with ABI of <0.90 are twice as likely to have a history of MI, angina, and heart failure than patients with an ABI of >1.0.[12,13] An abnormal ABI also provides complimentary information to Framingham risk score (FRS) and increases

cardiovascular risk prediction. A low ABI (≤0.90) was associated with approximately twice the 10-year total mortality, cardiovascular mortality, and major coronary event rate compared to the overall rate in each FRS category.[14] In the recently published German Epidemiological Trial on Ankle-Brachial Index (GET ABI), an abnormal ABI for both symptomatic and asymptomatic patients was associated with increased risk of major cardiovascular events.[15]

NATURAL HISTORY OF PAD

Less than 5% of patients with stable claudication will require amputation;[4] however, the annual risk increases dramatically to 30% to 40% among those with critical limb ischemia (CLI).[16] It has been demonstrated that patients with PAD have significant function and QOL impairment. The QOL impairment among PAD patients is similar to that of patients with congestive heart failure or recent MI.[17] Objective evidence of clinical depression is twice as common among patients with PAD.[18] PAD leads to functional impairment with decreased walking distance and speed in patients with claudication and even among patients with atypical leg symptoms.[19] Such functional impairment can diminish a patient's abilities to work, exercise regularly, and participate in recreational activities.

SYMPTOMS AND SIGNS OF PAD

The classic symptom of lower extremity PAD is claudication, which is derived from Latin and meaning to limp. Claudication is defined as recurrent burning, aching, fatigue, or heaviness in the leg muscles that is provoked with a predictable level of exercise and that resolves with a predictable duration of rest (generally <10 minutes). The Rose claudication questionnaire is a simple screening tool for claudication that can be used in clinical practice by asking the patient two simple questions: "Do you get pain in either leg when you walk?" and "Does the pain go away when you stop walking?" If the answer to both questions is yes, the likelihood of PAD is >95%.[20] Claudication must be distinguished from other potential diagnoses, including pseudoclaudication due to lumbar canal stenosis that can present with buttock, back, and thigh pain with both exertion and prolonged standing. While claudication is an important symptom of PAD, it is important to recognize that the majority of patients with PAD do not present with classic intermittent claudication (Fig. 50.1). The majority of patients with PAD will exhibit leg discomforts that do not meet the definition of claudication (atypical leg symptoms), while others remain completely asymptomatic and are identified only through measures such as the ABI.

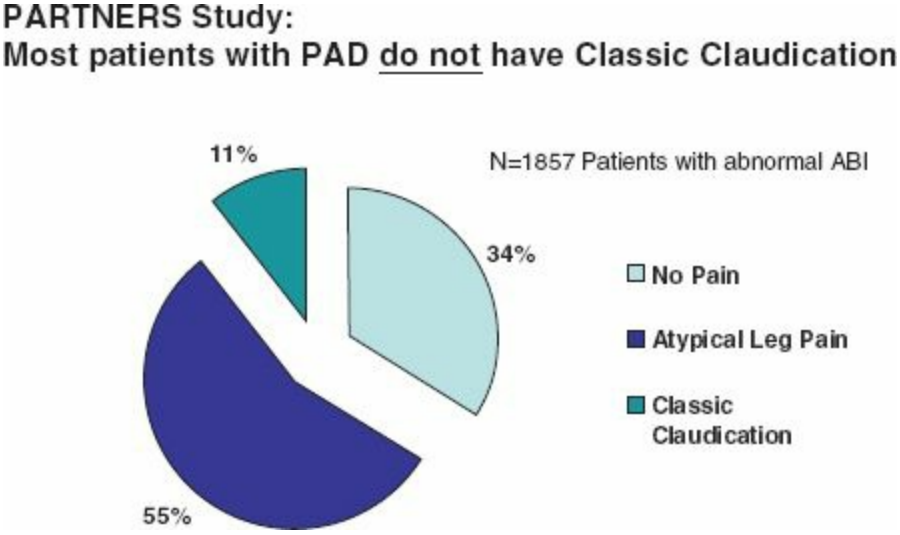

FIGURE 50.1 Clinical presentation of lower extremity PAD in the stable patient. In these data from the PARTNERS study, the majority of patients identified to have an abnormal ABI on a screening examination were either asymptomatic or had leg symptoms atypical for claudication. Only 11% in this study had classic intermittent claudication. These findings emphasize the variable clinical presentation of PAD and the need to incorporate modalities beyond screening for claudication (such as the ABI) to diagnose this disease. (Adapted from Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA. 2001;286(11):1317–1324.)

Acute Limb Ischemia and Critical Limb Ischemia

There are two severe clinical presentations of lower extremity PAD that must be clinically recognized in a timely fashion. Acute limb ischemia, characterized by the "6Ps" of pain, paresthesias, pallor, pulselessness, paralysis, and poikilothermia (or "polar"), is a vascular emergency due to thrombotic arterial occlusion that requires urgent revascularization with thrombolytic therapy and/or thrombectomy. CLI is a more common severe clinical presentation of PAD. CLI is defined as objectively proven PAD plus ischemic rest pain, nonhealing ulceration, or gangrene that has been present for at least 2 weeks.[21] The most important risk factors for development of CLI among patients with stable PAD are diabetes mellitus and ongoing tobacco use, but older patient age (>65 years), lower baseline ABI, and hyperlipidemia also increase risk.[21] CLI is vascular urgency that requires expedient evaluation for revascularization. Patients with CLI are at a very high risk of a major cardiovascular event in the year following diagnosis, including death, and careful assessment of cardiovascular risk factor control and symptoms is important in this population.

Physical Examination Findings in Peripheral Arterial Disease

A comprehensive history and vascular examination is key for diagnosis and appropriate management of PAD. The comprehensive physical examination in the PAD patient should include measurement of blood pressure in bilateral arms (to screen for subclavian stenosis/upper extremity PAD); assessment of the carotid, upper extremity,

and lower extremity (femoral, popliteal, dorsalis pedis [DP], posterior tibial) pulses; and assessment of the abdominal aorta. Using standardized definitions, pulses are graded on a scale from 0 to 3 with 2 = normal pulse, 1 = diminished pulse, 0 = nonpalpable pulse, and 3 = abnormally bounding or aneurysmal pulse.[16] If no pulse is palpable, Doppler examination using a handheld continuous-wave device should be performed. An absent posterior tibial pulse has high specificity for diagnosis of PAD. Abnormalities of the DP pulse are less specific due to a high prevalence of anomalous or absent DP arteries in healthy patients. In addition to pulse deficits, other physical examination findings consistent with lower extremity PAD include vascular bruits (heard over femoral or popliteal arteries), hair loss, nail hypertrophy, and rapid elevation pallor or dependent rubor of the leg. Socks must be removed at every visit to carefully inspect the feet for evidence of tissue loss (i.e., ulcers or gangrene) as well as for signs of concomitant foot pathology, such as peripheral neuropathy or excessive callous formation.

DIAGNOSTIC TESTING FOR PAD

Ankle–Brachial Index

The ABI is the ratio of ankle systolic pressure to brachial systolic pressure and is determined by measuring systolic blood pressures in bilateral brachial arteries and at bilateral DP and posterior tibial arteries using a handheld Doppler device. Calculation of the ABI is shown in Figure 50.2. Interpretation guidelines for the ABI are shown in Table 50.2. The range of normal values for an ABI is 1.0 to 1.4. A normal resting ABI does not always rule out PAD. If the ABI is borderline (e.g., 0.91 to 0.99) or normal and the clinical suspicion of PAD is high, repeat ABI after treadmill exercise should be performed. An ABI may fall by 20% or more in patients with significant PAD after exercise. This is especially true among patients with aortoiliac disease (“inflow disease”).

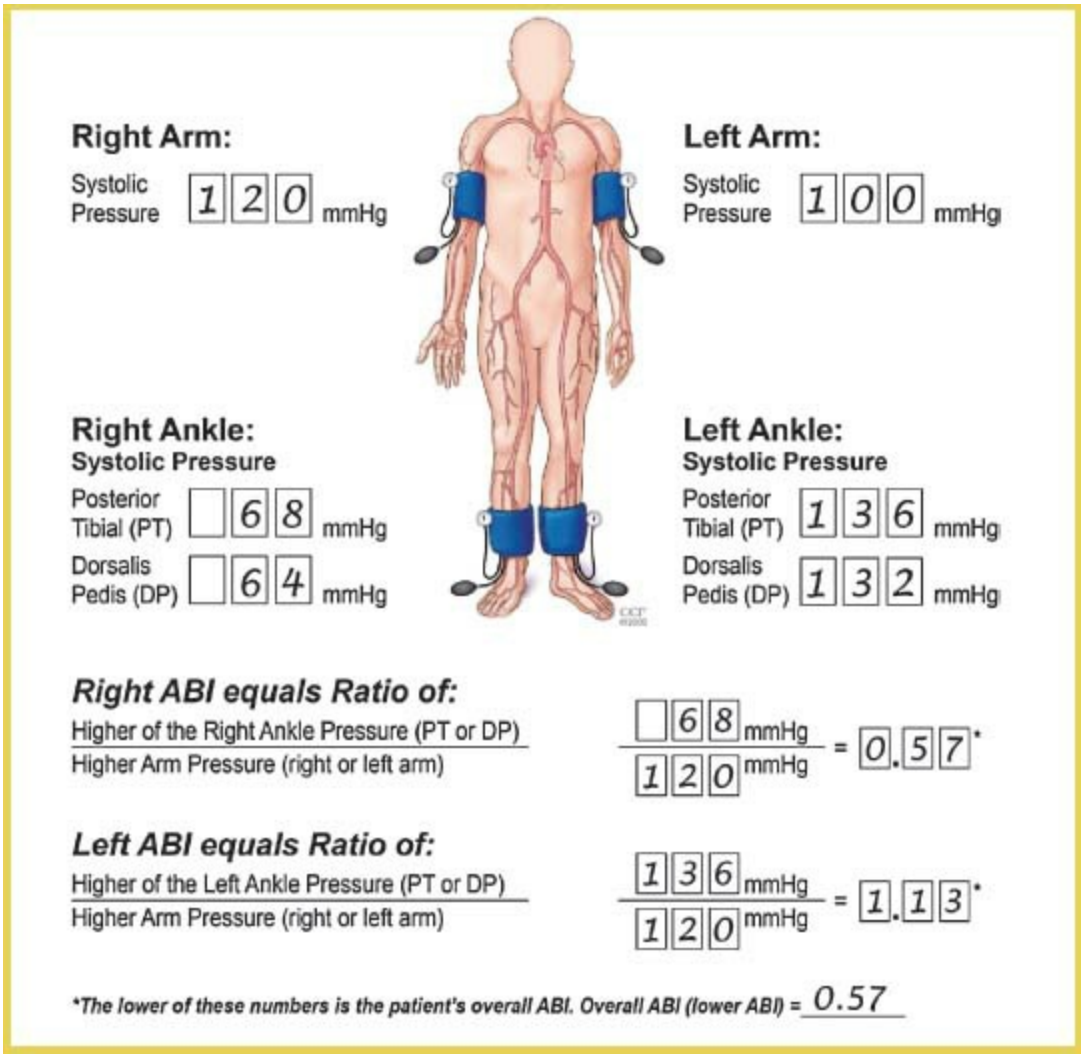

Figure 50.2 Calculation of the ABI. The ABI is the ratio of blood flow in the legs to the arms. The ankle blood pressure for each limb is the higher of the DP and posterior tibial artery pressures. For both the right and left ABI calculation, the higher of the two arm blood pressures is used for the denominator. (From Cleveland Clinic Foundation, with permission.)

TABLE
50.2 Interpretation of the ABI[a]

ABI Value	Interpretation
1.00–1.39	Normal
0.91–0.99	Borderline ABI, consider exercise ABI testing
≤0.90	Abnormal, PAD
≤0.4	Severe PAD
≥1.4	Noncompressible vessels, must use other modality to asses for PAD (such as TBI and/or PVR waveforms)

[a]ABI values are interpreted according to the 2011 update of the American College of Cardiology Foundation/American Heart Association Guideline for the management of Patients with Peripheral Artery Disease. Rooke TW, et al. J Am Coll Cardiol. 2011;58(19):2020–2045.

It should also be emphasized that an ABI of >1.4 is not normal and suggests noncompressible vessels either from vascular calcification ("medial calcinosis") or from inability to compress arteries due to obesity. This is commonly seen among patients with diabetes and chronic kidney disease. A high or falsely elevated ABI has been shown to confer increased cardiovascular risk in epidemiologic studies.[10,14] In clinical practice, an ABI > 1.4 cannot be interpreted and thus cannot confirm or rule out the diagnosis of PAD without another diagnostic test, such as pulse volume recordings (PVRs), the toe–brachial index (TBI), or an imaging modality.

Imaging Studies for PAD

Beyond the ABI, segmental leg pressures with PVRs or Doppler tracings may be used to localize disease by anatomic segments (e.g., aortoiliac disease, femoropopliteal disease, infrapopliteal disease). Transcutaneous oximetry may be helpful to determine tissue perfusion and limb viability in the setting of CLI and ulceration. In some cases, imaging modalities may be indicated to more definitively define anatomy and establish severity of disease. Diagnostic modalities for PAD are shown in Table 50.3. In general, imaging studies are most appropriately reserved for selected patients with PAD, such as for revascularization planning or for postprocedural graft or stent surveillance or for cases in which the diagnosis of PAD or the nature of disease is uncertain. For example, these imaging studies are particularly important for evaluation of nonatherosclerotic causes of PAD (e.g., arterial aneurysm, fibromuscular dysplasia, entrapment syndromes, and vasculitis). Imaging studies may also be indicated to establish the diagnosis of PAD in the setting of noncompressible vessels (i.e., ABI > 1.4).

TABLE
50.3 Diagnostic Modalities for PAD

Physiologic Testing (Nonimaging)
ABI at rest ±following treadmill exercise
TBI
Transcutaneous oximetry or laser Doppler
Segmental leg pressures with PVRs and/or Doppler waveforms
Imaging Modalities
Arterial duplex (complete or limited examination)
Magnetic resonance angiography (MRA)
Computed tomographic angiography (CTA)
Catheter-based digital subtraction angiography [invasive[a]]

[a]Angiography is generally reserved for cases in which revascularization is anticipated or noninvasive testing is inadequate to comprehensively evaluate the patient.

MANAGEMENT OF PAD: A THREE-PRONGED APPROACH

The comprehensive care of the PAD patient must address three important aspects: protection of the feet and prevention of limb loss, prevention of cardiovascular events, and improvement of functional capacity and QOL (Fig. 50.3).

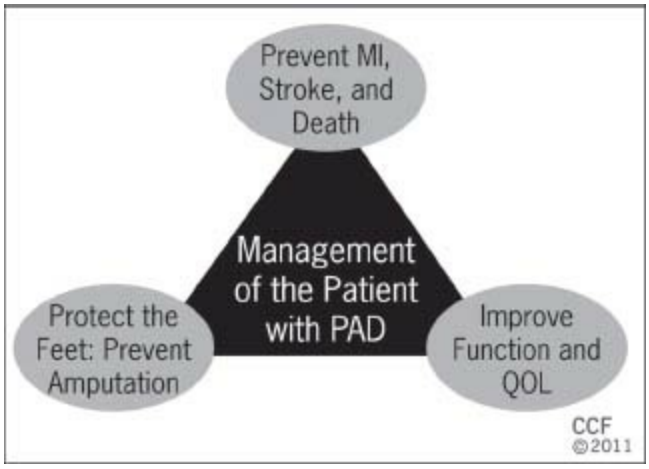

FIGURE 50.3 The three-pronged approach to PAD care. Comprehensive care of the PAD patient must include all three aspects of care. (From Cleveland Clinic Foundation, with permission.)

Foot Care and Ulcer Prevention

The feet of the PAD patient must be examined at every office visit. The importance of meticulous foot and nail care should be reviewed regularly, including the need for regular foot self-inspection, moisturization of the feet, and use of appropriate footwear. Patients should be educated regarding the symptoms and signs of CLI and advised to seek medical attention should these develop. Patients should be referred for podiatric care when indicated, and the use of diabetic footwear and orthotic devices should be considered for patients with diabetes mellitus, foot deformities, or excessive callous formation.

Prevention of Cardiovascular Events

Therapies to prevent MI and stroke are crucial for every patient with PAD, including those without known atherosclerotic carotid or coronary artery disease. While there are little data regarding the benefits of CV risk reduction therapies among asymptomatic patients with an abnormal ABI, the same therapies are generally recommended for these PAD patients. Elements of a risk reduction program for the PAD patient are shown in Table 50.4 and discussed in detailed in both the American College of Cardiology/American Heart Association (ACC/AHA) and the Inter-Society Consensus

for the Management of Peripheral Arterial Disease (TASC-II) guidelines.[16,21,21a] Cardiovascular risk reduction therapies are underprescribed among patients with PAD and in comparison to those with coronary artery disease.[22,23]

TABLE
50.4 Therapies to Prevent Cardiovascular Events Among Patients with PAD

Smoking cessation
■ Counseling programs
■ Pharmacotherapy (nicotine replacement, bupropion, varenicline)
Antiplatelet therapy
■ Aspirin
■ Clopidogrel
Lipid-lowering therapy
■ Statins
■ Nonstatin agents
Blood pressure control
■ ACE-inhibitors or angiotensin receptor blockers
■ Other agents
Glycemic control for diabetic patients
Annual influenza vaccination

Smoking Cessation

It is well established that smoking cessation decreases the risk of MI, stroke, and malignancy and improves survival. Among patients with PAD, smoking cessation has been shown (in epidemiologic studies) to lower the risk of amputation, need for revascularization, and bypass graft failure and to improve overall survival.[24–27] Asking patients about their smoking status at every visit and counseling them to quit is the first step in the management of PAD. Pharmacotherapy for smoking cessation such as nicotine replacement, bupropion, and varenicline should be considered and offered. The use of varenicline, a partial α4β nicotinic acetylcholine receptor agonist, has shown to be effective in smokers with cardiovascular disease, including PAD.[28] Referring patients to a formal smoking cessation program, when available, may be helpful.

Antiplatelet Agents

Clinical trials and meta-analyses have shown that antiplatelet medications like aspirin are efficacious in secondary prevention for coronary artery disease and carotid disease. Antiplatelet therapy reduces the incidence of major vascular events among symptomatic PAD patients by approximately 25% as shown in a large meta-analysis.[29] Based upon

these data, both the ACC/AHA and TASC II PAD guidelines recommend antiplatelet therapy with either aspirin or clopidogrel for patients with PAD.[16,21,21a] However, the optimal agent and dose of antiplatelet therapy for patients with PAD have not been definitively established. Data from the prevention of progression of arterial disease and diabetes (POPADAD) trial and Aspirin for Asymptomatic Atherosclerosis (AAA) trial demonstrated a lack of benefit of low-dose aspirin (100 mg/d) for prevention of cardiovascular events among patients with asymptomatic PAD and borderline abnormal ABI.[30,31] The CLIPS trial demonstrated a significant benefit of aspirin 100 mg/d versus placebo among patients with symptomatic or asymptomatic PAD with mean ABI = 0.63, although this study was stopped early due to poor recruitment and had some methodologic flaws.[32] A recently published meta-analysis of trials of aspirin for symptomatic and asymptomatic PAD patients has shown a need for additional studies to confirm the benefit of aspirin for CV risk reduction in PAD patients.[33] When clopidogrel was compared with aspirin among high-risk patients with atherosclerotic vascular disease in the CAPRIE study (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events),[33] there was a small but incremental benefit of clopidogrel, particularly among the subgroup of symptomatic PAD patients.[34] A focused update of the 2005 ACC/AHA PAD guidelines has been published that addresses these new antiplatelet data.[21a] Antiplatelet therapy with either aspirin or clopidogrel is recommended for patients with lower extremity PAD for reduction of cardiovascular events.[21a] Given a lack of compelling efficacy data, dual antiplatelet therapy is not recommended for PAD patients unless there is another compelling indication such as recent acute coronary syndrome or coronary stenting.[35]

Warfarin

Warfarin in combination with antiplatelet medication was compared with antiplatelet medication alone in PAD patients in the WAVE trial (Warfarin Antiplatelet Vascular Evaluation). The combination was not more beneficial but was associated with an increased risk of significantly life-threatening bleeding.[36] Based upon these data, warfarin is not recommended unless there is another compelling indication for its use (e.g., venous thromboembolism or atrial fibrillation).[16,21a]

Lipid-Lowering Therapy

All patients with PAD should be treated with an HMG coenzyme-A reductase inhibitor (statin), unless there is a compelling contraindication. The Heart Protection Study randomized high-risk and relatively normocholesterolemic patients (total cholesterol ≥135 mg/dL) to simvastatin and placebo, including 4,588 patients with lower extremity

PAD.[37] Statins were associated with a 13% reduction in all-cause mortality, 17% reduction in cardiovascular mortality, and 24% reduction in first major vascular event.[37] Among the subset of PAD patients, randomization to simvastatin was associated with a 20% reduction in noncoronary revascularization procedures.[38] Statin therapy has been shown to improve claudication symptoms and slowed the rate of functional decline among patients with PAD.[39,40] The 2005 ACC/AHA PAD guidelines recommend statin therapy to a goal low-density lipoprotein (LDL) cholesterol < 100 mg/dL for PAD patients (Class I, level of evidence [LOE] B) with an option to target cholesterol to <70 mg/dL for very high risk patients (Class IIa, LOE B). For PAD patients with low highdensity lipoprotein (HDL) cholesterol and/or significantly elevated triglycerides, additional lipid-lowering agents (e.g., niacin and fibrates) may be considered, but generally as adjunctive therapy to statins.

Blood Pressure Control

Current practice guidelines recommend antihypertensive therapy for hypertensive PAD patients to achieve a goal of <140/90 mm Hg for nondiabetic patients or of <130/80 mm Hg for PAD patients with concomitant diabetes mellitus or chronic renal disease.[16] Clinical trials have further established the benefit of more intensive blood pressure control, particularly with the angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers. The HOPE trial included 4,046 patients with symptomatic PAD among its population of patients with atherosclerotic vascular disease or diabetes and other risk factors and compared ramipril verses placebo for CV risk reduction among relatively normotensive patients. The trial showed a 22% reduction in major CV events among patients randomized to ramipril.[41] The ONTARGET trial established a role for angiotensin receptor blockers (telmisartan) as an alternative to ACE inhibitors in the management of CV risk in patients with atherosclerotic vascular disease, including PAD.[42] In this study, the combination of ramipril plus telmisartan showed no incremental benefit and increased the risk of significant adverse events including hypotension and hyperkalemia compared to the individual therapies. Intensive blood pressure control among diabetic patients with PAD is particularly important. The ABCD trial compared intensive blood pressure control to standard therapy among diabetic patients using nisoldipine or enalapril. In this trial, intensive BP control essentially eliminated the inverse relationship of ABI and adverse cardiovascular events[43] (Fig. 50.4).

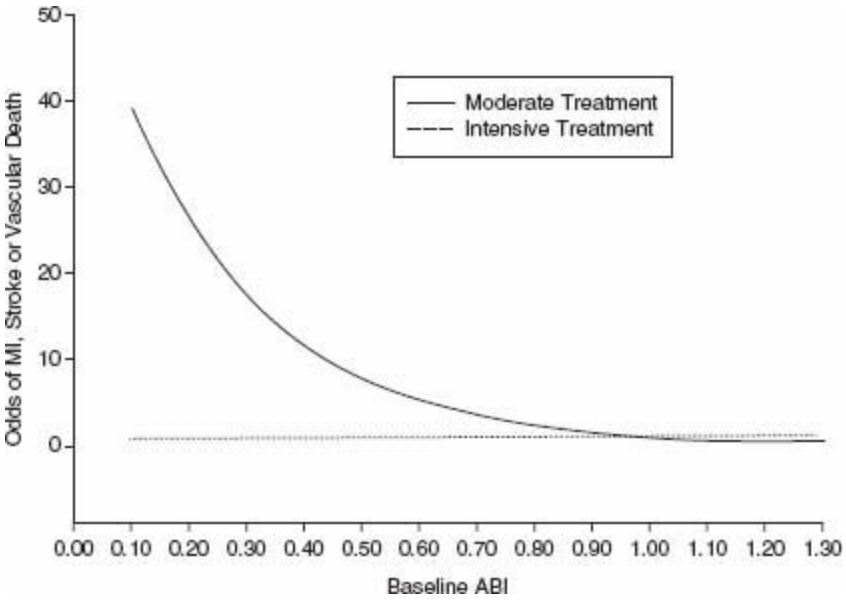

FIGURE 50.4 Intensive blood pressure control reduces risk of cardiovascular events among diabetic patients with PAD: Data from the ABCD trial. Intensive blood pressure control with nisoldipine or enalapril (dashed line) essentially eliminated the relationship of reduced ABI and risk of a major cardiovascular event that was seen in the standard therapy arm (solid line). (Reproduced from Mehler PS, Coll JR, Estacio R, et al. Intensive blood pressure control reduces the risk of cardiovascular events in patients with peripheral arterial disease and type 2 diabetes. Circulation. 2003;107(5):753–756, with permission.)

Beta-Blockers and PAD

Beta-blockers are important medications for PAD patients with prior MI, arrhythmias, and congestive heart failure as well as to prevent cardiovascular events among those undergoing major noncardiac surgery. They may also be used as a first- or second-line agent for blood pressure control. Historically, physicians were taught that beta-blockers may worsen claudication. It has recently been established that beta-blockers can be safely prescribed to patients with symptomatic or asymptomatic PAD. In a recently published meta-analysis of 11 randomized controlled trials, beta-blocker therapy did not worsen claudication in patients with PAD and had no significant effect on pain-free walking distance compared with placebo.[44]

Glycemic Control in Diabetic Patients with PAD

Epidemiologic data have demonstrated an increased risk of lower extremity amputation among diabetic patients with PAD with poor glycemic control and higher HgB A1C levels.[45] Intensive glycemic control has been shown to reduce the incidence of microvascular events among diabetic patients, but its role in prevention of macrovascular (cardiovascular) events is less established and somewhat controversial.[46–50]

It is recommended that diabetic patients with PAD be managed according to the

American Diabetes Association (ADA)/ACC/AHA guidelines for glycemic control and the prevention of cardiovascular events[51] (Table 50.5). Diabetic patients with PAD are at increased risk for development of CLI and patient education and meticulous foot care are particularly important in this population of patients.

TABLE
50.5 Key Recommendations from the American Diabetes Association/American College of Cardiology/American Heart Association (ADA/ACC/AHA) Guidelines for Glycemic Control and Prevention of Cardiovascular Events

- Recommended target HgB A1c < 7% stands for most patients
- Consider individualized glycemic targets:
  - More stringent control (normoglycemia) to minimize risk of microvascular outcomes in suitable candidates (e.g., short duration of diabetes, long life expectancy, no significant CV disease)
  - Less stringent HgB A1c goals for patients with a history of severe hypoglycemia, limited life expectancy, advanced micro- and/or macrovascular complications, or those in whom the goal is very difficult to achieve

Skyler JS, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA Diabetes Trials: a position statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association. J Am Coll Cardiol. 2009;53(3):298–304, with permission from Elsevier.

Therapies to Improve Function and Quality of Life

There are multiple treatments available for improvement of functional capacity and leg symptoms among patients with PAD including exercise training (supervised or unsupervised), pharmacotherapy (cilostazol), and revascularization (surgical or endovascular).

Supervised Exercise Rehabilitation for PAD

Supervised exercise rehabilitation is one of the most effective therapies for PAD but unfortunately is not widely available due to a lack of reimbursement by third-party payers. PAD rehabilitation programs generally consists of supervised exercise with training sessions focused on increasing intervals of treadmill walking with alternating periods of rest when the patient experiences moderately intense claudication. Optimal programs are continued for at least 12 weeks and meet for 30 to 45 minutes at a time at least three times weekly.[16] PAD exercise rehabilitation programs have been shown to

increase distance to claudication onset by up to 180% along with improvements in exercise performance, physical functioning, and QOL.[52] PAD rehabilitation has been shown to be highly cost-effective treatment when compared to catheter-based revascularization[53] and has been recommended as a first-line therapy by both major mulitisocietal consensus practice guidelines[16,21] as Class I, LOE A.[16,21] The efficacy of home-based or unsupervised exercise (walking) programs for PAD has not been as well established, although certainly all patients with PAD with or without claudication should be encouraged to begin a walking program.

Pharmacotherapy for PAD

In the United States, there are two FDA-approved medications for treatment of claudication (pentoxifylline and cilostazol). There are a number of investigational agents that have been and continued to be studied, including recent efforts exploring the use of angiogenic factors and stem cell therapy for the treatment of PAD patients. However, it should be noted that there have been no new agents FDA approved for treatment of claudication since cilostazol in 1999. Pharmacotherapy for claudication is a major area of unmet medical need. Recently, some medications that prevent cardiovascular events among PAD patients, such as statins and ACE inhibitors, have also been shown to have potential benefit in terms of claudication symptoms and walking performance.[39,54] A number of nutraceutical agents have been studied for claudication with limited success. The amino acid L-carnitine (especially its propionyl-L-carnitine form) has shown some promise.[55]

Cilostazol Cilostazol is a phosphodiesterase type III inhibitor. It increases cyclic AMP levels, inhibits platelet aggregation and smooth muscle cell proliferation, and has a weak vasodilator effect. In clinical trials, cilostazol has been shown to increase the maximal walk distance by 50.7% as compared to 24.3% for placebo.[56] The use of cilostazol to prevent coronary and superficial femoral artery stent restenosis is an ongoing area of research.[57,58] The standard dose of cilostazol is 100 mg twice a day. Dosage reduction should be implemented in the presence of drugs such as ketoconazole and omeprazole due to potential interactions (50 mg tablets also available). The most common side effects of cilostazol are diarrhea, palpitations/arrhythmias, and headache. Cilostazol is contraindicated in patients with congestive heart failure of any severity and carries a black box warning for this patient population. A trial of cilostazol therapy for claudication is given a Class I (LOE A) indication for patients with lifestyle-limiting claudication in the 2005 ACC/AHA PAD guidelines.[16]

Pentoxifyline Pentoxifyline is a methylxanthine derivative with mechanism of action felt

to be related to improvement of blood viscosity. Though there is a long-standing history of its use among patients with claudication, it is not highly efficacious, and it should be used only as a pharmacotherapy option for patients intolerant of cilostazol or those with a contraindication (e.g., congestive heart failure or left ventricular dysfunction).

Revascularization of PAD

A complete discussion of revascularization for PAD patients is beyond the scope of this chapter. The spectrum of PAD symptom severity and indications for revascularization are shown in Figure 50.5. Revascularization is clearly indicated for the patient with acute limb ischemia or chronic limb ischemia. Among claudicants, revascularization should be considered for the patient with significant (i.e., lifestyle- or vocationally limiting) symptoms after a trial of exercise and/or pharmacologic therapy or in cases where there is highly favorable anatomy of endovascular therapy (such as aortoiliac occlusive disease). Revascularization is never indicated as prophylactic therapy in an asymptomatic patient with a low ABI.[16] There are very few data to support endovascular therapy over medical therapy and/or supervised exercise training to improve functional outcomes and QOL in patients with intermittent claudication. In the recently published CLEVER trial, among patients with aortoiliac occlusive disease, both supervised exercise therapy and endovascular stenting improved functional outcomes in patients with claudication.[59]

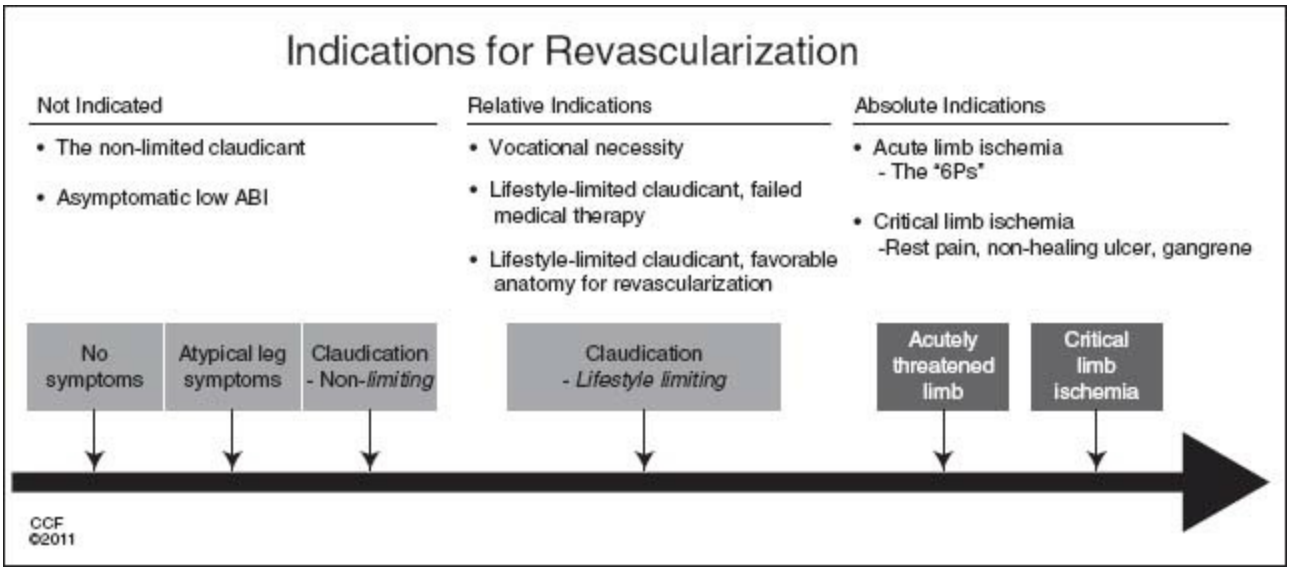

FIGURE 50.5 Indications for revascularization. Most patients with PAD can be managed with medical therapy. Acute and CLI are definite indications for lower extremity revascularization, either endovascular or surgical. In addition, revascularization may be considered for a severely limited PAD patient with stable claudication, particularly if a trial of medical therapy has failed or is unavailable or if the patient has aortoiliac disease that is readily amenable to endovascular treatment. (From Cleveland Clinic Foundation, with permission.)

While open bypass surgery may be necessary in some cases of severe PAD, endovascular therapy has emerged as a first-line approach to revascularization in cases with favorable anatomy, particularly aortoiliac occlusive disease. Endovascular therapy offers the advantage of less severe procedural complications and shorter recovery compared to lower extremity bypass surgery. The durability of endovascular versus surgical revascularization depends upon a number of factors, including anatomic location of disease (aortoiliac disease having better long-term patency outcomes than revascularization procedures below the inguinal ligament) as well as technical factors such as balloon angioplasty alone versus angioplasty with stenting and choice of surgical conduit (autogenous vein vs. prosthetic). Autogenous vein conduit is associated with improved long-term patency compared with prosthetic grafts.

EDUCATION ABOUT PAD

Increasing awareness about PAD among the public, patients, and health care providers is important. More than 70% of primary care providers in the PARTNERS (PAD Awareness, Risk, and Treatment study) study whose patients were screened were previously unaware of the presence of PAD.[2] In addition, in a recent survey of United States households, individuals were far less familiar with PAD than they were with relatively uncommon diseases such as Lou Gehrig's disease or cystic fibrosis.[60] There are many tools available to educate patients about PAD. One excellent source of patient information booklets and fact sheets, as well as health care provider resources, is the PAD Coalition (www.padcoalition. org). Most recently, multispecialty performance measures for providers who care for patients with PAD have been published.[61] Performance measures include evaluating patients at risk for PAD with the ABI, smoking cessation counseling, prescribing antiplatelet and lipid-lowering therapies, and referring for supervised exercise training for PAD patients with claudication.[37]

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QUESTIONS AND ANSWERS

Questions

1. A 66-year-old man comes to see you for evaluation of severe bilateral buttock and thigh discomfort

with exertion. He is a current tobacco smoker and underwent coronary artery bypass grafting (CABG) 5 years ago. He has had long-standing difficulties with low back pain, and he carries a diagnosis of mild lumbar canal stenosis. Your medical assistant measures ABIs in the office: right leg ankle–brachial index (ABI) = 1.01 and left leg ABI = 1.02. What is the most appropriate next step?

a. MRI of the lumbar spine
b. Computed tomographic angiography (CTA) of the aorta and lower extremities
c. Duplex arterial studies
d. Repeat ABIs after treadmill exercise
e. Measure toe–brachial indices (TBIs) bilaterally

2. A 68-year-old man with a history of uncontrolled diabetes mellitus, hypertension, and advanced chronic kidney disease requiring hemodialysis is referred to you for evaluation of a nonhealing ulcer of the left heal. All of the following are the appropriate next steps except:

a. Sharp debridement of the ulcer
b. Probe the ulcer
c. Plain radiograph of the foot to rule out osteomyelitis
d. Perform ABI with pulse volume recording (PVR) tracing
e. Check metabolic panel, lipids, and HbA1c

2. The ABI is done on the above patient. His right ABI is 1.54 and left ABI is 0.63. How would you interpret this test? Each of the following is true except:

a. ABI is not reliable as the patient has non-compressible arteries.
b. ABI is suggestive of calcified vessel and cannot be interpreted.
c. Right ABI is normal. Left ABI is abnormal.
d. Right ABI is not diagnostic in this patient and he will need other testing.
e. Measuring the TBI will be helpful.

3. A 58-year-old woman with long-standing bilateral calf claudication, which has been medically managed, reports progression of pain in her right calf and foot with less and less exertion. She also has intense burning in her right foot, occurring at night. These symptoms have developed over the past 4 weeks. The patient says she can help her right foot burning at night by dangling the foot over the side of the bed. What is the most likely diagnosis?

a. Phlegmasia cerulea dolens from proximal deep vein thrombosis
b. Restless leg syndrome
c. Critical limb ischemia (CLI)
d. Acute arterial embolism
e. Painful peripheral neuropathy

4. A 72-year-old man with multiple cardiovascular risk factors (former smoker, diabetes mellitus, hypertension, hyperlipidemia) presents with pain in calves after walking for two blocks. After resting for 5 minutes, he can resume his walk. His ABI in the right leg is 0.78 and left leg is 0.83. His medications are aspirin 162 mg/d, lisinopril, pioglitazone, and simvastatin. His blood pressure is 130/80 mm Hg, HbA1c of 7.2, and LDL is 66 mg/dL. Which of the following is the next step?

a. Refer to supervised exercise rehabilitation program and prescribe a trial of cilostazol.
b. Clopidogrel should be added.
c. Warfarin should be added if the risk of bleeding is acceptable.
d. Schedule arteriography and anticipated bilateral superficial femoral artery stenting.
e. The patient should be started on insulin therapy.

5. A 68-year-old woman is diagnosed with peripheral artery disease (PAD) on routine screening with ABI. She is a former heavy smoker who suffers from hypertension, congestive heart failure with mildly reduced left ventricular function, and hyperlipidemia. The right leg ABI is 0.88 and the left leg ABI is 0.82. She is currently taking aspirin, metoprolol, lisinopril, and atorvastatin. She has recently quit smoking after receiving the report of her ABIs. She was started on cilostazol by her primary care physician. She visits you for a second opinion. Which of the following is the most appropriate next

step?

a. The patient should be warned of the side effects of cilostazol, including postural hypotension and constipation.
b. Cilostazol is a reasonable FDA-approved option for medical treatment of PAD and should be continued.
c. Schedule the patient for lower extremity angiogram and possible percutaneous revascularization.
d. Stop cilostazol but continue remainder of medical regimen.
e. Tell the patient to continue cilostazol as it may prevent cardiovascular events.

6. A 72-year-old man with known PAD and a history of prior tobacco use and diabetes mellitus is admitted for intense right calf and foot pain and progressive gangrene of his right great toe for the last month. Right leg ABI is 0.33 and left leg ABI is 0.73. What is the next best step in managing his symptoms?

a. Begin intravenous heparin followed by coumadin.
b. Toe amputation
c. Add cilostazol to the medical regimen.
d. Arterial duplex or CTA examination
e. Arterial flow pump

7. A 26-year-old woman and avid cyclist complains of increasing fatigue in her left thigh after bicycling for <1 hour and has to slow down. Symptoms resolve within minutes of slowing down or stopping. She has never smoked tobacco and has no chronic medical conditions and otherwise feels well. Her resting vascular examination is normal. What is the most likely vascular diagnosis?

a. Atherosclerotic PAD
b. Coarctation of aorta
c. Neurologic claudication
d. External iliac endofibrosis
e. Vasculitis

Answers

1. Answer D: This patient has multiple risk factors for PAD. While his symptoms may be consistent with intermittent claudication (particularly aortoiliac occlusive disease), lumbar canal stenosis could also be contributing (pseudoclaudication). Normal ABIs at rest do not rule out a diagnosis of PAD. In this case, repeat ABIs after treadmill exercise are indicated to establish the diagnosis. In the setting of PAD, the postexercise ABIs would be expected to significantly fall. Duplex ultrasound and CTA are not needed to diagnose PAD but may be useful if revascularization is planned. The MRI of the spine could be performed to evaluate the severity of spinal stenosis if the patient does not have significant fall in ABIs with exercise and reproduction of symptoms. TBIs are most helpful to diagnose PAD when ABIs are not interpretable due to noncompressible vessels (i.e., resting ABI > 1.4).

2. Answer A: This patient has multiple PAD risk factors and it is important to first assess the circulation and severity of PAD. Vascular physiologic testing including the ABI with PVR tracings or Doppler waveforms should be obtained to rule out ischemia as a contributor to this nonhealing wound. Debriding the ulcer with compromised perfusion can lead to poor wound healing and increased risk of infection and amputation and should not be done until PAD status is known. Gently probing the ulcer to assess its depth should be done routinely in the evaluation of a wound. In this case, circulation should be first restored either by angioplasty or by bypass surgery before surgical debridement of ischemic ulcer. A plain radiograph may be helpful to assess for osteomyelitis in this chronic wound. Assessment of control cardiovascular risk factors is an important component of PAD care.

3. Answer C: The ABI of the right leg is not interpretable due to noncompressible vessels and is not normal. A noncompressible ABI (>1.4) has been associated with increased cardiovascular risk and a majority of these patients have significant PAD. The left leg ABI is abnormal and consistent with significant PAD, although partially noncompressible vessels can also lead to overestimation of ankle pressure and underestimation of severity of disease in diabetic patients, and it is possible that disease

may be more severe than the ABI indicates. In all patients with noncompressible vessels by ABI, the TBI should be measured to establish the diagnosis of PAD. In this case, segmental PVR tracings or Doppler waveforms, including tracings at the ankle, metatarsal, and digits would be helpful along with TBIs.

4. Answer C: This patient has known PAD that has progressed to the point of ischemic rest pain and CLI. The history of pain worsening with limb elevation and improved with dependency (i.e., dangling the foot over the side of the bed) is very typical for severe PAD/CLI. In this patient, repeat ABI measurement and expedient evaluation for revascularization are indicated.

5. Answer A: Supervised exercise training is the most cost-effective first-line treatment for management of claudication in the PAD patient. A trial of pharmacotherapy with cilostazol is also reasonable and recommended by the PAD guidelines (ref. ACC/AHA PAD Hirsch 2005). This approach would be first-line therapy with revascularization indicated (particularly for suspected SFA disease) only after medical therapy has failed. There is little evidence to support dual antiplatelet therapy for the PAD patient without concomitant coronary artery disease or stenting, and anticoagulation with warfarin is not superior to aspirin alone and has higher associated bleeding risk. This patient has reasonable diabetes mellitus control (by HgB A1c) on oral medication and thus insulin is not indicated.

6. Answer D: This patient has asymptomatic PAD but also has congestive heart failure and impaired LV systolic function. Cilostazol is approved for use in symptomatic patients to improve symptoms in patients with lower extremity claudication. It is contraindicated in this patient with CHF and LV dysfunction and is also not indicated given her lack of symptoms. There is no evidence that cilostazol improves cardiovascular outcomes among PAD patients. The most common side effects of cilostazol are headache, diarrhea, and palpitations. There is no role for revascularization in this asymptomatic patient with mildly reduced ankle–brachial indices.

7. Answer D: Not all patients with PAD are candidates for revascularization. In this patient, additional imaging is required given his CLI and to assess candidacy for revascularization. Arterial duplex or CTA of the extremities may be useful to diagnose anatomic location and degree of stenotic/occlusive lesions in the legs. Angioplasty or bypass of the proximal arteries (femoral, popliteal, and tibial) alone may not be helpful if the distal runoff is compromised and an imaging study can be used to further assess candidacy for revascularization. While the patient may ultimately require toe amputation, degree of ischemia and candidacy for revascularization must be considered first. Cilostazol is not known to be beneficial for treatment of CLI. An arterial flow pump may be an option for treating CLI and ischemic wound in patients who are not candidates for intervention.

8. Answer D: Atherosclerotic PAD is unlikely in this young woman with no risk factors. In such cases, it is important to think of alternative diagnoses. External iliac artery endofibrosis has been reported most commonly in bicyclists and leads to arterial narrowing and claudication or leg weakness, often at a high workload. This diagnosis should always be considered in a young athlete with claudication, especially a bicyclist. This entity has been traditionally treated with open surgery but can also be managed by endovascular means. Aortic coarctation and vasculitis are unlikely based on the given history and the normal vascular examination. Arterial physiological testing (i.e., ABI at rest and after treadmill exercise reproduces symptoms) and imaging studies can help to make this diagnosis.

CHAPTER

Carotid Disease

Amar Krishnaswamy and Mehdi Shishehbor

Carotid atherosclerotic disease is an important cause of ischemic stroke and transient ischemic attack (TIA). Diagnosis is made using ultrasound, computed tomography, magnetic resonance angiography (MRA), or angiography. Treatment consists of medical therapy to address the risk factors responsible for the formation and progression of carotid atherosclerosis, and carotid endarterectomy (CEA) or carotid artery stenting (CAS) in appropriately selected patients.

EPIDEMIOLOGY

Approximately 800,000 people in the United States experience a stroke each year, with a 30-day mortality of 10%.[1–3] Up to 500,000 more individuals suffer a TIA annually.[1] The male-to-female ratio for strokes is greater at ages <65 years (1.50) and less at ages >75 years (0.76); overall, approximately 55,000 more women than men have a stroke each year. With respect to race, blacks have an almost twofold higher risk of first stroke than whites.

PATHOPHYSIOLOGY OF CAROTID ARTERY DISEASE

An estimated 87% of strokes are ischemic in nature, about 15% to 20% of which are attributed to complications of carotid atherosclerotic disease.[1,4,5] Carotid stenosis can lead to ischemia via progressive narrowing and impairment of blood supply, or more commonly by providing a foundation for the formation of local plaque rupture and athero-thrombosis that embolizes distally. It is important to note that the severity of stenosis is predictive of ipsilateral stroke risk, with a 5-year risk of 7.8% in asymptomatic patients with <50% stenosis and 18.5% in patients with 75% to 94% stenosis.[6] In patients with an occluded artery, the risk is abrogated compared with severe stenosis, with an ipsilateral stroke risk of 9.4% at 5 years. Other studies of

patients with asymptomatic disease demonstrate the variability in stroke incidence. In the Veterans Affairs Cooperative Study (VACS) of patients with asymptomatic stenosis >50%, the risk of ipsilateral stroke at 4 years was 10.3% in those treated with medical therapy.[7] Similar findings were noted by the asymptomatic carotid artery stenosis (ACAS) investigators who found a risk of ipsilateral stroke of 6.2% at 2.7 years of follow-up in patients with >60% stenosis.[7] The risk of stroke provided above is indicative of older studies with medical therapy that predates the current era. In more contemporary studies with optimal medical therapy, the risk of ipsilateral stroke has been shown to be as low as 0.34% per year with a risk of ipsilateral TIA of 1.78% per year.[8]

Risk factors for carotid stenosis are similar to those for coronary artery disease (CAD), reflected in the fact that more than one-fifth of patients undergoing coronary artery bypass grafting (CABG) have >50% carotid stenosis.[9] Conversely, in patients with cerebral infarction, more than 50% have some degree of coronary stenosis, and more than one-fourth have coronary stenoses >50%.[10] Material extracted from embolic protection devices (EPDs) after CAS reveal lipid vacuoles, foam cells, fibrin, and platelets, similar to that of coronary lesions. Increasing age results in greater risk of stroke or TIA in both men and women as well as across race.[1] The relative risk of stroke is doubled among smokers and returns to baseline levels after 5 years of abstinence.[11] Hypertension, diabetes mellitus, hyperlipidemia, and the metabolic syndrome all impart an increased risk.[12–14]

CAROTID AND ARCH ANATOMY

Defining aortic arch anatomy is an important part of carotid and cerebrovascular angiography and is necessary in planning a carotid intervention. The aortic arch is defined as type I, II, or III depending on the relationship of the innominate artery to the inner and outer aortic arch curvature(s) (Fig. 51.1). While the normal arch branching pattern consists of the innominate, left common carotid (LCC), and left subclavian (LSC) arteries (proximal to distal), there are a number of variants. In about one-fourth of patients, the LCC and innominate share a common origin, and in about one-sixth of patients, the LCC originates directly from the innominate artery. Both of these configurations are termed “bovine arch,” though in reality bear no resemblance to the arch of cattle.[15] Other variations include an anomalous right subclavian artery that originates directly from the arch distal to the LSC artery, anomalous left vertebral artery originating directly from the arch, and a thyrocervical trunk originating from the aorta.

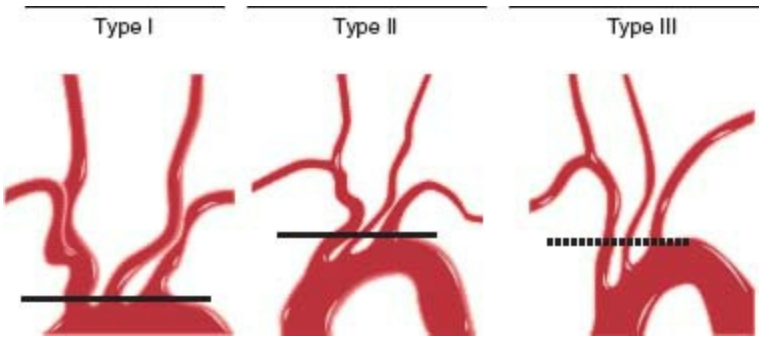

FIGURE 51.1 Classification of aortic arch type is based upon the relationship of the innominate artery to the inner and outer curvature of the arch. (Reproduced from Krishnaswamy A, Klein JP, Kapadia SR. Clinical cerebrovascular anatomy. Cath Cardiovasc Int. 2010;75:530–539, with permission from John Wiley and Sons.)

The common carotid artery bifurcates into the external and internal carotid arteries (ICAs) at the C3–C4 interspace, and is the most common site of carotid atherosclerosis. The external carotid artery courses anteriorly and supplies numerous important branches to the face and neck, which also serve as collaterals in the setting of severe ICA disease. The ICA is divided into the cervical, petrous, cavernous, and supraclinoid portions, and no branches arise from the cervical or petrous ICA. The supraclinoid portion of the ICA (carotid siphon) bifurcates into the middle cerebral artery (MCA) and anterior cerebral artery (ACA).

CLINICAL PRESENTATION

Carotid disease may be diagnosed incidentally during physical examination or by diagnostic testing, or as part of the workup of stroke or TIA. While carotid auscultation is a common and important part of a comprehensive cardiovascular physical examination, its sensitivity in patients with stenosis >60% is reported to be as low as 56%.[16] Therefore, in high-risk patients, carotid ultrasound is recommended for risk stratification. Population screening is not recommended by the United States Preventive Services Task Force (USP-STF), however.[17]

TIA is defined as symptoms that resolve within 24 hours (most commonly within 30 minutes) and does not have associated acute imaging changes. Carotid-territory TIA or stroke can be reasonably elucidated from a detailed history and physical examination (Table 51.1). Aphasia, dysarthria, or visual symptoms such as ipsilateral amaurosis fugax or contralateral homonymous hemianopia may be present. Sensory and motor symptoms are typically contralateral.

TABLE
51.1 Stroke Syndromes Involving the Major Vascular Territories

Vascular Distribution	Common Sequelae
Ophthalmic artery	Monocular blindness (amaurosis fugax)
Anterior choroidal artery	Contralateral hemiplegia and hemianesthesia, homonymous hemianopia
MCA—origin (M1 segment including lenticulostriate perforators)	Contralateral motor and sensory deficits predominantly affecting the face and arms, ipsilateral gaze deviation, homonymous hemianopia. Global aphasia if dominant hemisphere is involved
MCA—superior division	Contralateral motor and sensory deficits predominantly affecting the face and arms. Broca's (nonfluent) aphasia if dominant hemisphere is involved
MCA—inferior division	Contralateral homonymous hemianopia. Wernicke's (fluent) aphasia if dominant hemisphere is involved
ACA	Contralateral motor and sensory deficits predominantly involving the lower extremities, urinary incontinence, gait apraxia, abulia (implicates involvement of the recurrent artery of Heubner)
Posterior circulation (vertebrobasilar system and its branches)	Weakness, ataxia, oculomotor dysfunction and other cranial nerve deficits, dysphagia, vertigo, amnesia, altered consciousness, locked-in syndrome, "crossed" symptoms
ACA-MCA watershed infarction	"Man-in-a-barrel" syndrome of proximal greater than distal arm and leg weakness
MCA-PCA watershed infarction	Variable, may include visual field cuts, sensory deficits, weakness, apraxia, dysarthria.

MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery.

DIAGNOSTIC TESTING

There are various imaging modalities used in the diagnosis of, and procedural planning for, carotid disease.

Carotid Ultrasound

Ultrasonography is the standard noninvasive test for the evaluation of carotid disease. Large studies utilizing carotid ultrasound with angiography as a gold standard have reported sensitivity and specificity of >95% in diagnosing angiographic stenosis >50%.[18,19] Standard criteria for the diagnosis of carotid stenosis (the modified Stradness criteria) are listed in Table 51.2. It is important to note, however, that severe left ventricular (LV) dysfunction, severe aortic stenosis (AS), and significant common carotid stenosis can all spuriously decrease carotid velocities and therefore minimize the degree of stenosis calculated.

TABLE
51.2 Doppler Criteria for Diagnosis of Carotid Stenosis

Percent Stenosis	Velocity Measurement
0%–19%	PSV <105 m/s and no plaque visualized
20%–39%	PSV <105 cm/s and plaque visualized
40%–59%	105 ≤PSV ≤150 cm/s ICA/CCA PSV ratio >2.0
60%–79%	PSV ≥150 cm/s, EDV <135 cm/s ICA/CCA PSV ratio >4.0
80%–99%	PSV >240 cm/s, EDV ≥135 cm/s

PSV, proximal systolic velocity; ICA, internal carotid artery; CCA, common carotid artery.

Carotid Intima Media Thickness

Carotid intima media thickness (IMT) provides a measure of subclinical atherosclerosis and is usually measured in the common carotid artery. It is a measure of the thickness of the intima and media on two-dimensional (2-D) ultrasound imaging, normally increases with age, and is greater in men than women.[20] Carotid IMT may be used for risk stratification purposes in patients without established atherosclerotic disease and intermediate probability as it has been associated with a higher risk of myocardial infarction (MI), stroke, and cardiovascular death.[21–23]

Computed Tomography Angiography

Computed tomography angiography (CTA) is increasingly used in the evaluation of the coronary and peripheral arteries. In a recent evaluation of CTA, investigators reported a sensitivity and specificity of 77% and 95%, respectively, for diagnosing severe carotid stenosis.[24] One significant limitation in the accurate diagnosis of luminal narrowing is the presence of calcium blooming artifact. The diagnosis of moderate stenosis has lower accuracy (sensitivity 67%), similar to MRA in this setting.

Magnetic Resonance Angiography

Carotid imaging using MRA can be performed after gadolinium contrast administration or using time-of-flight (TOF) imaging without contrast. Unfortunately, noncontrast MRA may have poor sensitivity and specificity due to the lengthy time of acquisition (10 minutes), which increases artifact. On the other hand, gadolinium MRA has reasonable sensitivity (95%) and specificity (92%) for diagnosing severe stenosis (>70%).[25] Similar to CTA, diagnosis of moderate stenosis is poor (sensitivity 66%).

Angiography

Established as the gold standard for evaluating carotid stenosis, angiography should be performed using digital subtraction angiography (DSA) to "remove" the bones and soft tissues for better visualization of the arteries. Angiography provides highresolution images, allows an analysis of plaque quality (i.e., calcification, ulceration), and enables the operator to evaluate the arch, neck vessels, intracerebral circulation, and collateral filling at the same time. This method is not usually a first-line test given the historically reported risk of transient (1.3%) or permanent (0.6%) neurologic complications.[26,27] Notably, a more contemporary series of cerebrovascular angiography showed a much lower rate of complications, with 0.06% transient neurologic deficits and 0.2% iatrogenic dissection, though this series included no arch aortograms and only a small percentage of patients with ischemic cerebrovascular disease.[28]

MEDICAL TREATMENT

Primary and secondary prevention of carotid atherosclerosis includes risk factor modification and management. The use of CAS or CEA may be relevant in both situations, and are discussed further below.

Antiplatelet Therapy

Historically, aspirin is the cornerstone of antiplatelet therapy. In the Antithrombotic Trialist Collaboration's meta-analysis of 287 randomized trials enrolling >200,000 patients, they demonstrated a 25% reduction in nonfatal stroke and a 30% reduction in fatal or nonfatal ischemic stroke.[29] Additionally, low-doses of aspirin (75 to 150 mg) were just as effective as higher doses, though with the caveat that this conclusion was based on less robust data. It should be noted, though, that the benefit of aspirin has been noted mostly in patients considered to be at high risk. Conversely, patients at low-risk for events have greater potential for harm due to bleeding. As a result, the American College of Cardiology/American Stroke Association (ACC/ASA) guidelines provide a **Class I recommendation** for aspirin in patients for whom the benefits are likely to outweigh the risks (10-year risk 6% to 10%), though the recommendation is largely based on a reduction in all cardiovascular events and not specifically stroke alone.[17] Use of aspirin in women specifically is noted as a **Class IIa** indication, again for those in whom ischemic stroke risk reduction outweighs the risk of gastrointestinal bleeding or hemorrhagic stroke.[17] Recent trials have not convincingly shown that aspirin decreases the risk of first stroke in patients with diabetes (and without CAD), but have produced trends toward benefit. However, professional societies have found it difficult to completely abandon the use of aspirin in this setting. The ACC/ASA guidelines therefore provide a Class IIb recommendation for the use of aspirin in the primary prevention of stroke in diabetics at "high CV risk" with the caveat that the benefits

"remain unclear."[17,30,31] All patients with documented carotid disease should receive aspirin (or alternative regimen below).

Clopidogrel is an antiplatelet agent that irreversibly binds the $P2Y_{12}$ subunit of the ADP receptor, blocking GP IIb/IIIA-mediated platelet aggregation. In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial of patients with cardiovascular disease, clopidogrel demonstrated an 8.7% relative risk reduction (RRR) for the primary outcome of stroke, MI, or death.[32] There was a trend toward benefit (RRR 7.3%, $p = 0.26$) in patients with a history of stroke. On the basis of this and other studies, clopidogrel has been given an ACC/ASA **Class I recommendation** as an alternative agent to aspirin for secondary prevention in patients with a history of TIA or stroke.[33]

While dual antiplatelet therapy (DAT) with aspirin and clopidogrel is often used in patients after coronary artery stenting, two large studies have not found a benefit in patients with stroke. In both the MATCH (Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischaemic Attack or Ischemic Stroke) and CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trials, DAT did not significantly decrease stroke outcomes, but did result in a significantly increased bleeding.[34,35] The ACC/ASA guidelines therefore provide a **Class III recommendation** (not recommended) for the use of DAT for secondary prevention of stroke.[33]

Dipyridamole (DP) is an adenosine deaminase (ADA) and phosphodiesterase (PDE) inhibitor, which results in an increased concentration of cyclic AMP, adenosine, and adenine nucleotides; this inhibits platelet aggregation and causes vasodilation. Large studies using ASA and DP in patients with stroke have found a significant benefit to the use of combination therapy over monotherapy.[36,37] Therefore, the ACC/ASA guidelines provide a **Class I recommendation** for ASA/DP combination therapy for patients with TIA/stroke, and suggest its use over aspirin monotherapy.[33]

Anticoagulant Therapy

While anticoagulation with vitamin K antagonists is standard therapy for patients with cardioembolic source of TIA or stroke, there has been no suggestion of benefit over aspirin in patients with noncardioembolic stroke. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) randomized patients to warfarin (goal international normalized ratio (INR) 3.0 to 4.0) versus aspirin for secondary prevention.[38] Patients receiving warfarin had more than double the adverse events, mostly attributed to bleeding complications. The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) investigators made a similar randomization though with a more conservative INR goal (2.0 to 3.0) but were forced to terminate the trial early due to an almost threefold

increase in major hemorrhage.[39] Ultimately, due to complications of bleeding and a lack of benefit for patients with atherosclerotic disease, anticoagulation is reserved for patients with a cardioembolic source of stroke or hypercoagulability disorder and is otherwise **not indicated** for the routine secondary prevention of TIA or stroke.

Antihypertensive Therapy

A large percentage of the US population has hypertension, and numerous studies have documented a 30% to 40% reduction in stroke with blood pressure control.[40] While many studies using individual antihypertensive regimens (thiazides, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, etc.) have shown a reduction in stroke, there is a paucity of data to recommend one specific therapy over another. The treatment of hypertension for both primary and secondary prevention has been given a **Class I recommendation** by the ACC/ASA.[17,33] For primary prevention in patients, treatment to a goal blood pressure (BP) <140/90 mm Hg is recommended, with a goal BP <130/80 in patients with diabetes or renal disease **(Class I).**[17] Secondary prevention guidelines support a goal BP of <120/80 mm Hg with a **Class IIa recommendation.**[33] All of these recommendations are made on the basis of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). While no specific agents are recommended for either group due to the small number of trials and limited comparisons, diuretics or the combination of diuretics and angiotensin-converting enzyme inhibitor (ACEi) are provided a **Class IIa recommendation** (for secondary prevention).[33] The use of ACEi or angiotensin receptor blockers (ARBs) is given a **Class I recommendation** for patients with diabetes.[17,33]

Antihyperlipidemic Therapy

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) have become the mainstay of antihyperlipidemic treatment for the primary and secondary prevention of cardiovascular events. Studies of statin use in patients with CAD have shown a reduction not only in coronary events but also in the risk of first-time TIA and stroke. In one of the first trials of statin therapy in patients with a history of CAD, the Scandinavian Simvastatin Survival Study (4S), patients had an approximately 30% RRR in stroke or TIA.[41] Studies of statin use in patients without established cardiovascular disease have also shown promising reductions in the risk of first stroke. For instance, use of rosuvastatin among a large group of healthy men and women with elevated C-reactive protein in the JUPITER trial provided an almost 50% RRR in stroke.[42] The benefits of statin therapy in reducing stroke among patients with and without CAD was also demonstrated in a meta-analysis of >200,000 patients showing an RR of 0.75 in

patients with CAD and 0.77 in patients without CAD.[43] Ultimately, the use of statin therapy for the primary prevention of ischemic stroke is based upon the National Cholesterol Education Program (NCEP) recommendations (Table 51.3), and is given a **Class I recommendation.**

TABLE
51.3 NCEP Recommendations for Statin Therapy for Primary Stroke Prevention

Factor	Goal	Recommendations
LDL-C		
0–1 CHD risk factor	LDL-C <160 mg/dL	Diet, weight management, and physical activity. Drug therapy recommended if LDL-C remains ≥190 mg/dL. Drug therapy optional for LDL-C 160–189 mg/dL
2+ CHD risk factors and 10-year CHD risk <20%	LDL-C <130 mg/dL	Diet, weight management, and physical activity. Drug therapy recommended if LDL-C remains ≥160 mg/dL
2+ CHD risk factors and 10-year CHD risk 10%–20%	LDL-C <130 mg/dL, or optionally LDL-C <100 mg/dL	Diet, weight management, and physical activity. Drug therapy recommended if LDL-C remains ≥130 mg/dL (optionally ≥100 mg/dL).
CHD or CHD risk equivalent (10-year risk >20%)	LDL-C <100 mg/dL or optionally LDL-C <70 mg/dL	Diet, weight management, and physical activity. Drug therapy recommended if LDL-C ≥130 mg/dL. Drug therapy optional for LDL-C 70–129 mg/dL

From Goldstein LB, Bushnell CD, Adams RJ, et al. Guidelines for the primary prevention of stroke. A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2011;42(2):517–584, with permission.

RECOMMENDATION

Statin use for the secondary prevention of stroke or TIA is well-established, largely on the basis of the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial.[17,44] Approximately 5,000 patients with stroke (and without known CAD) were randomized to atorvastatin 80 mg daily versus placebo and followed for almost 5 years. The treatment group demonstrated an HR of 0.84 in the primary outcome of fatal or nonfatal stroke, a difference that was more pronounced in the group with carotid stenosis (HR 0.67). The use of statin treatment as secondary prevention is therefore given a **Class I recommendation** in the AHA/ASA guidelines, even for patients without CAD.[33] Treatment to a goal LDL <70 mg/dL can be considered **(Class IIa).**[33]

CAROTID ENDARTERECTOMY

Endarterectomy of the carotid artery was first performed in 1953 by Dr. Michael

DeBakey. Since then, numerous large trials have been performed to investigate the use of CEA in patients with prior TIA/stroke. The North American Symptomatic Carotid Endarterectomy Trial Collaborators (NAS-CET) performed a randomized, prospective trial of CEA versus medical therapy among patients with symptomatic carotid stenosis.[45] Over a 2-year follow-up, CEA resulted in a significantly lower risk of stroke (9% vs. 26%, p <0.001) and a lower risk of major or fatal stroke (2.5% vs. 13.1%, p <0.001) in 659 patients with 70% to 99% stenosis. Among 2,216 patients with symptoms and moderate stenosis (50% to 69%), 5-year follow-up showed benefit also to CEA but to a lesser degree (15.7% vs. 22.2%, p = 0.045). Among 6,092 patients with symptomatic disease in a pooled analysis of the three major randomized trials (NASCET, European Carotid Surgery Trial [ECST], and VACS), CEA provided a 48% reduction from stroke or death in patients with 70% to 99% stenosis (RR 0.52, 95% CI 0.40 to 0.64), and a 28% reduction in patients with 50% to 69% stenosis (RR 0.72, CI 0.58 to 0.86).[46] Patients with <50% stenosis did not benefit from CEA. Given the data gleaned from randomized trials, CEA is given a **Class I recommendation** for patients with symptomatic stenosis >50% and a perioperative morbidity and mortality risk of <6%.[33] CEA is **not indicated (Class III)** for patients with stenosis <50%.

The ACAS, the VA Trial, and the Asymptomatic Carotid Surgery Trial (ACST) are the three major trials of CEA in patients with asymptomatic carotid stenosis. In ACAS, 1,662 patients were randomized to CEA versus medical therapy. CEA was performed for patients with >60% stenosis as gauged by angiography. Surgery was found to provide a significant decrease in the risk of ipsilateral stroke, perioperative stroke, or death (5.1% vs. 11%, p = 0.004) at a calculated aggregate follow-up of 5-years.[47] The ACST assigned 3,120 patients with >70% stenosis (on ultrasound) to CEA or medical therapy ("deferred" CEA until indicated). The net 5 year risk for all strokes or perioperative death was significantly reduced in the CEA group (6.4% vs. 11.8%, p <0.001), including the 3.1% risk of 30-day stroke or death with CEA.[48] It should be noted, however, that this overall benefit was delayed. As shown in Figure 51.2, patients receiving CEA had a worse outcome until almost 2 years postsurgery, implying that patient selection should also account for comorbidities and life expectancy. Largely on the basis of these two trials and the VA trial, CEA is given a **Class IIa recommendation** by the AHA/ASA for asymptomatic patients with >70% stenosis by ultrasound and >60% stenosis by angiography and an estimated perioperative event rate of <3%.[17] A thorough assessment of risks and life expectancy, as well as an educated conversation with patients regarding the same, is imperative **(Class I recommendation).** It should be noted, also, that a major criticism of the large trials on which CEA was established (NASCET, ECST, ACAS, etc.) utilized medical therapy that is suboptimal based on today's standards, and may therefore overestimate the benefits of CEA.[17] For instance, a recent small study of patients with asymptomatic >

50% stenosis on contemporary medical therapy had an approximately 6% risk of ischemic event (stroke or TIA) at 3 years.[8] Newer trials are therefore warranted to test the benefits of CEA in the asymptomatic population (Tables 51.4 and 51.5).

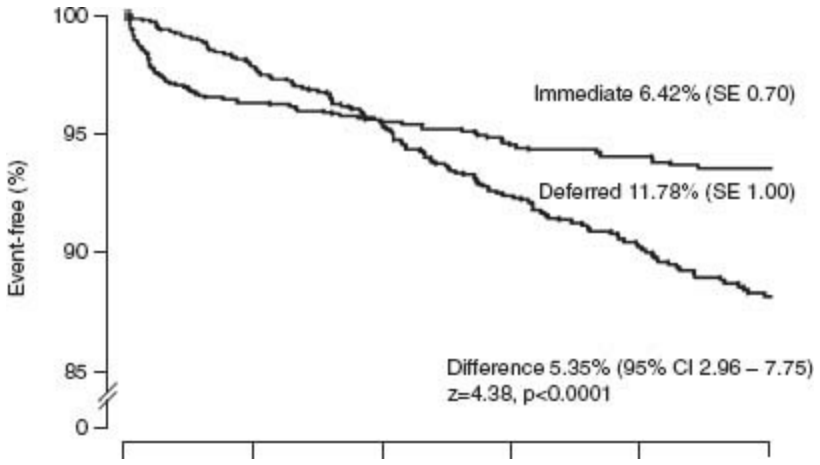

FIGURE 51.2 5-year event-free survival (free of all strokes or death) with immediate versus deferred CEA shows a benefit to CEA only after 2 years due to the 30-day risk of complications with surgery. (Reprinted from The Lancet, 363, Halliday A, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial, 1491–1502, © 2004, with permission from Elsevier.)

TABLE
51.4 Guideline Recommendations for Revascularization in Patients with Carotid Stenosis

Symptom Status	Revascularization Strategy	ACC/AHA Guideline Class
Asymptomatic	CEA for ultrasound stenosis >70% or angiographic stenosis >60% if estimated perioperative event rate is <3%	IIa
	CAS for "highly selected" patients with ultrasound stenosis >70% or angiographic stenosis >60%	IIb
Symptomatic	CEA for angiographic stenosis >50% if perioperative event rate is <6%	I
	CEA for angiographic stenosis <50%	III
	CAS for angiographic stenosis >50%	I
	CAS for stenosis >70% in patients with high surgical risk or anatomic considerations prohibitive to CEA	IIb

CEA, carotid endarterectomy; CAS, carotid artery stenting.

TABLE
51.5 Comparison of Risks and Benefits of CEA and CAS

Carotid Endarterectomy		CAS	
Pros	**Cons**	**Pros**	**Cons**
Risk of periprocedural stroke in symptomatic patients may be lower than with stenting[51,52]	Risk of periprocedural MI higher than with stenting[51]	Risk of periprocedural MI lower than with surgery[51,53]	Risk of periprocedural stroke higher than with surgery in symptomatic patients and octogenarians[49,51–53]
More data available from long-term follow-up than for stenting	Risk of cranial nerve damage higher than with stenting[49,51,53]	No risk of cranial nerve damage[51,52]	
	Risk of wound complications higher than with stenting[51]	Risk of wound complications lower than with surgery[45,51]	
	General anesthesia required in most cases[51]	General anesthesia almost never required	
	Longer recovery period than for stenting	Minimally invasive	

Aksoy O, Kapadia SR, Bajzer C, Clark WM, Shishehbor MH. Carotid stenting vs surgery: Parsing the risk of stroke and MI. Cleve Clin J Med 2010; 77:892–902. Reprinted with permission. Copyright © 2010 Cleveland Clinic Foundation. All rights reserved.

CAROTID ARTERY STENTING

Percutaneous transluminal angioplasty (PTA) of the carotid artery in humans was first reported in 1980. Since then, there has been a proliferation of stent technology to address issues of vessel recoil and dissection after balloon dilation and development of EPDs to reduce the risk of periprocedural embolic complications. Both are considered to represent the standard of care in the current era of CAS.

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial was the first randomized controlled trial comparing emboli-protected CAS to CEA.[49] The 334 patients enrolled were either asymptomatic with ≥80% stenosis by ultrasound or symptomatic with ≥50% stenosis. All patients were considered to have high risk for surgery, and approximately 70% were asymptomatic. The primary end point of major adverse cardiovascular events (MACE) (which included death, stroke, or MI within 30 days of the procedure plus death from neurologic causes or ipsilateral stroke up to 1 year) was lower in the CAS group (12.2% vs. 20.1%, $p = 0.05$). At 3-year follow-up, the prespecified major secondary endpoint of MACE (death, stroke, or MI within 30 days of the procedure or death or ipsilateral stroke between 31 and 1,080 days) occurred in 24.6% of the protected CAS group and 26.9% of the CEA group ($p = 0.71$).[50]

The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) was recently published and randomized roughly equivalent numbers of symptomatic (53%)

and asymptomatic (47%) patients to protected CAS or CEA.[51] Among the 2,502 patients enrolled, the primary endpoint (any periprocedural stroke, MI, or death or postprocedural ipsilateral stroke) at 4 years was not significantly different between the CAS and CEA groups (5.2% vs. 4.5%, p = 0.38). Notably, though, the risk of stroke was significantly higher with CAS (4.1% vs. 2.3%, p = 0.01), and the risk of MI was significantly lower (1.1% vs. 2.3%, p = 0.03). While these differences resulted in an overall similar primary outcome for the two groups, quality-of-life analysis at 1-year showed that stroke resulted in a large adverse effect than did MI. There was a suggestion in subgroup analysis that CAS tended to show greater efficacy in patients <70 years.

In contrast to SAPPHIRE and CREST, SPACE (the Stent- Protected Angioplasty Versus Carotid Endarterectomy in Symptomatic Patients trial), EVA-3S (the Endarterectomy Versus Stenting in Patients with Symptomatic Severe Carotid Stenosis trial), and ICSS (the International Carotid Stenting Study) all showed CAS to be inferior to CEA. All studies were in symptomatic patients and were conducted in Europe. Collectively, a number of criticisms have been raised surrounding these trials. These include lack of operator experience and minimal use of EPDs.

The current data on CAS have resulted in a **Class IIb** recommendation by the ACC/AHA for "highly selected" patients with asymptomatic carotid stenosis. The U.S. FDA does not provide reimbursement for CAS in these patients outside of clinical trial enrollment. Conversely, in symptomatic patients with stenosis >70% by ultrasound or >50% by angiography, CAS is indicated **(Class I)** as an alternative to CEA for patients with an average or low risk of complications with CAS.[33] In patients with severe symptomatic stenosis and anatomic considerations that make CEA technically challenging or comorbid conditions that result in high surgical risk, CAS may be considered **(Class IIb)** but is less highly recommended (likely due to the significant coexisting conditions that increase overall morbidity and mortality in this group of patients).[33] These factors include New York Heart Association (NYHA) III/IV heart failure, Class III/IV angina, left main coronary disease, two-vessel CAD, left ventricular ejection fraction <30%, recent MI, severe lung or renal disease, prior neck operation or irradiation, restenosis after CEA, contralateral carotid occlusion, tracheostomy, or surgically inaccessible lesions.

CONCLUSIONS

Stroke is a leading cause of morbidity and mortality, and carotid atherosclerotic disease is a common etiology of ischemic cerebrovascular events. Risk factors for the development of carotid disease include the usual causes of atherosclerosis such as hypertension, age, and diabetes, as well as tobacco use, renal disease, and others. The diagnosis of carotid stenosis should be considered in patients at high risk for vascular

disease as well as patients who have suffered a TIA or stroke. The diagnosis is usually made using ultrasound, though CTA, MRA, or conventional angiography may play a role in certain situations. The management of carotid disease includes antihypertensive, antihyperlipi- demic, and antiplatelet therapies. The use of CEA or CAS for revascularization depends on a myriad of factors including the degree of stenosis, symptom status, expected procedural risk, comorbidities, and life expectancy.

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QUESTIONS AND ANSWERS

Questions

1. Which of the following has no proven benefits in reducing the risk of a first stroke in patients with diabetes mellitus?
   a. Blood pressure control
   b. Aspirin
   c. Statin therapy
   d. Blood pressure control and statin therapy
2. Which of the following antiplatelet regimens is not recommended in patients with a history of transient ischemic attack (TIA)/stroke?
   a. Aspirin plus dipyridamole (DP)
   b. Clopidogrel

c. Aspirin alone
d. Aspirin plus clopidogrel

3. A 57-year-old gentleman is referred to your clinic for management after his primary medical doctor auscultated a right carotid bruit. He exercises regularly and "watches what he eats." On your exam, his blood pressure is 155/95 mm Hg and heart rate 70 beats/min (bpm). Laboratory testing reveals a serum LDL of 168 mg/dL and HDL of 50 mg/dL, a fasting blood glucose of 85, and normal GFR. Which of the following is recommended to decrease the risk of a first stroke in this patient?
   a. Blood pressure control to goal BP <140/90 mm Hg
   b. Statin therapy to goal LDL <160 mg/dL
   c. Statin therapy to goal LDL <130 mg/dL
   d. Blood pressure control to goal BP <140/90 mm Hg and statin therapy to goal LDL <160 mg/dL
   e. Blood pressure control to goal BP <140/90 mm Hg and statin therapy to goal LDL <130 mg/dL

4. For the patient above, what would be the next step in management?
   a. Duplex carotid ultrasonography
   b. Carotid angiography
   c. Computed tomography angiography (CTA)
   d. No further testing is necessary

5. The patient above undergoes carotid ultrasound testing that reveals a right carotid stenosis of 80% to 99%. What is the appropriate management?
   a. Continued medical therapy and surveillance for development of symptoms
   b. Referral for carotid endarterectomy (CEA)
   c. Referral for carotid artery stenting (CAS)
   d. All of the choices

6. Which of the following diagnostic modalities for assessing carotid disease has the lowest sensitivity for detecting severe stenosis?
   a. Carotid-CTA
   b. Contrast-enhanced magnetic resonance angiography (MRA)
   c. Invasive carotid digital subtraction angiography (DSA)
   d. Carotid ultrasonography

7. Which of the following favor CAS over CEA?
   a. Risk of periprocedural myocardial infarction (MI)
   b. Risk of periprocedural stroke
   c. Preferred procedure for restenosis after endarterectomy
   d. Risk of periprocedural MI and preferred procedure for restenosis after endarterectomy

8. A 75-year-old man with hypertension, previous coronary artery bypass grafting (CABG), and atrial fibrillation presents with new onset weakness and numbness of the left face and arm. Which vascular territory is likely to be compromised?
   a. Right anterior cerebral artery (ACA)
   b. Right vertebral artery
   c. Right middle cerebral artery (MCA)
   d. ACA-MCA watershed infarction

Answers

1. Answer B: Recent trials have not convincingly shown that aspirin decreases the risk of first stroke in patients with diabetes (and without CAD), but have produced trends toward benefit. However, professional societies have found it difficult to completely abandon the use of aspirin in this setting. The ACC/ASA guidelines therefore provide a Class lib recommendation for the use of aspirin in the primary prevention of stroke in diabetics at "high CV risk" with the caveat that the benefits "remain unclear." The treatment of hypertension for primary prevention has been given a Class I recommendation by the

ACC/ASA, and the use of ACEi or ARBs is given a Class I recommendation for patients with diabetes. The goals of statin therapy for the primary prevention of ischemic stroke is based upon the National Cholesterol Education Program (NCEP) recommendations, and is given a Class I recommendation.

2. Answer D: The ACC/ASA guidelines provide a Class I recommendation for aspirin plus dipyridamole (ASA/DP) combination therapy for patients with TIA/stroke. The use of the combination is suggested over aspirin monotherapy, though monotherapy is reasonable if clinical considerations preclude the use of the combination regimen. Clopidogrel has been given an ACC/ASA Class I recommendation as an alternative agent to aspirin for secondary prevention. Due to large studies that showed an increased risk of bleeding with ASA/clopidogrel combination therapy, and no significant decrease in the risk of stroke in comparison to aspirin alone, this combination has been given a Class III (not recommended) designation.

3. Answer E: The patient has two CHD risk factors (age and hypertension) in addition to hyperlipidemia. The treatment of hypertension substantially reduces the risk of a first stroke, and treatment to goal BP <140/90 mm Hg (<130/80 in patients with diabetes or renal disease) is given a Class I recommendation based on the JNC-7. With regard to lipid management, this patient meets criteria for a goal LDL <130 mg/dL based on NCEP guidelines, with the use of statin therapy (ACC/ASA Class I recommendation) as necessary in addition to lifestyle modifications. This patient actually has a Framingham 10 year risk of 12%, so would qualify for the optional treatment goal of LDL <100 mg/dL.

4. Answer A: This patient is in an intermediate-risk category given his risk factors for cardiovascular disease as well as an auscultory bruit on exam. He would therefore merit further investigation to determine the severity of disease. Carotid ultrasound has been validated through large studies, and in comparison to the "gold standard" of angiography has a sensitivity of >95% for the diagnosis of carotid stenosis >50%. Carotid angiography is not indicated as a first-line study given its invasive nature and the risk of transient (1.3%) or permanent (0.6%) neurologic complications. CT angiography has a lower sensitivity than ultrasound (77% for severe stenosis, 67% for moderate stenosis). In the absence of factors that might make interpretation of ultrasound examination less accurate (i.e., severe LV dysfunction or severe aortic stenosis [AS]), ultrasound would therefore be preferred.

5. Answer D: The patient has severe but asymptomatic carotid stenosis. Therefore, medical management or revascularization (with medical management) would be reasonable. CEA may be beneficial over medical therapy alone if the procedure can be completed with a <3% complication rate and the patient's life expectancy exceeds 3 years (as expected in this patient) (ACC/ASA Class IIa recommendation). The historic trials on which this benefit is based, however, are dated and may therefore overestimate the benefits of CEA for reducing stroke risk over contemporary medical therapies. CAS has compared favorably to CEA in this patient population, but trades a lower rate of procedural MI for a higher rate of procedural stroke (ACC/ASA Class IIb recommendation). Therefore, a detailed conversation with the patient is imperative to discuss the choice of procedure as well as the risks/benefits of a procedure in comparison to medical therapy alone. Of note, CAS in asymptomatic patients is reimbursed by CMS only under the auspices of a clinical trial.

6. Answer A: CT angiography has been shown in numerous studies to have poor sensitivity in the evaluation of carotid disease, with a sensitivity of 77% for severe stenosis and 67% for moderate stenosis. Calcium blooming artifact is a significant issue. MRA without contrast has poor sensitivity, but gadolinium-enhanced MRA has good sensitivity (95%) and specificity (92%) for diagnosing severe stenosis (>70%). Carotid angiography is considered the "gold standard" of diagnosis for carotid stenosis. Carotid ultrasound has been validated through large studies, and in comparison to angiography has a sensitivity of >95% for the diagnosis of carotid stenosis >50%.

7. Answer D: Numerous studies comparing CEA and CAS have shown a similar rate of overall clinical outcomes but increased risk of stroke with CAS and increased risk of MI with CEA. In patients with restenosis after CEA, stenting is the preferred treatment.

8. Answer C: Infarction of the right MCA territory results in contralateral motor and sensory deficits predominantly affecting the face and arms. Compromise of the right ACA would result in contralateral motor and sensory deficits predominantly affecting the legs. ACA–MCA watershed infarcts may present with proximal greater than distal arm and leg weakness. Furthermore, watershed infarcts generally present in settings of hypoperfusion (i.e., hypotension), while MCA infarcts are the most common

location for cardioembolic stroke (which is likely in this patient with a history of CABG, hypertension, and AFib).

CHAPTER

Hallmarks of Essential and Secondary Hypertension

Mohamed A. Rafey, Martin J. Schreiber, Jr., and Joseph V. Nally, Jr.

PATHOGENESIS OF HYPERTENSION

A number of pathophysiologic factors have been implicated in the development of essential hypertension, making selective mechanistically based antihypertensive therapy in any one patient difficult.[1] In a broad sense, increased sympathetic nervous system activity, autonomic imbalance (increased sympathetic tone, abnormally reduced parasympathetic tone), vascular remodeling, arterial stiffness, and endothelial dysfunction contribute to both the development and maintenance of essential hypertension. Increased sympathetic activity may stem from alterations in baroflex and chemoreflex pathways, both peripherally and centrally. The renin–angiotensin system plays a major role in vascular remodeling (alterations in structure, mechanical properties, and function of small arteries) and critical target organ damage (TOD) (myocardial fibrosis, renal injury). In addition, arterial stiffness—a primary contributor to increased vascular resistance, especially with advancing age—results from continued collagen deposition, smooth muscle hypertrophy, and changes in the elastin media fibers. Although intact vascular endothelium is critical to maintaining vascular tone (relaxation and contraction), we now know that multiple insults (decreased nitric oxide synthesis, increased endothelin, estrogen deficiency, high dietary salt intake, diabetes mellitus, tobacco use, and increased homocysteine) can damage vascular endothelium and contribute to important clinical findings. These vascular factors or conditions disrupt normal endothelial function, initiating the cascade of cardiovascular events that results in atherosclerosis, thrombosis, and heart failure.

Renal microvascular disease remains a viable theory as being responsible for the development of hypertension.[2] Renal vasoconstriction resulting from the renin–

angiotensin–aldosterone system (RAAS) activation, increased sodium reabsorption, and primary microvascular injury may all lead to renal ischemia (particularly in the outer medullary section). Local production of angiotensin-II plus reactive oxygen species at sites of renal injury potentially result in structural alterations and hemodynamic events that cause hypertension.[3]

Hyperuricemia in humans is associated with renal vasoconstriction, activation of the RAAS, cardiovascular disease (CVD) risk, and hypertension. Theoretically, uric acid stimulates renal afferent arteriopathy and tubular interstitial disease, resulting in hypertension. Renal lesions and hypertension could be prevented or reversed in a rodent model by decreasing uric acid levels coupled with use of angiotensin-converting enzyme (ACE) inhibition, but not hydrochlorothiazide (HCTZ).[4] Continued studies leveraging these observations in humans warrant further investigation. Moving forward, medication selection may be directed as much to specific detrimental microvascular effects as to the actual lowering of blood pressure (BP) to target levels.

GENETICS OF HYPERTENSION

Hypertension results from a complex interaction of genetic, environmental, and demographic factors. In patients with essential hypertension, heritability (h2) has been estimated to range from 30% to 50% indicating that a large proportion of variation in BP can be attributed to additive genetic effects. Variation in BP appears to be the result of contribution by several different genes (it is polygenic).[5] In addition, there are reported rare cases of simple Mendelian forms of high BP in which a single gene defect may be largely responsible for the hypertensive phenotype.

Improved techniques of genetic analysis (i.e., genetic-wide linkage analysis) have aided in the search for genes that contribute to the development of primary hypertension. Genetic causes of hypertension, though uncommon in the general population, may be more frequent in selective hypertensive populations, particularly patients with resistant hypertension. Genome scans have identified regions of specific human chromosomes that influence BP, which are called the BP quantitative trait loci (QTL) (i.e., chromosome 6.2). Lack of standardization in BP measurement, dichotomization of BP levels for diagnosis of hypertension, and inappropriate selection of cases and controls in clinical studies may result in substantial variation in the hypertension phenotype, which may have contributed to the slow progress in identification of genetic variants associated with BP. Consequently, genetic profiling is not currently beneficial in the diagnostic evaluation of hypertension.

From the clinical perspective, a family with a history of hypertension can be a surrogate marker for undefined, genetically linked risk factors shared by the family. Risk factors such as obesity, dyslipidemia, and insulin resistance are predictive of future hypertension. Having a single first-degree relative with hypertension is only a

weak predictor of hypertension, whereas a finding of two or more relatives with hypertension at an early age (before age 55 years) identifies a smaller subset of families who are at much higher risk for the future development of hypertension.[6]

Wilk et al.[7] reported findings to support a link between the quantitative trait age at hypertensive diagnosis and the qualitatively defined early-onset trait in African Americans. Several genes with specific salt interactions have been identified, for example, ones for glucocorticoid remedial hypertension and apparent mineralocorticoid excess.[8] In addition, the α-adducin gene is associated with an increased risk of renal tubular absorption of sodium, and angiotensinogen gene polymorphism (A-to-G substitution and methionine-to-threonine amino acid substitution) has been linked to an increase in plasma levels of angiotensinogen.[9]

Patients with specific gene patterns may respond preferentially to one class of drugs more than another. Patients with the α-adducin gene respond best to thiazide diuretics, those with (Met235 thr) angiotensinogen to ACE inhibitor and calcium channel blocker (CCB), and those with specific G-protein genes impart response to beta-blockers (BBs) and diuretics[10]

A number of syndromes represent genetic mutations of hypertension single-gene forms including glucocorticoid remedial hypertension (chimeric gene formation; autosomal dominant), 11-β-hydroxylase (mutation in gene encoding), 17-α-hydroxylase deficiency, Liddle syndrome (mutation in the sodium channel gene), hypertension exacerbated by pregnancy, syndrome of apparent mineralocorticoid excess, and pseudohypoaldosteronism.[11] Also, human atrial natriuretic peptide (hANP) is an attractive gene for linking specific population groups to an associated increased risk for hypertension. More recently, polymorphisms of the angiotensinogen gene have been detected in hypertensive patients and in children of hypertensive parents.

The continued advances in molecular biology and newer technologies make likely the possibility of gene expression profiling being applied to hypertensive research, diagnosis, and treatment selection in the future.[12]

SIGNIFICANCE OF SYSTOLIC, DIASTOLIC, AND PULSE PRESSURE

A shift in diagnostic emphasis from diastolic BP to systolic BP has occurred beginning in the 1990s.[13–15] A reanalysis of the Framingham Heart Study with longer follow-up data and more extensive cardiovascular data tracking showed that at all levels of systolic pressure (even within a normal range), the height of the systolic BP accurately predicted coronary heart disease (CHD).[16] In addition, these data also suggest that the pulse pressure (systolic BP–diastolic BP) is a major independent predictor of CHD. A wide pulse pressure is a marker for large artery stiffness and for vascular aging

(arteriosclerosis). Elevated coronary arterial calcification scores are associated with arterial stiffness and increased pulse pressure.[17] Age is a determinant of the importance of pulse pressure in hypertension. A growing body of evidence supports pulse pressure readings as an important predictor in patients >65 years of age.[18,19] Furthermore, pulse pressure may be a strong predictor of CV risk in the presence of compromised ventricular function with normal or low systolic BP.[20]

Therefore, systolic BP, diastolic BP, and pulse pressure are important in staging hypertension at different ages. Earlier generations of physicians favored the importance of diastolic BP over systolic BP, in part because hypertension was apparently a young person's disease. With the aging of the population, hypertension has become a disease of older patients specifically reflected by isolated systolic hypertension (ISH). As arteries stiffen and pulse wave amplification decreases with aging, a general shift in elevation occurs from diastolic BP to systolic BP, and eventually in some, to pulse pressure as predictors of CV risk.[21]

There are patients in whom pulse pressure does not represent arterial stiffness (discrepancy between central and brachial pulse pressure, mild arterial stiffness, increased cardiac output, variable heart rate, and vasodilation). Moreover, pulse pressure cannot replace systolic BP as a single measure of CHD risk. Systolic BP and diastolic BP together are frequently superior to systolic BP alone in predicting CV risk. From a practical standpoint, physicians should first measure systolic BP (especially in healthy middle-aged and elderly cohorts) and then adjust risk upward for pulse pressure if there is a discordantly low diastolic BP (postmyocardial infarction, heart failure, end-stage renal disease [ESRD], etc.). Only when there is a discordantly low diastolic BP does pulse pressure add to systolic BP in predicting CV risk.

EVALUATION OF HYPERTENSION

A complete history, physical examination, basic serum chemistries, urinalysis, and electrocardiogram (ECG) are recommended for the initial evaluation of a hypertensive patient. Urinalysis is especially important because of the impact that renal disease has on both treatment selection and target goals for BP lowering.

The patient's history should include a detailed family history, notation of early cerebrovascular hemorrhagic stroke (if <60 years old), nonprescription medications (nonsteroidal anti-inflammatory drugs, diet pills, decongestants, appetite suppressants, herbal therapy), birth control pills, alcohol/street drugs, and sleep history. The physician should always be alert to history or physical exam findings that suggest a secondary cause for the hypertension.

The physical examination should include two or more BP measurements separated by 2 minutes, with the patient either supine or seated, and after standing for at least 2 minutes, in accordance with recommended techniques. BP should be verified in the

contralateral arms; if values are different, the higher value should be used. Measurements of height, weight, and waist circumference should be obtained. Special attention should be directed to the funduscopic examination; the presence or absence of carotid bruits or distended neck veins, thyroid enlargements; and examination of the heart, lungs, abdomen, and extremities. Particular attention should be directed to peripheral pulses, presence of abdominal bruits, and presence or absence of edema. A neurologic assessment should also be performed.

The presence of significant arteriosclerosis or arterio-venous (AV) nicking on funduscopic examination indicates in most cases that the BP has been elevated for >6 months. Arteriolar changes are the most common manifestation of hypertensive retinopathy. The mean ratio of arteriole-to-venular diameter in nonhypertensive patients is 0.84. This ratio progressively decreases with increased mean arterial BP. AV nicking can be detected where branch retinal arteries cross over veins. The thickened arteriole wall compresses the thin-walled vein, causing a tapering or "nicked" appearance.

A basic laboratory evaluation should include a urinalysis, microalbuminuria measurement, complete blood count, blood chemistry (potassium, sodium, creatinine, fasting glucose, uric acid), a full fasting lipid profile, and an ECG. An elevated uric acid value may predict the development of hypertension, is frequently present in patients with hypertension, and the degree of elevation also correlates with the degree of BP elevation. Uric acid may also have a pathogenic role in progressive renal disease.

Ambulatory blood pressure monitoring (ABPM), an echocardiogram, and assessment of plasma renin activity (PRA) are not indicated for routine evaluation of most hypertensive patients at the first visit. Recent European guidelines for hypertension have emphasized the importance of estimating the degree of underlying arterial disease by measuring arterial brachi index (ABI) and pulse wave velocity (PWV) when available, to better stratify patients at risk for cardiovascular complications and to tailor aggressive antihypertensive therapy for these individuals.

ABPM is currently considered the gold standard for measuring BP accurately. An average 24 hour BP of ≥130/80 mm Hg is considered diagnostic of hypertension. Based on 24 hour ABPM results and office BP readings, several patterns of BP have been identified which that may have a bearing on managing patients with hypertension (see Fig. 52.1.). Individuals with white coat hypertension have persistently elevated office BP (≥140/90 mm Hg) and normal 24-hours ABPM (<130/80 mm Hg). Data are not yet clear on the clinical significance of white coat hypertension and its impact on TOD and cardiovascular outcomes. In current clinical practice, identifying patients with white coat hypertension helps in reducing overtreatment of these individuals with antihypertensive medications and avoiding iatrogenic complications including hypotension. Masked hypertension is defined as persistently normal or controlled office BP measurements with elevated outside office BPs. The prevalence of masked hypertension ranges from 8% to 16% based on the population sampled. Preliminary

studies indicate that the burden of TOD in these individuals may be similar to that of patients with essential hypertension. Nocturnal hypertension (average night-time BP of >120/70 mm Hg) is a subgroup of masked hypertension and was recently demonstrated to be high in prevalence among African Americans with hypertension and chronic kidney disease (CKD). There are no expert guidelines available yet regarding the management of masked hypertension.

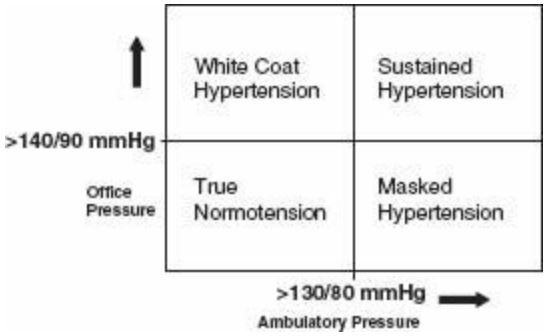

FIGURE 52.1 Patterns of blood pressure which may have a bearing on managing patients with hypertension.

Higher ambulatory systolic or diastolic BP predicts CV events even after adjustment for classic risk factors.[22] Data from clinical trials that treated patients based on office BP readings demonstrate that individuals who had better average 24-hour BP control during the study had improved cardiovascular outcomes.

A major drawback in the routine use of 24-hour ABPM is that it is expensive and not reimbursed by health insurance plans. Home blood pressure monitoring (HBPM), if performed correctly, is a much cheaper alternative and provides similar accuracy to 24-hour ABPM in managing patients with hypertension. Guidelines on HBPM were recently released by the American Heart Association and American Society of hypertension and have recommended a cutoff of 135/85 mm Hg to define hypertension. A major drawback of HBPM when compared to 24-hour ABPM is the lack of evaluation of BP during sleep.

RESISTANT HYPERTENSION

Resistant hypertension is defined as the persistence of BP >140/90 mm Hg while being treated with a rational triple-drug therapy, optimally including a diuretic. In addition, patients with hypertension who require four or more antihypertensive medications to control BP are also termed to have refractory hypertension. Resistant hypertension falls into two broad categories: apparent resistance and true resistance (Table 52.1).[23]

TABLE
52.1 Causes of Refractory Hypertension

Apparent Resistance	True Resistance
Cuff-related artifacts	Excess plasma volume
Pseudohypertension	Associated conditions[a]
White coat hypertension	Drug-related causes[b]
Nonadherence to therapy	Secondary hypertension
Prescription errors	

[a]Obesity, insulin resistance, ethanol excess, sleep apnea.

[b]Drug–drug interactions and specific drugs that may produce refractory hypertension include: nonsteroidal antiinflammatory drugs (NSAIDs), sympathomimetic drugs (decongestants, appetite suppressants), corticosteroids, chlorpromazine, over-the-counter dietary substances (i.e., ephedra, rehung, bitter orange), tricyclic antidepressants, cocaine, amphetamines, cyclosporine, tacrolimus, erythropoietin, anabolic steroids, monamine oxidase inhibitors, oral contraceptives, licorice, and some chewing tobaccos.

The exact prevalence of resistant hypertension is unknown. Clinical trials suggest that it is not rare, involving perhaps 20% to 30% of study participants. Review of clinical records of patients seen in an outpatient setting demonstrates resistant hypertension to be present in approximately 10% of patients in a primary care setting and in more than 30% of patients in subspecialty clinics. Patient noncompliance and suboptimal therapeutic regimens are the major causes for apparent resistant hypertension (Fig. 52.2).[24] More intensive therapy with emphasis on targeted volume control using diuretic therapy can achieve goal BP levels in a significant percentage of patients with apparent resistant hypertension.[25]

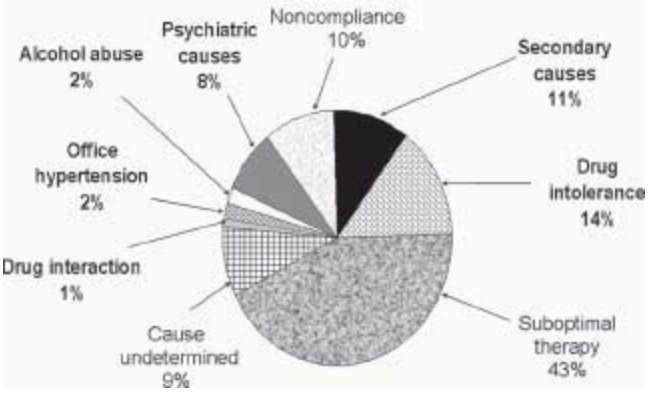

FIGURE 52.2 Of 436 patients treated at a hypertension clinic, 92 (21%) had refractory hypertension. In 83 patients, a cause was identified, the most frequent being suboptimal therapy. BP was brought under control or improved in 58 patients. (Data from Yakovlevitch M, Black HR. Resistant hypertension in a tertiary care clinic. Arch Intern Med. 1991;151:1786–1792.)

Awareness of the association among sleep-disordered breathing, sleep apnea, and hypertension has increased over the past few years.[26] Both hypoxia and CO_2 retention excite central and peripheral chemoreceptors activating the renin–angiotensin system,

which can lead to vasoconstriction and increased BP. Typically, the onset of sleep is associated with a significant decrease in BP of 10% to 20% in normotensive individuals. Patients with disrupted sleep patterns do not experience a nocturnal dip in BP. When treated with cPAP, the nocturnal dip in BP is restored (Fig. 52.3).[27]

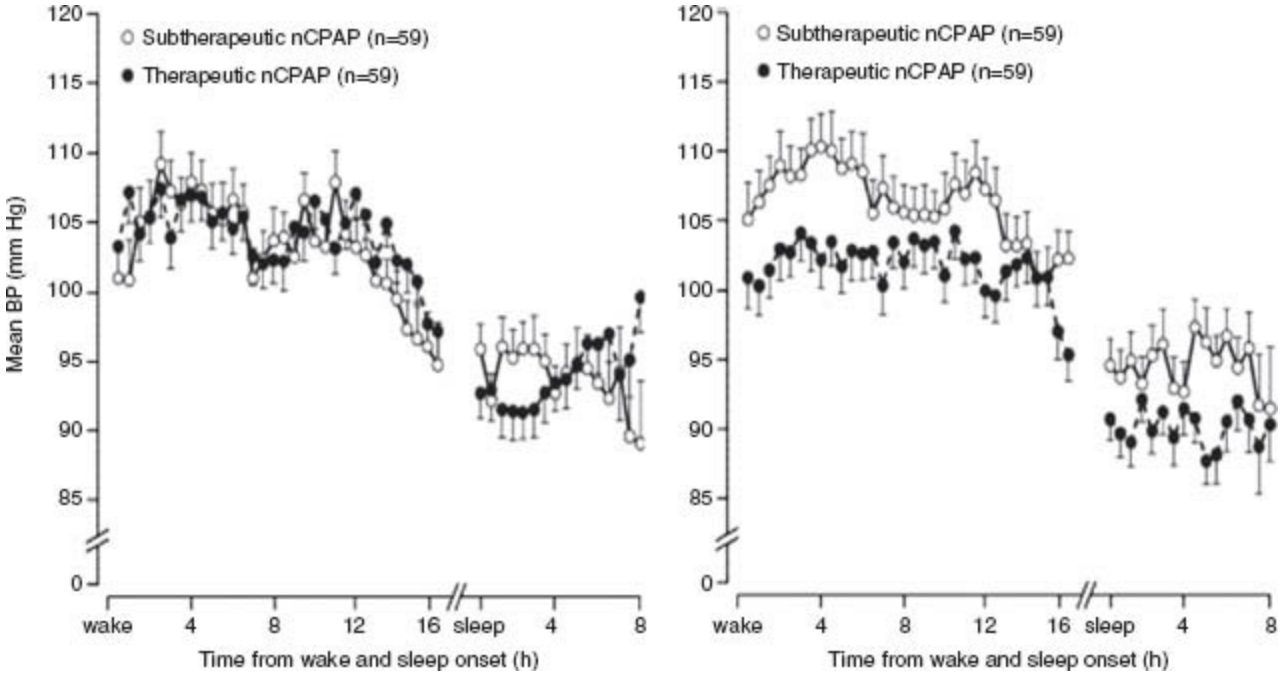

FIGURE 52.3 Randomized trial comparing treated (therapeutic vs. subtherapeutic CPAP (1 cm H_2O over a 1-month period) and untreated men with sleep apnea. Bars are standard errors for every 30-minute period, synchronized to wake and sleep times. (Reprinted from the Lancet, 359, Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial, 204–210, © 2002, with permission from Elsevier.)

Novel therapies are being developed to improve BP control in patients with resistant hypertension. Some recent reports indicate a high prevalence of primary aldosteronism in patients with resistant hypertension and others have demonstrated that mineralocorticoid receptor (MR) antagonists provide significant antihypertensive benefit when added to existing multidrug regimens. Catheter-based renal denervation for treatment-resistant hypertension appears to be another novel approach. Results of a recent multicentre, prospective, randomized trial demonstrate that a significantly higher percentage of patients with drug-resistant hypertension who underwent renal denervation had improved BP control when compared to those receiving usual medical therapy.

CLINICAL APPROACHES TO HYPERTENSION

Contrary to results from National Health and Nutrition Examination Survey (NHANES) surveys in the past, which demonstrated an increasing prevalence of hypertension in the

United States, results of the latest NHANES show that the prevalence of hypertension has remained at 29% over the past decade. Results from this survey also demonstrated that BP control (achieving a target BP of <140/90 mm Hg) has improved from 27.3% in 1988 to 1994 period to 50.1% in 2007 to 2008. Hypertension prevalence is highest among non-Hispanic blacks and women, and increases with age and elevated body mass index (BMI). Interestingly, hypertension control is lower in younger individuals (18 to 39 years) as compared to older individuals.[28]

Several landmark clinical trials have assessed the impact of different therapeutic agents on outcome in the presence of hypertension. These studies highlight the importance of treatment selection in the individual hypertension patient.[29] These trial findings, coupled with the recommendations of the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII),[30,31] underscore the importance of recognizing up-to-date BP classification, selecting the appropriate agents for the clinical setting and achieving effective target BP lowering.

The current classification of BP for adults 18 years of age or older in JNC VII defines a prehypertension category that precedes stages I and II.[32] When considering the number of patients with a BP of 120 to 139/80 to 89 mm Hg, prehypertension represents a major public health problem. Vigorous attempts at lifestyle modifications should be undertaken for individuals categorized as prehypertensive. Patients with systolic BPs between 120 and 140 mm Hg are not entirely free from a potential CV event; these prehypertensive individuals have a higher risk for developing hypertension than those with systolic BPs < 120 mm Hg. Figure 52.4 shows the importance of matching the initial drug selection with the stage of hypertension and the presence or absence of compelling indications (heart failure, diabetes mellitus type 1 or 2, proteinuria, renal disease, isolated hypertension, myocardial infarction, etc.). In the JNC VII, there was emphasis on attention to antihypertensive drug selection as well as intense BP control (defined as target BP <130/80 mm Hg) in the presence of compelling indications including diabetes mellitus, CKD with proteinuria, and congestive heart failure (CHF). However, recent results from two large prospective clinical trials, Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial and African-American Study of Kidney Disease and Hypertension (AASK), have brought into question the premise that intense BP lowering in these high-risk goups is beneficial. In the ACCORD trial, lowering of systolic BP to a goal of 120 mm Hg (intense BP-lowering group) in patients with diabetes was not associated with a reduction in cardiovascular outcomes when compared with the standard therapy group (systolic blood pressure [SBP] goal of 140 mm Hg). However, the risk of stroke was reduced in the intense BP-lowering group. The overall analysis of the follow up study of AASK participants (African American patients with CKD and hypertension) who were randonmized to intense and

usual/standard BP-lowering goals did not show any benefit with intense BP lowering in these patients. However, for individuals with an elevated urine protein-to-creatinine ratio (>0.22), more intensive therapy, with a BP goal/target of approximately 130/80 mm Hg, appeared to reduce the likelihood of death or progression to ESRD.

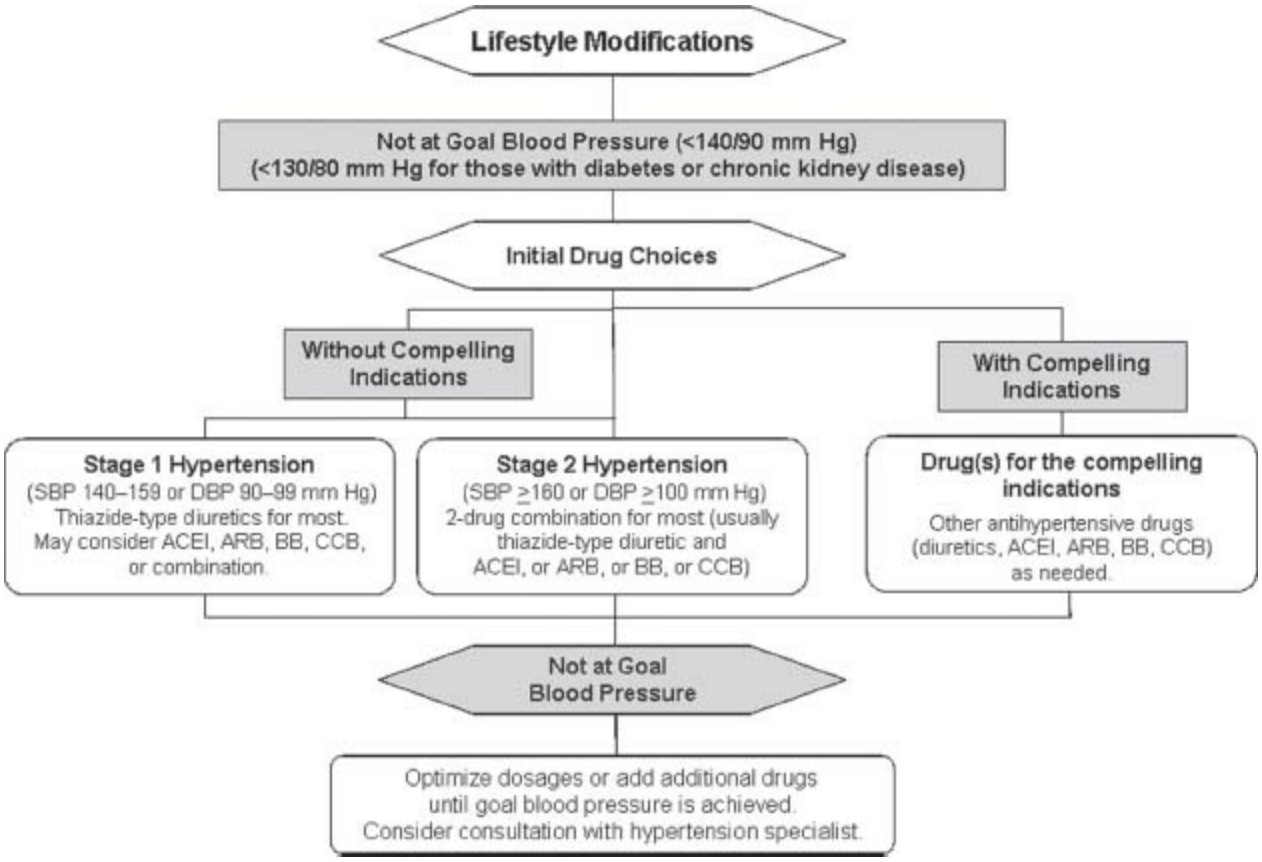

FIGURE 52.4 Algorithm for treatment of hypertension, based on randomized controlled trials. SBP, systolic blood pressure; DPB, diastolic blood pressure; ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; CCB, calcium channel blocker; HYTN, hypertension. (Adapted from Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. Lancet. 2002;359:204–210; Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. JAMA. 2003;289:2560–2571.)

Findings from recent clinical trials (Table 52.2) point out specific caveats for therapeutic selection in high-risk patients for CVD,[33] for those with diabetic renal disease,[34,35] and in high-risk ethnic groups (e.g., African Americans).[36] For patients with essential hypertension who are at high risk for CVD, the use of diuretic therapy resulted in outcomes at least equivalent to the use of ACE inhibitors or CCBs in the ALLHAT study.[37] Dihydropyridine calcium blockers should not be used as monotherapy in patients with proteinuric renal disease, whether associated with diabetes mellitus or hypertension. The role of BBs, especially those without vasodilating properties such as atenolol, in the management of hypertension in the absence of compelling cardiac

indications is still under debate and will need further clarification. Recent clinical trials with metoprolol and newer vasodilating BBs (carvedilol and bucindolol) have shown benefit in CHF patients when added to standard therapy including ACE inhibitors.[38,39] For patients with type 1 diabetes, ACE inhibitor therapy is the cornerstone of treatment. ACE inhibitors and angiotensin-II receptor blockers (ARBs) have demonstrated favorable results in both diabetic and nondiabetic renal disease. The greatest benefit for slowing progression of type 2 diabetes with renal disease can be seen with ARBs, based on findings from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) studies.[40,41] Aliskiren belongs to a new class of antihypertensive medication that act by direct renin inhibition (DRI). In clinical trials, BP reduction by aliskiren was equivalent to ARBs including valsartan, irbesartan, and losartan. Several trials have examined the effect of aliskiren in combination with other antihypertensive drugs. Aliskiren when used in combination with atenolol showed a significantly greater reduction in diastolic BP (14.1 mm Hg) when compared with aliskiren monotherapy (11.3 mm Hg) but not with atenolol alone (13.7 mm Hg).[12] The additive effects of a high-dose combination of aliskiren and valsartan demonstrated that the combination reduced BP by a mean of 17.2/12.2 mm Hg, a greater reduction than was observed with either component (aliskiren, 13.0/9.0 mm Hg; valsartan, 12.8/9.7 mm Hg; $p < 0.0001$). The Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study evaluated the additive effect of aliskiren in patients with hypertension and type 2 diabetes with nephropathy who were on an ARB (losartan). The study arm that received a combination of aliskiren and losartan had a significant reduction in albuminuria, a surrogate end point for renoprotection. Direct renin inhibitors offer an additional choice in the current armamentarium of antihypertensive medications, to treat those with hypertension and provide renoprotection in those with diabetic nephropathy. Data on the effects of DRI on cardiovascular and renal end points are lacking and need to be studied further before they can be considered a first-line agent in treating patients with compelling indications.

TABLE
52.2 Summary of Cardiovascular and Kidney Outcome Trials (2001–2010)

Study	Population	Special Note(s)	Effect on Clinical Practice
ALLHAT	North American subjects >55 y	Alpha-blocker terminated due to excess risk for hospitalized CHF	Hypertensive patients respond as well or better to diuretics compared to other agents ACE inhibitors, CCB
RENAAL	Type 2 diabetics, 31–70 y with nephropathy	Controlling BP may require 3–4 antihypertensive agents	Greater reduction in proteinuria for losartan vs. placebo
IDNT	Type 2 diabetics, hypertensive, proteinuria		Lower risk of SCr doubling with irbesartan vs. amlodipine or placebo
AASK	African Americans, 18–70 y, hypertensive with renal disease	Amlodipine arm terminated due to excess risk of ESRD/death vs. ramipril	Patients with proteinuria should not receive DHP CCB as monotherapy. Lower-than-usual BP control did not slow progression of renal disease. ACE inhibitors more effective at slowing progression compared to CCB or BB
HYVET	Very elder hypertensives (80 y and older)	Study discontinued as treatment was associated with reductions in stroke and all-cause mortality	The first morbidity/mortality trial to show antihypertensive therapy benefits very elderly hypertensive patients
ONTARGET	>55 y with CHD/DM plus risk factors	Combination of ACEI +ARB developed more adverse effects	ARB similar to ACEI in patients with vascular disease or those with high-risk diabetes

y, year(s); CHF, congestive heart failure; ACE, angiotensin-converting enzyme; CCB, calcium channel blocker; SCr, serum creatinine; ESRD, end-stage renal disease; DHP CCB, dihydropyridine calcium channel blocker; BP, blood pressure. Trial names: ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; IDNT, Irbesartan Diabetic Nephropathy Trial; AASK, African American Study of Kidney Disease and Hypertension; HYVET, Hypertension in the Very Elderly Trial; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial.

Because patients with CKD (serum creatinine ≥1.4 mg/dL or estimated glomerular filtration rate [eGFR] <60 mL/min) are more likely to die from CVD than from ESRD, hypertension should be aggressively controlled.[42] Despite this, awareness of kidney disease is low, especially with respect to other chronic diseases. Decreased CKD awareness is most prevalent in first-degree Spanish speakers, male gender, non-Hispanic blacks, and in patients with hypertension.[43] The risk for CV and renal disease events starts at systolic BP levels as low as 115 mm Hg.[44] ACE inhibitors or ARBs should be used in CKD patients whenever possible. An increase in baseline serum creatinine up to 35% on these agents is acceptable unless clinically resistant hyperkalemia develops. Hypertensive patients with eGFR <30 mL/min/1.73 m^2 will require increasing doses of loop diuretic in combination with other agents to optimize volume, a critical determinant of elevated BP.

The development of microalbuminuria is associated with abnormal vascular reactivity, salt sensitivity, increased presence of TOD, and loss of nocturnal dipping in BP.[45] An elevated urine albumin-to-creatinine ratio heralds the need for aggressive BP

control.

Effective BP control can be achieved in the majority of patients with hypertension, but more than two (2.7 to 3.8) medications may be needed to reach target BP levels.[46] When BP is >20/10 mm Hg above target, consideration should be given to initiating therapy with two drugs. Extensive clinical experience with available antihypertensive agents suggests that any single drug preparation will control only 30% to 65% of patients treated, whereas the addition of a second or third drug to the regimen can improve control rates into the range of 90% to 95%. Patients should return for follow-up monthly until the BP goal is achieved. Serum potassium and creatinine should be monitored at least twice per year.[47]

Among older persons, systolic BP is a better predictor of events (CHD, CVD, heart failure, stroke, ESRD, and all-cause mortality) than diastolic BP. The initial treatment goal in older patients should be the same as in younger individuals, namely, to achieve a BP below 140/90 mm Hg. However, the concept of a J curve for mortality with exaggerated BP lowering may be of greatest importance in the elderly. Findings from both the Systolic Hypertension in the Elderly Program (SHEP) trial[48] and the Rotterdam Study[49] suggest that there may be an increased CV risk in the lowest strata of BP and that reducing systolic BP to <130 mm Hg or diastolic BP to <65 mm Hg may not represent optimal strategy in the elderly.

Electrocardiographic or echocardiographic evidence of left ventricular hypertrophy (LVH) is associated with increased risk of coronary disease, ventricular dysrhythmias, and sudden death[50,51] and requires optimal target BP. Most of the antihypertensive drugs used for initial hypertension therapy induce regression of LVH. In the losartan intervention for endpoint reduction trial, ARBs were superior to BB therapy in reducing CV endpoints in hypertensive patients with electrocardiogram evidence of LVH.

Because the risk of heart disease and stroke increases with age among women, increasing attention has been focused on the nearly 30 million American women over age 50 years. In women 50 to 64 years of age, 47% have high BP—this figure increases to 58% in women 65 to 74 years of age, and to 75% for those 75 years and older. African American women have a death rate from hypertension that is approximately 4.5 times higher than the rate for white women, which makes hypertension the probable cause of up to 20% of all deaths in hypertensive African American women. There is no evidence that women respond any differently than men to the risk-reduction effect of antihypertensive drugs,[52] and the JNC VII guidelines should be applied equally to women.

SECONDARY HYPERTENSION

For hypertensive patients who are resistant to treatment with two or more agents, a

number of clinical clues can suggest the possible presence of secondary hypertension. Table 52.3 divides the causes of secondary hypertension into four broad categories. Secondary hypertensive disorders can be effectively treated or cured, leading to partial or complete normalization of resistant hypertension in most patients.

TABLE
52.3 Clues to Secondary Hypertension

Renal
Renal artery stenosis
Renal parenchymal obstruction
Polycystic kidney disease
Endocrine
Cushing syndrome
Adrenogenital syndrome
Pheochromocytoma
Adrenal and adrenal-like
Acromegaly
Hypercalcemia
Liddle syndrome
Gordon syndrome
Coarctation of the aorta
Other
Preeclampsia
Acute intermittent porphyria
Thyroid (hyper, hypo)
Drugs

Primary Aldosteronism

Primary aldosteronism is the most common cause of hypertension due to an endocrinopathy. The most common cause of primary aldosteronism is an aldosterone-producing adenoma (70% to 80%). However, glucocorticoid-remediable aldosteronism (GRA), adrenal hyperplasia, and adrenal carcinoma are other considerations. Although the clinical manifestations of primary aldosteronism are not distinctive, the best clues to the presence of primary aldosteronism include hypertension with spontaneous hypokalemia (<3.5 mEq/L), hypertension with provoked hypokalemia (<3.0 mEq/L during diuretic therapy), and hypertension with difficulty in maintaining normokalemia despite potassium supplementation.

Primary aldosteronism should be considered in any patient with both refractory hypertension and hypokalemia with inappropriate kaliuresis (urine potassium >30 mEq/L per 24 hours). One should be especially suspicious of primary aldosteronism if potassium is <3.5 mEq/L despite potassium supplementation, ACE inhibitor or ARB therapy, and/or a potassium-sparing diuretic. In addition, patients may develop muscle

spasms, periodic paralysis, or metabolic alkalosis. The clinician needs to remember that not all patients with primary aldosteronism have hypokalemia; 7% to 38% of patients with primary aldosteronism may have normal serum potassium.[53] Even 10% to 12% patients with positive tumors may not have hypokalemia during short-term salt loading. Individuals with hypertension and renal potassium wasting can be differentiated into high-renin and low-renin states (Table 52.4). Usually, the plasma renin concentration is <1 ng/mL/h in mineralocorticoid excess, and fails to rise above 2 ng/mL/h after salt depletion and upright posture.

TABLE
52.4 Biochemical Classification of Patients with Hypertension, Hypokalemia, and Renal Potassium Wasting

High Renin States	Low Renin States
Renovascular disease	Conn syndrome[a] (primary aldosteronism)
Malignant hypertension	Bilateral adrenal hyperplasia
	Renin-secreting tumors
	GRA[b]
	Mineralocorticoid excess syndrome
	Licorice ingestion
	Liddle syndrome[c]

[a]Aldosterone-secreting adrenal adenoma.

[b]Children, early-onset severe hypertension, history of early hemorrhagic stroke, adrenocorticotropic hormone (ACTH) and renin–angiotensin system is suppressed. Suppression of ACTH with glucocorticoids decreases aldosterone and cures the hypertension. Diagnose by high 18-hydroxycortisol/18-oxycortisol.

[c]Hypertension, decreased potassium, alkalosis, decreased aldosterone, and sodium channel mutation.

The best screening test for primary aldosteronism is the ratio between plasma aldosterone (PA) and PRA.[54] Patients with hypokalemia and resistant hypertension should undergo measurement of both PRA and aldosterone concentration. Both specific medications55 and variability of PA levels may affect the accuracy of the ratio. All diuretics should be discontinued 1 to 2 weeks prior to laboratory workup of hypokalemia. If the patient has uncontrolled hypertension, a CCB or a nonatenolol BB may be used. Although doxazosin and irbesartan have the least impact on the ratio, atenolol may lead to an increased rate of false-positive aldosterone/renin ratios. Spironolactone and ACE inhibitors also affect this ratio adversely. Physicians may be confused by values measured as PRA versus the new assay of direct renin measurement. The direct renin measurement divided by 8 is roughly equivalent to the PRA. An

elevated PA/PRA ratio alone does not establish a diagnosis of primary aldosteronism. The diagnostic suspicion should be confirmed by demonstrating inappropriate aldosterone secretion.

Table 52.5 lists the laboratory evaluation for patients with hypertension, hypokalemia, and kaliuresis. A high renin value does not exclude primary aldosteronism. The most important test in diagnosing primary aldosteronism is a nonsuppressed 24-hour urinary aldosterone excretion rate during a salt load. A rate >14 µg/24 hours following 3 days of salt loading (24 mL/kg of physiologic saline over 4 hours for 3 days, or a home oral salt load) distinguishes most cases of primary aldosteronism from essential hypertension. Those specific situations that warrant salt loading (>250 mEq/d) include individuals with hypertension and normal PA, with a PRA ≤ 1.0, those with high PA and normal–high PRA, and those with spontaneous hypokalemia who have normal PA and normal PRA. Individuals who warrant salt loading can be placed on a high-salt diet (1 level teaspoon of salt each day for 5 days). The urinary aldosterone excretion rate should be determined on days 4 and 5, along with urinary creatinine, potassium, and sodium measurements. If the sodium concentration is <250 mEq in 24 hours, mild increases in urinary aldosterone excretion rate may represent inadequate suppression.

TABLE
52.5 Hypertension; Hypokalemia (k_s < 3.5 mEq/L) with kaliuresis (uk_v >30 mEq/24 h)

Laboratory workup:
Serum electrolytes
Serum creatinine, urea
PA, cortisol, PRA
24-h urinary Na, K, Cr, aldosterone, and free cortisol during high-salt diet ($U_{Na}V$ >250 mg/kg/d)
High-salt diet

k_s, serum potassium concentration; uk_v, urinary potassium per 24 h; PRA, plasma renin activity; Na, sodium; K, potassium; Cr, creatinine; UNaV, urinary sodium per volume of urine.

Combining urinary aldosterone levels with urinary free cortisol results can distinguish nonaldosterone mineralocorticoid excess from aldosterone mineralocorticoid excess (Table 52.6). Patients with Liddle syndrome usually present with hypertension, hypokalemia, and metabolic alkalosis at an early age. Liddle syndrome is an autosomal dominant disorder associated with low/normal urinary excretion of aldosterone, increased kaliuresis occurring with increased collecting tubular sodium reabsorption via amiloride-sensitive channels, and normal urinary free cortisol measurements. The increased sodium reabsorption in collecting tubules results

in increased potassium secretion and hypokalemia. Amiloride has been used to close the sodium channels and correct the defect clinically. Liddle syndrome can be differentiated from congenital adrenal hyperplasia and 11-β-hydroxysteroid dehydrogenase deficiency (11-β-OHSD) by analyzing urinary aldosterone and urinary free cortisol values in addition to the clinical presentation.

TABLE
52.6 Combining Urinary Aldosterone Levels with Urinary Free Cortisol Results Can Distinguish Nonaldosterone Mineralocorticoid Excess from Aldosterone Mineralocorticoid Excess

		Urinary Free Cortisol		
		Low	**Normal**	**High**
Urinary aldosterone	Low-normal	Congenital adrenal hyperplasia	Liddle syndrome Exogenous mineralocorticoids	11-β-OHSD Cushing syndrome GRA
	High	—	Primary aldosterone GRA	Adrenal cancer Primary aldosteronism with Cushing syndrome

OHSD, hydroxysteroid dehydrogenate deficiency; GRA, glucocorticoid remediable aldosteronism.

The MRs in the distal nephron have equal affinity for both aldosterone and cortisol but are normally protected from cortisol by the presence of 11-β-dehydrogenase, which inactivates the conversion of cortisol to cortisone. The 11 to 18 hemiacetal structure of aldosterone protects it from the action of 11-β-dehydrogenase so that aldosterone gains specific access to the receptors. When this mechanism (normal 11-β-hydrogenase and aldosterone) is defective, either because of congenital 11-β-OHSD or because of enzyme inhibition (licorice or carbenoxalone), the intrarenal levels of cortisol increase and inappropriately activate the MRs, resulting in antinatiuresis and kaliuresis associated with hypertension and hypokalemia. Plasma cortisol concentrations in 11-β-OHSD are usually not elevated. The laboratory abnormalities and symptoms are reversed by spironolactone or dexamethasone but are exacerbated by physiologic doses of cortisone.

Licorice-induced hypermineralocorticoidism has both low PA and low PRA levels. The glycyrrhetinic acid inhibits the enzyme 11-β-dehydroxyase steroid dehydrogenase, allowing cortisol to act as the major endogenous mineralocorticoid avidly binding to the MRs and inducing inappropriate kaliuresis. It is interesting to note that essential hypertension patients are more sensitive to the inhibition of 11-β-hydroxysteroid dehydrogenase by licorice than normotensive subjects, and this inhibition causes more clinical symptoms in women than in men.[56] Glycyrrhetinic acid-containing compounds

include antipeptic ulcer medication, carbenoxalone sodium, antituberculosis medication, p-aminosalicylic acid, the French alcoholic beverage Boisson de coco, chewing tobacco,[57] and some Asian herbal preparations. Diagnosis depends on the elicitation of a thorough history and laboratory evidence of hypokalemia. In general, regular daily intake of 100 mg of glycyrrhizic acid produces adverse effects in sensitive individuals, whereas consumption of 400 mg/d produces adverse effects in most subjects.[58]

GRA is an inherited autosomal dominant disorder that mimics primary aldostoneronism. Aldosterone-like GRA should be suspected in any patient with a primary aldosterone-like presentation who presents with a positive family history and primary aldosteronism, early age (under 21 years) of hypertension onset, or severe hypertension with early death of affected members from a cerebrovascular accident. GRA is usually associated with bilateral adrenal hyperplasia. Patients with GRA have adrenocorticotropic hormone (ACTH)-sensitive aldosterone production occurring in the zona fasciculata rather than in the zona glomerulosa, which is the normal site of production. The isoenzyme in the zona glomerulosa catalyzes conversion of deoxycorticosterrone to corticosterone and of 18-hydroxycorticosterone to aldosterone. The hybrid gene in GRA results from a genetic mutation. This defect allows for an ectopic expression of aldosterone synthesis activity in the ACTH-regulated zona fasciculata. The plasma potassium concentration is normal in more than one-half of patients with GRA, in contrast to the pattern seen most commonly with primary aldosteronism. Genetic testing using molecular biologic techniques can detect a chimeric gene responsible for GRA. Standard laboratory testing includes a dexamethasone suppression test and measures of 18-hydroxycortisol and 18-oxycortisol. Both 18-hydroxycortisol and 18-oxycortisol are usually increased. Administration of dexamethasone in doses of 2 mg in 24 hours (0.5 mg every 6 hours) usually results in remission of hypertension and hypokalemia within 7 to 10 days. The suppression of ACTH with exogenous glucocorticoid should correct the metabolic defect and control hypertension in GRA. The use of spironolactone and/or amiloride may be supplemental treatment in addition to exogenous glucocorticoid therapy.

An adrenal computed tomography (CT) scan is helpful in differentiating among adrenal adenoma, adrenal hyperplasia, and adrenal carcinoma. The overall sensitivity of localizing aldosterone-producing tumors by high-resolution CT scanning exceeds 90%. Adrenal carcinomas are typically large (>5 cm) in comparison to a hypodense unilateral macroadenoma (>1 cm). Normally, abnormalities in both glands represent adrenal hyperplasia. Hounsfield units >10 usually indicate adrenal carcinoma, whereas Hounsfield units <10 most likely suggest an adrenal adenoma. The difference in density results from a vascular tumor versus a lipid-rich adenoma.

Adrenal vein sampling after administration of ACTH may be useful when no adrenal abnormality exists on CT scan or magnetic resonance imaging (MRI) or when there is an

asymmetric abnormality in both glands. The sampling of the adrenal vein is technically difficult and should be restricted to experienced centers. It is important to assess both aldosterone and cortisol values at the time of sampling from the right and left adrenal glands and high and low inferior vena cava. To be certain the samples are from the adrenal veins, cortisol should also be measured in the same samples. Serum cortisol concentrations should be roughly the same in both adrenal veins and approximately 10-fold higher than in the peripheral vein. The aldosterone concentrations should be two times higher from the adrenal vein versus periphery. An aldosterone ratio >10:1 in the presence of a symmetric ACTH-induced cortisol response is diagnostic of an aldosterone-producing adenoma.

Medical therapy with eplerenone (selective aldosterone-receptor antagonist) or spironolactone can be used in patients with bilateral adrenal adenomas, adenomas that cannot be excised surgically (poor surgical risk), in individuals with adrenal hyperplasia, and in those with significant responses to aldosterone-receptor antagonists who do not desire surgery. Surgical removal of an aldosterone-producing adenoma renders normotension and restoration of normal potassium homeostasis in most patients. Adrenal adenomas may be removed laparoscopically. Patients may require drug treatment for 3 to 6 months prior to surgery. Selective hypoaldosteronism usually occurs after aldosterone-producing adenoma removal.

Cushing Syndrome

Clinical clues for Cushing syndrome include a history of recent change in facial appearance and considerable weight gain, together with complaints of weakness, muscle wasting, peripheral bruising, impotence, and, in women, amenorrhea and hirsutism.[59] Typical physical features include truncal obesity, moon face, plethora, and purplish skin stria.

Screening and laboratory studies may indicate glucose intolerance or frank diabetes mellitus, and occasionally neutrophilia with relative lymphocytopenia. Pathologic fractures of a rib are common. A dexamethasone suppression test may be helpful. For diagnosis and localization, a 24-hour urinary free cortisol test, CT, and radioimmunoassay of plasma adrenocorticotropic hormone may be helpful.

The standard of care for most cases of Cushing syndrome is surgical resection of a pituitary gland or an ectopic source of adrenocorticotropic hormone or removal of a cortisol-producing adrenal cortical tumor. Transsphenoidal pituitary adenomectomy or radiation therapy to the pituitary bed may be considered in selected cases.

Pheochromocytoma

Pheochromocytoma can present in many ways, reflecting variation in the hormone it releases, the pattern of release, and differences in each individual's catecholamine sensitivities. Eighty percent of patients with pheochromocytoma present with headache, 57% with sweating, 48% with paroxysmal hypertension, 39% with persistent

hypertension, 64% with palpitations; 13% of patients may be normotensive, and 8% may be completely asymptomatic. In approximately 10% of patients, tumors are discovered incidentally during CT/MRI of the abdomen for unrelated symptoms. Those individuals who warrant a workup for pheochromocytoma include patients with (a) episodic symptoms of headache, tachycardia,diaphoresis; (b) family history of pheochromocytoma or multiple endocrine neoplasia (MEN) syndrome; (c) unexplained paroxysms of tachy/brady dysrhythmias; and/or (d) hypertension during intubation, induction of anesthesia, prolonged or unexplained hypotension after surgery, or adverse CV responses to ingestion or inhalation of certain drugs including anesthetic agents, glucagon, ACTH, thyrotropin-releasing hormone, antidopaminergic agents, miloxane, phenothiazine, guanethidine, and tricyclic antibiotics.

Currently available tests can establish the diagnosis of pheochromocytoma in >90% of cases. Figure 52.5 illustrates the approach to using plasma catecholamines and urinary metanephrines in the evaluation of patients suspected of having pheochromocytoma.[60] Fractionated plasma free metanephrines are the best test for familial (hereditary) pheochromocytoma, whereas 24-hour urinary metanephrines and catecholamines provide adequate sensitivity with low false-positive rates for sporadic pheochromocytoma. The combination of resting plasma catecholamines (NE plus E) at least 2,000 pg/mL and urinary metanephrines (normetanephrines plus metanephrines) at least 1.8 mg in 24 hours has a diagnostic accuracy of approximately 98% in both sporadic and hereditary pheochromocytoma. A number of medications interfere with the biochemical diagnosis of pheochromocytoma. Methylglucamine results in a decrease in metanephrines, whereas sotalol increases metanephrine concentration. ARBs, ACE inhibitors, and bromocriptine decrease catecholamine values, whereas α_1-blockers, BBs, and labetalol increase catecholamine values. Methyldopa and monamine oxidase inhibitors decrease vanillylmandelic acid (VMA) values, whereas nalidixic acid and anileridine increase VMA values. Phenothiazine, methyldopa, and tricyclic antibiotics have varying effects on these tests. A urinary metabolite of buspirone, an anxiolytic drug, is artificially measured as metanephrines, resulting in a marked increase in the measured metanephrine excretion. When blood specimens are drawn under standardized conditions, a total plasma catecholamine level ≥2,000 pg/mL is diagnostic of pheochromocytoma, whereas a value of <500 pg/mL excludes pheochromocytoma.

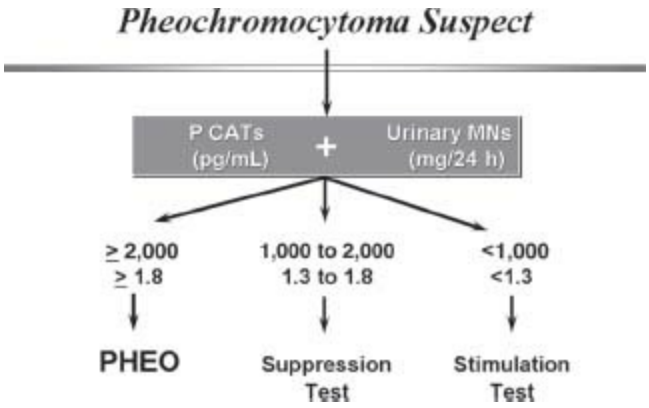

FIGURE 52.5 Pheochromocytoma suspected. (Adapted from Bravo EL. Pheochromocytoma. Cardiol Rev. 2002;10:44–50.)

For localization, CT scanning and MRI are equally sensitive (98% vs. 100%), whereas^{131} I-metaiodobenzyl-guanadine iothalamate (MIBG) has excellent specificity (100%) but low sensitivity (78%). Pheochromocytomas are typically hyperdense compared to the liver on T_2-weighted images, whereas benign tumors are isodense. If no tumor is detected (by either CT or MRI) in a highly suspicious setting, then MIBG scintigraphy should be used.

A provocative test is employed when the clinical findings are highly suggestive of pheochromocytoma but the BP is normal or slightly increased and plasma catecholamines are between 500 and 1,000 pg/mL. The glucagon test has a high specificity (100%) but low sensitivity (81%). Drugs that inhibit central sympathetic outflow (e.g., clonidine, bromocryptine, haloperidol, methyldopa) may decrease plasma catecholamines in normal and hypertensive subjects but have little effect on the excessive catecholamine secretion by pheochromocytoma. A clonidine suppression test is used for a patient whose plasma catecholamine level is between 1,000 and 2,000 pg/mL, with or without hypertension. A normal clonidine suppression test requires at least a 50% fall of plasma catecholamines from baseline to <500 pg/mL.

Such clinical situations as acute clonidine withdrawal, acute alcohol withdrawal, monotherapy with a pure arterial vasodilator (hydralazine or minoxidil), cocaine abuse, severe CHF, acute myocardial ischemia/infarction, and acute cerebrovascular accident can increase both plasma catecholamines and urine catecholamine metabolites.

Pheochromocytomas may develop in about 50% of patients with MEN type 2a and type 2b, in 25% of patients with von Hippel–Lindau (VHL) type 2, and in 5% with Von Recklinghausen disease (neurofibromatosis). However, in patients with Von Recklinghausen disease and hypertension, a pheochromocytoma has been identified in more than one-third of patients.

CCBs (nifedipine, verapamil, or diltiazem) are used with or without selective α_1-receptor blockers (prazosin, terazosin, doxazosin) in the preoperative management of pheochromocytoma patients. The CCBs relax arterial smooth muscle and decrease

peripheral vascular resistance by inhibiting norepinenephrine-mediated release of intracellular calcium and/or calcium transmembrane influx. These agents do not usually produce the overshoot hypotension seen with nonselective α-adrenergic blockade. Selective α_1-blockers do not enhance norepinenephrine release and usually are not associated with reflex tachycardia. Therefore, CCBs or selective α_1-receptor blockers are effective and safe, without the adverse effects associated with the relatively nonspecific complete and prolonged α_1-blockade with phenoxybenzamine.[61] Phenoxybenzamine, traditionally used to counteract the sudden release of massive quantities of catecholamines during surgical intervention, is associated with dramatic hypertension with tumor manipulation and therefore is used less today than previously.

Current medications and surgical techniques have significantly decreased the risk of surgical intervention in pheochromocytoma. Laparoscopic surgery can be used successfully for tumor removal in the majority of cases. Patients undergoing laparoscopy have less severe intraoperative hypotension, minimal blood loss, shorter duration of hospitalization, and earlier resumption of normal activities.

Several prognostic factors have been suggested for characterizing patients with malignant pheochromocytoma. These characteristics include large tumor size, local tumor extension at the time of surgery, and a DNA ploidy pattern with diploid DNA being benign and DNA anuloploidy/tetraploidy having a more progressive nature.[62]

Renal Parenchymal Disease

CKD defined by either a reduction in glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 (corresponding male creatinine >1.5 mg/dL or female >1.3 mg/dL) or the presence of albuminuria >300 mg/d or 200 mg of albumin per gram of creatinine has been associated with an increased risk for hypertension.

The HOPE study data demonstrated a continuous relationship between serum creatinine levels and CV outcomes in hypertensive and normotensive patients. An additive risk exists with increased serum creatinine and microalbuminuria.[63]

Hypertension is one of the main contributing factors to progressive renal injury, and lowering BP to <130/80 mm Hg is recommended. Patients with renal parenchymal disease usually present with renal insufficiency, proteinuria, or hematuria.[64,65] Renal parenchymal disease is a common secondary cause of hypertension, although not often reversible. The clinical clues are easily detected with a carefully performed urinalysis and screening tests of renal function (serum creatinine and eGFR). Verifying proteinuria with sulfosalicylic acid is important because it detects protein light chains present in dysproteinemic states. Urinary protein should be quantitated with a urine protein-to-creatinine ratio to establish the level of the proteinuria. Additional screening studies may include renal ultrasonography. For diagnosis, assessment of the iothalamate GFR and renal biopsy may be helpful.

Baseline systolic BP is a stronger predictor than diastolic BP of renal outcome in patients with type 2 diabetes mellitus and diabetic nephropathy. Patients with the highest baseline pulse pressure have the highest risk for nephropathy progression and experience the greatest risk reduction with systolic BP lowered to <140 mm Hg.[40] The underlying etiology of the renal disease (focal segmental glomerulosclerosis, chronic interstitial nephritis, amyloidosis, etc.), determines the immediate and long-term management of renal parenchymal disease. Aggressive treatment and control of BP can slow the progression of renal function loss, especially with ACE inhibitors or ARBs as specific additions to the regimen.[66] With advanced renal failure (GFR < 30 mL/min/1.73 m^2, corresponding to a serum creatinine of 2.5 to 3.0 mg/dL), the use of loop diuretics is usually warranted to optimize fluid volume, which is critical for BP control. There is a significant opportunity to improve the treatment of hypertension in proteinuric CKD by the increased use of ACE inhibitors and ARBs.[67] In diabetics, tight control of blood sugar can also slow the loss of renal function. For patients who do progress to ESRD, renal replacement therapies, including hemodialysis or peritoneal dialysis, are available, together with renal transplantation for selected patients.

Renovascular Disease

Renal artery stenosis that results in renovascular hypertension occurs in 1% to 5% of all patients with hypertension.[68] The most common causes of renovascular disease are either fibromuscular dysplasia (FMD) or atherosclerosis.

Atherosclerotic renal artery disease (RAD) accounts for 90% of all renovascular lesions, usually occurring at the ostium or within the proximal 2 cm of the renal artery.[69] Patients with atherosclerotic renal artery stenosis may present with hypertension, renal failure secondary to ischemia, and/or recurrent episodes of CHF, and "flash pulmonary edema."

FMD is found predominantly in young women.[70] Radiographically it is characterized by a "string of beads" appearance, with the beading extending beyond the normal caliber of the artery, located in the middle to distal portion of the artery. Less common forms of fibrous renal artery stenosis include perimedial fibroplasia, medial hyperplasia, intimal fibroplasia, and adventitial hyperplasia.

Clinical clues for renovascular hypertension include abrupt onset of hypertension, age <30 years or >55 years, accelerated/malignant hypertension (grade 3 or 4 retinopathy), hypertension refractory to a triple-drug regimen, hypertension and diffuse vascular disease (carotid, coronary, peripheral vascular), systolic/diastolic epigastric bruit, hypertension and unexplained renal insufficiency, renal insufficiency induced by ACE inhibitor therapy, severe hypertension, and recurrent "flash pulmonary edema."[64,71,72,]

A number of specialized diagnostic tests have been used to screen patients

suspected of having renovascular disease. Duplex Doppler ultrasonography, spiral CT angiography, and magnetic resonance angiography (MRA) are replacing traditional screening tests (i.e., intravenous pyelogram [IVP], PRA, captopril renogram). Renal arteriography remains the "gold standard" for diagnosing renal artery stenosis. Renovascular disease can be effectively diagnosed with an acceptable specificity and sensitivity utilizing most forms of newer diagnosis tests (Table 52.7).

TABLE
52.7 Specificity and Sensitivity of Screening Tests for Renovascular Hypertension

Test	Sensitivity (%)	Specificity (%)
MRA	100	96
Duplex Doppler ultrasonography	69–96	86–90
Spiral CT angiography	98	94
IVP	~75	~85
Captopril renogram	70–93	95
Captopril-stimulated PRA	75	89

IVP, intravenous pyelogram; PRA, plasma renin activity; MRA, magnetic resonance angiography.

Uncontrolled BP and progressive compromise in renal function are the primary indicators for intervention. For younger patients with FMD (medial fibroplasia, intimal fibroplasia, periarterial hyperplasia), percutaneous transluminal renal angioplasty (PTRA) is the mainstay of therapy, with surgical revascularization considered a secondary indication. Successful angioplasty results in reduction of both the disease and hypertension.[70]

The primary goal of therapy for patients with hemodynamically significant RAD is control of hypertension and preservation of kidney function. The four current therapeutic options available to treat patients with RAD include (a) medical management, (b) surgical revascularization, (c) PTRA, and (d) stents. The risks versus benefits of medical and interventional therapies, PTRA, and renal stents in treating patients with RAD have been under debate for a long time now. In the past, three randomized controlled trials (RCTs) of medical versus PTRA (no stents) demonstrated a slight benefit in BP control with less medication (2.5 vs. 3.0), but kidney function was unaffected in patients randomized to PTRA. Another RCT of medical versus surgical revascularization did not demonstrate any difference in composite "stop points,"

including uncontrolled hypertension, 50% decrease in GFR, CV event, or mortality. The "Stent Placement and Blood Pressure and Lipid-Lowering for the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery" (STAR) trial that randomized patients with RAD either to percutaneous revascularization or medical treatment demonstrated that at 2 years, 16% of the revascularized and 22% of the medical group reached the primary end point of 20% or more reduction in creatinine clearance, the difference not achieving statistical significance. Another large study, Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial randomized patients with significant atherosclerotic RAD to renal revascularization coupled with medical therapy versus medical therapy alone. In this study, renal revascularization provided no benefit in renal function, BP or cardiovascular events, and mortality, when compared to patients who were managed conservatively. Nonetheless, selected patients may derive benefit in BP control and/or kidney function following interventions.

Hypertension in Women

In the United States, CVD has accounted for more deaths in women than in men every year since 1984.[73] Hypertension is a strong determinant of CVD in women, although CVD is delayed approximately 10 years compared to men.[74] Although essential hypertension accounts for the majority of women with hypertension, the primary causes of hypertension that occur only in women are eclampsia in pregnancy and hypertension associated with oral contraceptives.

A point that is frequently forgotten in hypertension diagnosis and treatment is that women have lower brachial systolic BP, diastolic BP, and mean BP than men. Also, they exhibit lower brachial pulse pressure below age 40 years and a higher pulse pressure over age 55 years.[75]

Gueyffier et al. compared the effects of antihypertensive drug treatment in 20,802 women and 19,975 men from a meta-analysis of seven previous therapeutic trials.[52] The odds ratios for benefit in any category of CV event did not differ between men and women. Because many women with hypertension require more than one medication for optimal BP control, a number of reports have examined the relationship between baseline use of ACE inhibitors, BBs, CCB, diuretics, or a combination of these and the incidence of CHD, stroke, and CVD mortality. The Women's Health Initiative Observational Study (WHI-OS)[76] examined differences in CV mortality among postmenopausal women with hypertension but no history of CVD who were treated with different classes of anti-hypertensive agents, single agent or combination therapy. Among women with hypertension but no history of CVD, a two-drug class regimen of CCB plus diuretics was associated with a higher risk of CVD mortality versus BB with diuretics. Risks were similar for ACE inhibitors plus diuretics and BBs plus diuretics. Monotherapy with diuretics was equal or superior to other monotherapy in preventing

CVD complications of high BP. Further work examining the importance of antihypertensive drug treatment is essential to clarifying the link between treatment strategies and risk in the postmenopausal woman.

Hypertension disorders occur in 6% to 8% of all pregnancies, are the second leading cause of maternal death, and contribute to significant neonatal morbidity and mortality.[77] The U.S. National High Blood Pressure Education Program (NHBPEP) recommends the use of four categories in defining pregnancy-related hypertension: "chronic hypertension, preeclampsia/eclampsia, preeclampsia superimposed upon hypertension, and gestational (transient/chronic) hypertension." Chronic hypertension (>140/90 mm Hg) is defined as hypertension that was either present before conception or detected before the 20th week of gestation and did not resolve in the early postpartum period. Diagnosis of preeclampsia after the 20th week of gestation denotes the presence of hypertension.

Medication selection in pregnancy is critical to avoiding embryotoxic complications. Methyldopa, hydralazine, and labetalol have been used most often in controlling BP in pregnancy. ACE inhibitors are contraindicated in pregnancy. Angiotensin-II antagonists are believed to raise similar concerns. Beta-adrenergic blocking agents, especially atenolol, may be associated with retardation of fetal growth. CCB may adversely affect uterine placental blood flow. Diuretics have been used for treating hypertension prepregnancy or before midpregnancy. Thiazide diuretics are preferable to loop diuretics. Short-term studies have not found adverse effects from either methyldopa or hydralazine administered during lactation.

Oral contraceptives induce hypertension in approximately 5% of women using high-dose pills containing at least 50 μg of estrogen and 1 to 4 mg of progestin.[78] Systolic BP and diastolic BP are significantly higher in patients who use oral contraceptives for more than 8 years.[79] BP should return to pretreatment levels within 3 months of discontinuation of oral contraceptives if the hypertension is attributable to the oral contraceptive. All levels of progestational potency and low levels of estrogen potency have been associated with a significantly increased risk of hypertension.

Thyroid and Parathyroid Disorders

Thyroid dysfunction together with renovascular hypertension represent the most common forms of reversible secondary hypertension observed in hypertensive individuals >60 years of age.[80,81] Thyrotoxic patients have hyperdynamic hypertension and high cardiac output seen predominantly as an elevated systolic BP, whereas elevation in diastolic BP is uncommon. Overall, the prevalence of hypertension in hyperthyroidism varies from 20% to 26%. On the other hand, hypothyroid patients have a high prevalence of elevated diastolic BP, and this can be a valuable clue in the elderly, in whom primary diastolic hypertension is rare. Hypertension in hypothyroid disease is associated with decreased cardiac index, low stroke volume, and increased

systemic vascular resistance. Beta-adrenergic receptors are reported to be decreased, while α-adrenergic responses are increased.

Most patients with primary hyperparathyroidism are asymptomatic; clinical diagnosis should be strongly suspected in the presence of hypercalcemia. The side effects of hypercalcemia, such as polyuria, polydipsia, renal calculi, peptic ulcer disease, and hypertension, may offer diagnostic clues. MEN syndromes are the exception to the above, and the finding of a thyroid nodule, thyroid mass, or cervical lymphadenopathy should suggest the possibility of a medullary thyroid carcinoma.

Additional screening studies may include assessment of thyroid-stimulating hormone level, serum thyroid hormone level, and serum calcitonin level for thyroid disease. For hyperparathyroidism, serum calcium, serum phosphorus, and serum parathyroid hormone level should be assessed.

For diagnosis, decreased thyroid-stimulating hormone and increased free thyroxine index should be assessed in the hyperthyroid patient; increased thyroid-stimulating hormone, decreased free thyroxine index, presence of medullary thyroid carcinoma, and increased calcitonin in the hypothyroid patient; and hypercalcemia, hypophosphatemia, and increased parathyroid hormone level in the hyperparathyroid patient.

Coarctation of the Aorta

Although coarctation of the aorta may cause left ventricular failure in early life, adults with coarctation are often asymptomatic.[82,83] As a result, the medical history may be of little help in suggesting the presence of coarctation unless the diagnosis is suspected in association with other congenital malformations, such as bicuspid aortic valve, patent ductus arteriosus or ventricular septal defect, and mitral valve abnormalities. The most common location for a coarctation is distal to the left subclavian artery, but it may occasionally involve the origin of the left subclavian artery and may be missed if BPs are not checked in both upper extremities and at least one lower extremity. Absent or reduced pulses in the legs, together with hypertension in the upper extremities and low BP in the lower extremities, are obviously valuable clues to diagnosis. Systolic BPs are elevated disproportionately to the diastolic BP, resulting in wide pulse pressure and bounding pulses proximal to the coarctation. A thrill may be observed in the suprasternal notch, together with palpable pulsations or auscultated bruits over the intercostal arteries.

Additional screening studies may include an abnormal chest x-ray with a “three sign” (proximal aorta, coarctated segment with poststenotic dilation, and indentation of the aortic knob). For diagnosis and localization, two-dimensional echocardiography, aortography, and MRI may be helpful. Management should consist of surgical repair or angioplasty.

HYPERTENSIVE EMERGENCIES AND URGENCIES

A number of different terms including “accelerated hypertension,” “hypertensive crisis,” “malignant hypertension,” “hypertension emergencies,” and “hypertensive urgencies” generally denote severe hypertension. Conditions associated with systolic BP >200 mm Hg and diastolic BP >110 mm Hg are associated with TOD (papilledema, CHF, central nervous system dysfunction, etc.). These emergencies require immediate BP reduction, not necessarily to normal, to prevent or limit ongoing TOD.

The primary pathophysiologic abnormalities in patients presenting with hypertensive urgencies stem from defective autoregulation mechanisms of certain vascular beds that lead to arteritis and ischemia. Whereas normal arteries maintain blood flow over a broad range of mean arterial pressures from 60 to 150 mm Hg, excessive abrupt increases in BP above this autoregulation range result in TOD, especially within the brain and kidney. In these settings, the disruption of the blood–brain barrier, diffuse cerebral edema, and subsequent fibrinoid necrosis of medium arteries, small arteries, and arterioles can occur. The abruptness of the BP increase may be more critical than the actual level of BP rise. Because the risk–benefit ratio of immediate therapy for some forms of hypertensive emergencies has not been clearly established, an individual approach should be invoked to guide therapy (clinical setting, absolute level of BP increase, potential for worsening target organ perfusion). The target BP is usually lower for encephalopathy than for an acute stroke in evolution. Hypertensive emergencies are those occasional situations that require immediate BP reduction (not necessarily to normal) to prevent or limit TOD. Examples include hypertensive encephalopathy, intracranial hemorrhage, acute pulmonary edema, or a dissecting aortic aneurysm.[84] Hypertensive urgencies are those situations in which reduction of BP over several hours to 24 hours is desirable. Examples include patients with upper levels of stage II hypertension and those with progressive target organ complications but not acute deterioration in target organ disease. Elevated BP alone, in the absence of symptoms or new or progressive TOD, rarely requires emergency therapy. A number of effective agents are available for the management of hypertensive emergencies and urgencies (Table 52.8).

TABLE
52.8 Drugs for the Management of Hypertensive Emergencies and Urgencies

Agent	Dose	Onset/Duration of Action (After Discontinuation)	Precautions
		Parenteral Vasodilators	
Sodium nitroprusside	0.25–10.0 μg/kg/min as IV infusion,[a] maximal dose for 10 min only	Immediate/2–3 min after infusion	Nausea, vomiting, muscle twitching; with prolonged use may cause thiocyanate intoxication, methemoglobinemia acidosis, cyanide poisoning; bags, bottles, and delivery sets must be light resistant
Fenoldopam mesylate	0.1–0.3 mg/kg/min as IV infusion	<5 min/30 min	Headache, tachycardia, flushing, local phlebitis

Glyceryl trinitrate	5–100 µg as IV infusiona	2–5 min/5–10 min	Headache, tachycardia, vomiting, flushing, methemoglobinemia; requires special delivery system due to drug binding to polyvinyl chloride tubing
Nicardipine	5–15 mg/h IV infusion	1–5 min/15–30 min, but may exceed 12 h after prolonged infusion	Tachycardia, nausea, vomiting, headache, increased intracranial pressure; hypotension may be protracted after prolonged infusions
Verapamil	5–10 mg IV; can follow with infusion of 3–25 mg/h	1–5/30–60 min	First-, second-, third-degree heart block, concomitant digitalis or beta-blockers, bradycardia
Diazoxide	50–150 mg as IV bolus, repeated, or 15–30 mg/min by IV infusion	2–5/3–12 h	Hypotension, tachycardia, aggravation of angina pectoris, nausea and vomiting, hyperglycemia with repeated injections
Hydralazine	10–20 mg as IV bolus or 10–40 mg IM, repeat every 4–6 h	10 min IV/>1 h IV; 20–30 min IM/4–6 h IM	Tachycardia, headache, vomiting, aggravation of angina pectoris
Enalaprilat	0.625–1.250 mg every 6 h IV	15–60 min/12–24 h	Renal failure in patients with bilateral renal artery stenosis, hypotension
Parenteral Adrenergic Inhibitors			
Labetalol	20–80 mg as IV bolus every 10 min; 2 mg/min as IV infusion	5–10 min/2–6 h	Bronchoconstriction, heart block, orthostatic hypotension
Esmolol	500-mg/kg bolus injection IV or 25–100 mg/kg/min by infusion; may rebolus after 5 min or increase infusion rate to 300 mg/kg/min	1–5 /15–30 min	Greater than first-degree heart block, CHF, asthma
Methyldopa	250–500 mg as IV infusion every 6 h	30–60 min/4–6 h	Drowsiness
Phentolamine	5–15 mg as IV bolus	1–2/10–30 min	Tachycardia, orthostatic hypotension
Oral Agents			
Captopril	25 mg PO, repeat as needed SL, 25 mg	15–30 min/6–8 h SL 15–30 min/2–6 h	Hypotension, renal failure in bilateral renal artery stenosis
Clonidine	0.1–0.2 mg PO, repeat hourly as required to total dose of 0.6 mg	30–60 min/8–16 h	Hypotension, drowsiness, dry mouth
Labetalol	200–400 mg PO, repeat every 2–3 h	30 min to 2 h/2–12 h	Bronchoconstriction, heart block, orthostatic hypotension
Prazosin	1–2 mg PO, repeat hourly as needed	1–2 h/8–12 h	Syncope (first dose), palpitations, tachycardia, orthostatic hypotension

[a]Requires special delivery system.

From Vidt DG. Treatment of hypertensive urgencies and emergencies. In: Izzo JL Jr, Black HR, eds. Hypertension Primer: The Essentials of High Blood Pressure, Third Edition. Dallas: Council on High Blood Pressure Research, American Heart Association; 2003.

Hypertensive emergencies during pregnancy warrant careful drug selection and

hemodynamic monitoring to avoid any increase in fetal risk. Hydralazine, methyldopa, and magnesium sulfate are traditional therapeutic agents in pregnancy; however, labetalol has been used more recently. Bolus injections may achieve therapeutic BP-lowering goals sooner than continuous infusion. Consideration of timely delivery of the infant will often help with BP control.

Most hypertensive urgencies represent patients who are noncompliant with therapy or who are inadequately treated patients with essential hypertension. In most cases, immediate resumption of medication with appropriate outpatient follow-up represents appropriate therapy.

The use of fast-acting nifedipine in hypertensive urgencies has been discouraged by the U.S. Food and Drug Administration. A number of reported serious adverse effects and the inability to control the rate or degree of decline in BP make this agent unacceptable.[85,86] The routine use of sublingual or oral nifedipine in patients with chronic hypertension, when BPs increase beyond a predetermined level, is also considered unacceptable.

For patients who present with a hypertensive emergency, parenteral therapy may be initiated in the Emergency Department under supervision. Most patients with true hypertensive emergencies should be admitted to an intensive care unit (ICU) for continuous monitoring. The initial goal for BP reduction is not to immediately reduce the BP to normal, but rather to achieve a controlled, progressive decrease in BP to a safer level and to minimize the risk of hypoperfusion in the cerebral, coronary, and renal vascular circulation.

CONCLUSION

Hypertension is a major public health problem worldwide, affecting over 50 million individuals in the United States alone. Hypertension may result from a number of different pathophysiologic factors that lead to both microvascular and, in time, macrovascular damage. Discovering genetic, environmental, and demographic factors that truly affect both the development and the maintenance of BP should offer hope for future medication development. The classification of patients into a prehypertensive BP category has reemphasized the need for earlier recognition of patients who may have or develop BP elevations that warrant intervention. A significant percentage of hypertensive patients warrant two or three medications to achieve a 90% control rate. Physicians should not sacrifice BP control in their desire to limit the number of medications used in treating hypertension. In the case of resistant hypertension, a series of clinical clues suggests the presence of secondary hypertension, and in specific situations, a comprehensive workup is necessary. Since the early 1980s, coronary vascular disease has accounted for more deaths among women than among men, so renewed emphasis on the importance of diagnosing and effectively treating hypertension

in the female population is paramount. Although the availability of medications and increased public awareness of hypertension have decreased the total number of hypertensive emergencies, the importance of appropriate medication selection and achieving BP-lowering rates is critical to the success of avoiding end-organ damage in this setting. Even though hypertension requires simple diagnostic maneuvers and basic clinical skills, it remains a significant medical problem, with the potential for limiting long-term patient survival.

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QUESTIONS AND ANSWERS

Questions

1. A 55-year-old white man is referred for evaluation of hypertension (blood pressure [BP] 185/95 mm Hg), discovered during a BP screening at his workplace. The patient states that he is well and has not seen a physician in many years. He describes himself as “a fitness freak,” as he is an active jogger, abstains from alcohol, and limits his salt and fat intake. He denies any knowledge of hypertension, cardiovascular disease (CVD), renal disease, or diabetes mellitus. He takes no medications regularly. Family history is significant in that his father was known to be hypertensive and died of a stroke. His older brother is being treated for hypertension.

   On examination, the patient appears well, with a BP of 178/96 mm Hg while seated and standing. Body weight is 71 kg (157 pounds), and height is 178 cm (70 in). Optic fundus examination is significant for grade II hypertensive retinopathy. The remainder of the examination is normal.

   Complete blood count, electrolyte panel, blood urea nitrogen level, creatinine concentration, thyroid-stimulating hormone level, and results of urinalysis are normal. Electrocardiography demonstrates normal sinus rhythm with left ventricular hypertrophy (LVH).

   To reduce the patient’s cardiovascular morbidity and mortality, which therapy would you prescribe?
   a. Hydralazine
   b. Atenolol
   c. Losartan
   d. Doxazosin

2. A 51-year-old white man transfers to your practice after a change of insurance status. His medical history is positive for primary hypertension without target organ damage (TOD). He has no history of renal or prostatic disease. Laboratory values obtained from his former primary care physician show normal results for blood urea nitrogen, serum creatinine, electrolytes, urinalysis, prostate-specific antigen, and electrocardiography. He takes the α-blocker doxazosin, 2 mg at bedtime.

   On examination, BP is 152/93 mm Hg seated and standing. Body weight is 84 kg (185 pounds). The remainder of the examination is normal.

   What is the appropriate course of action regarding the patient’s antihypertensive therapy?
   a. Advise a low-sodium diet.
   b. Discontinue doxazosin therapy and consider an alternative agent.
   c. Advise high dietary intake of calcium and potassium.
   d. Increase the doxazosin to 4 mg a day.

3. Which of the following statements about microalbuminuria is true?
   a. To be of clinical value, microalbuminuria must be measured in a timed 12- to 24-hour sample.
   b. Microalbuminuria is a cardiovascular risk factor that is independent of traditional Framingham risk factors.
   c. Microalbuminuria is present when the "spot" urine albumin-to-creatinine ratio is >500 mg/g.
   d. Microalbuminuria is a predictor of cardiovascular risk only in patients with diabetes.

4. A 37-year-old woman calls Monday morning seeking help with "the worst headache ever" Friday night and Saturday. The headache was associated with severe lethargy and intermittent confusion. She recovered and has felt well for the past 24 hours. She states that she does not have fever or neurologic or cardiovascular symptoms. Her medical history is significant for hypertension, and recurrent urinary tract infections related to her known autosomal dominant polycystic kidney disease. She is concerned because her father died of a stroke during dialysis. Her serum creatinine concentration is 2.6 mg/dL. BP at home currently is 146/92 mm Hg.
   What do you recommend for this patient?
   a. Arrange urgent magnetic resonance angiography (MRA) of her head.
   b. Order computed tomography (CT) of her head without contrast.
   c. Arrange a consultation with the neurology/headache clinic.
   d. Make an office appointment for her to see you

5. 5. A 52-year-old rodeo rider is referred by his primary care physician for hypertension and hypokalemia over the past 6 months. BP and routine chemistries were normal last year at the time of a company physical. He has no history of CVD, stroke, or renal disease. Family history is negative for hypertension. He uses alcohol socially and does not smoke, but chews tobacco. He takes no medications regularly.
   On examination, the patient weights 77 kg (168 pounds). BP is 184/102 mm Hg seated and standing. Except for trace pedal edema, the remainder of examination is normal.
   The primary care physician provides the following laboratory values:
Blood urea nitrogen: 21 mg/dL
Serum creatinine: 0.9 mg/dL
Serum sodium: 141 mEq/L
Serum potassium: 3.1 mEq/DL
Serum chloride: 100 mEq/L
Serum bicarbonate: 28 mEq/L
A 24-hour urine test during salt loading reveals the following values:
Creatinine: 1.1 g
Sodium: 252 mEq
Potassium: 128 mEq
   The daily aldosterone excretion rate is 6 mg (normal, 5 to 10 mg), plasma renin activity (PRA) is 1 µg/L/h, and plasma aldosterone (PA) level is 9 ng/dL.
   Which diagnostic test would you order next?
   a. Adrenocorticotropin hormone stimulation test
   b. MRA with gadolinium
   c. Serum cortisol and urinary free cortisol measurement
   d. CT of the adrenal glands

Answers

1. Answer C: The educational objective of this question is to recognize the superiority of therapy with an angiotensin-receptor blocker (ARB) over a traditional beta-blocker (BB) for cardiovascular morbidity and mortality in treating patients with primary hypertension and electrocardiographic evidence of LVH.

Most previous antihypertensive trials that demonstrated reductions in cardiovascular morbidity and mortality were based on a "stepped care" approach using diuretics and BBs. The recent Losartan Intervention for Endpoint Reduction in Hypertension Study compared the angiotensinreceptor blocker losartan with the BB atenolol in patients with primary hypertension who had evidence of LVH. Despite

similar reductions in BP between the groups, losartan recipients had fewer primary cardiovascular events (death, myocardial infarction, or cerebrovascular accident), experienced a lower rate of new-onset diabetes mellitus, and tolerated the medication with fewer side effects.[88]

2. Answer B: The objective of this question is to recognize that withdrawal of monotherapy with an α-blocker is recommended to treat hypertension. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial documented an increased risk of cardiovascular events (especially congestive heart failure [CHF]) with use of α-blockers. This adverse finding was published before completion of the full trial. The authors recommended that clinicians discontinue use of α-blocker monotherapy for hypertension and consider alternative therapy. Use of α-blocker therapy in combination with other antihypertensive agents and as therapy for symptomatic benign prostatic hyperplasia was not precluded.[89]

3. Answer B: The educational objective is to identify microalbuminuria as a cardiovascular risk factor and appreciate its measurement in clinical practice.

Further analysis of data from the Heart Outcomes Prevention Evaluation (HOPE) trial demonstrated that microalbuminuria was an independent predictor of cardiovascular events in both diabetic and nondiabetic persons at risk for such events.

Clinical measurement of microalbuminuria is an important tool for assessment of chronic kidney disease (CKD) and estimation of cardiovascular risk. Recent guidelines from the National Kidney Foundation suggest that timed urine collections are not required and that a “spot” urine sample to calculate the albumin-to-creatinine ratio is preferred. The albumin-to-creatinine ratio varies by gender because of differences in muscle mass. The established criteria for albumin-to-creatinine ratios for normal, microalbuminuria, and overt clinical proteinuria are as follows: in men, a normal albumin-to-creatinine ratio is <17 mg/g, whereas in women, <25 mg/g is normal. In microalbuminuria, the ratio is 17 to 250 mg/g in men and 25 to 355 mg/g in women; in clinical proteinuria, the ratio is >250 mg/g in men, whereas in women, it is >255 mg/g ([90,91]).

4. Answer A: The educational objective is to recognize the presentation and diagnosis of berry aneurysm in a patient with autosomal dominant polycystic kidney disease.The patient’s neurologic symptoms 48 hours earlier probably represent a “sentinel bleed” from a berry aneurysm. The likelihood of central nervous system bleeding after such an event is high and warrants urgent evaluation. MRA with gadolinium provides acceptable imaging of the carotids, circle of Willis, and central nervous system vasculature to identify or exclude berry aneurysm, which might require intervention. Overall, aneurysm is found in approximately 10% of all patients with autosomal dominant polycystic kidney disease and in about 24% of patients with polycystic kidney disease who have a positive family history of aneurysm. Routine screening with MRA is often recommended for patients with this family history and autosomal dominant polycystic kidney disease. All patients with autosomal dominant polycystic kidney disease who have central nervous system symptoms should undergo MRA evaluation to exclude a life-threatening condition.[92-94]

5. Answer C: The educational objective of this question is to recognize corticoid excess in a patient with hypertension and hypokalemia.

This patient presents with hypertension, metabolic alkalosis with hypokalemia, and a low normal plasma and urinary aldosterone suggestive of corticoid excess due to tobacco chewing. Chewing tobacco is adulterated with licorice-containing glycyrrhizic acid. Licorice and its derivatives cause hypertension by inhibiting inactivation of cortisol by 11-β-dehydrogenase. This results in increased activation of corticosteroid receptors by cortisol, an effect that is most obvious for renal mineralocorticoid receptors (MRs), resulting in sodium retention and kaliuresis. Modest increases in the serum cortisol level and urinary level of free cortisol are diagnostic of the licorice-containing products. The biochemical data do not support the diagnosis of primary hyperaldosteronism. The low PRA and clinical presentation do not suggest renal artery stenosis.[95]

CHAPTER

The Dyslipidemias

Adam W. Grasso and Michael B. Rocco

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the industrialized world, accounting for approximately one-third of all deaths in the United States. Coronary heart disease (CHD), a subcategory of CVD, kills nearly 1 in every 5 Americans. Each year, 1.5 million people in the United States suffer a first or recurrent myocardial infarction (MI), and nearly 325,000 people experience sudden cardiac death (SCD). Stroke remains the third leading cause of mortality with 800,000 strokes per year in the United States. Despite reductions in mean serum total cholesterol (TC) from 222 mg/dL in 1962 to 199 mg/dL in 2006, nearly half of US adults still have abnormally high levels. Given the enormous burden of CVD, the high prevalence of lipid disorders, and effective evidence-based treatment strategies, recognition of and management of lipid disorders is an essential component of both primary and secondary prevention of CVD. In this chapter, we have sought to provide a clinically relevant discussion of dyslipidemias and their effective treatment to reduce CVD morbidity and mortality. In addition to defining lipoproteins and lipid disorders, the clinical trials and observational studies that form the cornerstone for modern treatment guidelines are reviewed.

LIPIDS AND LIPOPROTEINS

Lipids are molecules with hydrocarbon skeletons, which play crucial roles in the storage, metabolism, and production of energy, the structure and behavior of cell membranes, and the transduction of signals both inside and between cells. Lipids are fat-soluble, or lipophilic, compounds, which are classified as either simple or complex. Simple lipids include free cholesterol (FC) and fatty acids (FAs), and complex lipids, which are combinations of simple lipids, include cholesteryl esters (CEs) and triglycerides (TG). The lipids with greatest pathologic significance appear to be CE, the predominant components of macrophage foam cell inclusions, and TG, which form the

core of adipocyte inclusions. Packaged together with phospholipids and proteins known as apolipoproteins, lipids are transported between organs in the form of lipoproteins. Lipoproteins are classified according to their densities and electrophoretic mobilities and include, in decreasing density, high-density lipoproteins (HDL), low-density lipoproteins (LDL), intermediate-density lipo-proteins (IDL), very low-density lipoproteins (VLDL), and chylomicrons.

Lipid processing and transport can be envisioned as a bidirectional process. The first cycle begins with triglyceride-rich lipoproteins (TGRLs), namely, chylomicrons from the gut and VLDL from the liver (Fig. 53.1). These lipoproteins serve as substrates for lipoprotein lipase (LPL) and hepatic lipase (HL), two different enzymes bound to capillary endothelium. Free FAs are released for the use of skeletal muscle, adipose tissue, and other organs and FC and CE are delivered to distant tissues. Chylomicrons, VLDL, and their lipolysis products, such as chylomicron remnants, IDL, and LDL, bear apolipoprotein B (apoB) and apolipoprotein E (apoE) on their surfaces. ApoB has two isoforms: apoB100, which is present on lipoproteins secreted by the liver, and apoB48, which is present on gut-derived lipoproteins. LDL, IDL, and remnant particles can be taken up by hepatocytes via receptors that bind to apoB and apoE. Alternatively, they may migrate across the endothelium, undergo oxidation/modification, induce monocyte recruitment and foam cell formation, and initiate a cycle of inflammation, chemotaxis, and thrombotic activity leading to atherosclerosis and vascular events. IDL is the most atherogenic lipoprotein, but LDL (which carries 70% of plasma cholesterol) is the principle lipoprotein responsible for atherosclerosis. Cholesterol present in apoB-containing lipoproteins may be represented as non–high-density lipoprotein cholesterol (non-HDL-C). Small dense LDL (sdLDL) is defined as LDL with a low LDL-C to LDL-apoB ratio (<1.2) and represents a more atherogenic subclass of LDL.

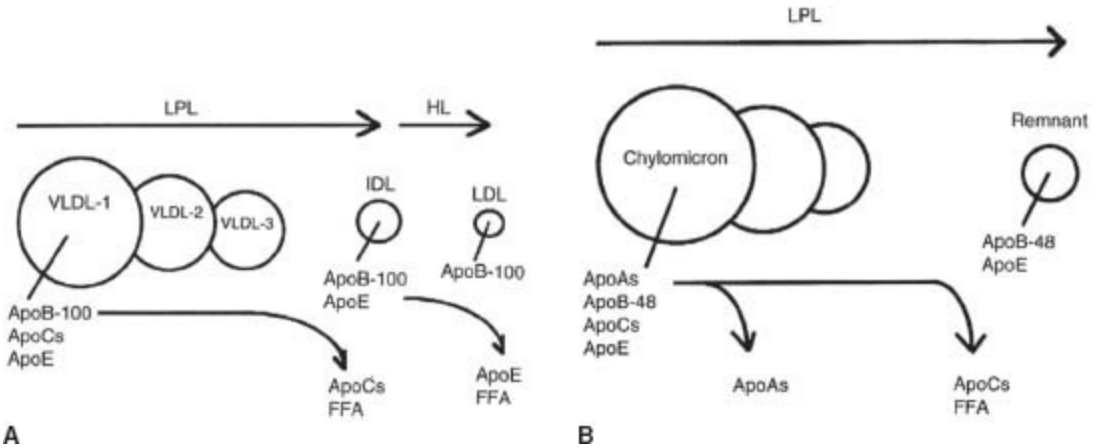

FIGURE 53.1 Remodeling of TGRLs. **A:** Stepwise lipolysis of VLDL subfractions 1, 2, and 3 by LPL. LPL catalyzes VLDL triglyceride hydrolysis with the concomitant transfer of the apoC proteins to HDL and the release of free fatty acids (FFA). Subsequently, HL catalyzes additional triglyceride hydrolysis that induces the transfer of apoE from IDL to HDL and the release of additional FFA. LDL contains apoB100 as its sole protein. **B:** Lipolysis of chylomicrons by LPL. Triglyceride hydrolysis is associated with the transfer of the apoC proteins to HDL and the

release of FFA. The remnant contains apoB48, which is the major protein of chylomicrons, and apoE, which mediates the binding of remnants to hepatic receptors. (Reprinted from Betteridge DJ, Illingworth DR, Shepherd J. Lipoproteins in Health and Disease. 1st ed. London: Arnold, 1999:4, with permission.)

The other major transport cycle, sometimes termed reverse cholesterol transport (RCT), serves primarily to return cholesterol to the liver (Fig. 53.2). RCT involves HDL, the major structural protein of which is apolipoprotein A (apoA). Starting with a lipid-poor HDL known as pre-β HDL, FC is progressively added from macrophages, and then esterified by the enzyme lecithin cholesterol acyltransferase (LCAT). These mature HDL-cholesterol (HDL-C) particles can return to the liver by direct hepatic uptake of HDL, or CE can be transferred to apoB-containing lipoproteins, which then can be taken up by the liver. One clinically relevant reaction is catalyzed by the cholesteryl ester transfer protein (CETP), which transfers CE from HDL to LDL or VLDL in exchange for TG. Thus, CE and TG are rapidly equilibrated between HDL and the apoB-containing lipoproteins, a major reason why patients with hypertriglyceridemia tend to have low HDL-C. The subsequent action of HL on TG-rich HDL leads to the production of smaller, denser HDL in such individuals. Individuals with diminished or absent levels of serum CETP generally have elevated HDL-C and lower rates of atherosclerosis. Pharmacologic inhibitors of CETP have been shown to significantly elevate HDL-C, but initial studies showed harm, not benefit. However, other CETP drugs "in the pipeline" may yet become important tools for the clinician. In addition to its role in lipid transport, HDL may mediate other antiatherosclerotic effects by inhibiting LDL oxidation, reducing endothelial dysfunction, reducing chemotaxis of inflammatory cells into plaques, and inhibiting thrombosis.

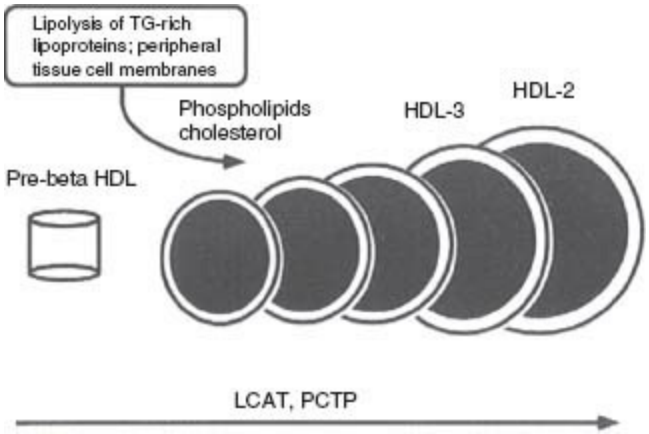

FIGURE 53.2 Remodeling of HDL by LCAT and phosphatidylcholine transfer protein (PCTP, also known as phospholipid transfer protein or PLTP). Small, premigrating HDL composed of apoA-I, cholesterol, and lecithin is a substrate for LCAT, which forms CEs within the core. Additional cholesterol and phospholipids from peripheral tissue cell membranes and lipolysis of TGRLs are added to the HDL. Multiple cycles of lipid transfer to HDL and LCAT activity eventually produce large, mature HDL, which is a major carrier of cholesterol to the liver. (Reprinted from Betteridge DJ, Illingworth DR, Shepherd J, eds. Lipoproteins in Health and Disease. 1st ed. London: Arnold, 1999:4, with permission.)

Lipoprotein (a), or Lp(a), is an LDL-like particle of hepatic origin. Unlike LDL, apoB100 on the surface of Lp(a) is bound to a protein called apolipoprotein (a), or apo(a), which has strong homologies to plasminogen. While apo(a) lacks enzymatic activity, Lp(a) can interfere with the binding of plasminogen to substrates such as fibrin, cell surfaces, and extracellular matrix, potentially promoting a prothrombotic state. Numerous retrospective and prospective studies have shown a clear association between high plasma Lp(a) levels and CHD, and such associations appear to be genetically mediated. At this time, though, we still lack evidence that pharmacologic reduction of Lp(a) levels can lower the incidence of coronary events.

DIAGNOSIS OF DYSLIPIDEMIAS

Clinical interest is focused on dyslipidemias in which a causal or proposed causal relationship exists between abnormal serum lipid levels and atherosclerosis. Appropriate treatment of a particular dyslipidemia requires accurately characterizing a patient's lipid disorder. In order to classify a patient's dyslipidemia and exclude secondary causes and determine treatment strategies, the clinical practitioner should investigate the following:

- Personal history: abnormal serum lipid levels; CHD; manifestations of cerebrovascular disease, including transient ischemic attack (TIA) or cerebrovascular accident (CVA); peripheral vascular disease (PVD), including limb claudication, aortic aneurysm, or carotid atherosclerosis; diabetes mellitus (DM); hypothyroidism; chronic renal insufficiency (CRI); nephrotic syndrome; hepatobiliary disease; pancreatitis; or pregnancy
- Medication history: especially of thiazide diuretics, β-blockers, oral contraceptives (OCPs), hormone replacement therapy (HRT), isotretinoin, glucocorticoids, or highly active antiretroviral therapy (HAART) for HIV
- Family history: dyslipidemias, CHD, TIA/CVA, PVD, sudden death, diabetes, hypertension, or central obesity. Suspicion of familial dyslipidemias should be followed up with lipid testing of family members.
- Lifestyle history: past and present tobacco use, excessive alcohol use (>40 g/d), sedentary lifestyle, or diets rich in saturated fats or carbohydrates
- Physical exam findings: body mass index (BMI), waist circumference, blood pressure, thyroid characteristics, xanthomas (cholesterol deposits of interdigital, tuberous, planar, or eruptive types), xanthelasmas (xanthomas of the palpebral fissures), arcus corneae, lipemia retinalis (pale-appearing retinal vessels), peripheral pulses, vascular bruits, or hepatosplenomegaly. See Figure 53.3 for representative examples of xanthomas
- Laboratory studies: fasting serum lipid panel, fasting glucose, thyroid-stimulating

hormone (TSH), creatinine, hepatic function panel, urinalysis, and a screen for microalbuminuria. Additional measurements such as lipoprotein subpopulation analysis, levels of serum Lp(a), apoB, and high-sensitivity CRP (hsCRP) may help refine risk assessment, particularly in an intermediate-risk population or to help tailor intensity of therapies, but would not be recommended as routine tests for all individuals.

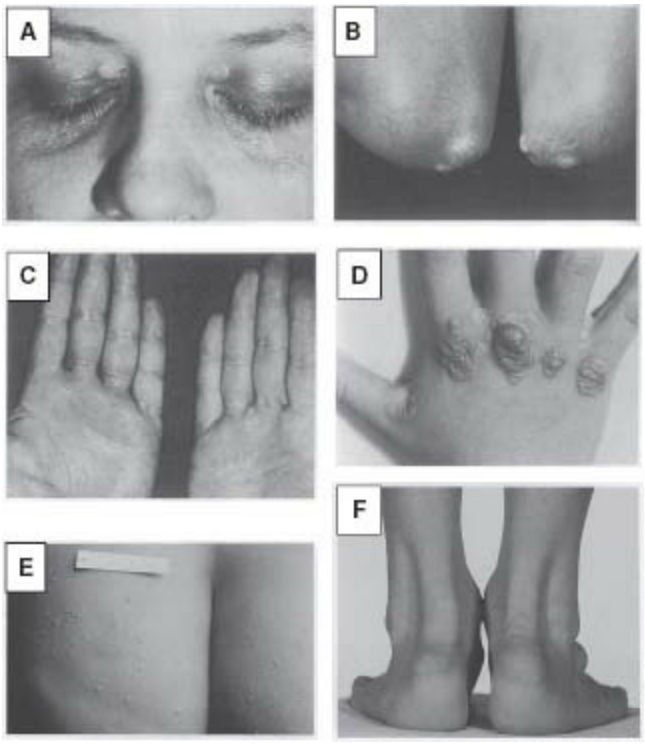

FIGURE 53.3 Representative xanthomas are illustrated: **A**: Xanthelasmas (xanthomas of the palpebral fissures). **B**: Tuberous xanthomas of the elbows. **C**: Palmar xanthomas. **D**: Interdigital xanthomas. **E**: Tuberoeruptive xanthomas of the buttocks. **F**: Tendon xanthomas of the Achilles tendon. (Reprinted from Fuster V, Ross R, Topol EJ, eds. Atherosclerosis and Coronary Artery Disease. 1st ed. Philadelphia: Lippincott-Raven; 1996, with permission.)

CLASSIFICATION OF DYSLIPIDEMIAS

In 1967, Fredrickson et al.[1] proposed a system to diagnose and classify lipid disorders based upon the specific lipoprotein or lipoproteins elevated in the patient's serum. While the Fredrickson classification system was useful shorthand for describing hyperlipidemias, it had two major shortcomings: its phenotypes did not provide or even imply etiology, and HDL was not included. In a more clinically relevant schema, lipid disorders can also be grouped into two broad categories. Primary dyslipidemias result from genetic variability in one or more loci controlling the expression of proteins involved in lipoprotein synthesis, metabolism, or clearance. Secondary dyslipidemias are the consequence of a separate pathologic process.

Primary Dyslipidemias

The primary dyslipidemias of non-HDL-C have been summarized in Table 53.1. Familial hypercholesterolemia (FH) is a common autosomal dominant disorder resulting from mutations in the LDL receptor (LDL-R), or apoB receptor, leading to impaired hepatic clearance of LDL from the circulation. Heterozygous FH (HeFH) occurs in 1 in 500 persons and is associated with serum LDL-C two to three times the average and a four- to sixfold increased risk for premature CHD. Without treatment, the average age for development of symptomatic CHD is 45 years in men, and 55 years in women. By age 39, 90% of FH heterozygotes exhibit detectable xanthomas on the extensor tendons of the hands, or on the Achilles tendons (Fig. 53.3). Several diagnostic criteria for FH exist, with that of the 15-year Simon Broome Register Group being the most commonly used.

TABLE
53.1 Primary Dyslipidemias of Non-HDL-C

Disorder	Molecular Basis	Inheritance/ Prevalence	Lipid Profile	Physical Findings	Symptomatic CHD Risk	Treatment (Nondietary)
Familial hypercholesterolemia (FH)	LDL-R mutations Dysfunctional receptor ↓ Hepatic LDL clearance.	AD HeFH 1:500 HoFH 1:1 million	TC 300–400 mg/dL LDL-C 200–300 mg/dL TC > 600 mg/dL LDL-C >600 mg/dL	Xanthomas of extensor hand tendons, Achilles tendons As in HeFH, plus interdigital, tuberous (hands, elbows, buttocks, feet), planar (thighs, buttocks, knees) xanthomas.	4–6x average risk Without treatment, fatal MI in nearly 100% by age 20	Statins, resins, apheresis Apheresis, statins, resins
Familial defective ApoB100	ApoB100 mutation ↓ LDL affinity for LDL-R ↓ Hepatic LDL clearance	AD 1:600	Similar to HeFH	Similar to HeFH	Similar to HeFH, often with slightly more benign course.	Statins, resins, apheresis
Polygenic hypercholesterolemia (PH)	Presence of ApoE4 allele, or Mildly defective LDL-R, or Mildly defective apoB100. ↑ apoB synthesis	Complex 1:20 to 1:100	TC 250–350 mg/dL LDL-C 150–250 mg/dL TG normal	No xanthomas	1.5–2x average risk	Statins, niacin, resins
Familial combined hyperlipidemia (FCH)	Multiple implicated genes	Complex 1:33 to 1:100	TC 250–350 mg/dL LDL-C 200–300 mg/dL and/or TG >130 mg/dL (often much higher)	Arcus cornea Xanthelasmas No xanthomas	2–5x average risk	Statins (for phenotypes IIa, IIb) Fibrates (for phenotypes IIb, IV)

Hyperapobeta-lipoproteinemia (HyperapoB)	↑ Synthesis apoB	Inheritance and prevalence unclear	LDL-C <160 mg/dL (normal to borderline ↑) LDL-apoB >130 mg/dL TG normal or ↑	Arcus cornea Xanthelasmas No xanthomas	If TG↑, >17x average risk If TG normal, 2–3x average risk	Statins Resins
Type III Hyperlipidemia (Familial Dys-betalipoproteinemia)	Defective apoE 90% of patients are E2/E2	Usually AR, but can be AD 1:1,000 to 1:5,000	TC 300–600 mg/dL TG 400–800 mg/dL and higher VLDL-C:TG > 0.3	Planar xanthomas of the palmar creases Tuberous xanthomas over knees and elbows, not attached to tendons	↑↑ compared to average (RR unknown)	Fibrates Statins Niacin
Familial Endogenous and Familial Mixed Hypertriglyceride-mias	↑ hepatic VLDL, TG ↑ hepatic VLDL, ↓ LPL activity	FEH: AD? 1:300 FMH: unclear rare	TG 200–500 mg/dL TG > 1,000 mg/dL	No xanthomas	CHD risk not consistently elevated. Some kindreds at higher risk than others.	Fibrates, niacin Fibrates
Familial Chylomicronemia	LPL or apoC-II mutations → serum accumulation of chylomicrons	AR 1 in 1 million	TG > 1,000 mg/dL	Eruptive xanthomas on extensor limb surfaces, hepatosplenomegaly, pancreatitis, lipemia retinalis	Unclear association with CHD	Drug therapy ineffective

AD, autosomal dominant; AR, autosomal recessive; HeFH, heterozygous FH; HoFH, homozygous FH; RR, relative risk.

Definite FH requires:

(a) TC > 290 mg/dL in adults or TC > 260 mg/dL in children under 16
OR LDL-C > 190 mg/dL in adults or >155 mg/dL in children
PLUS

(b) Tendon xanthomas in the patient, or first- or second-degree relative

(c) OR DNA-based evidence of LDL-R mutation or familial defective apoB100

Possible FH is defined as (a) above plus one of (d) or (e):

(d) MI before age 50 in second-degree relative, or before 60 in first degree

(e) Elevated cholesterol in first-degree relative, or >290 mg/dL in second degree

Homozygous FH (HoFH) occurs in one in one million individuals. Patients with HoFH do not express any functional LDL-Rs, and consequently exhibit a more severe phenotype. TC levels are generally >600 mg/dL, with LDL-C levels six- to eightfold higher than average. Without treatment, death from MI occurs in the first or second decades of life. In addition to the xanthomas observed in heterozygotes, FH homozygotes are commonly affected by interdigital xanthomas, tuberous xanthomas on the hands, elbows, buttocks, and feet, and planar xanthomas on the posterior thighs, buttocks, and knees.

Familial Defective Apolipoprotein B100 is associated with impaired LDL clearance due to reduced affinity of LDL for the LDL-R. The most common cause of this autosomal dominant condition is a single base mutation in the apoB100 gene. Although the prevalence of familial defective apoB100 is unclear, and varies by ethnic background, it may be as common as 1 in 600. The lipoprotein concentrations, clinical features, and treatment are similar to FH heterozygotes.

Polygenic hypercholesterolemia (PH) is the most common cause of an isolated elevation in TC or LDL-C, with prevalence in the United States estimated at between 1 in 20 and 1 in 100. TG levels are generally normal. Alterations in the function or expression of several key proteins involved in LDL metabolism have been associated with PH, including mildly defective LDL-R and apoB100, increased synthesis of apoB, and the presence of the apoE4 allele, which has a higher affinity for the LDL-R than the other apoE isoforms leading to downregulation of LDL-R synthesis and a secondary increase in serum LDL-C. Xanthomas are very rare or absent in patients with PH.

Familial combined hyperlipidemia (FCH) is the most common primary dyslipidemia in which multiple lipoprotein phenotypes exist, with a population prevalence of 1% to 3%. The three observed patterns of elevated VLDL, elevated LDL, or both can be seen within a family or within a single patient over time. Transmission is complex, with multiple genes likely to be involved. It is associated with an estimated two- to fivefold increased risk for CHD, accounting for one-third to one-half of familial CHD, and up to 20% of all premature CHD. Traditionally, diagnostic criteria include:

1. TC and/or TG levels >90th percentile for age- and sex-matched controls. TC of 250 to 350 mg/dL and TG > 130 mg/dL (often higher, especially in diabetics).
2. At least one first-degree relative with elevated VLDL-C, LDL-C, or both
3. Strong family histories of hyperlipidemia and premature CHD

Other major characteristics include elevated apoB (>120 mg/dL), a preponderance of sdLDL, and low HDL-C. FCH is usually diagnosed after age 20, and the patients are often hypertensive, overweight, insulin resistant, or diabetic. Arcus cornea and xanthelasmas are commonly seen, but tendon xanthomas are unusual. Hence, the absence of tendon xanthomas in a hypercholesterolemic patient is a useful feature to differentiate FCH from FH.

Other less common dyslipidemias of apoB metabolism are frequently characterized by elevations in TG, VLDL or in LDL-apoB concentrations. These include hyperapobetalipo-proteinemia (hyperapoB) , type III hyperlipidemia (also known as familial dysbetalipoproteinemia or remnant disease) , familial endogenous hypertriglyceridemia (FEH) , familial mixed hypertriglyceridemia (FMH), and familial chylomicronemia and are outlined in Table 53.1.

There exist a heterogeneous group of rare familial disorders of HDL-C, including Tangier Disease, Familial LCAT Deficiency , and Partial LCAT Deficiency or Fish-Eye Disease which have not been consistently associated with premature CHD and are beyond the scope of this chapter. $ApoAI_{Milano}$ is a rare genetic variant of the apoAI protein resulting in low HDL-C levels. However, individuals bearing the mutation display longevity and an exceptionally low risk of CHD. In a controlled trial of patients with a history of acute coronary syndrome (ACS), infusions of purified $ApoAI_{Milano}$

induced plaque regression, as assessed by intravascular ultrasound (IVUS). At present, such therapy is not available for clinical use but these studies suggest a future role for HDL-C modification to reduce cardiovascular risk.

Secondary Dyslipidemias

Evaluation of a dyslipidemia would not be complete without a thorough search for secondary and contributing causes. A careful history and physical, accompanied by selected laboratory studies, including a fasting lipid panel, will frequently reveal the etiology of a patient's dyslipidemia. Breakdown by the abnormal lipid may simplify diagnosis of the dyslipidemia's cause:

- Elevated TC and LDL-C: diet rich in saturated fat, drugs (oral contraceptives or OCPs, HRT, HAART), hypothyroidism, nephrotic syndrome, chronic liver disease, and chronic biliary tract disease (classically, primary biliary cirrhosis)
- Elevated TG: diet rich in carbohydrates, drugs (β blockers, thiazide diuretics, isotretinoin, glucocorticoids, HAART, OCP, HRT), excessive alcohol consumption, obesity, DM, hypothyroidism, CRI, chronic pancreatitis, and pregnancy
- Low HDL-C: very high carbohydrate, very low-fat diet, hypertriglyceridemia, obesity, sedentary lifestyle, smoking, DM

Often, these dyslipidemias can be at least partially controlled by institution of lifestyle changes (including dietary improvement, weight loss, increased exercise, and smoking cessation), withdrawal and replacement on an implicated medication, or recognition and treatment of an underlying disorder. A typical example is the hyperlipidemic patient who is resistant to lipid-lowering therapy, but later found to be hypothyroid. Treatment with levothyroxine then corrects the secondary dyslipidemia.

METABOLIC SYNDROME

Due to the growing recognition of its prevalence and the association of this syndrome with a particular dyslipidemic pattern, the metabolic syndrome (MetS) is reviewed here. During the late 1980s, Reaven observed that several CHD risk factors (namely dyslipidemia, hypertension, and hyperglycemia) frequently cluster together.[2] Originally referred to as Syndrome X or the insulin-resistance syndrome, these descriptors have been supplanted by the more general term metabolic syndrome. The National Cholesterol Education Program's Adult Treatment Panel III report (ATP III, discussed later) identified six components of the MetS which relate to CHD: abdominal obesity, atherogenic dyslipidemia (high TG, low HDL-C, and sdLDL), hypertension (HTN), insulin resistance, a prothrombotic state, and a proinflammatory state.[3] Given the ongoing "epidemic of obesity," MetS is common and becoming more so, with approximately one-third of American adults fulfilling ATP III and global criteria, [4] as

listed in Table 53.2. Observational data have shown that such persons have a three to fivefold risk of CHD mortality, compared to those without MetS. A major health danger to persons with MetS appears to be a vastly increased risk of developing diabetes. MetS was highly predictive of new-onset DM in both men and women of the Framingham offspring cohort, as nearly half of the population-attributable risk of type 2 diabetes (DM2) could be explained by the presence of ATPIII-defined MetS.[5] When overt DM develops, CHD risk increases sharply.

TABLE
53.2 ATP III Clinical Identification of the MetS

Risk Factor (Need 3)	Defining Level
Abdominal obesity[a]	Waist circumference[b]
Men	>102 cm (>40 inches)
Women	>88 cm (>35 inches)
TG	≥150 mg/dL
HDL-C	
Men	<40 mg/dL
Women	<50 mg/dL
Blood Pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL

[a]Overweight and obesity are associated with insulin resistance and the MetS. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated BMI. Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the MetS.

[b]Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, for example, 37 to 39 inches (94 to 102 cm). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similar to men with categorical increases in waist circumference. Adapted from the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III), Final Report, 2002. A publication of the National Heart, Lung, and Blood Institute (NHLBI), a division of the National Institutes of Health (NIH), and the U.S. Department of Health and Human Services.

TREATMENT STRATEGIES FOR DYSLIPIDEMIAS: THERAPEUTIC LIFESTYLE CHANGES

All dyslipidemic patients should be urged to adopt therapeutic lifestyle changes (TLC), consisting of increased physical activity, ideal weight maintenance (often necessitating weight loss), smoking cessation, and the pursuance of a low-saturated fat, low-cholesterol diet rich in fruits, vegetables, grains, and fiber (Table 53.3). In highly motivated individuals, TLC can result in an LDL-C reduction of nearly 30%, and should form the basis of all preventive treatment. Alcohol avoidance, smoking cessation, physical activity, and diet are essential in the management of dyslipidemias

characterized by very high TG.

TABLE
53.3 Therapeutic Lifestyle Changes

Component	Recommendation	Expected Change in Lipids
Diet		
Saturated fat	<7% of total calories	↓ LDL-C 8%–10%
Dietary cholesterol	<200 mg/d	↓ LDL-C 3%–5%
Polyunsaturated fat	up to 10% of total calories	
Monounsaturated fat	up to 20% of total calories	
n-3 FAs	"higher"	
Trans-FAs	"low"	
Total fat	25%–35% of total calories	
Carbohydrate	50%–60% of total calories	
Dietary fiber	20%–30 g/d	
Total protein	15% of total calories	
Therapeutic options to ↓ LDL-C		
Plant stanols/sterols	2–3 g/d	↓ LDL-C 6%–15%
Increased viscous soluble fiber (from whole grains, fresh fruits, legumes, green leafy vegetables)	5–10 g/d	↓ LDL-C~5%
Physical activity	Enough moderate activity to expend at least 200 kcal/d.	↓ TG 5%–15% ↓ TC 0%–5% ↓ LDL-C 0%–3% ↑ HDL-C 3%–5% (highly variable)
Weight loss	Goal BMI < 25 kg/m^2	↓ TG~7% ↓ LDL-C~6% ↓ TC~10% ↑ HDL-C~8% (with 10 kg/22 pounds weight loss)[a]
Smoking cessation	Immediate cessation of use of all tobacco products. Reasonable to use nicotine patch, gum, bupropion, or varenicline for assistance in quitting.	↑ HDL-C~5% (highly variable)

Adapted from the ATP III Final Report (2002).

[a]Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. Am J Clin Nutr. 1992;56:320–328.

Most primary dyslipidemias other than HoFH, as well as the dyslipidemia associated with MetS, are very sensitive to changes in diet and adiposity, and thus should always be treated with a TLC diet and weight management, with a goal BMI <25 kg/m^2. Lifestyle changes are first-line therapy for the MetS, with obesity the primary target of intervention.[6] The most critical goal of such modifications is to decrease the incidence of new-onset DM, which confers a similar risk of CHD events as known CHD. It may be challenging to successfully implement such changes, but every effort should be made to stress the clear health benefits of dietary modification, weight loss, and physical activity.

Whether TLC are sufficient alone, or should be accompanied by drug therapy, is determined by the dyslipidemic patient's CHD risk status, initial lipid levels, and treatment targets (to be discussed in later sections). Other nonpharmacologic approaches such as dietary intake of plant stanols/sterols (in certain labeled margarines and juices and pill supplements) and increased viscous soluble fiber (in oats, barley, psyllium, pectin-rich fruits, and legumes) may also aid in LDL-C reduction. High-dose omega-3 fish oil supplementation may aid in TG lowering. Consultation of a registered dietician or qualified nutritionist may be useful. In high-risk individuals pharmacologic therapy should be introduced simultaneously with TLC. In others, if goal LDL-C has not been reached after 3 months, pharmacologic therapy should be considered.

TREATMENT STRATEGIES FOR DYSLIPIDEMIAS: PHARMACOLOGIC THERAPY

Pharmacologic therapy should be initiated in patients whose lipids are inadequately lowered with TLC alone, those with lipids too high to be reasonably reduced with TLC alone, or those with CHD risk high enough to mandate drug initiation simultaneously with TLC. There are six major classes of drugs which can be used to regulate a patient's lipid profile, including (a) HMG-CoA reductase inhibitors, or "statins," (b) bile acid sequestrants or "resins," (c) fibric acid derivatives or fibrates, (d) nicotinic acid or niacin, (e) cholesterol absorption inhibitors of which ezetimibe is the only clinically available member, and (f) Omega-3 FAs of which Lovaza is the only available prescription formulation. Table 53.4 includes a description of these agents, their mechanisms of action, therapeutic indications and contraindications, effects on lipid levels, and adverse effects. The choice of a specific drug or combination of drugs is dependent on an understanding of each medication's mechanism of action, as well as the individual patient's lipid profile, cardiovascular risk, treatment goals, and contraindications. Medication choice should also be influenced by clinical outcome trials demonstrating reduction of cardiovascular events with specific treatments. Specific treatment guidelines are reviewed in a later section. Fasting lipid levels should be checked 6 weeks after drug initiation. Once the treatment goal has been achieved,

fasting lipids should be redrawn every 4 to 6 months. Importantly, TLC should always be used concomitantly with drug therapy of dyslipidemias. Referral to a lipid specialist should be considered for complex combined lipid disorders or nonresponders.

TABLE
53.4 Lipid-Regulating Drugs

Class	Specific Agents	Mechanism of Action	Indications/Contraindications	Changes in Lipid Levels	Adverse Effects
Statins	Lovastatin Pravastatin Fluvastatin Simvastatin Atorvastatin Rosuvastatin Pitavastatin	Inhibit HMG-CoA reductase, hepatic enzyme controlling rate-limiting step in cholesterol synthesis → upregulation of LDL-R and ↑ hepatic LDL clearance.	High TC, high LDL-C, low HDL-C high TG, high non-HDL-C, high apoB mixed lipidemias, known CHD AC: active or chronic liver disease, persistent ↑ transaminases, pregnancy, breast-feeding. RC: ↑ susceptibility to rhabdo-induced RF	↓ TC 15–60% ↓ LDL-C 20–60% ↑ HDL-C 5–15% ↓ TG 10–25%	Major: myopathy, life-threatening rhabdomyolysis (rare) Minor: ↑ hepatic transaminases, heartburn, abdominal pain, diarrhea, constipation, flatulence, headache, rash
Resins	Cholestyramine Colestipol Colesevelam	Bind intestinal bile acids, interrupt enterohepatic recycling, increase stool elimination of bile acids, leading to ↓ serum cholesterol.	High TC, high LDL-C Generally used only in familial disorders AC: complete biliary obstruction, fasting TG > 400 mg/dL. RC: fasting TG > 200 mg/dL	↓ TC 5%–10% ↓ LDL-C 15–30% ↑ HDL-C 3%–5% TG may be ↑	Major: bowel obstruction (rare) Minor: constipation, diarrhea, flatulence, abdominal pain, bloating, heartburn, steatorrhea, hypertriglyceridemia
Fibrates	Clofibrate Fenofibrate Gemfibrozil Bezafibrate[a] Ciprofibrate[a]	Stimulate transcription factor PPAR-α → ↑ catabolism of TGRL ↓ formation of VLDL TG ↑ apoA synthesis ↓ TG lead to ↑ HDL-C	High TG, low HDL-C AC: severe renal or hepatic dysfunction RC: diabetic nephropathy, breast-feeding	↓ TG 20%–50% ↑ HDL-C 10%–20% ↓ TC 15%–20% ↓ LDL-C 5%–20%	Major: myopathy (rare), but ↑ frequency with CRI, low albumin, or coadministration with statins. Minor: upper GI sx, HA, anxiety, fatigue, vertigo, sleep disorders, myalgia, ↓ libido, alopecia
Nicotinic acid	IR (crystalline) ER (Niaspan) SR (Slo-Niacin, enduracin)	↓ adipose tissue lipolysis. ↓ hepatic TG formation. ↓ hepatic HDL particle uptake and catabolism ↑ apoB100 catabolism ↓ Lp(a) synthesis.	High TG, low HDL-C, high TC, high LDL-C high Lp(a) AC: active or chronic liver disease, severe gout, peptic ulcer disease	↑ HDL-C 5%–35% ↓ LDL-C 5%–25% ↓ TG 20%–50% ↓ Lp(a) 20%–30%	Major: hepatotoxicity (seen more in sustained release), gout Minor: Flushing, pruritis, upper GI distress, hyperuricemia, hyperglycemia
Cholesterol absorption Inhibitors	Ezetimibe	↓ sterol transport across intestinal brush border	High TC, high LDL-C in patients with statin intolerance, or not at goal with statin AC or RC: none	↓ TC 10%–15% ↓ LDL-C 15%–20% ↓ TG 5%–10%	Major: none Minor: mild transaminase elevation
Omega-3 FAs	Lovaza Fish oil	↓ hepatic VLDL formation ↑ VLDL/chylomicron uptake and catabolism ↑ PPAR-gamma activation	High TG, low HDL-C	↓ TG 20%–40% ↑ HDL-C 1%–5% ↑ LDL-C 5%–10%	Major: none Minor: increased bleeding risk, upper GI distress, diarrhea

[a]not available in the U.S.; AC, absolute contraindication; RC, relative contraindication; CRI, chronic renal insufficiency; HA, headache; IR, immediate release; ER, extended release; SR, sustained release

Of the primary dyslipidemias, treatment of HeFH includes dietary approaches and aggressive pharmacologic therapy. Since the hepatocytes of these individuals still express the LDL-R, albeit at a lower concentration than normal, they are able to upregulate its level and thus increase clearance of LDL. Multiple studies involving adults with HeFH have shown high-dose statin therapy to be safe, well tolerated, and effective at reducing LDL-C levels, CHD morbidity/mortality. Children and adolescents with HeFH are also effectively treated with statins. Despite concerns over possible interference with hormonal pathways, the growth parameters and sexual maturation in statin-treated children were similar to those given placebo.[7] Often, combination drug therapy of a statin with ezetimibe, resins, and/or niacin is necessary to adequately lower LDL-C levels. As for HoFH, dietary changes are not effective at reducing LDL-C.

Given the complete absence of functional LDL-Rs, one would not predict that FH homozygotes could be treated effectively with statins. However, multiple small studies have shown that statins reduce LDL-C by 15% to 35% in such persons, probably via decreased hepatic synthesis of VLDL and LDL.

Drug treatment of persons with other primary dyslipidemias is determined largely by their individual lipid profiles (see Table 53.1). In general, elevated LDL-C should be treated with a statin unless contraindicated or not tolerated. Disorders of elevated TG are usually evaluated with a search for secondary causes, and treated with dietary modification, physical activity, and fibrates, niacin or omega-3 FAs. The dyslipidemia associated with MetS should always be initially treated with lifestyle approaches, especially weight loss. However, failure to achieve full reversal of the MetS characteristics may necessitate pharmacologic therapy. Subgroup analyses of statin trials have shown that statins reduce risk for CVD events in MetS patients. A post hoc analysis of recent fibrate trials strongly suggests that they reduce CVD endpoints in patients with atherogenic dyslipidemia and MetS.

In some cases, drugs from multiple classes used in combination may be required for adequate LDL-C lowering and/or treatment of combined dyslipidemias. Studies have supported acceptable tolerance and improvement of the lipid profile with combination therapy in certain subgroups. Although lipoprotein improvements have been even more dramatic on combined statin–fibrate, statin–niacin, or stain-resin/ezetimibe therapy, no CVD endpoint data from large, controlled trials are available. Smaller trials and those employing surrogate vascular endpoints suggest clinical benefit of combination therapy. It is important to be familiar with the adverse effects of lipid-regulating drugs (Table 53.4). Such adverse effects may occur more frequently with combination therapy, including rhabdomyolysis (more common with statin + fibrate) and hepatic injury (statin + niacin, statin + ezetimibe, statin + fibrate). Obese patients undergoing weight-loss (bariatric) surgery are observed to exhibit a dramatic decline in clinical features of MetS. Their total and LDL-C tend to be significantly lower. Most impressively, a systematic review has also demonstrated that most diabetic patients undergoing such surgery experience total postoperative reversal of their diabetes diagnosis.

APHERESIS THERAPY

The mainstay of therapy for FH homozygotes is extracorporeal, namely LDL apheresis. On average, LDL-C levels immediately after the procedure are decreased 50% to 80%. Since these values rebound fairly quickly, the process is performed every 2 weeks to keep intrapheresis LDL-C ≤120 mg/dL. FDA indications since 1996 include: HoFH; HeFH in the absence of CHD when LDL-C ≥ 300 mg/dL despite maximal pharmacologic and dietary therapy; and HeFH in the presence of CHD when LDL-C ≥ 200 mg/dL despite maximal pharmacologic and dietary therapy. The benefits of

apheresis to FH homozygotes, in terms of stabilization or regression of atherosclerotic lesions, and improvement in symptoms, have been clearly demonstrated. As for FH heterozygotes, combined apheresis and statin therapy have been shown to substantially reduce risk of coronary events, and to improve angiographic outcome.

LIPID-REGULATING TRIALS FOR THE PREVENTION OF CHD

The rationale for aggressive management of lipid disorders for the purpose of reducing cardiovascular events is based on a large body of research spanning the past decade. A complete review of the research establishing an association between dyslipidemia and CHD is beyond the scope of this chapter, but it is important to highlight the observations and trials supporting recent cholesterol treatment recommendations. As early as the 1930s, associations were observed between cholesterol levels and atherosclerotic disease. Multiple, large observational and epidemiologic studies helped to form the basis of the cholesterol hypothesis, which posited that elevated serum cholesterol plays a causative role in the development of CHD, and that cholesterol reduction will reduce CHD risk.[8] These studies included the Framingham Heart Study, the Seven Country Study, the Münster Heart Study (PROCAM), the Multiple Risk Factor Intervention Trial (MRFIT), and the Lipid Research Clinics (LRC) Prevalence Study. Data from these studies revealed a strong, graded, linear relationship between TC levels and risk of CHD, with an approximate 20% to 30% increase in CHD risk for each 10% increase in serum TC. An inverse correlation was observed for HDL-C, with every 1 mg/dL (0.026 mM) increase in HDL-C correlating with a 2% decrease in CHD risk for men, and a 3% decrease for women.[9] Hypertriglyceridemia was long suspected to be an independent CHD risk factor, but this was difficult to prove given the tight inverse correlation between levels of TG and HDL-C. A meta-analysis of 17 population-based studies showed that each 1 mmol/L (88.5 mg/dL) increase in serum TG significantly increased the risk of a CHD event, by 32% in men, and 76% in women. After multivariate analysis, including adjustment for HDL-C levels, a 1 mmol/L increase in TG continued to confer a significantly increased CHD risk, by 14% in men, and 37% in women.

Once these relationships had been identified, clinical trials were designed to test the hypothesis that lipid-lowering therapy would slow or reverse the atherosclerotic process and decrease the incidence of CVD events. Despite the diversity in entry criteria and treatments, initial animal and human intervention studies demonstrated plaque regression or improvements in angiographic outcomes associated with improved lipid profiles. Although some of these trials did demonstrate decreased coronary events, the primary endpoints were typically surrogate outcomes and the trials were not designed or powered to examine clinical outcomes. Subsequent intervention trials targeted “hard” clinical endpoints, including death and nonfatal MI. In primary prevention trials, individuals without known CVD underwent cholesterol reduction,

with the goal of preventing a first CHD event. In secondary prevention trials, subjects with known CVD were treated to lower cholesterol, in an effort to prevent repeat events.

EARLY TRIALS FOR PRIMARY AND SECONDARY CHD PREVENTION

A number of CVD endpoint trials, reviewed in detail in Table 53.5, were performed in the prestatin era, utilizing diet, bile acid sequestrants, fibrates or niacin. These trials, in predominantly male populations both with and without CHD, using various treatments or combination of treatments, provided strong support for the cholesterol hypothesis, giving rise to the rule of thumb that a 1% lowering of TC decreases the incidence of CHD events by 2% to 3%. In several of these studies, noncardiovascular death was increased in the group treated with lipid-lowering therapy, raising concern over the safety of such treatment. However, a causal link was never established between lipid-lowering drugs and increased mortality. The early trials set the stage for the large statin trials of the 1990s.

TABLE
53.5 Early Lipid-Regulating Trials

Study	N	Sex, Age	Entry Criteria	Treatment, Control	Y	Lipid Change with Treatment	Clinical Outcome with Treatmen[a]
				Primary CHD prevention			
LRC-CPPT	3,806	M, 35–59	TC ≥265 mg/dL LDL-C ≥190 mg/dL TG ≤300 mg/dL	Cholestyramine + Diet Placebo + Diet	7.4	TC ↓ 13% LDL-C ↓ 20%	1° NFMI/CHDD ↓ 19%, new angina ↓ 20%, new +stress ↓ 25% CABG ↓ 21% (NS), CHDD ↓ 24% (NS), TM ↓ 7% (NS)
WHO	>10K	M, 30–59	TC in upper tertile of those screened	Clofibrate Placebo	5.3	TC ↓ 9%	NFMI/CHDD ↓ 20% TM ↑ 47% but 13y TM ↑ 11% (NS)
HHS	4,081	M, 40–55	non-HDL-C >200 mg/dL	Gemfibrozil Placebo	5	TC ↓ 10% LDL-C ↓ 11% HDL-C ↑ 11% TG ↓ 35%	1° NFMI/CHDD ↓ 34% CHDD ↓ 26% (NS) TM slightly ↑ (NS)
Oslo	1,232	M, 40–49	TC 290–380 SBP <150 mm Hg Top quartile CHD risk (80% smokers)	Dietary and antismoking advice Usual care	5	TC ↓ 13% TG ↓ 20	1° NFMI/CHDD/SCD ↓ 47% CHDD ↓ 55% (NS), TM ↓ 33% (NS)
				Secondary CHD prevention			
CDP	8,341	M, 30–64	MI	Niacin Clofibrate D-thyroxine E 2.5 mg/d E 5.0 mg/d Placebo	5	TC ↓ 10% TG ↓ 22% TC ↓ 6% TG ↓ 22%	NFMI ↓ 27%, TM/CHDD unchanged 15y TM ↓ 11% NFMI/CHDD ↓ 9% (NS), TM unchanged ↑ TM, arm stopped ↑ TE, CA, TM, arm stopped ↑ NFMI, lack of efficacy, arm stopped
Stockholm	555	M/F	MI	Clofibrate + Niacin Placebo	5	TC ↓ 13% TG ↓ 19%	CHDD ↓ 36%, TM ↓ 26%
BIP	3,090	M/F	MI, stable angina, or both	Bezafibrate	6.2	TC ↓ 4.5% TG ↓ 21% HDL-C ↑ 18%	MI or sudden death ↓ 7.3% (NS)

N, number of patients in trial; Y, years of trial duration; aall outcomes significant except as noted; 1°, primary

endpoint; NFMI, nonfatal MI; CHDD, CHD death; SCD, sudden cardiac death; +stress, positive stress test; TM, total mortality; E, estrogen; NS, nonsignificant p-value.

These subsequent large, multicenter, randomized controlled trials irrefutably confirmed the cholesterol hypothesis, conclusively demonstrating that lowering LDL-C reduced the risk of coronary events, and in some cases, total mortality. The efficacy of statins was demonstrated in study populations with a wide range of risk factors and LDL-C levels, and in both primary and secondary CHD prevention. These trials also lay to rest concerns about the possible dangers of low cholesterol, the possibility of which had been raised by several of the prestatin trials.

THE LANDMARK STATIN TRIALS: PRIMARY PREVENTION

The major statin trials—all of which were large, multiyear, randomized, double-blinded, placebo-controlled studies— and their findings are summarized in Table 53.6.

TABLE
53.6 Landmark Statin Trials

Trial[a]	*n* (Sex)	Enrollment Lipids (mg/dL)	Drug, Dose (mg)	Y	Base LDL-C	Tx LDL-C	Δ LDL-C	Adverse Event, Relative Risk Reduction	Tx Rate (%)	PC Rate (%)	% ARR
Primary Prevention											
WOSCOPS	6,595 (M)	LDL-C ≥155	Prava 40	4.9	192	159	−26%	NFMI or CHDD ↓ 31%	5.3	7.5	2.2
								CABG or PTCA ↓ 37%	3.2	4.1	0.9
								All-cause mortality ↓ 22%*	1.4	1.5	NS
								CVA ↓ 11% (NS)			
AFCAPS/ TEXCAPS	6,605 (M/F)	TC 180–264 LDL-C 130–190 HDL-C ≤45 M, ≤47 F	Lova 20–40	5.2	150	115	−25%	NFMI, CHDD, USA, or SCD ↓ 37%	3.5	5.5	2.0
ASCOT-LLA	10,305 (M/F)	TC ≤ 250 (mean 212)	Atorva 10	3.3	133	87	−35%	NFMI or CHDD ↓ 36%	5.2	8.3	3.1
								CV events/procedures ↓ 21%	24.1	30.6	6.5
								Coronary events ↓ 29%	10.8	15.2	4.4
								CVA ↓ 27%	5.4	7.4	2.0
								Chronic stable angina ↓ 41%	2.0	3.4	1.4
Secondary Prevention and High-Risk Primary Prevention											
4S	4,444 (M/F)	TC 212–309 (mean 261)	Simva 20–40	5.4	188	122	−35%	All-cause mortality ↓ 30%	8.2	11.5	3.3
								NFMI, CHDD, or resusc SCD ↓34%	19.4	27.9	8.5
								CVA ↓ 30%	3.2	4.4	1.2
CARE	4,159 (M/F)	TC < 240— LDL-C 115–174	Prava 40	5.0	139	98	−32%	NFMI or CHDD ↓ 24%	10.2	13.2	3.0
								CVA ↓ 31%	2.6	3.8	1.2
LIPID	9,014 (M/F)	TC 155–270	Prava 40	6.1	150	110	−27%	CHDD ↓ 24%	6.4	8.3	1.9
								All-cause mortality ↓ 22%	11.0	14.1	3.1
								MI ↓ 29%	7.4	10.3	2.9
								CVA ↓ 19%**	3.7	4.5	0.8
HPS	20,536 (M/F)	TC ≥ 135	Simva 40	6	128 M 135 F	89	−40 mg/dL	All-cause mortality ↓ 12%	12.9	14.6	1.7
								Vascular death ↓ 17%	7.7	9.2	1.5
								Total CHD, CVA, or revasc ↓ 24%	19.9	25.4	5.5
								CVA ↓ 25%	4.3	5.7	1.4

[a]Trials: WOSCOPS, West of Scotland Coronary Prevention Study; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm; 4S, Scandinavian Simvastatin Survival Study; CARE, Cholesterol And Recurrent Events trial; LIPID, Long-term Intervention with Pravastatin in Ischemic Disease trial; HPS, Medical Research Council/Brit Heart Foundation (MRC/BHF) Heart Protection Study.

Other abbreviations: n, number of subjects in trial; Sex, sex of subjects in trial; Y, years of trial duration; Base LDL-C, average baseline LDL-C; Tx LDL-C, average LDL-C with drug treatment; A LDL-C, change in av age LDL-C with drug treatment compared to placebo, expressed in percent or mg/dL; Tx Rate, adverse event

occurrence rate in treatment group during study period; PC Rate, adverse event occurrence rate in place control group during study period; % ARR, percent absolute risk reduction; Prava, pravastatin; Lova, lovastatin; Simva, simvastatin; Atorva, atorvastatin; NFMI, nonfatal MI; CHDD, CHD death; CVA, nonfatal and] stroke; USA, unstable angina; SCD, sudden cardiac death; revasc, coronary revascularization; resusc, resuscitated; NS, not significant.

*p = 0.051.

**p = 0.048.

Adapted from Gotto AM and Pownall HJ. Manual of Lipid Disorders. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2003:171–174.

- The West of Scotland Coronary Prevention Study (WOSCOPS)[10] was a trial of pravastatin in men with high LDL-C and no previous diagnosis of CAD. WOSCOPS demonstrated that pravastatin was both safe and effective at preventing a first CHD event in hyperlipidemic men. Despite its borderline statistical significance, the result was nonetheless provocative that total mortality was decreased by 22% in the statin arm.
- The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[11] was the first primary prevention trial of lipid regulation to include women and subjects >65 years of age, but its most important feature was that it enrolled subjects with only average LDL-C and below-average HDL-C. AFCAPS/TexCAPS expanded the observations of WOSCOPS by demonstrating that statin therapy effectively prevented a first CHD event in both men and women with average LDL-C. Intriguingly, the subpopulation of individuals with the lowest HDL-C levels experienced the greatest reduction in coronary events.

THE LANDMARK STATIN TRIALS: SECONDARY PREVENTION AND HIGH RISK PRIMARY PREVENTION

- The Scandinavian Simvastatin Survival Study (4S)[12] utilized sim vastatin to treat middle-aged men and women with a history of angina pectoris or MI. 4S provided robust evidence that LDL-C reduction with simvastatin safely reduced CHD events by 34%, stroke by 30%, and total mortality by 30%, in both men and women with known CHD. Nonlipid risk factors did not mitigate these benefits, and coronary event risk reduction was similar in each quartile of baseline TC, LDL-C, or HDL-C. Individuals with impaired fasting glucose and diabetes enjoyed the greatest reduction in CHD events, 38% and 42%, respectively.
- The Cholesterol and Recurrent Events (CARE) trial.[13] enrolled a wide age-range of post-MI men and postmenopausal women with average LDL-C (mean 139 mg/dL), treating them with pravastatin. CARE demonstrated that both men and women (including the elderly) with a history of MI and only modest elevations in LDL-C

levels experience fewer CHD events and strokes when treated with a statin.

- The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial[14] was designed to be applicable to as many patients with CHD as possible. LIPID enrolled men and women with history of acute MI or hospitalization for unstable angina, with a broad range of serum lipids, as well as "average" LDL-C (mean 150 mg/dL). LIPID showed that a broad population of men and women with known CHD derived significant morbidity and mortality benefit from statin therapy, even in the context of average LDL-C levels and in addition to current non–lipid lowering therapy for CHD.
- The Medical Research Council/British Heart Foundation (MRC/BHF) Heart Protection Study (HPS)[15] was a "megastudy" of over 20,000 subjects, easily representing the largest trial of lipid-regulating therapy to date. It set out to test the hypothesis that statin therapy would benefit the at-risk individual, regardless of the pretreatment LDL-C level. Eligible patients included men and women between 40 and 80 years of age with fasting TC > 135 mg/dL (>3.5 mM) at high risk for CHD death over the next 5 years. Subjects fell into one of three categories: (1) history of CHD, (2) PVD or cerebrovascular disease, or (3) DM or treated HTN in men ≥65 years. HPS demonstrated that men and women at high risk for a major vascular event (including those with DM, HTN, PVD, or cerebrovascular disease) benefit from statin therapy, regardless of baseline LDL-C. Even those with baseline LDL-C <100 mg/dL experienced a substantial 21% reduction in vascular events. Data from HPS have helped shift our therapeutic paradigm towards the treatment of elevated CHD risk, rather than simply the treatment of elevated LDL-C levels.

LESSONS FROM SUBSEQUENT STATIN TRIALS: EARLIER OR MORE AGGRESSIVE MANAGEMENT OF LDL-C

In the preceding trials, statins were often started months to years after an acute coronary event and at moderate doses. Later studies addressed the safety and effectiveness of early high-dose statin therapy and set the stage for trials which would test the utility of more aggressive and early lipid lowering in the prevention of CHD.

- The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial tested the hypothesis that initiation of statin therapy in the acute post-ACS setting could be safe and provide clinical benefit. After only 16 weeks, the primary endpoint of combined death, nonfatal MI, resuscitated cardiac arrest, or ischemia was reduced by 16% ($p = 0.048$) in the atorvastatin group. In summary, the MIRACL study showed that early initiation of high-dose atorvastatin was safe and possibly beneficial for immediate post-ACS patients.
- The Atorvastatin Versus Revascularization Treatments (AVERT) trial was a small,

short-term trial that compared high-dose atorvastatin therapy (80 mg/d) with angioplasty and usual care in patients with stable CHD. LDL-C was reduced on an average of 46% in the atorvastatin group, compared to 18% in the usual care group. The rate of ischemic events was reduced by 36% in the atorvastatin group, compared to usual care/angioplasty, although the statistical significance was borderline ($p = 0.048$). AVERT contained the provocative result that, for patients with stable CHD, aggressive LDL-C reduction to levels well below 100 mg/dL with a high-dose statin was more effective at reducing coronary events than angioplasty. Since the NCEP ATP III guidelines appeared in 2001, a number of published trials in addition to the HPS have offered a rationale for modifications in these treatment recommendations (Table 53.7). Some have attempted to determine if more aggressive lipid lowering confers clinical benefit beyond moderate lipid lowering in patients after ACS (REVERSAL, PROVE IT/TIMI-22, Phase Z of the A to Z Trial) and in those with stable CHD (TNT). Others have tested the hypothesis that initiation of statin therapy at levels of LDL-C previously not recommended for pharmacologic therapy would reduce CVD events in moderate to high-risk individuals without known CHD (ASCOT-LLA in "primary care" hypertensive, nondyslip idemic patients with multiple risk factors, CARDS in patients with type 2 diabetes without significant elevation in LDL-C, and Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) in individuals with elevated hsCRP regardless of LDL-C level.

- The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial[16] compared the ability of moderate (pravastatin 40 mg/d) and intensive statin (atorvastatin 80 mg/d) treatment to reduce progression of coronary atherosclerosis as assessed by IVUS. REVERSAL showed that in patients with known CHD, there was a reduced rate of atherosclerotic progression associated with more aggressive statin treatment.
- The Pravastatin or Atorvastatin Evaluation and Infection Therapy— Thrombolysis in Myocardial Infarction 22 (PROVE-IT/TIMI-22) was a large trial[17] which randomized post-ACS patients to pravastatin 40 mg/d (standard therapy) or atorvastatin 80 mg/d (intensive therapy). Prior to this study, moderate-intensity statin treatment to a target LDL-C < 100 mg/dL was felt to be adequate for patients with established CHD. However, PROVE-IT/TIMI-22 demonstrated that intensive statin therapy, with a goal LDL-C < 70 mg/dL, provided greater protection against death or major cardiovascular events post ACS.
- The Treating to New Targets (TNT) study[18] sought to determine if lowering LDL-C well below 100 mg/dL would provide additional benefit to patients with stable CHD. The trial randomized patients to either 10 or 80 mg of atorvastatin per day, resulting in a 22% relative risk reduction in the primary endpoint of a major

cardiovascular event. The TNT study showed that patients with stable CHD benefit from LDL-C reduction to levels considerably below 100 mg/dL.

- The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA)[19] assessed the benefits of statin therapy for "the primary prevention of CHD in hypertensive patients not conventionally deemed dyslipidemic," defined as men and women with TC ≤250 mg/dL (mean LDL-C 133 mg/dL). Subjects were randomized to either atorvastatin 10 mg/d or placebo. The trial was stopped early (after 3.3 years, instead of the planned 5 years), because of a highly significant 36% reduction ($p = 0.0005$) in the primary endpoint of nonfatal MI and CHD death in the atorvastatin group. In conclusion, ASCOT-LLA demonstrated that men and women at moderately elevated risk for CHD should be considered for statin therapy, even if their LDL-C levels are only mildly elevated.
- The Collaborative Atorvastatin Diabetes Study (CARDS)[20] tested the hypothesis that statin treatment could prevent primary CHD events in patients with DM2, serum creatinine ≤1.7 mg/dL, and fasting LDL-C <160 mg/dL (mean 111 mg/dL). Two thousand eight hundred and thirty-eight diabetic patients without known CHD, aged 40 to 75 years, with at least one other high-risk feature (retinopathy, albuminuria, current smoking, or HTN) were randomized to placebo or atorvastatin 10 mg/d. Subjects treated with atorvastatin experienced a highly significant 37% reduction in the first occurrence of an acute CHD event, coronary revascularization, or CVA ($p = 0.001$). Treatment also conferred a favorable trend toward reduced total mortality (RR reduction of 27%, $p = 0.059$). Therefore, CARDS demonstrated that atorvastatin 10 mg/d was safe and effective in reducing the risk of a first CVD event for patients with DM2 and average-to-low LDL-C and that diabetic patients may benefit from statins, regardless of baseline LDL-C levels.
- Given the inflammatory nature of CVD, the JUPITER trial[21] sought to determine if statin therapy would benefit individuals with normal or low LDL-C levels and elevated levels of the inflammatory biomarker hsCRP. "Apparently healthy" men and women with LDL-C <130 mg/dL and hsCRP >2 mg/L were randomized to rosuvastatin 20 mg/d or placebo. Statin therapy reduced LDL-C by 50%, and hsCRP by 37%. In the statin arm, compared to placebo, there was a 47% reduction in CVD events, and a 20% reduction in total mortality. The JUPITER trial supported the expanded use of statins in patients not previously thought likely to benefit from statin treatment.

TABLE
53.7 Subsequent Statin Trials

Trial[a]	N (Sex)	Drug, Dose (mg)	Y	Base LDL-C	Tx LDL-C	Adverse Event, Relative Risk Reduction	Tx Rate (%)	PC Rate (%)	% ARR
PROVE-IT TIMI-22	4,162 (M/F)	Atorva 80 vs. Prava 40	2	133	62 vs. 95	NFMI or CHDD ↓ %	5.2	8.3	3.1
						CV events/procedures ↓ 16%	22.4 10.8	26.3 15.2	1.9 4.4
						Coronary events ↓ 29%	5.4	7.4	2.0
						CVA ↓ 27%	2.0	3.4	1.4
TNT	10,001 (M/F)	Atorva 80 vs. Atorva 10	4.9	99 on Atorva 10 mg	77 vs. 101	NFMI ↓ 22%	6.2	4.9	1.3
						Combined CV events ↓ 22%	8.7 3.1	10.9 2.3	2.2 0.8
						CVA ↓ 25%	2.5	2.0	0.5
						Fatal MI ↓ 20% NS			
ASCOT-LLA	10,305 (M/F)	Atorva 10	3.3	133	87	NFMI or CHDD ↓ 36%	5.2	8.3	3.1
						CV events/procedures ↓ 21%	24.1 10.8	30.6 15.2	6.5 4.4
						Coronary events ↓ 29%	5.4	7.4	2.0
						CVA ↓ 27%	2.0	3.4	1.4
						Chronic stable angina ↓ 41%			
CARDS	2,838 (M/F)	Atorva 10	3.9	111	122	Combined CV events ↓ 37%	5.8 3.6	9.0 5.5	3.2 1.9
						USA, NFMI, CHDD ↓36%	1.5	2.8	1.3
						CVA ↓ 48%	4.3	5.8	1.5
						Total mortality ↓27%*			

[a]Trials: PROVE-IT/TIMI-22, Provastain or Atorvastain Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22; TNT, Treating to New Targets; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm; CARDS, Collaborative Atorvastatin Diabetes Study.

*p = 0.059.

Other abbreviations: n, number of subjects in trial; Sex, sex of subjects in trial; Y, years of trial duration; Tx LDL-C, average LDL-C with drug treatment; Tx Rate, adverse event occurrence rate in treatment group during study period; PC Rate, adverse event occurrence rate in placebo control group or comparison group during study period; % ARR, percent absolute risk reduction; Prava, pravastatin; Atorva, atorvastatin; NFMI, nonfatal MI; CHDD, CHD death; CVA, nonfatal and fatal stroke; USA, unstable angina; SCD, sudden cardiac death; revasc, coronary revascularization; resusc, resuscitated; NS, not significant. Adapted in part from Gotto AM and Pownall HJ. Manual of Lipid Disorders. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2003:171–174.

TARGETING LIPIDS OTHER THAN LDL-C

As therapeutic target levels of LDL-C drop ever lower and the demographics of patients eligible for statin therapy grow ever wider, we may be soon approaching the limits of beneficial LDL-C treatment. In addition, with the increase in obesity, diabetes, MetS, and DM2, more individuals are presenting with combined hyperlipidemias. Given the knowledge derived from epidemiologic and biochemical studies, it would appear logical that altering concentrations of HDL-C and TG could reduce the incidence of CHD. There are a number of reasons to consider looking beyond LDL-C lowering in the quest to further reduce cardiovascular adverse events:

- Cardiovascular events still occur in individuals with low LDL-C and even in treatment groups after LDL lowering with statins.
- When patients with diabetes are treated with statins in clinical trials, CVD event rates remain higher than the CVD event rates of those patients without diabetes on placebo.
- In IVUS studies, LDL-C lowering to <70 to 80 mg/dL is required to see plaque regression, but the 20% of patients in this group who continue to have progression of plaque often have associated DM, less increase in HDL, less decrease in Apolipoprotein B.
- The impact of other atherogenic particles including low or abnormally functioning HDL, VLDL remnants, TG, small dense LDL
- The independent risk of low HDL, elevated TG
- Non-HDL-C, Apo B, LDL-C particle number, Apo B/Apo A1 ratio are better predictors of risk than LDL-C, particularly on therapy.

Consequently, after maximal achievable LDL-C lowering interest has focused on other therapies directed toward lowering TG and or raising HDL-C. Fibrates and niacin are the most potent agents available to achieve this end. Unfortunately, dissecting the relative contributions of changes in HDL-C and TG to decreasing CHD risk has been challenging. Earlier trials provided indirect data suggesting a benefit of such changes, but data from prospective studies directly testing this hypothesis have been limited. Monotherapy trials support a role for treatment with fibrates or niacin in select groups. An important clinical question is whether there is added benefit when other medications to modify HDL-C and TG are added to a background of statin therapy. However, long-term outcome trials examining combinations of these agents with statins are few, only recently completed or still forthcoming. See Table 53.8 for a summary of the trials discussed below.

TABLE
53.8 Studies Targeting Lipids Other Than LDL-C

Study	N	Drug	F/U (y)	ΔLDL	ΔTG	ΔHDL	Primary CVD Endpoint Entire Cohort (p-value)	Lipid Subgroup Criterion	Primary CVD Endpoint Subgroup (p-value)
HHS	4,081	Gemfibrozil	5.4	−10%	−43%	+>10%	34% ↓ fatal/ nonfatal CHD (0.02)	TG >200 mg/ dL LDL-C/HDL-C > 5.0	−71% (0.005)
BIP	3,122	Bezafibrate	6.2	−6.5%	−21%	+18%	9.4% ↓ nonfatal CHD (0.26)	TG ≥200 mg/ dL	−40% (0.02)
VA-HIT	2,531	Gemfibrozil	5.1	0%	−31%	+6%	22% ↓fatal/ nonfatal CHD (0.006)	Diabetes	−32% (0.004)
FIELD	9,795	Fenofibrate	5	−6%	−22%	+1%	11% ↓ CHD (0.16)	TG ≥204 mg/ dL and HDL-C <42 mg/dL	−27% (0.005)
ACCORD LIPID	5,518	Fenofibrate (as add-on therapy to simvas-tatin)	4.7	−19% vs. −21%	−26% vs. −10%	+8.4% vs. +6.0%	−8% ↓ CHD (0.32)	TG ≥204 mg/ dL and HDL-C ≤34 mg/dL	−31% (0.0567)

MONOTHERAPY TRIALS WITH FIBRATES

- The Helsinki Heart Study (HHS) and the Bezafibrate Infarction Prevention (BIP) trial were primary and secondary prevention studies, respectively, using fibrates. Although both trials showed respectable increases in HDL-C and decreases in TG, nonfatal MI/CHD death was decreased 34% ($p < 0.02$) compared to placebo in HHS, while no such benefit was observed in BIP. In HHS, the patients most likely to benefit from treatment were further defined as those with an LDL-C:HDL-C ratio >5 and TG > 200 mg/dL. In BIP, although there was no difference in the total cohort, a subgroup with TG > 200 mg/dL did have a 40% reduction in CVD risk.

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial of patients with diabetes,[22] fenofibrate compared to placebo was not associated with a significant reduction in CVD events in the entire cohort, but there was a significant 27% reduction in a subgroup with TG > 203 mg/dL and HDL-C < 42 mg/dL.

- The Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)[23] assessed the benefit of gemfibrozil therapy for secondary CHD prevention in patients with low HDL-C and without elevated LDL-C. When 2,531 men with mean HDL-C of 32 mg/dL, mean LDL-C of 112 mg/dL, and mean TG of 160 mg/dL were randomized to gemfibrozil 1,200 mg/d

or placebo, for an average period of 5.1 years, treatment was associated with 6% higher HDL-C and 31% lower TG and afforded a 22% reduction in nonfatal MI and CHD death over placebo ($p = 0.006$) and a 24% reduction in the combined primary outcome of nonfatal MI, CHD death, and stroke ($p < 0.001$). These studies collectively suggest that while monotherapy with fibrates may not benefit all individuals with dyslipidemia, subgroups with a metabolic pattern of elevated TG and low HDL-C may benefit.

MONOTHERAPY TRIALS WITH NIACIN

- The Coronary Drug Project (CDP), initiated in the late 1960s, was a large secondary prevention study among men with several treatment arms, one of which utilized 3 g/d of niacin. Compared to placebo, niacin lowered TC by 10% and TG by 26% (LDL-C and HDL-C data not available), and after 6 years, significantly reduced nonfatal MI by 27%. Although all-cause mortality was not significantly different from placebo at the study's conclusion, a 15-year follow-up analysis (9 years after the interventions had ended) revealed a significant 11% decrease ($p < 0.004$) in total mortality.

A subanalysis demonstrated equivalent reductions in CVD risk regardless of entry fasting glucose level, change in fasting glucose on therapy, or presence or absence of diabetes.

COMBINATION TRIALS WITH STATINS

Combination outcome trials are limited. The Familial Atherosclerosis Treatment Study (FATS) was an angiographic regression trial comparing treatment with lovastatin/colestipol or niacin/colestipol to conventional therapy.[24] After 2.5 years, the two treatment groups demonstrated 32% and 39% of patients with regression compared with 11% in the conventional group. The Cholesterol-Lowering Atherosclerosis Study (CLAS) compared niacin/colestipol combination to placebo and demonstrated significant regression in 16% of patients on combination therapy versus 2.4% in the placebo group.[25] The HDL-Atherosclerosis Treatment Study (HATS) demonstrated similar benefits of combined simvastatin/niacin treatment for persons with CHD, low HDL-C, and average LDL-C.[26] However, the relevant clinical question since statin therapy is the primary pharmacologic treatment is if there is incremental reduction in CVD risk when niacin or fibrates are added to adequate statin therapy.

- The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER-2)[27] study was a small secondary prevention trial of 167

persons (91% men) with known CHD and low HDL-C using the surrogate endpoint of carotid intima-media thickness (CIMT) as the primary outcome. (mean 40 mg/dL). 1,000 mg extended-release niacin or placebo was added to a background of statin treatment with prerandomization LDL-C of 87 mg/dL and HDL-C of 39 mg/dL. AT 1 year, HDL-C increased an average of 21% in the niacin group. Mean CIMT increased significantly in the placebo group, but was not significantly changed in the niacin group. Although the overall difference in CIMT progression between niacin and placebo groups was not statistically significant ($p = 0.08$), niacin significantly reduced the CIMT progression rate in subjects without insulin resistance ($p = 0.026$). ARBITER-3, a 1 year open label extension of ARBITER-2 with all subjects on niacin and statin, demonstrated regression as measured by change in mm of CIMT which was even more prominent in subjects with DM or MetS. ARBITER-6-HALTS compared the effects of niacin versus ezetimibe when added to background statin therapy and demonstrated regression in CIMT over 14 months when niacin was added to statins but not when ezetimibe was added. Although these studies were not designed or powered to examine differences in clinical events, niacin treatment when added to statin therapy appeared to slow the rate of atherosclerotic progression in persons with CHD and low HDL-C.

Few large placebo-controlled trials are available addressing the question of combination therapy with statins and the effect on CVD events. In the lipid arm of the ACCORD trial,[28] fenofibrate or placebo was added to a background of simvastatin therapy in 5,518 individuals with diabetes. The annual rate of the primary composite CVD outcome was not significantly different (2.2% in fenofibrate group vs. 2.4 in placebo group) and mortality was similar at 1.5% versus 1.6% in the two treatment groups. However, in a prespecified subgroup analysis of subjects with TG $\geq$ 204 mg/dL and HDL-C $\leq$ 34 mg/dL, the primary outcome was 12.4% in the fenofibrate group versus 17.3% in the placebo group, a 31% reduction, ($p = 0.0567$) compared with 10.1% in both groups in the entire cohort.

Two placebo-controlled outcome studies were designed to investigate the effects of adding niacin to a background of aggressive LDL-C treatment with statins. AIM-HIGH trial of 3,414 subjects with nonacute stable CVD was designed to test whether the addition of extended-release niacin after lowering LDL-C with simvastatin (±ezetimibe) to between 40 and 80 mg/dL would result in an additional 25% reduction in CVD events. This NIH-supported study was ended prematurely by the Data Safety Monitoring Board in May of 2011 due to futility or inability to demonstrate a significant difference between the study arms. The published final results of the trial showed no significant difference in events between the statin + placebo group and the statin + niacin group. The AIM-HIGH results suggest that adding niacin to statin therapy in patients with optimally controlled LDL may be of no benefit. However, given the impressive results

from earlier studies, niacin use in patients with suboptimally controlled LDL, or in those who are entirely intolerant of statins, may still be justified. The larger ongoing Heart Protection Study (HPS)-THRIVE will be examining whether the addition of niacin (combined with a prostaglandin receptor blocker to reduce flushing) to statin therapy will reduce CVD events in approximately 20,000 subjects.

DIABETES AND LIPID MANAGEMENT

Individuals with diabetes have been known to be at high risk for development of CVD. In 2001 the ATP III panel raised diabetes from a risk factor for CVD to a CHD risk equivalent. Factors supporting this decision include:

- Accelerated atherosclerosis is multifactorial and begins years to decades prior to the diagnosis of type 2 diabetes.
- >50% individuals with newly diagnosed type 2 diabetes have clinical CHD.
- Risk for CVD events is two- to fourfold greater in diabetics than in nondiabetics.
- Diabetics with MI or revascularization procedures do worse.
- Atherosclerosis accounts for approximately 65% to 75% of all diabetic mortality, 75% of which are due to complications of coronary atherosclerosis.
- Diabetes is one of most important risk factors for stroke in women.
- A diabetics risk of CV mortality or MI is equivalent to a nondiabetic having had a prior MI: Concept of Diabetes as a CHD risk equivalent.
- A diabetic with one of the CVD risk factors of hypertension, hyperlipidemia, or cigarette smoking has a CVD mortality rate as high as or higher than a nondiabetic with all three.

In multivariate models from the UKPDS study, the lipid parameters of LDL-C and HDL-C were more strongly associated with the development of new CHD during follow-up compared with HbA1c, hypertension, and smoking. The STENO-2 trial demonstrated that cardiovascular mortality could be significantly reduced by 53% in diabetic patients when a multifactorial approach designed to more aggressively treat lipids, glucoses, and hypertension was employed. A retrospective analysis determined that lipid management (LDL-C of 83 mg/dL in the treatment group vs. 126 mg/dL in the conventional therapy group) explained 70% of the reduction in risk with HbA1c and blood pressure lowering explaining the other 30%. Therapeutic decisions are further complicated by the typical atherogenic dyslipidemia in patients with DM and MetS that is characterized by elevated levels of TG, LDL particle number and apolipoprotein B, low HDL-C, and small dense LDL particle size. Despite this mixed dyslipidemia, statins remain the primary therapeutic choice for lipid treatment in diabetics as in the general population. Analysis of diabetic subgroups in the large statin trials have clearly

demonstrated the benefits of statin therapy.

A recent meta-analysis of 10 trials[29] compared 16,000 diabetics with 54,000 nondiabetics in statin trials and demonstrated similar 30% reduction in CHD, 19% reduction in CVA, and 12% reduction in mortality in the two groups. In another meta-analysis of 14 trials, a similar 22% reduction in CHD was noted in diabetics whether or not there was an existing history of CVD disease.

CURRENT TREATMENT GUIDELINES FOR DYSLIPIDEMIAS

The most recent full set of guidelines for the treatment of dyslipidemias is the National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III), a 284-page document initially published in 2001.[30] ATP III highlighted early identification of lipid abnormalities, offered new recommendations for screening and detection, modified lipid and lipoprotein classifications, and reemphasized the importance of nonpharmacologic management of lipid disorders. The main objective of ATP III was to promote more aggressive treatment of dyslipidemias in a broader spectrum of patients and over a wider range of cholesterol levels. LDL-C remained the primary target of therapy. This was based on knowledge of the linear relationship between serum cholesterol and coronary events (~1% drop in CHD event risk for each 1% reduction in LDL-C), as well as knowledge gleaned from many of the large, prospective, randomized statin trials unavailable at the time of previous guidelines. For all patients, optimal LDL-C was redefined as <100 mg/dL (a lower threshold of LDL-C levels had not yet been established), threshold for low HDL-C increased from <35 to <40 mg/dL, and TG classification cutpoints were reduced to bring more attention to moderate elevations (Table 53.9). Major CHD risk factors were once again identified (Table 53.10) and utilized as a basis for global risk assessment. Nonpharmacologic interventions such as TLC were intensified (see Table 53.3). One of the most important contributions of the newer guidelines was highlighting the importance of identifying the level of future cardiovascular risk and targeting therapeutic decisions to that risk level. In fact, applying the new risk assessment and treatment goals nearly tripled the number of adults suitable for initiation of simultaneous TLC and drug therapy to over 36 million individuals. In August 2004, the NCEP generated a report[31] proposing further modifications to the ATP III LDL-C treatment goals, based upon studies published after its release, including HPS, ASCOT-LLA, and PROVE IT/TIMI-22. These suggested changes consist of optional lower goals for LDL-C targets, initiation of pharmacologic treatment at lower LDL-C cutoffs, and a minimum 30% to 40% reduction in LDL-C from baseline, in high risk and moderately high-risk patients. These modifications in treatment recommendations are further reflected in the ACC/AHA secondary prevention guidelines, women cardiovascular prevention guidelines, and American Diabetes Association lipid treatment recommendations as well as others.

TABLE
53.9 ATP III Classification of LDL, Total, and HDL-Cholesterol, and Triglycerides (mg/dL)

LDL Cholesterol—Primary Target of Therapy	
<100	Optimal
100–129	Near optimal/above optimal
130–159	Borderline high
160–189	High
≥190	Very high
Total Cholesterol	
<200	Desirable
200–239	Borderline high
≥240	High
HDL Cholesterol	
<40	Low
≥60	High
Triglycerides	
<150	Normal
150–199	Borderline high
200–499	High
≥500	Very high

Adapted from Grundy SM, Becker D, Clark LT, et al. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Final Report, NIH Publication No. 02-5215. September 2002.

TABLE
53.10 Major CHD Risk Factors (Exclusive of LDL-C) that Modify LDL-C Goals

Cigarette smoking
HTN (BP ≥ 140/90 mm Hg or on anti-hypertensive medication)
Low HDL-C (<40 mg/dL)[a]
Family history of premature CHD (first degree relative, male < 55 y, female < 65 y)
Age (men ≥ 45 y, women ≥ 55 y)

[a]HDL-C ≥ 60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.

Adapted from Grundy SM, Becker D, Clark LT, et al. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults

(Adult Treatment Panel III): Final Report, NIH Publication No. 02-5215. September 2002.

Based on this additional emerging data, appropriate modifications of the 2001 guidelines include:

- LDL-C goal <70 mg/dL is therapeutic option for very high-risk patients.
- The above goal extends to patients at very high risk with baseline LDL-C <100 mg/dL
- Factors favoring the optional goal of <70 mg/dL include CVD associated with multiple major risk factors (especially diabetes), severe and poorly controlled other risk factors (especially smoking), MetS, or ACS.
- For moderately high-risk patients, LDL-C goal <100 mg/dL is a therapeutic option (e.g., hypertensive with multiple other risk factors).
- Statins are the first-line pharmacologic therapy.
- Increase to maximal tolerated doses of a potent statin as needed to achieve LDL-C goals before adding additional therapies
- In patients with elevated LDL-C at baseline (≥160 mg/dL) standard statin doses may not be sufficient for optimal LDL-C reduction. Therefore, consider high-dose statins and/or combination therapy (e.g., statins + ezetimibe or resins) to achieve aggressive LDL-C goals.
- Addition of fibrate or nicotinic acid should be considered for high-risk patients with high TG or low high-density lipoprotein cholesterol (HDL-C after achieving LDL-C goals).
- Although extensive outcome data are not yet available, consider addition of additional therapies to achieve LDL-C and Non–HDL-C goals after optimization of statin therapy.

The most recent cholesterol treatment guidelines and update identify four tiers of CHD risk with therapeutic life style and pharmacologic recommendations for each risk level (Table 53.11). These tiers of risk are largely based upon the known risk of clinically present CVD or diabetes and epidemiologic data from the Framingham Heart Study. Individuals with known CHD, including a history of MI, unstable angina, PCI or CABG, or evidence of clinically significant myocardial ischemia, are at the highest risk for coronary events. Because noncoronary atherosclerotic disease confers a risk for coronary events comparable to that of known CHD, conditions such as symptomatic carotid artery disease, peripheral arterial disease, and abdominal aneurysm are referred to as “CHD risk equivalents.” Starting with ATP III, diabetes also came to be regarded as a CHD risk equivalent based on previously described observations. Patients with known CHD, or CHD risk equivalents, fall into the highrisk group for coronary events, and should thus receive the most aggressive lipid lowering. These are individuals with

an estimated yearly risk of MI or death of 2% or greater.

TABLE
53.11 ATP III LDL-C Goals and Cutpoints for TLCs and Drug Therapy in Different Risk Categories land Proposed Modifications Based on Recent Clinical Trial Evidence

Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy[a]
High risk: CHD[b] or CHD risk equivalents[c] (10-y risk >20%)	<100 mg/dL (optional goal: <70 mg/dL)[d]	≥100 mg/dL[e]	≥100 mg/dL[f] (<100 mg/dL: consider drug options)[a]
Moderately high risk: 2+ risk factors (10-y risk 10%–20%)[g]	<130 mg/dL (optional goal: <100 mg/dL)	≥130 mg/dL[e]	≥130 mg/dL (100–129 mg/dL: consider drug options)[h]
Moderate risk: 2+ risk factors (10-y risk <10%)[g]	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower risk: 0–1 risk factor[i]	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160–189 mg/dL: LDL-lowering drug optional)

[a] When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C level

[b] CHD includes history of MI, unstable angina, PCI or CABG, or evidence of clinically significant myocardial ischemia.

[c] CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [TIA or CVA of carotid origin or >50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with 10-y risk for hard CHD >20%.

[d] Very high risk favors the optional LDL-C goal of <70 mg/dL, and in patients with high triglycerides, non-HDL-C <100 mg/dL.

[e] Any person at high risk or moderately high risk who has lifestyle-related risk factors (e.g., obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level.

[f] If baseline LDL-C is <100 mg/dL, institution of an LDL-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high TG or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.

[g] Electronic 10-year risk calculators are available at www.nhlbi.nih.gov/guidelines/cholesterol.

[h] For moderately high-risk persons, when LDL-C is 100–129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C <100 mg/dL is a therapeutic option on the basis of available clinical trial results.

[i] Almost all people with zero or 1 risk factor have a 10-y risk <10%, and 10-y risk assessment in people with zero or 1 risk factor is thus not necessary. Adapted from Grundy SM, Cleeman JI, Merz CN, et al. Circulation. 2004;110:227–239.

At the other end of the spectrum are those with 0 to 1 risk factors but no known CVD or diabetes. They are considered at lower risk for CHD events, with an estimated yearly MI or death rate of <0.5% to 1%, and require the least aggressive lipid control.

Between these two extremes are individuals with 2 or more risk factors, but without known CVD or diabetes, for whom the 10-year risk of having a MI or dying from an MI can be estimated using the Framingham risk calculator. This is a point-based system (available online and in the "ATP III Guidelines At-A-Glance Quick Desk Reference," NIH Publication No. 01–3305) to assess risk in men and women, based upon data from the Framingham Study, utilizing the parameters of age, TC, smoking status, HDL-C, and systolic BP. Those with 2+ risk factors and a 10-year risk >20% are grouped with the CHD and CHD risk equivalents (high risk), those with a 10-year risk of 10% to 20% are considered to be at moderately high risk, and those with a 10-year risk of <10% are said to be at moderate risk. Despite the utility of this calculator, important risk factors such as family history and obesity are not included, the calculation is heavily age and gender-weighted, and it may not apply equally to all ethnic groups. The guidelines have recommended the use of other novel risk markers (e.g., Lp(a)), measures of inflammation (e.g., hsCRP), and imaging for preclinical vascular disease (e.g., CT coronary calcification score, ankle–brachial index, carotid intima-medial thickness) to guide the intensity of therapy. These additional factors may be particularly useful in making more aggressive treatment decisions for intermediate risk individuals with other compelling risk factors such as a strong family history of premature CHD.

The primary target of treatment is LDL-C. The LDL-C goal for therapy and LDL-C level for initiation of drug therapy are dependent on the individual's risk category. For example, the 2001 guidelines recommended that individuals falling into the CHD or CHD risk equivalent category have a treatment goal of <100 mg/dL and have drug therapy initiated for an LDL-C of ≥130 mg/dL (between 100 and 129 mg/dL optional). After LDL-C goals have been met, non-HDL cholesterol (TC minus HDL-C) is a secondary target of therapy (Table 53.12). The non-HDL-C target should be 30 mg/dL higher than the LDL-C goal. For example, in the high-risk group, if the LDL-C target is <100 mg/dL, the non-HDL-C target would be <130 mg/dL. This may be achieved by further reductions in LDL-C, lowering of TG, increase in HDL-C, or a combination. Specific recommendations for TG management have been outlined. If TG are borderline elevated at 150 to 199 mg/dL, weight reduction and increased physical activity should be prescribed. If TG are 200 to 499 mg/dL, this can be achieved by intensifying therapy with an LDL-lowering drug (i.e., increasing the statin dose), or by adding niacin or a fibrate to further lower VLDL-C. If TG are ≥500 mg/dL, TG should be lowered first to prevent pancreatitis. Treatment options include a very low-fat diet (<15% of calories from fat), identification and treatment of secondary causes of elevated TG, weight reduction and physical activity, and the addition of niacin or a fibrate. Once TG have been lowered to <500 mg/dL, LDL-C-lowering therapy should be initiated. Treatment of low-HDL-C remains a tertiary goal in lipid management, mainly because of the paucity of large outcome studies involving treatment of low HDL-C and less-effective available medications. No specific target for ideal HDL-C has been proposed. Once

LDL-C goal has been achieved, weight reduction and increased physical activity should be employed in an attempt to boost HDL-C. If TG are 200 to 499, the non-HDL-C goal should be achieved. If TG are <200 mg/dL (isolated low HDL-C) in high-risk individuals, one should consider initiating niacin or a fibrate. In the future, as better medications to raise HDL-C become available and more large trials address the utility of treating HDL-C to reduce CHD events, the priority of treating a low HDL-C may increase. Finally, ATP III recognized the MetS as a growing contributor to CHD risk, and stressed the importance of its identification and treatment. The ATP III definition of MetS and its treatment goals have already been discussed (see Table 53.2).

TABLE
53.12 Comparison of LDL-C and Non-HDL-C Goals for Three Risk Categories

Risk Category	LDL-C Goal (mg/dL)	Non-HDL-C Goal (mg/dL)
CHD and CHD risk equivalent (10-y risk for CHD > 20%)	<100	<130
Multiple (2+) risk factors and 10-y risk ≤10%	<130	<160
0–1 risk factor	<160	<190

Adapted from Grundy SM, Becker D, Clark LT, et al. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Final Report, NIH Publication No. 02-5215. September 2002.

Recommendations for aggressive lipid management in the diabetic population have been reinforced in ADA/ACC concensus statement and ADA guidelines. The ADA suggests specific targets not only for LDL-C and non-HDL-C as outlined in Table 53.13 but also for TG of <150 mg/dL and HDL-C of <40 mg/dL in men and <50 mg/dL in women. Apolipoprotein B has been added as a secondary target.

TABLE
53.13 Therapeutic Lipid and Lipoprotein Goals in Diabetic Patients

Suggested Treatment Goal in Patients With Cardiometabolic Risk (CMR) and Lipoprotein Abnormalities	Goals		
	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	apo B (mg/dL)
Highest-risk patients: 1) Known CVD or 2) Diabetes plus one or more additional CVD risk factor(s)	<70	<100	<80
High-risk patients: 1) No diabetes or known CVD but 2 or more major CVD risk factors or 2) Diabetes but no other CVD risk factors	<100	<130	<90

Despite the enormous amount of information and widely disseminated treatment recommendations, a significant number of treatment-eligible patients are not identified or do not receive adequate treatment. ATP III suggests that all adults be screened with a full fasting lipid profile beginning at age 20. ATP III recommends screening the family members of individuals with genetic disorders such as FH, familial defective apolipoprotein B-100, or PH. The guidelines recommend early assessment of response and titration of nonpharmacologic and drug treatment strategies (every 6 weeks) and offer advice to help with patient, physician, and health care provider adherence to the guidelines.

The American Heart Association recommends that children of parents with premature CHD or significantly elevated cholesterol or children whose family history is unknown be screened after 2 years of age. Updated guidelines and recommendations for the treatment of high cholesterol in children 8 years of age and older were issued by the American Academy of Pediatrics in July, 2008. These guidelines recommend pharmacologic treatment if not achieving goals with lifestyle intervention (with statins as first-line therapy) of elevated LDL-C if the value is >190 mg/dL in patients with no risk factors for CVD, >160 mg/dL in those who have a family history of premature onset of CVD or at least one other risk factors including obesity, hypertension, or cigarette smoking, and >130 mg/dL in those who have diabetes.

Clearly we are faced with the challenge of finding better ways to implement cholesterol treatment recommendations. See Tables 53.3 and 53.4 for detailed information on TLC and drug therapy, respectively, and Table 53.9 for an overview of the ATP III/Update treatment recommendations.

FUTURE DIRECTIONS

In the past two decades, we have witnessed remarkable strides in the treatment of lipid

disorders and coronary disease. These accomplishments can be largely attributed in large part to the development of statins, and their overwhelming success in multiple large-scale randomized trials of CHD prevention. Over the next two decades, we can expect to see continued progress in lipid and CHD therapies. Basic science findings will continue to further our understanding of atherosclerotic mechanisms. Lipid absorption and metabolism; lipoprotein structure, function, and transport; inflammation, and the complex genetics of dyslipidemias and atherosclerosis are just a few of the fertile research areas which will undergo further exploration. Further understanding of the genetic underpinnings of atherosclerotic vascular disease may assist in specifically tailoring cardiac care to the individual patient. Clinical trials with agents with a capability to raise or modify HDL-C (such as the CETP inhibitors or ApoA1-Milano), long-term assessment of combination therapies along with statins, and better understanding of the role of hsCRP-directed therapy will likely further expand our treatment options for dyslipidemias and enhance our ability to reduce cardiovascular events.

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QUESTIONS AND ANSWERS

Questions

1. Casey S. is an obese 54-year-old man (BMI = 35) with a history significant for obstructive sleep apnea and multiple joint complaints. A lower extremity arterial duplex study, performed to work up the possibility of claudication, reveals noncritical peripheral arterial disease, with bilateral antel–brachial indices (ABIs) of 0.8. He denies ongoing exertional chest discomfort or dyspnea, but lives a fairly sedentary lifestyle. Physical exam reveals an obese man with normal BP, an unremarkable cardiac exam, and 1+ dorsalis pedis pulses. His fasting lipids are as follows: total cholesterol (TC) 240 mg/dL, triglycerides (TG) 250 mg/dL, highdensity lipoprotein-cholesterol (HDL-C) 35 mg/dL, low-density lipoprotein-cholesterol (LDL-C) (calculated) 155. Initial therapy should include:
   a. Therapeutic lifestyle change (TLC) only
   b. TLC plus a statin, with the goal of reducing LDL-C to <130 mg/dL
   c. TLC plus niacin or a fibrate, with the goals of reducing LDL-C to <100 mg/dL and TG to <150 mg/dL
   d. TLC plus a statin, with the goal of reducing LDL-C to <100 mg/dL (<70 mg/dL optional)
   e. e. TLC plus statin, as well as niacin or a fibrate, with the goals of reducing LDL-C to <100 mg/dL and TG to <150 mg/dL

2. Donna O. is a 71-year-old retired executive whose father died at age 52 of a “massive MI.” She is very worried about her own risk of a heart attack.
   She watches her weight (BMI = 23), does not smoke, and keeps physically fit, walking 3 miles on a treadmill three to four times a week. She denies angina or dyspnea on exertion, claudication, or history of TIA symptoms. Her BP is 120/80. Her fasting lipids are as follows: TC 250 mg/dL, TG 120 mg/dL, HDL-C 42 mg/dL, LDL-C (calculated) 151 mg/dL. Her calculated Framingham 10-year event risk is 5%. Initial therapy should include:
   a. Nothing beyond her current lifestyle measures
   b. Weight loss to bring BMI to <2 0.
   c. TLC plus a statin to reduce LDL-C to <130 mg/dL, or optionally to <100 mg/dL
   d. TLC to reduce LDL-C to <130 mg/dL
   e. Statin and niacin to reduce LDL-C to <130 mg/dL and increase HDL-C to > 50 mg/dL

3. If the same patient were found instead to have untreated HTN (systolic BP of 160), with all other data the same, what would be the preferred initial treatment, in addition to BP control? Her calculated 10-year Framingham risk score is now 11%.
   a. Nothing beyond her current lifestyle measures
   b. Weight loss to bring BMI to < 20
   c. TLC plus a statin to reduce LDL-C to <130 mg/dL, or optionally to <100 mg/dL
   d. TLC to reduce LDL-C to <130 mg/dL
   e. Statin and niacin to reduce LDL-C to <130 mg/dL and increase HDL-C to > 50 mg/dL

4. Richard D. is referred to you for lipid management. He denies any first-degree relatives with history of coronary heart disease (CHD) but reports that two uncles and a distant cousin have had heart attacks. He is currently asymptomatic. His BMI is 28. His physical exam reveals arcus cornea and xanthelasmas, but no xanthomas, and a BP of 150/80. His fasting lipid profile is as follows: TC 300 mg/dL, TG 430 mg/dL, HDL-C 50 mg/dL, LDL-C (direct) 200 mg/dL. Which primary dyslipidemia is this patient most likely to have?
   a. Polygenic hypercholesterolemia (PH)
   b. Heterozygous Familial Hypercholesterolemia (FH)
   c. Familial Combined Hyperlipidemia (FCH)
   d. Hyperapobetalipoproteinemia
   e. Familial endogenous hypertriglyceridemia

5. What should the initial therapy be for this patient?
   a. Statin
   b. Fibrate
   c. Statin and antihypertensive agent
   d. Niacin
   e. Apheresis

6. Which of the following statements is not correct?
   a. Scandinavian Simvastatin Survival Study (4S), CARE, LIPID, and HPS all involved secondary prevention of CHD.
   b. Data from HPS, ASCOT-LLA, and PROVE-IT/TIMI-22 were influential in lowering the recommended treatment goals for LDL-C in the 2004 ATP III updates.
   c. WOSCOPS and AFCAPS/TexCAPS were both primary CHD prevention studies which showed significant clinical benefits for statin therapy, with similar percentage reductions in LDL-C. The main difference between these trials was that subjects in AFCAPS/TexCAPS had considerably lower baseline LDL-C levels than those in WOSCOPS.
   d. Early angiographic trials of lipid lowering showed significant reductions in coronary events, though they were not designed to show this.
   e. ASCOT-LLA showed reductions in nonfatal myocardial infarction (MI), CHD death, and all-cause mortality when patients with average lipids and HTN were treated with atorvastatin 10 mg daily for an average of 3.3 years.

7. Gary P. is an obese, nonsmoking, gregarious 44-year-old talk show host with treated HTN and no family history of CHD. He has no personal history of known CHD. He has had elevated LDL-C in the past, and is taking atorvastatin 20 mg/d. His latest lipid panel is: TC 220, HDL-C 40, direct LDL-C 120, and TG 450. His calculated 10-year risk of a CHD event is 5%. After recommending lifestyle modifications, what is your first goal of drug treatment?
   a. Increase the HDL-C
   b. Lower the LDL-C
   c. Lower the non-HDL-C
   d. Lower the TG
   e. Lower the TG and increase the HDL-C

8. Which of the following would lower non-HDL-C?
   a. Increase the dose of atorvastatin
   b. Add a fibrate
   c. Add niacin
   d. Add ezetemibe
   e. All of the above

9. If the patient's TG were 600 mg/dL, what would be your next step in lipid management?
   a. Increase the HDL-C
   b. Lower the LDL-C
   c. Lower the non-HDL-C
   d. Lower the TG
   e. Lower the TG and increase the HDL-C

10. Which drug would you use?
   a. Raise the dose of atorvastatin to 40 mg/d
   b. Add a fibrate
   c. Add niacin
   d. Add ezetemibe
   e. Increase the statin dose and add a fibrate Answers

Answers

1. Answer D: Patients with a CHD equivalent (including clinically evident peripheral arterial disease) have an LDL-C goal of <100 mg/dL, with the optional goal of <70 mg/dL.

2. Answer D: The patient has two major risk factors: age (woman ≥55 years), and family history of CHD, with a 10-year CHD event risk of <10%. In such moderaterisk persons, TLC alone should be initiated if LDL-C is ≥130 mg/dL, and TLC plus drug therapy should be started for LDL-C ≥160 mg/dL. Since her LDL-C is ≥130 mg/dL, TLC measures should be initiated.

3. Answer C: Given her HTN, the patient now has three major risk factors and a 10-year risk of between 10% and 20%, placing her in the moderately high-risk category. By ATP III, her goal LDL-C is <130 mg/dL, with an optional goal of <100 mg/dL, per the 2004 updates. Since her LDL-C is ≥130 mg/dL, a statin should be started.

4. Answer C: FCH is a common dyslipidemia (1:33 to 1:100 persons) characterized by complex inheritance. Xanthomas are rarely present (unlike in heterozygous FH), but xanthelasmas and arcus cornea can be seen. Affected individuals generally exhibit a TC of 250 to 350 mg/dL, LDL-C of 200 to 300 mg/dL, and TG > 140 mg/dL (two-thirds of patients with FCH have TG of 200 to 500 mg/dL. Patients with PH have a similar lipid profile, except they do not generally have elevated TG.

5. Answer C: Since this patient's TG are <500, LDL-C reduction has first priority. A statin should be initiated, as well as an antihypertensive agent.

6. Answer E: While ASCOT-LLA showed reductions in nonfatal MI and CHD death, coronary events or procedures, stroke, and chronic stable angina, it did not show a reduction in total mortality.

7. Answer C: This man is currently at goal for his target LDL-C of <130 mg/dL. Given the fact that his TG are in the 200 to 499 range, the next priority is to lower his non-HDL-C from its current level of 180 to <160 mg/dL.

8. Answer E: Any of the therapeutic interventions would lower the non-HDL-C (TC minus HDL-C). However, risks of combination therapy and lack of long-term clinical trials assessing add-on therapy need to be considered. Emphasis on TLC with an increase in the statin dose would be an appropriate first step.

9. Answer D: When TG are ≥500 mg/dL, the priority is to reduce TG to <500 mg/dL, to avoid pancreatitis.

10. Answer B: This change could be most effectively achieved by adding a fibrate to his regimen.

CHAPTER

Preoperative Evaluation of Cardiac Patients for Noncardiac Surgery

Matthew C. Bunte and Richard A. Grimm

The evaluation of cardiac patients undergoing noncardiac surgery is an important part of the day-to-day practice of the consulting cardiologist. Unfortunately, poor outcomes can and do occur in high-risk patients. Therefore, predicting risk of potential nonfatal myocardial infarction (MI), heart failure, pulmonary embolism, or death is imperative when managing especially high-risk patients. Several risk prediction indexes have been proposed by various authors with this aim in mind. Coronary revascularization before noncardiac surgery is rarely necessary, however, even among high-risk populations. In this chapter, the revised American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Task Force on Practice Guidelines are used extensively as the primary reference for review of the literature and practice recommendations. These guidelines emphasize the importance of utilizing clinical predictors, evidence-based practice, along with a rational and common sense approach.

Approximately 30 million patients underwent noncardiac surgery in the United States in 2003. Of these, an estimated 4% had diagnosed coronary artery disease (CAD), 8% to 12% had multiple risk factors for CAD, and approximately 16% were over 65 years of age. Those at greatest risk for cardiac complications are 65 years or older with previously diagnosed CAD. This group accounts for nearly 80% of the estimated 1 million patients who suffer major cardiovascular complications annually. These cardiovascular complications cost an estimated $12 billion annually

Despite the increasing age of those undergoing noncardiac surgery, age alone represents a minor risk factor for perioperative complications. However, mortality associated with perioperative acute MI increases dramatically with advanced age. While the overall risk of suffering a postoperative MI is probably <1% with many elective operations, up to 50% of these events can be fatal. The highest risk of perioperative reinfarction occurs within the first 6 months of the index infarction and

subsequently falls with time. Guidelines published by the ACC/AHA recommend that elective surgery may be performed before the 6-month time period so long as a postinfarction risk stratification has been performed. A negative stress test for ischemia or complete revascularization does reduce the risk of reinfarction with elective surgery. Nonetheless, waiting at least 4 to 6 weeks before proceeding with elective surgery represents a prudent approach suggested by these guidelines.

For patients with cardiac disease undergoing noncardiac surgery, surveillance for cardiac complications should be performed for at least 48 hours following surgery. This assessment begins with a baseline preoperative resting 12-lead electrocardiogram (ECG) for future comparison, particularly among patients with at least one clinical risk factor and/or those undergoing procedures of intermediate risk or greater. The peak risk of MI occurs within the first 3 postsurgical days but may persist for as long as 5 to 6 days. Most postoperative MIs are non–Q-wave MIs, usually detected within the first 24 hours as a result of surveillance with electrocardiographic and cardiac enzyme testing. Routine acquisition of an ECG in the immediate postoperative period has been shown to be useful in reevaluation of risk in both low- and high-risk populations after major noncardiac surgical procedures. Patients with evidence of ischemia on the immediate postsurgical ECG were found to have a higher risk of subsequent major cardiac complications. Postoperative infarctions are frequently silent, and their presence may only be revealed by the detection of new onset heart failure, hypertension, nausea, altered mental status, or arrhythmias.

PREOPERATIVE CARDIAC RISK ASSESSMENT

Surgical risk assessment encompasses patient-specific, procedure-specific, and institution-specific factors that must be identified in order to estimate individual risk and in turn outline management plans. Variables associated with the perioperative state that require careful scrutiny include the type and urgency of operation, presence and severity of CAD, status of left ventricular (LV) function, advanced age, presence of severe valvular heart disease, significant cardiac arrhythmias, comorbid medical conditions (e.g., cerebrovascular disease, diabetes mellitus, chronic kidney disease), and overall functional status.

Clinical Markers of Increased Risk

Perioperative cardiovascular risk can be stratified further into major, intermediate, and low-risk categories. Acute conditions that often require hospitalization carry more risk than stable chronic conditions. For example, decompensated heart failure would be considered a major risk predictor, likely to require further evaluation and therapy, whereas compensated heart failure would be considered an intermediate-risk condition.

Major clinic predictors of high risk for perioperative morbidity and mortality include unstable coronary syndromes (unstable or severe angina or recent MI), decompensated heart failure, significant arrhythmias, and/or severe valvular heart disease. Intermediate predictors include mild angina pectoris, prior MI (by history or pathologic Q waves), compensated or prior heart failure, diabetes mellitus (particularly insulin-dependent), and renal insufficiency. Notably, a history of MI is defined as an intermediaterisk factor. However, an acute (a documented MI <7 days before the exam) or recent MI (>7 days but <1 month before the exam) is considered a major predictor. Minor clinical predictors include advanced age, abnormal ECG, rhythm other than sinus, low functional capacity, history of stroke, and uncontrolled systemic hypertension.

Procedure-Specific Risks

Risks associated with the planned surgical procedure require consideration and can be categorized into high, intermediate, and low-risk categories. High-risk procedures include emergency major operations (particularly in the elderly), aortic and other major vascular surgery, peripheral vascular surgery, aortic surgeries, as well as surgical procedures that are expected to be prolonged and associated with large fluid shifts and/or blood loss. Such high-risk procedures are often associated with a perioperative event rate (i.e., heart failure or MI) of over 5%. Blood loss, large intra- and extravascular fluid shifts, aortic cross clamping (in the case of aortic surgery), duration, and postoperative hypoxemia are factors believed to contribute to this increased risk. The risk of peripheral vascular surgical procedures relates to the likelihood of associated CAD in this patient population. Intermediate-risk procedures (cardiac risk generally <5%) include carotid endarterectomy, head and neck surgeries, intraperitoneal and intrathoracic surgery, orthopedic surgeries, and prostate surgery. Examples of low-risk surgeries (cardiac risk generally <1%) include endoscopic surgery, superficial procedures, breast surgery, and cataract surgery (Table 54.1).

TABLE
54.1 Cardiac Risk Stratification with Examples of Noncardiac Surgical Procedures

Risk Stratification	Cardiac Risk[a]	Procedure Examples
Vascular/high	>5%	■ Aortic or other major vascular surgery ■ Peripheral or infrainguinal vascular surgery
Intermediate	1%–5%	■ Intraperitoneal and intrathoracic surgery ■ Carotid endarterectomy ■ Head and neck surgery ■ Orthopedic surgery ■ Prostate surgery
Low	<1%	■ Endoscopic procedures ■ Superficial procedures ■ Cataract surgery ■ Breast surgery

[a]Reported cardiac risk, including combined incidence of nonfatal MI and death.

Modified from Fleisher LA, Beckman JA, Brown KA, et al. 2009 ACCF/AHA Focused Update on Perioperative Beta Blockade Incorporated Into the ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery. et al. J Am Coll Cardiol. 2009;54:e13–e118, with permission from Elsevier.

Functional Capacity and Stress Testing for Preoperative Assessment of Risk

A patient's functional capacity is a good indicator of his or her ability to safely tolerate noncardiac surgery. Estimating functional capacity can be accomplished using readily available energy requirement correlates of daily activities (Fig. 54.1). Exercise stress testing represents a particularly useful tool if it will change management among intermediate- or high-risk patients. It is important to note that noninvasive testing is not useful for patients who are at low cardiovascular risk undergoing low- or intermediate-risk procedure. Noninvasive stress testing provides an objective determination of functional status with concurrent assessment for myocardial ischemia or cardiac arrhythmias during stress evaluation. A final aim of supplemental preoperative stress testing is the provision of an objective measure of perioperative and long-term prognosis. The onset of myocardial ischemia at low exercise workload is associated with a significantly elevated risk of both perioperative and long-term cardiac events.

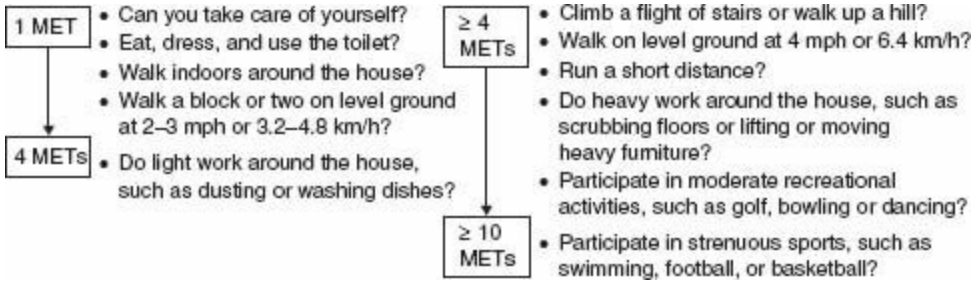

FIGURE 54.1 Estimated energy requirements for typical daily activities. (Adapted from Eagle KA, Berger PB, Calkins H, et al. Guideline update for perioperative cardiovascular evaluation for noncardiac surgery. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee to

Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery]. J Am Coll Cardiol. 2002;39:542–553, with permission from Elsevier.)

A majority of patients in need of further preoperative risk stratification are either unable to exercise or have an ECG that is not interpretable. In these instances, a pharmacologic stress agent is utilized in substitute for physical activity, thereby inducing a hyperemic response, which enhances discrepancies in coronary flow, and enabling detection of myocardial ischemia. Dobutamine stress echocardiography and intravenous vasodilator myocardial perfusion scintigraphy utilizing either single positron emission computed tomography (SPECT) or positron emission tomography (PET) detectors represent the two most common techniques in preoperative stress testing for those who cannot exercise. The negative predictive value of these tests is high (99% for dipyridamole thallium, and 93% to 100% for dobutamine stress echo), though the positive predictive value of these tests for perioperative events is low (4% to 20% for intravenous dipyridamole thallium and 7% to 23% for dobutamine stress echocardiography). Therefore, incorporating clinical markers of risk is essential for improving the specificity and positive predictive value of these diagnostic studies. As a guideline, noninvasive testing in preoperative patients is indicated if two or more of the following are present: (a) intermediate clinical predictors (Canadian Class I or II angina, prior MI based on history or pathologic Q waves, compensated or prior heart failure, or diabetes), (b) a poor functional capacity (<4 METs), or (c) a high–surgical-risk procedure (aortic repair or peripheral vascular, prolonged surgical procedures with large fluid shifts or blood loss).

Abnormalities in thallium redistribution and coronary flow among patients with one or more clinical risk factors are associated with a higher incidence of perioperative cardiac events as compared to patients without clinical risk factors. Furthermore, postoperative events increased from 29% to 50% in a population of patients with thallium perfusion defects in the group of patients that were found to have three clinical risk factors as opposed to only one or two variables present. These data, again, highlight the importance of eliciting clinical markers of risk. Finally, the extent of ischemia (i.e., number of abnormal segments), as well as the severity of ischemia, correlates with perioperative cardiac events.

Which Stress Test Is Best?

For most outpatients able to exercise with a normal resting ECG requiring further preoperative risk assessment, treadmill exercise ECG testing represents a cost-effective assessment of functional capacity, if not a slightly less sensitive and specific assessment for myocardial ischemia compared with stress testing utilizing advanced nuclear or echocardiographic imaging. Low-risk patients include those able to exercise without cardiac ischemic symptoms beyond stage II of the Bruce protocol (>7 METs), or achieve a heart rate (HR) over 130 bpm, or over 85% age-predicted maximum HR.

Among patients unable to perform sufficient exercise (at least 4 to 6 METs) for reliable test interpretation or those with abnormal resting ECGs (e.g., LV hypertrophy, left bundle branch block, or digitalis effect), stress testing utilizing an imaging modality such as myocardial perfusion imaging or dobutamine echocardiography is most effective. In many locations, specific expertise and familiarity with a particular stress imaging technique determines which test is used. Either stress imaging technique may be appropriate when used selectively, provided the expertise in a specific institution is satisfactory and commensurate with published investigations. Certain characteristics of these imaging techniques should be kept in mind when deciding on the ideal choice of a test. Both imaging techniques provide high sensitivity for detecting patients at risk for perioperative events, with a commensurate high negative predictive value but suffer from low specificity with corresponding low positive predictive values. Risk for perioperative events is proportional to the amount of myocardium at risk as detected by either modality. Myocardial perfusion imaging utilizing a vasodilator such as dipyridamole, adenosine, or regadenoson should be avoided in patients with significant bronchospasm, critical carotid disease, or in patients with a condition that prevents them from being withdrawn from theophylline preparations. Dobutamine should not be used as a stressor in patients with serious arrhythmias, severe hypertension, or hypotension.

Indications for Angiography

For patients with suggested or proven CAD, coronary angiography should be considered among those with high-risk results during noninvasive testing, unstable angina, and nondiagnostic or equivocal noninvasive tests in a high-risk patient undergoing a high-risk procedure. Coronary angiography may be considered in the setting of intermediate results during noninvasive testing, a nondiagnostic or equivocal noninvasive test in a patient at lower risk undergoing a high-risk procedure, urgent noncardiac surgery in a patient recovering from an acute MI, and in the setting of perioperative MI.

GENERAL APPROACH TO SUCCESSFUL PERIOPERATIVE EVALUATION OF CARDIAC PATIENTS UNDERGOING NONCARDIAC SURGERY

The joint ACC/AHA Task Force approach to the patient undergoing elective noncardiac surgery is based on a Bayesian strategy reliant on clinical markers, including prior CAD evaluation and treatment, functional capacity, and magnitude of the proposed surgical procedure. These general guidelines may be useful in a majority of preoperative assessment. Since publication of the original guidelines in 1996, several studies and subsequent guideline revisions have demonstrated that this stepwise approach is both

efficacious and cost effective (Fig. 54.2).

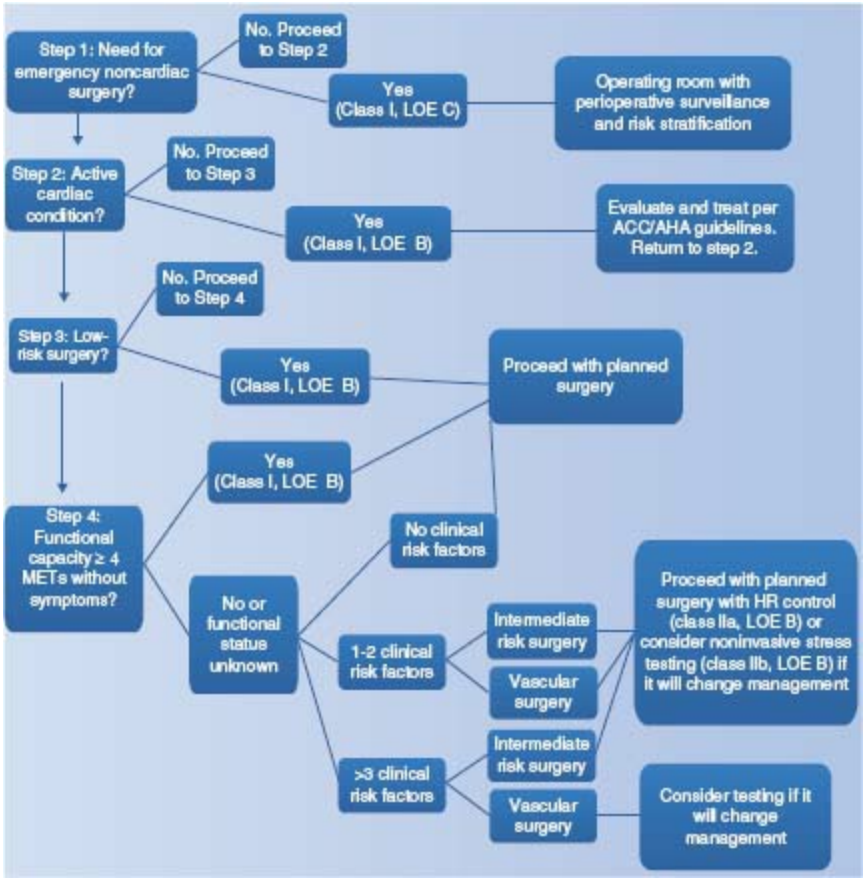

FIGURE 54.2 Algorithm of preoperative cardiac evaluation for patients over age 50 years undergoing noncardiac surgery. LOE: level of evidence; METs: metabolic equivalent of task. (Modified from Fleisher LA, Beckman JA, Brown KA, et al. 2009 ACCF/AHA Focused Update on Perioperative Beta Blockade Incorporated Into the ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery. J Am Coll Cardiol. 2009;54:e13–e118, with permission from Elsevier.)

The first step in preoperative assessment for noncardiac surgery is determining the urgency of the procedure. When encountering a patient in need of emergency surgery, time often does not allow for a preoperative evaluation. In such cases, proceeding directly to the surgical suite with careful perioperative surveillance and postoperative risk stratification is most appropriate. When the proposed surgery is determined to be elective, clinical risk stratification based on type of surgery is important (see Table 54.1).

Clinical risk factor assessment is especially critical for patients with three or more clinical risk factors if further testing will affect management. Patients with known CAD should be assessed for symptoms as well as a history of coronary revascularization within the preceding 5 years. Screening for interval development of ischemic heart disease signs or symptoms within that time frame may allow for further invasive or noninvasive testing prior to the planned operation. If the patient has one or two clinical

risk factors, often the patient can proceed with the planned surgery. If a history for interval ischemic heart disease signs or symptoms is determined to be negative, further testing is not necessary. If the patient has undergone a coronary evaluation within the previous 2 years (assuming risk was adequately assessed and findings were favorable) and is currently without symptoms, further testing is usually not necessary. The presence of one or more major clinic predictors of risk (i.e., unstable coronary disease, decompensated heart failure, symptomatic arrhythmias, and/or severe valvular heart disease) mandates more intensive preoperative evaluation and management. Cancellation or delay of surgery until these active cardiac conditions has been satisfactorily identified and treated is usually necessary to mitigate this risk.

A number of cardiovascular risk prediction models have been developed from broad screening for markers and multivariate analyses that predict preoperative cardiac mortality. The six independent risk correlates for perioperative MI of the Revised Cardiac Risk Index have been extensively studied and validated, and are among the most widely used. The presence or history of ischemic heart disease (by history or ECG), compensated or prior heart failure, cerebrovascular disease, insulin-dependent diabetes mellitus, and renal insufficiency (defined as preoperative creatinine >2 mg/dL) stratify clinical risk for perioperative coronary events. Assessment of functional capacity (see Fig. 54.1) and magnitude of surgeryspecific risk (see Table 54.1) along with clinical risk factor analysis together allows for a rational approach to identify patients most likely to benefit from noninvasive testing.

Patients without major predictors but with intermediate predictors of clinical risk, and moderate or excellent functional capacity, generally may undergo intermediaterisk surgery with little likelihood of perioperative death or MI. Conversely, further noninvasive testing is often considered for patients with poor or moderate functional capacity undergoing higher-risk surgery or patients with more than two intermediate predictors. Assessment of LV function is reasonable for patients with preoperative dyspnea of unknown origin. In addition, patients with heart failure with worsening dyspnea or change in clinical status who have not undergone noninvasive assessment of ventricular function within 12 months may also benefit from reassessment. Conversely, routine perioperative assessment of LV function is not recommended in patients without such histories.

Noncardiac surgery is generally safe for patients without major or intermediate clinical predictors and a functional capacity of more than 4 METs. Additional testing may be considered for patients without clinical markers but considered to have a poor functional capacity faced with high-risk operations, particularly those with several minor predictors of risk who are scheduled for vascular surgery. Finally, the results of noninvasive testing should be used to determine further preoperative management, including initiation of beta-blockers and pursuit of coronary revascularization if indicated.

Class I ACCF/AHA Recommendations for Perioperative Cardiac Assessment:

- Patients who have a need for emergency noncardiac surgery should proceed to the operating room and continue perioperative surveillance and postoperative risk stratification and risk factor management. (Level of Evidence: C)
- Patients with active cardiac conditions should be evaluated and treated per ACC/AHA guidelines and, if appropriate, consider proceeding to the operating room. (Level of Evidence: B)
- Patients undergoing low-risk surgery are recommended to proceed to planned surgery. (Level of Evidence: B)
- Patients with poor (< 4 METs) or unknown functional capacity and no clinical risk factors should proceed with planned surgery. (Level of Evidence: B)

MANAGEMENT OF OTHER CARDIOVASCULAR CONDITIONS

Hypertension

Severe hypertension (systolic blood pressure >180 mm Hg, diastolic blood pressure >110 mm Hg) should be controlled preoperatively when possible. While hypertension is not an independent risk factor for perioperative complications, the condition does serve as a marker for potential CAD. The decision to delay surgery because of severe hypertension needs to take into account the urgency of the noncardiac surgery. Continuation of preoperative antihypertensive treatment through the perioperative period is important.

Valvular Heart Disease

The indications for evaluation and treatment of valvular heart disease are the same as those in the nonoperative setting. Symptomatic stenotic lesions are associated with an increased risk of perioperative congestive heart failure or shock, and may require balloon valvuloplasty or valve replacement before the cardiac surgery. Symptomatic regurgitant lesions, on the other hand, are usually well tolerated perioperatively and can often be optimized with medical therapy and monitoring. This strategy assumes normal LV function, and therefore, relatively adequate cardiac reserve. These recommendations are appropriate if a delay in the noncardiac surgery is thought to have potentially dire consequences. In the case of severe valvular regurgitation and LV dysfunction in which cardiac reserve is limited, instability during noncardiac surgery is likely, and therefore, valve surgery prior to noncardiac surgery may be warranted.

Hypertrophic Obstructive Cardiomyopathy

Patients with hypertrophic obstructive cardiomyopathy generally tolerate surgery well, provided that attention is given to a few critical factors. Anesthetic-associated decrease

in peripheral vascular resistance, hypovolemia, and adrenergic stimulation may result in tachycardia and depletion of LV preload. These factors may precipitate hemodynamic deterioration and should be avoided if possible. HR control to allow for adequate ventricular filling is useful. For these reasons, perioperative beta-blockade may provide a reduced HR and negative inotropic effects that can help to avoid hemodynamic instability.

Dilated Cardiomyopathy

Patients with dilated cardiomyopathy also are at increased risk for perioperative heart failure. Management is directed at optimizing preoperative hemodynamics and providing intensive postoperative medical therapy and surveillance.

PERIOPERATIVE MEDICAL THERAPY

Although few randomized controlled trials have been performed to determine the optimal perioperative medical regimen for patients with cardiac disease undergoing noncardiac surgery, study data strongly support perioperative betablocker therapy among individuals at elevated risk for cardiovascular events. Among patients with more than one major clinical risk factor undergoing at least intermediate-risk surgery, beta-blockade reduces the frequency of postoperative ischemic events, MI, and perioperative death. A randomized trial of beta-blocker therapy versus standard treatment in a series of patients with positive dobutamine stress echocardiograms demonstrated a positive benefit to bisoprolol in reducing perioperative death and nonfatal MI. These data, as well as prior studies, support the use of beta-blocker therapy unless it is contraindicated. Beta-blocker therapy should be initiated days to weeks before the procedure and the dose titrated to a resting HR of 50 to 60 beats/min (bpm). Fixed-dose regimens of perioperative beta-blockade are to be generally avoided, as they have not been shown to be as efficacious in intermediate-risk groups. Perioperative withdrawal of beta-blockers should be avoided, because of associated risks of angina pectoris and MI. Hypotension (systolic blood pressure <100 mm Hg) and bradycardia (HR <50 bpm) associated with beta-blocker use is to be avoided, as hypotension is associated with increased perioperative morbidity and mortality.

Statin therapy and reduction of lipid levels has proven to be highly efficacious in secondary prevention of cardiac events in a number of large randomized trials. The effectiveness of statins to reduce cardiovascular events in the perioperative setting is less conclusive, although data suggest an overall protective effect against cardiac complications during noncardiac surgery. Statin therapy should be continued if already initiated. It may be reasonable to start statin therapy preoperatively for patients undergoing high-risk procedures and in those with one clinical risk factor or more undergoing intermediate-risk surgical procedures.

PERIOPERATIVE CORONARY REVASCULARIZATION

Preoperative risk stratification tools provide the greatest advantage to patients who are correctly stratified as high risk, allowing for preparation and preoperative management that may mitigate cardiac risk associated with noncardiac surgery. Those stratified to the highest-risk group often have known CAD with symptoms of ischemic heart disease, reduced LV function, or other clinical risk factors. Nevertheless, prophylactic preoperative revascularization of severe coronary stenosis may not reduce perioperative complications related to ischemia. Attempts to invasively characterize CAD and potentially perform revascularization should be reserved for a select group of patients and circumstances. In essence, only those patients who would otherwise gain a mortality benefit from coronary revascularization, regardless of whether a noncardiac surgery is planned, should undergo such attempts at preoperative coronary intervention.

Coronary revascularization before noncardiac surgery is useful for patients with stable angina and significant left main trunk stenosis or 3-vessel disease. Patients with stable angina and 2-vessel disease that includes proximal stenosis of the left anterior descending artery and either LV ejection fraction of 0.50 or demonstrable ischemia on noninvasive testing also enjoy a benefit from preoperative revascularization. Coronary revascularization should also be considered before noncardiac surgery for those with high-risk unstable angina, non–ST-segment elevation MI, or acute ST-segment elevation MI as is recommended in the general percutaneous intervention (PCI) guidelines. Routine prophylactic coronary revascularization among patients with stable CAD is not recommended.

Class I ACCF/AHA Recommendations for Preoperative Coronary Revascularization with coronary artery bypass graft (CABG) or PCI:

- Coronary revascularization before noncardiac surgery is useful in patients with stable angina who have significant left main coronary artery stenosis. (Level of Evidence: A)
- Coronary revascularization before noncardiac surgery is useful in patients with stable angina who have 3-vessel disease. (Level of Evidence: A)
- Coronary revascularization before noncardiac surgery is useful in patients with stable angina who have 2-vessel disease with significant proximal left anterior descending coronary artery stenosis and either ejection fraction <0.50 or demonstrable ischemia on noninvasive testing. (Level of Evidence: A)
- Coronary revascularization before noncardiac surgery is recommended for patients with high-risk unstable angina or non–ST-segment elevation MI. (Level of Evidence: A)
- Coronary revascularization before noncardiac surgery is recommended for patients with acute ST-segment elevation MI. (Level of Evidence: A)

When coronary revascularization before noncardiac surgery is indicated, the mode of revascularization depends on guideline consensus statements. Indications for CABG before noncardiac surgery are identical to those reviewed in the ACC/AHA 2004 Guideline Update for CABG Surgery Preoperative PCI in patients undergoing elective noncardiac surgery follows the ACC/AHA 2005 Guideline Update for PCI.

In the uncommon event that preoperative PCI with stent placement is indicated, important considerations may affect the timing of coronary intervention and the proposed operation (see Fig. 54.3). Premature discontinuation of antiplatelet therapy, including aspirin or thienopyridine, may unnecessarily increase the risk of in-stent thrombosis and subsequent acute MI. Elective noncardiac surgery is not recommended within 4 to 6 weeks of bare metal stent or within 12 months of drug-eluting stent implantation in patients in whom thienopyridine or aspirin therapy requires discontinuation perioperatively. Balloon angioplasty represents an alternative modality for coronary revascularization, although noncardiac surgery is not recommended within 4 weeks of such a procedure.

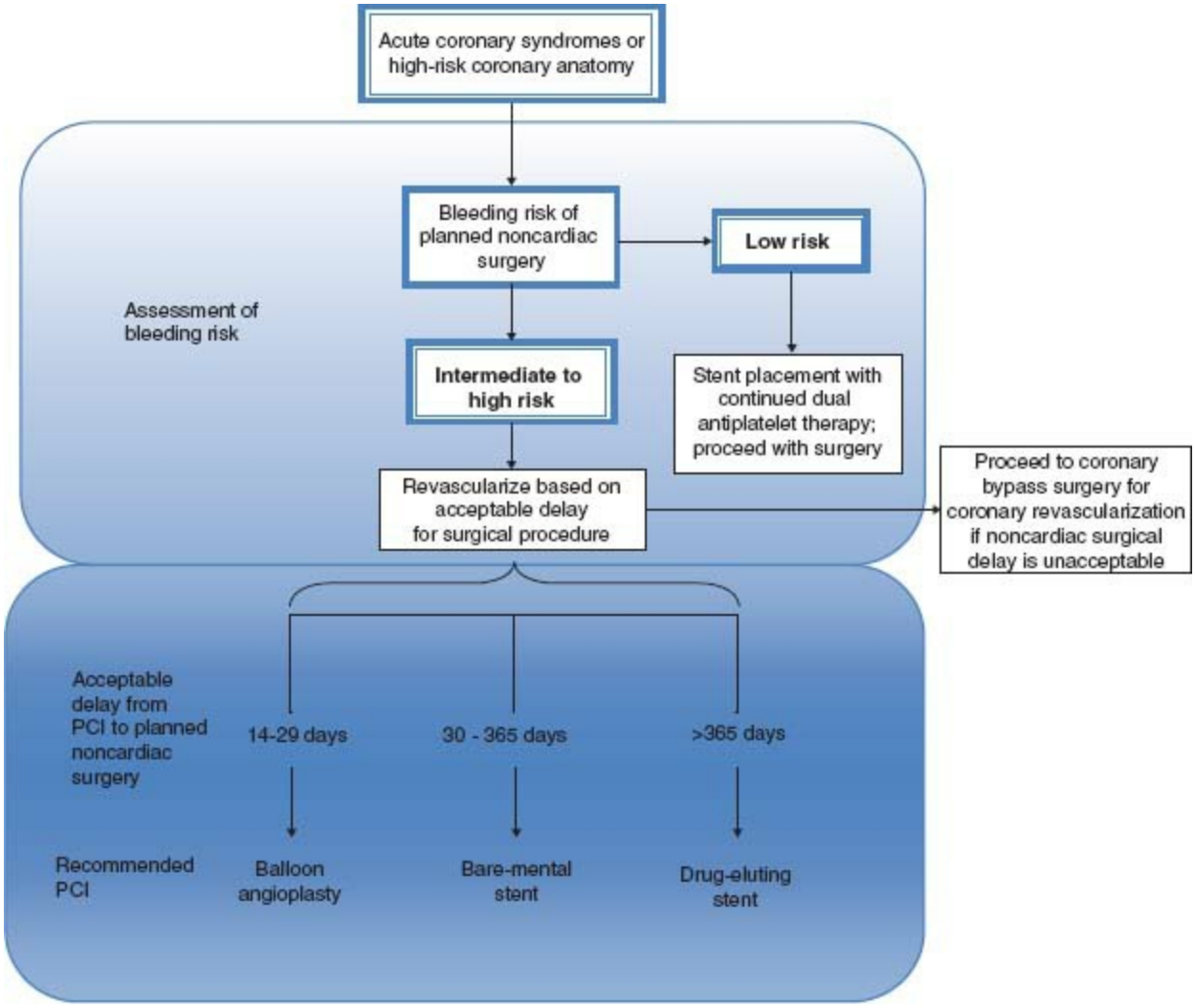

figure 54.3 Pathway for coronary arterial revascularization prior to non-elective noncardiac surgery in setting of acute

coronary syndromes or high-risk coronary anatomy. PCI: percutaneous intervention. (Modified from Fleisher LA, Beckman JA, Brown KA, et al. 2009 ACCF/AHA Focused Update on Perioperative Beta Blockade Incorporated Into the ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery. J Am Coll Cardiol. 2009;54:e13–e118, with permission from Elsevier.)

POSTOPERATIVE MYOCARDIAL INFARCTION MANAGEMENT

Perioperative MI is commonly associated with minimal symptoms, nonspecific ST- or T-wave changes, and exhibit small increases in cardiac enzyme leaks. Surveillance for perioperative MI with troponin measurement is recommended in patients with ECG changes or chest pain typical for acute coronary syndrome. Patients undergoing intermediate-risk or vascular surgical procedures who are otherwise asymptomatic may also benefit from such monitoring.

Patients with CAD, especially those with prior MI, are at risk for postoperative MI. Most commonly, perioperative MI is secondary to increased myocardial oxygen demand outstripping coronary arterial oxygen supply Whether as a case of "supply–demand mismatch" or a more traditional scenario of coronary thrombosis and acute vascular occlusion, perioperative MI engenders a high rate of cardiovascular morbidity and mortality. Coronary stent thrombosis represents a unique problem after discontinuation of aspirin or thienopyridine antiplatelet therapy that carries a fatality rate as high as 45%. Stent thrombosis may also represent an untoward consequence of PCI, which lends credence to a strategy of careful screening before performing prophylactic preoperative coronary revascularization.

AREAS OF CONTROVERSY AND FURTHER RESEARCH

The latest release of the ACC/AHA Perioperative Guidelines for Cardiovascular Evaluation and Care for Noncardiac Surgery includes a number of important studies that have clarified the importance of perioperative beta-blockade and the limited role of coronary revascularization prior to noncardiac surgery. Nevertheless, a number of important questions and topics would benefit from further research seeking to clarify remaining concerns. The following lists important topics to be addressed with further research pertaining to cardiac risk of noncardiac surgery:

1. The efficacy and cost-effectiveness of various noninvasive stress testing methods in determining risk and reducing cardiac complications
2. Establishment of optimal guidelines for selected subgroups of patients undergoing noncardiac surgery, especially among the elderly and women
3. The optimal time delay between an acute (≤7 days) or recent (8 to 30 days) for myocardial infarction among patients undergoing elective noncardiac surgery is uncertain and requires further evaluation

4. Establishing improved guidelines for patients with valvular heart disease undergoing noncardiac surgery
5. Establishment of the efficacy of surveillance and monitoring of patients for myocardial ischemia and infarction perioperatively

CONCLUSIONS

The effective preoperative cardiovascular evaluation requires careful regard to individual clinical risk factors, surgery-specific considerations, and communication to determine the appropriate timing of further cardiac testing and treatments before proceeding to noncardiac surgery. Preoperative testing should be limited to those instances in which the results of testing will impact subsequent care. The patient is best served by recommendations that lower their immediate perioperative risk while assessing the need for subsequent postoperative surveillance and risk stratification. The recently updated 2009 ACC/AHA Guidelines on Perioperative Cardiac Evaluation and Care for Noncardiac Surgery provide a rational, conservative, and systematic approach. These guidelines promote clinical risk-factor stratification while highlighting the importance of perioperative beta-blockade in selected groups and acknowledgment that neither routine noninvasive stress testing nor prophylactic coronary artery revascularization is routinely required to lower the risk for most patients undergoing a noncardiac operation.

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QUESTIONS AND ANSWERS

Questions

1. You are asked to evaluate a 55-year-old man with a history of prior myocardial infarction (MI) in preparation for an abdominal aortic aneurysm repair. A dobutamine stress echocardiogram demonstrates a single segment of basal inferior akinesis on rest and stress imaging. Your recommendation to the referring physician is:
   a. Clear the patient for surgery with beta-blocker prophylaxis.
   b. Stress single positron emission computed tomography (SPECT) thallium nuclear imaging
   c. Coronary angiography
   d. Cancellation of surgery
   e. Stent grafting, in hopes of avoiding major aortic surgery

2. A 70-year-old man with hypertension and a recently diagnosed solitary pulmonary nodule is scheduled for pulmonary wedge resection. He is otherwise healthy, active, and regularly plays 18 holes of golf. His Electrocardiogram (ECG) reveals left ventricular (LV) hypertrophy with secondary repolarization changes consistent with a strain pattern. Your recommendation is:
   a. Stress echocardiography for risk stratification
   b. Clear the patient for surgery.
   c. Coronary angiography
   d. Echocardiogram
   e. Stress SPECT thallium imaging

3. An 80-year-old woman with hypertension, coronary artery disease (CAD), and chronic heart failure recently suffered a hip fracture requiring open reduction and internal fixation. She lives with family but is known to be inactive, primarily because of arthritis. Your recommendation is:
   a. Clear the patient for the orthopedic procedure with beta-blocker initiated prior to her operation.
   b. Coronary angiography
   c. Dobutamine stress echocardiography for risk stratification
   d. Echocardiogram, and if LV function is normal, clear the patient for surgery.
   e. Exercise stress SPECT thallium

4. A 78-year-old woman with a history of chronic systolic heart failure, chronic obstructive pulmonary disease, insulin-dependent diabetes mellitus, and chronic kidney disease is scheduled for cataract surgery. She describes chronic angina after ascending over two flights of stairs that resolves with rest. Your recommendation is:
   a. Dipyridamole stress SPECT thallium imaging

b. Coronary angiography
c. Clear the patient for cataract surgery.
d. Echocardiogram, and if LV function is normal, clear the patient for surgery.
e. Exercise stress echocardiography

5. A 55-year-old male with iliofemoral peripheral arterial disease and claudication presents for preoperative evaluation with plan for infrainguinal arterial bypass surgery. Which of the following provides greatest utility for further cardiac risk stratification in this patient?
   a. Exercise ECG
   b. Diagnostic coronary angiography
   c. Dobutamine stress echocardiography
   d. Dipyridamole thallium myocardial perfusion imaging
   e. Clinical evaluation

Answers

1. Answer A: The dobutamine echocardiogram demonstrates a fixed regional wall motion abnormality involving the base of the inferior wall and base of the septum consistent with a right coronary artery territory scar. The remaining LV wall segments were contracting normally at rest with a resting ejection fraction of approximately 55%. Peak dobutamine stress images reveal an appropriate improvement in wall motion involving the left anterior descending and circumflex coronary territories with no change in the wall motion involving the inferior and basal septum. These results are consistent with right coronary artery territory scar and no evidence for ischemia. Based on this negative echocardiogram for ischemia, this patient with an intermediate clinical predictor, namely, prior MI may be considered at a relatively low perioperative risk for a cardiac event and therefore could be cleared for his procedure with beta-blocker prophylaxis.

2. Answer B: This 70-year-old man with hypertension is scheduled for an intermediate-risk surgery. He has a history of hypertension with ECG changes consistent with LV hypertrophy. Other than his age and an abnormal baseline ECG, this gentleman has no other significant clinical predictors of perioperative risk. Reportedly, he has a very good exercise capacity, which would place him in the moderate to excellent category for functional capacity based on his ability to regularly play 18 holes of golf without difficulty. Based on the absence of significant clinical predictors, as well as a good exercise capacity, this patient can be cleared for his wedge resection with a low perioperative risk of sustaining a cardiac event.

3. Answer C: Because of the one reported critical predictor, namely, the prior history of congestive heart failure, as well as a suspected poor functional capacity, this patient should undergo further risk stratification using a pharmacologic stress imaging study. Stress echocardiography can be considered a good stress imaging modality in a patient with hypertensive heart disease, as the microvascular disease associated with hypertensive heart disease may result in abnormalities in coronary flow reserve that may in turn lead to a false- positive result when using nuclear perfusion imaging.

4. Answer C: This 78-year-old woman does have > 3 clinical predictors of risk. However, she was noted to have good functional capacity and is undergoing a very lowrisk surgical procedure, so she can be cleared for the cataract surgery with a low anticipated risk for adverse events.

5. Answer E: In any patient undergoing preoperative evaluation, an assessment of clinical predictors of risk is central to initiating an appropriate workup prior to the noncardiac surgery. If this man with vascular disease were found, on clinical evaluation, to have a history of one or more intermediate or major clinical predictors of risk, or were found to be unable to exercise to a moderate level, further risk stratification with pharmacologic stress imaging would be indicated.

CHAPTER

Pregnancy and Heart Disease

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Approximately 2% of pregnancies are complicated by maternal heart disease. In North America, congenital heart disease is the most common underlying cause, with a declining incidence of rheumatic heart disease. Over recent decades, substantial advances in the care of patients with congenital heart diseases have occurred, with the majority of babies born with heart defects now surviving into their reproductive years. In most cases, the presence of heart disease does not preclude pregnancy, but careful and individualized management is essential in achieving optimal maternal and fetal outcomes. When treating this patient population, the safety of the mother should be the first priority, and drugs, investigations, and interventions should be limited to absolute necessity. Whenever possible, a thorough and informed discussion of the risks of pregnancy and potential risk-minimizing strategies should occur prior to conception. It is also recommended that the care of these patients before, during, and after pregnancy should be delivered by an experienced multidisciplinary team including obstetricians, cardiologists, anesthesiologists, pediatricians, primary care providers, and genetic counselors where appropriate. Cardiac disease may become evident for the first time during pregnancy; conversely many signs and symptoms of normal pregnancy can be suggestive of cardiac pathology.

NORMAL PHYSIOLOGIC CHANGES DURING PREGNANCY

Demands on the cardiovascular system increase steadily during pregnancy, labor, and delivery, and in the postpartum period. Remarkable maternal adaptations to pregnancy occur with major changes in hemodynamics, respiratory parameters, and glucose metabolism (Table 55.1). Because these changes peak late in the second trimester of pregnancy, hemodynamic deterioration in diseased or structurally abnormal hearts most often clinically manifests at this time.

TABLE
55.1 Normal Changes in Hemodynamic, Respiratory, and Metabolic Parameters during Pregnancy

Hemodynamic Parameter	Change During Pregnancy	Change During Labor and Delivery	Change Postpartum
Blood volume	↑↑	↑ further	↓ to baseline
Heart rate	↑	↑ further	↓ to baseline
Cardiac output	↑	↑ further	↑ initially, then ↓
Blood pressure	↓	↑	↓ to baseline
Stroke volume	↑ 1st and 2nd trimester ↓Third trimester	↑	↓ to baseline
Systemic vascular resistance (SVR)	↓	↑	↓ to baseline
Respiratory Parameter	**Change During Normal Pregnancy by 7–9 mo**		
Thoracic cage	Upward displacement of diaphragm, increase in anteroposterior and transverse diameters		
Thin layer chromatography (TLC)	↓ by 4–5%		
Functional residual capacity (FRC)	↓ by 20%		
DLCO	↔		
Minute ventilation	↑ 50%		
Tidal volume	↑ 50%		
Respiratory rate	↔		
Glucose Metabolism	**First Trimester Normal Pregnancy**	**2nd and 3rd Trimester Normal Pregnancy**	
Insulin sensitivity	Normal	↓	
Insulin secretion	↑	↑↑	
Fasting plasma glucose	↔	↓	

During normal pregnancy, plasma volume increases 40% to 50%, in part due to estrogen-mediated activation of the renin–aldosterone axis. Because red blood cell mass increases 20% to 30%, hemodilution contributes to an overall fall in hemoglobin concentration. Cardiac output rises 30% to 50% above baseline, peaking by the 20th week of gestation and remaining at a plateau until delivery. The change in cardiac output is mediated by (a) increased preload due to the rise in blood volume, (b) reduced afterload due to a fall in systemic vascular resistance (SVR), and (c) a rise in the maternal heart rate by 10 to 15 beats/min (bpm). Stroke volume begins to rise by 5 weeks' gestation and peaks by 31 weeks. In the third trimester, caval compression by the gravid uterus causes stroke volume to fall slightly. However, a compensatory rise in heart rate allows maintenance of cardiac output. The direct effect of pregnancy on cardiac contractility is controversial. Blood pressure typically falls to 10 mm Hg below baseline by the end of the second trimester, due to decreased SVR induced by hormonal changes and by the addition of low-resistance vessels in the uteroplacental bed. Redistribution of cardiac output is facilitated by uterine vasodilatation, with an increase from 100 mL/min uterine blood flow in the nonpregnant state to approximately 1,200 mL/min at term. Maternal oxygen consumption, which includes the oxygen demands of

the developing fetus, peaks at 30% above the nonpregnant level. These hemodynamic changes are better tolerated by volume overload lesions than by fixed obstructions to output.

During labor and delivery, dramatic variations in hemodynamic status add further stress to the cardiovascular system. Each uterine contraction displaces 300 to 500 mL of blood into the general circulation. In combination with elevated heart rates, cardiac output during contractions can increase up to 75% over baseline during labor, with typical values around 9 L/min. Use of epidural anesthesia slightly reduces cardiac output due to peripheral vasodilatation, and general anesthetic may lower output more substantially. Mean systemic pressure usually rises during labor with maternal pain and anxiety. Blood loss during delivery (averaging 300 to 400 mL for vaginal delivery and 500 to 800 mL for cesarean section) can further compromise hemodynamics.

During the postpartum period, cardiovascular hemodynamics is altered once again by the relief of vena caval compression. The increase in venous return augments preload and cardiac output, resulting in an increase in renal blood flow and a brisk diuresis. Cardiovascular homeostasis is largely restored to the prepregnant baseline within 3 to 4 weeks following delivery, although it is suggested that a slight augmentation of cardiac output may persist for as long as 12 months.

The hemodynamic response to exercise is altered in pregnancy In the sitting position, any given level of exertion results in a greater cardiac output than the nonpregnant state, and maximal output is attained at lower levels of activity Animal models show a decrease in uterine blood flow with exercise, and regular aerobic endurance exercise in humans during pregnancy has been shown to reduce birth weight. The long-term implications of this observation are unclear, although they are likely greater for mothers with heart disease than those without. Activity recommendations for pregnant women with heart disease should be based on the level of symptoms.

Pregnancy induces marked changes in respiratory parameters. The gravid uterus gradually limits diaphragmatic excursion, resulting in reductions in total lung capacity and functional residual capacity. These changes are countered by hormonally induced increases in airway dilatation. In addition, minute ventilation increases 45% via an increase in tidal volume.

Pregnancy is also characterized by a complex series of hormonal and metabolic changes that govern glucose regulation. Typically, a state of maternal insulin resistance develops during the second and third trimesters. Insulin resistance is a physiologic response that favors a shift in the glucose supply to the fetus. In normal women, however, insulin resistance is countered by a steady increase in basal insulin secretion and a marked increase in insulin secretion immediately after a glucose load (first phase). In contrast, women with gestational diabetes exhibit impaired pancreatic β-cell secretory function and demonstrate a blunted first-phase insulin secretion response to glucose loading. The cardiovascular consequences of gestational diabetes can include

macrosomia, shoulder dystocia, future development of maternal type 2 diabetes, and an increased risk of obesity and type 2 diabetes in the offspring.

Fatigue, dyspnea, and decreased exercise capacity are common in normal pregnancies and can mimic cardiac disease. Pregnant women usually have peripheral edema, lateral displacement of the point of maximum impulse, and a brisk and full carotid upstroke. Most pregnant women have audible physiologic systolic murmurs, created by augmented blood flow. This systolic murmur is typically located on the left sternal border, is wide-peaking, and is associated with exaggerated physiologic splitting of S_2. A physiologic third heart sound (S_3) can often be appreciated, as can a continuous venous hum or mammary soufflé. Symptoms that are unusual during normal pregnancy and may signal true cardiac pathology include chest pain, orthopnea, or paroxysmal nocturnal dyspnea. A fourth heart sound, a loud systolic murmur, a purely diastolic murmur, fixed splitting of S_2, or pulmonary edema, are not expected findings and should be promptly investigated.

ASSESSMENT OF RISK IN PATIENTS WITH PREEXISTING CARDIAC DISEASE

Planning for Optimal Maternal and Fetal Outcomes

It is advised that individuals with structural cardiac disease who have undergone surgical or catheter-based repair should not be considered "corrected," as some residual disease almost always remains and the responses to the physiology of pregnancy can be unpredictable. Whenever possible, women with known preexisting cardiac lesions should receive preconception counseling. This should include contraceptive advice, quantification of maternal and fetal risks during pregnancy, and discussion of possible long-term morbidity and mortality after pregnancy. Unfortunately, many women with preexisting heart disease do not appear to be aware of the risks of pregnancy. In one questionnaire-based study of 116 adult females with congenital heart disease, of which 55% had been pregnant at least once, 37% of respondents reported that they had never been informed that they were at increased risk for maternal cardiac complications during pregnancy. The following conditions are generally considered contraindications to pregnancy: severe pulmonary hypertension of any etiology, severe fixed obstructive cardiac lesions, heart failure New York Heart Association (NYHA) class III-IV, left ventricular ejection fraction (LVEF) <40%, prior peripartum cardiomyopathy (PPCM), dilated unstable aorta of 40 to 45 mm or above, or severe cyanosis. The cardiac disease in pregnancy (CARPREG) risk score is composed of four clinical features found to be predictive of maternal cardiac complications (Table 55.2). Each risk factor was assigned a value of one point. The maternal cardiac event rate associated with 0, 1, and >1 points was 5%, 27%, and 75%, respectively. The more

recent ZAHARA predictors were developed in a population of 1,802 congenital heart disease patients. Although such scores serve as an overall assessment of risk, prepregnancy counseling should be tailored according to specific cardiac lesions. In the following section, congenital and acquired cardiac lesions are classified as low, intermediate, or high risk (Table 55.3).

TABLE
55.2 Predictors of Maternal Risk for Cardiac Complications

Criterion	Example	Points[a]
Prior cardiac event or arrhythmia[a]	Heart failure, transient ischemic attack, stroke before present pregnancy, or symptomatic sustained tachyarrhythmia or bradyarrhythmia requiring treatment	1
NYHA Class III–IV *or* cyanosis	—	1
Valvular and outflow tract obstruction	Aortic valve area <1.5 cm^2, mitral valve area <2 cm^2, or LV outflow tract peak gradient >30 mm Hg	1
Myocardial dysfunction	LVEF <40% or restrictive cardiomyopathy or HCM	1

[a]Maternal cardiac event rate for 0, 1, and >1 point is 5%, 27% and 75%, respectively.

LVEF, left ventricular ejection fraction.

Adapted from Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation. 2001;104:515–521, with permission.

TABLE
55.3 Maternal Cardiac Lesions and Risk of Cardiac Complications during Pregnancy

Lesion	Low Risk	Intermediate Risk	High Risk
Left-to-right shunt	ASD; VSD; PDA	Large left-to-right shunt	
AS	Asymptomatic AS with low mean gradient (<50 mm Hg) and normal LV function (EF >50%)	Mild to moderate AS	Severe AS, with or without symptoms; LVEF <40%
MS	Mild/moderate MS (Mitral valve area (MVA) >1.5 cm^2, mean gradient <5 mm Hg) without severe pulmonary hypertension	Moderate/severe MS	MS with NYHA Class II–IV symptoms; LVEF <40%
AR	AR with normal LV function and NYHA Class I or II	—	AR with NYHA Class III–IV symptoms or LVEF <40%
MR	MR with normal LV function and NYHA Class I or II	—	MR with NYHA Class III–IV symptoms or LVEF <40%
Cyanotic congenital heart disease	Repaired acyanotic congenital heart disease without residual cardiac dysfunction	—	Complex cyanotic heart disease (TOF, Ebstein anomaly, TA, TGA, tricuspid atresia)
PPCM	—	—	Prior PPCM with or without persistent LV dysfunction
Marfan syndrome	—	Normal aortic root	Aortic root or valve involvement
Pulmonary hypertension	—	—	Severe pulmonary hypertension or Eisenmenger syndrome
Mechanical prosthetic valve	—	—	Requiring anticoagulation

AS, aortic stenosis; LV left ventricle; EF, ejection fraction; AR, aortic regurgitation; NYHA, New York Heart Association; MVP, mitral valve prolapse; MS, mitral stenosis; MVA, mitral valve area; PS, pulmonary stenosis; TOF, tetralogy of Fallot; TA, truncus arteriosus; TGA, transposition of the great arteries; PPCM, peripartum cardiomyopathy.

The likelihood of cardiac disease in the developing fetus is dependent upon the exact nature of the mother's condition, but overall 5% of women with cardiac disease themselves have offspring with a congenital heart condition. A fetal anomaly scan is routinely offered around 20 to 26 weeks, which screens for cardiac defects.

Vaginal delivery is optimal for most expectant mothers with heart disease. Left lateral decubital positioning helps to maintain venous return. The second stage of labor should be assisted if necessary with forceps or vacuum extraction in order to avoid a long labor. Indications for cesarean section can include obstetric indications, warfarin anticoagulation (due to the risk of neonatal intracranial hemorrhage during delivery), severe maternal pulmonary hypertension, severe fixed obstructive cardiac lesions, or an unstable aorta. At the 24th week of gestation or beyond, a life-threatening cardiac complication should prompt consideration of steroids for fetal lung maturity and emergent cesarean section delivery. Successful delivery does not resolve the maternal

risk; even in women unaffected by cardiac disease, a significant proportion of pregnancy-related deaths occur in the first week postpartum.

The 2007 American Heart Association (AHA) guidelines on prevention of infective endocarditis provided revised recommendations for the conditions and procedures with which antibiotic prophylaxis should be administered. Cardiac conditions associated with the highest risk of adverse outcomes from endocarditis are stated as prosthetic valves, previous infective endocarditis, unrepaired or incompletely repaired congenital heart disease, congenital defects repaired with prosthetic material for the first 6 months post repair, and cardiac transplant recipients who develop valvulopathy. Patients meeting these criteria are still recommended to receive prophylaxis with dental procedures; however, the guidelines state that antibiotics solely to prevent endocarditis are not recommended for genitourinary (GU) or gastrointestinal (GI) tract procedures. Vaginal delivery is not specifically mentioned within these guidelines. The 2008 American College of Cardiology (ACC)/AHA guidelines for the management of adults with congenital heart disease state that it is reasonable to consider antibiotic prophylaxis before vaginal delivery at the time of membrane rupture in the patients within this high-risk patient group. In clinical practice, physicians should discuss the recommendations and pathophysiology with expectant mothers who meet these high-risk criteria early in pregnancy, and jointly form an individualized plan regarding antibiotic prophylaxis for vaginal delivery.

Specific Congenital or Acquired Cardiac Lesions

Low-Risk Lesions

Atrial Septal Defect Ostium secundum atrial septal defect (ASD), the most common congenital cardiac lesion encountered during pregnancy, is usually well tolerated. An uncorrected ASD does carry a small increased risk of paradoxical embolism and so deep vein thrombosis (DVT) prevention should be meticulous. With advancing maternal age (especially >40 years), uncomplicated ASD may be accompanied by a higher incidence of supraventricular arrhythmias (e.g., atrial fibrillation or atrial flutter). Although it is unusual for secundum ASD to cause pulmonary hypertension during the childbearing years, the presence of pulmonary hypertension substantially increases the risk of cardiac complications during pregnancy. A secundum ASD that has been repaired prior to pregnancy is not associated with any increased risk of cardiac complications. Device or operative repair of an ASD prior to conception is preferable. It has recently been highlighted that individuals with simple secundum ASDs appear to be at elevated risk of bacterial endocarditis. Holt–Oram syndrome, a rare heart-upper limb malformation complex that includes ASD, requires additional consideration given the potential for autosomal dominant transmission of the TBX5 gene defect to offspring.

Ventricular Septal Defect Isolated ventricular septal defect (VSD) is also a low-risk lesion that is usually well tolerated during pregnancy. However, VSD accompanied by

pulmonary hypertension and/or Eisenmenger syndrome carries a high risk for cardiac complications. VSD can occur in conjunction with other congenital cardiac lesions, including ASD, patent ductus arteriosus (PDA), mitral regurgitation (MR), and transposition of the great arteries. The risk associated with a VSD that was repaired prior to the development of pulmonary hypertension is negligible.

Patent Ductus Arteriosus

The presence of a PDA during pregnancy is not associated with additional maternal risk, provided that the shunt is small to moderate and that the pulmonary artery pressures are normal. Percutaneous closure is now first-line, and it is considered reasonable to close even asymptomatic small PDAs. Following repair of more significant PDAs, women are at no additional risk for complications during pregnancy.

Mitral Valve Prolapse In isolation, mitral valve prolapse (MVP) rarely causes any difficulties during pregnancy. MVP is specifically stated as a low risk condition for endocarditis in the AHA 2007 guidelines, and is not an indication for antibiotic prophylaxis at delivery.

Mitral Regurgitation Chronic regurgitant lesions are generally well tolerated during pregnancy. In chronic MR, the physiologic reduction in systemic vascular resistance (SVR) partially compensates for the additional volume overload generated by the regurgitant valve. However, the development of new atrial fibrillation or severe hypertension can disrupt this balance and precipitate hemodynamic deterioration. In contrast, acute MR (e.g., from rupture of chordae tendineae) is not well tolerated and can produce flash pulmonary edema and/or life-threatening cardiac decompensation. The most common causes of MR are rheumatic heart disease and myxomatous degeneration. Hypertrophic cardiomyopathy (HCM) and mitral annular dilatation secondary to dilated cardiomyopathy can also result in MR.

Women with preexisting severe MR may develop heart failure symptoms during pregnancy, especially during the third trimester. In general, these symptoms can be managed medically with judicious use of diuretics and afterload-reducing agents. Nitrates, hydralazine, and dihydropyridine calcium channel-blocking agents can serve as relatively safe afterload-reducing agents in pregnant women. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) are strictly contraindicated during pregnancy. Women with severe symptomatic MR prior to pregnancy may consider operative repair prior to conception. Although repair is strongly preferred to valve replacement before pregnancy, the success of operative repair is dependent on suitable valve anatomy.

Aortic Regurgitation Like chronic MR, chronic aortic regurgitation (AR) is also generally well tolerated during pregnancy. In addition to the physiologic fall in SVR, the tachycardia of pregnancy shortens diastole and reduces the aortic regurgitant fraction. Marfan syndrome should be considered as an etiology, because of the implications regarding aortic root stability during pregnancy. AR is generally well tolerated and is usually medically managed during pregnancy with diuretics and afterload reducers. Operative repair prior to pregnancy is feasible in certain patients, especially when the valve is anatomically bicuspid. However, the long-term durability of repair may not be superior to valve replacement. During pregnancy, surgical intervention for both mitral and AR is usually performed only for refractory heart failure, which is a rare occurrence.

Pulmonary Stenosis As an isolated lesion, pulmonic stenosis is well tolerated during pregnancy. Severe, symptomatic pulmonary stenosis (PS) may be treated with percutaneous pulmonary valvuloplasty prior to conception. If necessary during pregnancy, percutaneous pulmonary valvuloplasty should be delayed until after the first trimester to avoid fetal radiation exposure during early development. PS frequently coexists with other congenital cardiac lesions that may cause cyanotic heart disease.

Moderate-Risk Lesions

Mitral Stenosis Mitral stenosis (MS) in women of childbearing age is most often rheumatic in origin. It is the most common valve disease complicating pregnancy worldwide and one of the most poorly tolerated. Symptoms occur in up to a quarter of affected patients, and usually become apparent by the 20th week. Patients with a mitral valve area <1.5 cm^2 face a substantial risk of heart failure, cardiac arrhythmia, and/or intrauterine growth retardation during pregnancy. Increased blood volume and heart rate during pregnancy lead to left atrial pressure elevation, which can result in pulmonary edema. Additional displacement of blood volume into the systemic circulation during uterine contractions makes labor particularly hazardous.

MS requires close and regular follow-up during pregnancy. Echocardiography should be performed at the end of the first and second trimesters, and monthly during the third trimester. Beta-blockers and diuretics should be used to control signs and symptoms of pulmonary congestion and to maintain the estimated pulmonary artery pressure below 50 mm Hg.

Although mild MS can often be managed with conservative medical therapy during pregnancy, patients with moderate to severe MS should consider correction prior to conception. When pregnancy has already occurred and medical therapy is insufficient to control severe symptomatic MS, intervention during pregnancy may be necessary. Percutaneous mitral balloon valvuloplasty (PMBV) is the therapeutic option of choice.

Its safety and feasibility during pregnancy have been well established. Radiation exposure to the fetus is minimized by abdominal lead shielding, use of transesophageal echocardiographic guidance, and omission of invasive hemodynamic measurements and angiography. When PMBV cannot be performed, open surgical commissurotomy is the preferred surgical correction. Although this procedure is considered safe for the mother, it carries a 2% to 12% risk of fetal mortality. Cardiopulmonary bypass during pregnancy should be performed with normothermic perfusion and high flow volumes, to reduce fetal morbidity and mortality. Women past 20 weeks' gestation should be positioned in the lateral decubitus position during surgery, to avoid uterine compression of the inferior vena cava. If possible, hyperkalemic arrest should be avoided, because of the potential for hyperkalemic solutions to reach the fetal circulation. In the current era it appears that maternal mortality with cardiopulmonary bypass is equivalent to that expected from a nonpregnant female, unless the operation is emergent.

The combination of atrial fibrillation and MS in the pregnant patient may result in a rapid rise in left atrial pressure and acute pulmonary edema. Treatment consists of heart rate control with digoxin and beta-blockers plus gentle reduction of blood volume and left atrial pressure with diuretics. Hemodynamic deterioration is an indication for electrocardioversion, which can be performed safely during pregnancy. The development of atrial fibrillation is an indication for the initiation of anticoagulation, which is discussed in greater detail in the section, "Anticoagulation during Pregnancy."

Most patients with MS can undergo vaginal delivery. However, Swan–Ganz hemodynamic monitoring during labor, delivery, and for several hours into the postpartum period is advisable in patients with symptoms of heart failure or with moderate to severe MS. In these patients, epidural anesthesia during labor and delivery is usually better tolerated than general anesthesia.

Aortic Stenosis The most common etiology of aortic stenosis (AS) in women of childbearing age is a congenitally bicuspid valve. Other, less common etiologies include rheumatic heart disease, calcific valvular disease, and a unicuspid aortic valve. Mild to moderate AS with preserved left ventricular (LV) function usually is well tolerated during pregnancy. However severe AS (aortic valve area <1.0 cm2, mean gradient >50 mm Hg) significantly increases the maternal and fetal risks of pregnancy and women with uncorrected severe AS should be counseled against conception. Classic symptoms of AS such as dyspnea, angina pectoris, or syncope usually become apparent late in the second or early third trimester.

Ideally, women with known severe AS should undergo valve correction prior to conception. Although percutaneous aortic balloon valvuloplasty (PABV) prior to pregnancy can decrease the risk of pregnancy, labor, and delivery, it has limited durability and is unlikely to relieve AS in the long term. Therefore, surgical correction

is the preferred approach.

Bioprosthetic valves have limited durability; young patients will likely require reoperation within 10 to 15 years. However, implantation of a bioprosthetic valve avoids the need for anticoagulation during pregnancy. Mechanical valves have greater durability but require anticoagulation, which independently increases both the maternal and fetal complication risk during pregnancy. The decision to implant a bioprosthetic versus mechanical valve is complex and should be made in consultation with both a cardiologist and a cardiothoracic surgeon.

Management of mild to moderate AS during pregnancy is largely conservative. When severe symptomatic AS is diagnosed during pregnancy, PABV should be performed prior to the demands of labor and delivery. Aortic insufficiency that occurs as a postprocedural complication of PABV usually is well tolerated during labor and delivery. Vaginal or assisted vaginal delivery is usually well tolerated, although spinal and epidural anesthesia are discouraged during labor and delivery because of their vasodilatory effects. Invasive hemodynamic monitoring and is recommended during labor and delivery.

Coarctation of the Aorta Coarctation of the aorta is a narrowing in the region of the ligamentum arteriosum, just distal to the origin of the left subclavian artery usually presenting with resistant hypertension in childhood. Coarctation is well tolerated during pregnancy, although hypertension, heart failure, angina, and aortic dissection are possible complications. Coarctation can be associated with intracerebral aneurysms, which may rupture during pregnancy. Hypotension in vascular beds distal to the coarctation can compromise uteroplacental blood flow, resulting in intrauterine growth retardation. Coarctation of the aorta is often associated with a congenitally bicuspid aortic valve, which increases the risk of infective endocarditis.

If at all possible, coarctation of the aorta should be corrected prior to pregnancy with standard surgical repair or balloon angioplasty with endovascular stent placement. Correction of coarctation during pregnancy is indicated in patients with severe uncontrollable hypertension, heart failure, or uterine hypoperfusion. The aortic wall adjacent to an area of coarctation has histologic features of cystic medial necrosis, which renders it vulnerable to dissection. Thus, women who underwent surgical repair of an aortic coarctation in childhood remain at risk for complications during pregnancy.

Marfan Syndrome Marfan syndrome is a connective tissue disorder resulting from mutations in the fibrillin gene that are inherited in an autosomal dominant fashion (i.e., 50% of offspring will inherit the disorder, regardless of gender). Thus, women with Marfan syndrome should receive genetic counseling well in advance of pregnancy consideration. The clinical manifestations of Marfan syndrome include skeletal

abnormalities, ectopia lentis, and cardiovascular abnormalities, such as aortic root dilatation with or without AR, aortic dissection, and MVP. However, Marfan syndrome is a heterogeneous disorder with highly variable disease penetrance.

It is estimated that pregnancy in patients with Marfan syndrome carries a 1% risk of serious cardiac complications; this risk rises with increasing aortic root dimensions. Women with Marfan syndrome are more vulnerable to aortic dissection and/or rupture during pregnancy because of the additional weakness in the aortic wall imposed by hormonal changes. Interestingly, the occurrence of dissection appears to peak at 3 to 20 days postpartum, with a hypothesis being that oxytocin stimulation during breast-feeding may activate the extracellular signal-regulated kinase (ERK) pathway, which has been recently implicated in the pathophysiology of this condition. In addition, women with Marfan syndrome may be more prone to spontaneous abortion and preterm labor.

Screening echocardiography should be performed prior to pregnancy. Enlargement of the aortic root >4.5 cm is associated with maternal mortality as high as 10%. There is some evidence that pregnancy in women with Marfan syndrome may be relatively safe up to 4.5 cm, and therefore in women with an aortic diameter of 4.0 to 4.5 cm pertinent risk factors for dissection (family history of dissection, rapid growth) should be taken into account, and body surface area factored in too. The 2011 European Society of Cardiology guidelines strongly recommend preconception elective aortic root repair above 4.5 cm and support individualization of management in the range 4.0 to 4.5 cm; the 2010 ACC/AHA guidelines on thoracic aortic disease state that it is “reasonable” to prophylactically replace the aortic root and ascending aorta when the diameter exceeds 4.0 cm. The aortic root should be monitored by serial echocardiography throughout pregnancy, with progressive dilatation warranting termination of pregnancy and/or timely aortic repair or replacement.

Medical management involves the use of beta-blockers throughout pregnancy to reduce the risk of aortic rupture, careful control of blood pressure, and consideration of general anesthesia and cesarean section at the time of delivery to maximize hemodynamic control. Women with Marfan syndrome who do not manifest any cardiac abnormalities have a low rate of complications and can usually tolerate a normal vaginal delivery. Spinal or epidural anesthesia is advised, to minimize the pain and stress of labor.

High-Risk Lesions

Eisenmenger Syndrome The Eisenmenger syndrome is a consequence of uncorrected long-standing left-to-right shunts. Over time, pulmonary artery pressures approach and can exceed systemic pressures, resulting in reversal of the shunt flow direction from right to left and cyanosis. Eisenmenger syndrome is a possible common endpoint of multiple congenital lesions, including ASD, VSD, and PDA. Maternal mortality in

women with Eisenmenger syndrome ranges from 30% to 50%, with a 50% risk of fetal loss if the mother survives. Mortality is frequently caused by complications of thromboembolic disease. Decompensation occurs most frequently during the first week after delivery. Fetal risk due to maternal hypoxemia is substantial, with a high incidence of fetal loss, premature delivery, intrauterine growth retardation, and perinatal death.

Because of the considerable risk to both the mother and the fetus, pregnancy is not advised for women with Eisenmenger syndrome. If pregnancy should occur, therapeutic abortion is recommended. Women who choose to continue with pregnancy are advised to restrict physical activity, use continuous oxygen for at least the third trimester and consider use of pulmonary vasodilating drugs such as iloprost and prostacyclin. Anticoagulation is recommended during the third trimester and for 4 weeks after delivery. The most vulnerable period for the mother is labor and delivery and the first week postpartum. Vaginal delivery, facilitated by vacuum or low forceps extraction, is the delivery method of choice. Cesarean delivery is associated with a substantially higher mortality than the vaginal route. Anesthetic management includes central venous and arterial pressure monitoring, with maintenance of adequate SVR and intravenous volume and prevention of sudden increases in pulmonary vascular resistance (PVR).

Complex Cyanotic Congenital Heart Disease More women born with cyanotic congenital heart disease are surviving to childbearing age. In general, pregnancy is not recommended for women with uncorrected lesions. A low maternal oxygen saturation (<85%) correlated with a very low rate of live-born infants (12%) in one study of pregnancy in cyanotic heart disease. The most common cyanotic congenital defect is tetralogy of Fallot, which is characterized by a VSD, pulmonic stenosis, right ventricular outflow tract obstruction, and an overriding aorta. Women with tetralogy of Fallot who have undergone successful repair during childhood may tolerate pregnancy well, provided that they have little or no residual right ventricular outflow tract gradient, no pulmonary hypertension, and preserved ventricular function. Genetic counseling and screening for the 22q11 deletion should be offered as its transmission is autosomal dominant. Ebstein anomaly, characterized by abnormal right ventricular function, apical displacement of the tricuspid valve septal leaflet, and tricuspid regurgitation, is often associated with the Wolf–Parkinson–White syndrome. Pregnancy can precipitate supraventricular arrhythmias that may be rapidly conducted over the accessory pathway. Surgical correction reduces the maternal risk of pregnancy, but does not reduce the risk of congenital anomalies in the fetus. Individuals with a single functional ventricle will usually have been palliated with a version of the Fontan procedure during childhood. Heart failure, thromboembolism, and atrial arrhythmias occur in 10% to 20% pregnant patients with this anatomy, and fetal loss is up to 50%. Experience during pregnancy in women with surgically corrected D-transposition of the great arteries, truncus arteriosus, or tricuspid atresia is limited. Women with

congenitally corrected transposition (L-transposition) and no cyanosis, heart failure, or conduction disease should tolerate pregnancy well. Preterm delivery rates in these complex conditions range from 22% to 65%, and an elevated rate of premature rupture of membranes has been associated with Fontan patients and transposition.

Cardiomyopathy Women with heart failure of any etiology and ejection fraction <40% or NYHA class III-IV symptoms should be counseled to avoid pregnancy. PPCM and its implications for subsequent pregnancies are discussed further in the following section. HCM is associated with increased maternal morbidity and mortality. Although an increase in blood volume helps to reduce intracavitary or LV outflow tract gradients, tachycardia and a reduction in SVR can exacerbate outflow tract obstruction. Avoidance of volume depletion helps to prevent hemodynamic deterioration in these patients. Vaginal delivery is usually well tolerated. Whenever possible, women should receive genetic counseling prior to conception, because the heritability of certain forms of HCM approaches 50%.

CARDIOVASCULAR DISORDERS ACQUIRED DURING OR AFTER PREGNANCY

Peripartum Cardiomyopathy

PPCM is defined as the development of idiopathic LV systolic dysfunction (demonstrated by echocardiography) in the last month of pregnancy or up to the first 5 months postpartum in women without preexisting cardiac dysfunction. The incidence of PPCM in the United States is estimated to be 1 in 3,000 to 1 in 4,000 live births; the incidence appears to be highest in Africa and Haiti (occurring in 1 in 300 pregnancies). Certain risk factors are appreciated: maternal age >30 years, obesity, multiparity, multiple fetuses, history of preeclampsia, eclampsia, or chronic hypertension, African descent, low socioeconomic status, or tocolytic therapy with beta-agonists. There does not appear to be a hereditary predisposition.

PPCM has long been regarded as a disease of unknown etiology, with possible triggers including viral infection and autoimmunity. Recent mouse model research has demonstrated a role for a 16 kDa protein derived from proteolytic cleavage of prolactin under oxidative stress. This derivative is cardiotoxic, antiangiogenic, proaptotic, and proinflammatory and is observed in higher levels in PPCM patients. Furthermore, small numbers of postpartum women with PPCM have shown favorable cardiac outcomes with bromocriptine, which inhibits prolactin secretion via dopamine receptor agonism.

Medical therapy for PPCM is similar to therapy for cardiomyopathies of other etiologies. Digoxin and diuretics may be used safely during pregnancy and while breastfeeding. Beta-blockers are generally considered safe during pregnancy, although there have been case reports of fetal bradycardia and growth retardation. ACE

inhibitors and ARBs are strictly contraindicated throughout pregnancy. ACE inhibitor fetopathy includes oligohydramnios, intrauterine growth retardation, hypocalvaria, renal dysplasia, anuria, and death. Hydralazine is an effective afterload-reducing agent, although it is currently listed as a category C agent (adequate and well-controlled studies in pregnant patients are lacking, and it should be used only when the expected benefit outweighs the potential risk to the fetus). Anticoagulation should be considered. When medical therapy is not successful, women with PPCM may ultimately require advanced mechanical support or cardiac transplantation.

The prognosis after development of PPCM is variable. Approximately 50% of women recover completely normal heart size and function, usually within 6 months of delivery. The remainder either experience stable LV dysfunction or continue to experience clinical deterioration. Mortality at 2 years appears to be around 15%. Women with PPCM who attempt a subsequent pregnancy face a high risk of complications, including deterioration of LV function, symptomatic heart failure, and death. Some experts counsel affected women against subsequent pregnancies. However the majority of maternal deaths have occurred in women whose LV function remained abnormal prior to becoming pregnant again, and LVEF at first PPCM diagnosis seems to be a major prognostic indicator. Therefore, an EF <25% at initial presentation, and/or persistence of any degree of EF reduction at the time of consultation, are considered definite contraindications to future pregnancy.

Hypertension in Pregnancy

Hypertension during pregnancy can be classified into three main categories: chronic hypertension, gestational hypertension, and preeclampsia, with or without preexisting hypertension. Hypertensive disorders can complicate 5% to 15% of pregnancies and are a major cause of maternal morbidity and mortality

Chronic, or preexisting, hypertension is defined as blood pressure ≥140/90 mm Hg present prior to pregnancy, before the 20th week of gestation, or persisting beyond the 42nd postpartum day. Drug therapy for diastolic blood pressure ≥110 mm Hg has been shown to reduce the risk of stroke and cardiovascular complications. Options for drug therapy are shown in Table 55.4.

TABLE
55.4 Drug Therapy for Mild to Moderate Chronic Hypertension in Pregnancy

Drug Class	Example	Fetal Risk	Breast-Feeding	Risk Class[a]
		First-Line Agents		
α_2-Adrenergic blockers	Methyldopa	Most commonly used Drug of choice Longest safety track record Avoid in women with prior history of depression	Safe	B oral form C intravenous
		Second-Line Agents		
Calcium channel blockers	Nifedipine	Avoid sublingual nifedipine (sudden hypotension) Good safety data	Safe	C
	Amlodipine	Has been used effectively, but safety data are lacking Calcium channel blockers have tocolytic effects	No data; avoid	C
Arteriolar vasodilators	Hydralazine	Possible associations: (a) first-trimester use and hypospadias, (b) third-trimester use and neonatal thrombocytopenia, (c) maternal and neonatal lupus-like syndrome, (d) more maternal hypotension and lower 1-min Apgar scores compared to labetalol or nifedipine (17)	Safe	C
Beta-blockers	Atenolol Metoprolol	Associated with intrauterine growth retardation and newborn bradycardia; avoid atenolol	Safe, but infants should be observed for bradycardia	D (atenolol) C (metoprolol)
α, β-Blockers	Labetalol	Associated with intrauterine growth retardation and newborn bradycardia May induce fetal lung maturation	Safe, but infants should be observed for bradycardia	C
Thiazide diuretics	Hydrochlorothiazide	Associated with neonatal hypoglycemia, thrombocytopenia, hemolytic anemia, and with maternal electrolyte disturbances	Safe, but may suppress lactation	B
		Drug Classes to Avoid		
ACE inhibitors	Captopril Lisinopril	Second- and third-trimester use causes prematurity, intrauterine growth retardation, renal tubular dysplasia and neonatal anuria, severe oligohydramnios, lung and skull hypoplasia, limb contractures, neonatal hypotension	No data	D (C first trimester)
Angiotensin-receptor blockers (ARBs)	Losartan Valsartan	No human data, but potentially associated with fetal renal and skull defects, neonatal hypotension and anuria	No data	D (losartan C first trimester)

[a]Risk Class C: Either studies in animals have revealed adverse effects on the fetus and there are no controlled studies in women, or studies in women are not available. Drug should be given only if the potential bei justifies the potential risk to the fetus. Risk Class D: There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk.

Gestational hypertension is defined as hypertension that (a) develops beyond 20 weeks gestation, (b) can be with or without proteinuria but is not associated with other features of preeclampsia, and (c) usually resolves within 42 days postpartum. This condition may portend the future development of chronic hypertension, but is otherwise associated with good maternal and fetal outcomes.

Preeclampsia occurs in 3% to 8% of pregnancies in the United States. The classic clinical triad involves gradual onset of hypertension, proteinuria (>300 mg in 24 hours), and edema. Symptoms usually begin in the third trimester and resolve with delivery. The etiology of preeclampsia is still unclear, although it has been observed that the extravillous trophoblast cells of the placenta fail to invade the myometrium normally, resulting in low spiral artery blood flow and subsequent placental hypoperfusion. Eclampsia is the rare development of grand mal seizures in a woman with preeclampsia, which has an estimated incidence of 4 to 5 cases per 10,000 live births. Preeclampsia risk appears to be elevated in patients with aortic coarctation, PS, or pulmonary atresia with VSD and transposition.

Untreated preeclampsia is a risk to both the fetus and the mother. When

preeclampsia is accompanied by risk factors, including seizures, severe hypertension, HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), placental abruption, cerebral hemorrhage, pulmonary edema, renal failure, or liver failure, the fetus must be delivered immediately. Antihypertensive agents are usually initiated after the diastolic blood pressure exceeds 105 mm Hg and the systolic pressure is >160 to 180 mm Hg. Labetalol, nifedipine, and methyldopa are first-line agents in the treatment of hypertension in pregnant women. Hypertension due to preeclampsia typically improves within a few days of delivery and should return to baseline by 12 weeks following delivery.

Coronary Artery Disease

Manifestations of coronary artery disease (CAD) rarely arise during pregnancy. However the increasing prevalence of diabetes, smoking, and obesity, and the trend toward advanced maternal age, have all contributed to recent observations of increased mortality in pregnancy attributable to acute coronary syndromes. Acute myocardial infarction (MI) is estimated to have occurred in 6.2 per 100,000 deliveries in the USA between 2000 and 2002. Pregnancy itself is an MI risk factor (risk three to four times above the nonpregnant state), with most MIs in pregnancy occurring during the third trimester in women over age 33 years who have had multiple prior pregnancies. Coronary spasm, in situ coronary thrombosis, and coronary dissection are possible etiologies (in addition to classic obstructive atherosclerosis). Acute myocardial infarction may also be the initial clinical manifestation of an underlying hypercoagulable state, such as the antiphospholipid antibody syndrome. The diagnosis and management of acute myocardial infarction in the pregnant patient should follow established guidelines.

Therapy for acute myocardial infarction must be modified in the pregnant patient. Thrombolytic agents are relatively contraindicated in pregnancy due to the increased risk of maternal hemorrhage but remain a reasonable choice in the setting of an ST elevation MI without timely percutaneous coronary intervention availability. Cardiac catheterization and percutaneous intervention must be performed with lead shielding of the patient's abdomen. Medications that are considered generally safe include low-dose aspirin, nitrates, beta-blockers, and short-term heparin. ACE-inhibitors are strictly contraindicated; conversely statins have not been firmly established as teratogens, although given the scarcity of data, avoidance in pregnancy is generally recommended. There is no established data on the safety of clopidogrel and glycoprotein IIb/IIIA inhibitors in pregnancy. In general, bare metal (rather than drug-eluting) stents should be used if required during pregnancy to lower the risk of in-stent thrombosis when clopidogrel is discontinued at the time of delivery.

Arrhythmias in Pregnancy

The most frequent rhythm disturbances during pregnancy are premature atrial and/or

ventricular complexes. They are not associated with adverse maternal or fetal outcomes and do not warrant antiarrhythmic drug therapy. Atrial fibrillation and atrial flutter are not common during pregnancy and can be treated with rate-controlling agents, such as beta-blockers or digitalis, or direct-current cardioversion, which can be performed safely during any stage of pregnancy. Anticoagulation is recommended for chronic atrial fibrillation in the setting of underlying structural heart disease. Atrioventricular nodal reentrant tachycardia (AVNRT), the most common supraventricular arrhythmia in pregnant women, can be treated with adenosine and/or beta-blockers. Direct current cardioversion is safe throughout pregnancy, and should be performed with the patient in the left lateral position for any arrhythmia compromising maternal and fetal perfusion. Catheter ablation is the strategy of choice for drug-refractory, hemodynamically significant supraventricular tachycardias and should preferably occur during the second trimester.

Ventricular tachycardia (VT) is rare during pregnancy, but when it arises it most commonly originates in the right ventricular outflow tract with a left bundle morphology and inferior axis. Other etiologies include PPCM, long QT syndrome (LQTS), thyrotoxicosis, or hyperemesis gravidarum. VT associated with structural heart disease is associated with a significant risk of death, and should be promptly treated with cardioversion or medications. Most antiarrhythmic medications used to treat ventricular tachycardia are safe during pregnancy, although amiodarone's iodine component may cause neonatal goiter.

Bradyarrhythmias are uncommon during pregnancy. Pacemaker support is recommended only if the escape rhythm has an intraventricular conduction delay, the bradyarrhythmia is symptomatic, or there is hemodynamic deterioration.

Commonly used antiarrhythmic cardiovascular drugs during pregnancy and their potential side effects are shown in Table 55.5.

TABLE
55.5 Antiarrhythmic Drugs in Pregnancy

Drug	Use	Fetal Risks	Risk Class[a]	Use During Breast-Feeding
Adenosine	SVT	None reported	C	No data
Amiodarone	SVT, VT	IUGR, prematurity, hypothyroidism	D	Significant amiodarone and iodine secretion; not recommended
Beta-blockers	AF, SVT, VT	Fetal bradycardia, hypoglycemia, IUGR	C metoprolol and carvedilol; D atenolol	Safe; observe for bradycardia
Calcium-channel blockers	AF, SVT	None reported; tocolytic effect	C verapamil and diltiazem	Safe; observe for bradycardia
Digoxin	AF, atrial flutter	Possibly low birth weight, prematurity	C but has been used in pregnancy for decades	Safe
Dofetilide	AF	Teratogenic >2 mg/kg/d in animal studies	C	No data; not recommended
Flecainide	AF, SVT, VT	Fetal death; limited data	C	Safe
Lidocaine	VT	Neonatal CNS depression	B	Safe
Procainamide	SVT, VT	None reported; limited data	C has been safely used in third trimester	Safe
Propafenone	AF, SVT, VT	Possibly embryotoxic at very high doses	C	No data; not recommended
Quinidine	SVT, VT	Neonatal thrombocytopenia, mild oxytocic effect	C	Relatively safe
Sotalol	AF, SVT, VT	Fetal bradycardia, IUGR	B (all trimesters, previously D in second and third)	Not recommended

IUGR, intrauterine growth retardation; SVT, supraventricular tachycardia; VT, ventricular tachycardia; AF, atrial fibrillation; CNS, central nervous system.

[a]Risk Class B: Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of risk in later trimesters). Risk Class C: Either studies in animals have revealed adverse effects on the fetus and there are no controlled studies in women, or studies in women are not available.

Drug should be given only if the potential benefit justifies the potential risk to the fetus. Risk Class D: There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk.

Data retrieved from Micromedex 2.0, correct as of October 1st, 2011.

Abnormal Glucose Regulation During Pregnancy

In normal pregnancy, hormonally induced insulin resistance is countered by a compensatory increase in insulin secretion. Inadequate compensation caused by dysfunction of pancreatic β cells likely contributes to the development of gestational diabetes. Women who develop gestational diabetes prior to the 24th week of pregnancy face an 80% chance of developing type 2 diabetes mellitus within 5 years. Moreover, women who develop gestational diabetes have a greater risk of hypertension, hyperlipidemia, electrocardiographic abnormalities, and overall mortality. Maternal hyperglycemia is associated with an increase in fetal and neonatal morbidity, including macrosomia, congenital malformations, fetal HCM, and neonatal hypoglycemia. Women

diagnosed with gestational diabetes require close follow-up for primary prevention of type 2 diabetes, including dietary modification, maintenance of body weight control, and regular exercise. There is some evidence that insulin-sensitizing agents may reduce the rate of conversion from gestational diabetes to type 2 diabetes.

ANTICOAGULATION DURING PREGNANCY

Several conditions require the initiation or the maintenance of anticoagulation during pregnancy, including mechanical prosthetic valves, hypercoagulable states, prior or current deep venous thrombosis, and Eisenmenger syndrome. The three most common agents considered for use during pregnancy are unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and warfarin. The Eighth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy recommended three potential strategies for anticoagulation during pregnancy (Table 55–6): (a) adjusted-dose LMWH administered twice daily throughout pregnancy, (b) adjusted-dose UFH administered subcutaneously twice daily throughout pregnancy, or (c) UFH or LMWH until the 13th week, warfarin from week 13 to just before delivery and then UFH or LMWH until after delivery. There is the additional caveat that individuals with the highest risk metallic valves (such as older valve designs in the mitral position, or patients who have already suffered a stroke) may be managed with warfarin throughout pregnancy. Nevertheless, the choice of anticoagulation regimens depends on the preferences of the patient and physician after consideration of the maternal and fetal risks associated with each drug.

TABLE
55.6 Anticoagulation Strategies during Pregnancy

Trimester 1	Trimester 2	Trimester 3	Dosing	Monitoring
Unfractionated heparin	UFH	UFH	Subcutaneous: BID with an initial dose of 17,500–20,000 U; intravenous drip	aPTT 2.0–3.0 times control 6 h postinjection; Xa level 0.35–0.70 U/mL
Low-molecular-weight heparin	LMWH	LMWH	Subcutaneous: BID	Xa level 1.0–1.2 U/mL 4 h postinjection
Wk 6–12: Unfractionated heparin/Low-molecular-weight heparin Consider warfarin if total daily dose <5 mg	Warfarin	Warfarin up to wk 35–36, then UFH/LMWH	UFH and LMWH as above; warfarin daily	UFH and LMWH as above; warfarin to goal INR 3.0 (range 2.5–3.5)

UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; BID, twice daily.

Warfarin crosses the placental barrier freely and can result in warfarin embryopathy (abnormalities of fetal bone and cartilage formation). The risk of warfarin embryopathy

has been estimated at 4% to 10%, but is minimized when the daily dose is <5 mg. Although the highest-risk period is during the first trimester (weeks 6 to 12), warfarin use during the second and third trimesters has been associated with fetal central nervous system abnormalities, such as optic atrophy, microencephaly, mental retardation, spasticity, and hypotonia. Warfarin's anticoagulant effect is more potent for the fetus than the mother; the fetus has lower levels of vitamin K-dependent clotting factors, and warfarin can cause spontaneous abortion, prematurity, still birth, neonatal intracranial hemorrhage, or a retroplacental hematoma. Note that the package insert for warfarin states pregnancy as a contraindication to use. However, given the dose-dependency of adverse events some experts, and the 2011 European Society of Cardiology (ESC) guidelines, recommend that women with a prepregnancy daily dose under 5 mg should remain on warfarin until just before delivery.

UFH does not cross the placenta and is considered safer for the fetus. However, it is less safe for the mother, being associated with maternal osteoporosis, hemorrhage, heparin induced thrombocytopenia and a high incidence of thromboembolic events with older-generation mechanical valves. UFH may be administered parenterally or subcutaneously throughout pregnancy. The appropriate subcutaneous dose of UFH is based on a 6-hour postinjection activated partial thromboplastin time (aPTT) of 2.0 to 3.0 times the control level or an anti-Xa level of 0.35 to 0.70 U/mL. UFH should be initiated in high doses (17,500 to 20,000 U subcutaneously every 12 hours). Parenteral infusions are standard of care peridelivery and should be stopped 4 hours before cesarean sections. In the event of preterm labor, spontaneous hemorrhage, or significant bleeding during delivery, UFH can be reversed with protamine sulfate.

Low-molecular-weight heparin also does not cross the placenta. It produces a more predictable anticoagulant response than UFH and is less likely to cause thrombocytopenia. Its effect on bone mineral density is unclear. LMWH can be administered subcutaneously and is dosed to achieve a 4-hour postinjection anti-Xa level of 1.0 to 1.2 U/mL (or the manufacturer's specific target range if appropriate). Although data exists to support the use of LMWH in pregnant women with deep venous thrombosis, data on the safety and efficacy of LMWH in pregnant patients with mechanical valve prostheses are controversial. In fact, one LMWH carries a warning regarding the safety of LMWH in patients with mechanical heart valves. Because of the small number of patients on which this warning was based, the true incidence of valve thrombosis in patients receiving LMWH during pregnancy is unclear. Subsequent small studies continue to demonstrate individuals with catastrophic valve thrombosis despite therapeutic anti-Xa levels, further underlining the limitations of the LMWH strategy. However, retrospective auditing of pregnancies managed with LMWH versus warfarin strategies has indeed shown better neonatal outcomes with the LMWH option.

Warfarin, UFH, and LMWH can be administered safely to nursing mothers. Furthermore, low-dose aspirin (<150 mg/day) has been found to be safe during the

second and third trimesters. In certain women with mechanical valves and high risk of thrombosis, the addition of low-dose aspirin to warfarin is advisable.

In summary, anticoagulation in the pregnant patient can be difficult because of the risk profile associated with each drug regimen. In planned pregnancies, a careful discussion about the risks and benefits of warfarin, UFH, and LMWH will help the patient and physician to choose an anticoagulation strategy. Usual practice is to stop warfarin when the pregnancy is discovered and to use UFH or LMWH at least until the 12th week.

SUGGESTED READINGS

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QUESTIONS AND ANSWERS

Questions

(Adapted from the syllabus of The Cleveland Clinic Intensive Review of Medicine, Drs. Raymond and Maroo,2005.)

1. All of the following lesions are contraindications to pregnancy except:
   a. Primary and secondary pulmonary hypertension
   b. Shunt lesions complicated by Eisenmenger syndrome (ES)
   c. Mild to moderate mitral stenosis (MS)
   d. Complex cyanotic congenital heart disease
   e. Previous peripartum cardiomyopathy (PPCM) with any residual impairment of left ventricular (LV)

function

2. A 28-year-old G3P2 Hispanic woman with known mild MS presents to your office after referral by her obstetrician. She is now 18 weeks pregnant and has noted 2 weeks of progressive dyspnea on exertion, which she states is much worse than during her last pregnancy. During physical examination you note 3 cm jugular venous distension at 45 degrees, rales halfway up the posterior lung fields, and a Grade II-III diastolic rumble murmur at the apex. An echocardiogram is consistent with moderate to severe MS. All of the following therapeutic modalities are appropriate except:
   a. Immediate admission to the hospital with plans for urgent open mitral commissurotomy
   b. Initial admission to the hospital including bedrest in the left lateral decubitus position and gentle diuresis
   c. Consider percutaneous mitral valvuloplasty if initial conservative measures sch as bedrest and diuresis do not result in complete resolution of her symptoms.
   d. The initiation of oral digoxin as prophylaxis against atrial fibrillation

3. A 29-year-old G2P1 with a mechanical mitral valve prosthesis presents with rapidly progressive dyspnea in her 28th week of gestation. She takes coumadin with an international normalizing ratio (INR) of 1.8. Her physical exam reveals a heart rate of 100 beats/min (bpm), prominent jugular venous distention, rales up the back, and a displaced apical impulse. The mechanical prosthetic sounds are blunted, in addition to a soft systolic murmur. Echocardiography revealed an 18-mm transvalvular mitral gradient (5 mm prior to pregnancy) and mechanical leaflets that were difficult to visualize. LV function was normal. All of the following are appropriate treatment options except:
   a. Cardiac catheterization to measure the mitral valve gradient and coronary angiography
   b. Emergency high-risk obstetric evaluation
   c. Thrombolytic therapy
   d. Emergency cardiovascular surgery
   e. Administration of both furosemide and heparin

4. A 36-year-old woman presents to an emergency department at the 28th week of her first pregnancy. She has noticed increasing dyspnea on exertion and ankle swelling for the past 4 weeks, and has episodes of palpitations lasting 2 to 3 minutes. These symptoms are new during pregnancy. She denies chest pains, dyspnea at rest, dizziness, or loss of consciousness. Her obstetrician has been satisfied with fetal growth and movements so far. On examination, her vital signs are 106/60, pulse 98, oxygen saturation 97% on room air. Her cardiac exam is notable for a prominent but undisplaced apical impulse, an I/VI systolic murmur at the left mid sternal border that is wide-peaking, and a third heart sound. She has 1+ lower extremity edema bilaterally. The most appropriate management would be:
   a. Transthoracic echocardiogram
   b. Recommendation for cesarean section at time of delivery due to advanced maternal age and cardiac risk factors
   c. Referral for fetal cardiac anomaly scan
   d. Ventilation–perfusion scan for pulmonary embolus
   e. None of the choices

5. The following cardiac condition is considered to have the highest maternal mortality rate associated with pregnancy:
   a. Marfan syndrome with aortic root diameter 4.6 cm
   b. Family history of PPCM in a first degree female relative
   c. Ventricular septal defect (VSD) with right-to-left shunt
   d. Severe mitral regurgitation (MR), with LV end systolic diameter 42 mm
   e. Uncorrected coarctation of the aorta

6. A 32-year-old G2P1 woman is found to have several blood pressure readings in the range of 145 to 158 systolic, 80 to 92 diastolic at 32 weeks of pregnancy. She had no known hypertension pre-existing this pregnancy, or associated her prior pregnancy. Her physician diagnoses gestational hypertension

and commences labetalol orally. Which of the following statements is true?

a. Hypertension complicates approximately 1.5% of pregnancies.
b. During pregnancy, the diastolic blood pressure is defined as the pressure at which the fourth Korotkoff sound becomes barely audible.
c. Gestational hypertension is a blood pressure ≥140/90 developing after 20 weeks of pregnancy and resolving within 42 days postpartum.
d. Preeclampsia is a multisystem disorder characterized by hypertension and new-onset proteinuria exceeding 3 g/24 hours, occurring beyond 20 weeks gestation.
e. Extremity edema is the key diagnostic feature in preeclampsia.

7. A 23-year-old G1P0 woman is referred for evaluation at 11 weeks with a history of tetralogy of Fallot (TOF) repair in childhood. A recent echocardiogram showed no residual right ventricular outflow tract gradient, and no pulmonary hypertension or right ventricular dysfunction. The following are all correct, except:

a. Tetralogy of Fallot is the most common cyanotic congenital defect after infancy.
b. Transmission of this condition can be autosomal dominant.
c. Screening for the 22q11 deletion should be offered.
d. Antibiotic prophylaxis is recommended by American Heart Association (AHA) guidelines at the time of delivery.
e. Serial echocardiograms should be performed during pregnancy for early detection of the development of pulmonary hypertension.

8. A 29-year-old woman, G2P2, presents to an emergency department with 20 minutes of severe substernal chest pain 10 days postpartum. The onset of pain occurred while carrying two bags of shopping up a flight of stairs. Her two pregnancies had been uneventful and she has never experienced chest pain previously. She has no smoking history, family history of premature coronary artery disease (CAD) or hyperlipidemia, but does report blood pressures in the region of 110-130/60-80 in the third trimester. She had an uncomplicated spontaneous vaginal delivery at term. An electrocardiogram shows 2 mm ST-segment elevations V_2 to V_5 and 1 mm depressions inferiorly.

The D-dimer is elevated at 900 ng/mL (normal range <500). The chest radiograph is unremarkable. Which of the following is the most likely diagnosis?

a. Aortic dissection
b. Acute atherosclerotic coronary plaque rupture
c. Pulmonary embolus
d. Spontaneous coronary artery dissection
e. Pericarditis

9. Which of the following is least appropriate in the management of the patient in question 8?

a. Emergent coronary angiography
b. Thrombolysis
c. Aspirin, clopidogrel, and high-dose statin
d. Drug-eluting stent placement
e. Aspirin, heparin, and beta-blocker

10. A 29-year-old woman with a severely stenotic bicuspid aortic valve consults with her cardiologist to discuss the options surrounding her upcoming aortic valve replacement surgery. She is nulliparous and hopes to become pregnant in the near future. Select the single best option from the following statements:

a. Aortic valve replacement with a bioprosthesis would be associated with a 50% likelihood of structural valve deterioration at 10 years postoperation.
b. The Ross procedure is a potential alternative to prosthetic aortic valve replacement in this individual.
c. If she receives a mechanical aortic valve and establishes a daily maintenance dose of 2.5 mg warfarin to achieve a target INR 2.0 to 3.0, continuation of warfarin from conception until the 36th

week of pregnancy would be an acceptable strategy during pregnancy.
d. If she receives a mechanical aortic valve and converts to twice-daily low-molecular-weight heparin during pregnancy, the dosage must be adjusted to therapeutic anti-Xa levels.
e. Only (a) and (b) are true statements.
f. All of the statements are true.

11. All of the following are true regarding a woman with a new diagnosis of PPCM, left ventricular ejection fraction (LVEF) of 35%, 3 weeks postpartum, except:
a. Further pregnancy is contraindicated due to the high risk of recurrence and tubal ligation should be considered.
b. There may be an etiologic role for a breakdown product of prolactin, cleaved under oxidative stress.
c. Bromocriptine, a dopamine receptor antagonist, is a new therapy that may be appropriate for this patient.
d. Initial medical management should include a diuretic and an ACE-inhibitor.
e. This patient has a 50% chance of recovering normal heart size and function within the coming 6 months.

Answers

1. Answer C: Listed in this question are four clear contraindications to pregnancy, including primary and secondary pulmonary hypertension; shunt lesions complicated by Eisenmenger syndrome (ES), because of the high pulmonary pressures and right-to-left shunting; complex cyanotic congenital heart disease; and residual poor LV function following PPCM and other cardiomyopathies. Mild to moderate MS is usually well tolerated during pregnancy and can be treated with percutaneous mitral valvuloplasty in the event the patient becomes dyspneic in the second or third trimester.

2. Answer A: Pregnancy complicated by symptomatic MS is first managed by bedrest and general diuresis as well as the initiation of digoxin for atrial fibrillation prophylaxis. Percutaneous mitral valvuloplasty should be considered if symptoms do not resolve with initial measures. Open mitral commissurotomy is seldom necessary in the modern day of valvuloplasty.

3. Answer A: This emergency situation needs to be evaluated by a cardiac surgeon and high-risk obstetrics specialist. Thrombolysis should be considered emergently unless the patient is at a facility where cardiac surgery is an option. A transesophageal echocardiogram is preferable if it can be performed safely. However, the entire history and physical scenario is consistent with thrombosis of a mechanical prosthesis. Urgent intervention is necessary to save both the mother and fetus. Mild diuresis may be helpful initially. Thrombolysis has been shown to be safe during pregnancy, without adverse effects on the mother or fetus in this emergency situation. If necessary, emergency cardiovascular surgery can be performed, but with an adverse risk primarily to the fetus. Perioperative uterine and fetal heart tone monitoring is necessary.

4. Answer E: These examination findings are all consistent with normal pregnancy. In the absence of more concerning symptoms, echocardiography is not indicated. Reasons to recommend a cesarean section can include obstetric indications, warfarin anticoagulation, severe maternal pulmonary hypertension, severe fixed obstructive cardiac lesions, or an unstable aorta. A fetal anomaly scan is routinely performed between 20 and 26 weeks and so should already have occurred. This woman does not appear to have any features that would elevate above baseline the risk of her baby having a cardiac malformation. Mild shortness of breath and minimally symptomatic palpitations are not uncommon during pregnancy. The heart rate typically rises by 10 to 15 bpm above the nonpregnant state. Although pregnancy is a procoagulant state, there is no suggestion that the woman in this scenario has symptoms or signs beyond those that are considered normal for the pregnant state.

5. Answer C: Scenario c. describes Eisenmenger syndrome due to an uncorrected VSD. Eisenmenger syndrome carries a maternal mortality rate of 30% to 50% and is therefore considered an absolute contraindication to pregnancy. An aortic root measuring above 4.5 cm carries a maternal mortality as high as 10% and should be repaired prior to conception. When discovered in pregnancy, medical management with beta-blockade, serial echocardiograms, and cesarean section delivery are all

indicated. However, per the literature the higher risk condition is answer c. PPCM is not considered to have a hereditary predisposition. Uncorrected regurgitant valvular lesions tend to be reasonably well tolerated in pregnancy and can usually be successfully managed medically. Coarctation is also usually well tolerated in pregnancy, although maternal outcomes depend on the degree of hypertension and the potential for aortic dissection.

6. Answer C: Hypertension is diagnosed in up to 15% of pregnancies, depending on the population and is responsible for about a quarter of all antenatal hospital admissions. It is the Korotkoff V sound—the silence encountered as the cuff pressure drops below the diastolic blood pressure—that should be used as the determinant of diastolic pressure in pregnant women. Preeclampsia is associated with new-onset significant proteinuria exceeding 300 mg/24 hours. Edema is no longer considered to be part of the diagnostic criteria for preeclampsia because it occurs in more than half of normal pregnancies.

7. Answer D: The 2007 AHA guidelines recommend dental infectious endocarditis prophylaxis for unrepaired or palliatively repaired patients or patients within 6 months of prosthetic material placement. No specific recommendations are made regarding antibiotics at the time of childbirth.

8. Answer D: The severe chest pain in the setting of anterior ST elevations with reciprocal depression is strongly suggestive of acute left anterior descending artery pathology. Plaque rupture is very unlikely in this patient with minimal atherosclerotic risk factors. Aortic dissection can extend into a coronary artery, but the right coronary artery is most commonly affected. The D-dimer remains elevated in the postpartum state and is not indicative of a pulmonary embolus.

9. Answer B: Thrombolysis is an appropriate first line treatment of an ST elevation MI for a patient who does not have timely access to emergent coronary angiography. Although it has added risks, it is also an acceptable management strategy for a pregnant woman with an ST-segment elevation myocardial infarction (STEMI). In this postpartum patient, it is, however, the least desirable option, as a coronary dissection is strongly suspected. Thrombolysis could lyse a thrombus in the true lumen and help to restore patency, and could also lyse a thrombus in the false lumen, so relieving compression on the true lumen. However, a thrombolysis could also precipitate increased flow into the false lumen and propagate the dissection. Clinical deterioration with thrombolysis has been reported. The management of choice is emergent coronary angiography; during pregnancy lead shielding of the patient's abdomen would be essential. Treatment of a coronary dissection is largely empiric, with aspirin and heparin usually initiated for an acute coronary syndrome before the diagnosis is revealed at angiography. Anti-ischemic therapy with a beta-blocker is usually indicated, and beyond pregnancy a statin is a reasonable addition for its anti-inflammatory properties. If an intimal tear is visualized, a stent may be placed at the entry site to promote false lumen obliteration. In the absence of an intimal tear, stenting of the entire length of the dissection may be performed. In pregnancy a bare metal stent is preferred over a drug-eluting stent due to the need to discontinue clopidogrel at the time of delivery; either type of stent may be considered postpartum.

10. Answer F: A bioprosthesis is commonly chosen when valve replacement is necessary in a young woman who intends to undergo pregnancy, but with the understanding that a redo operation will almost certainly be required due to structural deterioration of the valve. The Ross procedure may be an alternate option for avoiding the anticoagulation required with metallic valves, and involves switching the patient's native pulmonary valve into the aortic position, and replacing the pulmonary valve with a homograft. If a mechanical valve is used, continuation of warfarin anticoagulation carries the lowest risk of valve thrombosis for the pregnant mother and is the strategy favored by the 2011 European Society of Cardiology (ESC) guidelines. There is a risk of embryopathy if warfarin is continued during the first trimester, although the risk is minimal at a daily dose of <5 mg. Warfarin should be discontinued in the final days of pregnancy in favor of intravenous heparin, which can be held during labor to minimize the risk of fetal intracranial hemorrhage. If low-molecular-weight heparin (LMWH) is used, it should be dose adjusted to achieve an anti-Xa level of 1.0 to 1.2 U/mL. Adjusted LMWH twice daily throughout pregnancy is very reasonable treatment option and a choice that is supported by the American College of Chest Physicians (ACCP) 2008 guidelines. However it is recognized that a minority of pregnant women receiving LMWH have suffered catastrophic valve thrombosis despite therapeutic anti-Xa levels.

11. Answer A: It is too early to make decisions regarding future pregnancies. If the initial ejection fraction were <25%, or if the EF of 35% does not fully recover in the coming 6 months, then future pregnancies

would be contraindicated. Bromocriptine is indeed a new therapy that may be appropriate for this patient by decreasing prolactin levels, but it is a dopamine agonist. PPCM should be managed similarly to a new-onset cardiomyopathy of another etiology. Diuresis and an ACE-inhibitor (the patient is postpartum) are both appropriate.

CHAPTER

Women and Heart Disease

JoEllyn Moore Abraham and Ellen Mayer Sabik

EPIDEMIOLOGY/SCOPE OF PROBLEM

Cardiovascular disease (hypertension, cerebrovascular disease, and coronary artery disease [CAD]) is the leading cause of death for women in the United States, killing approximately 500,000 women annually. CAD is responsible for half of those deaths. This may in part be due to the lack of awareness among women: although ultimately 1 in 2.4 women will die from cardiovascular disease, compared to 1 in 30 women from breast cancer, many women consider breast cancer to be their greatest potential health problem. These attitudes are beginning to change as the National Health Lung and Blood Institute (NHLBI) in 2001 and the American Heart Association (AHA) in 2004 have undertaken national education campaigns to educate women and their physicians regarding women's risk for cardiovascular disease.

One reason that heart disease has usually been thought of as a disease that primarily affects men is that clinical manifestations typically occur in women 10 years later than in men. As a consequence, historically there has been a tendency for women to be underrepresented in national trials studying risk factors, diagnosis, and treatment for CAD, heart failure, and arrhythmias. Despite this neglect, "optimal care" for treating women with these problems has been extrapolated from predominantly male patient data. More recent studies have attempted to improve the recruitment of female patients as well as to conduct separate analyses on the specific treatment effects on women, in order to identify possible differences in outcomes based on gender.

RISK FACTORS FOR CORONARY ARTERY DISEASE

The standard risk factors for CAD include diabetes, elevated cholesterol, hypertension, smoking, and a positive family history of the disease. Although risk factors for CAD are similar in men and women, the effects of the individual risk factors as well as

interventions can differ dramatically based on gender. Thus, in order to appropriately diagnose and treat CAD in women, we need to understand the pertinent risk factors and determine the effects of modifying these factors on disease progression. Although these risk factors are common in women of all racial and ethnic groups in the United States, they are more prevalent among socioeconomically and educationally disadvantaged women. Data from 2008 for women ≥18 years old in the United States showed that more than a third had hypertension, more than a third had low-density lipoprotein (LDL) cholesterol ≥130 mg/dL, approximately a fifth were cigarette smokers, more than 60% were either overweight or obese, and more than two-thirds led a sedentary lifestyle.

Diabetes

Diabetes is the most powerful risk factor for CAD in women. Not only does diabetes increase the risk of CAD fivefold, the risk of myocardial infarction (MI) twofold as well as the risk for developing congestive heart failure or dying post-MI, but it also eliminates the 10-year gender gap in risk for CAD.

Hyperglycemia decreases estradiol-mediated nitric oxide production, thus causing endothelial dysfunction and platelet aggregation. Diabetes is also associated with abnormalities of platelet function and coagulation factors. Diabetics have elevated levels of fibrinogen, factor VII, and fibrinopeptide A, all markers of a hypercoagulable state. Also, women have increased platelet response and reactivity compared to men, which compounds the effects of hyperglycemia.

Elevated Cholesterol

While there is a strong association between total cholesterol and LDLs and CAD in men, there is only a very weak association in women and none at all in women ≥65 years of age. In older women, low HDL and elevated triglycerides are strong risk factors for CAD. Total cholesterol/high-density lipoprotein (HDL-C) ratio (which should be ≤4) is a more accurate predictor of CAD risk in women of all ages. The average HDL-C level in adult premenopausal women is 20% higher than in age-matched men. Although HDL-C declines following menopause, it still remains higher than in men.

Several secondary prevention studies have assessed the effect of treatment of lipid abnormalities in women. The CARE (Cholesterol and Recurrent Events) trial, which studied pravastatin as treatment in patients with average cholesterol levels and prior MI, found a 46% reduction in death or recurrent MI in treated patients (as compared with a 26% reduction in men). The 4S trial (Scandinavian Simvastatin Survival Study) investigated the use of simvastatin in patients with known CAD. The outcome was a 35% reduction in relative risk for coronary events in women (compared with a 34% reduction in men). The LIPID (Long Term Intervention with Pravastatin in Ischemic Disease) trial studied patients with prior MI or unstable angina who were treated with pravastatin and found a 24% decrease in CAD events.

Primary prevention studies include the AFCAPS/Tex-CAPS (Air-Force/Texas Coronary Atherosclerosis Prevention Study). Patients were men and postmenopausal women with average total cholesterol and LDL-C levels but belowaverage HDL. Long-term lipid-lowering treatment decreased the incidence of a first major acute CAD event by 46% in women and by 37% in men. There are no data to support aggressive lipid lowering in premenopausal women without CAD or family history or multiple risk factors.

Hypertension

More than 50 million people in the United States have been diagnosed with hypertension, and >60% of these individuals are women. However, there is a lower prevalence of hyper tension in women until the sixth decade at which point the prevalence in women begins to exceed that in men. Hypertension is more likely to cause a cardiovascular event in women and is a risk factor for congestive heart failure in women. Nonetheless, women are more likely than men to be aware of their diagnosis, to receive treatment, and to reach target blood pressure.

Etiology

The origin of hypertension is predominantly essential. Etiologies that are seen exclusively or disproportionately in women include hypertension associated with pregnancy or use of oral contraceptives (especially older agents with higher doses of estrogens and progestins) and renovascular hypertension, which has a female:male ratio of 8:1.

Treatment

Antihypertensive treatment recommendations are generally similar for women as compared to men except in certain situations.

- Pregnancy: Methyldopa is generally preferred and ACE-inhibitors and angiotensin receptor blockers are contraindicated.
- Elderly: Thiazide diuretics may be helpful as they have been shown to reduce hip fracture.

The following side effects have been demonstrated to be more frequent in women:

- Hyponatremia
- Hypokalemia
- ACE-inhibitor induced cough
- Peripheral edema from calcium channel blockers

- Hirsutism from minoxidil

Smoking

Cigarette smoking is the leading preventable cause of death in men and women in the United States. Women who are heavy smokers (>20 cigarettes a day) have two- to fourfold increased risk of coronary disease compared with nonsmokers. Even light smokers (1 to 4 cigarettes a day) have a two- to three-fold risk of fatal coronary heart disease (CHD) or nonfatal MI. Second-hand smoke may increase risk of CAD by 20%.

The prevalence of smoking has declined in the United States since 1965, but more men have been successful at quitting than women. There are multiple factors in women's failure to quit, including fear of weight gain and lack of confidence.

Mechanisms by Which Smoking May Increase Risk of CAD

Chronic smokers are insulin resistant, hyperinsulinemic, and dyslipidemic compared to nonsmokers. (There is a dose–response relationship between number of cigarettes smoked and plasma cholesterol, possibly due to increased lipolysis.)
Second-hand smoke may cause intimal wall damage and accelerate atherosclerotic plaque formation. In young women, the combination of smoking and use of oral contraceptives promotes thrombogenesis.

Smoking Cessation Decreases Risk

The Nurses' Health Study showed a 30% decrease in risk for CAD in 2 years following cessation of smoking. There is continued decline in risk over next 10 to 15 years, and then the risk is at the same level as that of a nonsmoker.

Most studies show a 30% to 50% decrease in risk for CAD in the first 2 years following cessation.

Obesity and Sedentary Lifestyle

Obesity is an independent risk factor for CAD in women. In the Framingham Heart Study, relative weight in women was positively and independently associated with the development of CAD as well as mortality from CAD and cardiovascular disease. In the Nurses' Health Study, women with a body mass index (BMI) of 25 to 29, had an age-adjusted relative risk for CAD of 1.8, whereas those with BMI $\geq$ 29 had a relative risk of 3.3, compared with women of ideal BMI.

Truncal obesity correlates with increased LDL-C and decreased HDL-C and also is associated with hyperinsulinemia and hypertension. Although obesity is associated with diabetes (insulin resistance), hypertension, and hypercholesterolemia, the waist/hip

ratio still correlates positively with CAD after controlling for smoking, hypertension, glucose intolerance, lipids, and BMI.

AHA 2011 GUIDELINES FOR HEART DISEASE PREVENTION IN WOMEN

The 2011 American Heart Association/American College of Cardiology (AHA/ACC) guidelines for heart disease prevention in women are evidence based and provide individual recommendations for women (see Tables 56.1 and 56.2). In general, the recommendations differ very little from those for men.

TABLE
56.1 Guidelines for Prevention of CAD in Women: Clinical Recommendations

Lifestyle Interventions

Cigarette smoking

Women should be advised not to smoke and to avoid environmental tobacco smoke. Provide counseling at each encounter, nicotine replacement, and other pharmacotherapy as indicated in conjunction with a behavioral program or formal smoking cessation program (*Class I, Level at Evidence B*).

Physical activity

Women should be advised to accumulate at least 150 min/wk of moderate exercise, 75 min/wk of vigorous exercise, or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity. Aerobic activity should be performed in episodes of at least 10 min, preferably spread throughout the week (*Class I, Level of Evidence B*).

Women should also be advised that additional cardiovascular benefits are provided by increasing moderate-intensity aerobic physical activity to 5 h 300 min/wk, 2 1/2 h/wk of vigorous-intensity physical activity, or an equivalent combination of both (*Class I, Level of Evidence B*).

Women should be advised to engage in muscle-strengthening activities that involve all major muscle groups performed on ≥2 d/wk (*Class I, Level of Evidence B*).

Women who need to lose weight or sustain weight loss should be advised to accumulate a minimum of 60–90 min of at least moderate-intensity physical activity (e.g., brisk walking) on most, and preferably all, days of the week (*Class I, Level of Evidence B*).

Cardiac rehabilitation

A comprehensive CVD risk-reduction regimen such as cardiovascular or stroke rehabilitation or a physician-guided home- or community-based exercise training program should be recommended to women with a recent acute coronary syndrome or coronary revascularization, new-onset or chronic angina, recent cerebrovascular event, peripheral arterial disease (*Class I, Level of Evidence A*), or current/prior symptoms of heart failure and an LVEF ≤35% (*Class I, Level of Evidence B*).

Dietary intake

Women should be advised to consume a diet rich in fruits and vegetables; to choose whole-grain, high-fiber foods; to consume fish, especially oily fish, at least twice a week; to limit intake of saturated fat, cholesterol, alcohol, sodium, and sugar; and avoid *trans*-fatty acids. See Appendix (*Class I, Level of Evidence B*).

Note: Pregnant women should be counseled to avoid eating fish with the potential for the highest level of mercury contamination (e.g., shark, swordfish. king mackerel, or tile fish).

Weight maintenance/reduction

Women should maintain or lose weight through an appropriate balance of physical activity, caloric intake, and formal behavioral programs when indicated to maintain or achieve an appropriate body weight (e.g., BMI <25 kg/m^2 in US women), waist size (e.g., <35 in), or other target metric of obesity. (*Class I, Level of Evidence B*).

Omega-3 fatty acids

Consumption of omega-3 fatty acids in the form of fish or in capsule farm (e.g., EPA 1,800 mg/d) may be considered in women with hypercholesterolemia and/or hypertriglyceridemia for primary and secondary prevention (*Class IIb, Level of Evidence B*).

Note: Fish oil dietary supplements may have widely variable amounts of EPA and DHA (likely the only active ingredients).

Major Risk Factor Interventions

Blood pressure: optimal level and lifestyle

An optimal blood pressure of <120/80 mm Hg should be encouraged through lifestyle approaches such as weight control, increased physical activity, alcohol moderation, sodium restriction, and increased consumption of fruits, vegetables, and low-fat dairy products (*Class I, Level of Evidence B*).

Blood pressure: pharmacotherapy

Pharmacotherapy is indicated when blood pressure is ≥140/90 mm Hg (≥130/80 mm Hg in the setting of chronic kidney disease and diabetes mellitus). Thiazide diuretics should be part of the drug regimen for most patients unless contraindicated or if there are compelling indications for other agents in specific vascular diseases. Initial treatment of high-risk women with acute coronary syndrome or MI should be with β-blockers and/or ACE inhibitors/ARBs, with addition of other drugs such as thiazides as needed to achieve goal blood pressure (*Class I, Level of Evidence A*).

Note: ACE inhibitors are contraindicated in pregnancy and ought to be used with caution in women who may become pregnant.

Lipid and lipoprotein levels: optimal levels and lifestyle

The following levels of lipids and lipoproteins in women should be encouraged through lifestyle approaches: LDL-C <100 mg/dL, HDL-C >50 mg/dL, triglycerides <150 mg/dL, and non-HDL-C (total cholesterol minus HDL) <130 mg/dL (*Class I, Level of Evidence B*).

Lipids: pharmacotherapy for LDL-C lowering, high-risk women

LDL-C–lowering drug therapy is recommended simultaneously with lifestyle therapy in women with CHD to achieve an LDL-C <100 mg/dL (*Class I, Level of Evidence A*) and is also indicated in women with other atherosclerotic CVD or diabetes mellitus or 10-y absolute risk >20% (*Class I, Level of Evidence B*).

A reduction to <70 mg/dL is reasonable in very-high-risk women (e.g., those with recent ACS or multiple poorly controlled cardiovascular risk factors) with CHD and may require an LDL-lowering drug combination (*Class IIa, Level of Evidence B*).

Lipids: pharmacotherapy for LDL-C lowering, other at-risk women

LDL-C lowering with lifestyle therapy is useful if LDL-C level is ≥130 mg/dL, there are multiple risk factors, and the 10-y absolute CHD risk is 10%–20% (*Class I, Level of Evidence B*).

LDL-C lowering is useful with lifestyle therapy if LDL-C level is ≥160 mg/dL and multiple risk factors even if 10-y absolute CHD risk is <10% (*Class I, Level of Evidence B*).

LDL-C lowering with lifestyle therapy is useful if LDL 190 mg/dL regardless of the presence or absence of other risk factors or CVD (*Class I, Level of Evidence B*).

In women >60 y of age and with an estimated CHD risk >10%, statins could be considered if hsCRP is >2 mg/dL after lifestyle modification and no acute inflammatory process is present (*Class IIb, Level of Evidence B*).

Lipids: pharmacotherapy for low HDL-C or elevated non–HDL-C

Niacin or fibrate therapy can be useful when HDL-C is low (<50 mg/dL) or non–HDL-C is elevated (>130 mg/dL) in high-risk women after LDL-C goal is reached (*Class IIb, Level of Evidence B*).

Diabetes mellitus

Lifestyle and pharmacotherapy can be useful in women with diabetes mellitus to achieve an HbA_{1c} <7% if this can be accomplished without significant hypoglycemia (*Class IIa, Level of Evidence B*).

Preventive Drug Interventions

Aspirin: high-risk women

Aspirin therapy (75–325 mg/d) should be used in women with CHD unless contraindicated (*Class I, Level of Evidence A*).

Aspirin therapy (75–325 mg/d) is reasonable in women with diabetes mellitus unless contraindicated (*Class IIa, Level of Evidence B*).

If a high-risk woman has an indication but is intolerant of aspirin therapy, clopidogrel should be substituted (*Class I, Level of Evidence B*).

Aspirin: other at-risk or healthy women

Aspirin therapy can be useful in women ≥65 y of age (81 mg daily or 100 mg every other day) if blood pressure is controlled and benefit for ischemic stroke and MI prevention is likely to outweigh risk of gastrointestinal bleeding and hemorrhagic stroke (*Class IIa, Level of Evidence B*) and may be reasonable for women <65 y of age for ischemia stroke prevention (*Class IIb, Level of Evidence B*).

Aspirin: atrial fibrillation

Aspirin 75–325 mg should be used in women with chronic or paroxysmal atrial fibrillation with a contraindication to warfarin or at low risk of stroke (<1%/y or CHADS2 score of <2) (*Class I, Level of Evidence A*).

Warfarin: atrial fibrillation

For women with chronic or paroxysmal atrial fibrillation, warfarin should be used to maintain the INR at 2.0–3.0 unless they are considered to be at low risk for stroke (<1%/y or high risk of bleeding) (*Class I, Level of Evidence A*).

Dabigatran: atrial fibrillation

Dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance 15 mL/min), or advanced liver disease (impaired baseline clotting function) (*Class I, Level of Evidence B*).

β-Blockers

β-Blockers should be used for up to 12 mo (*Class I, Level of Evidence A*) or up to 3 y (*Class I, Level of Evidence B*) in all women after MI or ACS with normal left ventricular function unless contraindicated.

Long-term β-blocker therapy should be used indefinitely for women with left ventricular failure unless contraindications are present (*Class I, Level of Evidence A*).

Long-term β-blocker therapy may be considered in other women with coronary or vascular disease and normal left ventricular function (*Class IIb, Level of Evidence C*).

ACE inhibitors/ARBs

ACE inhibitors should be used (unless contraindicated) in women after MI and in those with clinical evidence of heart failure, LVEF ≤40%, or diabetes mellitus (*Class I, Level of Evidence A*).

In women after MI and in those with clinical evidence of heart failure, an LVEF ≤40%, or diabetes mellitus who are intolerant of ACE inhibitors, ARBs should be used instead (*Class I, Level of Evidence B*).

Note: ACE inhibitors are contraindicated in pregnancy and ought to be used with caution in women who may become pregnant.

Aldosterone blockade

Use of aldosterone blockade (e.g., spironolactone) after MI is indicated in women who do not have significant hypotension, renal dysfunction, or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and β-blocker and have LVEF ≤40% with symptomatic heart failure (*Class I, Level of Evidence B*).

LVEF, left ventricular ejection fraction; BMI, body mass index; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CHD, coronary heart disease; CVD, cardiovascular disease; ACS, acute coronary syndrome; hsCRP, high-sensitivity C-reactive protein; HbA_{1c}, hemoglobin A_{1C}; MI, myocardial infarction; CHADS2, Congestive Heart Failure, Hypertension, Age, Diabetes, Prior Stroke; and INR, international normalized ratio. Reprinted from **2011 Writing Group Members, Wright RS, Anderson JL, Adams CD, et al.** 2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (Updating the 2007 Guideline): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;123:2022–2060, with permission.

TABLE
56.2 Class III Interventions (Not Useful/Effective and May Be Harmful) for CAD or MI Prevention in Women

Menopausal Therapy

Hormone therapy and selective estrogen-receptor modulators (SERMs) should not be used for the primary or secondary prevention of CVD (*Class III, Level of Evidence A*).

Antioxidant Supplements

Antioxidant vitamin supplements (e.g., vitamin E, C, and beta carotene) should not be used for the primary or secondary prevention of CVD (*Class III, Level of Evidence A*).

Folic Acid[a]

Folic acid, with or without B6 and B12 supplementation, should not be used for the primary or secondary prevention of CVD (*Class III, Level of Evidence A*).

Aspirin for MI in Women <65 y of Age

Routine use of aspirin in healthy women <65 y of age is not recommended to prevent MI (*Class III, Level of Evidence B*).

CVD indicates cardiovascular disease; MI, myocardial infarction.

[a]Folic acid supplementation should be used in the childbearing years to prevent neural tube defects.

Reprinted from **2011 Writing Group Members, Wright RS, Anderson JL, Adams CD, et al.** 2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation.

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Women are grouped into high-risk (includes risk for CHD event of ≥10% over the next 10 years, women with CHD, cerebrovascular disease, diabetes mellitus, peripheral arterial disease, chronic kidney disease, or abdominal aortic aneurysm), at-risk (includes women with systemic autoimmune collagen-vascular disease, history of preeclampsia, pregnancy-induced hypertension, or gestational diabetes along with other traditional risk factors), and ideal cardiovascular health. As compared to the 2007 guidelines, the 2011 guidelines have decreased the threshold at which women are considered to be high-risk (from risk for CHD event over the next 10 years of ≥20% to ≥10%).

HISTORICAL PERSPECTIVE: ESTROGEN THERAPY FOR PREVENTION OF CARDIOVASCULAR DISEASE

Physiologic Effects of Estrogen

Benefits

- Beneficial effects on lipid profile
- Antioxidant effects
- Reduction of serum fibrinogen
- Inhibition of neointimal hyperplasia, smooth muscle cells, and collagen biosynthesis
- Potentiation of endothelium-derived relaxing factor
- Calcium channel blocking effect
- Increases prostacyclin biosynthesis
- Decreases insulin resistance
- May cause favorable distribution of body fat

Risks

- Breast cancer: relative risk is 1.35 with >10 years of hormone-replacement therapy (HRT).
- Endometrial cancer: relative risk is 8.22 with >8 years of HRT.
- Risk of deep vein thrombosis (DVT)/pulmonary embolism (PE) is doubled with HRT.
- Risk of gall bladder disease is doubled with HRT.

Population Data

Observational studies (e.g., the Nurses' Health Study) showed a significant reduction in

MI or death among postmenopausal estrogen users.

Some randomized controlled trials of HRT for secondary prevention of cardiovascular disease have been undertaken. The HERS (Heart and Estrogen/progestin Replacement Study) was the first randomized controlled trial of HRT for prevention of CHD. It looked at estrogen and progestin versus placebo in postmenopausal women with prior MI, coro nary revascularization, or angiographic evidence of CAD. Results showed, over a mean follow-up period of 4.1 years, no difference in the rates of nonfatal MI and coronary death, and a 52% increase in cardiovascular events in the first year of HRT.

The ERA (Estrogen Replacement and Atherosclerosis) trial was the first randomized angiographic-endpoint trial to test the effect of estrogen replacement therapy (ERT) and HRT on the progression of atherosclerosis in postmenopausal women with documented CAD. Neither the HRT (estrogen and progestin) nor the ERT (estrogen only) showed any angiographic benefit on disease progression.

In a randomized controlled trial of HRT for the primary prevention of CHD, the Women's Health Initiative (WHI) studied estrogen plus progestin in >16,000 postmenopausal women aged 50 to 79 years. Primary outcomes were nonfatal MI or death from CHD. Mean follow-up was 5.2 years, but the trial was stopped early because the overall risks exceeded the benefits, with a hazard ratio for CHD of 1.24. The study's conclusions stated: "Estrogen plus progestin does NOT confer cardiac protection and may increase the risk of CHD among generally healthy postmenopausal women, especially during the first year of treatment." The separate Estrogen Only arm of the WHI was stopped because the hormone increased the risk of CVA and did not reduce the risk of CHD.

Thus, based on the randomized, placebo-controlled trials, hormone replacement therapy (estrogen and progestin or estrogen alone) is not indicated for either primary or secondary prevention of cardiovascular disease in women and may in fact increase risk.

CLINICAL PRESENTATION OF CAD IN WOMEN

The most common presentation of CAD in women is angina pectoris (typical and atypical), in contrast to men, who present most commonly with MI or sudden cardiac death. Women who present with acute coronary syndrome (ACS) are more likely to be older and to have more comorbidities than men, including hypertension, diabetes, hyperlipidemia, and congestive heart failure. Women are less likely to have had a prior MI or revascularization. In MI, both men and women present with chest pain as the most common symptom; however, women are more likely to have atypical symptoms, including shoulder, neck, and abdominal pain. Women may also present with profound fatigue or dyspnea without pain. Atypical symptoms often contribute to delay in women seeking medical attention for acute MI.

A Women and Ischemia Syndrome Evaluation (WISE) substudy demonstrated that women with chest pain and nonobstructive CAD on coronary angiogram were likely to have atherosclerosis as assessed by intravascular ultrasound and abnormal flow reserve. Additionally, it has been demonstrated that women with persistent chest pain have an increase in cardiovascular events, even when documented to have nonobstructive CAD by coronary angiogram.

CAD TREATMENT RESULTS

During hospitalization for MI, women had more complications and higher 30-day mortality rates than men, but similar rates of reinfarction. In Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) IIb, once the data were adjusted for age and baseline characteristics, however, men and women had similar mortality rates. Complications seen more commonly in women include shock, heart failure, recurrent chest pain, cardiac rupture, and stroke.

A recent meta-analysis demonstrated that gender is an independent risk factor for complications after both coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) but these differences were attenuated after adjustment for risk factors such as age, presence of diabetes and body habitus.

Thrombolytics

GUSTO I showed comparable infarct-related artery patency and significant reduction in early mortality with thrombolytic treatment in women as in men; however, unadjusted 30-day mortality for women was double that for men (13% vs. 4.8%). Multiple factors may be contributing to women's increased mortality: later presentation and diagnosis, more comorbidities and older age, as well as more bleeding complications (including intracranial hemorrhage), due in part to lack of weight-adjusted dosing. Thrombolysis in Myocardial Infarction (TIMI) II and Gruppo Italiano per lo Studio (GISSI) also showed mortality benefits for both men and women with thrombolytics, however both showed higher 6-week and 1-year mortality rates for women. Data from the National Registry of Myocardial Infarction showed that women have greater mortality with acute MI than men, even when matched for age, both with and without thrombolysis. Women were less likely to receive thrombolytics and were more likely to have major bleeding when they did. Younger women (<70 years of age) had higher mortality rates during hospitalization than age-matched men.

Primary Angioplasty for Acute Myocardial Infarction

The possibility of a referral bias has been explored. In the GUSTO IIb trial, fewer women than men underwent coronary angiography (53% vs. 59%). Women at catheterization had less severe coronary disease than men. Although previously women

with abnormal noninvasive test findings suggesting CAD were less likely to be referred for catheterization, this bias has changed so that currently men and women have comparable referral rates for angiography following abnormal nuclear stress tests. Similarly, referral rates for revascularization have been comparable between men and women based on coronary anatomy once angiography has been performed.

Similar procedural success rates have been found for men and women treated with primary angioplasty Primary percutaneous transluminal coronary angioplasty (PTCA) decreased risk of intracranial hemorrhage seen in women with thrombolytics, and improved survival. Note that women still had higher 30-day and 7-month mortality, although this is likely due to differences in baseline characteristics.

A recent meta-analysis comparing early invasive versus conservative treatment in patients presenting with unstable angina or non ST-elevation MI suggests that, unlike men and high-risk women, low-risk women (defined as myocardial necrosis biomarker negative) should be treated according to a conservative strategy. It is possible that some of this trend toward harm with early invasive therapy for low-risk women is driven by increased bleeding risk that has been seen in women with ACS.

NONINVASIVE EVALUATION OF WOMEN SUSPECTED OF HAVING CORONARY ARTERY DISEASE

The gender-specific challenges of noninvasive evaluation in women are due to the fact that women are more likely to have single-vessel disease and nonobstructive CAD than men (who have more multivessel disease or left main disease), and there is a decreased diagnostic accuracy of noninvasive testing in women, with a higher rate of false positives. Therefore it is important to determine the likelihood of disease before testing.

Data support the use of stress testing with stress electrocardiography or cardiac imaging in patients with intermediate risk for CAD, to provide the best chance of determining the presence of disease. In patients at high risk for CAD, cardiac imaging is more useful for determining prognosis and guiding therapy than determining if the disease is present. The use of testing in low-risk patients is more likely to produce a false positive and should be avoided.

Exercise electrocardiograms (ECGs) are less accurate for women than for men. Using ECG alone, sensitivity and specificity are 61% and 70% in women, compared to 72% and 77% in men. Improved accuracy can be achieved by integrating multiple other clinical parameters of the stress test, including the Duke treadmill score, heart rate recovery, and maximal exercise capacity, all of which have significant prognostic as well as diagnostic value.

Recommendations based on stress ECG include the following:

1. If the Duke treadmill score is high or high risk stress ECG indicates high risk, there

is increased likelihood of obstructive disease, and the patient should be referred for cardiac catheterization.

2. If the Duke treadmill score is intermediate, further risk stratification using cardiac imaging is recommended.
3. If pretest probability is low and the Duke treadmill score is also low, no further evaluation for CAD is usually necessary. Exercise ECG in women has a high negative predictive value in women with low pretest probability.
4. Lower work capacity on exercise tests (average 5 to 7 minutes) challenges the ability of the test to provoke ischemia. Therefore, patients who are expected to perform <5 metabolic equivalents (METs) at exercise are better evaluated using pharmacologic stress imaging.
5. Women who exercise at <5 METs are at increased risk of death.

Stress echocardiography can indicate not only the presence or absence of ischemia but may also provide information on overall systolic and diastolic function, valvular structure and function, and the extent of infarct or stress-induced ischemia. Meta-analysis of stress echo studies in women found that mean sensitivity and specificity are 81% and 86%, respectively. Stress echo testing is gender neutral; there is no gender effect on diagnostic accuracy. Echo data provide incremental value over the exercise ECG and clinical variables, and may be the most cost-effective tool to diagnose CAD in women with intermediate pretest likelihood of disease. The use of dobutamine echo for patients who are unable to exercise is recommended.

Radionuclide imaging, myocardial perfusion and ventricular function imaging, have special features in women. Single photon emission computed tomography (SPECT) imaging parameters include perfusion defects, global and regional left ventricular (LV) function, and LV volumes. In women, however, a generally smaller LV cavity decreases the accuracy of the test. Breast attenuation can be improved by using a higher count isotope (technetium-99 m: ^{99m}Tc) with less attenuation, allowing gating that improves accuracy. In addition, performing studies on a combination SPECT/computed tomography (CT) scanner allows attenuation correction to be performed. This correction can also be useful when imaging obese women.

Vasodilator pharmacologic stress SPECT can be used for patients who are unable to exercise adequately. Because women with suspected CAD are typically older and have diminished exercise capacity, pharmacologic stress SPECT is useful. Vasodilator stress perfusion imaging is more accurate than exercise stress and is the test of choice in men and women with left bundle branch block.

SPECT imaging provides incremental prognostic value to clinical and exercise variables. The annual cardiac event rate for a person with a normal SPECT is <1%. The prognosis worsens as the number of vascular territories with provocable ischemia increases. Rather than a dichotomous result of positive or negative, evaluation of extent

and severity of perfusion defects allows gradation of risk.

Emerging Technologies for the Evaluation of Women with Suspected Coronary Artery Disease

Limited data are now appearing on the use of CT and magnetic resonance imaging (MRI) as well as carotid intimamedia thickness (IMT—combined thickness of intima and medial layer of the carotid) in the diagnosis of CAD in women. These techniques appear promising; however, further studies, which are currently ongoing, are required to determine their differential role in diagnosis and riskassess ment in women.

- Cardiac CT: Appears to be equally useful in men and women although there are no specific studies evaluating this question.
- Coronary artery calcium: There is evidence that coronary artery calcium screening is equally accurate in men and women.
- Cardiac MRI: Appears to be equally useful in men and women although there are no specific studies evaluating this question.
- Carotid IMT: Carotid IMT is predictive of CAD and it appears to be both a more sensitive and specific risk marker for women as compared to men.

As with all tests involving radiation exposure, patients should be informed of the risks associated with radiation exposure as well as the increasing risk with increasing cumulative dose of radiation from multiple modalities of diagnostic tests.

WOMEN AND DEVICE THERAPY

Recent studies have demonstrated that implantable cardioverter defibrillators (ICDs) are less likely to be offered to women than men. The reasons for this discrepancy are not clear. According to the National Cardiovascular Data Registry, overutilization in men does not explain this gap. Also, women appear to have more in-hospital adverse events related to ICD implantation. Nonetheless, although females comprised only one-quarter of the subject pool, data from the MADIT-CRT trial suggest that female subjects benefit more from CRT as compared to male subjects.

At least two studies found that women received fewer dual-chamber (as opposed to single-chamber) pacemakers with a trend toward increased complications in women.

WOMEN AND HEART FAILURE

Risk factors for heart failure differ by gender. Hypertension and diabetes mellitus are major risk factors in women (with diabetes in younger women markedly increasing the risk of congestive heart failure), while CAD is a more important risk factor in men.

Note, however, that women, especially diabetic women, have a greater risk of developing heart failure post-MI than men. There are also gender-specific causes of heart failure, such as peripartum cardiomyopathy and X-linked cardiomyopathy.

Structural responses to loading differ by gender; women, for example, are more likely to develop concentric LV hypertrophy and less likely to have cardiac dilation.

Heart failure is more prevalent in men as compared to women across all age groups and has almost twice the prevalence in men between ages 60 and 79 (9.1% vs. 4.9%)—although this gap narrows in octogenarians and older (14.7% men vs. 12.8% women). However, it is estimated that of the women with heart failure, approximately 57% will have a preserved ejection fraction.

Survival

There are discrepancies in the literature as to whether women have a better prognosis with heart failure than men. A problem is that many studies lump different etiologies of heart failure as well as systolic and diastolic heart failure (i.e., patients with impaired systolic function lumped with those with preserved left ventricular ejection fraction, LVEF). In the Framingham Heart Study (controlled for age and etiol ogy of heart failure), National Health and Nutrition Examination Survey (NHANES) I, Cardiac Insufficiency Bisoprolol Study II (CIBIS-II), Inception cohort, and the Malmo Prevention project, women had better survival than men with congestive heart failure. These were epidemiologic studies and did not stratify by LV function. The SOLVD (Studies of Left Ventricular Dysfunction) and Cleveland Clinic cohort data showed no differences in overall survival based on gender. The patients in both of these cohorts had reduced LVEF as enrollment criteria.

Treatment

The large therapeutic trials suffer from the problem of limited numbers of women enrolled as subjects. Attempts to pool data, such as Gali et al.'s examination of the use of ACE inhibitors for patients with decreased LVEF, found no reduction of mortality or combined endpoint of all-cause mortality and heart failure hospitalizations in women. Metoprolol Controlled Release/Extended Release Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF) looked at benefits from the addition of beta-blockers to heart failure regimens, but only 23% of the patients studied were women. A subgroup analysis did not show a mortality benefit for women. It is possible that the study was underpowered to detect benefit.

Thus, the standard treatment for women with heart failure with depressed LVEF (including ACE inhibitors, beta-blockers, spironolactone, and possibly digitalis) is based on overall population benefits shown in studies that predominantly enrolled men. Morbidity and mortality benefits have not been specifically proven for women, and further study is needed. Heart failure in women with preserved systolic function is a

different entity seen mostly in older women, often women with hypertension. Only small numbers of clinical trials have addressed treatment of these patients, and thus there are no conclusive data to guide therapy. Nonetheless, at least two studies have demonstrated that women are less well managed according to recommended guidelines than men. The 2009 ACC/AHA guidelines for this patient population recommend using standard guideline-driven care for heart failure for women as well as their inclusion in ongoing clinical trials. Further study is required to optimize treatment of this patient population to improve their quality of life.

SUGGESTED READINGS

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QUESTIONS AND ANSWERS

Questions

1. All of the following are true regarding women with a myocardial infarction (MI) except:
   a. Women are more likely to have complications such as ventricular septal defect (VSD), heart failure, cardiac rupture, and shock than men.
   b. Women are more likely than men to have had a prior MI.
   c. Women have unadjusted 30-day and 1-year mortality rates post-MI that are higher than those for

men.
   d. Primary percutaneous transluminal coronary angioplasty (PTCA) decreased the risk of intracranial hemorrhage that is seen with thrombolytics.

2. Women with hypertension are:
   a. Less likely than men to be aware of their diagnosis
   b. More likely than men to reach their target blood pressure
   c. Less likely than men to have a cerebral vascular accident (CVA) than men with hypertension
   d. Less likely than men to have renovascular hypertension

3. All of the following are true regarding diabetes as a cardiac risk factor in women except:
   a. Eliminates the 10-year gender gap
   b. Increases the risk of coronary artery disease (CAD) fivefold over women without diabetes
   c. Increases the risk for developing congestive heart failure post-MI
   d. Increases the risk of MI 10-fold over women without diabetes

4. All of the following are true regarding the use of hormone replacement therapy for prevention of CAD except:
   a. Estrogen therapy increases the risk of breast and endometrial cancer.
   b. Hormone replacement therapy is useful for secondary prevention of CAD in women.
   c. The HERS trial showed no difference in nonfatal MI or coronary death in postmenopausal women with prior MI or revascularization or angiographic CAD who had hormone replacement therapy.
   d. Hormone replacement therapy may increase risk of CAD in healthy postmenopausal women.

5. The use of thrombolytics in women who present with an MI:
   a. Is associated with comparable infarct-related artery patency as seen in men
   b. Is associated with fewer bleeding complications than are seen in men
   c. Did not show mortality benefit as seen in men
   d. Is contraindicated in menstruating women or women of reproductive age

6. The following statements are true except:
   a. Women with chest pain are at an increased risk of cardiovascular events even if documented not to have obstructive CAD.
   b. Women are more likely than men to have atypical symptoms of acute coronary syndrome (ACS).
   c. Women are more likely to have systolic, as compared to diastolic, dysfunction.
   d. In low-risk women, routine use of aspirin is not recommended for primary prevention.

7. Which of the following is more likely in men than in women following antihypertensive therapy?
   a. Hyponatremia
   b. Hypokalemia
   c. ACE-inhibitor induced cough
   d. Peripheral edema from calcium channel blockers
   e. None of the above

8. Which of the following is true about the use of pacemakers and implantable defibrillators in women?
   a. Women are more likely to receive an advanced pacemaker device such as a dual chamber pacemaker than men.
   b. Women are less likely to have a therapeutic response to biventricular pacemaker insertion than men.
   c. Women are more likely to have complications following device insertion than men.
   d. Women are more likely to be offered an implantable defibrillator than men.

9. Risk factors for CAD in older (>65 years) women are all of the following except:
   a. High low-density lipoprotein (LDL)
   b. Low high-density lipoprotein (HDL)
   c. High triglycerides

d. Morbid obesity
e. Total cholesterol/HDL ratio > 4

10. Which of the following is true about stress testing in women?
    a. False positive stress electrocardiography is less common than in men.
    b. False positive stress echocardiography is more common in women than in men.
    c. Women who exercise for <5 METS have little implication for adverse outcomes.
    d. Women are less likely to have multivessel or left main disease than men and this in part explains the greater diagnostic challenge in noninvasive assessment of CAD in women.

Answers

1. Answer B: Women who present with an MI are less likely to have had a prior MI, and are more likely to have mechanical complications including VSD, congestive heart failure, cardiac rupture, and shock. Women also have higher 30-day and 1-year unadjusted mortality rates compared to men who present with an MI. Primary PTCA has decreased the risk of intracranial hemorrhage that is seen with thrombolytics.

2. Answer B: Women with hypertension are more likely than men to be aware of their diagnosis, to have appropriate treatment, and to reach their target blood pressure. Women with hypertension are more likely to have a stroke than men with hypertension. Women have renovascular hypertension much more commonly than men (ratio 8:1).

3. Answer D: Diabetes increases a woman's risk of CAD fivefold and of MI twofold, not 10-fold, over nondiabetics. The other statements are all true.

4. Answer B: Hormone replacement therapy has no role in either primary or secondary prevention of CAD. It may, in fact, increase the risk of CAD in healthy postmenopausal women. HRT has certain noncardiac risks associated with it, including increased risk of breast cancer, endometrial cancer, and gallbladder disease, as well as increased risk of DVT and pulmonary embolism.

5. Answer A: The use of thrombolytics in women produces equivalent rates of infarct-related artery as when used in men, as well as mortality benefit. More bleeding complications were seen in women, but this is likely related to the uniform dosing (i.e., not weight adjusted) that was used in the early studies. These bleeding complications included intracranial hemorrhages as well as groin bleeds at the site of catheterization.

6. Answer C: Approximately 57% of women with heart failure have preserved ejection fraction.

7. Answer E: None of the above. All of the others are more common in women than in men.

8. Answer C: Women are more likely to respond positively to biventricular pacemaker insertion than men. They are less likely to be offered advanced pacemaker options and ICDs than men and are at higher risk of post device complications than men.

9. Answer A: While there is a strong association between total cholesterol and LDL and CAD in men, there is only a very weak association in women and none at all in women ≥ 65 years of age. In older women, low HDL and elevated triglycerides are strong risk factors for CAD. Total cholesterol/high-density lipoprotein (HDL-C) ratio (which should be ≤4) is a more accurate predictor of CAD risk in women of all ages. Obesity is an independent risk factor for CAD in women. In the Nurses' Health Study, women with a body mass index (BMI) of 25 to 29, had an age-adjusted relative risk for CAD of 1.8, whereas those with BMI ≥ 29 had a relative risk of 3.3, compared with women of ideal BMI.

10. Answer D: The gender-specific challenges of noninvasive evaluation in women are due to the fact that women are more likely to have single-vessel disease and nonobstructive CAD than men (who have more multivessel disease or left main disease), and there is a decreased diagnostic accuracy of noninvasive testing in women, with a higher rate of false positives. Exercise ECGs are less accurate for women than for men. Using ECG alone, sensitivity and specificity are 61% and 70% in women, compared to 72% and 77% in men. Women who exercise at <5 METs are at increased risk of death. Stress echo testing is gender neutral; there is no gender effect on diagnostic accuracy.

CHAPTER

Pericardial Diseases

Evan Lau and Allan L. Klein

INTRODUCTION

Pericardial disease is a small but important subset of cardiovascular illness. Clinical trial data and published society guidelines[1] are sparse; board questions should focus on the most basic aspects of these diseases. We review the three most common presentations that are encountered by the cardiologist: acute pericarditis, pericardial effusions, and constrictive pericarditis.

Acute Pericarditis

Presentation and Diagnosis

Acute pericarditis is a common chest pain syndrome, occurring in up to 5% of cases presenting with non-myocardial infarction chest pain to an emergency setting.[2] The diagnosis of acute pericarditis is made by a constellation of clinical symptoms, presence of a pericardial friction rub, characteristic ECG changes, and the presence of a pericardial effusion (Table 57.1). Elevation of inflammatory biomarkers serves as a supportive criterion for the diagnosis. Reasonable diagnostic certainty of acute pericarditis is present if findings in two of these four categories support the diagnosis. In practice, the transience of a pericardial friction rub makes it an unreliable marker of disease and significant weight is put on the rise of inflammatory markers during periods of symptom activity. The classic symptoms of acute pericarditis include the presence of sharp, pleuritic chest pain that is exacerbated by recumbency and improved by leaning forward. The pain often times radiates to one or both trapezius muscles. A pericardial friction rub is pathognomonic for pericarditis, but its inconsistency and transience make it less reliable as a diagnostic criterion. The electrocardiogram demonstrates a characteristic progression over time, with diffuse ST elevation and PR depression (representing epicardial injury of the ventricles and atria, respectively) early on (Fig.

57.1), followed by symmetric T-wave inversions, which eventually progress to normalization of the ST/T-wave segments. Serologic testing demonstrates elevation in the erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP). Finally, echocardiographic demonstration of a pericardial effusion supports the presence of pericardial inflammation. The use of delayed enhancement imaging with gadolinium by cardiac magnetic resonance imaging is emerging as another imaging tool to demonstrate pericardial inflammation (Fig. 57.2).[3]

TABLE

57.1 Diagnostic Criteria for Acute Pericarditis[a]

- Typical chest pain
- Pericardial friction rub
- Classic ECG changes (diffuse ST elevations, PR depression)
- Pericardial effusion (by echocardiography, CT, or cardiac MRI)

[a]Rise in inflammatory markers, including ESR and CRP are supportive of the diagnosis. Two out of four major criteria are required for reasonable diagnostic certainty.

Adapted from Imazio M, et al. Controversial issues in the management of pericardial disease. Circulation. 2010;121:916–928.

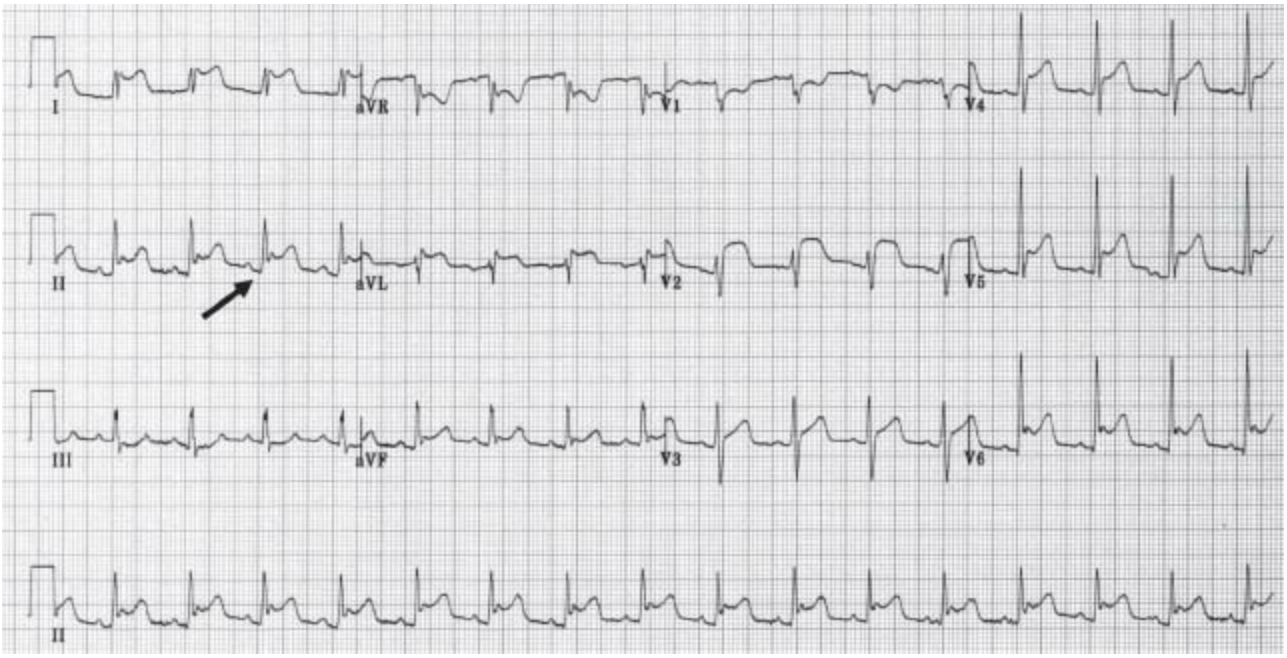

FIGURE 57.1 Classic ECG changes consistent with earliest stage of acute pericarditis. Diffuse ST-segment elevation with ST depression in aVR. Diffuse PR depression (blackarrow) with PR elevation in aVR.

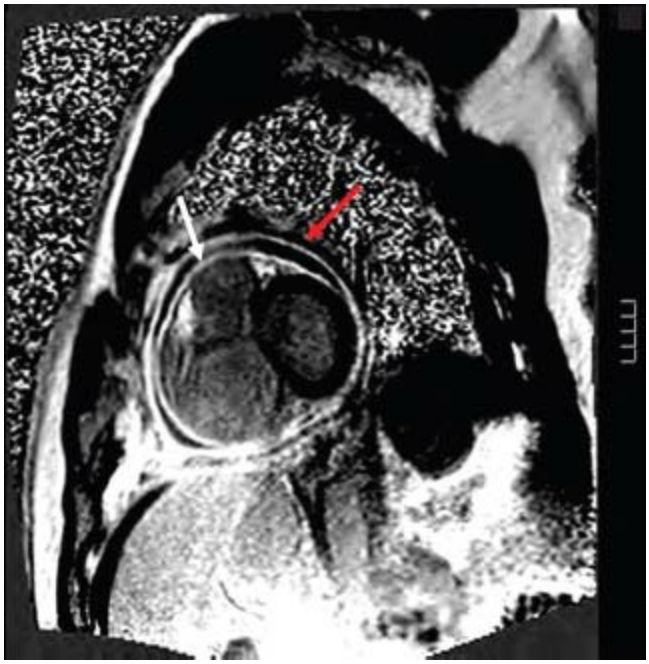

FIGURE 57.2 Cardiac MRI. Delayed imaging following administration of gadolinium, short axis view. There is uptake of contrast in both the visceral (white arrow) and parietal layers (red arrow) of the pericardium, suggesting active inflammation of the pericardium.

Etiology

There is a long differential diagnosis for the etiology of acute pericarditis (Table 57.2).[4] The frequency of etiology depends on the geographic population selected. In developed countries, idiopathic pericarditis represents the vast majority of cases. It is believed that most cases of idiopathic pericarditis represent the sequelae of a viral infection. An exhaustive virologic workup is rarely done in clinical practice, so the terms "idiopathic" and "viral" pericarditis are often used synonymously. Systemic autoimmune disease, chest radiation, open heart surgery, neoplastic disease, hypothyroidism, uremia, and acute myocardial infarction occur with enough frequency that they should be entertained in most cases. Tuberculous pericarditis is more common in developing countries and should be considered in patients with the appropriate exposure. Overall, the prognosis for idiopathic pericarditis is good. However, the risk of complications, including recurrence, tamponade, and constriction, is higher in patients with the following characteristics: female gender, large effusion or tamponade, and aspirin/nonsteroidal anti-inflammatory drug (NSAID) failure. Patients who have a specific underlying etiology (as opposed to idiopathic or viral pericarditis) are more likely to present with fevers, subacute onset, large pericardial effusion, elevation in cardiac troponin, and failure of NSAID treatment. These patients are also at increased risk for pericarditis-related complications of recurrence, tamponade, and constriction.[5]

TABLE

57.2 Etiology of 100 Consecutive, Hospitalized Acute Pericarditis Patients

Idiopathic	78%
Neoplastic	7%
Lung[a]	(4%)
Breast[a]	(1%)
Cystic duct adenocarcinoma[a]	(1%)
Cardiac angiosarcoma[a]	(1%)
Tuberculosis	4%
Other infection	3%
Toxoplasmosis gondii[a]	(1%)
Bacterial pneumonia[a]	(1%)
Purulent (unknown organism)[a]	(1%)
Collagen vascular disease	3%
Systemic lupus erythematosus[a]	(2%)
Rheumatoid arthritis[a]	(1%)
Thyroid disorder	4%
Dissecting aortic aneurysm	1%

[a]Denotes specific etiologies under subcategory. Percentages in parentheses demonstrate how cases are divided within the subcategory. Adapted from Zaya R, et al. Incidence of specific etiology and role of methods for specific etiologic diagnosis of primary acute pericarditis. Am J Cardiol. 1995;75:378–382.

Treatment

The mainstay of treatment for acute pericarditis is the use of nonsteroidal anti-inflammatory medications. The choice of drug is usually based on clinician experience and drug toxicity; there is a lack of head-to-head comparative trials that would demonstrate the superiority of one over the other. Typical regimens include aspirin (2,400 to 3,200 mg daily), indomethacin (150 mg/d), and ibuprofen (3,200 mg/d). Specific circumstances for choosing aspirin over other NSAIDs include acute pericarditis occurring in the postmyocardial infarction period, as well as chronic kidney disease.[6,7] The optimal duration of treatment is unknown. One general approach is to maintain the maximum dose of NSAID until normalization of CRP or ESR (usually 1 to 2 weeks), followed by gradual tapering of the medication, usually over a period of 3 to 4 weeks.[8,9] Treatment failure and recurrent symptoms are oftentimes related to inadequate dose and duration of NSAID treatment.

Colchicine has been demonstrated to be beneficial by randomized controlled trials in both first presentation and recurrent presentations of pericarditis.[8-10] Patients taking colchicine (loading dose 1 to 2 mg on day 1, followed by maintenance dose 0.5 to 1 mg daily thereafter), demonstrate fewer recurrent episodes. The total duration of colchicine should be for at least 3 months, certainly well past the resolution of symptoms and elevation of inflammatory markers. In the special circumstance of acute pericarditis

occurring in the postpericardiotomy setting, the COlchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) trial also demonstrates the efficacy and safety of colchicine in preventing pericarditis and its complications following open heart surgery.[11]

Corticosteroids are oftentimes used in acute pericarditis but their role is controversial. Observational data would suggest that they may actually increase the risk for recurrent pericarditis.[8] Furthermore, the dosages used are controversial, as one retrospective study suggests that lower doses of corticosteroids may be as effective as higher doses (prednisone 0.2 to 0.5 mg/kg/d vs. 1 mg/kg/d), with lower occurrences of side effects.[12] In our opinion, their use in patients with acute pericarditis, particularly those thought to be idiopathic or viral, should be restricted to cases with refractory symptoms (particularly when patients have been receiving optimal doses of NSAIDs and colchicine with evidence of ongoing inflammation) or to cases where they are used to treat a systemic autoimmune process. In the post–myocardial infarction setting, glucocorticoids should be avoided, as their use may be associated with the development of free wall rupture.

Recurrent Pericarditis

Recurrent pericarditis manifests in two different patterns, intermittent or incessant. In cases of intermittent pericarditis, patients will have symptom-free intervals of 6 weeks or greater while off all treatment. In contrast, incessant pericarditis is marked by return of symptoms within a 6 week period, either in the tapering or discontinuation phase of some or all anti-inflammatories.[13] Incessant pericarditis is particularly common in patients treated with corticosteroids; observational studies would suggest that corticosteroids are a risk factor for this complication of acute pericarditis. Recurrence of symptoms often coincides with objective findings of pericardial inflammation, particularly elevations of CRP and/or ESR. However, in some cases, patients will demonstrate their stereotypic symptoms without objective findings of inflammation. The treatment approach for recurrent pericarditis is similar to acute pericarditis. Nonsteroidal anti-inflammatories should be the backbone of therapy, along with the use of colchicine. Treatment with maximum doses tolerated should be maintained for at least 1 to 2 weeks or until symptoms and inflammatory markers normalize. Tapering of NSAIDs should be performed over at least a 3 to 4 week period. For some patients with recalcitrant disease, the period of tapering may require several months. Colchicine has been demonstrated to decrease the recurrence rate in patients with recurrent pericarditis.[10] Patients should take it for 3 months; for those who require longer periods for NSAID taper, colchicine is continued until NSAIDs have been successfully weaned. Corticosteroids should be reserved only for refractory cases; they may also be considered in patients who demonstrate highrisk features, including evidence for

transient constrictive pericarditis on echocardiography or CMR. Weaning of corticosteroids can be problematic, as symptoms often recur when doses are being tapered. We recommend the use of concomitant NSAIDs and colchicine when attempting to wean corticosteroids (triple therapy). Minimizing time on glucocorticoids is an important goal. Even in the presence of recurrent symptoms, we recommend continuing to wean doses as long as objective markers of inflammation are controlled by other anti-inflammatory agents. The prognosis for recurrent, idiopathic pericarditis is good, with no reported cases of constrictive pericarditis and approximately 3.5% cases of tamponade (usually occurring during initial attack).

Pericardial Effusion

Pericardial effusions come to attention in a variety of ways: they are discovered incidentally or as part of an evaluation for pericarditis, or they present symptomatically with symptoms and signs of tamponade.

Presentation and Diagnosis

The classic symptoms of tamponade include hypotension and dyspnea; patients may present with lower extremity edema, if the effusion has had a very slow rate of growth. Physical signs include tachycardia, elevated jugular venous pressure, and the presence of an exaggerated pulsus paradoxus. Electrocardiographic manifestations of a pericardial effusion include low voltage and, in extreme cases, electrical alternans. Pericardial effusion can be detected by a variety of testing, including echocardiography, CT, and MRI. Echocardiography is generally the test of choice with its widespread availability and its ability to provide twodimensional (2-D) imaging with concomitant hemodynamic data. The diagnostic echocardiographic findings for tamponade include the presence of a pericardial effusion, evidence of ventricular interdependence (demonstrated by variation of mitral and tricuspid inflow velocities by pulsed-wave Doppler), inferior vena cava (IVC) plethora, and collapse of the right atrium (Fig. 57.3), left atrium, and/or right ventricle (RV) (Fig. 57.4). In clinical practice, the diagnosis of early tamponade is challenging and is made by an appraisal of the clinical scenario and available data. Unfortunately, no single clinical or echocardiographic sign is completely reliable and a summation of all accessible information is necessary. On rare occasions, the diagnosis of tamponade is in question and a Swan–Ganz catheter is used to adjudicate a diagnosis. Classic hemodynamic findings include tachycardia; elevated right atrial (RA) pressure; an “M” pattern in the RA waveform, with a preserved x descent and blunted y descent; equalization of diastolic pressures in the RA, RV, and pulmonary capillary wedge pressure (PCWP); and a low normal or depressed cardiac output/index. No single hemodynamic finding is pathognomonic or completely sensitive for tamponade either. In cases where a patient is symptomatic and

has a moderate to large effusion by echocardiography, the demonstration of an elevated RA pressure and a low normal or depressed cardiac index should, without other explanation, be sufficient to make a diagnosis.[14]

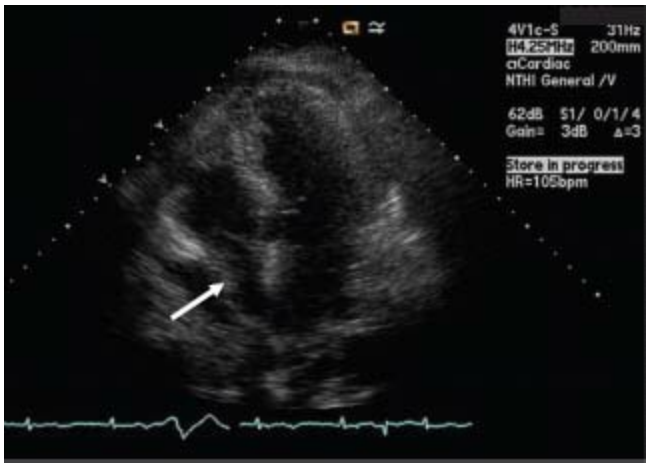

FIGURE 57.3 Transthoracic echocardiography, 4 chamber view. Collapse of the RA free wall (white arrow) during late atrial diastole.

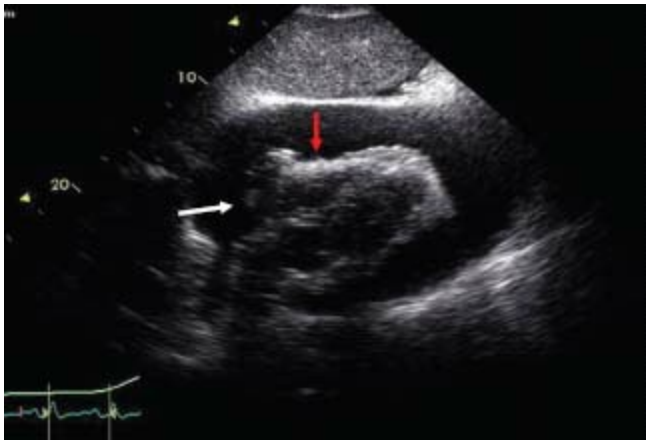

FIGURE 57.4 Transthoracic echocardiography, subcostal view. There is inversion of the RA (white arrow) and RV free wall (red arrow) during mid-diastole.

Etiology

The etiology of pericardial effusions includes the differential diagnosis of acute pericarditis; commonly encountered scenarios being idiopathic or viral pericarditis, malignancy, rheumatologic disease, tuberculosis, myocardial infarction, and post open heart surgery. Iatrogenic causes, including cardiac perforations from interventional and electrophysiology procedures, may manifest dramatically with tamponade from relatively small effusions accumulating within minutes. On occasion, effusion may be present as a result of elevated intracardiac filling pressures, such as in pulmonary hypertension or congestive heart failure. Finally, patients with myxedema or hypothyroidism may occasionally manifest with pericardial effusions. According to

published series, compared to cases of acute pericarditis, patients with large pericardial effusions often have specific etiologies that are identifiable rather than the majority of cases being idiopathic (Table 57.3).[15]

TABLE
57.3 Differences in Etiologic Diagnosis of Large Pericardial Effusions in Two Major Series

	Corey et al.[16] (*N* = 58)	Sagrista-Sauleda et al.[17] (*N* = 322)
Idiopathic	7%	29%
Neoplastic	23%	13%
Infectious	27%	2%
Connective tissue disease	12%	5%
Metabolic	24%	6%
Iatrogenic	0%	16%
Other	9%	29%

Adapted from Imazio M, et al. Medical therapy of pericardial disease Part II: noninfectious pericarditis, pericardial effusion and constrictive pericarditis. J Cardiovasc Med. 2010;11:785–794.

Cases of suspected tamponade in the post–open heart surgery setting deserve special attention. These cases are particularly challenging as effusions or hemorrhagic pericardial collections are frequently localized and the imaging by surface echocardiography is often suboptimal. Findings usually seen in tamponade, particularly relating to ventricular interdependence, such as pulsus paradoxus, and mitral and tricuspid inflow variation, are not reliable for a variety of reasons. They may be exaggerated or obliterated by changes in pulmonary and intrathoracic dynamics (pleural effusions, mechanical ventilation). Furthermore, localized collections, causing collapse of the right or left atria, may not manifest with ventricular interdependence. In this setting, for patients who have unexplained hemodynamic instability, chamber compression and/or a localized pericardial collection is the most important finding. When imaging by routine surface echocardiography is inadequate, further imaging, such as with transesophageal echocardiography, is recommended.

Treatment

Clinical tamponade, with hemodynamic compromise, is an absolute indication to drain a pericardial effusion. Relative indications include pretamponade physiology (typically seen by echocardiography), large effusions that fail to regress with medical therapy, and the need for diagnostic sampling (particularly to make a diagnosis of bacterial or

neoplastic pericarditis). There are multiple approaches that may be taken. Percutaneous drainage via pericardiocentesis is the most expedient and least morbid procedure. This may be accomplished via echocardiographic or fluoroscopic guidance; the two general approaches are via the subxiphoid or para-apical spaces. Surgical drainage is pursued for a variety of reasons: the expectation for recurrence and need for ongoing drainage (neoplastic pericarditis), inability to safely access the pericardial space via pericardiocentesis (typically posteriorly located effusions), the need for a pericardial biopsy, and loculated effusions. In surgical procedures, a portion of the pericardium is excised to create a "window," through which fluid may continually drain. The two incisional approaches include a subxiphoid window and via left thoracotomy (or thoracoscopy). There is a percutaneous option to more durable drainage: balloon pericardiotomy, where a balloon is used to create a tear in the pericardium (similar to a pericardial window) that may be performed by selected practitioners.

Constrictive Pericarditis

Constrictive pericarditis is one of the most challenging diagnoses to make in cardiology because it is rare, has a variety of presentations, and the diagnostic criteria are nonspecific and insensitive.

Presentation and Diagnosis

The classic and most typical presentation of constrictive pericarditis is predominant right-sided heart failure, with symptoms of lower extremity edema and abdominal distension, usually from ascites. Other common presentations include dyspnea (from left-sided heart failure or pleural effusions), abnormal liver function tests, and cirrhosis. Patients oftentimes are treated by noncardiologists for a prolonged period of time before the diagnosis of constriction becomes evident. In truth, patients with constriction have a wide spectrum of disease severity, spanning from patients with subclinical disease to severe refractory heart failure.

The diagnosis of constrictive pericarditis requires the appraisal of clinical, imaging and hemodynamic data. On clinical examination, the patient should demonstrate signs of right-sided heart failure, including elevated jugular venous pressure, lower extremity edema, and/or signs of ascites. The absence of all of these would make clinically significant constrictive physiology highly unlikely. The presence of a pericardial knock, a diastolic heart sound similar to an S_3, is helpful but insensitive. Chest x-ray, particularly the left lateral view, may demonstrate calcified pericardium, though this finding is not universal to all cases of constrictive pericarditis (Fig. 57.5). Transthoracic echocardiography is the initial test of choice and is ideally performed with a respirometer. Relevant findings include conical compression of the chambers, increased pericardial thickening/calcification, "tethering" of the atria and/or ventricles,

diastolic septal bounce, mitral and tricuspid inflow, and pulmonary vein and hepatic vein flow variation (Fig. 57.6) by pulsedwave Doppler, normal or exaggerated mitral annular tissue Doppler velocities (Fig. 57.7A and B), IVC plethora, and increased hepatic vein flow reversal with expiration. The preservation (or even exaggeration) of tissue Doppler velocities deserves some special attention, as annular velocities are generally reduced in cardiomyopathies that are part of the differential diagnosis.[18,19] In other conditions, as the left ventricular pressure rises, the tissue velocities (e′) fall and the resulting ratio of E/e′ becomes elevated. Conversely, in constrictive pericarditis, increased left ventricular pressure results in paradoxical elevation in tissue velocity; this phenomenon is known as annulus paradoxus and is unique to constriction. Cardiac MRI may show findings of diastolic septal bounce, diastolic restraint, conical deformity of the ventricles (Fig. 57.8), thickening of the pericardium (>4 mm, Fig. 57.9), and exaggerated septal motion with inspiration (Fig. 57.10A,B). There are a number of hemodynamic findings by cardiac catheterization, including but not limited to elevation and equalization of diastolic pressures, "square root sign," and "M" pattern of the RA pressure tracing with prominent Y descent. The most specific hemodynamic findings for constrictive pericarditis include discordance of RV and LV systolic pressure variation with respiration (Fig. 57.11) and a decrease in pulmonary–capillary wedge pressure to LV end-diastolic pressure gradient with inspiration.[20] It should be emphasized that no single test or finding is completely sensitive or diagnostic for constrictive pericarditis. Often, a diagnosis is made with the help of multiple tests and with only some of the characteristic findings present. In considering the entities that are causing the patient's symptoms, the typical differential diagnoses that present similarly to constriction are right ventricular failure, severe tricuspid regurgitation, and infiltrative cardiomyopathies (most commonly cardiac amyloidosis). Much attention is paid toward differentiating "constrictive" versus "restrictive" physiology (Table 57.4). Although many of the hemodynamic findings overlap, in clinical practice, the distinction is made by the clinical context and echocardiography appearance of the heart. The exception to this rule is in the setting of patients who have had previous chest radiation. For these patients, both constriction (pericardial involvement) and restriction (by myocardial involvement) are real diagnostic possibilities; they may even coexist in a particular patient. Discerning the dominant pathology in these cases is extraordinarily challenging.

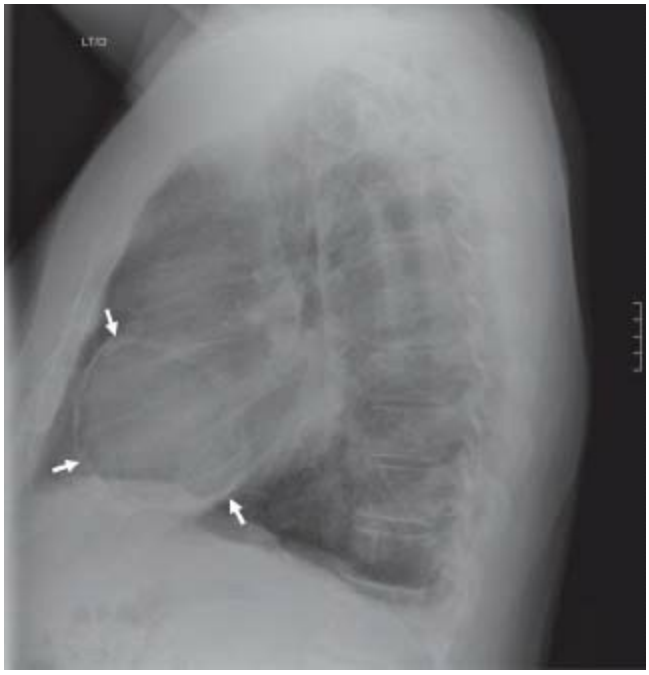

FIGURE 57.5 Chest x-ray, left lateral view. A patient with constrictive pericarditis who has severe calcification (white arrows) of the pericardium, which can be best seen on the left lateral view of the chest x-ray.

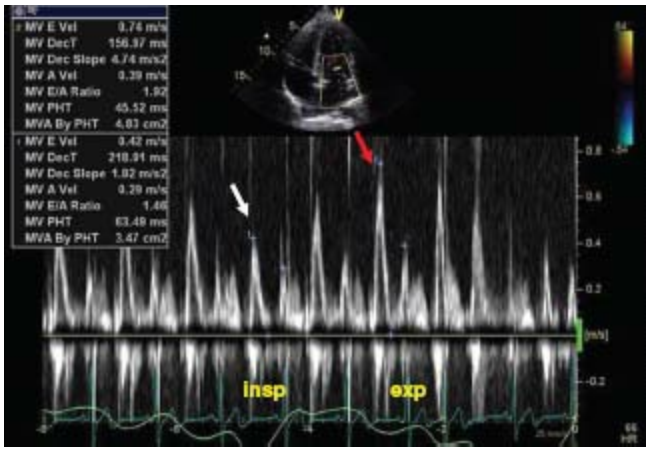

FIGURE 57.6 Transthoracic echocardiography, pulsed-wave Doppler at the mitral valve leaflet tips. Significant respiratory variation of the mitral E velocity (43%), which decreases with onset of inspiration (white arrow) and increases with onset of expiration (red arrow). Insp, inspiration; exp, expiration.

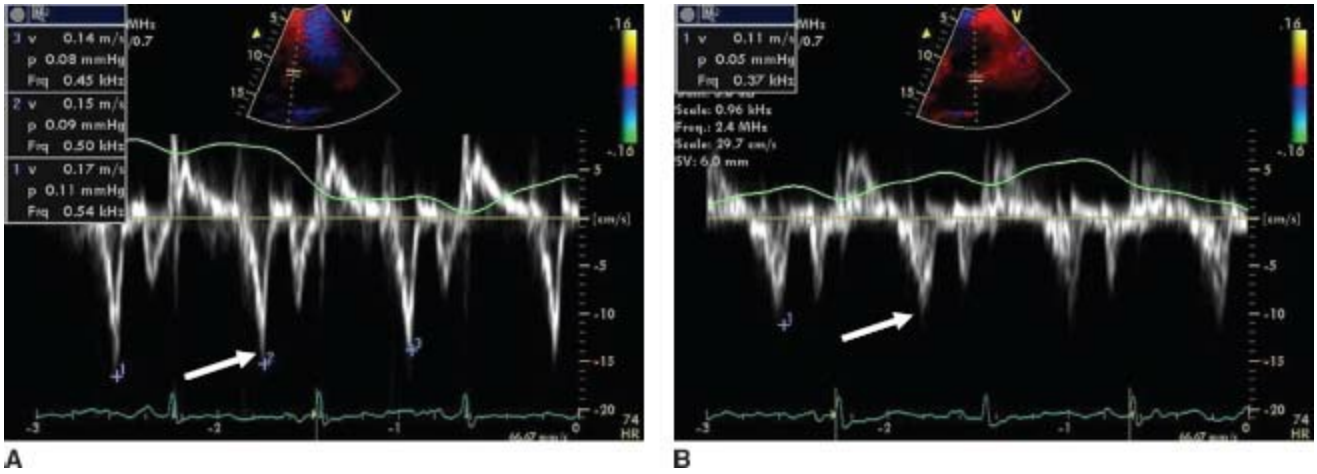

FIGURE 57.7 Transthoracic echocardiography, tissue Doppler imaging recorded at the septal **(A)** and lateral mitral annulus **(B)**. There is supranormal e' velocity (white arrow), suggesting rapid early diastolic ventricular filling. The septal e' velocity (15 cm/s) is greater than the lateral e' velocity (11 cm/s), a phenomenon known as "annulus reversus." This is unique to constrictive pericarditis and is thought to be related to tethering of the lateral ventricular wall to the pericardium.

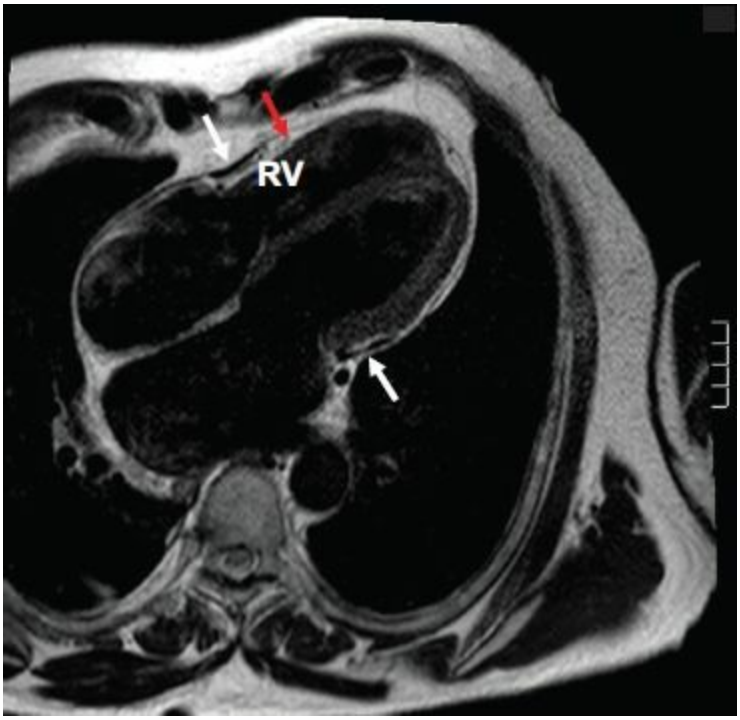

FIGURE 57.8 Cardiac MRI,dark-blood sequence, 4 chamber view. There is thickening of the pericardium (white arrows) and conical deformity of the RV (red arrow).

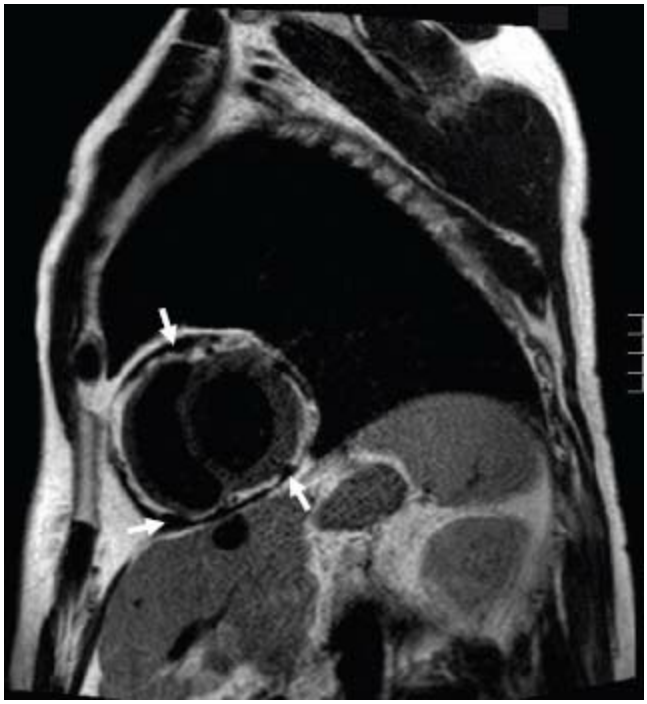

FIGURE 57.9 Cardiac MRI, dark-blood imaging, short axis view. The black border (white arrows) surrounding the ventricles represents severe thickening of the pericardium, measuring 8 mm in maximal thickness.

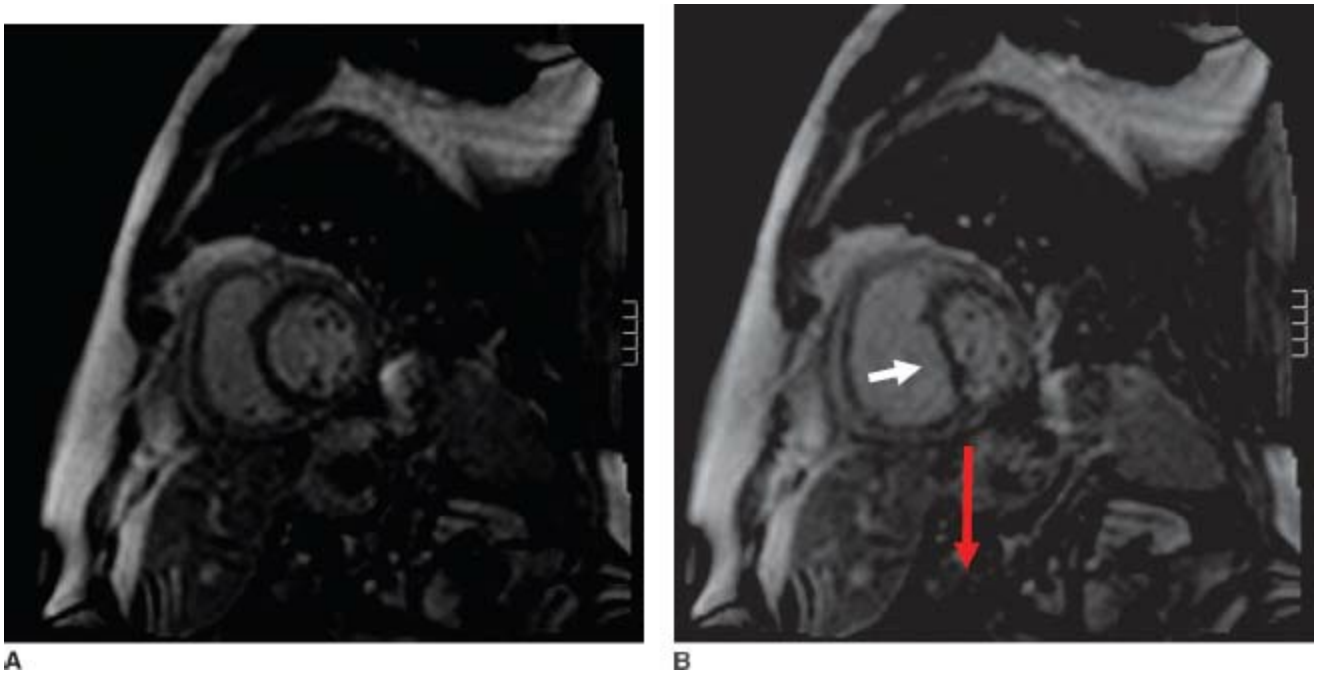

FIGURE 57.10 A, B: Cardiac MRI, cine sequences taken during one respiratory cycle. Ventricular interdependence, a hallmark of constrictive pericarditis, is demonstrated by the changes in morphology of the interventricular septum during the respiratory cycle. At end expiration (10A), the interventricular septum has its usual morphology. During inspiration, there is an increase in venous return to the RV; the confinements of the pericardial space prohibit RV expansion, except for bowing of the interventricular septum toward the LV, causing impairment LV filling. This is demonstrated by exaggerated interventricular septal flattening (white arrow) during diaphragmatic lowering (red arrow).

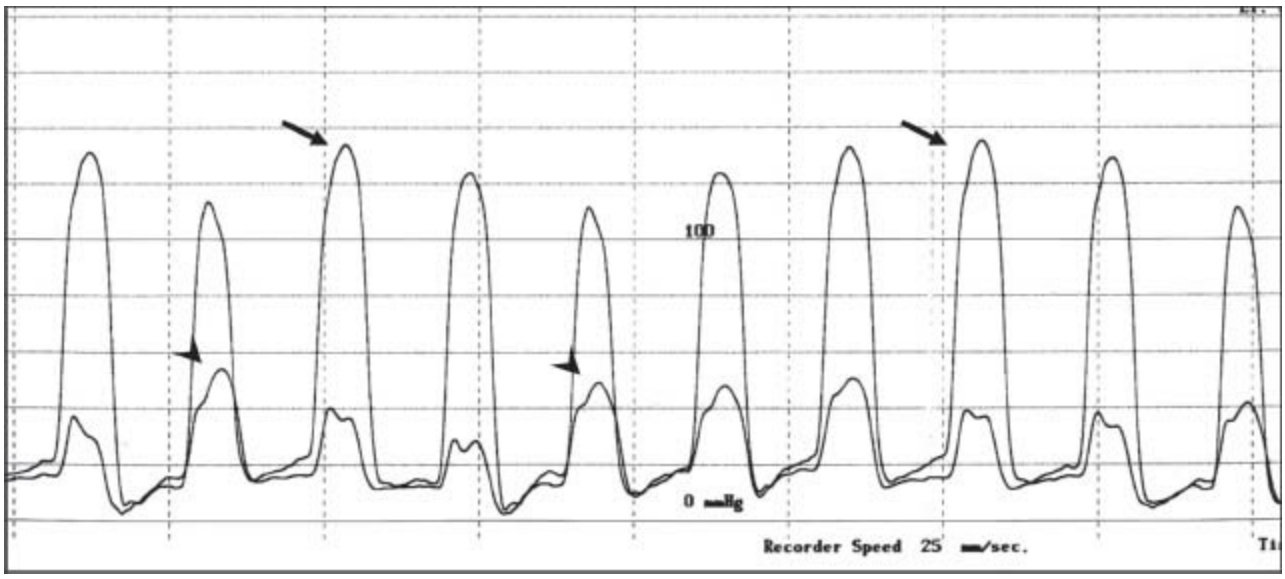

FIGURE 57.11 Simultaneous LV and RV pressure tracings. There is discordance in the timing of peak LV (arrows) and RV (arrowheads) pressures, with respect to respiratory variation. This can be quantitatively demonstrated by changes in the areas under the curves of both LV and RV pressures during respiration.

TABLE 57.4 Differential Imaging Characteristics Between Restrictive Cardiomyopathy and Constrictive Pericarditis

Imaging Modality	Restrictive Cardiomyopathy	Constrictive Pericarditis
Chest X-ray		Pericardial Calcification (sometimes)
Echocardiography (2-D imaging)	■ Increased wall thickness ■ Thickening of valves (amyloid) ■ Speckled pattern of myocardium (amyloid) ■ Increased thickness of interatrial septum (amyloid)	■ Pericardial thickening ■ Diastolic septal bounce
Doppler		
Mitral inflow	<25% variation in (E) velocity	■ Inspiratory decrease in early (E) velocity ■ Expiratory increase in early (E) velocity ■ ≥25% variation in E velocity
Pulmonary veins	■ Blunted S/D (0.5) ■ Prominent atrial reversal	■ S/D = 1 ■ Inspiratory decrease in S/D ■ Expiratory increase in S/D
Tricuspid inflow	■ Mild variation	■ Inspiratory increase in early (E) velocity ■ Expiratory decrease in early (E) velocity ■ ≥50% variation in E velocity
Hepatic Vein		■ Expiratory reversal of diastolic flow
Annular motion	■ Low early filling (e′) velocity (<8 cm/s) ■ Septal e′ < lateral e′	■ Normal or elevated early filling (e′) velocity (>8 cm/s) ■ Septal e′ > lateral e′ (Annulus Reversus)
E/e′	■ Elevated	■ Low or normal
Catheterization Hemodynamics	■ LVEDP > 5 mm Hg than RVEDP	■ RVEDP = LVEDP ■ Discordance of RV peak systolic pressure and LV peak systolic pressure with respiration ■ RV systolic pressure during inspiration ■ Peak LV systolic pressure during expiration
CT/MRI		■ Conical deformity of ventricles ■ Pericardial thickening

Adapted from Klein AL, Asher C. Diseases of the pericardium, restrictive cardiomyopathy and diastolic dysfunction.

In: Topol EJ, ed. Textbook of Cardiovascular Medicine. 3rd ed. Philadelphia, PA. Lippincott, Williams and Wilkins; 2007:420-459.

Once a diagnosis of constrictive pericarditis has been made, an important determination to make is the clinical context of the constrictive physiology. On occasion, patients with acute pericarditis, manifesting with severe pericardial inflammation, may demonstrate constrictive physiology.[21] In this setting, the physiology of constriction may be reversible with aggressive anti-inflammatory measures, as it is related to inflammation and tissue edema. In more typical cases, patients with constriction will present with established pericardial scarring that is irreversible. Short of surgical inspection, there is no perfect method of making the distinction between these two entities. Thus, for patients presenting with acute pericarditis symptoms with signs of inflammation (pericardial-type chest pain, ESR and/or CRP elevation, pericardial effusion, and/or MRI enhancement) and constrictive pericarditis, a trial of anti-inflammatories should be considered prior to surgical therapy. In limited experience, pericardiectomy performed in patients with acute inflammation can result in significant postoperative complications.

Effusive–constrictive pericarditis is another clinical entity that deserves special attention. Patients with this condition demonstrate signs of constrictive physiology, clinically and by imaging, in the setting of a significant pericardial effusion. As many of the hemodynamic changes seen in both tamponade and constriction overlap, it is difficult to determine the relative contribution of the pericardial effusion versus the thickened pericardium to the patient's clinical presentation. When a significant contribution of pericardial effusion is postulated, the patient may require pericardiocentesis in order to determine the significance of pericardial constriction.

As with pericardial effusions, the differential diagnosis of the etiology of constrictive pericarditis is similar to that of acute pericarditis. As pericardial scarring is a process that usually occurs over a period of time, the history usually reveals an episode of pericarditis that occurred remotely. Classically, the separation between initial insult and presentation of constrictive pericarditis is by years, even decades. This is true for patients with constriction as a result of idiopathic pericarditis and radiation-induced pericarditis. However, on occasion, patients may present as soon as months out from their initial episode, particularly following cardiac surgery. Common causes of constriction that are seen in practice include idiopathic/viral pericarditis, postradiation therapy, and post–open heart surgery.

Treatment

Patients with constrictive pericarditis may manifest along a wide spectrum of disease severity, from the asymptomatic patient with detectable constriction by imaging tests to the debilitated patient with severe right heart failure symptoms. As stated previously,

the patient with the possibility of transient constriction in the setting of acute pericarditis deserves a several month course of aggressive antiinflammatory treatment to see if their physiology improves. In patients with established pericardial scarring, medical management of constriction revolves around diuretic therapy to relieve congestive symptoms. It is still unclear what the appropriate disease severity threshold should be to recommend surgical pericardiectomy. Most would agree that patients with refractory symptoms, and/or New York Heart Association (NYHA) Class III/IV heart failure should be considered for surgical referral. However, the appropriate management of patients who are discovered earlier in the natural history of the disease course or who have minimal symptoms remains undetermined. Observational data suggest that patients who are operated on later in their disease course have worse outcomes.[22,23] Some of the reluctance for surgical referral revolves around an early surgical series demonstrating a high rate of morbidity and mortality following pericardiectomy. However, more contemporary data suggest that surgical risk in a high volume setting is much lower.[24,25] In determining a patient's surgical risk, some consideration should be given to the etiology of pericardial constriction. In one series, constrictive pericarditis related to mantle radiation had significantly worse perioperative and long-term mortality compared with patients with idiopathic constrictive pericarditis undergoing pericardiectomy.[25] Those with constriction as a result of previous open heart surgery had an intermediate short and long-term mortality.

ACKNOWLEDGMENT

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QUESTIONS AND ANSWERS

Questions

1. A 65-year-old man has just undergone primary percutaneous intervention for an acute, ST elevation myocardial infarction. Several hours following the procedure, he complains of new onset chest pain, different from his presenting complaint, worse with inspiration and radiating to both of his shoulders. His electrocardiogram demonstrates subtle, diffuse ST elevations in the inferior, lateral, and anterior leads. You perform an echocardiogram that demonstrates a small pericardial effusion, without evidence for a mechanical complication following his myocardial infarction. Which of the following would be the next best step?
   a. Initiate ibuprofen 800 mg three times daily
   b. Initiate prednisone 1 mg/kg daily
   c. Initiate aspirin 800 mg four times daily
   d. Return to the cardiac catheterization laboratory for repeat coronary angiography

2. A 77-year-old man with a history of end-stage renal disease presents with fevers and chest pain for 2 weeks. He has been on hemodialysis for more than 5 years and has not missed any recent sessions. He appears uncomfortable and diaphoretic. His vital signs are T103F, HR 82, BP 143/96 RR 12. His pulsus paradoxus is 6 mm Hg. His examination is remarkable for a pericardial friction rub. His electrocardiogram demonstrates diffuse ST elevations with PR depression. A complete blood count demonstrates a WBC of 14K. An echocardiogram demonstrates a large pericardial effusion but no signs of tamponade physiology. The next best step in managing this patient is:
   a. Initiate ibuprofen 800 mg three times daily with colchicine 0.6 mg twice daily.
   b. Initiate prednisone 0.5 mg/kg daily for 4 weeks followed by a tapering regimen over 3 months.
   c. Call the referring nephrologist for more intensive hemodialysis.
   d. Perform a pericardiocentesis.

3. A 43-year-old woman presents to your office complaining of lower extremity edema and increased abdominal girth. She had undergone mantle radiation for Hodgkin's lymphoma 20 years prior. On examination, you find an elevated jugular venous pressure, severe lower extremity edema, and a fluid wave suggesting abdominal ascites. The following echocardiographic findings support a diagnosis of constrictive pericarditis except:
   a. A septal tissue Doppler velocity of 4 cm/s
   b. Plethora of the inferior vena cava
   c. A decrease in mitral inflow early (E) velocity with inspiration
   d. An increase in tricuspid inflow early (E) velocity with inspiration
   e. Increased hepatic vein flow reversal with expiration

4. Central venous pressure examination in tamponade reveals:
   a. Prominent X descent (rapid ventricular filling during systole) and absent Y descent (absent diastolic filling)
   b. Prominent X and Y descents
   c. Prominent Y but blunted X descent
   d. These waveforms can only be discerned with right heart catheterization

5. What is the most common cause of constrictive pericarditis in the United States?

a. Previous cardiac surgery
b. Mantle radiation
c. Tuberculosis
d. Idiopathic or viral

Answers

1. Answer C: Although the incidence of acute pericarditis in the postmyocardial infarction setting has decreased with early revascularization, it is still a commonly encountered scenario. In this setting, there is some concern that the use of nonsteroidal antiinflammatory drugs (NSAIDs) and/or corticosteroids may increase the risk of free wall rupture. As such, using high-dose aspirin is the most appropriate therapy in this situation. The presenting symptoms and ECG do not support stent thrombosis or a complication of the revascularization procedure, so there is no indication for repeat angiography.

2. Answer D: A patient who has been on hemodialysis for a prolonged period of time, particularly if they have not missed any hemodialysis sessions, is unlikely to present with uremic pericarditis. In this case, bacterial pericarditis should be considered on the differential diagnosis. Prior to initiating typical anti-inflammatory therapy, a pericardiocentesis should be performed to rule out bacterial seeding of the pericardial space.

3. Answer A: In constrictive pericarditis, the tissue Doppler velocity of the mitral annulus is typically normal or even exaggerated (8 cm/s or greater). This represents normal diastolic function of the myocardium itself; the diastolic abnormalities in pure constrictive pericarditis are related to constraint from the pericardium. Occasionally, pericardial scarring adjacent to the lateral wall of the LV can cause tethering of the mitral annulus to the pericardium; in these cases, the lateral tissue Doppler velocity may be decreased (a phenomenon known as annulus reversus). As such, for constrictive pericarditis, it is more reliable to use the septal measurement of the tissue Doppler velocity. Choices b-e represent typical echocardiographic findings in patients with constrictive physiology.

4. Answer A: Prominent X descent (rapid ventricular filling during systole) and absent Y descent (absent diastolic filling).

5. Answer D: Idiopathic or viral pericarditis. In one series (Bertog et al.), the etiology was idiopathic in 46%, previous cardiac surgery in 37%, mantle radiation in 9%, and miscellaneous (including tuberculosis) in 8% of the patients. In some series, the representation of constriction as a result of previous PiSSSI cardiac surgery is even higher.

CHAPTER

Effects of Systemic Diseases on the Heart and Cardiovascular System

Jay Sengupta and Curtis M. Rimmerman

Many inherited and acquired organ system disorders result in clinically significant changes in the heart and cardiovascular system. These changes often demand specific cardiovascular imaging and therapies in addition to disease-specific treatment. Successfully completing the Cardiovascular Board examination requires an understanding of associated clinical situations. In this chapter, the most commonly tested topics are reviewed, categorized by primary organ system.

INHERITED DISORDERS/GENETIC SYNDROMES

Marfan Syndrome

Marfan syndrome is an autosomal dominant disorder that primarily affects connective tissues as a result of various mutations involving the fibrillin-1 (FBN-1) gene. Mutations in the transforming growth factor (TGF)-beta receptor 2 (TGFBR2) and TGFBR1 genes have been linked to the Marfan phenotype in a minority of cases and a related condition termed Loeys-Dietz syndrome associated with a bifid uvula and cleft palate. The histopathology demonstrates cystic medial necrosis. Mitral valve prolapse and aortic root and aortic annular dilation may be seen, leading to incompetence of the mitral and aortic valves. Aortic disease is the most common cause for morbidity and mortality among Marfan patients and includes aneurysm formation, intramural hematoma, dissection, and rupture. This risk increases significantly with pregnancy.

The 2010 American College of Cardiology/American Heart Association/American Association for Thoracic Surgery (ACC)/(AHA)/(AATS) guidelines for thoracic aortic disease recommend an echocardiogram at the time of diagnosis and in 6 months to determine the aortic root and ascending aortic diameters and their rate of enlargement. Beta-blockers are recommended in all patients with Marfan syndrome and aortic

aneurysm to reduce the rate of aortic dilatation. Elective surgical repair is recommended for patients with an external aortic diameter of 5 cm and in patients with aortic diameter <5 cm if there is rapid growth (>0.5 cm/year), family history of aortic dissection at a smaller diameter, or progressive aortic insufficiency In patients with Loeys-Dietz syndrome, aortic dissection has been observed for aortic diameters <5 cm, and therefore surgical repair is recommended at smaller diameters than recommended for Marfan syndrome (>4.2 cm). In all conditions, the height of the individual should also be considered in determining the optimal timing of surgery. Thus, an aorta size of 4.8 cm may be more concerning in an individual who is 60 inches tall in comparison to someone who is 75 inches tall. Algorithms that allow normalization of aorta size for height are available and are useful in these circumstances.

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome is also an autosomal dominant syndrome that affects the connective tissues and thereby results in similar heart abnormalities. Mitral and tricuspid valve prolapse causing mitral and tricuspid regurgitation, aortic root dilation causing aortic regurgitation, and dissection of the aorta and great vessels comprise the most common cardiovascular complications. When aortic surgery is indicated, patients with Marfan, Loeys-Dietz, or Ehlers-Danlos vascular-type syndromes with a normal aortic valve should undergo valve-sparing aortic root surgery with excision of the sinuses together if feasible or replacement with a valvegraft conduit if the valve is abnormal.

Noonan Syndrome

Noonan syndrome is an autosomal dominant disorder that includes characteristic facies and cognitive impairment in addition to its cardiovascular abnormalities. Heart lesions include pulmonic valve or infundibular stenosis, atrial septal defect, patent ductus arteriosus, tetralogy of Fallot, and hypertrophic cardiomyopathy Vascular abnormalities include peripheral pulmonary arterial stenosis.

Williams Syndrome

Williams syndrome, the result of spontaneous mutations, is characterized by cognitive impairment, an elf-like facies, hypercalcemia, and dental abnormalities. Cardiovascular manifestations include congenital supravalvular aortic stenosis, atrial septal defect, ventricular septal defect, and peripheral pulmonary arterial stenosis.

Osler-Weber-Rendu Syndrome

Also known as hereditary hemorrhagic telangiectasia, Osler-Weber-Rendu syndrome is characterized by mucocutaneous telangiectasias (on the tongue, lips, and fingertips) and arteriovenous malformations (AVMs) in the upper and lower gastrointestinal tracts and pulmonary vasculature. These pulmonary AVMs may result in paradoxical emboli in the presence of venous thrombosis.

NEUROMUSCULAR DISORDERS

Muscular Dystrophy

The three most common variations of muscular dystrophy—Duchenne, Becker, and Emery-Dreifuss—are each X-linked disorders associated with significant cardiac abnormalities. Conduction disturbances are common, especially atrioven-tricular (AV) nodal block and atrial dysrhythmias; atrial paralysis and atrial fibrillation/flutter are particularly common in the Emery-Dreifuss variant. Each muscular dystrophy syndrome may also result in a cardiomyopathy, leading to heart failure. The cardiomyopathy that occurs in Duchenne muscular dystrophy preferentially affects the posterobasal left ventricle, which may exacerbate heart failure by causing posteromedial papillary muscle-mediated mitral regurgitation. Baseline assessment of cardiac function at the time of diagnosis or by the age of 6 years followed by echo or MRI annually or biannually is recommended.

Treatment of the conduction disturbances and cardiomyopathy is supportive; permanent pacing may become indicated. Angiotensin-converting enzyme (ACE) inhibitors may slow the development of LV dysfunction, while the use of ACE inhibitors and beta-blockers may lead to reverse remodeling in patients who have developed dilated cardiomyopathy. Cardiac transplant may be an option in Becker patients with severe dilated cardiomyopathy and no evidence of skeletal muscle disease.

Friedrich Ataxia

Friedrich ataxia is an autosomal recessive neuromuscular disorder, caused by intramitochondrial iron accumulation, resulting in progressive ataxia, areflexia, upper motor neuron injury, and loss of proprioception. From a cardiovascular perspective, it is associated with a hypertrophic cardiomyopathy. Although fatal ventricular dysrhythmias are rare, the cardiomyopathy itself often causes death, especially in cases that progress to dilated cardiomyopathy.

Myotonic Dystrophy

Myotonic dystrophy, also known as Steinert disease, is an autosomal dominant disorder caused by a mutation in the myotonin gene; the resultant phenotype includes myotonia, weakness, frontal balding, cataracts, and gonadal dysfunction in addition to its cardiovascular manifestations. Electrocardiogram changes include pathologic Q waves in the absence of coronary artery disease or myocardial infarction. It also is associated with conduction disturbances, manifested primarily by AV block and intraventricular conduction delay Progression of AV conduction abnormalities is unpredictable and pacing is reasonable in asymptomatic patients with neuromuscular diseases and any degree of AV block.

Kearns-Sayre Syndrome

Kearns-Sayre syndrome is a mitochondrial encephalopathy characterized by ophthalmologic abnormalities. AV block is seen, often requiring pacemaker placement.

Myasthenia Gravis

Myasthenia gravis is an autoimmune process that reduces the number of acetylcholine receptors present at the neuromuscular junction. Affecting more females than males, it presents as progressive weakness and fatigue that worsens with repetitive muscle use and improves with rest. In addition to the autoimmune effect that it has on the neuromuscular endplate, myasthenia gravis can cause a myocarditis that responds to conventional myasthenia gravis treatment modalities.

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is an acute, autoimmune-mediated demyelinating disorder of the peripheral nervous system, characterized by ascending motor weakness, paresthesias, and areflexia. The adverse effects that GBS has on the nervous system include autonomic dysfunction involving the cardiovascular system. Hypertension, orthostatic hypotension, resting sinus tachycardia, and potentially fatal dysrhythmias are all potential complications of GBS. Supportive treatment, including plasmapheresis and intravenous immunoglobulin, is the mainstay of care.

ENDOCRINE AND METABOLIC DISORDERS

Acromegaly

Acromegaly results from an excess of circulating growth hormone, usually from overproduction in the pituitary gland. The most common cardiovascular manifestation of this excess is hypertension, with premature atherosclerosis and cardiomegaly also commonly seen. The cardiomegaly is out of proportion to the overall organomegaly and results in congestive heart failure and cardiac dysrhythmias, occasionally resulting in sudden cardiac death.

Treatment consists of destruction of the growth hormone source (i.e., the pituitary gland), either via transsphenoidal surgical resection or external-beam radiation. The associated cardiovascular abnormalities generally can be controlled with conventional therapies; hypertensive patients respond favorably to diuretics and sodium restriction.

Cushing Syndrome

Cushing syndrome is characterized by excess glucocorticoids and androgens, either primarily from adrenal hyperplasia or secondarily from adrenocorticotrophic hormone (ACTH)-producing neoplasms or exogenous administration. Patients with this syndrome are characterized by central obesity with slender extremities and proximal muscle weakness. Associated cardiovascular disorders include hypertension, accelerated atherosclerosis, and dyslipidemia. Cardiac dysrhythmias associated with hypokalemia

are seen.

Therapy is directed at the specific cause of the hormonal excess. From a cardiovascular standpoint, efforts should be aimed at controlling hypertension, which is often difficult without first reducing cortisol production and maintaining normal potassium levels.

Hyperaldosteronism/Conn Syndrome

Usually caused by an aldosterone-secreting adenoma, hyperaldosteronism features hypertension, hypokalemia, and metabolic alkalosis. The hypertension can be resistant to multiple medications and severe enough to cause renal insufficiency or stroke. Typical electrocardiogram changes associated with hypokalemia can also occur and manifest as flattened T waves and prominent U waves.

Surgical resection of the adenoma or medical therapy with aldosterone antagonists (e.g., spironolactone, eplerenone) is the treatment of choice, in addition to appropriate potassium replacement.

Adrenal Insufficiency

Adrenal insufficiency can result from (a) primary adrenal cortex failure (Addison disease), (b) hypopituitarism (secondary adrenal insufficiency), (c) selective/isolated hypoaldosteronism (a hyperreninemic state usually caused by a congenital inability to produce aldosterone with preserved glucocorticoid function), or (d) enzymatic deficiency (congenital adrenal hyperplasia). Cardiovascular effects include hypotension with orthostasis and several possible electrocardiogram changes—small/inverted T waves, sinus bradycardia, prolonged QT interval, low-voltage QRS complexes, and first-degree AV block. Treatment consists of replacement with corticosteroids.

Hyperthyroidism

Excess circulating thyroid hormone results in a physiologic state that resembles activation of the sympathetic nervous system. Hyperthyroidism has a peak incidence in the third and fourth decades, and women are four to eight times more likely to be affected.

Cardiac features include palpitations, dyspnea, tachycardia, and systolic hypertension, consistent with the increased chronotropic and inotropic state expected with increased adrenergic tone. Cardiac dysrhythmias and electrocardiogram changes also occur, including atrial fibrillation and other supraventricular tachyarrhythmias, intraventricular conduction delay, and right bundle branch block. Finally, anginal chest pain and congestive heart failure symptoms can occur, even in a structurally normal heart.

Goals of treatment consist of reversal of the hyperthyroid state and resolution of symptoms. The latter is generally accomplished with β-adrenergic-blocking agents; the former can be done medically with targeted antithyroid agents such as methimazole and

propylthiouracil, radioactively with ^{131}I ablation of thyroid tissue, or surgically via thyroidectomy. ACC/AHA/European Society of Cardiology (ESC) guidelines consider thyrotoxicosis a risk factor for throm-boembolism in atrial fibrillation and when associated with one moderate-risk factor recommend anticoagulation until a euthyroid state is restored.

Hypothyroidism

A lack of thyroid hormonal effect will also adversely affect the cardiovascular system. Interstitial myocardial fibrosis can result in gross biventricular dilation. Facial and peripheral edema can progress to brawny, nonpitting myxedema, and myxedematous pericardial effusions can be found in as many as one-third of patients. Electrocardiogram changes may include sinus bradycardia, low-voltage QRS complexes, a prolonged QT interval, and intraventricular conduction delay or right bundle branch block. Hypertension or hypotension may result. Dyslipidemia (hypercholesterolemia and/or hypertriglyc-eridemia) is common.

Thyroid hormone replacement should be instituted at a low initial dose, with small increases in dosage at long intervals, especially in elderly patients or those with known coronary artery disease, as abrupt elevation of thyroid hormone levels can precipitate myocardial ischemia and/or heart failure.

CONNECTIVE TISSUE AND ASSOCIATED VASCULAR DISORDERS

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a well-described autoimmune disorder characterized by antibodies against cellular antigens, resulting in an inflammatory state that is manifested by effects on multiple organ systems. Most commonly, patients with SLE present with arthritis and dermatitis. The most common cardiovascular complication of SLE is pericarditis, with or without pericardial effusion. The effusion, usually exudative, is characterized by an elevated protein concentration, a low/normal glucose concentration, and low complement. Other cardiac abnormalities seen in SLE patients include early coronary artery disease, caused by both progressive atherosclerosis (with chronic corticosteroid use) and coronary arteritis. Myocardial infarction may occur via embolism of noninfectious (Libman-Sacks) endocarditis vegetations, or via SLE-related antiphospholipid antibody (APLA)-mediated thrombosis. The noninfectious endocarditis tends to cause insufficiency of the aortic and mitral valves more commonly, generally sparing the ventricular surface of each valve. Valvular lesions that can be detected by echocardiography are much more common than clinically significant disease. In those patients with clinically significant disease, the tendency is toward valve repair or replacement with bioprosthetic valves rather than

mechanical valves, given the propensity of SLE patients to suffer bleeding complications from associated serositis or cerebritis. In patients with the APLA syndrome, mechanical valves are preferred, since anticoagulation is already indicated. Infants born to female patients with SLE (especially those having anti-Ro or anti-La antibodies) may suffer congenital heart block as a result of fibrosis of the conduction system in utero.

SLE-related pericarditis and pericardial effusions should be treated with nonsteroidal anti-inflammatory agents (NSAIDs) initially, with a plan to switch to corticosteroids should more aggressive treatment be necessary. Percutaneous or surgical drainage may be necessary should there be evidence of cardiac tamponade physiology or should maximized medical therapy (corticosteroids and cyclophosphamide) fail to result in resorption of the effusion. Coronary artery disease treatment consists of conventional measures, except in cases of arteritis (which demands an intensive course of corticosteroids) or APLA-mediated thrombosis that requires systemic anticoagulation. In cases of endocarditis, serial echocardiography should be used to monitor for progressive valvular incompetence and indications for surgical valve repair or replacement. Women with SLE who become pregnant should undergo intensive gestational screening; intrauterine dexamethasone has been used successfully to slow progression of congenital heart block.

Some common cardiovascular medications can cause a drug-induced lupus-like syndrome including hydralazine, atenolol, procainamide, statins, captopril, and enalapril. This can occur after months or years of use and is associated with positive antinuclear antibodies (ANA) and antihistone antibodies.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a progressive autoimmune arthritis, resulting in joint destruction, deformation, and immobility. In patients with RA, pericardial disease is the most prominent cardiac complication, ranging in complexity from a chronic asymptomatic effusion to constrictive pericarditis. Early coronary artery disease and myocardial infarction can result from the chronic inflammatory state of RA and the long-term use of corticosteroid therapy. Rarely, secondary amyloidosis will occur, causing an infiltrative cardiomyopathy that may be accompanied by conduction abnormalities.

The mainstay of initial treatment is NSAIDs, followed by more intensive immunosuppression if necessary.

Seronegative Spondyloarthropathies

The seronegative spondyloarthropathies—ankylosing spondylitis, Reiter syndrome, and the inflammatory bowel disease arthritides (ulcerative colitis and Crohn's disease)—appear to be closely related from a clinical standpoint and are associated with the HLA-B27 antigen. Ankylosing spondylitis results in ankylosis, sacroiliitis, peripheral arthritis, iritis, and aortitis. Reiter syndrome includes asymmetric arthritis,

conjunctivitis, and genital ulcers. Aside from the well-described gastrointestinal findings in inflammatory bowel disease, they also feature an asymmetric arthritis and enthesitis. In general, this set of connective tissue disorders also shares a similar cadre of cardiac involvement: a thickened/dilated aortic root, leading to aortic regurgitation, and AV conduction abnormalities.

Polymyositis

Polymyositis is an idiopathic inflammatory myopathy characterized by proximal muscle weakness and elevation of muscle enzyme serum levels. Cardiac involvement consists of a myopericarditis that can either be focal or generalized, at times involving the conduction system and resulting in conduction system abnormalities including heart block. Corticosteroids are generally administered if myocarditis is proven on endomyocardial biopsy.

Scleroderma/CREST Syndrome

Systemic sclerosis, especially when complicated by the CREST syndrome (calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias), can cause pericardial effusions and pericarditis. Patchy myocardial fibrosis may occur as well as conduction system abnormalities at all levels. Pulmonary hypertension can be a prominent feature.

A careful physical examination and echocardiography should be used both to assess for pericardial drainage indications and to monitor pulmonary pressures for significant elevations, possibly requiring the institution of vasodilator therapy.

Takayasu Arteritis

Takayasu arteritis is an idiopathic, granulomatous largevessel vasculitis that generally occurs in young people, with a 10-fold female preponderance and highest incidence found in Japan. Hypertension and aortic regurgitation secondary to aortic annular and aortic root dilation are its most prominent cardiac complications. There is a panarteritis typically affecting the aorta and its major branches. Involvement of the coronary arteries is exceptionally rare.

Clinical classification criteria include age <40 years, claudication especially of the upper extremities, decreased pulses in the brachial artery, blood pressure difference >10 mm Hg between arms, and bruit over the subclavian arteries or the abdominal aorta. Onset is associated with constitutional symptoms such as fever, arthralgias, and weight loss and vessel inflammation can manifest as pain and tenderness, most commonly found over the carotid arteries. Angiography is the gold standard for detecting diseased vessels. Corticosteroids with or without further immunosuppression (cyclo-phosphamide, methotrexate) constitute primary therapy.

The differential diagnosis for vascular symptoms arising from Takayasu's arteritis includes giant cell/temporal arteritis, Behget disease, fibromuscular dysplasia (FMD),

sarcoid vasculopathy, mechanical thoracic outlet syndromes, and infectious or other inflammatory causes for aortitis. Giant cell arteritis shares many clinical, histopathologic, and radiographic findings seen in Takayasu arteritis except that it typically affects individuals older than 50 years of age. It is also associated with new headaches, visual disturbances, and symptoms of polymyalgia rheumatica. Markers of inflammation such as erythrocyte sedimentation rate (ESR) and/or C-reactive protein may be significantly elevated in either condition, and additional findings include constitutional symptoms and jaw and upper extremity claudication. CT or MR angiography can help to distinguish the etiology by demonstrating multisegment stenoses alternating with areas of normal luminal caliber in inflammatory vasculitis versus single stenosis or vascular cutoff at focal sites of functional or mechanical compression.

Fibromuscular Dysplasia

FMD is a noninflammatory, nonatherosclerotic process in which various fibrous lesions in the different layers of the vascular wall lead to arterial stenoses. Any vascular bed can be affected but the most commonly involved vessels are the renal (60% to 75% of cases) and carotid arteries (30% to 60%) followed by mesenteric or brachial arteries and rarely coronary arteries. FMD is more common among females, and the mean age at presentation is 58 years. Renal FMD can manifest as severe or resistant hypertension while involvement of the extracranial vessels can lead to ischemia, spontaneous dissection and occlusion, rupture of aneurysms, or embolic phenomenon. Digital subtraction angiography is the gold standard in diagnosis and shows a classic string-of-beads appearance which differentiates FMD from the inflammatory vasculitides.

Vasculitis Affecting Small to Medium-Sized Vessels

Polyarteritis nodosa (PAN) is a rare necrotizing vasculitis associated with weight loss, myalgias, neuropathy, testicular pain, elevated diastolic blood pressure, renal insufficiency without glomerulonephritis, and false-positive serum hepatitis B testing. The vessels affected by PAN include the coronary arteries. Coronary arteritis and coronary artery aneurysms are seen, which can lead to an acute myocardial infarction. Atherosclerosis is also accelerated in PAN as a result of the associated hypertension, steroid therapy, and renal failure. Corticosteroids are primary therapy.

Churg-Strauss syndrome is an eosinophilic granulomatous inflammation of the respiratory tract, characterized by a necrotizing vasculitis of small and medium-sized vessels. The eosinophilia results in an association with asthma and other atopic diseases. Eosinophilic myocarditis, causing a restrictive cardiomyopathy, pericarditis with or without an associated effusion, and coronary arteritis characterize the cardiac manifestations. Heart failure secondary to the cardiomyopathy is the most common cause of death. Corticosteroids are primary therapy.

Wegener granulomatosis is characterized by systemic granulomatous inflammation of the upper and lower respiratory tract as well as a vasculitis that may result in

necrotizing glomerulonephritis. Its cardiac manifestations include pericarditis, myocarditis with left ventricular dysfunction, and an uncommon valvulitis, most often aortic. Serial electrocardiograms and echocardiography to monitor electrophysiologic and ventricular function are warranted, respectively, to guide supportive therapy. Corticosteroids are primary therapy, and cyclophosphamide may be added for progressive disease.

Sarcoidosis

Sarcoidosis is an idiopathic noncaseating granulomatous disorder that predominantly affects the lungs and mediastinal lymph nodes, causing a restrictive pulmonary physiology similar to that of interstitial lung diseases. Sarcoidosis may involve the vascular system, pericardium causing pericarditis, the myocardium causing myocarditis or restrictive cardiomyopathy, and the conduction system causing varying levels of AV and intraventricular block. Ventricular arrhythmias, both benign and malignant, can occur in the presence of myocardial sarcoid infiltration. Endomyocardial biopsy demonstrates granulomatous inflammation but has poor sensitivity. Positron emission tomography in conjunction with CT-imaging can anatomically localize intracardiac and extracardiac inflammation through detection of fludeoxyglucose (18-F) uptake. Cardiac MRI can also be used to improve the sensitivity of diagnosis and typically demonstrates myocardial delayed enhancement with gadolinium. In addition to monitoring for permanent pacing and implantable cardioverter-defibrillator indications, corticosteroids are the mainstay of treatment. In cases of drug-refractory ventricular tachycardia, catheter radiofrequency ablation through endocardial and/or epicardial access may be considered. Patients with advanced heart failure or malignant ventricular arrhythmias may also be considered for cardiac transplantation.

Relapsing Polychondritis

Relapsing polychondritis is an idiopathic, degenerative, inflammatory disease characterized by destruction of cartilage, which results in damage to organs of special sense (outer/inner ear, eyes, nose) in addition to the musculoskeletal system. Relapsing polychondritis can cause aneurysms of the ascending aorta and subsequent aortic regurgitation (because of its effect on the cartilaginous support structures of the mediastinum) as well as vasculitis of vessels ranging in size from the aorta to postcapillary venules. The vasculitis may result in either thrombosis or thrombotic emboli. Corticosteroids are primary therapy.

Behçet Disease

Behçet disease is a chronic inflammatory disease—considered a multisystem vasculitis—characterized by oral aphthous ulcers as well as ulcers of the skin, genitals, and eyes. The vasculitis can result in aneurysms of the arch vessels and the abdominal aorta as well as a proximal aortitis that may cause aortic regurgitation from dilation of the aortic

root. Corticosteroids are primary therapy.

HEMATOLOGIC/ONCOLOGIC DISORDERS

Iron Overload

Iron overload may result from primary hemochromatosis, multiple transfusions, intestinal hyperabsorption, and from diseases characterized by bone marrow failure. The most common cardiac complication of iron overload is a restrictive cardiomyopathy secondary to myocardial iron deposition. Pericarditis, AV conduction disorders, and angina, despite normal coronary arteries, also occur. Phlebotomy and chelation therapy with deferoxamine can remove excess iron and a new oral iron chelator, deferiprone, is being tested in patients with sickle cell anemia.

Anemia

Severe anemia can result in left ventricular dysfunction and ultimately congestive heart failure and is associated with a lower quality of life and an impaired survival. Angina may also occur in severe anemia as a consequence of a marked reduction in oxygen transport capacity. For hemolytic anemias related to prosthetic valves, transfusion can increase blood viscosity and reduce valve-related hemolysis. Recent studies of erythropoietin to restore near-normal hemoglobin values in patients with renal failure was associated with increased mortality, hypertension, and thrombosis and in another study did not reduce the composite endpoint of death or a cardiovascular event.

In sickle-cell disease, myocardial infarction may occur with sickling of cells in coronary arteries, leading to coronary artery thrombosis. Acute mitral regurgitation from papillary muscle involvement can complicate myocardial infarctions in sickle-cell disease. Pulmonary infarction may also occur, from either pulmonary arterial thrombosis or embolization of venous thrombi.

Polycythemia

In addition to polycythemia vera, other polycythemic states may result in adverse cardiovascular effects. Like polycythemia vera, thrombocytosis, leukocytosis, plasma cell neoplasms, monoclonal gammopathies such as multiple myeloma, and cryoglobulinemia each may cause a hyperviscosity syndrome, leading to vascular thrombosis. Coronary arterial thrombosis may result in myocardial infarction, deep venous thrombosis can lead to pulmonary embolism, and peripheral arterial thrombosis may cause skeletal muscle or organ-specific infarction.

Therapy is focused on reducing the polycythemic load with treatment specific to the involved cell line. Polycythemia vera and thrombocytosis may respond to hydroxyurea. Leukocytoses and plasma cell neoplasms should be treated with appropriate chemotherapeutics, and, in the case of paraproteinemias, plasmapheresis is an important adjunctive therapy.

Neoplastic Disease

Tumors originating in the heart and those that commonly metastasize to the myocardium are discussed in the Cardiac Tumors chapter. Pericardial disease may take the form of metastatic infiltration causing a constrictive physiology or it may be effusive, resulting in possible cardiac tamponade. Noninfectious, nonmetastatic, thrombotic endocarditis, also known as marantic endocarditis, may occur. Marantic endocarditis generally does not destroy valve architecture or disrupt valvular function but does predispose to peripheral embolism. Myocardial ischemia is a potential complication of thrombotic emboli or extrinsic compression of epicardial coronary arteries. Dysrhythmias are common with metastases to the myocardium. The superior vena cava (SVC) syndrome, caused by extrinsic compression of the SVC by tumor or enlarged lymph nodes resulting in venous stasis in the head, arms, and upper torso, may also complicate malignancies.

Effusive pericardial disease is treated with percutaneous or surgical drainage, whereas infiltrative pericardial disease requires surgical pericardial stripping. The presence of marantic endocarditis requires no specific therapy, though treating ischemic syndromes that may result or occur concomitantly requires anticoagulation that may precipitate further embolic phenomena. The SVC syndrome requires urgent combination therapy with external-beam radiation and chemotherapy, and endovascular stenting has become a common adjunctive treatment.

External-Beam Radiation Therapy

Patients who receive external-beam radiation (XRT) for chest wall or mediastinal tumors often suffer heart-specific side effects. Pericardial disease may range from an effusion to calcific constrictive pericarditis. Coronary arteries may undergo accelerated atherosclerosis or narrowing, a form of radiation fibrosis. Heart valves may also be damaged, resulting in valvulitis that can cause either stenosis or regurgitation. XRT may also cause a cardiomyopathy from direct myocardial damage, though this can be difficult to distinguish from a cardiomyopathy caused by simultaneously used chemotherapeutic agents.

Pericardial disease is treated with drainage or pericardial stripping. Coronary artery disease should be managed with conventional therapies, and valvulitis requires serial echocardiography to determine timing of surgical repair or replacement. XRT-related cardiomyopathy is managed by usual congestive heart failure therapies.

Chemotherapy

Anthracycline chemotherapeutics and mitoxantrone (a chemically similar antineoplastic medication) are known to cause a well-described dilated cardiomyopathy that is related to cumulative dose. The cardiomyopathy should be treated with conventional congestive heart failure therapy. These drugs may also cause an acute toxicity, characterized by electrocardiogram changes that include a prolonged QT interval and nonspecific ST-

segment and T-wave changes. Other chemotherapeutics are also identified as cardiotoxins. Ischemic coronary syndromes may be precipitated by 5-fluorouracil in patients with preexisting coronary artery disease. Treatment consists of usual coronary artery disease management. Cyclophosphamide and ifosfamide have been shown to cause a cardiomyopathy similar to that observed with the anthracyclines and should be managed similarly. Small-molecule kinase inhibitors and antibody-based therapies targeting signaling pathways in cancer such as sunitinib, imatinib, trastuzumab, and sorafenib have been associated with drug-induced cardiac injury in a subset of treated individuals.

RENAL FAILURE

Although congestive heart failure may lead to renal insufficiency, the reverse may also occur. Uremic cardiomyopathy may result from volume and pressure overload related to insufficient fluid clearance, and circulating uremic toxins have a negative inotropic effect. As with most secondary cardiomyopathies, treatment consists of conventional congestive heart failure management measures.

Accelerated atherosclerosis can result from the hyper-lipidemia that constitutes a component of the nephrotic syndrome, which should be treated with aggressive medical therapy. Hypertension can also occur as a result of renal failure, especially in cases caused by arterionephrosclerosis, glomerulopathies, or transplant-associated renal failure. Treatment consists of antihypertensive medications and early hemodialysis as the renal failure progresses.

Calcification of the heart's valvular apparatus, coronary arteries, conduction system, and pericardium may develop as the calcium phosphorus product increases with worsening renal failure. Diet modification and phosphate-binding agents are the treatments of choice.

Furthermore, pericardial disease in renal failure ranges from constriction to uremic pericarditis with effusion. Percutaneous or surgical drainage may be required. Effective hemodialysis can reduce the likelihood of developing further effusions.

Because of the rapid changes in electrolytes and pH that accompany dialysis and the high prevalence of underlying heart disease among patients with renal failure, dysrhythmias are common, requiring supportive care and close monitoring of electrolytes both pre- and postdialysis.

HIV

Among the protean clinical manifestations of HIV, the heart is not spared. Left ventricular dysfunction results as HIV infection progresses to individual cardiac myocytes, causing focal myocarditis. This cardiomyopathy is more common as the

CD4+ cell count decreases and tends to occur more frequently in infected children. Treatment consists of usual measures for dilated cardiomyopathy.

As HIV progresses, the release of cytokines to fight opportunistic infections and to signal maximal activation of the immune system compromises endothelial integrity at the capillary level. This results in pleural, peritoneal, and pericardial effusions. The presence of a pericardial effusion markedly increases predicted mortality. Screening echocar-diography is a reasonable consideration in the later stages of HIV, and percutaneous or surgical drainage may become necessary in the presence of hemodynamic compromise or to examine fluid for treatable opportunistic etiologies (e.g., tuberculosis, malignancy).

The chronic inflammatory state present in HIV and lipid-raising tendency of protease inhibitors may result in accelerated atherosclerosis of the coronary arteries. Patients on antiretrovi-ral therapy should receive aggressive lipid-lowering therapy, and a high degree of suspicion should exist in even young HIV+ patients presenting with possible anginal syndromes.

A heart-specific opportunistic infection occurring in the setting of HIV is Salmonella endocarditis, as the transient bacteremia that may occur after ingestion of affected food will not be effectively cleared. Fungal endocarditis is also included on the list of HIV-associated opportunistic infections. Treatment consists of broad-spectrum antibiotic therapy pending isolation of a specific pathogen.

Finally, HIV-associated malignancies may involve the heart as well, most commonly metastatic Kaposi sarcoma and lymphomas, which may be heralded by pericardial effusions. Treatment is specifically directed at the identified malignancy.

Antiretroviral therapy is implicated in increasing metabolic and cardiovascular risk. All HIV-infected individuals should be evaluated regularly for lipid abnormalities, hyperglycemia, hypertension, and obesity as part of risk stratification for coronary artery disease. Selection of retroviral medications to minimize metabolic risk without compromising suppression of viral replication must be considered.

CONCLUSION

Given the spectrum of noncardiac disease that may significantly affect the heart and cardiovascular system, a working knowledge of these interactions is essential for treatment of patients with cardiovascular disease and for success on the Cardiovascular Medicine Board Examination. Effective care for patients with systemic disease demands cooperation with internists as well as medical and surgical subspecialists.

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QUESTIONS AND ANSWERS

Questions

1. Match the syndrome with the phenotype.
   a. Marfan
   b. Osler-Weber-Rendu
   c. Noonan
   d. Williams
2. Infundibular stenosis, atrial septal defect, patent ductus arteriosus, tetralogy of Fallot
   a. Mitral valve prolapse, aortic regurgitation, aortic aneurysm/dissection
   b. Paradoxical emboli
   c. Elfin facies, hypercalcemia, supravalvular aortic stenosis, atrial septal defect, ventricular septal defect
3. In a patient with myotonic dystrophy, which of the following is not an associated electrocardiographic abnormality?
   a. Intraventricular conduction delay
   b. Left ventricular hypertrophy by voltage criteria

c. Pathologic Q waves
d. Atrioventricular (AV) conduction block

4. Typically, Guillain-Barré syndrome (GBS) is not associated with which of the following abnormalities?
   a. Hypertension
   b. Sinus tachycardia
   c. Sinus bradycardia
   d. Orthostatic hypotension
   e. Ventricular tachycardia

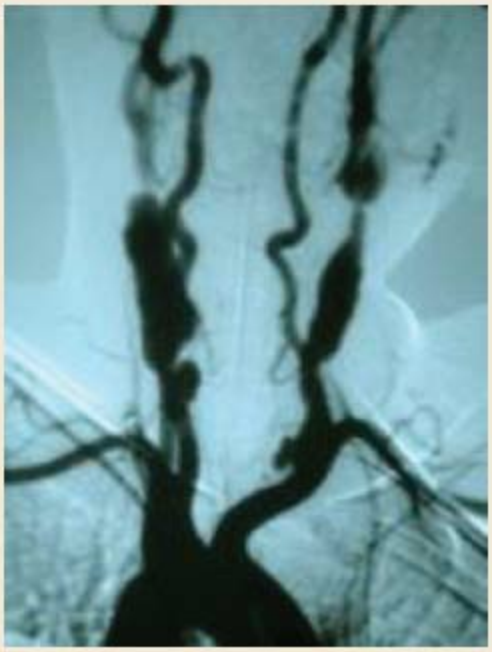
5. A 35-year-old woman with rheumatoid arthritis (RA) presents for evaluation of hypertension and resting tachycardia. Her RA is controlled on 5 mg/day of prednisone. She does not experience chest pain or dyspnea. Her vital signs include an irregular apical pulse of 120 beats/min (bpm) and a blood pressure of 165/70 mm Hg. Serum electrolytes and a complete blood count are within normal limits. What is the most appropriate initial therapy?
   a. Increase the steroid dosage.
   b. Discontinue steroid therapy.
   c. Transsphenoidal pituitary resection followed by corticosteroid and T4 replacement
   d. β-Adrenergic blockers and methimazole

6. A 27-year-old white man presents to the outpatient department with dyspnea on exertion. He has no symptoms of chest pain or presyncope, and reports only a migratory joint discomfort on review of systems. Vital signs demonstrate a heart rate of 90 bpm and a blood pressure of 125/44 mm Hg. His jugular venous pressure is normal, his lungs are clear, and his heart rhythm is regular. What findings would you expect on further examination and testing?
   a. Malar rash, holosystolic murmur radiating to the axilla, positive serum anti-dsDNA antibody
   b. Telangiectasias, sclerodactyly, diffuse ST-segment elevations on electrocardiogram
   c. Loss of lumbar lordosis, diastolic murmur at the left sternal border, iritis, positive serum HLA-B27 marker
   d. Digital ulnar deviation, positive serum rheumatoid factor, electrical alternans on electrocardiogram. AV conduction block and a restrictive pulmonary function test pattern

7. A 45-year-old woman with a history of Hodgkin's disease presents with dyspnea. She underwent chemotherapy and external-beam radiation 10 years ago, and her Hodgkin's disease has been in clinical remission ever since. Which of the following is not likely to be the cause of her dyspnea?
   a. Complete heart block
   b. Coronary artery disease
   c. Aortic stenosis
   d. Constrictive pericarditis

8. Which of the following is not a cardiac complication of HIV infection and antiretroviral therapy?
   a. Diffuse coronary artery disease
   b. Intraventricular conduction delay
   c. Pericardial effusion
   d. Dilated cardiomyopathy with regional wall motion abnormalities

9. A 35-year-old woman of Asian descent presents with subacute onset of fevers, arthralgias, headaches, and jaw claudication and presents to the emergency room for further evaluation and management. The following imaging study is performed. The most likely diagnosis is:



a. Fibromuscular dysplasia
b. Takayasu's arteritis
c. Sarcoid vasculopathy
d. Giant cell arteritis

10. A 27-year-old male with myotonic muscular dystrophy is referred to your clinic after his neurologist noted second degree, Mobitz I (Wenckebach) as an incidental finding on ECG during a routine office visit. There were no other apparent conduction abnormalities. The patient is asymptomatic with his routine daily activities. Which of the following is the most appropriate management strategy at this time?
    a. Implant permanent pacemaker
    b. Electrophysiology (EP) study followed by permanent pacemaker if AV block at intra-or infra-His levels is found
    c. Holter monitor and close follow-up to evaluate for more advanced degree of heart block
    d. Exercise stress testing to evaluate exercise capacity and dromotropic response.

11. A 24-year-old woman with Marfan syndrome presents to your office because she would like to explore options regarding pregnancy. She has a history of mild aortic root dilatation to 3.7 cm. She has no family history of acute aortic syndromes. What is the most appropriate recommendation at this time?
    a. Recommend against pregnancy due to increased risk of acute aortic syndromes
    b. Recommend increased cardiovascular monitoring during pregnancy and into the puerperium
    c. Prophylactic repair of the aortic root prior to pregnancy
    d. Beta-blocker and reassess progression of aortic dilatation in 6 months

12. In which of the following clinical situations is the role for prophylactic surgical repair of an aortic aneurysm less clear in preventing an acute aortic syndrome?
    a. Loeys-Dietz syndrome with ascending aortic diameter 4.5 cm
    b. Marfan syndrome with ascending aortic diameter of 5.0 cm
    c. Thoracic aortic aneurysm with ascending aortic diameter of 5.5 cm
    d. Ehlers-Danlos syndrome, vascular form with ascending aortic diameter of 4.5 cm

Answers

1. Answers: A-2, B-3, C-1, D-4

2. Answer B: Unlike the muscular dystrophies, myotonic dystrophy is not associated with a hypertrophic cardiomyopathy. It is, however, associated with the electrocardiogram abnormalities above.

3. Answer C: The autonomic instability that characterizes the polyneuropathy in GBS may result in hypertension, orthostatic hypotension, and sinus tachycardia; sinus bradycardia is usually not observed. Ventricular tachycardia may also occur.

4. Answer D: This patient has hyperthyroidism. Her RA increases her risk of other autoimmune disorders; the most common cause of hyperthyroidism is Graves disease, an autoimmune disorder characterized by autoantibodies against the thyrotropin receptor. Her associated hypertension and atrial fibrillation are best managed initially with β-adrenergic-blocking agents and then by antithyroid medications.

5. Answer C: This patient has ankylosing spondylitis. The wide pulse pressure results from a regurgitant aortic valve, which would also cause the diastolic murmur. The arthritis associated with ankylosing spondylitis is asymmetric and migratory, and loss of lumbar lordosis occurs with sacroiliitis. The clinical findings listed would not account for scleroderma-associated pericarditis (as in choice b), for RA-associated pericardial effusion (as in choice d), or for sarcoid-associated heart block (as in choice e).

6. Answer A: Complete heart block is not a complication of external-beam radiation. Diffuse coronary artery disease, valvulitis causing aortic stenosis, and constrictive pericarditis may all result from radiation-induced mediastinal damage.

7. Answer B: Although HIV and protease inhibitors may cause diffuse coronary artery disease, pericardial effusion, and focal myocarditis, intraventricular conduction delay is not an associated complication of the infection or therapy.

8. Answer B: The question highlights several characteristics that are consistent with Takayasu's arteritis including, young female, Asian origin, inflammatory constitutional symptoms, and the imaging study demonstrates serial arterial stenoses alternating with regions of normal arterial diameter representing an inflammatory vasculitis.

9. Answer A: Guidelines have a Class I recommendation for permanent pacing in neuromuscular diseases with AV block, such as myotonic muscular dystrophy, Kearns-Sayre syndrome, Erb's dystrophy, and peroneal muscular atrophy with or without symptoms, because there may be unpredictable progression of AV conduction disease. There is a Class IIb recommendation for permanent pacing in neuromuscular diseases with any degree of AV block (including first-degree AV block) with or without symptoms.

10. Answer B: Pregnant patients with Marfan syndrome are at increased risk for aortic dissection if the aortic diameter exceeds 4 cm and it is reasonable to prophylactically replace the aortic root and ascending aorta if the diameter exceeds 4.0 cm. All women with Marfan syndrome warrant frequent cardiovascular monitoring throughout pregnancy and into the puerperium.

11. Answer D: Most of the fatal complications are caused by arterial rupture or dissection. These arterial ruptures lead to reduced life expectancy; however, often no aneurysms are documented.

CHAPTER

Cardiac Neoplasms

Michael Samara and Brian P. Griffin

Primary cardiac tumors are rare occurring with a prevalence ranging from 0.001% to 0.03% in unselected autopsy series. Metastatic involvement of the heart is significantly more common, present at autopsy in roughly 20% of patients dying from extracardiac malignancies. The vast majority of primary cardiac tumors are of mesenchymal origin and accordingly display a variety of histopathologies. Over 75% of primary tumors are benign. Symptoms when present may be related to obstruction, interference with valvular structures resulting in regurgitation, direct invasion of the myocardium with associated impaired contractility, arrhythmia and conduction disorders, pericardial effusion, or embolization.[1,2]

BENIGN TUMORS (TABLE 59.1)

TABLE
59.1 Benign Primary Cardiac Tumors

Cardiac Tumor	Epidemiology	Clinical Associations	Location	Pathology
Myxoma	Bimodal 20s/50s F > M 7%–10% familial	Carney complex NAME syndrome LAMB syndrome	LA (80%)/RA (15%)/ventricle (5%) Interatrial septum inferior to fossa ovalis	Scattered cells in mucopolysaccharide stroma Pedunculated solitary tumor
Papillary fibroelastoma	Frequency ↑ w/age M = F		Valvular endocardium (90%) Aortic valve most common Single in 91% of cases	Avascular connective tissue core covered by endothelium Fronds extending from central stalk
Lipoma	All ages M = F	Tuberous sclerosis	Subendocardial/subepicardial > intramyocardial	Encapsulated mature adipocytes
Rhabdomyoma	80% before 1 y	Tuberous sclerosis	Intramyocardial or AV valves	Striated muscle cells in myxomatous stroma
Fibroma	90% in children M = F	Gorlin syndrome	Interventricular septum and LV free wall	Solitary intramural lesions
Hemangioma	All ages M = F	Kasabach–Merritt syndrome	Ventricle > atria	Multiple in 30% of cases Capillary and cavernous morphologies

Myxomas

Myxomas represent the most common primary cardiac tumors in adults, accounting for approximately 25% of all cardiac neoplasms and 75% of all benign primary cardiac tumors. While once thought to represent organized thrombus, gene expression and immunohistochemical studies have firmly concluded that they are neoplasms arising from multipotent mesenchymal cells.[3] Myxomas have a bimodal peak onset in the third and sixth decades of life with 65% occurring in women. Seven to ten percent of myxomas are familial in origin.[4] The autosomal dominant Carney complex represents the majority of these familial cases and is characterized by cardiac and extracardiac myxomas (breast and skin), lentigines, hyperendocrine states, and nonmyxomatous extracardiac tumors including testicular Sertoli cell tumors, schwannomas, pituitary adenomas, and thyroid tumors. Other familial syndromes associated with myxoma formation include the LAMB (lentigines, atrial myxoma, mucocutaneous myxoma, and blue nevi) and NAME (nevi, atrial myxoma, myxoid neurofibromata, and ephelides) syndromes. In contrast to sporadic cases, familial myxomas have no clear predilection for sex or age, are multicentric, apically located, and more likely to recur following resection (20% of cases in the Carney complex).[5]

Over 90% of myxomas are solitary with 80% located in the left atrium, most commonly attaching to the interatrial septum at the inferior border of the fossa ovalis. They may however arise from any endocardial surface within the heart with 15% occurring in the right atrium and the remaining 5% arising from the ventricles or atrioventricular (AV) valves.[6] Myxomas are pedunculated with surfaces that may be smooth or villous. On gross examination they have a gelatinous consistency with foci of hemorrhage, calcification, ossification, and frequently cystic components. Size at the

time of diagnosis is typically 4 to 8 cm in diameter though myxomas as large as 16 cm have been described in the literature.

As with all cardiac tumors, symptoms are highly variable and depend largely on tumor size, location, and mobility. The classic triad of symptoms includes obstructive symptoms (syncope, sudden cardiac death, or symptomatic heart failure [HF]), embolic phenomenon, and constitutional symptoms (fever, weight loss, arthralgias, and Raynaud syndrome) thought secondary to release of IL-6. Findings on auscultation include diastolic and systolic murmurs. The characteristic low-pitched "tumor plop " occurring 80 to 120 ms after S_2 (i.e., after an opening snap and prior to a third heart sound) and correlating with tumor movement through the mitral valve and contact with the ventricular wall is heard in only a minority of cases.[4]

Laboratory abnormalities include elevated erythrocyte sedimentation rates and C-reactive protein, anemia (often hemolytic), polycythemia, and thrombocytopenia. The diagnosis is made by echocardiography, contrast-enhanced computed tomography (CT), or cine gradient-echo cardiac MR (CMR) where myxomas appear as heterogeneous density spherical or ovoid masses (Fig. 59.1). Thrombus is the primary differential diagnosis with protrusion through the mitral annulus being the most specific finding favoring the diagnosis of myxoma.

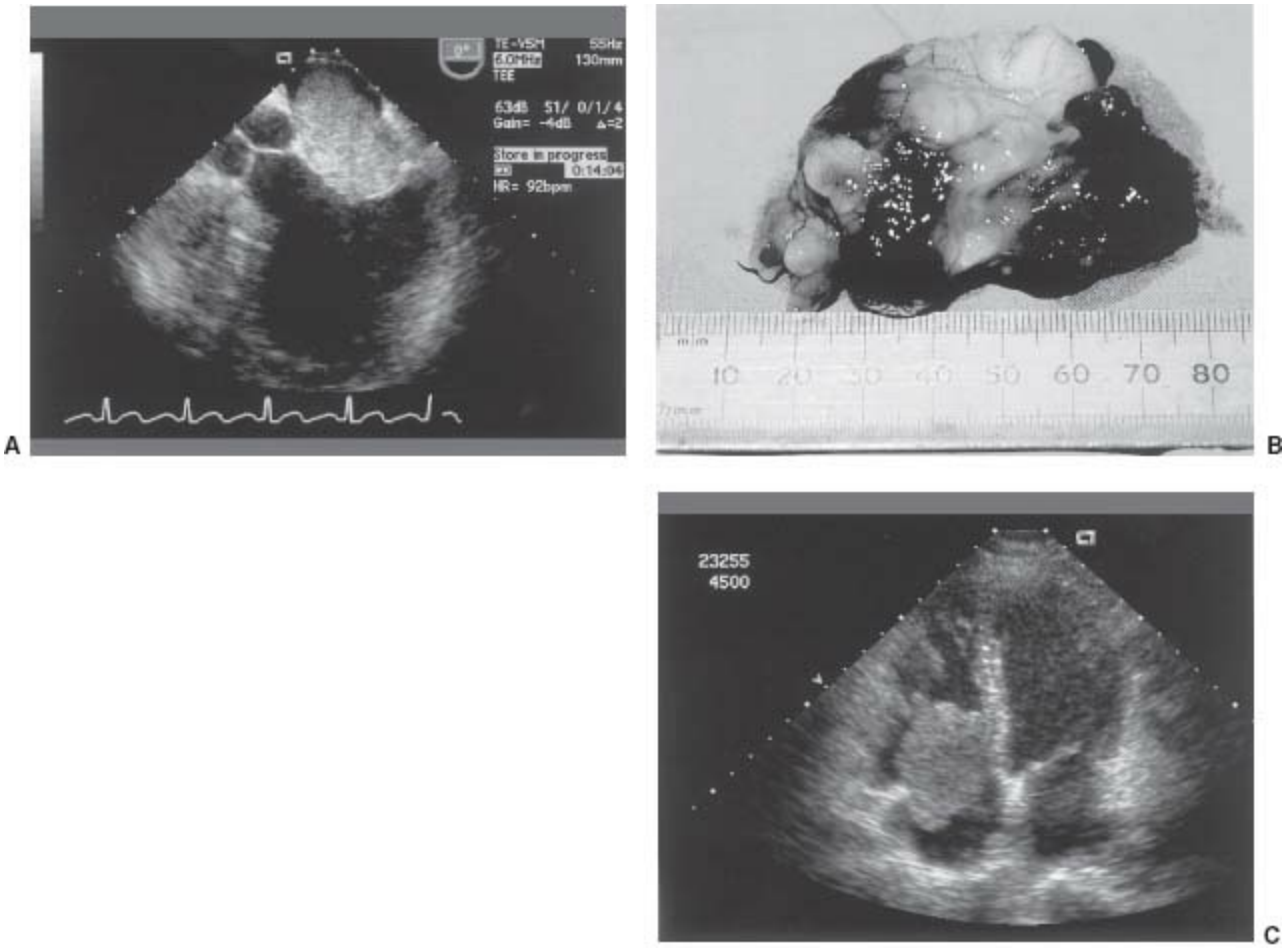


FIGURE 59.1 A: Left atrial myxoma. **B:** Surgical specimen, left atrial myxoma (same as part A). **C:** Right atrial myxoma.

Treatment consists of surgical resection, which is associated with a low operative mortality, and, with the exception of familial cases, a low recurrence rate (0% to 3%). Complete resection of the tumor and avoidance of excessive manipulation is essential to preventing local and distant recurrences, respectively. As with all cardiac tumors, this is best achieved with extracorporeal circulatory support via femoral or azygous vein cannulation in order to avoid tumor fragment embolization, facilitate direct visualization, and rule out metasynchronous tumors. As with all resected cardiac tumors, annual noninvasive imaging is recommended for follow-up.[6]

Papillary Fibroelastoma

Papillary fibroelastoma is the second most common benign primary cardiac tumor and the most common to involve the cardiac valves. Eighty percent of fibroelastomas occur in the left cardiac chambers with the aortic and mitral valves being the most common sites. Fibroelastomas are typically found on the downstream aspect of the valve and appear as frondlike projections of collagen and elastic fibers emanating from a short central stalk (often described as sea anemone like) (Fig. 59.2). Their small size and highly mobile nature make them best suited to visualization with echocardiography. They can be differentiated from Lambl excrescences by their location on noncontact surfaces of the valve. Symptoms when present are due to systemic embolization with stroke and myocardial infarction being the most feared complications. The current therapeutic approach is surgical excision for fibroelastomas that are highly mobile, > 1 cm in size or associated with prior embolization. In nonsurgical candidates with prior embolic events long-term anticoagulation may be considered.[7]

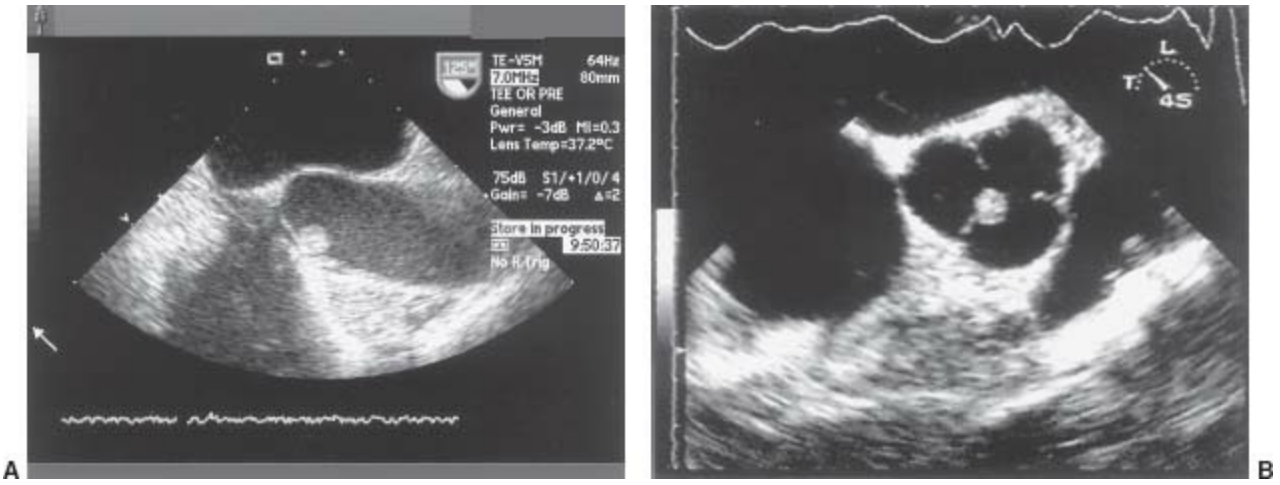


FIGURE 59.2 A, B: Aortic valve papillary fibroelastoma.

Other Benign Primary Cardiac Tumors

Lipoma

Cardiac lipomas are the third most common benign primary cardiac tumors and as their name implies represent well-encapsulated collections of mature adipocytes. Subepicardial and subendocardial locations predominate though intramyocardial locations can also occur. Clinical presentations are largely dictated by location with subepicardial lipomas rarely resulting in symptoms unless very large and associated with pericardial effusion or chamber compression. Subendocardial lesions may result in hemodynamic obstruction when large and intramyocardial lipomas may occasionally present with conduction disorders or arrhythmia. Because lipomas have a nonspecific echocardiographic appearance, CT has become a favored diagnostic modality demonstrating a well-circumscribed mass with low attenuation similar to subcutaneous fat. Surgical resection is reserved for symptomatic cases.[8]

Lipomatous hypertrophy of the interatrial septum (LHAS) is a nonneoplastic excessive accumulation of nonencapsulated fat > 2 cm in diameter in the superior and inferior portions of the atrial septum, sparing the fossa ovalis. LHAS is more common in elderly, obese, and male patients. Rhythm disturbances and hemodynamic obstruction necessitating surgical intervention are rare.

Rhabdomyoma

Cardiac rhabdomyomas are quite rare in adult populations but represent the most common benign primary cardiac tumors in the pediatric population with more than 80% occurring in patients < 1 year of age. They are thought to represent hamartomatous growths as opposed to true neoplasms with an absence of mitotic activity and a tendency to spontaneously regress. The later characteristic has led to the recommendation that asymptomatic lesions be followed conservatively.[4] There is a clear association with tuberous sclerosis with 80% of rhabdomyoma patients having the disease. In these cases multiple tumors are the rule.[9]

Fibroma

Cardiac fibromas are the second most common benign primary cardiac tumor in pediatric populations and again are rarely seen in adults. They are typically located in the left ventricular (LV) free wall, ventricular septum, or apex with the LV involved five to ten times more frequently than the RV. They can grow to large sizes with clinical presentations including signs and symptoms of mechanical obstruction, congestive HF due to systolic or diastolic dysfunction, or malignant arrhythmias. While nonspecific, the diagnosis is often suggested by the presence of calcification (Fig. 59.3). Definitive treatment involves resection as unlike rhabdomyomas they rarely regress. Cardiac

fibromas may occur as part of the Gorlin syndrome (cardiac fibromas, multiple basal cell carcinomas, jaw cysts, and skeletal abnormalities).[4]

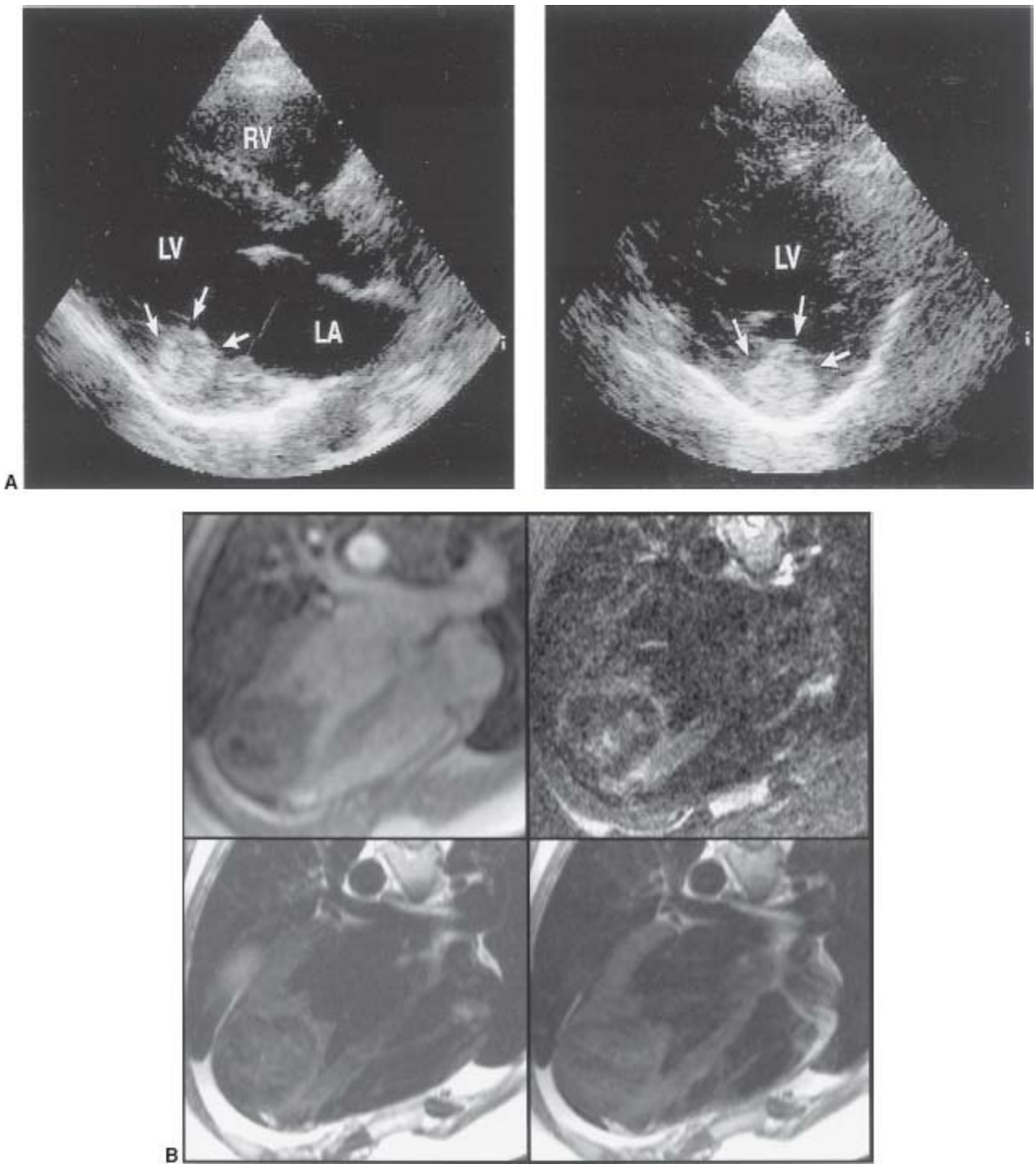


FIGURE 59.3 A: Left ventricular fibroma **(B)** MRI, left ventricular fibroma.

Hemangioma

Cardiac hemangiomas are vascular malformations composed of endothelial-lined

channels with interspersed fat and fibrous septa. They represent < 2% of benign primary cardiac tumors and can occur at any age, in any chamber, and at any level from pericardium to endocardium. They appear hyperechoic by echocardiography and have characteristic intense contrast enhancement on CT. Similarly coronary angiography may demonstrate findings consistent with perfusion although in both cases contrast enhancement may vary with "low flow " cavernous hemangiomas having relatively reduced perfusion. Given that they often regress spontaneously, conservative management is favored in asymptomatic patients.

MALIGNANT TUMORS (TABLE 59.2)

TABLE
59.2 Malignant Primary Cardiac Tumors

Cardiac Tumor	Epidemiology	Clinical Presentation	Location	Notes
Angiosarcoma	30–50 y M:F 2:1	Right-sided HF Hemorrhagic effusion Continuous precordial murmur Includes Kaposi sarcoma	90% in RA	RA location may contribute to late diagnosis with large tumor burden and symptoms of right-sided failure
Rhabdomyosarcoma	Children and young adults M > F	Obstructive symptoms Constitutional symptoms Hypereosinophilic syndrome	No chamber predilection Multiple in 60% of cases	Generally infiltrative but may have polypoid appearance
Leiomyosarcoma	30–40 M = F	Obstructive symptoms Constitutional symptoms Metastatic disease	LA (70%–80%)	Differentiated from LA myxoma by broad base and propensity for extending into pulmonary trunk
Lymphoma	All ages M > F Immunocompromised hosts (HIV, post-transplant, PTLD)	Obstructive symptoms Arrhythmia Embolic phenomena Pericardial effusion	Right-sided chambers 60% Pericardium 20%	Most commonly diffuse large B cell lymphoma
Mesothelioma	Frequency ↑ w/age M = F	Constrictive pericarditis Hemorrhagic effusion Conduction disorders	Typically in pericardium Rarely near AV node	Association with asbestos exposure not as well defined as pleural disease

Malignant cardiac tumors account for approximately 25% of primary cardiac tumors. Morphologic features suggesting malignancy include right-sided location (with the exception of leiomyosarcoma), broad-based attachment, involvement of multiple chambers, size > 5 cm, associated pericardial effusion, and extension into the

mediastinum, great vessels, or pulmonary veins. As metastatic disease involving the heart is significantly more common, detailed clinical examination and appropriate imaging are warranted to rule out the possibility of a distant noncardiac primary.[9,10]

Transesophageal echocardiography (TEE) is the initial diagnostic test of choice; however, owing to its inability to demonstrate infiltration, regional invasion, and distant metastases, it is important to supplement with CT and CMR. Currently, no TNM classification exists, and treatment strategies remain poorly defined with surgery recommended when complete resection is feasible or when severe symptoms require palliation.[10]

The vast majority of primary malignant cardiac tumors are rapidly proliferating sarcomas. They typically result in death secondary to wide spread infiltration, obstructive symptoms, or diffuse metastases with a median survival of 6 to 12 months. Survival is improved significantly in cases where complete surgical resection is possible. In well-selected patients, cardiac transplantation or autotransplantation has been successfully employed. A team approach to care is required as adjuvant/neoadjuvant chemotherapy and external beam radiation therapy are often used in conjunction with surgery (Fig. 59.4).

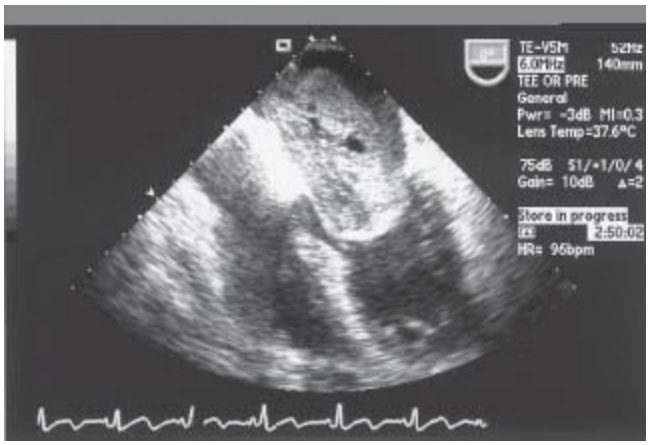


FIGURE 59.4 Left atrial sarcoma.

Primary cardiac lymphomas represent the second most common class of primary malignant cardiac tumors with a frequency that has increased in the era of solid organ transplantation. The disease is more common in immunocompromised hosts such as those with HIV associated lymphoma or post transplant lymphoproliferative disorder (PTLD) where extracardiac involvement is the rule at the time of diagnosis. Treatment typically consists of systemic chemotherapy.[10]

SECONDARY CARDIAC TUMORS

Tumor metastases to the heart are 20 to 40 times more common than primary malignant

tumors. Primary tumors that metastasize to the heart in order of descending frequency include lung, breast, lymphoma/leukemia, esophageal, uterine, melanoma, gastric, sarcoma, and colon. Melanoma has the greatest propensity to metastasize to the heart (60% to 70% cardiac involvement with metastatic disease). Metastases reach the heart via hematologic or lymphatic spread (melanoma, lymphoma, and breast), invasion through venous structures (renal, hepatocellular, adrenal, uterine), or direct invasion (lung, breast, esophageal) (Fig. 59.5). The pericardium is the most common site of involvement, followed by myocardial involvement, and rarely endocardial and valvular surfaces (Fig. 59.6).[11]

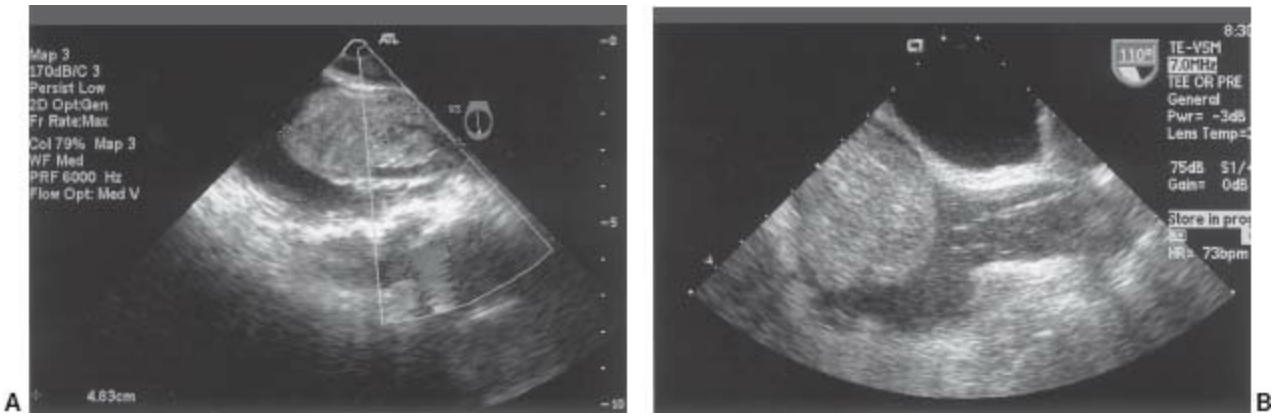


FIGURE 59.5 A, B: Inferior vena cava/right atrial tumor, renal cell carcinoma.

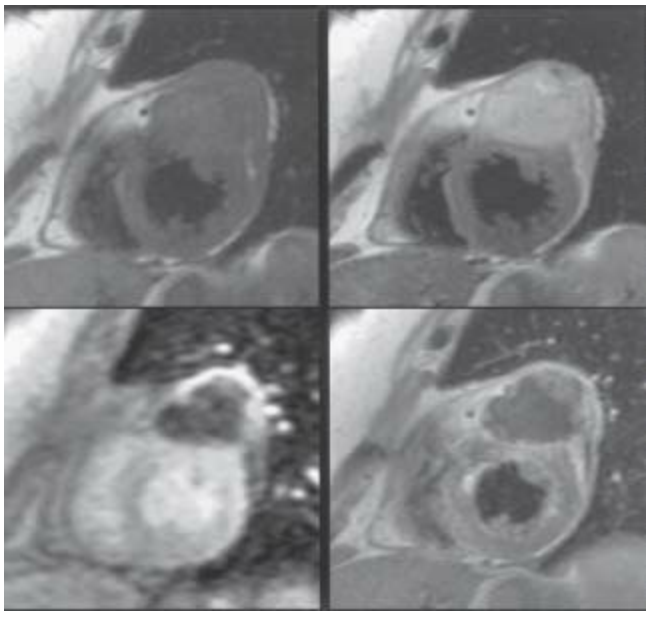


FIGURE 59.6 MRI, pericardial metastasis.

Since nearly all patients with cardiac metastases have widespread disease, therapy is generally directed at the primary tumor. Removal of a malignant pericardial effusion by pericardiocentesis or pericardial window with or without pericardial sclerosis may

palliate symptoms and delay or prevent recurrence.

Renal Cell Carcinoma

Renal cell carcinoma is unique in its propensity to invade the vena cava with locally advanced disease being classified in part on the basis of tumor thrombus extension below (Stage IIIb) and above (Stage IIIc) the diaphragm. For the approximately 5% of patients with inferior vena cava (IVC) involvement, radical nephrectomy with tumor thrombus resection is the preferred treatment strategy. In most cases this can be achieved without cardiopulmonary bypass. Hypernephromas and leiomyomatous sarcomas (uterine) may also invade the heart via the IVC.[12]

CARCINOID HEART DISEASE

Carcinoid tumors are rare gastrointestinal neuroendocrine tumors typically arising from the enterochromaffin cells of the gastrointestinal tract. While metastases to the heart are exceedingly rare, carcinoid heart disease resulting from deposition of fibrous tissue occurs in approximately 50% of patients with the disease and represents a major source of morbidity and mortality. Interestingly 20% of carcinoid patients present with cardiac manifestations in contrast to the classic vasomotor symptoms (flushing) and gastrointestinal hypermotility that may only be present in a small minority of patients with carcinoid tumors.

Carcinoid heart disease is characterized by the plaquelike deposition of fibrous tissue on the valvular endocardium and more rarely on the intima of the pulmonary arteries and aorta. These deposits appear to be mediated by high circulating concentrations of serotonin and typically require hepatic metastases or a primary ovarian carcinoid (via direct venous drainage into the IVC) to bypass inactivation in the liver. The right-sided valves are preferentially affected due to further inactivation of humoral mediators in the lung, though in the setting of overwhelming elevations in circulating serotonin levels, intracardiac shunting (patent foramen ovale/atrial septal defect [PFO/ASD]), or bronchial carcinoids, left-sided lesions have been described.

The diagnosis of carcinoid syndrome is best made using the 24-hour urine excretion of 5-hydroxyindoleacetic acid (HIAA) the terminal product of serotonin metabolism. The characteristic echocardiographic features include thickening and retraction of immobile tricuspid valve leaflets with associated tricuspid regurgitation. Tricuspid stenosis is less common.

Involvement of the pulmonic valve is typical with coexistent pulmonary regurgitation or stenosis. The causative plaques are composed of accumulations of smooth muscle cells and mucopolysaccharides and are histopathologically and echocardiographically identical to those observed in the setting of chronic ingestion of ergotamines or fenfluramine-phentermine.

Management of localized tumors typically involves surgical resection. Patients experiencing carcinoid syndrome typically have disseminated metastatic disease necessitating treatment with chemotherapy. The somatostatin analog octreotide can be used in cases with prominent flushing or diarrhea. Patients with carcinoid heart disease may remain asymptomatic for extended periods of time but ultimately present with symptoms of severe tricuspid regurgitation and right-sided HF. While surgical mortality is high, patients treated with valve replacement have superior survival to their medically treated counterparts.[13]

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QUESTIONS AND ANSWERS

Questions

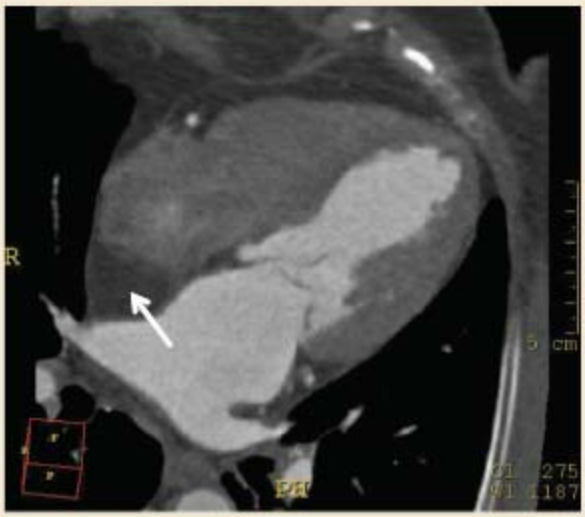
1. True statements regarding cardiac myxomas include all of the following except:
   a. They can arise anywhere within the heart.
   b. They are the most common primary cardiac tumor.
   c. Approximately 80% occur in the left atrium.
   d. The majority are familial.
   e. They may be associated with syncope, fever, or stroke.
2. True statements regarding papillary fibroelastomas include all of the following except:
   a. They have a fronded appearance.
   b. They have a benign histology.
   c. The vast majority arise on the right side.
   d. They have significant embolic potential.
   e. They are the most common tumor involving the cardiac valves.
3. Which of the following is not part of the Carney complex?
   a. Lentigines
   b. Extracardiac myxomas
   c. Testicular Sertoli cell tumors
   d. Schwannomas
   e. Hypoadrenalism
4. Which of the following malignancies has the highest propensity for cardiac metastasis?
   a. Lung cancer
   b. Renal cell carcinoma
   c. Melanoma
   d. Breast cancer
   e. Colon cancer
5. Leiomyosarcomas can be differentiated from myxomas on the basis of which of the following echocardiographic features?
   a. Propensity for right-sided heart chambers
   b. Broad based attachment
   c. Extension into the pulmonary vein
   d. Attachment to the interatrial septum
   e. b and c
6. A 32-year-old asymptomatic man with tuberous sclerosis is incidentally found to have a 1 × 1.5 cm intramyocardial mass in the left ventricular (LV) free wall on a transthoracic echocardiogram performed during an executive physical. How should you proceed with his diagnosis/management?
   a. Surgical consultation for resection
   b. Transesophageal echocardiogram to better characterize lesion
   c. Positron Emission Tomography with F-18 fluorodeoxyglucose to assess for metabolic activity
   d. Conservative management and reassurance
   e. Computerized tomography (CT) scan to better characterize lesion
7. A 59-year-old female with a history of liver transplantation for cryptogenic cirrhosis presents with a 3-month history of progressive dyspnea on exertion and lower extremity edema. On history, she also endorses fever, night sweats, and a 10 pound unintentional weight loss. Transthoracic echocardiography demonstrates a 3 × 4 cm mass occupying the right atrium and a moderate pericardial effusion without tamponade physiology. An extensive evaluation for extracardiac tumors is unrevealing. What is the most likely diagnosis?
   a. Angiosarcoma

b. Primary cardiac lymphoma
c. Mesothelioma
d. Rhabdomyosarcoma
e. Myxoma

8. A 43-year-old man with a history of multiple basal cell carcinomas is admitted to your service with progressive heart failure (HF) symptoms and syncope. The evening following admission he is noted to have multiple episodes of nonsustained monomorphic ventricular tachycardia. His transthoracic echo demonstrates 4 × 6 cm intramyocardial tumor in the LV myocardium with extensive calcification. What is the preferred treatment?
   a. Initiation of amiodarone and continued telemetry monitoring
   b. Referral to electrophysiology for implantation of an implantable cardioverter defibrillator
   c. Initiation of HF pharmacotherapy including beta antagonist therapy once euvolemic
   d. Referral for surgical resection

9. A 43-year-old female with biopsy proven carcinoid tumor with liver metastases presents to your clinic requesting a second opinion on the management of her valvular heart disease. She reports a 3-month history of progressive lower extremity edema and dyspnea on exertion. She denies flushing or diarrhea. On examination she has holosystolic murmurs at the left sternal border and apex and a fixed split second heart sound. The jugular venous pulsations are elevated with a prominent V-wave, her liver is pulsatile, and she has bilateral lower extremity pitting edema. Her echocardiogram demonstrates retracted and immobile tricuspid and mitral leaflets with severe tricuspid and mitral regurgitation. There is mild pulmonic insufficiency. Her right ventricle is moderately dilated with preserved systolic function. How would you counsel her?
   a. Advise that she immediately begin therapy with octreotide as inhibition of serotonin release will result in prompt reversal of her valvular disease.
   b. Advise her that given her metastatic carcinoid she is not a candidate for valvular surgery owing to her poor short-term prognosis.
   c. Advise her that her valvular disease is unlikely to be related to carcinoid given the involvement of the mitral valve.
   d. Advise her that surgical replacement of the valves, while high risk, will improve her survival. Ensure that she has appropriate oncologic follow-up for management options.

10. A 75-year-old obese man is referred to your clinic for further recommendations regarding the following incidental finding on cardiac CT imaging (see figure, arrow). He denies palpitations, syncope, or HF symptoms. What is the most likely diagnosis?



   a. Fibroma
   b. Lipomatous hypertrophy of the interatrial septum (LHAS)

c. Lipoma
d. Leiomyosarcoma

Answers

1. Answer D: Cardiac myxomas are the most common primary cardiac tumor, accounting for 50% of primary cardiac tumors in adults. Though they can be found anywhere in the heart, the most common location is in the left atrium. Myxomas can present with a classic triad of symptoms including obstructive, embolic, or constitutional symptoms. Only 7% to 10% are associated with autosomal dominant familial syndromes.

2. Answer C: Cardiac papillary fibroelastomas are the second most common primary cardiac tumor and the most common tumor of the cardiac valves. The majority involve the left heart chambers most commonly the aortic valve. They have embolic potential prompting referral for surgery in select cases.

3. Answer D: The Carney complex is characterized by cardiac and extracardiac myxomas, lentigines, nonmyxomatous extracardiac tumors including testicular Sertoli cell tumors, schwannomas, pituitary adenomas, and thyroid tumors. Frequently the Carney complex involves Adrenocorticotropic hormone-independent primary adrenal hypercortisolism and not hypoadrenalism.

4. Answer C: Melanomas have the highest propensity for cardiac metastases with 60% to 70% of cases of metastatic disease being associated with cardiac involvement. Owing to the fact that they are more common malignancies, lung and breast cardiac metastases are numerically more common.

5. Answer E: Leiomyosarcomas are unique amongst primary malignant cardiac tumors in that they predominantly occur in the left heart with 70% to 80% of tumors occurring in the left atrium. They can be differentiated from left atrial myxomas by their broad-based attachment and tendency to extend into the pulmonary veins.

6. Answer D: Both cardiac lipomas and rhabdomyomas can be seen in the context of tuberous sclerosis. Lipomas most commonly have an epicardial location with a narrow stalk and growth into the pericardial space. In some cases they may be intramyocardial and associated with conduction disorders or arrhythmia. Rhabdomyomas are quite rare in the adult population but may complicate tuberous sclerosis. They are typically intramyocardial and are defined by their propensity to regress spontaneously. Given that the patient is asymptomatic, further workup can be deferred and the patient can be followed conservatively with serial echocardiograms. Symptoms suggestive of conduction disease or arrhythmia (e.g., palpitations, syncope, etc.) should be aggressively pursued if they occur and may necessitate resection.

7. Answer B: Immunocompromised hosts including patients with HIV and those status postsolid organ transplantation are at risk of developing primary cardiac lymphomas. Angiosarcomas and rhabdomyosarcomas are diagnostic possibilities but less likely in this context. Mesotheliomas typically present with epicardial/pericardial masses in patients with a history of asbestos exposure. Atrial myxomas are less common in the right atrium but this too is a diagnostic possibility. Importantly, the presence of systemic complaints such as fever and weight loss may accompany both myxomas and malignant primary and secondary cardiac tumors. Tissue diagnosis is critical as unlike other malignant primary cardiac neoplasms, these lymphomas are best managed with attenuation of the immunosuppressive regimen and systemic chemotherapy. As with all primary malignant cardiac tumors, their rarity mandates that an exhaustive evaluation be performed to rule out an extracardiac primary tumor.

8. Answer D: This patient's tumor is most likely a fibroma given its intramyocardial location, extensive calcification, and the associated malignant arrhythmias. His history of recurrent basal cell carcinomas raises the possibility of the Gorlin complex (basal cell carcinomas, bifid ribs, cardiac fibromas, and mandibular cysts). Cardiac fibromas frequently present with malignant arrhythmias and HF due to obstruction or restrictive filling. Treatment focuses on surgical resection which is curative. In contrast to rhabdomyomas, fibromas are unlikely to regress spontaneously and conservative management is not appropriate.

9. Answer D: In the absence of severe right ventricular dysfunction, patients with severe tricuspid regurgitation secondary to carcinoid have an improved prognosis with valve replacement. Octreotide is

a synthetic somatostatin analogue that binds to carcinoid tumor cells and inhibits the production of serotonin and other biologic amines. It is effective in treating the vasomotor symptoms and diarrhea associated with carcinoid syndrome but will not lead to regression of her valvulopathy. Carcinoid tumors are typically indolent, and the short-term prognosis is excellent even in the setting of metastatic disease with 1- and 5-year survival rates of 80% and 60%, respectively for patients undergoing treatment. Carcinoid heart disease typically targets the right-sided valves but in the setting of intracardiac shunts or bronchial tumors, left-sided valves may be affected. In this patient, the fixed splitting of the second heart sound is the result of a small secundum atrial septal defect (ASD).

10. Answer B: The noncontrasted cardiac CT image demonstrates LHAS, a nonneoplastic excessive accumulation of nonencapsulated fat > 2 cm in diameter in the superior and inferior portions of the atrial septum. As seen in this image, there is typically sparing of the fossa ovalis. LHAS is more common in elderly, obese, male patients. The need for surgical resection is extraordinarily uncommon and predicated on the presence of associated arrhythmic or obstructive symptoms.

CHAPTER

Pharmacokinetic and Pharmacodynamic Essentials

Michael A. Militello

Basic understanding of pharmacokinetic and pharmacodynamic concepts is essential to the design of rational, patient-specific pharmacotherapy. The study of pharmacokinetics was first introduced some 40 years ago and is defined as the time course of drug absorption, distribution, metabolism, and elimination. In basic terms, this is described as how the body handles the drug. The concepts of pharmacokinetics can be applied to individual patients in order to maximize efficacy and limit drug toxicities. Drug plasma concentration can help to predict efficacy and toxicity of selected medications. Even though there are limited data for therapeutic drug monitoring for all medications, pharmacokinetic principles can be applied to a wide range of medications.

The primary principle of pharmacodynamics is that a relationship exists between drug concentration at the site of action (receptor) and pharmacologic response. The concentration at the receptor site is most important for elucidating pharmacologic response, with the assumption that serum concentration is directly proportional to receptor concentration. This assumption is not always true. For example, although abciximab has an initial half-life of 10 minutes and second-phase half-life of about 30 minutes, measurement of plasma concentrations of abciximab is not of clinical importance, whereas measurement of platelet activity potentially could be. The focus of this chapter is to review pharmacokinetic and pharmacodynamic concepts and relate them to specific cardiovascular medications. This chapter does not cover current guidelines for use of medications. Please refer to individual chapters in this review book for guideline reference.

PHARMACOKINETICS

Pharmacokinetics refers to the concepts of drug absorption, distribution, metabolism, and elimination (known as “ADME”). Such principles can be applied to drug therapy by

such examples as determining loading and maintenance doses of medications, adjusting doses for altered elimination (e.g., renal or hepatic insufficiency), and interpreting plasma drug concentrations. The concepts of ADME are reviewed below.

Absorption

Absorption of medications can occur via multiple routes of administration. Medications administered via the intravenous route are considered to have 100% absorption because the drug is delivered directly into the patient's circulation. Other routes of administration include oral, transdermal, buccal, sublingual, subcutaneous, intradermal, and rectal. Depending on the type of medication, there are advantages and disadvantages of each of these administration techniques related to absorption. For example, the administration of nitroglycerin via the oral route would provide little systemic effect because of the high degree of presystemic clearance through hepatic metabolism. However, when nitroglycerin is administered intravenously, transdermally, or sublingually, the amount delivered is greatly increased, as presystemic clearance is bypassed.

A number of factors affect the amount of drug absorbed. These include:

- Dose administered
- Fraction of the administered dose that is "active drug" (S)
- Bioavailability of the drug (F)

The equation for amount of drug absorbed is

$$\text{Amount of drug absorbed} = (S)\ (F)\ (\text{Dose})$$

The fraction of administered dose that is "active drug" (S) is typically described as the salt form of a drug and varies with different salts. For example, quinidine sulfate has 82% active drug, and quinidine gluconate has 62%. By using the above equation, you can convert one salt form to another salt, assuming you know the bioavailability (F). For example, quinidine sulfate is 82% quinidine base with a bioavailability of 0.73, and quinidine gluconate is 62% quinidine base with a bioavailability of 0.7. With this information, you can compare the amount of quinidine in each tablet to make your conversion. Below is a comparison of quinidine bases, assuming you have 200-mg tablets of both quinidine sulfate (a) andquinidine gluconate (b).

a. Amount of quinidine base absorbed = $0.82 \times 0.7 \times 200 \rightarrow 114.8$ mg
b. Amount of quinidine base absorbed = $0.62 \times 0.7 \times 200 \rightarrow 86.8$ mg

Bioavailability (F) is defined as the fraction of an administered dose that reaches the systemic circulation of a patient. Values of bioavailability can be found in a number of pharmacology texts and drug reference handbooks. Factors that can alter bioavailability

include:

- Inherent characteristics of the dosage form administered (e.g., tablet dissolution characteristics)
- Administration route (e.g., oral versus transdermal versus intravenous). The bioavailability of most parenterally administered drugs is 100% (i.e., F = 1).
- Issues related to the gastrointestinal (GI) tract

The bioavailability of orally administered medications can be affected by gastric pH, GI transit time, gut metabolism, and the presence of food. Certain medications may be unstable in low-pH environments and therefore may be enteric coated in order to prevent breakdown in the stomach. Conversely, certain medications, such as itraconazole, require an acid environment for optimal absorption. Likewise, changes in GI motility with promotility agents or patients experiencing diarrhea may have decreased absorption secondary to decreased transit time through the GI tract. Enzymatic metabolism of medications in the GI tract can also alter absorption and can be responsible for drug interactions. A well-described example of this is the fact that administration of grapefruit juice with certain medications may actually enhance bioavailability secondary to preventing GI metabolism of the compound, thereby increasing the amount of drug available for absorption. Finally, the amount of bioavailable drug may be reduced as a result of the extent of metabolism before reaching the systemic circulation. Examples of this include metabolism via GI bacteria (e.g., digoxin) or "first-pass metabolism" by the liver.

Drugs are absorbed from the GI tract into the portal circulation, and certain drugs are extensively metabolized in the liver before reaching systemic circulation. These drugs have a high first-pass effect or high first-pass metabolism, which can significantly decrease the amount of medication reaching the systemic circulation and hence drug bioavailability. Drugs with high first-pass metabolism have much lower intravenous doses compared to oral doses. Examples of medications with high first-pass metabolism are diltiazem, nitroglycerin, propranolol, verapamil, hydralazine, isoproterenol, labetalol, lidocaine, metoprolol, and nifedipine.

Distribution

After absorption, medications distribute to various tissues in the body to produce a pharmacologic effect. Not all distribution sites for a given medication produce a therapeutic effect. In fact, some distribution sites may produce no effect or untoward effects. The volume of distribution (Vd), or apparent volume of distribution, refers to the total amount of drug in the body, assuming that the drug is present at the same plasma drug concentration (Cp) throughout the body. The Vd is expressed in terms of volume (e.g., liters or liters per kilogram) and is a function of the solubility (lipid versus water

solubility) and binding (tissue versus plasma protein binding) characteristics of the drug. Actual sites of distribution cannot be determined from the Vd value.

The volume of distribution equation is

$$\text{Volume of distribution} = \frac{\text{amount of drug in body}}{\text{plasma drug concentration}}$$

Factors that tend to increase Cp will decrease apparent Vd and include drugs that have:

- Low lipid solubility
- High plasma protein binding
- Low tissue binding

Factors that tend to decrease Cp will increase apparent Vd and include drugs that have:

- High lipid solubility
- Low plasma protein binding
- High tissue binding

Volume of distribution can be used to estimate a loading dose needed to achieve a desired plasma concentration rapidly. A medication, such as amiodarone, which has a large volume of distribution (66 L/kg) requires a longer duration (weeks) to load adequately, as there is a large number of distribution sites. In contrast, a person receiving procainamide, which has a volume of distribution of 2 L/kg, can be adequately loaded with a single dose in the appropriate amount. Although a loading dose does not decrease the time to achieve steady-state plasma concentration, it does reduce the time to reach a therapeutic plasma concentration or therapeutic range. For many medications, there is not a target concentration that is defined, and therefore, loading-dose equations are typically not used. In this circumstance, which is true for most drugs, initial and maximal doses are chosen based on dose ranging and randomized studies comparing the expected response to the dose. For instance, early trials of metoprolol tartrate used starting doses of 25 to 50 mg twice daily for hypertension, and these doses produced the clinical response desired to obtain the specified endpoints. Therefore, using both pharmacokinetic and pharmacodynamic data can help to establish appropriate dosing of medications when obtaining serum drug levels is not available.

To determine the loading dose, the following equation is used:

$$\text{Loading dose} = \frac{(Vd)(Cp)}{(S)(F)}$$

The target plasma concentration for a given drug is often referred to as the therapeutic range, and can be thought of as a range of drug concentrations in which there is a relatively high probability of achieving a desired clinical response and a relatively low probability of developing unacceptable toxicity. Narrow-therapeutic-range drugs are

ones in which this desired drug concentration range is small (e.g., lidocaine, procainamide, digoxin, quinidine, etc.) and the therapeutic concentration and toxic concentration are similar. This concept is reviewed later in this chapter under pharmacodynamics.

Metabolism and Elimination

Clearance (Cl) is the intrinsic ability of the body (or eliminating organs such as kidneys or liver) to remove drug, and is expressed in volume per unit of time (e.g., liters per hour). Hepatic metabolism of a drug can lead to formation of active or inactive metabolites. Metabolites may contribute to the therapeutic efficacy or toxicities associated with the parent drug (e.g., procainamide and N-acetylprocainamide).

At steady state, the rate of drug administration (RA, or dose per time) and rate of drug elimination are equal, and the concentration of drug remains constant. Clearance can be thought of in terms of these factors in the following equation, where Cpss refers to steady-state plasma drug concentrations:

$$Cl = \frac{(RA)}{(Cpss)}$$

The relative clearance of drug is an important factor in calculating the rate of administration or maintenance dose to produce a desired average plasma drug concentration:

$$\text{Maintenance dose or RA} = (\text{Cl})(\text{Cpss})$$

Another consideration in determining dosing interval is evaluating the half-life of a medication. Half-life ($t_{1/2}$) refers to the amount of time required for the total amount of drug in the body or the plasma drug concentration to decrease by half. Half-life can be calculated with the following equation:

$$t_{1/2} = \frac{0.693 \times Vd}{Cl}$$

Half-life can be used to determine the amount of time it will take to reach steady-state plasma concentrations. Typically, three to five half-lives are required to reach steady state. It takes one half-life to reach 50%, two to reach 75%, three to reach 87.5%, four to reach 93.75%, and five half-lives to reach 97% of steady state. Half-life can also be used to determine how long it will take to eliminate drug from the body after the drug has been discontinued. It takes one half-life to eliminate 50%, two to eliminate 75%, and so on.

Metabolism of medications typically occurs in the liver, producing more hydrophilic compounds to allow for elimination through the kidneys. However, many drugs may undergo exclusive renal elimination without any form of biotransformation or metabolism. Biotransformation may also convert prodrugs (precursors to active drug

forms) to drugs with biologic activity (e.g., enalapril, losartan). Other routes of drug elimination include biliary routes.

PHARMACODYNAMICS

The main principle of pharmacodynamics is the relationship between drug concentration at the site of action (receptor site) and pharmacologic response. Simply stated, pharmacodynamics is the study of plasma concentration and pharmacologic response. This relationship can be described by the equation

$$E = \frac{(E_{max} \times C)}{(C + EC_{50})}$$

where E is the pharmacologic effect, E_{max} is the maximum effect the drug can cause (determines efficacy), EC_{50} is the concentration at which one-half of the maximal response will occur (determines drug potency), and C is the concentration of the drug at the receptor site.

Drugs with low EC_{50} are considered more potent than the comparison drug (i.e., these drugs elicit the same response at lower concentrations). Drugs with a similar E_{max} are considered to have similar efficacy (Fig. 60.1). Some medications may have the same EC_{50} but very different E_{max} values.

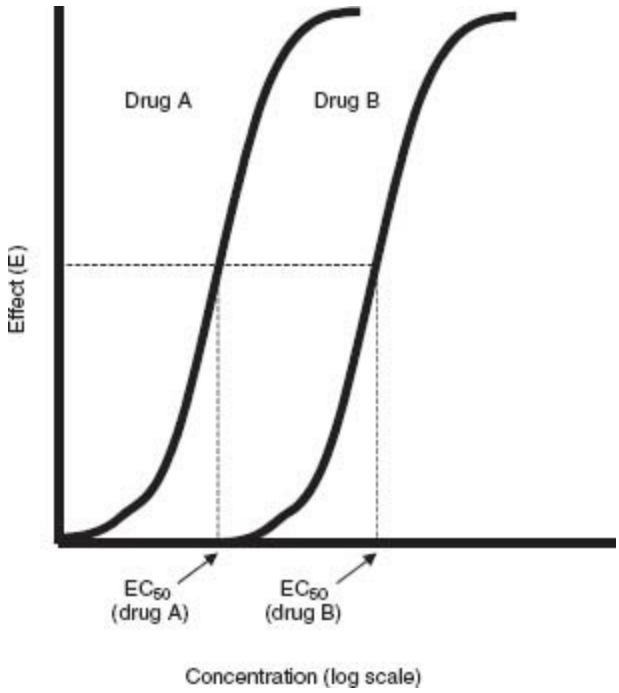


FIGURE 60.1 Potency and efficacy curves. Drug A is considered to have the same efficacy as drug B, because the maximal effect is the same. However, drug A is considered to be more potent, because the EC_{50} is less than that of drug B.

These same efficacy principles can be applied to toxicity and used to evaluate therapeutic ranges or indexes. The dose that produces toxic effects in 50% of evaluated subjects (typically animals) is called the toxic dose 50 or TD_{50}. The ratio of the TD_{50} to the ED_{50} is the typical definition of therapeutic index. As this ratio approaches one, the therapeutic index is considered narrow. The risks versus benefits of the therapy as well as the severity of the disease state determine an acceptable therapeutic index. For example, medications to treat chronic diseases or non–life-threatening diseases typically have therapeutic indexes that are large. In contrast, physicians accept a narrower therapeutic index when treating a disease state that has a high mortality (e.g., certain malignancies).

PHARMACOGENETICS

Pharmacogenetics is the third side of the pharmacology triangle. The other two sides of this triangle, pharmacokinetics and pharmacodynamics, are described above. Drug response may be altered in an individual patient based on their genetic variation. Variations in the genetic code for drug targets (receptors), drug metabolizing enzymes (CYP 450), and drug transport genes can explain in many cases the difference in interindividual response to drug therapy. There are a number of examples of genetic variation that may alter response to drug therapy; these include clopidogrel response and CYP 2C19 activity, warfarin response and CYP 2C9 activity, as well as VKOR (vitamin K epoxide reductase) activity and digoxin levels as it relates to P-glycoprotein activity We are currently limited in our ability to utilize pharmacogenetic information in daily practice because in most cases there are limited data to support improved patient outcomes.

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QUESTIONS AND ANSWERS

Questions

1. Which of the following best describes bioavailability?
   a. The amount of drug absorbed

b. The amount of drug that reaches systemic circulation
c. The amount of drug that is cleared by the liver upon first-pass metabolism
d. The amount of drug within the tablet

2. Which of the following answers best describes this statement?
Beta-blockers slow ventricular response in patients with atrial fibrillation.
a. Pharmacodynamics of beta blockers
b. Pharmacokinetics of beta blockers
c. Tolerance to beta blockers
d. Pharmacogenetics of beta blockers

3. Amiodarone has a volume of distribution of about 66 L/kg and gentamicin has a volume of distribution of 0.25 L/kg. Based on this information, which answer describes the above statement best?
a. Amiodarone is cleared by the kidneys.
b. Amiodarone distributes only into intravascular volume.
c. Amiodarone is expected to have a short half-life.
d. Amiodarone is expected to have a long half-life.

4. Which of the following angiotensin-converting enzyme inhibitors (ACE-I) needs to undergo biotransformation to become active (i.e., which of the following is a prodrug)?
a. Enalaprilat
b. Lisinopril
c. Captopril
d. Ramipril

5. The average half-life of metoprolol is 6 hours. If you initiated 50 mg three times daily, how long will it take to reach steady state?
a. 12 hours
b. 18 hours
c. 24 hours
d. 30 hours

Answers

1. Answer B: Bioavailability is the amount of drug that reaches the systemic circulation.The amount of drug absorbed is related to the bioavailability; however, if a medication undergoes first-pass effect, some of that medication will not be bioavailable. Answer c also relates to bioavailability but this describes presystemic clearance.

2. Answer A: The pharmacodynamic response to beta-blocker therapy is to decrease heart rate and blood pressure. Pharmacodynamics is the relationship between drug concentration at the site of action (receptor site) and pharmacologic response. Pharmacokinetics is simply the effect that the body has on the medications.This is described in terms of absorption, distribution, metabolism, and elimination (ADME).

3. Answer D: Based on the equation $t_{1/2}$ = (0.693xVd)/Cl medications that have a large volume of distribution will be expected to have a long half-life.There is a direct relationship with volume of distribution and half-life and an inverse relationship with clearance.The volume of distribution will not give you the mechanism of how the drug is cleared. Finally, you would not expect a medication that has a large volume of distribution to be found only in the intravascular volume and would need to have a great deal of tissue binding.

4. Answer D: Most of the ACE-I are prodrugs and require transformation in the liver to the active compound. Answers a, b, and c are all the active forms and do not require biotransformation.

5. Answer D: In the strictest sense, it takes five half-lives to reach steady state.Thus, 30 hours is the answer. However, the following is true: after one half-life, 50% of steady state is achieved; after two half-lives, 75% of steady state is achieved; after three half-lives, 87.5% of steady state is achieved; and after

four half-lives, 93.75% of steady state is achieved.

CHAPTER

Cardiovascular Medicine—Essential Pharmaceuticals

Katherine M. Greenlee and Michael A. Militello

Cardiovascular disease (CVD) accounts for nearly 50% of all death in Western societies and 25% of all death worldwide. Furthermore, cardiac medications rank second in frequency of use worldwide, after antibiotics. Medical therapy plays an essential role, not only in the management of CVD but also in prevention.

Pharmacology accounts for about 12% of the questions on the Cardiology Boards. The topic is vast and may be approached in various ways. Pharmacokinetics and dynamics, drug interactions, and antiarrhythmics are addressed in other chapters. In this chapter, we cover most of the available cardiovascular drugs used in clinical practice in the United States. We review names (brand and generic), starting and maximum doses, mechanisms of action, labeled and unlabeled indications, and side effects. When appropriate, we comment on the major clinical trials involving the particular drug. The classes and drugs are classified alphabetically according to mechanistic class and/or therapeutic class, as shown in Table 61.1.

TABLE
61.1 Major Classes of Cardiac Medications, Listed Alphabetically

Drug Class[a]	Subclasses
Adrenergic agonists	
Adrenergic antagonists	α_1 antagonist
	Selective β antagonists (beta-blockers)
	Nonselective beta-blockers
	Mixed α_1-/beta-blockers
Angiotensin-converting enzyme inhibitors (ACEIs)	
Angiotensin II receptor blockers (ARBs)	
Aldosterone-receptor antagonists	
Anticoagulants	UFH/LMWH
	Pentasaccharide
	Direct thrombin inhibitors
	Oral anticoagulants
Calcium channel blockers	Dihydropyridines
	Nondihydropyridines
Diuretics	Loop diuretics
	Thiazide diuretics
	K^+-sparing diuretics
Inotropic agents and vasopressors	Catecholamines
	Phosphodiesterase inhibitors
Lipid-lowering agents	Bile acid resin
	HMG CoA reductase
	Fibrates
	Other
Nitrates	
Platelet inhibitors	Cyclooxygenase inhibitors
	Thienopyridines
	GP (IIb/IIIA) inhibitors
Thrombolytics	
Vasodilators	
Miscellaneous drugs	

[a]Antiarrhythmics are covered in Chapter 10.

ADRENERGIC AGONISTS

Before detailing specific medications, we review basic information on adrenergic receptors that is useful for understanding the mechanism and side effects of this class as

well as classes discussed subsequently. The adrenoceptors are classified into alpha (**α**) and beta (**β**) subtypes. There are two main subtypes of **α**-adrenoceptors, α_1 and α_2, and three main types of **β**-adrenoceptors, β_1, β_2, and β_3. The primary effects of receptor activation are shown in Table 61.2. The adrenergic agonists of cardiac interest in this section are the α_2 agonists, which act centrally. In later sections, we discuss other adrenergic agonists that stimulate **α** and **β** receptors, such as epinephrine, norepinephrine, dobutamine, and other inotropes and pressors.

TABLE
61.2 Main Effects of Receptor Activation of Adrenoceptors

Receptor Class	Biologic Effect When Stimulated
α_1	Vasoconstriction, relaxation of GI smooth muscle, stimulation of salivary secretion
α_2	Inhibition of norepinephrine release from autonomic nerves, contraction of smooth muscle, platelet aggregation
β_1	Increased heart rate and contractility, GI smooth muscle relaxation
β_2	Bronchodilation, vasodilation, relaxation of visceral smooth muscle
β_3	Lipolysis

The α_2 Agonists (Clonidine, Guanabenz, Guanfacine)

Mechanism of Action

The α_2 receptors are presynaptic and are found in the central nervous system (CNS). Stimulation of the a_2 receptors decreases sympathetic outflow from the CNS, thus lowering blood pressure and, in some patients, heart rate.

Side Effects

Common side effects include sedation, dry mouth, hypotension, dizziness, sexual dysfunction, bradycardia, nausea, headache, and depression. Abrupt withdrawal of therapy causes rebound hypertension. Rebound hypertension can be severe with concurrent administration of beta-blockers secondary to unopposed α_1-receptor stimulation.

Indication and Precautions

Clonidine (Catapres and Catapres-TTS) Clonidine is labeled for use in hypertension. For patients with severe renal insufficiency (i.e., CrCl <10 mL/min), doses should be reduced by 25% to 50%. Transdermal patches are replaced weekly.

Methyldopa (Aldomet) (Oral); Methyldopate HCL (Intravenous) Methyldopa is labeled for use in hypertension and hypertensive emergency (IV only) and is one of the few drugs that can be used for hypertension in pregnant women. In addition to the general side effects of α_2-receptor agonists, methyldopa has specific side effects: peripheral edema, hemolytic anemia, drug fever, systemic lupus erythematosus (SLE)-like syndrome, nightmares, hepatocellular injury, hepatitis (rare), and anxiety. Positive Coombs tests occur within 6 to 12 months in 10% to 20% of patients.

ADRENERGIC ANTAGONISTS

This section is divided according to the various subgroups of adrenergic antagonists, based on the adrenergic receptors they block, and include α_1-receptor antagonists, **β**-receptor antagonists, and nonselective **α/β** antagonists.

α_1-Receptor Antagonists

Selective α_1, Antagonists: Doxazosin (Cardura), Prazosin (Minipress), Terazosin (Hytrin)

Mechanism of Action Selective α_1-receptor antagonists act peripherally and lead to arterial and venous vasodilation.

Side Effects Side effects of α_1-receptor antagonists include orthostatic hypotension, dizziness, light-headedness, drowsiness, headache, dry mouth, and malaise. The first dose should be given at bedtime to limit effects associated with orthostatic hypotension. Tachyphylaxis may develop with long-term administration in patients with heart failure (e.g., prazosin).

Indications and Precautions These drugs are labeled for use in hypertension and benign prostatic hypertrophy (BPH) (terazosin and doxazosin).

Major Clinical Trials

VHeFT I.[1] In this trial, hydralazine combined with nitrates and prazosin was compared to placebo for the treatment of heart failure. No effect on the primary endpoint of mortality was observed, and no difference in left ventricular (LV) ejection fraction was observed when prazosin was compared to placebo.

ALLHAT.[2] This trial was designed to evaluate different antihypertensive medications to reduce cardiovascular events. An interim analysis 2 years before the final publication demonstrated that patients receiving doxazosin had a significantly higher rate of stroke cardiovascular events, and the rate of congestive heart failure (CHF) was two times higher. The doxazosin arm was stopped early as a result of the findings.

Nonselective α Antagonists: Phentolamine (Regitine)

Mechanism of Action Nonselective **α**-adrenergic antagonist with similar affinities for α_1 and α_2 receptors, producing vasodilation and an increase in heart rate

Side Effects Side effects of these drugs include hypotension, tachycardia, arrhythmias, angina, and nausea/vomiting/diarrhea. They may exacerbate peptic ulcer disease (PUD) and produce nasal congestion.

Indications and Precautions Phentolamine is labeled for use in hypertensive crisis in patients with pheochromocytoma and for treatment of skin necrosis in patients with norepinephrine, dopamine, epinephrine, and phenylephrine extravasation.

β-Receptor Antagonists

Beta-blockers were first discovered in 1958 (dichloroiso-prenaline). The effects produced depend on the degree of endogenous sympathetic activity and are less dramatic at rest. Beta-blockers are classified as selective and nonselective as well as having α_1-blocking properties.

Mechanism of Action Nonselective beta-blockers antagonize both β_1 and β_2 receptors, inhibiting the effects of catecholamines on these receptors. Cardiovascular effects include decreases in contractility and heart rate. Noncardiovascular effects mediated through β_2 blockade include increased peripheral vascular resistance or bronchospasm. Selective beta-blockers antagonize β_1 receptors to a greater extent than β_2 receptors, when administered in typical or usual doses. Cardiovascular effects are the same as with nonselective beta-blockers. Both classes generally lead to a decrease in blood pressure, sinus node automaticity, conduction through the atrioventricular (AV) node, and increased AV nodal refractoriness. The antiarrhythmic properties are a class effect. Other pharmacologic properties of selective beta-blockers include intrinsic sympathomimetic activity (ISA). Agents that have ISA are partial **β** agonists during low catecholamine states, preventing resting bradycardia; however, they act as full agonists when endogenous catecholamine levels increase. Beta-blockers without ISA activity have been shown to decrease recurrent myocardial infarction (MI), sudden death, and overall mortality in acute-MI survivors. They also have been shown to reduce mortality and hospitalizations secondary to heart failure. A new beta-blocker, nebivolol, is a

selective β_1 antagonist that also reduces systemic vascular resistance (SVR) by producing an endothelium-derived nitric oxide (NO)-dependent vasodilation. A list of the various beta-blockers that are used is provided in Table 61.3.

TABLE
61.3 Pharmacokinetics of Commonly Used Beta-Blockers

Drug	Selectivity	ISA	Lipid Solubility	Dose, Initial–Maximum mg/d	Onset of Action	Half-Life (h)
Acebutolol	β_1	+	Low	400–1,200 mg/d	Oral, 1–3 h	3–4
Atenolol	β_1	0	Low	25–200 mg/d	1–3 h	6–9
Bisoprolol	β_1	0	Low	5–20 mg/d	2–4 h	9–12
Esmolol	β_1	0	Low	[a]	IV, 2–5 min	0.15
Metoprolol[b]	β_1	0	Moderate	50–450 mg/d	Oral, 1 h IV, 5 min	3–7
Nadolol	β_1 β_2	0	Low	40–320 mg/d	1–2 h	20–24
Pindolol	β_1 β_2	+++	Moderate	10–60 mg/d	>3 h	3–4
Propranolol	β_1 β_2	0	High	30–480 mg/d	Oral, 1–2 h IV, 2–5 min	3–5

[a]Esmolol is an IV-formulated drug. The loading dose is 500 μg/kg given over 1 min. Then, the maintenance dose is 25–300 μg/kg/min.

[b]Metoprolol is available as an immediate-release preparation and as an extended-release preparation. The extended-release product is labeled for both hypertension and heart failure.

ISA, intrinsic sympathomimetic activity.

Side Effects Side effects of these drugs include fatigue, bradycardia, heart block, bronchospasm, depression, lipid abnormalities, masking the symptoms of hypoglycemia, a rebound effect with abrupt discontinuation, precipitation of heart failure, and impotence.

Indications and Precautions Indications for beta-blockers include hypertension, ischemic heart disease, acute myocardial infarction (AMI), stable and unstable angina (UA), heart failure, arrhythmia, and stable heart failure (see Table 61.3). Absolute contraindications include hypersensitivity to beta-blockers, asthma, heart block greater than first degree, insulin-dependent diabetics with frequent hypoglycemic episodes, and overt heart failure. Relative contraindications include chronic obstructive lung disease, diabetes mellitus, and severe peripheral arterial disease. Beta-blockers have significant interactions with other drugs, including medications that slow AV nodal conduction such as digoxin, diltiazem, and verapamil, as well as nonsteroidal anti-inflammatory drugs (NSAIDs), other antihypertensive medications, other negative inotropic agents, rifampin, phenobarbital, phenytoin, cholestyramine, and colestipol, to name a few.

Combined α-/β-Receptor Antagonists

Mechanism of Action The combination preparations are specific α_1-receptor antagonists, but nonselective b-receptor antagonists. Labetalol is 7:1 selective b to a receptor in the IV preparation and 3:1 in the oral preparation.

Side Effects Refer to side effects of beta-blockers.

Indications and Precautions The labeled indication of labetalol is hypertension. Carvedilol has labeled indications for hypertension, as well as LV dysfunction following MI (clinically stable patients), and mild to severe chronic heart failure. Refer to precautions for beta-blockers.

Major Clinical Trials

MERIT-HF.[3] Metoprolol CR/XL improved survival and New York Heart Association (NYHA) functional class and reduced the number of hospitalizations and days in the hospital due to worsening heart failure.

CIBIS-II.[4] This trial demonstrated that bisoprolol therapy was well tolerated and reduced mortality and hospitalization rates in patients with stable CHF.

CAPRICORN.[5] This trial showed that long-term therapy with carvedilol, in addition to angiotensin-converting enzyme inhibitor (ACE-I) and standard therapy, reduced mortality and recurrent MI in stable patients with LV systolic dysfunction after acute MI.

COPERNICUS.[6] This trial studied the effect of carvedilol on survival in patients with severe chronic heart failure. Carvedilol reduced mortality in patients with severe CHF by 34% and also reduced the number of days spent in hospital because of CHF and for any cause.

COMET.[7] Carvedilol improved survival and LV ejection fraction to a greater degree than immediate-release metoprolol during long-term therapy for heart failure.

BHAT.[8,9] The Beta-blocker Heart Attack Trial, using propanolol, and the Norwegian Multicenter Study Group, using timolol, both showed a reduction in mortality rate, reinfarction rate, or both with the use of the beta-blocker.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

The renin–angiotensin system (RAS) is a hormonal system that interacts very closely with the sympathetic nervous system, angiotensin II formation, and aldosterone secretion. It has an essential role in sodium and volume management. Renin, an enzyme, is secreted by the juxtaglomerular apparatus located in the wall of the arteriole of the glomerulus. It is secreted secondary to multiple stimuli, low sodium concentration of the fluid in the distal tubule, stimulation of the **β**-adrenoceptors, and circulating prostacyclin and NO, as shown in Figure 61.1.

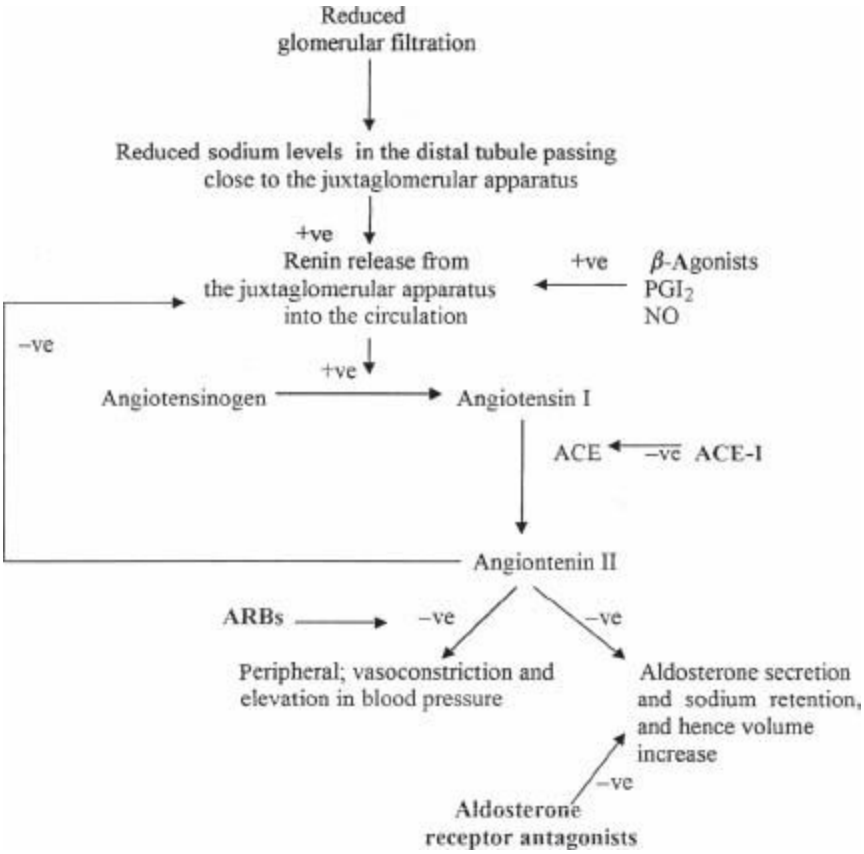

FIGURE 61.1 The renin–angiotensin–aldosterone pathway and mechanism of action of ACE-I and ARBs. ACE is a membranebound enzyme on the surface of endothelial cells abundant in the lung (+ve, positive or stimulatory effect; –ve, negative or inhibitory effect).

The RAS pathway is important in the pathogenesis of heart failure and hypertension; hence all aspects of this pathway are targets for therapy in CHF and hypertension, whether in renin release such as beta-blockers, angiotensin II formation such as ACE-I, or angiotensin II blockade such as angiotensin II receptor blockers (ARBs) and aldosterone antagonists.

Mechanism of Action

ACE-I block the conversion of angiotensin I to angiotensin II by inhibiting ACE, as shown in Figure 61.1. In response to this blockade, there is decreased formation of angiotensin II, leading to vasodilatation. Also, there is a decrease in the breakdown of bradykinins, which may produce additional vasodilatory effects.

Side Effects

Side effects include cough (because of decrease in breakdown of bradykinin), acute renal failure (particularly if there is bilateral renal artery stenosis), angioedema, hyperkalemia, proteinuria, hypotension (which needs to be monitored after the first dose and in water-depleted patients), headache, rash, neutropenia/agranulocytosis, and

dizziness.

Angioedema is rare but may occur at any time; when it does occur, however, it is usually early in therapy. Severe hypotension may be seen in volume-depleted patients; hence the volume status of a heart failure patient should be carefully assessed before initiating therapy. Neutropenia or agranulocytosis has been reported with many ACE-I and is usually associated with collagen vascular disorders, higher doses, and renal dysfunction.

Indications and Precautions

ACE-I are labeled for use in hypertension, heart failure, LV dysfunction, post-AMI, and diabetic nephropathy (Table 61.4). ACE-I are contraindicated in pregnancy and in patients with bilateral renal artery stenosis or unilateral renal artery stenosis in patients with a solitary kidney.

TABLE
61.4 Preparations and Dosing of Available ACE-I

Medication	Side Group	Half-Life (h)	Comments
Benazepril (Lotensin) 5, 10, 20, 40 mg	Carboxyl	10–11	
Captopril (Capoten) 12.5, 25, 50, 100 mg	Sulfhydryl	1.7–2	Best taken on empty stomach; not a prodrug
Enalapril (Vasotec) 2.5, 5, 10, 20 mg	Carboxyl	11	Also available in IV form (1.25 mg/mL); IV form is not a prodrug.
Fosinopril (Monopril) 10, 20 mg	Phosphinyl	12	
Lisinopril (Prinivil, Zestril) 2.5, 5, 10, 20, 40 mg	Carboxyl	12	Not a prodrug
Moexipril (Univasc) 7.5, 15 mg	Carboxyl	2–9	Best taken on empty stomach
Perindopril (Aceon) 2, 4, 8 mg	Carboxyl	10–25	
Quinapril (Accupril) 5, 10, 20, 40 mg	Carboxyl	2	
Ramipril (Altace) 1.25, 2.5, 5, 10 mg	Carboxyl	13–17	
Trandolapril (Mavik) 1, 2, 4 mg	Carboxyl	10–16	

Major Clinical Trials

SAVE.[10,11] The SAVE trial showed that the long-term use of captopril in patients with asymptomatic LV dysfunction following acute MI was associated with lower mortality and morbidity.

GISSI-3.[12] This trial showed that lisinopril therapy reduced mortality and improved outcome after MI. The mortality benefit manifested primarily during the early phase (6 weeks), whereas the LV remodeling benefit manifested later.

TRACE.[13] The TRACE trial update confirmed that trandolapril reduced death and major cardiovascular complications in diabetic patients after infarction.

HEART.[14] The HEART trial showed that in patients with acute anterior MI, early use of ramipril (titrated to 10 mg) attenuated LV remodeling and resulted in swift LV recovery.

AIREX.[15] This trial showed that beneficial effects of ramipril started early after MI in patients with heart failure, and

that the benefit was sustained over several years.

CONSENSUS.[16] CONSENSUS studied the effects of enalapril on mortality in severe CHF. Enalapril reduced mortality and improved symptoms in severe CHF, when added to conventional therapy.

V-HeFT II.[17] This trial compared enalapril with hydralazine–isosorbide (H-ISDN) for the treatment of CHF. Mortality with enalapril was significantly lower than in the H-ISDN group.

Stop-Hypertension-2.[18] This trial showed that ACE-I and calcium channel blockers have similar efficacy in prevention of cardiovascular mortality compared to older-generation antihypertensive drugs (diuretics and beta-blockers) in elderly patients. ACE-I was associated with less MI and CHF than calcium channel blockers, but not compared to conventional therapy with diuretics and beta-blockers.

ANGIOTENSIN-II RECEPTOR BLOCKERS

Mechanism of Action

ARBs block angiotensin II (A-II) from binding to angiotensin II type 1 receptors (AT_1), thereby inhibiting the vasoconstrictor and aldosterone-secreting effects of angiotensin II (see Fig. 61.1; Table 61.5). ARBs do not alter the metabolism of bradykinin or neuropeptides, so they should not cause side effects related to this effect, such as cough. However, there are case reports of angioedema occurring with ARB therapy.

TABLE
61.5 Formulations of ARBs

Medication	Half-Life (h)
Azilsartan (Edarbi)	11
Candesartan Cilexetil (Atacand)	9
Eprosartan (Teveten)	6
Irbesartan (Avapro)	11–15
Losartan (Cozaar)	6–9
Olmesartan (Benecar)	12–18
Telmisartan (Micardis)	24
Valsartan (Diovan)	6

Side Effects

Side effects include hypotension, acute renal failure (particularly if there is bilateral renal artery stenosis), hyperkalemia, proteinuria, hypotension, dizziness, headache, and angioedema (rare).

Indications and Precautions

The labeled use for all ARBs is hypertension; however, both candesartan and valsartan are also labeled for heart failure. Candesartan is labeled for cardiovascular mortality reduction for patients with reduced LV dysfunction post-MI. Losartan is also labeled for

hypertension in patients with LV hypertrophy, as well as prophylaxis of diabetic nephropathy in patients with a history of hypertension. Additionally, irbesartan also carries an indication for prophylaxis against diabetic nephropathy in patients with a history of hypertension.

Major Clinical Trials

ELITE-II.[19] This trial demonstrated that losartan was not superior to captopril in reducing mortality in patients with CHF who were >60 years of age.

CHARM.[20] This trial had multiple arms. The CHARM-alternative looked at candesartan in patients with symptomatic heart failure who were intolerant of ACE-I. Patients were randomized to either candesartan or placebo. There was decreased risk of cardiovascular death or hospitalization from heart failure in the candesartan group compared to the placebo group. The CHARM-added trial randomized patients with symptomatic heart failure who were already on ACE-I to either candesartan or placebo. In contrast to the results of Val-HeFT, mortality was significantly reduced by addition of an ARB to an ACE-I compared to the ACE-I alone. The CHARM-preserved arm of the study looked at patients with symptomatic heart failure with preserved ejection fraction. They were randomized to either candesartan or placebo. There was no difference in the primary endpoint (cardiovascular death or hospitalization secondary to CHF).

LIFE.[21] This trial showed that losartan was more effective than atenolol in preventing death, cardiovascular accidents (CVA), and MI as a combined endpoint. In terms of single outcomes, the reduction in CVA was significant, whereas the reduction in death or MI was only a trend without statistical significance.

Val-HeFT.[22] This trial showed that valsartan reduced the combined endpoint of death and morbidity and improved symptoms and signs of CHF. The benefit was seen only in patients who were not receiving ACE-I. In patients who were on ACE-I and beta-blockers, the addition of valsartan was associated with increased mortality.

RESOLVD.[23] This trial showed that both candesartan and enalapril were effective, safe, and tolerated in the treatment of CHF. Combination of candesartan and enalapril reduced LV dilatation greater than either agent alone.

RENAAL.[24] This trial showed that losartan preserved renal function in patients with type II diabetes and diabetic nephropathy, as well as decreasing hospitalization for CHF.

ALDOSTERONE RECEPTOR ANTAGONISTS

Mechanism of Action

As shown in Figure 61.1, this class of drugs antagonizes aldosterone at the mineralocorticoid receptor, consequently inhibiting aldosterone effects in the late distal convoluted tubule and cortical collecting duct, reducing sodium reuptake (hence the diuretic effect) and reducing potassium excretion (hence the side effect of hyperkalemia).

Side Effects

Side effects of spironolactone include hyperkalemia, hypotension, fatigue, rash, gynecomastia, amenorrhea, breast tenderness, sexual dysfunction, headache, nausea/vomiting, and diarrhea. With eplerenone, hyperkalemia is the predominant effect, with gynecomastia much less common. Drug–drug interactions are common with eplerenone, especially when concomitant medications increase serum potassium levels

and when it is given with potent inhibitors of the CYP 3A4 isoenzyme system.

Indications and Precautions

Spironolactone is labeled for primary aldosteronism, edema, hypertension, severe heart failure (NYHA Class III-IV) to increase survival and reduce hospitalization when added to standard therapy, and hypokalemia associated with loop diuretics. Use at a dose of 25 mg daily as an adjunct therapy for patients with Class III to IV CHF. Eplerenone is labeled for use in hypertension and for treatment in patients with LV dysfunction after MI. It is important to point out that this class of drugs should be avoided in patients with renal dysfunction (creatinine >2.5 mg/dL) or hyperkalemia.

Major Clinical Trials

RALES.[25] RALES found that the addition of spironolactone to standard-therapy ACE-I, loop diuretic, and digoxin reduced mortality and hospitalizations due to heart failure, with a 30% decrease in mortality in patients with NYHA Class III or IV heart failure.

EPHESUS.[26] This trial was designed to assess the safety and efficacy of eplerenone in patients with CHF after acute MI. The study showed a 15% decrease in mortality in patients with CHF post-MI.

EMPHASIS-HF.[27] This trial added eplerenone (up to 50 mg daily) or placebo to recommended therapy in patients with NYHA functional Class II heart failure and an ejection fraction of no more than 35%. Primary outcome was the composite of death from cardiovascular causes or first hospitalization for heart failure. For patients in the eplerenone group, primary outcome occurred in 249 patients (18.3%) and in 356 patients (25.9%) in the placebo group with a hazard ratio for primary outcome for eplerenone compared to placebo of 0.63 (95% confidence interval, 0.54 to 0.74; $p < 0.001$). Of note, serum potassium levels above 5.5 mmol/L occurred in 158 patients (11.8%) in eplerenone group compared to 96 patients (7.2%) in the placebo group, ($p < 0.001$).

RENIN INHIBITORS

Mechanism of Action

Aliskiren is a direct renin inhibitor blocking the conversion of angiotensinogen to angiotensin I, which, in turn, decreases formation of angiotensin II.

Side Effects

Side effects include increased BUN and serum creatinine, hyperkalemia, hypotension, and angioedema.

Indications and Precautions

The labeled indication for aliskiren is for hypertension. This medication has not been studied in patients with severe renal impairment. It is recommend to avoid use in patients with worsening renal function, or renal artery stenosis (bilateral or unilateral).

ANTICOAGULANTS

Anticoagulant drugs are subclassified into unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), direct thrombin inhibitors, and oral anticoagulants. A diagram of the coagulation cascade is shown in Figure 61.2.

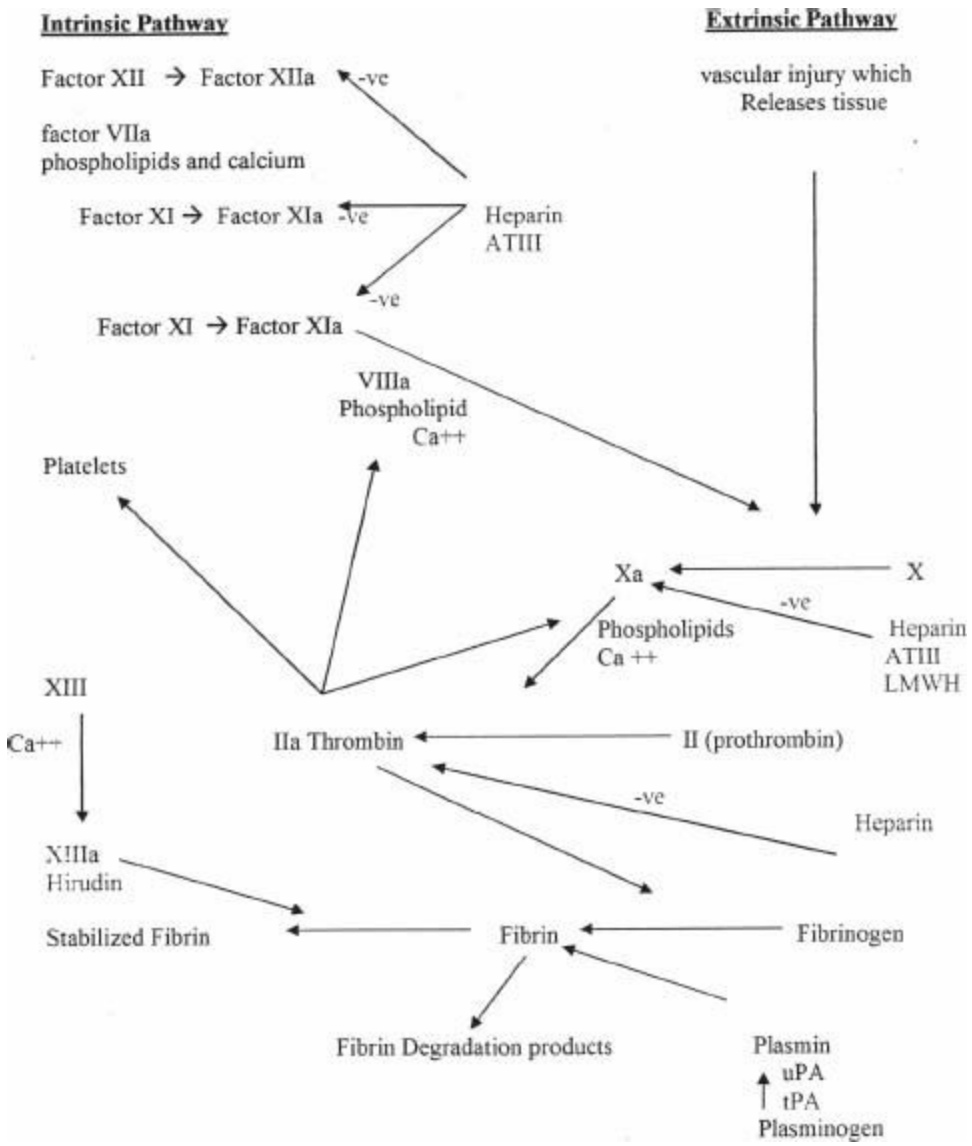

FIGURE 61.2 The blood coagulation pathways, intrinsic and extrinsic, and the sites of impact of anticoagulant. When the arrow is not marked, it indicates either a positive effect of a factor on a step in the pathway or a transformation into another factor. The negative effect is marked on the relevant arrows (+ve, positive or stimulatory effect; –ve, negative or inhibitory effect).

Unfractionated Heparin

Mechanism of Action

UFH is a thrombin inhibitor that binds to antithrombin, increasing antithrombin's activity to inactivate thrombin in addition to activated factors IX, X, XI, and XII.

Side Effects

Common side effects include bleeding, thrombocytopenia (benign type I and more severe type II, which may cause thrombosis), elevation in aspartate aminotransferase (AST)/alanine aminotransferase (ALT), osteoporosis (long-term therapy), and hyperkalemia.

Indications and Precautions

Heparin is administered subcutaneously or as an IV preparation. Generally, a weight-based nomogram is utilized that is titrated to a specific activated partial thromboplastin (aPTT) level. It is labeled for use in the treatment and prophylaxis of venous and arterial thrombosis. Heparin-induced thrombocytopenia (HIT) occurs in two forms, type I (non–antibody-mediated reaction) and type II (antibody-mediated reaction—typically IgG). Thromboembolic complications (e.g., deep vein thrombosis [DVT], MI, stroke) are associated with type II HIT and can be life-threatening. The incidence of thrombocytopenia is 10% to 15%, but the incidence of developing type II HIT is around 1% to 3%.

FACTOR XA INHIBITORS

Fondaparinux (Arixtra)

Mechanism of Action

Fondaparinux inhibits activated factor Xa through the neutralization capacity of antithrombin III.

Side Effects

Common side effects include bleeding, injection site–related bleeding, rash, and pruritus. Asymptomatic increases in AST and ALT may occur.

Indications and Precautions

Fondaparinux is used for prophylaxis of DVT in patients undergoing orthopedic or abdominal surgery. It is also indicated for treatment of acute pulmonary embolism (PE) and acute DVT (with or without PE). Fondaparinux is contraindicated in patients with a creatinine clearance <30 mL/min and in patients weighing <50 kg. As with direct thrombin inhibitors, there is no known antidote for fondaparinux.

Rivaroxaban (Xarelto)

Mechanism of Action

This prevents clot formation by selective inhibition of factor Xa.

Side Effects

Common side effects include bleeding (6%), ALT or AST elevation greater than three times upper limit of normal (3%).

Indications and Precautions

Rivaroxaban is indicated for thromboprophylaxis post knee or hip replacement. Avoid use in patients with moderate to severe hepatic dysfunction or severe (CrCl<30 mg/dL) renal dysfunction.

Major Clinical Trials

OASIS-5.[28] This trial compared efficacy and safety of fondaparinux to enoxaparin in patients with UA or non–ST-elevation myocardial infarction (NSTEMI).

The primary efficacy endpoint composite of death, MI, and refractory ischemia at 9 days validated noninferiority of fondaparinux (5.8%) compared with 5.7% for enoxaparin (HR 1.01; 95% CI 0.90 to 1.13; p = 0.007). The safety endpoint of major bleeding at 9 days was reduced with fondaparinux (2.2%) compared to 4.1% with enoxaparin (HR 0.52; 95% CI 0.44 to 0.61; p < 0.001). Of note, major bleeding in patients with CrCl < 30 mL/min was less with fondaparinux (2.4%) compared to 9.9% with enoxaparin (p = 0.001). Patients in whom percutaneous coronary intervention (PCI) was performed who received enoxaparin 6 or more hours before the procedure were administered UFH during the procedure, which may lead to a higher risk of bleeding. Of concern was the rate of guiding-catheter thrombus formations that occurred in the fondaparinux group (29 episodes [0.9%] vs. 8 episodes [0.3%]).

OASIS-6.[29] This study evaluated efficacy of fondaparinux with UFH in patients with acute ST-elevation myocardial infarction (STEMI). This was a randomized, double blind trial. There were two treatment groups, stratum 1, in which patients had no indication to receive UFH, and stratum 2, in which patients had an indication for UFH such as use of fibrinolytic therapy, patients not eligible for fibrinolysis but eligible for UFH, or primary PCI patients. Stratum 1 patients received fondaparinux for up to 8 days. Stratum 2 received either fondaparinux or placebo, with a control group receiving UFH for 24 to 48 hours. The primary endpoint at 30 days of death or reinfarction for fondaparinux was 9.7% compared to UFH or placebo group, which was 11.2% leading to a 14% risk reduction (0.86 HR; 95% CI, 0.77 to 0.96, p = 0.008). No difference was found between fondaparinux (2.1%) and the UFH or placebo group (1.8%) (0.83 HR; 95% CI, 0.64 to 1.06, p = 0.14) for major bleeding. For fondaparinux compared to control, significant benefit was found for patients without reperfusion (15.1% control, 12.2% fondaparinux, HR, 0.80; 95% CI, 0.65 to 0.98; p = 0.003), with fibrinolytic (13.6% vs. 10.9%; HR, 0.79; 95% CI, 0.68 to 0.92; p = 0.003), but not for the primary PCI patients (4.9% vs. 6.0%; HR, 1.24; 95% CI, 0.95 to 1.63; p = 0.12). With regard to PCI, as seen in OASIS-5, there was a significant rate of guiding-catheter thrombosis with fondaparinux (22 vs. 0; p < 0.001).

ROCKET AF.[30] Rivaroxaban was compared to warfarin in patients with nonvalvular atrial fibrillation at moderate to high risk for stroke. Elevated risk was signified by history of stroke, transient ischemic attack, or systemic embolism, or at least two of the following: heart failure or ejection fraction of 35% or less, hypertension, age 75 or more, or diabetes mellitus. The composite of stroke (ischemic or hemorrhagic) and systemic embolism was the primary endpoint. This occurred in the rivaroxaban group (1.7% per year) versus in the warfarin group (2.3% per year) (HR for rivaroxaban group, 0.79; 95% CI, 0.66 to 0.96; p <0.001 for non-inferiority). Major bleeding was similar between the groups (3.6% and 3.4%, p = 0.58). Rates of intracranial hemorrhage were lower in the rivaroxaban group (0.5% vs. 0.7% per year; HR, 0.67; 95% CI, 0.47 to 0.93). Major bleeding from a gastrointestinal site was significantly higher for rivaroxaban (3.2% vs. 2.2, p < 0.001). Of note, patients in the warfarin group were in therapeutic range for INR 55% of the time, which is lower than previous studies (range, 64% to 68%).

Direct Thrombin Inhibitors: Bivalirudin (Angiomax), Lepirudin (Refludan),

Argatroban (Argatroban), Dabigatran (Pradaxa)

Mechanism of Action

These drugs bind directly to thrombin (factor IIa), causing it to be inactivated (see Fig. 61.2). Bivalirudin, dabigatran, and argatroban bind directly and reversibly, whereas lepirudin binds directly and irreversibly.

Side Effects

Common side effects include bleeding. Patients on lepirudin may develop antibodies against lepirudin that decrease the elimination of lepirudin, hence increasing the duration of activity. Recent data demonstrated that patients may develop anaphylactic reactions with administration of lepirudin, and the occurrence is higher in patients who have previously been treated with the drug. Dabigatran has an increased incidence of dyspepsia (11%), but absorption of dabigatran is decreased by 20% to 25% when given in combination with proton pump inhibitors.

Indications and Precautions

Bivalirudin, lepirudin, and argatroban are given intravenously, and dabigatran is available orally. They are listed in Table 61.6. The labeled indication for bivalirudin is for percutaneous transluminal coronary angioplasty (PTCA) in the setting of UA. Dabigatran is indicated for prevention of stroke and systemic embolization in nonvalvular atrial fibrillation. There are no reversal agents for the direct thrombin inhibitors.

TABLE
61.6 Preparations, Dosing, and Indications for Direct Thrombin Inhibitors

Drug	Hirudin Derivative	Half-Life	Elimination Route	aPTT	PT	Dosing	Indications
Argatroban	No	21–60 min	Hepatic	↑	↑	Indication determines dosing (HIT or PCI). For HIT, initial dose is 0.5–2 μg/kg/min and maximum dose is 10 μg/kg/min. For PCI, initial bolus dose is 350 μg/kg and maintenance is at 25 μg/kg/min. Adjustments during PCI are based on ACT.	Anticoagulation for prophylaxis of thrombosis in patients with HIT. Anticoagulation for treatment of thromboembolic disease (to prevent further complications) in patients with HIT.
Bivalirudin	Yes	25–210 min[a]	Proteolytic cleavage within plasma (80%) and renal	↑	Dose dependent	For PCI, the initial bolus is 0.75 mg/kg and maintenance dose is 1.75 mg/kg/h for duration of procedure.	Anticoagulant for patients with UA undergoing PTCA. Unlabeled use is for patients undergoing PCI or for patients with HIT.
Dabigatran	No	12–17 h	Renal	↑	Dose dependent	150 mg orally twice daily. 75 mg orally twice daily for CrCl < 30 mL/min	Prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
Lepirudin	Yes	>80 min[a]	Renal	↑	Dose dependent	Loading dose is 0.4 mg/kg over 15–20 s. Maintenance dose is 0.15 mg/kg/h. Dosing should be altered if the patient has renal dysfunction.	Indicated for anticoagulation in patients with HIT and associated thromboembolic disease in order to prevent further thromboembolic complications

[a]Half-life depends on renal function.

aPTT, activated partial thromboplastin; PT, prothrombin time; HIT, heparin-induced thrombocytopenia; PCI, percutaneous coronary intervention; ACT, activated clotting time; PTCA, percutaneous transluminal coronary angioplasty.

Major Clinical Trials

Thrombin Inhibitors Trialist (DTIT) Collaborative Group.[31] This meta-analysis reviewed the use of direct thrombin inhibitors in acute coronary syndrome (ACS). A total of 5,674 patients were included, of whom 4,603 underwent PCI. Bivalirudin reduced the risk of death and MI by about 30% in the few weeks after the procedure compared to heparin.

HERO-2.[32] This trial compared bivalirudin to heparin in patients receiving streptokinase therapy for acute MI. The conclusion of the study was that the use of bivalirudin was associated with reduction of reinfarction rates within 96 hours, but it was not associated with reduction in mortality. It was associated with a slight increase in the risk of bleeding.

HASI.[33] This trial showed that bivalirudin is as effective as heparin in preventing ischemic complications in UA or after PCI. It was found to be superior to heparin in reducing immediate post-MI complications. In this study,

bivalirudin was associated with increased incidence of bleeding. In an update of the study that was published,[34] bivalirudin was better than heparin in reducing death, MI, revascularization, and bleeding (as a combined endpoint) in patients with UA or post infarction angina who were undergoing PCI. The difference stemmed mainly from a reduction in the rate of revascularization.

OASIS.[35] This study compared lepirudin to heparin in ACS. Lepirudin reduced mortality and reinfarction at 3 days after the event compared to heparin but was associated with an increased cost and risk of major bleeding, which required transfusion.

REPLACE-II.[36] In this trial, bivalirudin, given during PCI as an IV bolus followed by an infusion, was compared to heparin and glycoprotein (GP) IIb/IIIa inhibitors given 12 to 18 hours after the procedure. The study was set to assess for noninferiority for primary endpoint of death, MI, urgent revascularization, or major bleeding. Bivalirudin was found to be associated with a significant reduction in major bleeding compared to heparin and GP IIb/IIIa inhibitor.

RE-LY.[37] This study compared warfarin to dabigatran 150 mg twice daily and dabigatran 110 mg twice daily in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke. The primary outcome was stroke or systemic embolism. Dabigatran in both doses were found to be noninferior to warfarin for primary outcome, with the 150 mg dabigatran dose superior to warfarin with similar rates of bleeding.

ACUITY.[38] In this trial, patients with ACS undergoing early invasive strategy were treated with one of three regimens: UFH or enoxaparin plus a GP IIb/IIIa inhibitor, bivalirudin plus a GP IIb/IIIa inhibitor, or bivalirudin alone. Primary end-points included a composite ischemia endpoint (death, MI, and unplanned revascularization for ischemia), as well as major bleeding, and the combination of composite ischemia or major bleeding. Bivalirudin plus GP IIb/IIIa inhibitor compared to heparin plus IIb/IIIa inhibitor was found to be non-inferior for the composite ischemia endpoint as well as for major bleeding. Bivalirudin alone was found to have significantly reduced rates of major bleeding and was noninferior compared to heparin plus GP IIb/IIIa inhibitor for ischemic events.

HORIZONS-AMI.[39] This trial compared the use of bivalirudin to heparin plus GP IIb/IIIa inhibitor in patients with STEMI who presented within 12 hours of symptoms and were to undergo primary PCI. Major bleeding and combined adverse cardiovascular events (combination of major bleeding or major adverse cardiovascular events, including death, reinfarction, target-vessel revascularization for ischemia, and stroke) within 30 days were the two primary endpoints. The rate of net adverse clinical events with bivalirudin alone compared to heparin plus IIb/IIIa inhibitor was reduced (9.2% vs. 12.1%; RR, 0.76; 95% CI, 0.63 to 0.92; $p = 0.005$). Major bleeding was reduced with bivalirudin use (4.9% vs. 8.3%; RR, 0.6; 95% CI, 0.46 to 0.77; $p < 0.001$). Rates of major adverse cardiac events were similar between the groups. The 30-day rate of death from cardiac causes was also reduced with bivalirudin (1.8% vs. 2.9%; RR, 0.66; 95% CI, 0.40 to 0.95; $p = 0.03$). The rate of stent thrombosis in the first 24 hours occurred more in the bivalirudin group (1.3% vs. 0.3%, $p < 0.001$). However, the 30-day rate of stent thrombosis was similar between the groups (2.5% vs. 1.9%, $p = 0.30$).

Low-Molecular-Weight Heparin: Dalteparin (Fragmin), Enoxaparin (Lovenox), Tinzaparin (Innohep)

Mechanism of Action

Each of these three drugs binds to antithrombin, increasing antithrombin's activity.

Side Effects

Common side effects include bleeding and thrombocytopenia (type II occurs less often than with UFH but is still a concern), rash, hematoma at the injection site, and fever.

Indications and Precautions

Dalteparin is indicated for prophylaxis of DVT in high-risk patients undergoing abdominal surgery, hip replacement surgery, and patients who are immobile during acute illness. Dalteparin is also indicated in UA/non–Q-wave myocardial infarction (NQWMI) for the prevention of ischemic complications in patients on concurrent aspirin therapy. It should be avoided in patients with HIT or suspected HIT. Although there is a lower reported incidence of thrombocytopenia with LMWH than with UFH, it can still occur. Cross-reactivity of patients developing HIT type II on UFH to those receiving LMWH is >90%. Because it is cleared renally, it is contraindicated in patients with severe renal insufficiency (creatinine clearance <30 mL/min).

Enoxaparin is labeled for prevention of DVT in patients undergoing hip replacement surgery, during and following hospitalization for knee replacement surgery, or in patients undergoing abdominal surgery who are at risk for thromboembolic complications, as well as in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness. Other indications include the prevention of ischemic complications of UA and non–ST elevation and ST-elevation MIs when coadministered with aspirin. Furthermore, it is labeled for use with warfarin for inpatient treatment of acute DVT ± PE or outpatient treatment of acute DVT without PE when administered in conjunction with warfarin. Enoxaparin is renally cleared, dose reductions are required for creatinine clearance < 30 mL/min, and it has not been approved for use for patients on dialysis.

Tinzaparin is labeled for treatment of acute symptomatic DVT with or without PE when administered in conjunction with warfarin sodium. The safety and effectiveness of tinzaparin were established in hospitalized patients. The same precautions apply as for other LMWH products.

Major Clinical Trials

ESSENCE.[40] In this trial, IV UFH was compared with enoxaparin in patients with angina at rest or NQWMI. The primary end-point, the composite of risk of death, (MI, or recurrent angina at 14 days was reduced with enoxaparin by 16.2% (OR 0.8; 95% CI, 0.67 to 0.96; p = 0.02). Secondary endpoints that included the triple composite at 30 days were reduced with enoxaparin by 15% (OR 0.81; 95% CI, 0.68 to 0.96; p = 0.02). However, individual endpoints of death or MI were not significant at 14 or 30 days. Only 16.7% of patients received PCI. No difference was found in major hemorrhage or hemorrhagic stroke, although a higher risk of hemorrhage overall was found with enoxaparin versus heparin (18.4% vs. 14.2%, p = 0.001) due to the increase in minor hemorrhage at 30 days.

A to Z Trial.[41] The A to Z trial compared enoxaparin to IV UFH with concomitant tirofiban and aspirin in patients with Non–ST-elevation acute coronary syndrome (NSTE-ACS). The primary endpoint composite of all-cause death, MI, or refractory ischemia for enoxaparin was 8.4% compared to UFH that was 9.4% (HR 0.88, 95% CI, 0.71 to 1.08), which met criteria for noninferiority. The rate for thrombosis in myocardial infarction (TIMI) grade bleeding was reported in 3.0% of enoxaparin patients (vs. 2.2% for UFH) p =0.13.

ASSENT-3.[42] The safety and efficacy of tenecteplase in combination with enoxaparin, abciximab, or UFH were studied in patients with AMI. Patients received full-dose tenecteplase with enoxaparin, half-dose tenecteplase with low-dose weight-adjusted UFH and abciximab for 12 hours, or full-dose tenect-eplase with weight-adjusted UFH for 48 hours. The primary efficacy endpoint was the composite of mortality, in-hospital reinfarction, or in-hospital refractory ischemia at 30 days. The addition of in-hospital intracranial hemorrhage or in-hospital major bleeding

other than intracranial bleed made up the primary plus safety endpoint. The primary endpoint for the enoxaparin, abciximab, and UFH groups were (11.4%, 11.1%, and 15.4%; p = 0.001). Enoxaparin may have performed better due to the 7-day treatment as opposed to the 48 hours of UFH. The primary efficacy and safety endpoints were enoxaparin (13.8%), abciximab (14.2%), and UFH (17.0%), p = 0.0081. There was no difference found between the groups for 30-day mortality. A significant difference was found in major bleeding other than intracranial hemorrhage with enoxaparin (3.0%), abciximab (4.3%), and UFH (2.2%), p = 0.0005. The bleeding was not found to be significantly different between the enoxaparin and UFH groups. However, the abciximab group, specifically, was found to have an increase in major bleeding compared to the UFH group, especially in patients >75 years (13.3% vs. 4.1%) and in patients with diabetes (7.0% vs. 2.2%).

EXTRACT.[43] Enoxaparin was compared to UFH as adjunct therapy with fibrinolytic therapy in patients with STEMI. With fibrinolytic therapy, patients received either UFH for at least 48 hours or enoxaparin. Enoxaparin was continued through the hospital stay, or a maximum of 8 days. Primary endpoint was composite of death from any cause, or nonfatal recurrent MI through 30 days that was 9.9% for enoxaparin and 12.0% for UFH (0.83 RR; 95% CI, 0.77 to 0.90, p < 0.001). There was no difference in death between enoxaparin (6.9%) and UFH (7.5%) (p = 0.11). There was a significant increase in the rate of bleeding with enoxaparin (2.1%) compared to 1.4% for UFH (1.53 RR; 95% CI, 1.23 to 1.89, p < 0.001).

SYNERGY.[44] Enoxaparin was compared to UFH for efficacy and safety in high-risk patients with non–ST-segment elevation ACS managed with an early invasive strategy. Primary endpoint of death or nonfatal MI by 30 days was 14.0% (696/4,993) in the enoxaparin group and 14.5% (722/4,985) in the UFH group (HR, 0.96; 95% CI, 0.86 to 1.06). Enoxaparin was not superior but did meet noninferiority criteria. Enoxaparin had an increase in TIMI major bleeding (9.1% vs. 7.6%, p = 0.008), but not in GUSTO (Global Utilization of Streptokinase and t-Pa for Occluded Arteries) severe bleeding (2.7% vs. 2.2%).

CALCIUM CHANNEL BLOCKERS

This class of drugs is chemically and pharmacologically diverse. Before we classify the drugs, we will review some information on the various calcium channels. The main ports of entry for calcium into the cell are via voltagegated calcium channels, which open when the membrane depolarizes. Another is a sodium–calcium channel, which moves one calcium ion out in exchange for three sodium ions entering into the cell. The electrical balance within a cell is accomplished by the sodium/potassium ATP channel. Calcium is normally stored in the sarcoplasmic reticulum, which also helps control the level of intracellular calcium. There are three types of calcium channels, L, N, and T. They differ in distribution in various tissues, duration of opening, and voltage range. Only L and T are of interest in cardiology.

L-Type Channels

L-type channels are found in heart muscle and in parts of the conducting system, smooth muscle, brain, adrenals, and kidneys. Although all calcium channel blockers bind to the calcium channel receptor, they have different binding sites. Blocking the L channels or receptors inhibits inward calcium currents into the cell, thus reducing the concentration of calcium needed for muscle contraction, which leads to smooth muscle dilation, decreasing contractility of heart muscle, slowing of the sinoatrial (SA) node firing rate, and increasing AV nodal conductance time.

T-Type Channels

T-type channels are found in blood vessels, adrenals, brain, kidneys, the heart conduction system, and in heart muscle under pathologic conditions such as cardiomyopathy. There is only one identified binding spot for medications, and blocking this receptor leads to dilation of peripheral and coronary blood vessels, thus decreasing SVR and increasing myocardial blood flow. Also, blockade of T-type channels produces a lowering of heart rate.

Mechanism of Action

The various classes of calcium channel blockers and the drugs in each class, as well as their mechanism of action, are shown in Table 61.7.

TABLE
61.7 Calcium Channel Blockers

Subclass	Drugs Available in Subclass	Mechanism of Action
Dihydropyridines	Amlodipine (Norvasc) Felodipine (Plendil) Isradipine (Dynacirc) Nicardipine (Cardene) Nifedipine (Procardia, Adalat) Nimodipine (Nimotop) Nisoldipine (Sular)	Blocks Ca^{2+} channel in smooth muscle, which leads to vasodilatation of peripheral and coronary arteries. Effect on sinus and AV nodes is negated by reflex increase in sympathetic tone.
Nondihydropyridines	Diltiazem (Cardizem, Dilacor, Tiazac) Verapamil (Calan, Isoptin, Verelan)	Blocks Ca^{2+} channel in smooth muscle, which leads to vasodilatation of peripheral and coronary arteries as well as decrease in heart rate and prolonging conduction across the AV node.

AV, atrioventricular.

Side Effects

The side effects and contraindications for calcium channel blockers are shown in Table 61.8.

TABLE
61.8 Side Effects, Contraindications, and Major Drug Interactions of Calcium Channel Blockers

Subclass	Side Effects	Contraindications	Drug Interactions
Dihydropyridines	Headache, peripheral edema, flushing, reflex tachycardia (short-acting agents have higher incidence), rash, dizziness, hypotension, gingival hyperplasia (nifedipine)	Hypersensitivity to the medications; short-acting agents should not be used for hypertensive urgencies; AMI; acute stroke.	Grapefruit juice with certain dihydropyridines. Fentanyl has been reported to cause severe hypotension when given with certain calcium channel blockers. This reaction may occur with all calcium channel blockers, but data are not available. H_2-receptor antagonists may increase the bioavailability of many of the dihydropyridine calcium channel blockers.
Diltiazem and verapamil	Negative inotropic effects, nausea, bradycardia, dizziness, peripheral edema, hypotension, heart block, constipation	AMI; heart block greater than first degree; heart failure; pulmonary edema	H_2-receptor antagonist may increase bioavailability of diltiazem. Beta-blockers may increase negative inotropic and chronotropic effects. Inhibit metabolism of carbamazepine, cyclosporin, digoxin, quinidine, and theophylline.

Indications and Precautions

The various preparations and respective doses along with the labeled uses are shown in Table 61.9.

TABLE
61.9 Preparations, Dosing, and Labeled Uses for Calcium Channel Blockers

Drug	Indications
Amlodipine	Hypertension, stable and vasospastic angina
Felodipine	Hypertension
Isradipine	Hypertension
Nicardipine	Hypertension and stable angina
Nifedipine	Hypertension and vasospastic angina; unlabeled uses include prevention of migraine headaches, primary pulmonary hypertension
Nisoldipine	Hypertension
Diltiazem[a]	Hypertension, angina, and supraventricular tachyarrhythmias
Verapamil[a]	Hypertension, angina, and supraventricular tachyarrhythmias; unlabeled uses are for migraine and cluster headaches, exercise-induced asthma, and hypertrophic obstructive cardiomyopathy.

[a]Diltiazem and verapamil are available as IV formulations that can used in the acute management of atrial fibrillation and supraventricular tachyarrhythmias.

Mechanism of Action

Major Clinical Trials

ASCOT-BPLA.[45] The calcium channel blocker amlodipine was compared to atenolol as an antihypertensive regimen in patients with risk factors for coronary artery disease other than hypertension. The study was stopped early because the all-cause mortality rate was significantly lower with the amlodipine strategy than with the atenolol strategy. The amlodipine-based regimen was associated with reduced rates of strokes, cardiovascular death, and new-onset diabetes, and also total cardiovascular events and procedures.

DIURETICS

By definition, diuretics (except osmotic diuretics) are drugs that lead to a net loss of sodium (Na^+) and water from the body. These drugs (except spironolactone) work primarily in the kidneys, acting from within the tubular lumen. Hence, for these drugs to reach their target, they are secreted into the proximal tubule. The sites of action for these drugs are shown in Figure 61.3.

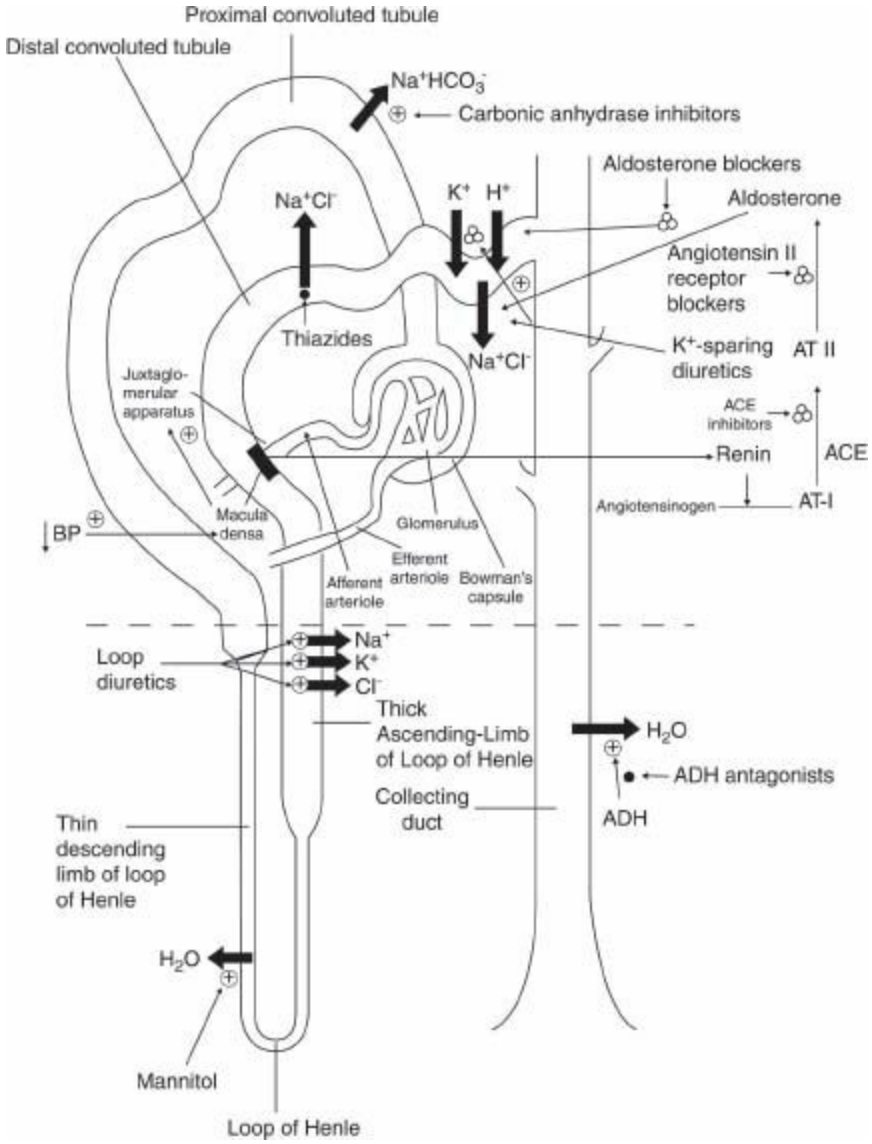

FIGURE 61.3 The human nephron and the sites of action of diuretics.

Loop Diuretics

Loop diuretics are the most powerful diuretics, causing about 15% to 20% of sodium in the tubule to be excreted, hence the name "high-ceiling diuretics."

Mechanism of Action

Loop diuretics act in the thick segment of the ascending loop of Henle and inhibit the transport of sodium out of the lumen of the nephron by blocking the chloride (Cl^-) component of the sodium/potassium/2 chloride ($Na^+/K^+/2Cl^-$) pump in the luminal membrane of the tubule. The net outcome is sodium and water loss. It is important to remember that loop diuretics gain access to the lumen of the nephron by organic acid pumping, without relying on glomerular filtration.

Side Effects

Common side effects of loop diuretics include hypokalemia, hypomagnesemia, hypochloremic metabolic alkalosis (with overdiuresis), ototoxicity (when given in high doses and in conjunction with other ototoxic drugs), hyperuricemia, allergic reaction, azotemia, hypocalcemia, and photosensitivity. They are contraindicated for use in patients with severe sulfonamide allergic reaction (except ethacrynic acid) and anuria.

Indications and Precautions

This subgroup of diuretics is labeled for use in edema to enhance diuresis. Furosemide and torsemide are also labeled for use in hypertension. Common uses are in heart failure, acute renal failure, hyperkalemia, anion overdose, and acute pulmonary edema.

Thiazide Diuretics

Mechanism of Action

Thiazide diuretics decrease active reabsorption of sodium and accompanying chloride by binding to the chloride site of the $Na+/Cl^-$ cotransport system in the distal convoluted tubule. Furthermore, they increase calcium reabsorption in the same region of the nephron. Drugs of this class are effective at low doses, for which reason they are called "low-ceiling diuretics."

Side Effects

Side effects of thiazide diuretics include hypokalemia, hypouricemia, glucose intolerance, hyperlipidemia, hyponatremia, allergic reaction, weakness, fatigue, and photosensitivity.

Indications and Precautions

The various drugs in this subgroup are shown in Table 61.10. Thiazides are not effective in patients with clearance <30 mL/min. Patients may be allergic to the drug if they are allergic to sulfonamide derivatives. Thiazides should be avoided in patients with elevated serum calcium levels. They have known drug interactions with lithium, NSAIDs, probenecid, digoxin, and calcium supplements.

TABLE
61.10 Preparations, Dosing,and Indications for Thiazide and Thiazide-Like Diuretics

Drug	Indications
Chlorothiazide (Diuril)[a] Chlorthalidone (Hygroton) Hydrochlorothiazide (Hydrodiuril) Indapamide (Lozol) Metolazone (Zaroxolyn)	Labeled: hypertension and edema; synergistic diuresis when added to loop diuretics Unlabeled: diabetes insipidus, prophylaxis of renal stones in hypercalcemia

[a]Available as IV and oral preparation.

Major Clinical Trials

ALLHAT.[2,46] In ALLHAT, 42,419 people with stage 1 or 2 hypertension were randomized to a diuretic (chlorthalidone), an ACE-I (lisinopril), a calcium channel blocker (amlodipine), or an **α**-blocker (doxazosin). After 3 years, the doxazosin arm was discontinued because of an increase in heart failure. At the end of the study at 6 years, there was no difference in primary end-points (fatal coronary heart disease and nonfatal MI) or all-cause mortality among ACE-I, diuretics, and calcium channel blockers. In secondary endpoints (stroke, heart failure), however, the diuretic proved to be better than the ACE-I at preventing strokes and heart failure and was also noted to be superior to the calcium channel blocker in preventing heart failure. The diuretic was also noted to have better overall outcomes in African American patients.

INOTROPIC AGENTS AND VASOPRESSORS

The maintenance of tissue perfusion in the body depends on the availability of adequate arterial pressure, which in turn depends on adequate cardiac output and vascular tone. We will approach this group of drugs from two perspectives, that of the inotropic agents and vasopressor agents. The goal of inotropic agents is to improve contractility of the ventricle to enhance cardiac pump function. Vasopressors, as the name suggests, are aimed at supporting the failing circulation by causing vasoconstriction. Many catecholamines have both of these properties.

Inotropic Agents

Physiologically, the mechanism of inotropic response is mediated via increases in intracellular cyclic AMP (cAMP). Hence, increasing the level of cAMP directly with catecholamines, or decreasing its degradation with phosphodiesterase inhibitors, will increase the contractility of the myocardium. However, because cAMP inhibits calcium-mediated contraction of arterial smooth muscle, vasodilatation of arterial vasculature may occur.

Dopamine (Intropin)

Mechanism of Action Dopamine has mixed **α**-, **β**-, and dopaminergic (DA_1)-agonist effects. Through the **α** effect (α_1), it leads to vasoconstriction. Through the **β** effect ($\beta_1 > \beta_2$), it increases cAMP and cardiac contractility. Through the DA_1 and DA_2 effects, it leads to increased renal perfusion and some peripheral dilatation (at low doses).

Side Effects Common side effects of dopamine include tachycardia, arrhythmias, hypertension, headache, and nausea.

Indications and Precautions Dopamine is labeled for use in hypotension, cardiogenic shock, septic shock, and trauma. It should be given by central line because skin necrosis may occur with extravasation. It has a graded dose■response curve, with lower doses causing renal vascular vasodilation, moderate doses having predominantly β_1-adrenergic effects, and higher doses causing vasoconstriction and elevations in blood pressure.

Dobutamine (Dobutrex)

Mechanism of Action Dobutamine is a relatively selective β_1 agonist, but it has much less effect on β_2 and α_1 receptors.

Side Effects Common side effects of dobutamine include tachycardia, hypo-or hypertension, ventricular arrhythmia, nausea, headache, and myocardial ischemia.

Indications and Precautions Dobutamine is labeled for use as a short-term inotropic support in patients with acute cardiac decompensation. Tachyphylaxis may occur with prolonged use. Chronic use has been associated with increased mortality.

Epinephrine (Adrenaline)

Mechanism of Action Epinephrine is a mixed **α**-and **β**-receptor agonist ($\beta_1 = \beta > \alpha$). Hence it leads to increased myocardial contractility and vasoconstriction.

Side Effects Common side effects of epinephrine include tachycardia, flushing, hypertension, restlessness, exacerbation of narrow-angle glaucoma, and ventricular arrhythmia.

Indications and Precautions Epinephrine is indicated for use in ventricular standstill

(cardioplegia or cardiac arrest) and shock (particularly anaphylaxis).

Isoproterenol (Isuprel)

Mechanism of Action Isoproterenol is a nonselective **β**-receptor agonist ($\beta_1 > \beta_2$). It has the most potent inotropic effect of any inotrope.

Side Effects Common side effects of isoproterenol include tachycardia and ventricular arrhythmia (the reason it is used in the electrophysiologic laboratory to stimulate tachycardia), hypotension, myocardial ischemia, mild tremor, nervousness, and flushing.

Preparation, Dosing, Indications, and Precautions Isoproterenol is labeled for use in shock, heart block, Adams–Stokes attacks, and bronchospasm. Unlabeled uses include for bradycardia and for torsades de pointes until temporary pacing can be established.

Milrinone (Primacor)

Mechanism of Action Milrinone is a phosphodiesterase inhibitor that results in increased levels of intracellular cAMP by blocking its degradation, thus increasing contractility as well as vasodilatation because of its effect on arterial smooth muscle.

Side Effects Common side effects of milrinone include hypotension, ventricular arrhythmia, supraventricular tachycardia, angina, chest pain, headache, and thrombocytopenia.

Indications and Precautions Milrinone is labeled for short-term use in the management of CHF. Similar to dobutamine, it was found to increase mortality with long-term therapy, secondary to increasing ventricular arrhythmias.

Vasopressors

Norepinephrine (Levophed)

Mechanism of Action Norepinephrine is a mixed **β** and **α** agonist ($\beta_1 = \alpha > \beta_2$). Its primary effect is vasoconstriction.

Side Effects

Common side effects of norepinephrine include hypertension, headache, trembling, and ventricular arrhythmias.

Indications and Precautions

The labeled use for norepinephrine is hypotension. It should be administered via a central line because of the risk of skin necrosis with extravasation. It should also be used with caution in patients with hepatic dysfunction or ischemic bowel, because it leads to splanchnic and hepatic vasculature constriction.

Phenylephrine (Neo-Synephrine)

Mechanism of Action

Phenylephrine is a pure a-receptor agonist that has a vasoconstrictor effect.

Side Effects Common side effects include bradycardia, hypertension, and myocardial ischemia.

Indications and Precautions Phenylephrine is labeled for use in hypotension, particularly when associated with septic shock (vasodilatation), and anesthetic hypotension. Furthermore, it may be used to counter hypotension due to vasodilatation in severe obstructive hypertrophic cardiomyopathy.

NITRATES

Nitrates are a group of drugs that are a source of NO, which produces vasodilatation in the coronary circulation as well as arterioles and veins. NO mediates vasodilatation via cAMP. These effects contribute to their antianginal properties as well as their role in heart failure. Nitrates that are in use are summarized in Table 61.11.

TABLE
61.11 Nitrates: Mechanism of Action, Side Effects, Dosing, and Indications

Drug	Mechanism of Action	Side Effects and Precautions	Dosing and Indications
ISDN (Isordil, Sorbitrate)	Biotransformation of nitrates releases NO, causing vasodilatation through cAMP. Venous dilation predominates.	Headache, hypotension (large doses), flushing, dizziness, rash, nausea, methemoglobinemia, reflex tachycardia	Labeled: prevention of anginal attacks Unlabeled: heart failure, in combination with hydralazine)
Isosorbide mononitrate (Imdur, Ismo, Monoket)	Same	Same	Labeled: prevention of anginal attacks
Nitroglycerin paste (Nitrol)	Same	Same; inconvenient for long-term therapy secondary to ointment formulation	Labeled: prevention of anginal attacks
Nitroglycerin patch (various)	Same	Same	Labeled: prevention of anginal attacks
Nitroglycerin SL (Nitrostat, Nitrolingual spray)	Same	Same	Labeled: acute treatment or prophylaxis of anginal attacks
Nitroglycerin IV (Tridil)	Same	Same; methemoglobinemia may occur with high doses. May increase intracranial pressure	Labeled: perioperative hypertension, CHF with acute MI, angina
	Same	IV formulation is poorly soluble	Unlabeled: hypertensive crisis, pulmonary hypertension

Some of the major trials studying the role of nitrates in the treatment of heart failure are

V-HeFT I[1] The addition of hydralazine and isosorbide dinitrate (ISDN) to standard therapy (digoxin and diuretics) improved mortality and LV function compared to placebo or prazosin in patients with heart failure.

V-HeFT II.[17] Hydralazine and ISDN were compared to enalapril in men with chronic CHF receiving digoxin and diuretics. In the enalapril patients, mortality at 2 years was reduced (18%) compared to H-ISDN patients (25%), p = 0.016.

A-HeFT.[47] The addition of a fixed dose of ISDN and hydralazine to standard therapy for heart failure, including neurohormonal blockers, is efficacious and increases survival among black patients with advanced heart failure.

PLATELET INHIBITORS

Thrombus formation is a complex process that involves platelets, the vasculature including collagen and tissue factors (primary hemostasis), as well as the coagulation pathways (secondary hemostasis), as shown in Figure 61.2. The initiation of thrombus formation in the arterial system mainly involves platelet aggregation with a small amount of fibrin (white clot), whereas in the venous system, it is composed mainly of fibrin and red cells (red clot). The primary functions of the platelets are to form a plug by adhesion and aggregation, as well as providing a phospholipid surface to facilitate procoagulant reaction.

For the platelets to participate in coagulation, they have to be activated. This usually happens with exposure of the platelets to collagen in the vasculature (injury). Platelets adhere to the collagen via GP Ib-IX, leading to change in shape and granular release of ADP and thromboxane. Thrombin (from the coagulation pathway), angiotensin II, norepinephrine, and contents of granules released from platelets (including ADP and serotonin) stimulate the endothelium to release calcium and hence allow platelet activation. Factors that inhibit platelet activation are prostacyclin and NO. When platelets are activated, arachidonic acid in the endothelium is transformed to thromboxane A2 (TXA2), by cyclooxygenase enzyme (COX). Thromboxane leads to more platelet activation. This step is the target for aspirin use as an antiplatelet therapy. Serotonin, thrombin, and ADP bind to receptors on the endothelium, and via secondary messengers lead to release of calcium from the endoplastic reticulm. The binding of ADP to receptors on the endothelium is the site of action for clopidogrel, prasugrel and ticlopidine as antiplatelet therapy. As mentioned earlier, when platelets are activated, TXA2 is released. TXA2 leads to the expression of GP IIb/IIIa receptors, which allows linkage of adjacent platelets (aggregation) by fibrinogen and von Willebrand factor (vWF) to the GP IIb/IIIa. The GP IIb/IIIa receptors are the site of action of IV antiplatelet therapy (abciximab, tirofiban, and eptifibatide).

Oral Antiplatelet Therapy

Cyclooxygenase Inhibitor/Aspirin

Mechanism of Action Aspirin irreversibly acetylates platelet cyclooxygenase, decreasing the formation of TXA2 from arachidonic acid.

Side Effects Side effects include bleeding, gastric ulceration, nausea/dyspepsia/heartburn, hemolytic anemia, and tinnitus (large doses or overdose).

Indications and Precautions Aspirin is labeled for analgesic, antipyretic, and anti-inflammatory use, as well as for MI, transient ischemic attacks, CVAs, and adjunct therapy for revascularization procedures (coronary artery bypass grafts, PTCA, and carotid endarterectomy) and stent implantation.

Clopidogrel (Plavix)

Mechanism of Action Clopidogrel acts by inhibiting the $P2Y_{12}$ component of adenosine diphosphate receptors, which decreases the expression of the GP IIb/IIIa receptors on the platelet cell surface and thereby prevents platelet aggregation.

Side Effects Common side effects of clopidogrel include bleeding, diarrhea, headache,

dizziness, abdominal pain/nausea/dyspepsia, purpura, rash, and sometimes thrombocytopenia.

Indications and Precautions The drug is labeled for use in ACS and to reduce the risk of MI, stroke, and/or peripheral arterial disease in patients with a completed MI, stroke, and/or peripheral arterial disease. It reduces rates of athero-thrombotic events in patients with UA or non–ST-elevation MI who are medically managed or with PCI (with or without stent placement). Most side effects when compared to aspirin in clinical trials were less in the clopidogrel-treated group. Maximal effects are seen 3 to 7 days after initiation of therapy. Cases of thrombotic thrombocytopenic purpura (TTP) have been reported. Recent data demonstrate that clopidogrel should be continued for 12 months after coronary artery stenting with a drug-eluting stent.[64]

Prasugrel (Effient)

Mechanism of Action This is a prodrug which when converted to its active metabolite, irreversibly inhibits the $P2Y_{12}$ portion of the ADP receptor on platelets to prevent activation of the GP IIb/IIIa receptor, reducing platelet activity.

Side Effects Common side effects include bleeding, hypertension, headache, and nausea.

Indications and Precautions Prasugrel is indicated to reduce rates of thrombotic cardiovascular events in patients with UA, NSTEMI, or STEMI managed with PCI. Due to the increased concern for bleeding, use with other anticoagulants should be cautioned. Use is contraindicated in patients with history of transient ischemic attack or stroke. Use in patients >75 years of age is not recommended due to increased risk of fatal and intracranial bleeding and uncertain benefit. For patients of low weight (<60 kg), a lower maintenance dose should be considered.

Ticagrelor (Brilinta)

Mechanism of Action This reversibly binds to the ADP $P2Y_{12}$ receptor to reduce platelet aggregation by inhibiting the activation of the IIb/IIIa receptor complex on platelets.

Side Effects Common side effects include major bleeding, dyspnea, and headache.

Indications and Precautions Ticagrelor is indicated for use with aspirin for secondary prevention of thrombotic events in patients with UA, NSTEMI, and STEMI who are

medically managed or managed with PCI and/or coronary artery bypass graft. Use is contraindicated in patients with active pathologic bleed or presence or history of intracranial hemorrhage. Efficacy may be reduced if used with aspirin doses higher than 100 mg daily. Maintenance doses of aspirin <100 mg daily are recommended. Cardiac events may increase with premature discontinuation of therapy.

Ticlopidine (Ticlid)

Mechanism of Action See clopidogrel.

Side Effects Common side effects of ticlopidine include bleeding, diarrhea, nausea, vomiting, anorexia, rash, neutropenia, and purpura. Rare but severe life-threatening cases of neutropenia, TTP, aplastic anemia, and agranulocytosis can occur. A complete blood count with differential should be measured at baseline and every 2 weeks for the first 3 months of therapy.

Indications and Precautions The labeled use for ticlopidine is to reduce the risk of thrombotic stroke in patients with completed thrombotic stroke or stroke precursors. It is also used as adjunctive therapy for coronary artery stent placement and as an alternative to aspirin in patients who are unable to take aspirin or clopidogrel. Patients should be monitored for fevers or other signs of infection. Maximal effects are seen 3 to 7 days after initiation of therapy.

Cilostazol (Pletal)

Mechanism of Action The mechanism for intermittent claudication is not fully known. However, as an antiplatelet therapy, cilostazol acts as a phosphodiesterase III inhibitor, suppressing breakdown of cAMP and thus leading to vasodilation and platelet inhibition.

Side Effects Common side effects of cilostazol include headache, palpitations, diarrhea, peripheral edema, and dizziness.

Indications and Precautions Cilostazol is labeled for use to reduce symptoms of intermittent claudication. Unlabeled use is an adjunct to aspirin in patients receiving coronary stenting. It should be taken on an empty stomach and should not be used in patients with CHF because phosphodiesterase inhibitors have been associated with increased mortality rates in CHF patients.

Major Clinical Trials of Antiplatelet Medications

ISIS-2.[48] Aspirin and streptokinase independently reduced mortality in patients with AMI. The combination of the two drugs was better than either alone (synergistic effect) in terms of mortality, without increasing the risk of hemorrhagic stroke.

Antithrombotic Trialists' Collaboration.[49] This was a collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, MI, and stroke in high-risk patients. It found that aspirin is protective in patients who are at increased risk of AMI or ischemic stroke, or who have unstable or stable angina, previous MI, stroke or cerebral ischemia, peripheral arterial disease, or atrial fibrillation. Low-dose aspirin (75 to 150 mg daily) is an effective antiplatelet regimen for long-term use, but in acute settings, an initial loading dose of at least 150 mg aspirin may be required.

CURE.[50] The study's goal was to assess the efficacy and safety of clopidogrel in addition to aspirin in patients with ACS without ST elevation. The study found that the long-term use of clopidogrel with aspirin reduced the risk of events in patients with ACS. The use of clopidogrel was associated with an increased risk of bleeding.

CURE-PCI.[51] This trial looked at the effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing PCI. The results showed that long-term use of clopidogrel after PCI was associated with a lower rate of cardiovascular death, MI, or any revascularization.

CREDO.[52] This trial showed that, after PCI, long-term (1-year) clopidogrel therapy significantly reduced the risk of adverse ischemic events.

CLASSICS.[53] This study showed that the combination of aspirin and clopidogrel was superior to the combination of aspirin and ticlopidine in terms of safety and tolerability. There was no difference in terms of impact on cardiac events.

ISAR-REACT.[54] This trial evaluated the efficacy of abciximab in 2,159 patients undergoing elective PCI. From the clopidogrel point of view, all patients were pretreated with 600 mg of clopidogrel at least 2 hours before PCI. There was no significant difference among groups that received clopidogrel at various intervals.

CLARITY-TIMI 28.[55] This trial randomized 3,491 patients (<75 years of age), presenting within 12 hours of symptoms of STEMI, to either clopidogrel (300-mg loading dose and 75 mg daily thereafter) or placebo. Clopidogrel was given after receiving aspirin and thrombolysis. The clopidogrel group had higher rates of vessel patency at angiography as well as lower rates of reinfarction at 30 days. A subgroup analysis of this study[56] looked at patients who had PCI and stenting within a few days after the clopidogrel loading and fibrinolysis. Early clopidogrel loading after fibrinolysis in patients who subsequently proceeded to PCI was associated with lower risk of cardiovascular death, MI, or stroke at 30 days.

TRITON-TIMI 38.[57] This trial compared prasugrel to clopidogrel in a randomized, double-blind fashion, in 13,608 ACS patients who were scheduled for PCI. A loading dose of prasugrel (60 mg) or clopidogrel (300 mg) was given prior to PCI followed by a maintenance dose of either prasugrel (10 mg) or clopidogrel (75 mg) daily. Aspirin use was required with recommended doses of 75 to 162 mg daily. The primary efficacy end-point was a composite (rate of death from cardiovascular causes, nonfatal MI, or nonfatal stroke). Prasugrel significantly reduced rates of the primary endpoint, as well as rates of MI, urgent target-vessel revascularization, and stent thrombosis. However, prasugrel had a significant increase in major bleeding. Patients with a history of cerebrovascular events (transient ischemic attack or stroke) had net harm with prasugrel and patients age > 75 years or weight < 60 kg did not derive a net clinical benefit with prasugrel.

PLATO.[58] In this trial, ticagrelor was compared to clopidogrel in patients with ACS, with or without ST-segment elevation for prevention of cardiovascular events. The primary endpoint was the composite of death from vascular causes, MI, or stroke, which occurred less in the ticagrelor group (9.8% of patients vs. 11.7% of patients at 12 months, HR, 0.84; 95% CI, 0.77 to 0.92; $p < 0.001$). All-cause mortality was also reduced with ticagrelor versus clopidogrel (4.5% vs. 5.9%, $p < 0.001$). For patients randomized to early invasive strategy, the primary end-point was also reduced with ticagrelor (8.9% vs. 10.6% with clopidogrel; $p = 0.003$). There was no significant difference in major bleeding between the groups. However, in the ticagrelor group, there was a significant increase in episodes of intracranial bleeding (26 [0.3%] vs. 14 [0.2%], $p = 0.06$), as well as fatal intracranial bleeding (11

[0.01%] vs. 1 [0.01%], p = 0.02). The incidence of dyspnea was greater with ticagrelor versus placebo (13.8% vs. 7.8%). In a prespecified subgroup analysis,[59] ticagrelor was found to have less of an effect in North American patients in the United States. Patients in the United States, compared to the rest of the world (ROW), were more frequently taking higher maintenance doses (>300 mg in 61% vs. 4% in ROW) of aspirin. Ticagrelor patients in the cohort on >300 mg doses of aspirin had worse primary efficacy outcomes compared to clopidogrel (HR 1.45, 95% CI, 1.01 to 2.09). Clopidogrel in combination with high- or low-dose (<100 mg daily) aspirin did not have any difference in outcomes. Ticagrelor compared to clopidogrel with low-dose aspirin had the lowest risk of cardiovascular death, MI, or stroke.

Intravenous Antiplatelet Therapy/Glycoprotein IIb/IIIa Inhibitors

Refer to Table 61.12 for details.

TABLE
61.12 Glycoprotein IIb/IIIa Inhibitors: Preparations, Mechanism of Action, and Side Effects

Drug	Mechanism of Action	Side Effects
Abciximab (Reopro)	Murine-derived monoclonal antibody Fab fragment binds to the human GP IIb/IIIa receptor on the platelet surface, inhibiting platelet aggregation.	Bleeding, thrombocytopenia, hypersensitivity reactions
Eptifibatide (Integrilin)	Heptapeptide antagonist that reversibly inhibits GP IIb/IIIa receptor on the platelet surface, inhibiting platelet aggregation	Bleeding, thrombocytopenia
Tirofiban (Aggrastat)	Nonpeptide antagonist that reversibly inhibits GP IIb/IIIa receptor on the platelet surface, inhibiting platelet aggregation	Bleeding, thrombocytopenia

Major Clinical Trials

PRISM.[60] This study compared the effects of tirofiban with aspirin versus heparin with aspirin on clinical outcomes in patients with UA. There was no difference between the two groups in terms of the combined endpoints at 30 days. Mortality alone was significantly reduced in the tirofiban group.

RESTORE.[61] The study focused on the effects of tirofiban on adverse cardiac events in patients with UA who were undergoing PCI. The study showed that tirofiban reduced the primary outcome, which was a composite of death, MI, PCI failure, and coronary artery bypass grafting (CABG). However, the reduction in emergency revascularization seen early in the study was no longer significant at 30 days.

TARGET.[62] TARGET compared tirofiban and abciximab for prevention of ischemic events with PCI. Abciximab was more effective than tirofiban in preventing nonfatal MI as well as in the composite endpoint of death, MI, or urgent target vessel revascularization.

TACTICS-TIMI-18.[63] This trial compared early invasive to conservative therapy in patients with ACS treated with tirofiban. The study showed that the strategy of early catheterization and revascularization was associated with fewer major cardiac events than the conservative approach.

PURSUIT.[64] This study aimed to determine the effects of eptifibatide in patients with ACS between those undergoing PCI versus those being managed conservatively. The study found that eptifibatide reduced the composite endpoint of death or MI at 30 days with either strategy of management.

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undergoing PCI versus those being managed conservatively. The study found that eptifibatide reduced the composite endpoint of death or MI at 30 days with either strategy of management.

ESPIRIT.[65] This study was aimed at assessing the efficacy and safety of high-dose eptifibatide in elective coronary stent implantation. The study showed that eptifibatide reduced ischemic complications after elective stent placement, as well as the combined endpoint of death and MI.

IMPACT-II.[66] This study aimed at assessing eptifibatide impact on the prevention of ischemic complications following PCI. The study showed that the use of eptifibatide was associated with reduced early abrupt closure and reduced the rates of 30 days ischemic events without increasing the risk of bleeding. However, there was no effect on reduction of 30-day mortality or MI, or 6-month cumulative ischemic event rate.

EPIC.[67] This study showed that abciximab bolus and infusion at the time of PTCA improved outcomes for as long as 3 years. It also showed that there was reduction in NQWMI and distal embolization in patients undergoing PCI on saphenous vein grafts.

EPILOG.[68] This trial was aimed at studying whether the clinical benefit of abciximab on reducing ischemic complications in patients undergoing high-risk PCI can be extended to all patients undergoing PCI. Furthermore, the study looked at whether adjusting the heparin dose reduced the hemorrhagic complications associated with abciximab. The study showed that abciximab with low-dose heparin reduced ischemic complications in patients undergoing PCI without increasing the risk of bleeding.

EPISTENT.[69] The purpose of this trial was to compare the outcomes of stenting with or without the use of abciximab, and the outcomes of PTCA with abciximab. The study showed that abciximab significantly improved the outcome of PCI. Furthermore, PTCA with abciximab was better and safer than stenting without abciximab.

CAPTURE.[70] Abciximab infusion started 18 to 24 hours before PCI and continued for 1 hour after PCI reduced the rates of periprocedural MI and the need for revascularization in patients with UA having PTCA, without affecting the rates of MI.

RAPPORT.[71] This trial showed that abciximab in the setting of primary PCI for acute STEMI did not alter the primary endpoint at 6 months—a composite endpoint of revascularization (elective or urgent), death reduction, or reinfarction. There was an increased risk of bleeding.

ADMIRAL.[72] This trial compared the effects of early administration of abciximab before primary stenting to stenting alone without IIb/IIIa-inhibitor therapy. The results showed that early abciximab (before primary PCI for STEMI) improved vessel patency before and after stenting and at 6 months follow-up after the procedure. It was associated with improved clinical outcomes and LV function preservation compared to primary PCI alone.

THROMBOLYTICS/FIBRINOLYTICS

When the coagulation pathways are activated, there is a naturally occurring counter process of "clot dissolving" that begins spontaneously (Fig. 61.2). This process involves plasminogen activators, tissue-type plasminogen activator (t-PA), and urokinase-type plasminogen activator (u-PA). t-PA is the major player in fibrinolysis, whereas u-PA is involved in cell migration and tissue remodeling. These activators break down plasminogen to plasmin, which in turn breaks down fibrin (thrombus) to fibrin degradation products. Fibrinolytics are drugs that mimic biologic activators and hence increase the level of plasmin, which in turn enhances thrombus breakdown. The goal of this therapy is to establish reperfusion to the myocardium, brain, or lung in acute MI (STEMI), CVA, or PE, respectively.

Alteplase/t-PA (Activase)

Mechanism of Action

t-PA binds to clot-bound plasminogen to catalyze conversion to plasmin. The specificity for clot-bound plasminogen decreases systemic fibrinolysis.

Side Effects

Common side effects of t-PA include bleeding, intracranial hemorrhage (0.7%), hypotension, nausea/vomiting, and epistaxis.

Indications and Precautions

The labeled use of t-PA is for AMI, PE, and acute ischemic stroke. Acute MI patients should receive aspirin and heparin during t-PA infusion. In PE, heparin should be started at the end of the alteplase infusion. It is considered superior to streptokinase, but the risk of intracranial hemorrhage is greater than with streptokinase. Age >65 years and weight <70 kg are independent risk factors for intracranial hemorrhage.

Reteplase, r-PA (Retavase)

Mechanism of Action

r-PA is a single-stranded mutant of wild-type t-PA with action similar to that of t-PA, with less high-affinity fibrin binding but increased potency.

Side Effects

Common side effects include bleeding and intracranial hemorrhage.

Indications and Precautions

The labeled use is for AMI. Combination of half-dose reteplase and full-dose abciximab was evaluated in the GUSTO-V trial and found not to be inferior to full-dose reteplase, but there was no mortality benefit, and risk of bleeding was increased.

Streptokinase (Streptase)

Mechanism of Action\

Streptokinase binds to clots and circulating plasminogen; this complex then catalyzes the conversion of plasminogen to plasmin. It is not specific for clot-bound plasminogen and therefore produces a systemic fibrinolytic state.

Side Effects

Common side effects of streptokinase include bleeding, bronchospasm, periorbital

swelling, angioedema, anaphylaxis, hypotension, rash, intracranial hemorrhage (0.2%), fever, and urticaria.

Indications and Precautions

Labeled uses of streptokinase are AMI, PE, DVT, arterial thrombosis or embolism, and occlusion of AV cannulae. Patients should not receive streptokinase if they have received anisoylated plasminogen streptokinase activator complex (APSAC) or streptokinase within the last 12 months. Heparin is not given with streptokinase; if it is needed, the heparin is initiated 4 hours after streptokinase infusion.

Tenecteplase (TNK-ase)

Mechanism of Action

Tenecteplase binds to clot-bound plasminogen to catalyze conversion to plasmin.

Side Effects

Common side effects of tenecteplase include bleeding and intracranial hemorrhage. Hypotension may occur.

Indications and Precautions

Tenecteplase is labeled for use in acute MI. It has the same rate of intracranial hemorrhage as t-PA, but it should not be used with enoxaparin in patients >75 years old. The advantage is that it can be given as a single weight-adjusted bolus injection over 5 to 10 seconds.

Major Clinic Trials

GUSTO-I.[73] This trial found that the mortality in patients with acute STEMI was lower in patients who received t-PA and IV heparin than in those who received streptokinase with either IV heparin or subcutaneous heparin. Furthermore, early PCI when appropriate led to improved survival of patients with MI with cardiogenic shock at 30 days.

GUSTO-III.[74] Reteplase did not show superiority over alteplase in terms of mortality benefit. The two therapies had comparable rates of hemorrhagic strokes.

GUSTO-V.[75] In this trial, half-dose reteplase was given with a 12-hour infusion of abciximab. This combination was not superior to the standard dose of reteplase in terms of mortality. The combination therapy was associated with an increased risk of bleeding complications.

VASODILATORS, MISCELLANEOUS

In this section, we discuss a more diverse group that does not fall into any specific pharmacologic class.

Hydralazine (Apresoline)

Mechanism of Action

Hydralazine works by direct relaxation of the arteriolar smooth muscle, causing a fall in blood pressure, reflex tachycardia, and an increase in cardiac output. The exact mechanism of action at a cellular level has not been determined completely.

Side Effects

Common side effects of hydralazine include palpitation, tachycardia, flushing, myocardial ischemia, nausea, vomiting, anorexia, hypotension, and drug-induced lupus-like syndrome with prolonged use.

Indications and Precautions

Hydralazine has a labeled indication for moderate to severe hypertension and unlabeled use in heart failure.

Fenoldopam (Corlopam)

Mechanism of Action

Fenoldopam is a dopamine (DA_1) receptor agonist that causes smooth muscle relaxation, leading to vasodilatation and increased renal blood flow.

Side Effects

Common side effects of fenoldopam include hypotension, headache, flushing, nausea, tachycardia, and, rarely, hypokalemia.

Indications and Precautions

Fenoldopam is labeled for use as short-term therapy for severe hypertension. It is very expensive while having similar efficacy to nitroprusside in terms of hypotensive effect.

Minoxidil (Loniten)

Mechanism of Action

Minoxidil acts as a vasodilator, primarily affecting arterial smooth muscle. It antagonizes the effect of ATP on the ATP-sensitive channel, which leads to hyperpolarization and muscle relaxation.

Side Effects

Common side effects of minoxidil include significant reflex tachycardia, sodium and

water retention, weight gain, hirsutism, breast tenderness, gynecomastia, and headache.

Indications and Precautions

The labeled use for minoxidil is severe hypertension, and usually it is the last resort in treating hypertension that is not responsive to other medications. It should be used with beta-blockers to reduce the reflex tachycardia and diuretics to reduce sodium and water retention.

Nitroprusside (Nipride)

Mechanism of Action

Direct vasodilatation occurs secondary to the liberation of the nitroso group from the nitrosocyanide structure. Nitroprusside has a balanced effect on both veins and arteries.

Side Effects

Common side effects of nitroprusside include hypotension, headache, nausea, confusion, and metabolic acidosis. Less common side effects are thiocyanate and cyanide toxicity.

Preparation, Dosing, Indications, and Precautions

The labeled use for nitroprusside is hypertensive urgencies and the management of acute CHF. Patients with hepatic failure are at increased risk for developing cyanide toxicity, and this should be suspected in patients with metabolic acidosis, venous hyperoxemia, increased serum lactate levels, air hunger, confusion, seizures, and ataxia. Patients with suspected cyanide toxicity should receive inhaled amyl nitrite while being given 300 mg of sodium nitrite IV, followed by 12.5 mg of sodium thiosulfate IV. If symptoms reappear, then administer half the amounts of sodium nitrite and sodium thiosulfate again. These modalities shift cyanide conversion to thiocyanate. Cyanide levels are not helpful acutely, because it may take up to 5 days to achieve results. Thiocyanate is a neurotoxin that causes confusion, psychosis, lethargy, tinnitus, convulsions, and hyperreflexia. Hemodialysis removes thiocyanate from the blood. Levels are not typically monitored unless infusion of >3 days or when high doses are used in patients with renal failure.

Bosentan (Tracleer)

Mechanism of Action

Bosentan is an endothelin-receptor antagonist (ET-A and ET-B), which leads to vasodilatation (endothelin is a potent vasoconstrictor).

Side Effects

Common side effects of bosentan include severe hepatotoxicity (11% of patients), teratogenicity, headache, flushing, hypotension, fatigue, pruritus, edema, and anemia.

Indications and Precautions

Bosentan is labeled for management of pulmonary hypertension in patients with Class III or IV symptoms. It is necessary to monitor the liver function tests (LFTs); if there is three- to fivefold increase in these, dosage reduction or discontinuation is required. It is available only through the Tracleer Access Program (TAP), a restricted distribution program.

Ambrisentan (Letairis)

Mechanism of Action

Ambrisentan is an endothelin-receptor antagonist (ET-A and ET-B), which leads to vasodilation. Affinity for ET-A is greater than ET-B.

Side Effects

Common side effects include peripheral edema, headache, decrease in hemoglobin/hematocrit, and palpitations.

Indications and Precautions

Indicated for the treatment of pulmonary artery hypertension World Health Organization Group I for improving exercise ability and decrease rate of clinical deterioration. Ambrisentan is contraindicated in pregnancy.

Nesiritide (Natrecor)

Mechanism of Action

Nesiritide is a recombinant human b type of BNP or rhBNP. It binds to guanylate cyclase receptors in vascular smooth muscle and endothelial cells, increasing the intracellular level of cGMP and thereby causing venous and arterial vasodilatation, resulting in dose-dependent reduction in pulmonary capillary wedge pressure (PCWP) and systemic blood pressure. It also causes mild natriuresis.

Side Effects

Common side effects of nesiritide include hypotension, headache, dizziness, and renal dysfunction.

Indications and Precautions

Nesiritide is labeled for use in acutely decompensated heart failure patients who have

dyspnea at rest or with minimal activity. It should be avoided in patients with cardiogenic shock, aortic stenosis, and severe hypotension (systolic blood pressure <90 mm Hg).

Major Clinic Trials

VMAC.[76] In this trial, nesiritide, intravenous nitroglycerin, or placebo was added to standard therapy for patients with dyspnea at rest due to decompensated heart failure. The primary endpoints were absolute change in PCWP (in catheterized patients) and dyspnea (all patients). Nesiritide significantly reduced PCWP at 3 hours (mean change from baseline -5.8 (6.5) mm Hg vs.placebo, $p < 0.001$; vs. nitroglycerin $p = 0.03$). At 24 hours, nesiritide reduced PCWP significantly more than nitroglycerin (-8.2 mm Hg vs. -6.3 mm Hg; $p = 0.04$). Dyspnea at 3 hours was improved with nesiritide over placebo ($p = 0.03$), but not compared to nitroglycerin ($p = 0.56$).

ASCEND-HF.[77] Nesiritide was compared to placebo in addition to standard care in hospitalized patients with acutely decompensated heart failure. The primary endpoints included change in dyspnea at 6 and 24 hours, and composite endpoint of rehospitalization for heart failure or death within 30 days. Nesiritide was not found to have a significant effect on dyspnea. Mortality and rehospitalization were not significantly different between the two groups. In regard to safety, hypotension occurred more frequently in the nesiritide group versus placebo (26.6% vs. 15.3%; $p < 0.001$) as did symptomatic hypotension (7.3% vs. 4.0%; $p < 0.001$).

Epoprostenol (Flolan)

Mechanism of Action

Epoprostenol is prostaglandin I_2. It is a vasodilator of the systemic as well as pulmonary arteries. It also inhibits platelet aggregation.

Side Effects

Common side effects of epoprostenol include jaw pain, hypotension, headache, rash, diarrhea, joint pain, and non-cardiogenic pulmonary edema.

Indications and Precautions

The primary use for epoprostenol is for pulmonary hypertension and pulmonary hypertension secondary to scleroderma in NYHA Class III and IV patients who have not responded to conventional therapy. The half-life of the drug is very short, 3 to 5 minutes; hence abrupt cessation is not well tolerated by patients.

Treprostinil (Remodulin)

Mechanism of Action

Treprostinil is a prostacyclin that directly vasodilates both pulmonary and systemic arterial vascular beds, as well as inhibiting platelet aggregation.

Side Effects

Common side effects include flushing, headache, rash, diarrhea, nausea, infusion site

pain (subcutaneous administration), jaw pain, edema, and hypotension.

Indications and Precautions

The labeled indication is for pulmonary arterial hypertension in patients with NYHA Class II to IV symptoms to decrease exercise-associated symptoms (intravenous and subcutaneous use). Abrupt withdrawal may worsen symptoms. It may cause symptomatic hypotension. Use with caution in patients with low blood pressure.

Digoxin (Lanoxin)

Mechanism of Action

Digoxin, a digitalis glycoside, is used as adjunctive treatment for heart failure and to slow ventricular rate in patients with atrial fibrillation. Digoxin inhibits the sodium–potassium pump on the cell membrane, blocking sodium transport out of the cell, thus increasing intracellular sodium concentrations, and eventually resulting in increased intracellular levels of calcium. This results in an increase in cardiac contractility. Digoxin enhances parasympathetic tone, leading to an increase in AV nodal refractory period, as observed by increases in the P–R interval.

Side Effects

The most common side effects related to digoxin include atrial and ventricular arrhythmias, blurred vision, anorexia, nausea and vomiting, and visual color distortion.

Indications and Precautions

Digoxin is no longer first-line therapy in the treatment of heart failure unless the patient has underlying atrial fibrillation and rapid ventricular response. Patients with continued symptoms of heart failure or with frequent admissions to the hospital may be considered candidates for digoxin after they have been maximized on therapies that improve survival.

Dosing of digoxin can be challenging, as one needs to consider patient weight, renal function, and concomitant medications. The inherent half-life of digoxin is 36 hours in patients with normal creatinine clearance. In patients with impaired renal function, the half-life of digoxin increases, and it will prolong to about 5 days if the patient has end-stage renal disease (ESRD). Concomitant medications may alter digoxin levels, and therefore when initiating new medications or discontinuing medications, one needs to assess the dose. Common drug interactions include those with amiodarone, quinidine, diltiazem and verapamil, erythromycin, and clarithromycin, to name a few.

Intravenous Nitroglycerin

Mechanism of Action

Nitroglycerin liberates NO, which activates guanylyl cyclase, increasing intracellular cGMP levels. The resulting effect produces smooth muscle relaxation leading to vasodilation. Standard doses of nitroglycerin primarily produce venodilation, leading to a decrease in ventricular wall tension by lowering LV end diastolic volume.

Side Effects

The most common side effects include headache, hypotension, tachycardia or bradycardia, dizziness, and rash.

Indications and Precautions

Nitroglycerin, by decreasing myocardial oxygen demand, is typically used to treat chest pain associated with ACSs and to relieve dyspnea associated with CHF.

Nitroglycerin is rapidly metabolized in the liver to less active and inactive metabolites. Because of extensive first-pass metabolism, nitroglycerin cannot be given orally for a therapeutic effect. Sublingual, transdermal, and IV administration of nitroglycerin bypass the portal circulation, avoiding first-pass metabolism. Chronic use of nitroglycerin or isosorbide di- and mononitrates without interruptions in therapy frequently leads to tolerance. Multiple mechanisms of tolerance have been described and include cellular sulfhydryl group depletion, volume expansion, free-radical generation, and neurohormonal activation. The exact mechanism is unknown, but daily nitrate interruptions (8 to 12 hours) will restore the efficacy of nitrates.

Ranolazine (Ranexa)

Mechanism of Action

Ranolazine has antianginal and anti-ischemic effects that do not affect hemodynamics. Ranolazine causes inhibition of the late phase of the inward sodium channel (I_{Na}) in ischemic cardiac myocytes. This reduces intracellular sodium concentration that reduces calcium influx. Decrease in intracellular calcium causes reduction in ventricular tension and myocardial oxygen consumption.

Side Effects

Common side effects include dizziness, constipation, nausea, and headache.

Indications and Precautions

Ranolazine is indicated for the treatment of chronic stable angina. Ranolazine does not relieve acute angina. Prolongation of AT interval has been shown in a concentration-dependent manner. Patients with hepatic impairment may have more significant

increases. Use is contraindicated in patients with clinically significant hepatic impairment. Use with caution in patients with renal impairment as plasma levels can increase by 50%. Ranolazine increases the levels of dabigatran, digoxin, and simvastatin. Simvastatin doses should be reduced to 20 mg daily.

Major Clinic Trials

MERLIN—TIMI 36.[78] Ranolazine was studied in NSTE-ACS patients. The primary efficacy endpoint was first occurrence of the composite of cardiovascular death, MI, or recurrent ischemia. This occurred in 696 (21.8%) ranolazine patients and 753 (23.5%) patients in the placebo group (HR, 0.92; 95% CI, 0.83 to 1.02); p = 0.11). Recurrent ischemia was significantly lower in the ranolazine group. Death from any cause was not significantly different between the groups. However, clinically significant arrhythmias during Holter monitoring in the first 7 days were lower in the ranolazine group.

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QUESTION AND ANSWERS

Questions

1. A 52-year-old woman with a history of ischemic cardiomyopathy and congestive heart failure (CHF) is on stable doses of lisinopril, carvedilol, furosemide, and digoxin. She was admitted to the hospital with shortness of breath, orthopnea, and lower extremity edema and is bradycardic with a heart rate of 42. Her jugular venous pressure was 15 cm H_2O, with bilateral basilar crackles on lung examination. She was 5.6 L in negative fluid balance over 48 hours of hospitalization, and her symptoms were much resolved. On the third day of hospitalization, the patient described dizziness, with vitals showing bradycardia with heart rate of 45. Which of the following is the best next step?
   a. Stop carvedilol.
   b. Stop lisinopril.
   c. Stop digoxin.
   d. Reduce or decrease furosemide dose.
   e. Discharge home with no change in medication.

2. A 64-year-old man presented to the emergency room with crushing chest pain that he had been experiencing for the last 20 minutes. Electrocardiogram (ECG) showed 3-mm ST elevation in leads V_1 to V_3 with reciprocal ST depression in the inferior leads. The patient received aspirin and was started on a heparin drip in the emergency room and forwarded to primary angioplasty. The patient was found to have an acute occlusion of the middle of the left anterior descending artery (LAD). The patient underwent percutaneous coronary intervention (PCI) with a Cypher stent (sirolimus-coated stent) to the middle LAD. How long should you recommend the patient take clopidogrel?
   a. The patient should take 75 mg of clopidogrel for at least 6 months.
   b. The patient should take 75 mg of clopidogrel for at least 3 months.
   c. The patient should take 75 mg of clopidogrel for at least 12 months.

3. A 62-year-old man has a history of chronic renal insufficiency (CrCl 25 mL/min). He has had an aortic valve replacement with a St Jude mechanical prosthetic valve. In addition, he has a history of heparin-induced thrombocytopenia (HITT) complicated with pulmonary embolus. In anticipation of an elective abdominal surgery, warfarin was discontinued. The patient's INR is now <2. Which of the following choices for anticoagulation would you recommend?
   a. Argatroban, 2 mg/kg/min
   b. Dabigatran 75 mg orally twice daily
   c. Heparin bolus and drip per weight nomogram
   d. Enoxaparin, 1 mg/kg SC every 12 hours

4. A 74-year-old male presents to your office after a recent (4 weeks ago) admission for ACS. He was discharged on medical management. He is on the following medications: aspirin 325 mg daily, atorvastatin 80 mg daily, lisinopril 40 mg daily, isosorbide mononitrate 30 mg daily, ticagrelor 90 mg twice daily, and metoprolol tartrate 50 mg twice daily. His blood pressure is 115/77 and heart rate 65 and has not experienced any additional angina and feels well. What adjustments should be made to his medications?
   a. Discontinue the isosorbide mononitrate.
   b. Decrease the lisinopril to 10 mg daily.
   c. Decrease the aspirin to 81 mg daily.
   d. Decrease the metoprolol tartrate to 25 twice daily.

5. Tolerance (tachyphylaxis) occurs with nitrates that can be avoided by:

a. Taking an aspirin 30 minutes prior to nitroglycerin dose
b. Avoiding using the transdermal patch
c. Using only low-dose nitroglycerin
d. Implementing a nitrate-free interval of 8 to 12 hours

6. A patient with normal renal function has hyperkalemia and is currently taking an angiotensin-converting enzyme inhibitor (ACE-I) for his or her hypertension. The best clinical decision would be to:
   a. Discontinue the ACE-I and start a thiazide diuretic
   b. Change from an ACE-I to an angiotensin receptor blocking (ARB) agent
   c. Add a thiazide diuretic to the ACE-I
   d. Add a renin inhibitor

7. An 80-year-old female presents to the emergency department with non–ST-elevation myocardial infarction (NSTEMI) and is being transported for PCI. Her past medical history includes hypertension, atrial fibrillation, stroke, and diabetes. Which antiplatelet option would you choose to initiate?
   a. Prasugrel 60-mg loading dose and 5-mg daily dose
   b. Clopidogrel 600-mg loading dose and 75 mg daily
   c. Prasugrel 60-mg loading dose and 10 mg daily

8. A 56-year-old female with end-stage renal disease (ESRD) on hemodialysis (HD) presents with atrial fibrillation with a rapid ventricular response and is undergoing a transesophageal echo and cardioversion. Your choice of anticoagulation prior to cardioversion is:
   a. Enoxaparin 1 mg/kg twice daily
   b. Dabigatran 75 mg twice daily
   c. Enoxaparin 1 mg/kg once daily
   d. Unfractionated heparin (UFH) infusion

9. A 61-year-old female with a previous history of coronary artery disease, myocardial infarction (MI), CHF (ejection fraction 25%), and chronic renal insufficiency (CrCl 35 mL/min) presents to your office as recommended by her primary care physician. Her current medications include aspirin 81 mg daily, atorvastatin 40 mg daily, lisinopril 40 mg daily, and atenolol 50 mg daily. She states that she has been feeling more tired recently. Her renal function is stable and her potassium is within normal limits. Her vitals show blood pressure of 110/78 and heart rate of 46. What adjustments should be made to her medications?
   a. Decrease lisinopril dose.
   b. Discontinue lisinopril and initiate ISDN and hydralazine combination.
   c. Decrease atenolol dose.
   d. Change atenolol to metoprolol succinate XL 50 mg daily.

10. A 68-year-old male with coronary artery disease, hypertension, and hyperlipidemia presents to your office for follow-up. He is currently taking metoprolol tartrate 100 mg twice daily, lisinopril 20 mg daily, simvastatin 40 mg daily, aspirin 81 mg daily, amlodipine 10 mg daily, and ranolazine 1,000 mg twice daily. His lipid panel shows low-density lipoprotein (LDL) of 85 mg/dL with a goal LDL of <70 mg/dL. How should his lipid-lowering therapy be modified?
    a. Change to atorvastatin 40 mg.
    b. Increase simvastatin to 80 mg.
    c. Add ezetimibe.
    d. Add fenofibrate.

Answers

1. Answer C: Digoxin has not shown survival benefit in heart failure, can cause bradycardia, and should be discontinued. The patient has been on stable doses of standard heart failure medications shown to reduce mortality (ACE-I, beta-blocker). Although carvedilol can reduce heart rate, without the interaction with the digoxin, the heart rate should improve. Furosemide does not cause bradycardia.

2. Answer C: Though previous guidelines recommended taking 75 mg of clopidogrel for 3 months after stenting with a sirolimus-eluting stent and for 6 months after a paclitaxel-eluting stent, the current guidelines recommend at least 12 months.

3. Answer A: Argatroban is recommended because the patient has chronic renal insufficiency and argatroban is cleared hepatically. Choice b, dabigatran, is cleared renally, and the patient has a mechanical aortic valve as well as HITT, which dabigatran has not been evaluated or approved for. Heparin is contraindicated because the patient has a history of HITT and is at increased risk for thrombotic complications, particularly with prosthetic valve. Enoxaparin is not advised because there is a significant degree of cross-reactivity with UFH with regard to HITT and concern with the dose not being renally adjusted.

4. Answer C: It is recommended to use doses of aspirin <100 mg daily for maintenance therapy when in combination with ticagrelor. In the prespecified subgroup analysis of the PLATO trial,[59] ticagrelor was found to have less of an effect in North American patients in the United States. Ticagrelor patients for the cohort on >300 mg doses of aspirin had worse primary efficacy outcomes compared to clopidogrel. Ticagrelor compared to clopidogrel with low-dose aspirin had the lowest risk of cardiovascular death, MI, or stroke. The patient's vitals are stable and he has no side effects from his other medications, so there is no need to discontinue or decrease doses of his other medications.

5. Answer D: Tachyphylaxis can be avoided by including a nitrate-free interval.

6. Answer A: Thiazide diuretics are considered first-line therapy for hypertension for patients without compelling indications such as heart failure, diabetes, and ischemic heart disease. Adding the thiazide to the ACE may cause hypotension but may not correct the hyperkalemia. Changing to an ARB or adding a renin inhibitor would also potentiate hyperkalemia.

7. Answer B: Clopidogrel is the optimal choice because in the TRITON-TIMI 38[57] trial, patients with a history of cerebrovascular events (transient ischemic attack or stroke) had net harm with prasugrel with an increased risk of bleeding compared to clopidogrel. Patients age > 75 years or weight < 60 kg did not derive a net clinical benefit with prasugrel compared to clopidogrel. Therefore, prasugrel is not recommended for use in patients >75 years old and is contraindicated in patients with a history of stroke. It is recommended by the manufacturer to lower prasugrel maintenance dose to 5 mg daily for patients who weigh <60 kg, although this is not supported by existing clinical trial data.

8. Answer D: UFH infusion should be used because it is not renally cleared and can be utilized for ESRD patients on HD. Enoxaparin is not approved for use in dialysis patients. If the patient was not on dialysis and CrCl was < 30 mL/min, enoxaparin 1 mg/kg once daily would be appropriate. Dabigatran is not recommended in patients with CrCl <15 mL/min or on HD. For patients not on dialysis with CrCl 15 to 30 mL/min, dabigatran 75 mg twice daily would be appropriate.

9. Answer D: Metoprolol succinate is approved for and has shown mortality benefit in patients with heart failure, whereas atenolol is not approved for treatment of heart failure. Atenolol is renally cleared and may be causing her bradycardia and fatigue symptoms due to accumulation of drug with her renal insufficiency. Decreasing the lisinopril dose or changing to the combination of ISDN and hydralazine is not necessary with a stable blood pressure and no signs of hyperkalemia or worsening renal failure.

10. Answer A: Changing to atorvastatin 40 mg will intensify the LDL lowering by adding the more potent agent at a higher dose without the potential risk of increased side effects or drug interactions. Amlodipine and ranolazine both have drug interactions with simvastatin in the face of new contraindications for increasing simvastatin dose above 10 mg daily in combination with amlodipine or 20 mg daily in combination with ranolazine. The current simvastatin dose (40 mg) is still too high with both drug interactions. Adding fenofibrate would potentially increase risk for myopathies, myalgias, and rhabdomyolysis. If adding ezetimibe, the dose of simvastatin would still be above the recommended maximum.

CHAPTER

Cardiovascular Drug Interactions

Michael A. Militello

Drug interactions occur when the combination of two or more medications alters the pharmacokinetic parameters or changes the pharmacologic response of either drug. These changes can produce undesirable responses including exaggerated or reduced pharmacologic effect or an added toxic response. It is clear that with the aging population and the increasing number of prescribed medications, the likelihood of having a significant drug interaction increases. In general, drug interactions account for a reported 7% to 17% of all adverse drug events and are probably higher considering underreported events.

Drug interactions are categorized as either pharmacokinetic or pharmacodynamic. Pharmacokinetic interactions occur when combining two or more medications results in an alteration of the drug's disposition in the body. Examples include the use of amiodarone with warfarin resulting in an increased international normalizing ratio (INR) secondary to decreased hepatic metabolism of warfarin, or itraconazole decreasing the metabolism of certain HMG-CoA reductase inhibitors. Pharmacodynamic interactions occur when the addition of a medication leads to changes in the pharmacologic response of either medication. Examples include the addition of digoxin for heart rate control to beta-blockers or nondihydropyridine calcium channel blockers, which may lead to an unacceptable lowering of heart rate.

This chapter outlines typical types of drug–drug interactions observed in clinical practice and includes information on selected food–drug interactions that are commonly encountered.

PHARMACOKINETIC DRUG INTERACTIONS

As reviewed in Chapter 60, the basic characteristics of pharmacokinetics include absorption, distribution, metabolism, and elimination. Alterations in one or more of these characteristics may lead to a significant drug interaction. Many of the documented

interactions occur as a result of changes in metabolism or elimination of medications.

Absorption-related interactions result in decreases or increases in the amount of drug absorbed as well as delays in absorption. The presence of food or certain types of food may change medication absorption characteristics, leading to either a decrease in the extent or an increase in absorption time. Certain medications must be taken on an empty stomach for adequate bioavailability. For example, captopril, a non–prodrug angiotensin-converting enzyme inhibitor, is a prototypical drug that must be taken on an empty stomach because food may decrease the bioavailability by 25% to 50%. Additional medications that should be taken on an empty stomach are listed in Table 62.1. In addition, other medications such as bile acid binders and fiber laxatives may alter absorption of medications. Bile acid binders such as cholestyramine interfere with the absorption of a number of medications, and as a general rule, medications should be taken 2 hours before or 2 hours after the bile acid resin to minimize a decrease in absorption. Another mechanism that may alter absorption is chelation, whereby di- or trivalent cations such as calcium and aluminum bind and decrease bioavailability. Tetracycline and quinolone antibiotics are prototypical for chelating interactions. Also, medications that may increase gastric motility, such as metoclopramide and erythromycin, may alter the bioavailability of medications because gastrointestinal transit times are hastened.

TABLE
62.1 Cardiovascular Medications that should be Taken on an Empty Stomach

Captopril	Moexipril
Felodipine	Perindopril

Certain medications require either an acidic or basic gastrointestinal pH for absorption. Alterations in pH may change the bioavailability of these medications. For example, itraconazole requires an acidic pH for optimal absorption, and medications such as H_2-blockers and proton pump inhibitors may decrease bioavailability and possibly result in treatment failure. Finally, antibiotics can alter the flora of the gastrointestinal tract and may change the bioavailability or efficacy of certain medications. Digoxin is metabolized in the gastrointestinal tract by the bacteria Eubacterium lentum in approximately 10% of patients. Both tetracycline and erythromycin can decrease the levels of this bacterium, therefore increasing the bioavailability of digoxin. Antibiotic-induced vitamin K depletion may interfere with warfarin. Gut flora that produce vitamin K may be killed, leading to an increased sensitivity to the effects of warfarin.

Alterations in protein binding may also play a role in drug–drug interactions. Drugs that are highly protein or tissue bound are more affected by other drugs that displace the

original drug from the protein-binding site. Levels of the unbound fraction of drug will increase either transiently or permanently when the two medications are given concomitantly. These interactions are more difficult to identify, and medications with high protein binding such as warfarin and digoxin should be taken into consideration when adding or discontinuing medications.

Drug metabolism occurs via phase I or II reactions. Phase I reactions include oxidation, reduction, or hydrolysis and convert parent compounds into more water-soluble compounds such as losartan. These metabolites may be inactive, have more activity than the parent compounds (prodrugs), or have less activity than the parent compound. Phase II reactions typically result in development of inactive compounds via glucuronidation, sulfation, or addition of other endogenous substances such as lorazepam.

Most phase I reactions occur via the cytochrome P450 (CYP) enzymes found in the liver, gastrointestinal tract, brain, kidneys, and other organs throughout the body. The vast majority of the enzymes are hepatic; however, there are large concentrations in the gastrointestinal tract as well. The CYP enzymes are a group of heme-containing compounds located on the membrane of the endoplasmic reticulum. The nomenclature for CYP includes a lead number referring to the family, followed by a letter referring to the subfamily, and finally an additional number that refers to the individual enzyme. Examples include CYP3A4 or 2D6. Most drug metabolism occurs via enzymes in the families 1, 2, and 3. CYP3 enzymes account for nearly 70% of the total CYP in the liver.

An individual drug can be a substrate, inhibitor, or inducer for a specific enzyme. A drug may act as an inhibitor of one or more groups of enzymes and may be a substrate for one or more groups of enzymes. For example, amiodarone is a substrate for CYP3A4 and is an inhibitor of CYP2C9 and 2D6 enzymes. Genetic variation also exists in the expression of certain CYP enzymes. Polymorphism is seen with both CYP2D6 and 2C19, and expression of the enzyme can be variable. Between 3% and 10% of Caucasians and 2% of Asians and African Americans have either low or no activity of CYP2D6. Patients with low or no activity of a particular isoenzyme are known as “poor metabolizers.” Some individuals are also poor metabolizers of medications that are eliminated through the CYP2C19. Many commonly used cardiovascular medications are eliminated through the CYP system. Table 62.2 lists the drugs and the enzyme(s) responsible for their elimination as well as other enzyme(s) they may inhibit.

TABLE
62.2 Commonly Observed Drug–Drug Interactions with Cardiovascular Medications[a]

Cardiovascular Drug	Interacting Drug	Mechanism	Considerations
Amiodarone	Warfarin	Amiodarone inhibits CYP2C9 and increases warfarin levels	Monitor closely; consider decreasing warfarin dose early
	Digoxin	P-glycoprotein inhibition	Monitor closely; consider decreasing dose by 50% when initiating amiodarone
	Simvastatin, lovastatin	Amiodarone inhibits CYP3A4, leading to elevations in levels	Use lower doses of statins to decrease risk of rhabdomyolysis; atorvastatin not as significant, as less is metabolized through 3A4.
	Diltiazem, verapamil	Amiodarone inhibits CYP3A4, increasing levels of verapamil and diltiazem; amiodarone also slows heart rate	Both pharmacokinetic and pharmacodynamic interactions occur with amiodarone and diltiazem and verapamil
	Cyclosporine	Amiodarone inhibits CYP3A4, increasing levels of cyclosporine	Monitor cyclosporine levels closely
	Metoprolol	Amiodarone inhibits CYP2D6, increasing levels of metoprolol; amiodarone also slows heart rate	Both pharmacokinetic and pharmacodynamic interactions occur with amiodarone and metoprolol
Digoxin	Amiodarone	P-glycoprotein inhibition	Digoxin levels may be increased with the addition of these agents; Consider dosing adjustment when adding or discontinuing medications to digoxin
	Clarithromycin	P-glycoprotein inhibition	
	Cyclosporine	P-glycoprotein inhibition	
	Diltiazem	P-glycoprotein inhibition	
	Erythromycin	P-glycoprotein inhibition	
	Itraconazole, ketoconazole	P-glycoprotein inhibition	
	Propafenone	P-glycoprotein inhibition	
	Quinidine	P-glycoprotein inhibition	
	Verapamil		
	Beta-blockers	Additive effects	Pharmacodynamic interaction with additive effects on slowing heart rate; also occurs with other rate-controlling medications such as diltiazem and verapamil
Dofetilide	Cimetidine	Inhibition of renal tubular secretion and CYP 3A4 metabolism	Contraindicated to give concurrently
	Hydrochlorothiazide	Inhibition of renal tubular secretion	Contraindicated to give concurrently
	Itraconazole	QT-prolonging effects possible; inhibition of CYP3A4	Contraindicated to give concurrently; dofetilide has minimal metabolism through 3A4; itraconazole may prolong QT interval
	Ketoconazole	Inhibition of renal cation transport system; additive effect on QT prolongation	Contraindicated to give concurrently
	Trimethoprim (alone or in combination with sulfamethoxazole)	Inhibition of renal tubular secretion	Contraindicated to give concurrently
	Triamterene	Inhibition of renal cation transport system	Contraindicated to give concurrently
	Verapamil	Unknown; however, may increase absorption of dofetilide	Contraindicated to give concurrently
	Prochlorperazine	Inhibition of renal tubular secretion	Contraindicated to give concurrently
	QT-interval–prolonging drugs	Additive effects on QT interval	Contraindicated to give concurrently; many drugs, such as Class Ia and III antiarrhythmics, certain antipsychotics, certain quinolones, phenothiazine, many others
	Megesterol	Inhibition of renal tubular secretion	Contraindicated to give concurrently
Statins	Amiodarone	CYP3A4 major metabolic pathway of statins listed on left	Do not exceed 10 mg of simvastatin
	Bosentan	CYP3A4 enzymes are induced by bosentan	May require higher dose for pharmacologic response
	Cyclosporine	Cyclosporine inhibits CYP3A4	Contraindicated with simvastatin
	Amlodipine	Inhibits CYP 3A4	Do not exceed 20 mg of simvastatin.
	Diltiazem, verapamil	Both verapamil and diltiazem are inhibitors of CYP3A4	Reduce dose of listed statins. Do not exceed 10 mg of simvastatin
	Itraconazole, ketoconazole	Inhibits all CYP enzymes	Avoid statins during therapy with these antifungals
	Gemfibrozil	Increased risk of myopathy and rhabdomyolysis	Contraindicated with simvastatin

	Erythromycin, clarithromycin	Certain macrolide antibiotics inhibit the CYP3A4	Avoid statin use during therapy with these antibiotics. Contraindicated with simvastatin
	Nefazodone	Nefazodone decreases CYP elimination of certain statins	Avoid statin use. Contraindicated with simvastatin.
	HIV-protease inhibitors	Certain protease inhibitors decrease metabolism of statins	Avoid statin use. Contraindicated with simvastatin.
	Ranolazine		Do not exceed 20 mg of simvastatin
Warfarin	Amiodarone	See Amiodarone	See Amiodarone
	Bile acid binders	Concomitant use decreases the absorption of warfarin	Take warfarin 2 h before or 2 h after a bile acid binder
	Antiplatelet medications	Increased risk of bleeding	Monitor for signs and symptoms of bleeding
	Metronidazole	Inhibition of warfarin metabolism	Change antibiotic if possible; if not, consider reducing dose of warfarin and monitor INR more frequently
	Gemfibrozil	Inhibition of warfarin metabolism and protein-binding displacement	Monitor INR more frequently while on therapy; consider alternative therapy; interaction may be seen with fenofibrate as well
	Trimethoprim and sulfamethoxazole	Inhibition of warfarin metabolism and protein-binding displacement	Avoid use if possible; if not, consider reducing warfarin dose and monitor INR more frequently while on therapy
	Rifampin	Increased metabolism of warfarin	Monitor INR more frequently, as patients will need higher doses.
	Phenobarbital	Increased metabolism of warfarin	Monitor INR more frequently, as patients will need higher doses.
	Phenytoin	Increased metabolism of warfarin	Monitor INR more frequently, as patients will need higher doses.
	Azole antifungals	Decreased metabolism of warfarin	Monitor INR more frequently, as patients will need lower doses.
	Macrolide antibiotics	Decreased metabolism of warfarin	Monitor INR more frequently, as patients will need lower doses.
	Cyclosporine	Unknown mechanism, probably reduced warfarin metabolism	Monitor INR more frequently, as patients will need lower doses.

[a] This table provides a limited list of medications and interactions and is by no means complete. A review of the complete medication list for drug interactions should be performed frequently, especially when adding or discontinuing medications, to avoid unnecessary adverse drug events.

Besides being inhibitors or substrates, medications can also be inducers of the CYP enzyme system. Inducers increase metabolism of medications that are eliminated by these enzymes (Table 62.3). Enzyme inducers increase the activity of certain CYP isoforms and may require dosing increases of affected medications. Ethanol and smoking can influence metabolism of medications. The amount of ethanol intake and the number of cigarettes smoked daily directly influences the degree of enzyme induction. However, caution must be exercised with patients who are binge ethanol users. Although chronic ethanol intake will induce hepatic enzyme metabolism, acute or binge use of ethanol will inhibit metabolism of medications.

TABLE
62.3 Truncated List of Medications that Induce CYP

Phenytoin	1A2, 3A4, 2D6, 2C9
Phenobarbital	1A2, 3A4, 2D6, 2C9
Carbamazepine	3A4, 2D6, 2C
Rifampin	1A2, 3A4, 2D6, 2C9
Ritonavir	1A2, 2D6
Smoking	1A2

Pharmacodynamic Drug Interactions

Interactions classified as pharmacodynamic do not alter the medication's disposition in the body but instead alter the expected pharmacologic response. The addition of a second agent may act synergistically to increase the response of the first drug, as in the addition of digoxin to a beta-blocker to control ventricular rate in patients with atrial fibrillation. Adverse reactions may be additive, as in the case of adding a medication that prolongs the QT interval to a regimen already consisting of a Class III antiarrhythmic agent such as sotalol. Table 62.4 contains a truncated list of medications that prolong the QT interval.

TABLE
62.4 Truncated List of Medications that Prolong the QT Interval

Amiodarone	Ketoconazole
Disopyramide	Procainamide
Dofetilide	Phenothiazine antipsychotics
Droperidol	Quinidine
Erythromycin	Quinolone antibiotics
Haloperidol	Sotalol
Ibutilide	Tricyclic antidepressants
Itraconazole	Ziprasidone

Sildenafil, tadalafil, and vardenafil enhance the effects of nitric oxide to produce their pharmacologic response. Nitrates that produce similar effects are considered contraindicated, as the additive effects of the combination may lead to life-threatening hypotension.

FOOD–DRUG INTERACTIONS

Food may increase or decrease the extent of medication absorption. These types of interactions may depend on the characteristics of the medication and the meal. Considerations of food vitamin and electrolyte content can be as important as significant drug–drug interactions. Increased risk or toxicities may occur, as in the case of high-potassium foods or salt substitutes with angiotensin-converting enzymes inhibitors, or

treatment failures as in the case of warfarin and excessive vitamin K intake. Finally, there have been occurrences of gastrointestinal interactions with CYP3A4 and P-glycoprotein. P-glycoprotein is a drug efflux pump found in high concentrations in the villi in the gastrointestinal tract, which is responsible for transporting lipophilic compounds from the enterocyte back to the intestinal lumen (reverse transport). Hence these two enzymes work together to change the amount of medication that reaches the systemic circulation.

Grapefruit juice is the classic example of a drug–food interaction, with inhibition of gastrointestinal CYP3A4 and P-glycoprotein leading to an increase in medication bio-availability. Grapefruit juice may increase the levels of certain dihydropyridine calcium channel blockers, statins, cyclosporine, and other medications. This interaction may be observed with as little as 200 mL daily, with an effect possibly lasting hours after ingestion. Medications that interact with grapefruit juice have increased toxicities, as in the case of felodipine, for which there can be two times the amount of drug absorbed, increasing the hypotensive risk. Other calcium channel blockers, such as amlodipine, are less affected by grapefruit juice. A similar case can be made for coadministration of certain statins with grapefruit juice. Simvastatin, lovastatin, and to a lesser extent atorvastatin will have increased levels with the coadministration of grapefruit juice and have an increased potential for the development of adverse events.

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QUESTIONS AND ANSWERS

Questions

1. Simvastatin levels can be increased by which of the following?
   a. Water
   b. Grape juice
   c. Grapefruit juice
   d. Orange juice
2. A 50 year old man was initiated on Amiodarone for paroxysmal atrial fibrillation. He complains of severe nausea after each dose and would like to try a different antiarrhythmic. You decide that sotalol would be a good alternative agent. He is currently taking warfarin, aspirin, hydrochlorothiazide, and lisinopril. Which of his current therapies will need to be adjusted after Amiodarone is discontinued?
   a. Aspirin
   b. Hydrochlorothiazide
   c. Lisinopril
   d. Warfarin
3. A 65 year old man has a history of hypercholesterolemia and is currently on simvastatin 40 mg daily. At his most recent appointment, he is now noted to have hypertension and you want to initiate amlodipine 5 mg daily. How should you alter the dose of Simvastatin?
   a. No change needs to be done.
   b. Increase the dose to 80 mg daily.
   c. Decrease the dose to 20 mg daily.
   d. Decrease the dose to 10 mg daily.
4. A 42 year old woman has a mechanical mitral valve and is on warfarin to prevent valve thrombosis. She is now diagnosed with tuberculosis and will need to receive rifampin as part of her therapy. Which of the following statements is correct?
   a. Rifampin will increase the elimination of warfarin.
   b. Rifampin will decrease the elimination of warfarin.
   c. There is no concern regarding rifampin and warfarin.
   d. Change warfarin to Dabigatran.
5. The interaction between Sotalol and Diltiazem would be considered a:
   a. Pharmacogenomic interaction
   b. Pharmacodynamic interaction
   c. Pharmacokinetic interaction
   d. None of the choices

Answers

1. Answer C: Grapefruit juice will inhibit p-glycoprotein and the CYP 3A4 enzyme system. In June of 2011 the FDA safety alert reiterated the product label for simvastatin stating that patients should drink <1 quart of grapefruit juice daily to prevent adverse effects of simvastatin.

2. Answer D: Amiodarone inhibits the metabolism of warfarin and upon discontinuing therapy you will need to monitor his international normalizing ratio (INR) more frequently and be ready to increase the dose of warfarin as the INR starts to decrease. This may not be immediately recognized as the half-life of Amiodarone is 25 to 100 days.

3. Answer C: Based on the new dosing recommendations the maximum dose of simvastatin when

taken with amlodipine is 20 mg daily. The exact mechanism of this interaction is unclear, however, most likely is related to interactions with the CYP 450 enzyme system. The dose of 80 mg should not be initiated on any patients at this time as there is an increased risk of rhabdomyolysis.

4. Answer A: Rifampin is a powerful inducer of the CYP 450 enzyme system. The addition of rifampin will increase the elimination of warfarin and occurs rapidly. This combination would require increased monitoring of the INR. Doses of warfarin will need to be greatly increased while the combination is continued. Dabigatran does not have an indication for the prevention of valve thrombosis and is not an appropriate therapy at this time.

5. Answer B: The addition of diltiazem to sotalol would cause an additive effect on slowing of the atrioventricular (AV) node. This interaction is a synergistic effect on prolongation of the AV node refractory period. This is not a pharmacokinetic effect as there is no alteration in the levels of either drug.

INDEX

AA. See Abdominal aortic aneurysm
bciximab (Reopro)
bdominal aortic aneurysm (AAA)
blation
  atrial flutter
  atrioventricular junction
  catheter
bsolute risk reduction (ARR)
CC/AHA. See American College of Cardiology/American Heart Association
ccelerated AV junctional rhythm
ccelerated idioventricular rhythm (AIVR)
CCP. See American College of Chest Physicians
CE. See Angiotensin-converting enzyme
CIP trial
CP Journal Club Criteria
cromegaly
CS. See Acute coronary syndrome
ction potential (AP), membrane
  calcium-dependent AP myocardial tissues vs. sodium channel tissues
  conduction system anatomy and physiology
  electrical coupling cells
  Na^+ channel activity regulation
  sodium-dependent cells
CTION trial
ctivase. See Alteplase
cute chest pain syndromes
cute cor pulmonale
cute coronary syndrome (ACS). See also Non-ST-elevation acute coronary syndrome
CC/AHA classification for
  angiotensin-converting enzyme inhibitors (ACE-I)
  clinical presentation for
  discharge planning and noninvasive stress testing
  epidemiology and prognosis
  management of
    anti-ischemic agents
    antiplatelet agents
    antithrombin therapy
    aspirin for
    DTIs
    glycoprotein IIb/IIa inhibitors for
    heparins
      low molecular weight
      unfractionated
    initial approach

invasive therapy
miscellaneous agents
thienopyridines
pathophysiology
risk stratification
biomarkers as
ECG and
TIMI risk score
summary on
terminology and overview
Acute mitral regurgitation. See also Mitral regurgitation
diagnosis for
symptoms and signs of
treatment for
Acute myocardial infarction (AMI)
dobutamine for
dopamine for
epinephrine for
management of
norepinephrine for
phenylephrine for
Acute pericarditis. See also Pericarditis
Adalat. See Nifedipine
Adenosine
Adenosine diphosphate (ADP)
Adenosine triphosphate (ATP)
for cardiac pacing
hydrolysis of
myocardial perfusion imaging
ADME (drug absorption, distribution, metabolism, and elimination)
ADMIRAL trial
ADP. See Adenosine diphosphate
Adrenal insufficiency
Adrenaline. See Epinephrine
Adrenergic agonists
Adrenergic antagonists
-Adrenergics
-Adrenoreceptor kinase (βARKI)
AF. See Atrial fibrillation
AFCAPS/TexCAPS. See Air Force/Texas Coronary Atherosclerosis Prevention Study
AFFIRM (Atrial Fibrillation Follow-Up
Investigation of Rhythm Management)
AFRP. See Atrial Functional Refractory Period
Aggrastat. See Tirifiban
-agonists
AHA. See American Heart Association
Air Force/Texas Coronary Atherosclerosis Prevention Study
AIREX
AIVR. See Accelerated idioventricular rhythm
Aldomet. See Methyldopa
Aldosterone

antagonists
receptor
ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)
Alteplase/t-PA (Activase)
Ambrisentan (Letairis)
American College of Cardiology/American Heart Association (ACC/AHA)
American College of Chest Physicians (ACCP)
American Heart Association (AHA)
American Society of Nuclear Cardiology
AMI. See Acute myocardial infarction
Aminoglycosides
Amiodarone
Amlodipine
Ampicillin
Amyl nitrite
Amyloidosis
Anemia
Angina
classifications
refractory
enhanced external counterpulsation
miscellaneous proposed therapies
spinal cord stimulation
stable
definition of
diagnostic testing/risk stratification
conclusion on
coronary angiography
echocar diography
electrocardiography
exercise ECG testing
stress testing
medical treatment for
antianginal therapies
conclusion on
medical therapies
pathophysiology of
revascularization
conclusion on
coronary artery bypass grafting vs. medical therapy
PCI vs. CABG
PCI vs. medical therapy
unstable
variant/prinzmetal
Angiography
indications for
pulmonary
Angiomax. See Bivalirudin
Angiotensin
I

II
Angiotensin-converting enzyme (ACE)
for stable angina
for STEMI
Angiotensin-receptor blockers (ARBs)
for HTN
II
Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA)
Annuloplasty
Antianginals, stable angina
beta-blockers
calcium channel blockers
combination therapy
nitroglycerin and nitrates
ranolazine
Antiarrhythmic drugs, A F
CHADS II score
class IA
class IC
class III
inpatient vs. outpatient initiation
proarrhyrhmia risks associated with
selection
Antibiotics
Anticoagulants
during pregnancy
for valves
Anticoagulation
chronic
recommendations for
Antihyperlipidemic therapy
Anti-ischemic agents
for ACS
for STEMI
Antiplatelet agents
for ACS
aspirin
glycoprotein IIb/IIIa inhibitors
thienopyridines and ADP inhibitors
for STEMI
Antiplatelet medications
Antiplatelet therapy
Antiproliferative agents
Antithrombin therapy
Antithrombotic therapies
for stable angina
for STEMI
Antithrombotic Trialists Collaboration
Aorta. See also Coarctation of aorta
anatomy of
diseases of

pathologic processes for
Aortic aneurysms
Aortic dissection
chronic
classifications of
clinical presentations of
diagnostic testing
iatrogenic
management of
in young
Aortic insufficiency
chest X-ray for
clinical findings on
ECG for
echocardiography for
etiology of
pathophysiology of
physical exam
treatment for
vasodilators for
Aortic regurgitation (AR)
pregnancy and
severe
Aortic stenosis (AS)
chest radiography
classifications of
clinical findings in
ECG for
etiologies of
invasive assessment of
pathophysiology of
pseudostenosis vs. low gradient
subvalvular
supravalvular
treatment of
TTE for
vasodilators for
Aortic valve(s)
anatomy
morphology of
resistance
Aortic valve area (AVA)
AP. See Action potential
Apresoline. See Hydralazine
AR. See Aortic regurgitation
ARBITER-2. See Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol
ARBs. See Angiotensin-receptor blockers
Arginine
Arixtra. See Fondaparinux
ARR. See Absolute risk reduction

Arrhythmias
Arrhythmic complications
  bradyarrhythmias
  tachyarrhythmias
Arrhythmogenic right ventricular cardiomyopathy (ARVC)
Arrhythmogenic right ventricular dysplasia (ARVD)
Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER-2)
Arterial pulse(s). See also Pulse(s)
  anacrotic pulse
  Corrigan
  dicrotic pulse
  disease states
  double-peaked pulse
  Duroziez sign
  Hill sign
  loud systolic sound
  Mayen sign
  normal
  osler sign
  pressure/pulse difference in two arms
  principles
  pulse deficit
  pulsus alternans
  pulsus paradoxus
  pulsus tardus and parvus
  radial-to-femoral delay
  supravafvular AS and
  traube sign and
  water-hammer pulse
ARTS (Arterial Revascularization Therapies Study)
  I
  II
ARVC. See Arrhythmogenic right ventricular cardiomyopathy
ARVD. See Arrhythmogenic right ventricular dysplasia
AS. See Aortic stenosis
ASCOT-LLA. See Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm
ASD. See Atrial septal defect
Aspirin
  for ACS
  for PCI
  for stable angina
  for STEMI
ASSENT (Assessment of Safety and Efficacy of a New Thrombolytic)
  2
  -3 trial
Atheromatous aortic disease
Atherosclerosis
Atorvastatin
  for NSTEMI
  for STEMI
Atorvastatin Versus Revascularization Treatments (AVERT)

ATP. See Adenosine triphosphate
Atrial arrhythmias
  ablation of
    maze procedure
    pacemaker therapy
    pulmonary vein isolation
  catheter ablation of
Atrial bradycardia, ectopic
Atrial extrastimulus testing
Atrial fibrillation (AF)
  antiarrhythmic drugs for
    class IA
    class IC
    class III
    inpatient vs. outpatient initiation of
    proarrhythmia risks associated with
    selection of
  AV node ablation
  catheter ablation
  definitions
  epidemiology
  evaluation
  factors predisposing
  management
  morbidity and mortality
  nonpharmacologic rate control
  onset of
  pathogenesis
  pharmacologic conversion
  sinus rhythm
    maintenance of
    restoration of
Atrial flutter
  ablation of
  cavotricuspid isthmus-dependent atrial flutter
  clinical presentation and diagnosis
  differential diagnosis
  mechanism
  noncavotricuspid isthmus-dependent atrial flutter
  nonpharmacologic management
  reentrant mechanism
  treatment
Atrial Functional Refractory Period (AFRP)
Atrial pacing
  EP and
  incremental
Atrial rhythm, ectopic
Atrial septal defect (ASD)
  coronary sinus ASD
  primum
  primum ASD

secundum
secundum ASD
sinus venosus ASD
types of
trial tachycardia
clinical presentation and diagnosis
mechanisms
treatment
trial-dependent arrhythmias
atrial flutter
atrial tachycardia
trioventricular block (AVB)
first degree
second degree
Mobitz Type I (Wenckebach)
Mobitz Type II
third degree (complete heart block)
trioventricular junction ablation
trioventricular junctional bradycardia
trioventricular junctional rhythm, accelerated
trioventricular junctional tachycardia
trioventricular nodal reentrant tachycardia (AVNRT)
trioventricular reentrant tachycardia (AVRT)
V junctional bradycardia
V junctional tachycardia
V nodal refractory periods
V node ablation
V node-dependent tachycardias (AVNRT)
clinical presentation and diagnosis
mechanism
treatment
V reciprocating tachycardia (AVRT). See also Wolff-Parkinson-White syndrome
accessory pathways
antidromic tachycardia
clinical presentation and diagnosis
electrophysiologic characteristics and diagnostic maneuvers
mechanism
treatment
Wolff-Parkinson-White syndrome and sudden cardiac death
V reentrant tachycardia
differential diagnosis
VERT. See Atorvastatin Versus Revascularization Treatments
VNRT. See Atrioventricular nodal reentrant tachycardia
V R T. See Atrioventricular reentrant tachycardia
zathioprine (Imuran)
zole antifungals
ztreonam

all-in-cage valve
alloon valvotomy

Balloon valvuloplasty
BARI (Bypass Angioplasty Revascularization Investigation)
Baseline intervals
Basiliximab (Simulect)
Bayes theorem
BBB. See Bundle branch block
Behçet disease
Benzathine penicillin
Bernoulli principle
Beta-adrenergic blockers
Beta-blockers
  for MI
  for syncope
Bezafibrate Infarction Prevention (BIP)
BHAT (Beta-Blocker Heat Attack Trial)
Bias
  in biostatistics
  observation
  recall
  selection
  verification
Bicuspid aortic valve
Bileaflet mechanical valve
Biomarkers
Biostatistics
  bias in
  causality and validity in
  confounding and interaction in
  current controversies associated with
  data presentation/outcomes reporting in
  exposures and outcomes
  multivariable regression in
  specific types issues in
  statistical tests for
  types of clinical studies in
    case reports as
    case series as
    case-control study as
    cohort study as
    cost-effectiveness studies on
    GWAS
    meta-analysis
    prospective vs. retrospective
    randomized controlled trials as
    studies of diagnostic tests
BIP. See Bezafibrate Infarction Prevention
Bivalirudin
Bjork-Shiley valves
Blood
  flow
    definition of

pulmonary
microbiology
BMD. See Bone mineral density
BMI. See Body mass index
Body mass index (BMI)
Bone mineral density (BMD)
Bosentan (Tracleer)
Bradbury- Eggleston syndrome. See Primary autonomic failure
Bradyarrhythmias
Bradykinins
Brain natriuretic peptide (BNP)
Braunwald classification of unstable angina
BRAVE trial
Brockenbrough response
Brucella,
Brugada syndrome
B-type natriuretic peptide (BNP)
Bundle branch block (BBB)

C
CABG. See Coronary artery bypass graft
CAD. See Coronary artery disease
CADILLAC trial
Calan. See Verapamil
Calcification
coronary artery
left atrial wall
mitral annular
patterns
Calcineurin inhibitors
Calcium
blockers, dihydropyridine
dependent ap myocardial tissues vs. sodium channels tissues
elemental
homeostasis, in cardiac biochemistry
Calcium channel blockers (CCBs)
class of
for H F
for stable angina
for syncope
CAMP. See Cyclic adenosine 3′5′-monophosphate
Canadian Cardiovascular Society (CCS)
Candida,
CAPITAL-AMI (Combined Angioplasty and Pharmacological Interventions vs. Thrombolytics Alone in Acute MI)
CAPRICORN (Carvedilol Post-Infarct Survival
Control in Left Ventricular Dysfunction)
CAPRIE trial
Captopril
CAPTURE trial
CAR. See Coxsackie adenovirus receptor
Carbamazepine

Carbomedic valves
Carcinoid heart disease
Carcinomas
Cardene. See Nicardipine
Cardiac allograft vasculopathy (CAV)
Cardiac amyloidosis
Cardiac anatomy. See also Heart
  cardiac chambers
    left atrium
    left ventricle
    right atrium
    right ventricle
  cardiac valves
    aortic valve
    mitral valve
    pulmonic valve
    tricuspid valve
  conducting system
  great vessels
    aorta
    cardiac lymphatic system
    cardiac veins
    coronary arteries
    pulmonary arteries
    pulmonary veins
    vena cavae
  heart and great vessels
  innervation
  pericardium
Cardiac biochemistry
  β-adrenergic signaling (β-AR)
  cardiac contractility and calcium homeostasis
  digitalis AND Na^{+}-K^{+} ATPase
  nitric oxide
  phosphodiesterase inhibitors (PDIs)
  renin-angiotensin system (RAS)
Cardiac catheterization
Cardiac chamber enlargement
Cardiac CT
  aortic disease
  coronary artery disease
  coronary calcium scoring
  indications
  limitations
  pulmonary vein assessment
  technical considerations
Cardiac diseases, . See also specific types
Cardiac free wall rupture
  diagnosis of
  signs and symptoms of
  treatment for

Cardiac hemangiomas
Cardiac intervals, measurement of
Cardiac lipomas
Cardiac masses
Cardiac MRI
  aortic disease
  constrictive pericarditis
  coronary artery disease
  heart failure
  limitations
  myocardial disease
    arrhythmogenic right ventricular cardiomyopathy (ARVC)
    dilated cardiomyopathy
    hypertrophic cardiomyopathy
    restrictive cardiomyopathy
  technical considerations
    MRI physics
    pulse sequences
  viability assessment
Cardiac output (CO)
  low
  measurement
Cardiac pacing. See also Implantable cardioverter defibrillators
  basic concepts of impulses and timing
  device features
  indications
  permanent pacing
  programming
  summary on
  temporary pacing
  troubleshooting and complications
Cardiac papillary fibroelastoma
Cardiac physical examination
  arterial pulse
    anacrotic pulse
    Corrigan
    dicrotic pulse
    disease states
    double-peaked pulse
    Duroziez sign
    Hill sign
    loud systolic sound
    Mayen sign
    normal
    osler sign
    pressure/pulse difference in two arms
    principles
    pulse deficit
    pulsus alternans
    pulsus paradoxus
    pulsus tardus and parvus

radial-to-femoral delay
supravafvular AS and
traube sign and
water-hammer pulse
atrial septal defect
continuous heart sounds
diastole
diastolic murmurs
dynamic auscultation
extra heart sounds
diastole
ES as
nonejection clicks
OS as
pacemaker sounds as
pericardial friction rubs
prosthetic heart sounds
systole
first heart sound
intensity
principles
splitting
fourth heart sound
heart murmurs
inspection
jugular venous pulse
disease states
jugular venous pressure
jugular venous waveforms
Kussmaul sign
principles
physical examination
precordial motion
dilation
disease states
hypertrophy
principles
pregnancy
second heart sound
intensity
principles
single S_2
splitting
specific diseases and
acute myocardial infarction
atrial septal defect
cardiac tamponade
constrictive pericarditis
dilated cardiomyopathy
pulmonary hypertension
restrictive CM

RV infarction
type A aortic dissection
ventricular septal defect
systole
systolic murmurs
third heart sound
Cardiac rhabdomyomas
Cardiac sarcoidosis
Cardiac tamponade
Cardiac tumors
benign
malignant
secondary
Cardiac valves
aortic valve
mitral valve
pulmonic valve
tricuspid valve
Cardiac veins
Cardiomediastinal silhouette patterns
Cardiomyopathy (CM), . See also Dilated cardiomyopathy; Hypertrophic cardiomyopathy
ischemic vs. nonischemic
myocarditis and forms of
restrictive
Cardionet system
Cardiovascular diseases (CVDs)
after pregnancy
board exam
first-time taker pass rates
format
general information
pitfalls
tips
risk factors
novel
traditional modifiable
diabetes mellitus
hypertension
lipids
obesity and metabolic syndrome
tobacco
in United States
age and gender variation of
cost and health care resources for
prognosis and risks associated with
racial and socioeconomic disparities of
silent myocardial ischemia/infarction
temporal trends of
young people and
Cardiovascular drug interactions
food-drug interactions

pharmacodynamic drug interactions
pharmacokinetic interactions of
Cardiovascular Medicine Board Examination
Cardiovascular physiology, myocardial performance
autonomic nervous system
cardiomyopathy
determinants of
afterload
contractility
heart rate
myocardial performance
preload
graphic illustration
Force-Tension curves
pressure-volume loops
starling law and Frank-Starling curves
pressure-volume loop
compliance
elastance and contractility
intracardiac pressures
stroke work
ventricular volumes
valvular heart disease
Cardizem. See Diltiazem
CARDS. See Collaborative Atorvastatin Diabetes Study
Cardura. See Doxazosin
CARE. See Cholesterol and Recurrent Events
Carney syndrome
Carotid
aortic arch anatomy
artery stenting
clinical presentation
diagnostic testing
endarterectomy
epidemiology
medical treatment
anticoagulant therapy
antihyperlipidemic therapy
antihypertensive therapy
antiplatelet therapy
pathophysiology of
recommendation
Carotid artery stenting
Carotid endarterectomy
Carotid intima-media thickness (CIMT)
Carvedilol
Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS)
CASS (Coronary Artery Surgery Study)
Catapres. See Clonidine
Catecholamines
Catheter(s)

ablation of A F
maze
Causality
CAV. See Cardiac allograft vasculopathy
CBC. See Complete blood count
CCBs. See Calcium channel blockers
CDC. See Centers for Disease Control
CDP. See Coronary Drug Project
Cellcept. See Mycophenolate mofetil
Centers for Disease Control (CDC)
Certican. See Everolimus
CETP. See Cholesteryl ester transfer protein
cGMP. See Cyclic guanosine 3′5′-monophosphate
Chagas heart disease
CHARM trials (Candesartan in Heart Failure
Assessment in Reduction of Mortality)
CHD. See Congenital heart disease; Coronary heart disease
Chemotherapy
Chest discomfort. See also Acute chest pain syndromes
associated symptoms
atypical
causes of
cocaine-associated
context of
diagnostic workup
differential diagnosis
family/social/medication history and
history of
location of
medical history
physical examination
plaintive and palliative factors
presyncopal/syncopal symptoms
quality of
radiation of
severity of
special circumstances
timing of
variant/prinzmetal angina
in women
work-up for
Chest radiography (CR)
approach and projections
atrial fibrillation
calcification patterns
calcific constrictive pericarditis
calcified post-MI left ventricular true
aneursym
coronary artery calcification
left atrial wall calcification
mitral annular calcification

cardiomediastinal silhouette patterns
aortic stenosis
coarctation
mitral regurgitation
mitral stenosis
normal cardiac silhouette
pectus excavatum
pericardial cyst
pseudocoarctation
valvar pulmonic stenosis
Kussmaul sign
Pulmonary vascular patterns
cardiovascular disease states
pulmonary arterial hypertension (PAH)
pulmonary edema
pulmonary venous hypertension
Chest x-ray (CXR)
CHF. See Congestive heart failure
Cholesterol
absorption inhibitors for dyslipidemias
embolization syndrome
Cholesterol and Recurrent Events (CARE)
Cholesteryl ester transfer protein (CETP)
Cholestyramine
Chronic mitral regurgitation
Chronic renal dysfunction
Churg-Strauss syndrome
Chylomicrons
CI. See Confidence interval
CIBIS-II
Cilostazol (Pletal)
Cimetidine
CIMT. See Carotid intima-media thickness
CIN. See Contrast induced nephropathy
Ciprofibrate
Circle of Willis
Circulatory-assist devices
CK. See Creatine kinase
Clarithromycin
CLARITY trial
CLASSICS
Clearance
Clofibrate
Clonidine (Catapres)
Clopidogrel (Plavix)
CM. See Cardiomyopathy
CO. See Cardiac output
COA. See Coarctation of aorta
Coagulopathies
Coanda effect
Coarctation, Chest radiography

Coarctation of aorta (CoA)
HTN and
pregnancy and
Colesevelam
Colestipol
Collaborative Atorvastatin Diabetes Study (CARDS)
Collimators
COMET (Carvedilol or Metoprolol European Trial)
Complete blood count (CBC)
Complex cyanotic congenital heart disease
Complex lesions
acyanotic
cyanotic
Computed tomography pulmonary angiography (CTPA)
Computerized tomography (CT)
cardiac
clinical applications for
evaluation of
indications of
limitations of
technical considerations for
Confidence interval (CI)
Congenital heart disease (CHD)
in adult
complex lesions (acyanotic)
complex lesions (cyanotic)
concepts
general management strategies
hereditary and chromosomal defects
shunt lesions
stenotic lesions
operations for
Congenital valve disease
Congenitally corrected D-TGA
Congestive heart failure (CHF)
abnormal cellular mechanisms
adaptive responses
autonomic nervous system dysfunction
biomarkers
B-type natriuretic peptide and
counterregulatory systems
definition of
demographics of
index event and
inflammation and oxidative stress
left ventricular remodeling during
peripheral vascular adaptations in
prognosis
renin-angiotensin-aldosterone system and
salt/water retention during
skeletal muscular adaptations in

SNS and
stage of
summary on
Conn syndrome
Connective tissue disorders
CONSENSUS. See Cooperative North Scandinavian Enalapril Survival Study
Constrictive pericarditis
Constrictive physiology
Continuity equation
Contrast induced nephropathy (CIN)
Contrast materials
Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)
COPERNICUS. See Carvedilol Prospective Randomized Cumulative Survival
Corlopam. See Fenoldopam
Coronary angiography
Coronary arteries
calcification of
Coronary artery bypass graft (CABG)
MPI after
PCI vs.,
PCI/post
Coronary artery disease (CAD)
global burden of
risk factors
novel
traditional modifiable
diabetes mellitus
hypertension
lipids
obesity and metabolic syndrome
tobacco
SE for
in United States
age and gender variation of
cost and health care resources for
prognosis and risks associated with
racial and socioeconomic disparities of
silent myocardial ischemia/infarction
temporal trends of
young people and
Coronary calcification on CT
Coronary calcium scoring
Coronary Drug Project (CDP)
Coronary heart disease (CHD)
morbidity/mortality and
prevention of
early trials for primary and secondary
lipid-regulating trials for
primary, landmark statin trials
secondary, landmark statin trials
subsequent statin trials for

Coronary stenoses
Corrigan pulse
Corticosteroids
Coumadin
Coxiella burnetti,
Coxsackie adenovirus receptor (CAR)
Creatine kinase (CK)
CREDO (Clopidogrel for the Reduction of Events during Observation)
CREST syndrome
CsA. See Cyclosporine
CT. See Computerized tomography
CTPA. See Computed tomography pulmonary angiography
CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events)
CURRENT-OASIS trial
Cushing syndrome
CVDs. See Cardiovascular diseases
CXR. See Chest x-ray
Cyclic adenosine 3′5′-monophosphate (CAMP)
Cyclic guanosine 3′5′-monophosphate (CGMP)
Cyclosporine (CsA)
Cystic medial degeneration

D
Daclizumab (Zenapax)
Dallas criteria
Dalteparin (Fragmin)
DB. See Decibels
DCM. See Dilated cardiomyopathy
D-Dimer
Decibels (dB)
Deep vein thrombosis (DVT)
  clinical presentation and diagnosis
  D-Dimer
  diagnostic testing
  duplex ultrasonography
  venography
DEFINITE trials
Dextrocardia
Diabetes mellitus (DM)
  CAD and
  occurrence
Diazoxide
Digitalis
  effect of
  NA^{+}-K^{+} ATPase
  toxicity
Digitalis Investigation Group (DIG) trial
Digoxin (Lanoxin)
Dihydropyridines
  calcium blockers
Dilacor. See Diltiazem

Dilated cardiomyopathy (DCM)
definition of
idiopathic
inherited forms of
SCD and
VT and
Diltiazem (Cardizem, Dilacor, Tiazac)
Dimensionless index
DINAMIT trials
Dipyridamole
myocardial perfusion imaging and
for stress echocardiography
Direct thrombin inhibitors (DTIs)
Disability-adjusted life year (DALY)
Disopyramide
Diuretics
loop
thiazide
DM. See Diabetes mellitus
Dobutamine (Dobutrex)
physiologic effects
SE
Dofetilide
Dopamine (Inotropic)
for AMI
physiologic effects of
Doppler echocardiography
flow principles of
imaging artifacts
principles of jets
strain imaging
three-dimensional chocardiography
ultrasound
basic principles of
harmonic imaging
imaging modalities
tissue interaction
transducers
Doppler shift
Doxazosin (Cardura)
Dressler syndrome
Dronedarone
Droperidol
Drug(s). See also specific drugs
antiarrhythmic for AF
class IA
class IC
class III
inpatient vs. outpatient initiation of
selection of
cardiovascular

pharmacodynamic interactions of
pharmacokinetic interactions of
)TIs. See Direct Thrombin Inhibitors
)TIT. See Thrombin Inhibitors Trialist Collaborative Group
)uke criteria
)uke Treadmill Scores
)uplex ultrasonography
)uroziez sign
)VT. See Deep vein thrombosis
)ynacirc. See Isradipine
)ynamic range
)yslipidemias
apheresis therapies for
classification of
primary
secondary
diabetes and lipid management
diagnosis of
fibrates monotherapy trials
future directions for
lipid
lipoproteins and
other
regulating trials
metabolic syndrome (metS)
metS and
niacin monotherapy trials
pharmacologic therapies for
regulating trials
TLC for
treatment guidelines
treatments for

:
:BCT. See Electron-beam CT
:bstein anomaly
:CG. See Electrocardiogram
:chocardiography. See also Stress Echocardiography; Transthoracic echocardiography
doppler
flow principles of
imaging artifacts
principles of jets
strain imaging
three-dimensional chocardiography
ultrasound
basic principles of
harmonic imaging
imaging modalities
tissue interaction
transducers
stress

three-dimensional
two-dimensional
valve prostheses, complications of
CSS. See European Coronary Surgery Study
ctopic atrial bradycardia
ctopic atrial rhythm
DP. See End-diastolic pressure
DPVR. See End-diastolic pressure-volume relationship
drophonium chloride (Tensilon)
DV. See End-diastolic volume
ECP. See Enhanced external counterpulsation
F. See Ejection fraction
ffective refractory period (ERP)
accessory pathway anterograde/retrograde AVN
fast/slow AVN
hlers-Danlos syndrome
isenmenger syndrome
jection fraction (EF)
jection sounds (ES)
LATE. See Extended Low-Intensity Anticoagulation for Thromboembolism
lectrical coupling cells. See GAP junction
lectrocardiogram (ECG)
for AS
for ACSs
board preparation
exercise stress test
current guidelines/essential evidence
diagnostic interpretation
essential facts
indications and contraindications
methods
prognostic interpretation
summary on
interpretation of
assessment of standardization/recorded leads and
atrial/ventricular rates/rhythms in
measurement of cardiac intervals in
P-wave/QRS-complex axes in
P-wave/QRS-complex/T-wave morphologies in
intracardiac
twelve-lead
lectrocardiography
lectron-beam CT (EBCT)
lectrophysiology (EP)
atrioventricular block and
atrioventricular conduction
atrioventricular nodes and
basis of
bradyarrhythmia evaluation by
indications for
sinus node function and

summary
tachyarrhythmia evaluation by
LISA. See Enzyme-linked immunosorbent assay
LITE. See Evaluation of Losartan in the Elderly study
LITE-II
mbolic protection devices
nalapril
nalaprilat
nd-diastolic pressure (EDP)
nd-diastolic pressure-volume relationship (EDPVR)
nd-diastolic volume (EDV)
ndless loop tachycardia
ndocarditis
Loffler
prophylaxis
ndomyocardial fibrosis
ndothelin-1 (ET-1)
nd-systolic pressure-volume relationship (ESPVR)
nhanced external counterpulsation (EECP)
noxaparin (Lovenox)
nzyme-linked immunosorbent assay (ELISA)
P. See Electrophysiology
PHESUS trial (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study)
pidemiology, clinical
bias
causality and validity
confounding and interaction
data presentation/outcomes reporting
exposures and outcomes
multivariable regression, uses and pitfalls
statistical tests
types of clinical studies
case reports
case series
case-control study
cohort study
cost-effectiveness studies
diagnostic tests
genome-wide association studies (GWAS)
meta-analysis
prospective-versus-retrospective studies
randomized controlled trials
PILOG trial
pinephrine (Adrenaline)
for AMI
physiologic effects of
PISTENT trial
poprostenol (Flolan)
ptifibatide (Integrilin)
rgonovine
RP. See Effective refractory period

rythromycin
S. See Ejection sounds
SETCID. See European Study on the Epidemiology and Treatment of Cardiac Inflammatory Disease
smolol
SPIRIT study
SPVR. See End-systolic pressure-volume relationship
strogen therapy
uropean Coronary Surgery Study (ECSS)
uropean Study Group on Diastolic Heart Failure
uropean Study on the Epidemiology and Treatment of Cardiac Inflammatory Disease (ESETCID)
valuation of Losartan in the Elderly study (ELITE)
vent monitoring
verolimus (Certican)
xtended Low-Intensity Anticoagulation for Thromboembolism (ELATE)
xternal-beam radiation therapy (XRT)
xtrastimulus
zetimibe

A. See Fatty acids
allot, tetralogy of
amilial Atherosclerosis Treatment Study (FATS)
amilial combined hyperlipidemia (FCH)
amilial Defective Apolipoprotein B100
amilial hypercholesterolemia (FH)
ATS. See Familial Atherosclerosis Treatment Study
atty acids (FAs)
C. See Free cholesterol
CH. See Familial combined hyperlipidemia
DA. See U.S. Food and Drug Administration
DG. See ^{18}F-2-fluoro-2-deoxyglucose
elodipine
enofibrate
enoldopam (Corlopam)
FR. See Fractional flow reserve
H. See Familial hypercholesterolemia
ibrates
ibrinolysis
ibrinolytic therapy
  for PVE
  for STEMI
ibroelastomas
ibromas
ibromuscular dysplasia (FMD)
ick technique
lecainide
lolan. See Epoprostenol
lorinef
low reserves
^{8}F-2-fluoro-2-deoxyglucose (FDG)
luoroscopy

luvastatin
MD. See Fibromuscular dysplasia
ondaparinux (Arixtra)
orce
  tension curves
  velocity relationship
ractional flow reserve (FFR)
ragmin. See Dalteparin
ramingham Heart Study
ramingham risk score (FRS)
rank-Starling curves
rank-Starling mechanism
ree cholesterol (FC)
requency (f),
riedrich ataxia
RISC (Fast Revascularization during Instability in Coronary Artery Disease)
ull-width, half-maximum (FWHM)
unctional mitral regurgitation
  diagnosis for
  symptoms and signs of
  treatment for
urosemide
WHM. See Full-width, half-maximum

G
adolinium DTPA
AP junction
ARCIA-1 trial
BS. See Guillain-Barré syndrome
emfibrozil
entamicin
ISSI. See Italian Group for the Study of Streptokinase in Myocardial Infarction
lobal registry of acute coronary events (GRACE) score
lucocorticoids
lucose, regulation of
lycoprotein IIb/IIIa inhibitors
  for ACS
  for PCI
  for STEMI
orlin formula
rating lobes
rowth hormones
uanabenz
uanfacine
uillain-Barré syndrome (GBS)
USTO (Global Utilization of Streptokinase and TPA for Occluded Arteries)
  I trial
  IIb trial
  V trial

H
HAART. See Highly active antiretroviral therapy

[ACEK organisms
[akki formula
[aloperidol
[ASI
[ATS. See HDL-Atherosclerosis Treatment Study
[BE. See His bundle catheter
[CM. See Hypertrophic cardiomyopathy
[CTZ. See Hydrochlorothiazide
[DL. See High-density lipoproteins
[DL cholesterol (HDL-C)
[DL-Atherosclerosis Treatment Study (HATS)
[DL-C. See HDL cholesterol
[EART
[eart
  blocks
  cardiac chambers
    left atrium
    left ventricle
    right atrium
    right ventricle
  cardiac valves
    aortic valve
    mitral valve
    pulmonic valve
    tricuspid valve
  conducting system
  diseases
    carcinoid
    radiation
    rheumatic
    structural
  great vessels
    aorta
    cardiac lymphatic system
    cardiac veins
    coronary arteries
    pulmonary arteries
    pulmonary veins
    vena cavae
  heart and great vessels
  innervation
  murmurs
    diastolic
      AR and
      mitral stenosis
      PR and
      TS and
    systolic
      aortic sclerosis
      aortic valvular stenosis
      ejection

hypertrophic cardiomyopathy
innocent (in children)
MR and
pulmonic stenosis
regurgitant
ventricular septal defect
pericardium
rate
sounds
continuous
extra
diastole
ES as
nonejection clicks
OS as
pacemaker sounds as
pericardial friction rubs
prosthetic heart sounds
systole
first
intensity
principles
splitting
fourth
second
intensity
principles
single S_2
splitting
third
transplantation
complications post
donor
immunosuppresant agents
organ allocation
recipient
rejection
survival after
[eart failure (HF)
ACE for
acute medical therapy
agents
decongestion
inotropes
neurohormonal blockade
supportive treatment
vasodilators
beta-blockers
chronic medical therapy
digitalis glycosides
investigational agents

neurohormonal blockade
related conditions, treatment of
vasodilators
devices for
circulatory support implantation
clinical trials
components and configurations
considerations regarding
operative risk, assessment of
patient selection
types of
diastolic
clinical presentation of
function
heart failure
laboratory examination for
phases of
physiology of
prognosis for
treatment
digitalis for
lifestyle measures
exercise
fluid restriction
sodium restriction
medications
antiarrhythmic
calcium channel blockers
chemotherapy agents
NSAIDs
oral hypoglycemics
monitoring and follow-up
preserved LVEF
women and
[eart failure with normal ejection fraction (HFNEF)
clinical presentation
diastole, phases of
diastole, physiology of
diastolic function
diastolic heart failure
laboratory examination
physical examination
prognosis
restrictive cardiomyopathies
[eart transplantation
donor
organ allocation
posttransplant complications
chronic renal dysfunction
fungal infections
hyperlipidemia

hypertension
infection
malignancies
osteoporosis
protozoal infections
tricuspid regurgitation (TR)
viral infections
posttransplant management issues
antiproliferative agents
calcineurin inhibitors
combination regimen
corticosteroids
immunosuppressive strategies
individual immunosuppresant agents
rejection
TOR inhibitors
recipient
survival
[eartMate II
[eberden, William
[eFH. See Heterozygous FH
[elsinki Heart Study (HHS)
[emangiomas, cardiac
[ematologic disorders
[ematomas, intramural
[emochromatosis
[emodynamic criteria
[eparin. See also Low molecular weight heparin
intravenous
low molecular weight
subcutaneous
unfractionated
[eparin agents
[epatic lipase (HL)
[ERO-2
[ertz (Hz)
[eterozygous FH (HeFH)
[F. See Heart failure
[HS. See Helsinki Heart Study
[igh- resolution collimators
[igh- sensitivity C-reactive protein (hs-CRP)
[igh-density lipoproteins (HDL)
[ighly active antiretroviral therapy (HAART)
[igh-sensitivity collimators
[is bundle
[is bundle catheter (HBE)
[is-Purkinje system (HPS)
[istograms
[IV (human immunodeficiency virus)
[L. See Hepatic lipase
[LAs. See Human leukocyte antigens

[OCM. See Hypertrophic Obstructive Cardiomyopathy
[oFH. See Homozygous FH
[omografts
[omozygous FH (HoFH)
[OPE (Heart Outcomes Prevention Evaluation)
[ormone-replacement therapy (HRT)
[ospitalization
[PS. See His-Purkinje system
[RT. See Hormone-replacement therapy
hs-CRP. See High- sensitivity C-reactive protein
[TN. See Hypertension
[uman leukocyte antigens (HLAs)
[ydralazine (Apresoline)
[ydrochlorothiazide (HCTZ)
[ydrofludrocortisone
1-β-hydroxysteroid dehydrogenase deficiency (11-β-OHSD)
[yperaldosteronism/Conn syndrome
[ypercalcemia
[yperenhancement
[yperkalemia
[yperlipidemia
[ypertension (HTN)
ARBs for
CAD and
clinical approaches
oA and
diastolic/systolic, pulse pressure and
emergencies/urgencies associated with
evaluation of
genetics of
isolated systolic
pathogenesis of
refractory
resistant
secondary
in women
[yperthyroidism
[ypertrophic cardiomyopathy (HCM)
and athletics
atrial fibrillation
classification
diagnostic testing
cardiac catheterization
cardiac magnetic resonance
echocardiography
labs, chest X-ray, and electrocardiogram
genetics
infective endocarditis prophylaxis
medical therapy
nonobstructive HCM
pathophysiology and histology

percutaneous alcohol septal ablation
permanent pacemaker implantation
physical examination
and pregnancy
prevalence and definition
screening of family members
septal myectomy
vs. alcohol ablation
sudden cardiac death (SCD)
symptoms and clinical course
[ypertrophic obstructive cardiomyopathy
HOCM)
[ypertrophy
[ypocalcemia
[ypokalemia
[ypotension
[ypothermia
[ypothyroidism
[ytrin. See Terazosin
[z. See Hertz

ABP. See Intra-aortic balloon pump
ɔutilide
CDs. See Implantable cardioverter defibrillators
CE. See Intracardiac echocardiography
CH. See Intracranial hemorrhage
diopathic hypertrophic subaortic stenosis (IHSS)
dioventricular rhythm
DL. See Intermediate-density lipo-proteins
DU. See Injection drug users
E. See Infective endocarditis
HSS. See Idiopathic hypertrophic subaortic stenosis
naging, . See also specific types of imaging
artifacts
modalities
perfusiom imaging
radionuclide
nmunosuppressive therapy
MPACT-II study
npaired coronary flow reserve
nplantable cardioverter defibrillators (ICDs)
devices
function of
implantation
indications
lead systems
summary on
troubleshooting
ndicator dilution methods
ndomethacin

ıfarct-related artery (IRA)
ıfection
  fungal
  protozoa
  viral
ıfective endocarditis (IE)
  blood cultures/microbiology
  clinical features of
  complications with
  conclusions of
  definitions of
  diagnosis for
  epidemiology of
  health care–associated
  pathogenesis of
  prophylaxis
  risk factors for
  surgery indications for
  treatment for
  TTE for
  uncommon causes
ıferior vena cava interruption (IVC Filters)
ıflammatory aortitis
ıheritted and acquired channelopathies
  Brugada syndrome
  idiopathic ventricular fibrillation
  long-QT syndrome
  short-QT syndrome
ıjection drug users (IDUs)
ınohep. See Tinzaparin
ıotropic. See Dopamine
ı-stent restenosis (ISR)
ısulin
ısulin resistance syndrome. See Metabolic syndrome
ıtegrilin. See Eptifibatide
NTERHEART study
ıtermediate-density lipo-proteins (IDL)
ıternational Society for Heart and Lung
ransplantation (ISHLT)
ıternational Study of Syncope of Undetermined Etiology (ISSUE)
ıtra-aortic balloon pump (IABP)
ıtracardiac echocardiography (ICE)
ıtracardiac waveforms
ıtracranial hemorrhage (ICH)
ıtramural hematoma
ıtravascular ultrasound (IVUS)
ıtravenous nitroglycerin
ıtraventricular conduction delay (IVCD)
RA. See Infarct-related artery
:on overload
SAR REACT study

SAR trial
SAR-COOL trial
SAR-REACT trial
SHLT. See International Society for Heart and Lung Transplantation
soproterenol (Isuprel)
soptin. See Verapamil
sosorbide dinitrate
sotretinoin
SR. See In-stent restenosis
sradipine (Dynacirc)
SSUE. See International Study of Syncope of Undetermined Etiology
talian Group for the Study of Streptokinase in
Myocardial Infarction (GISSI)
traconazole
VC Filters. See Inferior Vena Cava Interruption
VCD. See Intraventricular conduction delay
VUS. See Intravascular ultrasound

et
  principles of
  velocity
oint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7)
ugular venous pulse (JVP)
  disease states
  jugular venous pressure
  jugular venous waveforms
  Kussmaul sign
  principles
unctional premature complexes
VP. See Jugular venous pulse

K
K^+. See Potassium
Kaplan–Meier event rates
KE. See Kinetic energy
Kearns–Sayre syndrome
etoconazole
Killip classification
Kinetic energy (KE)
Koch triangle

abetalol
LAFB. See Left anterior fascicular block
LBBB. See left bundle branch block
LDL. See Low-density lipoprotein
LDL-C management
eft anterior fascicular block (LAFB)
eft atrial abnormality
eft atrial wall calcification

eft atrium
eft bundle branch block (LBBB)
eft posterior fascicular block (LPFB)
eft ventricle
eft ventricular aneurysm
  diagnosis for
  signs and symptoms of
  treatment for
eft ventricular dysfunction
eft ventricular ejection fraction (LVEF)
eft ventricular function
eft ventricular hypertrophy (LVH)
eft ventricular infarction, with hemodynamic compromise
  diagnosis for
  signs/symptoms of
  treatments for
eft ventricular outflow tract (LVOT)
  diagnosis for
  signs/symptoms of
  treatments for
eft ventricular remodeling
eft ventricular size/systolic function
egionella IE
epirudin (Refludan)
evophed. See Norepinephrine
idocaine
ikelihood ratio (LR)
IPID. See Long-term Intervention with Pravastatin in Ischemic Disease
ipid(s). See also Dyslipidemias
  lipoproteins and
  other
  regulating trials
ipid Research Clinics Prevalence Study (LRC)
ipoma
ipoprotein lipase (LPL)
ipoproteins. See also specific types of lipoproteins
MWH. See Low Molecular Weight Heparin
offler endocarditis
ong-QT syndrome (LQTS)
ong-term circulatory-assist devices
ong-term Intervention with Pravastatin in Ischemic Disease (LIPID)
oniten. See Minoxidil
sartan intervention for endpoint (LIFE)
ovastatin
ow molecular weight heparin (LMWH)
  for acs
  during pregnancy
ow-density lipoprotein (LDL)
PFB. See Left posterior fascicular block
PL. See Lipoprotein lipase
QTS. See Long-QT Syndrome

LR. See Likelihood ratio
LRC. See Lipid Research Clinics Prevalence Study
L-type channels
LVEF. See Left ventricular ejection fraction
LVH. See Left ventricular hypertrophy
LVOT. See Left ventricular outflow tract

M
MACE. See Major adverse cardiovascular events
Magnesium
Magnetic resonance angiography (MRA)
Magnetic resonance imaging (MRI)
  cardiac
    clinical application for
    evaluation of
    indications of
    limitations of
Magnetic resonance venography (MRV)
Major adverse cardiovascular events (MACE)
Malignant tumors
Mammary souffle
Mapping
Marfan syndrome
  inherited
Markers
MAs. See Mycotic aneurysms
MASS. See Medicine, Angioplasty or Surgery Study
MAT. See Multifocal atrial tachycardia
Maximum predicted heart rate (MPHR)
Mayo Clinic
Maze procedure
MDCT. See Multidetector Computed Tomography
MDPIT trial
Mechanical ventilation
Medical Research Council/British Heart Foundation (MRC/BHF)
Medicare
Medicine, Angioplasty or Surgery Study (MASS)
Medtronic Hall valves
Megesterol
MEN. See Multipleendocrineneoplasia
MERIT-HF (Metoprolol CR/XL Randomised
ntervention Trial in Congestive Heart Failure)
Metabolic syndrome (metS)
Methyldopa (Aldomet)
Metoprolol
  metS. See Metabolic syndrome
Midodrine
Milrinone (Primacor)
Minoxidil (Loniten)
MIRACL (Myocardial Ischemia Reduction with Acute Cholesterol Lowering trial)
Mitral regurgitation (MR)

acute
chest radiography
chronic
functional
mechanisms
quantitation of
TTE for
Mitral stenosis (MS)
features and history of
management of
Mitral valve(s)
anatomy
Mitral valve prolapse (MVP)
diagnosis of
signs and symptoms of
Mitral valve replacement (MVR)
MMF. See Mycophenolate mofetil
MPA. See Mycophenolic acid
MPHR. See Maximum predicted heart rate
MR. See Mitral regurgitation
MRA. See Magnetic resonance angiography
MRV. See Magnetic resonance venography
MS. See Mitral stenosis
MSA. See Multisystem atrophy
MSS. See Muscular subaortic stenosis
Multidetector Computed Tomography (MDCT)
Multifocal atrial tachycardia (MAT)
Multipleendocrineneoplasia (MEN)
Multisystem atrophy (MSA)
Münster Heart Study (PROCAM)
Muscular dystrophy
Muscular subaortic stenosis (MSS)
MUSTT Trial
MVP. See Mitral valve prolapse
Myasthenia gravis
Mycophenolate mofetil (MMF)
Mycophenolic acid (MPA)
Mycotic aneurysms (MAs)
Myocardial disease
Myocardial hibernation
Myocardial infarction (MI). See also Acute myocardial infarction
antiplatelet therapies for
beta-blockers
calcified post
left ventricular pseudo-aneurysm
left ventricular true aneurysm
complications
additional
arrhythmic
of left ventricular dysfunction
mechanical

therapies for
medical therapies
revascularization and
summary on
post
conclusions on
non–ST-elevation ACS
ST-elevation MI
therapies for
therapy
risks for
statins for
Myocardial injury and infarction
Myocardial performance. See also Pressure-volume loops
determinants of
afterload
contractility
heart rate
myocardial performance
preload
graphic illustration
Force–Tension curves
pressure–volume loops
starling law and Frank–Starling curves
Myocardial perfusion imaging
absolute vs. relative
adenosine and
ADP and
after CABG
after PCI
agents for pharmacologic stress testing
ATP and
coronary artery disease
detection of coronary stenoses during
dipyridamole and
dobutamine and
indications
non-ST-elevation myocardial infarction
preoperative testing prior to noncardiac surgery and
principles
resting perfusion defects
for specific populations and situations
ST-elevation myocardial infarction
stress options for
summary on
women and
Myocarditis
clinical presentation of
epidemiology and classification of
etiologies and pathophysiology of
evaluation of

forms of cardiomyopathy related to
giant-cell
hypersensitive/eosinophilic
treatment and prognosis for
Myocarditis Treatment Trial
Myotonic dystrophy
Myxedema
Myxomas

N

Na^+. See Sodium
Na^+/K^+ ATPase. See Sodium pump
N-acetyl procainamide (NAPA)
Nafcillin
NAME syndrome (nevi, Atrial myxoma, myxoid neurofibromata, and ephelides)
NAPA. See N-acetyl procainamide
Narula method
National Cholesterol Education Program (NCEP)
National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III)
National Health Lung and Blood Institute (NHLB)
National Institutes of Health (NIH)
NCEP. See National Cholesterol Education Program
NCEP ATP III. See National Cholesterol Education Program's Adult Treatment Panel III
NCXl. See Sodium-calcium pump
Negative predictive value (NPV)
Neoplastic disease
Neo-Synephrine. See Phenylephrine
Nervous system, autonomic
Nesiritide
Nesiritide (Natrecor)
Neuropeptide
New York Heart Association (NYHA)
NFAT. See Nuclear factor of activated T cells
NHBPEP. See U.S. National High Blood Pressure Education Program
NHLB. See National Health Lung and Blood Institute
Niacin
Niacin monotherapy trials
Nicardipine (Cardene)
Nifedipine (Procardia, Adalat)
NIH. See National Institutes of Health
Nimodipine (Nimotop)
Nipride. See Nitroprusside
Nisoldipine (Sular)
Nitrates
for ACS
for stable angina
Nitric oxide (NO)
cardiac biochemistry
production of
Nitric oxide synthases (NOS)
Nitroglycerin

Nitroprusside (Nipride)
sodium
NO. See Nitric oxide
Nocardia
Noncardiac surgery
evaluation of patients undergoing
management of other cardiovascular conditions and
myocardial perfusion imaging and
perioperative coronary revascularization
perioperative medical therapy and
postoperative myocardial infarction management
preoperative cardiac risk assessment
Non-HDL-C. See Non-high-density lipoprotein cholesterol
Non-high-density lipoprotein cholesterol (non-HDL-C)
Nonischemic cardiomyopathy
arrhythmogenic right ventricular dysplasia
dilated cardiomyopathy
hypertrophic cardiomyopathy
Non-ST-elevation acute coronary syndrome (NSTE-ACS)
risk stratification
risk stratification for
Non-ST-elevation myocardial infarction (NSTEMI)
clinical presentation
epidemiology and prognosis
fibrinolytic therapy for
management of
ACE-I for
anti-ischemic agents
antiplatelet agents
antithrombin therapy
aspirin for
atorvastatin for
beta-blockers
glycoprotein IIb/IIa inhibitors for
initial approach
invasive therapy
mechanical devices for
miscellaneous agents for
PCI for
predischarge risk stratification for
patients with
risk assessment for
risk stratification
summary on
thienopyridines for
Nonsteroidal anti- inflammatory drugs (NSAIDs)
Noonan syndrome
Norepinephrine
for AMI
physiologic effects
Normal sinus rhythm (NSR)

NOS. See Nitric oxide synthases
NPV. See Negative predictive value
NSAIDs. See Nonsteroidal anti- inflammatory drugs
NSR. See Normal sinus rhythm
NSTEACS. See Non-ST-elevation acute coronary syndrome
NSTEMI. See Non-ST-elevation myocardial infarction
Nuclear factor of activated T cells (NFAT)
Nuclear imaging. See also Myocardial perfusion imaging
  interpretation
  myocardial perfusion imaging
  overview
  PET
    myocardial viability
    radioactive tracers in
  radionuclide ventriculography
  SPECT
    radioactive tracers
Nuclear stress testing
  myocardial perfusion imaging
    agents for pharmacologic stress testing
    coronary artery disease
    coronary stenoses, detection of
    indications
    non-ST-elevation myocardial infarction
    principles
    relative vs. absolute myocardial perfusion
    resting perfusion defects
    ST-elevation myocardial infarction
  nuclear cardiac imaging in heart failure
    congestive heart failure
    etiology, ischemic vs. nonischemic cardiomyopathy
    reversible left ventricular dysfunction
    ventricular function, assessment of
Nyquist limit

O
OASIS
Obesity
  CAD and
  sedentary lifestyle and
OCP. See Oral contraceptives
OCT. See Optical coherence tomography
Ohm's law
OHSD. See -β-hydroxysteroid dehydrogenase deficiency
Oncologic disorders
Opening snap (OS)
OPO. See Organ procurement organizations
Optical coherence tomography (OCT)
OPTIMAAL study
OPTIME-HF trial
OPUS-TIMI (Oral Glycoprotein IIb/IIIa Inhibition with Orbofiban in Patients with Unstable Coronary Syndromes)

)ral contraceptives (OCPs)
)rgan procurement organizations (OPOs)
)rthostatic hypotension
)S. See Opening snap
)sler–Weber–Rendu syndrome
)steogenesis imperfecta
)steoporosis
)varian diseases
)xacillin
)xygen-15 water

'

waves
A. See Plasma aldosterone
acemaker(s)
permanent
sound
syndrome
therapy
AD. See Peripheral artery disease
AF. See Primary autonomic failure
AN. See Polyarteritis nodosa
apillary fibroelastoma
arathyroid disorders
arvus
atent Ductus Arteriosus (PDA)
CI. See Percutaneous coronary intervention
CW. See Pulmonary capillary wedge
DA. See Patent Ductus Arteriosus
DE3. See Phosphodiesterase
DIs. See Phosphodiesterase inhibitors
E. See Pulmonary embolism
EACE. See Prevention of Events with Angiotensin Converting Enzyme inhibition
ectus excavatum
enetrating aortic ulcer
clinical presentations of
intramural hematoma
management of
enicillin
entoxifyline
ercutaneous alcohol septal ablation
ercutaneous coronary intervention (PCI)
adjunct therapy for
antithrombin therapies for
bleeding
complications following
indications for
periprocedural myocardial infarction
for STEMI
technical aspects of
ercutaneous transluminal coronary angioplasty (PTCA)

ercutaneous transluminal renal angioplasty (PTRA)
erfusion defects, resting
ericardial diseases
ericardial effusion
ericardial friction rubs
ericardial tamponade
ericarditis. See also Acute pericarditis
  diagnosis for
  STEMI and
  symptoms and signs of
  treatment for
ericardium
erindopril
eripartum cardiomyopathy (PPCM)
eripheral artery disease (PAD)
  Ankle-Brachial Index
  definition
  epidemiology and risk factors
  foot care and ulcer prevention
  history
  imaging studies for
  marker of cardiovascular risk
  prevention of cardiovascular events
    antiplatelet agents
    beta-blockers and
    blood pressure control
    cilostazol
    education about
    glycemic control in diabetic patients with
    lipid-lowering therapy
    pentoxifyline
    pharmacotherapy for
    rehabilitation for
    revascularization of
    smoking cessation
    warfarin
  symptoms and signs of
eripheral vascular disease (PVD)
eripheral vasculature
ES. See Programmed electrical stimulation
H. See Pulmonary hypertension
harmacodynamics
harmacogenetics
harmacokinetics
  absorption of
  distribution of
  elimination/metabolism of
henobarbital
henothiazine antipsychotics
hentolamine (Regitine)
henylephrine

for AMI
physiologic effects of
henytoin
heochromocytoma
hosphodiesterase (PDE3)
hosphodiesterase inhibitors (PDIs)
hotons
annihilalation
emission of
KA. See Protein kinase A
lasma aldosterone (PA)
lasma drug concentration
lasma renin activity (PRA)
latelet inhibitors
lavix. See Clopidogrel
letal. See Cilostazol
MI. See Point of maximal cardiac impulse
oint of maximal cardiac impulse (PMI)
olyarteritis nodosa (PAN)
olycythemia
olygenic hypercholesterolemia
olymerase chain reaction (PCR)
olymorphic ventricular tachycardia
olymyositis
ositron emission tomography (PET)
ost thrombotic syndrome (PTS)
osttransplant lymphoproliferative disease (PTLD)
ostural orthostatic tachycardia syndrome (POTS)
otassium (K^+)
concentration
diuretics
OTS. See Postural orthostatic tachycardia syndrome
PCM. See Peripartum cardiomyopathy
R. See Pulmonic regurgitation
RA. See Plasma renin activity
RAISE
rasugrel (Effient)
ravastatin
razosin (Minipress)
recordial motion, during cardiac physical examination
dilation and
disease states and
hypertrophy and
principles of
rednisone
regnancy
anticoagulation during
AR and
arrhythmias
'OA and
'VDs after

[CM and
hypertension
LMWH during
physiologic changes during
pre-existing cardiac diseases and
unfractionated hepuin during
women and
reload, left ventricular
ressure
measurements
wave artifacts
ressure recovery
ressure-volume loops
cardiomyopathy
compliance
elastance and contractility
intracardiac pressures
stroke work
valvular heart disease
ventricular volumes
REVENT (prevention of recurrent venous thromboembolism)
revention of Events with Angiotensin Converting Enzyme inhibition (PEACE)
rimacor. See Milrinone
rimary aldosteronism
rimary autonomic failure (PAF)
rimary CHD prevention
trials for
RISM trial
roAmatine
roarrhythmia
rocainamide
ROCAM. See Münster Heart Study
rocardia. See Nifedipine
rochlorperazine
rogrammed electrical stimulation (PES)
ropafenone
ropranolol
rostacyclin
rosthetic valve endocarditis (PVE)
fibrinolytic therapy
surgery
rotein kinase A (PKA)
ROVED
ROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy)
S. See Pulmonic stenosis
seudoaneurysm
diagnosis for
signs/symptoms of
treatment for
seudocoarctation
seudomonas aeruginosa,

seudostenosis
TCA. See Percutaneous transluminal coronary angioplasty
TLD. See Posttransplant lymphoproliferative disease
TRA. See Percutaneous transluminal renal angioplasty
TS. See Post thrombotic syndrome
ulmonary angiography
ulmonary arterial hypertension
ulmonary arteries
ulmonary blood flow
ulmonary capillary wedge (PCW)
ulmonary edema
ulmonary embolism (PE)
  cardiospecific biomarkers
  clinical presentation and diagnosis
  CTPA
  echocardiography
  ventilation/perfusion scan
ulmonary hypertension (PH)
  chronic thromboembolic pulmonary hypertension
  definition and classification
  diagnosis and evaluation
    clinical evaluation
    echocardiography
    hemodynamic evaluation
  left heart disease
  lung diseases and/or hypoxia
  pathophysiology
    endothelin-1 (ET-1)
    hemodynamic consequences
    nitric oxide
    prostacyclin and thromboxane A_2
    serotonin (5-hydroxytryptamine)
  prognosis
  pulmonary arterial hypertension
  treatment
    combination therapy randomized clinical trials
    general measures
    pulmonary vasodilators
    randomized clinical trials
    surgical therapies
  with unclear multifactorial mechanisms
ulmonary insufficiency
ulmonary stenosis (PS)
ulmonary vascular resistance (PVR)
ulmonary vasculature
ulmonary veins
ulmonary venous hypertension
ulmonic regurgitation (PR)
  diastolic murmurs in
ulmonic stenosis (PS)
ulmonic valve disease

ulse(s). See also Arterial pulse(s)
anacrotic
deficit
dicrotic
double-peaked
duration
width
ulsus alternans
ulsus paradoxus
ulsus tardus/parvus
urkinje fibers
URSUIT
VD. See Peripheral vascular disease
VE. See Prosthetic valve endocarditis
VR. See Pulmonary vascular resistance

)
)ALY. See Quality-adjusted year of life
)RS complex
axes
interval
morphologies
)T interval
)T syndrome. See also Long-QT syndrome
long
short
)uality-adjusted year of life (QALY)
)uinidine
)uinolone
)-waves

:
.A. See Rheumatoid arthritis
.AAS. See Renin-angiotensin-aldosterone system
.AD. See Renal artery disease
.ADIANCE study
.adiation safety
conclusion on
dose estimation and displays
ionizing radiation and radiation effects
deterministic/nonstochastic risk
stochastic risk
management
collimation
dose and frame rate settings
fluoroscopy time and number of acquisitions
grid use
magnification modes
operator radiation management
patient radiation
source and distance
x-ray beam, path length and approach

production
generator
image receptor
operating console
x-ray tube
regulatory recommendations
.ALES trial (Randomized Aldactone Evaluation Study)
.andomized Assessment of Syncope Trial (RAST)
.anolazine (Ranexa)
.apamycin (Sirolimus)
.APPORT trials
.AS. See Renin-angiotensin system
.AST. See Randomized Assessment of Syncope Trial
.BBB. See Right bundle branch block
.CT. See Reverse cholesterol transport
.eflection
.efraction
.efractory angina
ACC/AHA recommendations
enhanced external counterpulsation (EECP)
spinal cord stimulation (SCS)
transcutaneous electrical nerve stimulation (TENS)
.egional wall motion abnormalities (RWMA)
.egitine. See Phentolamine
.elapsing polychondritis
.elative risk
.elative risk reduction (RRR)
.enal artery disease (RAD)
.enal cell carcinoma
.enal failure
.enal parenchymal disease
.enin-angiotensin system (RAS)
.enin-angiotensin-aldosterone system (RAAS)
.enins
.enovascular disease
.eopro. See Abciximab
.eperfusion therapy
.EPLACE-2 trial
.EPLACE-II
.ER. See Respiratory exchange ratio
.esin
.esolution
.ESOLVD
.espiration
.espiratory exchange ratio (RER)
.ESTORE trial
.eteplase, r-PA (Retavase)
.evascularization
MI complications and
stable angina and
CABG vs. MEDS

conclusions on
PCI vs. CABG
PCI vs. MEDS
.EVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering trial)
.everse cholesterol transport (RCT)
.habdomyomas
.heumatic heart disease
.heumatoid arthritis (RA)
.hythms of ventricular origin
.ifampin
.ight atrial abnormality
.ight atrium (RA)
.ight bundle branch block (RBBB)
.ight upper quadrant (RUQ)
.ight ventricle
.ight ventricular function
.ight ventricular hypertrophy (RVH)
.ight ventricular infarction
diagnosis for
symptoms and signs of
treatment for
.ight ventricular pacing
.isk ratio (RR)
.ITA (Randomized Intervention Treatment of Angina)
II
III
.itonavir
.ivaroxaban (Xarelto)
.oss procedure
.osuvastatin
·PA. See Reteplase
.R. See Risk ratio
.RR. See Relative risk reduction
.ubidium-82
.UQ. See Right upper quadrant
.VH. See Right ventricular hypertrophy
.WMA. See Regional wall motion abnormalities

A. See Sinoatrial node
A block. See Sinoatrial block
ACT. See Sinoatrial conduction time
alt, retention of
arcoidosis
arcoplasmic reticulum (SR)
AVE. See Survival and Ventricular Enlargement
BP. See Systolic blood pressure
candinavian Simvastatin Survival Study
cattering
CD. See Sudden cardiac death
CD-HeFT trials

cleroderma
CS. See Spinal cord stimulation
dLDL. See Small dense low-density lipoprotein
econdary cardiac tumors
econdary CHD prevention
  trials for
ensing
eptal myectomy
eronegative spondyloarthropathies
erotonin reuptake inhibitors
even Country Study
HOCK (Should We Emergently Revascularize Occluded Coronary Arteries for Cardiogenic Shock)
  Trial Registry
hort-term circulatory-assist devices
hunt
  calculations
  left-to-right
  lesions
  operations for
hy-Dragger syndrome. See Multisystem atrophy
ick sinus syndrome
ignal aliasing
ildenafil
IMA (Stenting v. Internal Mammary Artery study)
imon Broome Register Group
imulec. See Basiliximab
imvastatin
ingle-photon-emission computed tomography (SPECT)
  cameras
  myocardial perfusion scan
  radioactive tracers in
inoatrial block (SA block)
inoatrial conduction time (SACT)
inoatrial node (SA)
inus arrest/pause
inus arrhythmia
inus bradycardia
inus node
  dependent
  functions, EP and
  recovery time
  reentrant rhythm
  reentrant tachycardia
  refractory period
inus rhythm. See also Normal sinus rhythm
inus tachycardia
inus-dependent arrhythmias
irolimus. See Rapamycin
keletal muscular adaptations
LE. See Systemic lupus erythematosus
mall dense low-density lipoprotein (sdLDL)

moking
  CAD and
  pregnancy and
odium (NA^+)
  calcium pump
  channel activity regulation levels AP membrane and
  channel tissues
  dependent cells
  nitroprusside
odium pump (Na^+ /K^+ ATPase)
odium-calcium pump (NCXl)
OLVD. See Studies of Left Ventricular Dysfunction
otalol
PECT. See Single-photon-emission computed tomography
pectral analysis
pinal cord stimulation (SCS)
plitting
  first heart sound and
  paradoxical
  second heart sound and
R. See Sarcoplasmic reticulum
t. Jude's Medical valves
table angina
  CCS classification of
  definition of
  diagnostic testing/risk stratification
    CAD
    coronary angiography
    echocardiography
    electrocardiography
    exercise ECG testing
    stress testing with nuclear/echocardiographic imaging
  medical treatment
    antiplatelet therapy
    lipid-lowering therapy
    renin–angiotensin–aldosterone system blockade
  pathophysiology of
  refractory angina
  revascularization in
    ACC/AHA recommendations
    coronary artery bypass grafting versus medical therapy
    percutaneous coronary intervention versus medical therapy
  symptomatic medical therapies, antianginals
    beta-blockers
    calcium channel blockers
    combination therapy
    nitroglycerin and nitrates
    ranolazine
TAMINA-HF trial
taphylococcus aureus,
taphylococcus aureus bacteremia

taphylococcus epidermidis
prosthetic valve endocarditis
tarr-Edwards valve
tatin(s). See also specific types
combination trials
for dyslipidernias
high- risk primary prevention
LDL-C management
for MI
primary prevention
secondary prevention
trials for
T-elevation myocardial infarction (STEMI)
acute
clinical presentations of
diagnosis for
epidemiology/introduction to
fibrinolytic therapy for
management of
ACE for
anti-ischemic agents for
antiplatelet agents for
antithrombotic agents for
aspirin for
atorvastatin for
glycoprotein IIb/IIa inhibitors for
glycoprotein IIb/IIIa inhibitors
initial approach to
mechanical devices for
PCI for
pericarditis and
predischarge risk stratification for
reperfusion therapy for
pericarditis for
predischarge risk stratification for
risk assessment after
risk stratification
risk stratification for
summary on
thienopyridines for
TEMI. See ST-elevation myocardial infarction
tenotic lesions
tenting, coronary
tents
timulation threshold
tokes-Adams attack
top-Hypertension-2
trauss method
trength–duration curve
treptokinase
treptomycin

tress
  options for myocardial perfusion imaging
  testing
tress echocardiography
  adenosine for
  for CAD
  dipyridamole for
  dobutamine
  exercises
  forms of
  imaging technique
  imaging techniques for
  interpretation of
  ischemic cascade
  pharmacologic
  uses
  in valvular heart disease
  vasodilators for
tress perfusion defect
troke work
trokes
T-segment
  depression
  elevation
tudies of Left Ventricular Dysfunction (SOLVD)
ubaortic aortic stenosis
ubclinical hemolysis
udden cardiac death (SCD)
  arrhythmogenic right ventricular cardiomyopathy
  assessment for
  Brugada syndrome
  and coronary artery disease
  DCM and
  definition
  epidemiology
  evaluation and management of
  HCM and
  idiopathic ventricular fibrillation
  long-QT syndrome
  nonischemic cardiomyopathy
  risk factors and pathophysiology
  short-QT syndrome
  survivors of
  valvular heart disease
  Wolff–Parkinson–White syndrome
ular. See Nisoldipine
ummed stress score
uperior vena cava (SVC)
upraventricular tachycardia (SVT). See also Ventricular tachycardia; Wide-complex tachycardia
  algorithm
  approach

atrial-dependent arrhythmias
AV node-dependent
sinus-dependent arrhythmias
wide-complex tachycardia
bundle branch block
differential diagnosis
with pre-excitation.
urvival and Ventricular Enlargement (SAVE)
VC. See Superior vena cava
VR. See Systemic vascular resistance
VT. See Supraventricular tachycardia
wedish Angina Pectoris Aspirin Trial
ympathetic nervous system (SNS)
yncope
beta-blockers
CCBs for
clinical features
conclusions on
diagnostic testing for
driving and
epidemiology of
history of
neurally mediated
syndromes
physical examination
specific etiologies of
vasovagal
yndrome X. See Metabolic syndrome
YNERGY trial
yphilitic aortitis
ystemic lupus erythematosus (SLE)
ystemic vascular resistance (SVR)
ystolic blood pressure (SBP)

'
' waves
'AA. See Thoracic aortic aneurysm
'achyarrhythmias
evaluation of
'acrolimus (Tac)
'ACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy)
TIMI trial
'akayasu arteritis
'ansthoracic echocardiogram (TTE)
'ARGET analysis
'arget lesion revascularization
'-cell receptor (TCR)
'CR. See T-cell receptor
'echnetium-99m-labeled agents
sestamibi
teboroxime

tetrofosmin
'EE. See Transesophageal echocardiography
'enecteplase
'enecteplase (TNK-ase)
'ENS. See Transcutaneous electrical nerve stimulation
'erazosin (Hytrin)
'etralogy of Fallot
'GA. See Transposition of the great arteries
'GRLs. See Triglyceride-rich lipoproteins
'hallium
'heophylline
'herapeutic lifestyle changes (TLC)
'hiazide diuretics
'hienopyridines
for NSTEMI
for STEMI
'hiocyanate
'horacic aortic aneurysm (TAA)
'horatec device
'hrombin Inhibitors Trialist Collaborative Group (DTIT)
'hromboembolism
'hrombolytics
'hrombolytics/fibrinolytics
'hromboprophylaxis
'hyroid disorders
'hyroid-stimulating hormone (TSH)
'icagrelor (Brilinta)
'iclid. See Ticlopidine
'iclopidine (Ticlid)
'ID. See Transient ischemic dilatation
'IMI (Thrombolysis in Myocardial Infarction)
16
18
22
'inzaparin (Innohep)
'irifiban (Aggrastat)
'issue-type plasminogen activator (t-PA)
'LC. See Therapeutic lifestyle changes
'MP-SMX. See Trimethoprim-sulfamethoxazole
'NF alpha. See Tumor necrosis factor (TNF) alpha
'NT. See Treating to New Targets
'obacco
'oxoplasma,
-PA. See Tissue-type plasminogen activator
'R. See Tricuspid regurgitation
'racleer. See Bosentan
'ranscatheter aortic valve replacement (TAVR)
'ranscutaneous electrical nerve stimulation (TENS)
'ransesophageal echocardiography (TEE)
'ransient ischemic dilatation (TID)
'ransposition of the great arteries (TGA)

'ransthoracic echocardiography (TTE)
of HCM
for MR
'ransverse images
'rauma
'readmill
'reating to New Targets (TNT)
'reprostinil (Remodulin)
'riamterene
'riangle of Koch
'ricuspid regurgitation (TR)
etiology of
signs/symptoms of
treatments for
'ricuspid valve stenosis (TS)
diastolic murmurs
signs/symptoms of
'ricyclic antidepressants
'riglyceride-rich lipoproteins (TGRLs)
'rimethoprim
'rimethoprim-sulfamethoxazole (TMP-SMX)
'S. See Tricuspid valve stenosis
'SH. See Thyroid-stimulating hormone
'TE. See Transthoracic echocardiography
'-type channels
'umor necrosis factor (TNF) alpha
'umors, cardiac
benign
malignant

J
J waves
Jltrafiltration
Jltrasound
doppler echocardiography
basic principles of
harmonic imaging
imaging modalities
tissue interaction
transducers
Jnited Network for Organ Sharing (UNOS)
Jnited States (U.S), CVDs in
age/gender variation of
cost/health care resource for
prognosis/risk associated with
racial/socioeconomic disparities of
silent myocardial ischemia/infarction
JNOS. See United Network for Organ Sharing
Jrokinase
J.S. Food and Drug Administration (FDA)
J.S. National High Blood Pressure Education Program (NHBPEP)

ʳ
ʳA Study. See Veterans Administration Cooperative Study
ʳA-HIT. See Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial
ʳal-HeFT
ʳALIANT trial (Valsartan in Acute Myocardial Infarction)
ʳalidity
ʳalsalva maneuver
ʳalve(s)
  anticoagulation
  biologic
  bioprosthetic
  Bjork-Shiley
  Carbomedic
  complications with prostheses
  gradients
  mechanical
  Medtronic-Hall
  replacement options
  St. Jude's Medical
  Starr-Edwards
  types, selection of
ʳalve orifice area (VOA)
ʳalvular heart disease
  stress echocardiography in
ʳalvular pulmonic stenosis
ʳancomycin
ʳANQWISH
ʳascular resistance
ʳasoactive intestinal peptide
ʳasoconstriction
ʳasodilators
  for AS
  SE
ʳasopressin
  antagonists
ʳasopressors
ʳC. See Vena contracta
ʳelocity time integral (VTI)
ʳena cava interruption (IVC Filters)
ʳena cavae
ʳena contracta (VC)
ʳenography
ʳenous hum
ʳenous thromboembolism (VTE)
  diagnosis of
  DVT
    clinical presentation and diagnosis
    D-Dimer
    diagnostic testing
    duplex ultrasonography
    venography

essential facts about
treatment of
mechanical/surgical
pulmonary embolism
cardiospecific biomarkers
clinical presentation and diagnosis
CTPA
echocardiography
ventilation/perfusion scan
risk factors for
thromboprophylaxis
treatment of
anticoagulants
DTI
fondaparinux
LMWH
thrombolytic therapy for
unfractionated heparin
VKA
ʳentilation/perfusion scans (V/Q)
ʳentricular activation
ʳentricular extrastimulus testing
ʳentricular fibrillation (VF)
ʳentricular function
ʳentricular oversensing
ʳentricular pacing
ʳentricular parasystole
ʳentricular rate
ʳentricular sensitivity
ʳentricular septal defect (VSD)
diagnosis for
membranous
muscular
signs/symptoms of
supracristal
treatment for
types of
ʳentricular tachycardia (VT). See also Supraventricular tachycardia; Wide-complex tachycardia
coronary artery disease
dilated cardiomyopathy
idiopathic left ventricular tachycardia
morphology of
outflow-tract
short-QT syndrome
structurally normal heart and
ʳerapamil (Calan, Isoptin, Verelan)
ʳerelan. See Verapamil
ʳery low-density lipoprotein (VLDL)
ʳeterans Administration Cooperative Study (VA Study)
ʳeterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)
ʳF. See Ventricular fibrillation

V-HeFT
I
II
Vitamin D
Vitamin K Antagonists (VKA)
VKA. See Vitamin K Antagonists
VLDL. See Very low-density lipoprotein
VMAC
VOA. See Valve orifice area
Voltage output
Volume
of distribution
PVs and
V/Q. See Ventilation/perfusion scans
VSD. See Ventricular Septal Defect
VT. See Ventricular tachycardia
VTE. See Venous thromboembolism
VTI. See Velocity time integral

W
Wandering atrial pacemaker (WAP)
WAP. See Wandering atrial pacemaker
Warfarin
Warfarin and Antiplatelet Therapy in Heart Failure Trial (WATCH)
WATCH. See Warfarin and Antiplatelet Therapy in Heart Failure Trial
Water, retention of
Waveforms
intracardiac
venous
WCT. See Wide-complex tachycardia
Wegener granulomatosis
West of Scotland Coronary Prevention Study (WOSCOPS)
WHI-OS. See Women's Health Initiative Observational Study
White blood cell (WBC)
WHO. See World Health Organization
Wide-complex tachycardia (WCT). See also Supraventricular tachycardia (SVT); Ventricular tachycardia (VT)
algorithms
conclusions on
diagnosis
clinical presentation
ECG criteria
provocative maneuvers
differential diagnosis
special cases
Williams syndrome
Wolff-Parkinson-White syndrome (WPW)
and sudden cardiac death
Women. See also Pregnancy
AHA/ACC guidelines for
chest discomfort in
clinical presentation of

coronary artery disease
device therapy and
epidemiology/problem of
heart failure and
HTN
pregnancy
prevention of
estrogen therapy for
risk factors associated with
treatment results for
Women's Health Initiative Observational Study (WHI-OS)
World Health Organization (WHO)
global burden of disease
World Heart Foundation Marburg Criteria
WOSCOPS. See West of Scotland Coronary Prevention Study
WPW. See Wolff-Parkinson-White syndrome

X-ray imaging system
generator
image receptor
operating console
x-ray tube
XRT. See External-beam radiation therapy