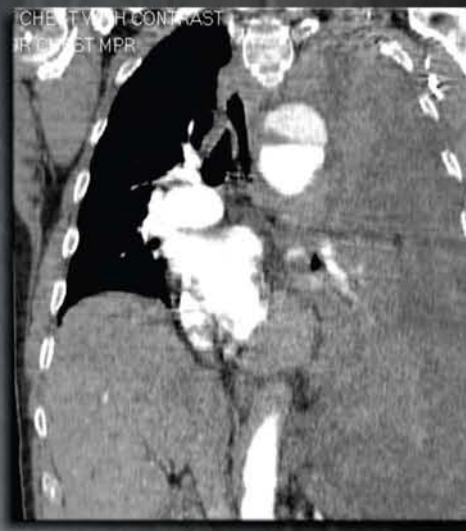
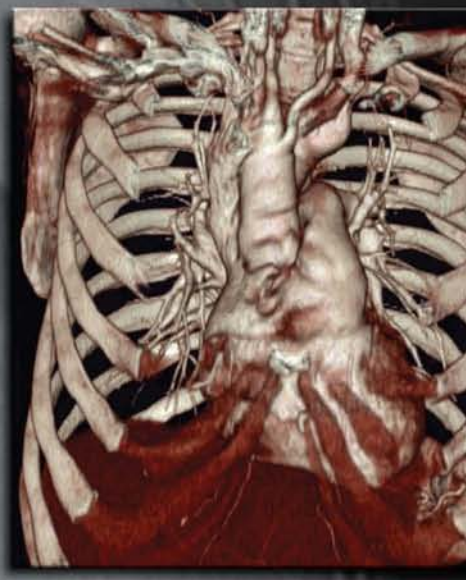
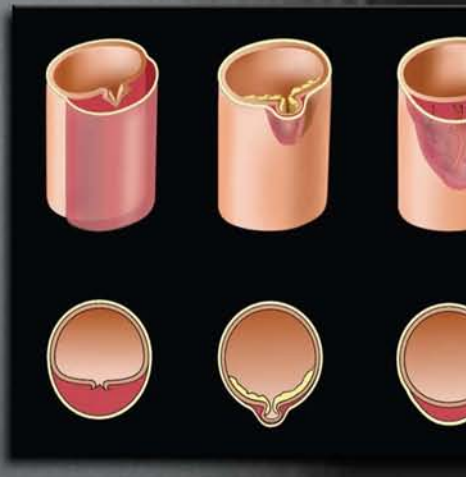
Acute Aortic Disease







Edited by

John A. Elefteriades

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Acute Aortic Disease

Fundamental and Clinical Cardiology

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Acute Aortic Disease

Edited by

John A. Elefteriades

Yale University School of Medicine
New Haven, Connecticut, U.S.A.

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To Sophie and Elias,
for their selfless devotion to their children

Introduction

Informa Healthcare has developed various series of beautifully produced books in different branches of medicine. These series have facilitated the integration of rapidly advancing information for both the clinical specialist and the researcher.

John A. Elefteriades, MD has written and edited a much-needed, practical, and timely book, *Acute Aortic Disease*. This complex clinical set of cardiovascular problems is approached methodically, with beautifully illustrated sections on diagnosis, imaging, biology, and treatment. Dr. Elefteriades has coauthored many of the chapters, which provides the text with unparalleled cohesion and uniformity. As a clinical cardiologist, I will keep this book open and on my office desk, not perched on my bookshelf, because of the practical information it provides to assist me in patient care.

The Editor has recruited the world's leading experts in epidemiology, pathophysiology, imaging, medical therapy, and surgery to approach this subject with depth and special insight. The textbook summarizes the present state-of-the-art and looks toward future advances in molecular diagnosis, gene therapy, and even more sophisticated diagnostic modalities.

My goal as Editor-in-Chief of the Fundamental and Clinical Cardiology Series is to assemble the talents of world-renowned authorities to discuss virtually every area of cardiovascular medicine. I feel we have achieved this objective with *Acute Aortic Disease*. Future contributions to this series will include books on

molecular biology, interventional cardiology, and clinical management of such problems as coronary artery disease, venous thromboembolism, peripheral vascular disease, and cardiac arrhythmias.

Samuel Z. Goldhaber, MD
Professor of Medicine
Harvard Medical School
Staff Cardiologist
Brigham and Women's Hospital
Boston, Massachusetts, U.S.A.

Editor-in-Chief
Fundamental and Clinical Cardiology Series

Foreword

There is no disease more conducive to clinical humility than aneurysm of the aorta.

The above quotation from Osler, the renowned physician, expresses the attitude of the medical profession toward aortic aneurysms during the first half of the 20th century. In 1952, however, the advent of a curative surgical approach (1) stimulated new interest in aortic diseases, and a more aggressive approach ensued. As physicians began to realize the seriousness of aortic lesions and their high morbidity and mortality, increasing attention was focused on the processes that lead up to acute conditions. Also, as physicians began to appreciate the varied etiology of aortic diseases, they gained a better understanding of the multiple factors (wall stress, age-related degeneration, hypertension, inflammation, and infection) that predispose to complications, mostly related to rupture.

Since the early years of aortic surgery, operative treatment has undergone extensive changes, ranging from excision of sacciform lesions to imposition of fabric or biologic grafts designed to restore the vascular continuity of all major tributaries. Conventional aortic surgery, involving the use of cardiopulmonary bypass and induced hypothermia, has yielded impressive results but is highly invasive and necessitates prolonged recuperation. Newer approaches, entailing intravascular placement of fabric-covered stents, promise to supplant the older techniques. Anatomic locations that are hard to access, such as the ascending aorta and proximal arch and the thoracoabdominal segments, may be more easily repaired in hybrid suites, which allow surgeons and interventionalists to perform combined repairs.

In addition, researchers are studying genetic factors and proposing preventive measures for averting aortic diseases. With digitized and computerized techniques, diagnoses are being made more precisely, more definitively, and less invasively than with conventional aortography. These techniques allow better prognostic

assessment and may help the physician decide on the best treatment after preventive measures fail.

Because of this intense interest and progress, the management of aortic diseases has a solid foundation. It will be interesting to see what new preventive measures and treatment strategies lie ahead. Indeed, the present book may provide the stimulus for future breakthroughs. I congratulate Dr. John Elefteriades on producing such an excellent volume, which belongs on the shelves of all who deal with aortic diseases.

Denton A. Cooley, MD
President and Surgeon-in-Chief
Texas Heart Institute

REFERENCE

1. Cooley DA, DeBakey ME. Surgical considerations of intrathoracic aneurysms of the aorta and great vessels. Ann Surg 1952; 135:660–680.

Preface

Over 100 years ago, the great physician Sir William Osler observed "there is no condition more conducive to clinical humility than aneurysm of the aorta." The lithograph in Figure 1 illustrates the "electroshock therapy" applied in that era for the treatment of large aortic aneurysms. Although we have made great progress since that era, Osler's observation regarding the challenge posed by aortic diseases remains true to this day. The powerful potential for aortic aneurysm and related

Figure 1 In Osler's time, electroshock therapy was employed to stop aneurysm progression and prevent rupture. Will our current therapies be looked at in another 100 years as similarly archaic?

Figure 2 (*See color insert*) Albert Einstein, Lucille Ball, Jonathan Larson (author of "Rent"), Flo Hyman (Olympic volleyball player), George C. Scott, and John Ritter are just a few among scores of brilliant people whose lives were cut short by acute aortic diseases.

disorders to injure or kill patients is expressed through a variety of acute aortic conditions. It is on these conditions that this volume is focused.

Acute aortic disease has affected so many individuals of great intelligence, creativity, and physical prowess (Fig. 2) that some authors have even speculated that the propensity for aortic aneurysm or dissection is genetically associated with intellectual or physical brilliance.

This volume is intended for cardiologists, emergency physicians, and cardiac surgeons. Of course, this book is also appropriate for trainees in those disciplines. We anticipate that it will also prove useful to a wide variety of other professionals, including internists, vascular surgeons, radiologists, physician associates, nurses, and students and residents in these various disciplines. The book provides basic information for the novice as well as cutting-edge insight for the expert.

This book takes up four perspectives to understanding aortic diseases: we explore the underlying biology of aortic disease, the imaging of aortic aneurysms and dissections, the appropriate means for diagnosis of these entities, and, of course, the treatment, both medical and surgical, of acute aortic conditions. Via these investigations, we will "read the playbook" of this virulent opponent that constitutes the acute aortic condition. By reading the playbook, we aim to render the professional better able to do battle with these conditions.

We make liberal use of illustrations of all types, including line drawings, x-rays, and operative photographs, in order to emphasize the narrative observations made in the text.

Some distinguishing features of this book, intended to engage the reader in an almost interactive exchange with the author experts, include the Editor's Counterpoint (in which comments on the material are presented by each chapter author) and the inclusion of a question and answer section at the end of most chapters (Questions for the Author).

The aorta, we are finding, is "much more than a tube." It is not simply a passive conduit for carrying blood to important organs. Rather, it is an active organ in its own right, even assisting the heart itself in propelling blood via its elastic properties in the "game of catch" it plays with the left ventricle. These organ-type functions of the aorta are explored in this book.

We place special emphasis on the difficult problem of diagnosing acute aortic conditions on the front lines—in the office, in the emergency room, or in the coronary care unit. Aside from their inherent virulence and complexity, these conditions pose special challenges by virtue of their relative infrequency and myriad clinical presentations. In many ways, for the internist, cardiologist, or emergency physician on the front lines, looking for aortic dissections is like trying to find a needle in a haystack. In fact, for every 100 patients presenting with chest pain, 99 will have some cause other than aortic aneurysm and dissection. Also, aortic dissection has been called "the great masquerader" because it can mimic such a broad spectrum of diseases. Dissection can present with chest pain, back pain, neck pain, abdominal distress, stroke-like symptoms, paraplegia, and vascular insufficiency of the extremities. Our intent is that readers of this book will always maintain an index of suspicion for aortic conditions and become better prepared to recognize affected individuals among the vast number of disparate patients they are called to evaluate.

The challenges of diagnosis and treatment in acute aortic conditions are such that litigation abounds in this arena. In this book, we pay special attention to the nature of lawsuits in aortic diseases and make special recommendations regarding measures for their prevention. An entire chapter is devoted to this topic.

The biologic, radiologic, and medical and surgical sciences have indeed made great strides since the observations of Osler regarding the challenge posed by aortic diseases. This book intends to present those strides to the reader, so as to better equip medical professionals to recognize and treat these disorders.

Through scientific advances, the balance of power is slowly changing vis-à-vis aortic diseases, with a better outlook than ever before, for both physicians and for the patients with whom they are entrusted, and progressively less danger from the inherent aortic disease.

John A. Elefteriades

Acknowledgments

The Editor expresses extreme gratitude to Sandra Beberman, who conceived and commissioned this book. This is but one of many contributions she has made to scientific education.

The Editor expresses thanks to Vanessa Sanchez and Ginny Faber for their production and editorial contributions.

The Editor is grateful to the many chapter contributors, acknowledged international authorities in their respective fields, whose contributions constitute the substance of this book. They have made time in their very busy lives to devote attention to the generation of their exceptional manuscripts.

The Editor wishes to thank Ms. Marianne McCarthy, our Academic Specialist in the Section of Cardiothoracic Surgery at Yale University, for her tireless efforts on behalf of this book. Thanks also go to Suzanne Giannotti for her administrative oversight that makes all our projects possible. Special thanks go to Ms. Marianne Tranquilli, RN, for extraordinary contributions not only to this book but also to all the functions of the Yale Center for Thoracic Aortic Disease. Thanks are extended also to our current research staff—Amar Trivedi, Shannon Widman, and Andrew Percy—for their review and scrutiny of the individual chapters of this book. A special thank you goes out to the dozens of prior research students and residents whose efforts are reflected in many chapters of this book, including Dr. George Koullias, Dr. Gonzalo Albornoz, Dr. Remo Moomiaie, and Dr. Ryan Davies, among others. Dr. John Rizzo, epidemiologist extraordinaire, has been a vital component of the Yale Center since its very inception. My colleague, Dr. Michael Coady, has contributed not only his clinical acumen and skills, but also his considerable statistical and investigational talents, to all the efforts of the Yale Center for Thoracic Aortic Disease. Appreciation is expressed to Drs. Emily Farkas and Ali Shahriari for their manuscript review and their contributions to Questions for the Authors.

Above all, thanks go to the thousands of aortic disease patients who have entrusted their care to the Yale Center for Thoracic Aortic Disease and whose clinical material forms the substrate for many of the investigations reported in this book.

John A. Elefteriades

Contents

Contributors

Nili Avidan Division of Medical Genetics, Department of Internal Medicine, University of Texas Medical School, Houston, Texas, U.S.A.

Joseph E. Bavaria Division of Cardiac Surgery, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania, U.S.A.

Donald M. Botta, Jr. Section of Cardiothoracic Surgery, Yale University, New Haven, Connecticut, U.S.A.

Derek R. Brinster Division of Cardiothoracic Surgery, Virginia Commonwealth University Medical Center/Medical College of Virginia, Richmond, Virginia, U.S.A.

Michael A. Coady Harvard University, Landmark Hospital, Boston, Massachusetts, U.S.A.

Peter G. Danias Department of Medicine, Tufts University Medical School, Boston, Massachusetts, U.S.A., and Cardiac MR Center, Hygeia Hospital, Maroussi, Athens, Greece

Kim Eagle Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan, U.S.A.

Andrew J. Einstein The Zena and Michael A. Wiener Cardiovascular Institute and Marie-Josee and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai School of Medicine, New York, New York, U.S.A.

John A. Elefteriades Section of Cardiothoracic Surgery, Yale University, New Haven, Connecticut, U.S.A.

Emily A. Farkas Section of Cardiothoracic Surgery, Yale University, New Haven, Connecticut, U.S.A.

Valentin Fuster The Zena and Michael A. Wiener Cardiovascular Institute and Marie-Josee and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai School of Medicine, New York, New York, U.S.A.

Randall Griepp Department of Surgery, Mt. Sinai School of Medicine, New York, New York, U.S.A.

Dong-chuan Guo Division of Medical Genetics, Department of Internal Medicine, University of Texas Medical School, Houston, Texas, U.S.A.

Amy E. Hackmann Departments of Surgery (Section of Vascular Surgery), Radiology, and Cell Biology and Physiology, Washington University School of Medicine, St. Louis, Missouri, U.S.A.

Hüseyin Ince Division of Cardiology, University Hospital Rostock, Rostock School of Medicine, Rostock, Germany

Eric M. Isselbacher Department of Medicine, Harvard Medical School and Thoracic Aortic Center, Massachusetts General Hospital, Boston, Massachusetts, U.S.A.

George Koullias Department of Thoracic and Cardiovascular Surgery, AHEPA University Hospital, Aristotle University Medical School, Thessaloniki, Greece

Scott A. LeMaire Division of Cardiothoracic Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, and Cardiovascular Surgery Service, The Texas Heart Institute at St. Luke's Episcopal Hospital, Houston, Texas, U.S.A.

Dianna M. Milewicz Division of Medical Genetics, Department of Internal Medicine, University of Texas Medical School, Houston, Texas, U.S.A.

Christoph A. Nienaber Division of Cardiology, University Hospital Rostock, Rostock School of Medicine, Rostock, Germany

Hariyadarshi Pannu Division of Medical Genetics, Department of Internal Medicine, University of Texas Medical School, Houston, Texas, U.S.A.

Arun Raghupathy Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan, U.S.A.

John A. Rizzo Department of Epidemiology, State University of New York at Stony Brook, Stony Brook, New York, U.S.A.

Javier Sanz The Zena and Michael A. Wiener Cardiovascular Institute and Marie-Josee and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai School of Medicine, New York, New York, U.S.A.

Ali Shahriari Section of Cardiothoracic Surgery, Yale University, New Haven, Connecticut, U.S.A.

Wilson Y. Szeto Division of Cardiac Surgery, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania, U.S.A.

Paul C. Y. Tang Section of Cardiothoracic Surgery, Yale University, New Haven, Connecticut, U.S.A.

George Tellides Section of Cardiothoracic Surgery, Yale University, New Haven, Connecticut, U.S.A.

Robert W. Thompson Departments of Surgery (Section of Vascular Surgery), Radiology, and Cell Biology and Physiology, Washington University School of Medicine, St. Louis, Missouri, U.S.A.

Van Tran-Fadulu Division of Medical Genetics, Department of Internal Medicine, University of Texas Medical School, Houston, Texas, U.S.A.

1

Classification of Aortic Dissection

Christoph A. Nienaber and Hüseyin Ince
Division of Cardiology, University Hospital Rostock,
Rostock School of Medicine, Rostock, Germany

INTRODUCTION

Since aortic dissection is one of the most challenging (and most rewarding) medical emergencies, with a spectrum of heterogeneous clinical features, the small community of experts in this field has tended to categorize and structure the complex appearances of aortic dissection. Interestingly, but also typically, those categorization attempts were made from the viewpoint of various disciplines, from surgery to genetics to epidemiology. The goal has always been to better comprehend the disorder, improving communication and education (1–4). This chapter deals with the four most common domains of classification and introduces the most popular and relevant stratification schemes for classifying aortic dissection.

CLASSIFICATION ACCORDING TO ETIOLOGY

Connective Tissue Disease

All mechanisms weakening the aorta's medial layers via micro-apoplexy of the vessel wall and encompassing many different disease entities lead to higher wall stress, which can induce aortic dilatation and aneurysm formation. Intramural hemorrhage, aortic dissection, or rupture of aortic wall layers may result. Three major inherited connective tissue disorders are currently known to affect the arterial wall: Marfan's syndrome (MFS), Ehlers-Danlos syndrome (EDS), and familial thoracic aneurysm and dissection.

Table 1 Risk Conditions for Aortic Dissection

Connective tissue disorders
Hereditary fibrillinopathies
Marfan's syndrome
Ehlers-Danlos syndrome
Hereditary vascular diseases
Bicuspid aortic valve
Coarctation
Chronic hypertension and atherosclerosis
Smoking, dyslipidemia, cocaine/crack
Vascular inflammation
Giant cell arteritis
Takayasu arteritis
Behcet's disease
Syphilis
Ormond's disease
Deceleration trauma and iatrogenic origin
Deceleration trauma (car accident, fall from height)
Iatrogenic factors
Catheter/instrument intervention
Valvular/aortic surgery
Side or cross clamping/aortotomy
Graft anastomosis
Patch aortoplasty
Cannulation site

Among hereditary diseases, MFS is the most prevalent connective tissue disorder, with an estimated incidence of 1/7000 and an autosomal dominant inheritance with variable penetrance. More than 100 mutations on the fibrillin-1 (*FBN-1*) gene have been identified encoding for a defective fibrillin in the extracellular matrix; this may affect the ocular, cardiovascular, skeletal, and pulmonary systems, as well as skin and dura mater. The diagnosis of MFS is currently based on revised clinical criteria of the "Gent nosology" (5). The Gent criteria pay particular attention to genetic information, such as MFS in kindreds of an unequivocally affected individual. Moreover, both skeletal and cardiovascular features are major (e.g., diagnostic) criteria if more than four of eight typical manifestations are present.

Considering, however, clinically challenging borderline manifestations—such as the Myopia Aneurysm Striae Skeletal involvement (MASS) phenotype, or subtle phenotypic features ("forme fruste" of Marfan's)—the molecular analysis of suspected MFS and its differentiation from other related entities become pertinent (6–11). The clinical variety of the MFS is only partially explained by the number of mutations on the *FBN-1* gene. Genetic heterogeneity and the involvement of a second gene (*MFS2,* Marfan syndrome type 2) may further add to the broad spectrum of symptoms (11).

A common denominator of all phenotypic forms of aortic wall disease is elastolysis of aortic wall components (12), as shown in an *FBN-q*-deficient animal model (13). Moreover, enhanced expression of metalloproteinases in vascular smooth muscle cells of the Marfan's aorta may promote both fragmentation of medial elastic layers and elastolysis, thus initiating an activated phenotype of smooth muscle cells (14). In parallel, expression of peroxisome proliferators–activated receptor-γ (PPAR-γ) is upregulated in smooth muscle cells of Marfan's aorta and in cystic medial degeneration. Thus, PPAR-γ expression might reflect the pathogenesis of cystic medial degeneration and disease progression in the aorta of Marfan's and nonMarfan's patients (15).

EDS is a heterogeneous group of hereditable connective tissue disorders characterized by articular hypermobility, skin hyperextensibility, and tissue fragility. Eleven types of EDS have been characterized. The true prevalence of EDS is unknown. An aggregate incidence of 1/5000 births is often cited, with no racial or ethnic predisposition. Aortic involvement is seen primarily in autosomal dominant EDS type IV (16).

More than five mutations in the *FBN-1* gene have now been identified in patients presenting with either sporadic or familial forms of thoracic aortic aneurysms and dissection (17,18). Histological examination of the aortic wall reveals elastolysis, or loss of elastic fibers, deposits of mucopolysaccharide-like materials, and cystic medial degeneration similar to MFS. However, no abnormalities of types I and III collagen or any specific fibrillopathy were found in fibroblast cultures.

Differentiation of familial forms of abdominal aortic aneurysm/dissection from thoracic aortic aneurysms/dissection with an abdominal component is difficult, considering that only one mutation within the *COL3A1* gene is known (17). In fact, many candidate genes encoding for collagens, fibrillins, fibrullins, microfibril-associated glycoproteins, matrix metalloproteinases and their inhibitors, have been investigated, but no mutation has been identified. Similar pathogenetic processes have been described with coarctation (18) and with the bicuspid aortic valve architecture (19) (Table 1).

Chronic Hypertension and Atherosclerosis

Chronic hypertension affects the arterial wall composition, causing intimal thickening, fibrosis, calcification, and extracellular fatty acid deposition. In parallel, the extracellular matrix undergoes accelerated degradation, apoptosis, and elastolysis, with hyalinization of collagen. Both mechanisms may eventually lead to intimal disruption, most often at the edges of plaques (as seen in coronary plaques, as well). Intimal thickening increases, which further compromises nutrient and oxygen supply to the arterial wall. Adventitial fibrosis may obstruct vessels feeding the arterial wall as well as small intramural vasa vasorum. Both processes result in necrosis of smooth muscle cells and fibrosis of elastic structures of the vessel wall, leading to increased stiffness. Increased stiffness confers vulnerability to pulsatile forces, creating a substrate for aneurysms and dissections (18,20–22).

In addition to chronic hypertension, smoking, dyslipidemia, and use of crack cocaine are modulating risk factors.

Atherosclerosis is the main cause of 435aortic aneurysms (23,24). The intima of the aorta shows massive fibrosis and calcification, and increased amounts of extracellular fatty acids. The integrity of this layer can be compromised by the extracellular matrix degraded by histiocytic cells, while additional degenerative changes can develop within the fibrous tissue. These mechanisms may lead to intimal rupture, most often at the edges of plaques. Intimal thickening increases the distance between the endothelial layer and the media, compromising the nutrient and oxygen supply. Adventitial fibrosis may obstruct vessels feeding small intramural vasa vasorum; reduced nutritional supply of the media results in medial thinning secondary to necrosis—primarily due to necrosis of the smooth muscle cells. Another consequence is a fibrotic change in the elastic structures of the medial layer (25). All these changes contribute to increased vessel stiffness, higher vulnerability, and shear stress, eventually leading to the formation of aneurysms and dissections. Ruptures are more common in the ascending aorta (65%) and less frequent in the abdominal aorta (32%). Fusiform thoracic aortic aneurysms have a higher rupture risk (61%) compared to abdominal aortic aneurysms. Aortic rupture is found in 0.9% of cases of sudden death. Aortic dissections are present in 62% of these patients, atherosclerotic aneurysms in 37%, and false aneurysms in 1.6% (24). The main risk factor for aneurysm formation in atherosclerosis is additional hypertension, found in 85% of those with ruptured or 52% of those with nonruptured aneurysms. Risk factors, such as smoking and hypercholesterolemia, are also associated with an increased incidence of aortic aneurysms. However, 60% of aneurysm patients have a cholesterol level of less than 240 mg/dL (6.2 mmol/L) (24,25).

Trauma and Iatrogenic Origin

Fifteen to twenty percent of deaths from high-speed motor vehicle accidents are related to aortic trauma. About 95% of the injuries occur at the site of greatest stress, the aortic isthmus, and only 5% at the ascending aorta (26). Aortic disruption can be limited to the intima or include all layers of the arterial wall. Chronic traumatic aneurysms tend to become symptomatic or rupture within five years. Aortic rupture will ultimately occur in most patients are after pseudoaneurysms formed, which can enlarge and compress surrounding structures such as the pulmonary artery (27). Aortic rupture, after blunt chest trauma, is frequently associated with myocardial contusion, which can lead to cardiac failure, myocardial infarction, and tamponade. Aneurysm formation and aortic rupture can also occur after aortic surgery and even after cardiopulmonary resuscitation (28–30). Extracorporal shock waves for lithotripsy can produce aortic injury as well (31). Another possible cause of trauma is cardiac catheterization, both diagnostic and interventional procedures (32,33). Aortic dissection may be observed in patients who have undergone prior aortic valve replacement, while the interval between valve replacement and dissection varies greatly (34–36). A precipitating mechanism for this dissection

Table 2 Etiology of Iatrogenic Aortic Dissection in the International Registry of Acute Aortic Dissection

Cause	*Type A*	*Type B*
Cardiac surgery	18 (69%)	1 (12%)
Coronarography/intervention	7 (27%)	7 (87%)
Renal angioplasty	1 (4%)	–
Complication	*Iatrogenic*	*Spontaneous*
Myocardial ischemia	36%[a]	5%
Myocardial infarction	15%[a]	3%
Limb ischemia	14%	8%
Mortality (30 days)	35%	24%

[a]$P \leq 0.001$.
Source: From Ref. 23.

may be changes within the aortic wall resulting from the original jet lesion that caused the poststenotic ascending aortic dilatation. Interestingly, distal aortic dissection has also been observed after aortic valve replacement, suggesting additional risk factors (34,36). Toxic aortic disease is seen in animals after the administration of beta-aminopropionitrile fumarate, which leads to changes in the media that are morphologically similar to mucoid degeneration of the aortic wall (37). In humans, different drugs, such as cocaine and amphetamine, have been associated with aneurysm formation and aortic dissection (38,39).

Inflammatory diseases can destroy the medial layers of the aortic wall and lead to weakening, expansion, and dissection of the aortic wall (12,40). Autoimmune processes may affect vasa vasorum and promote nutrient deficiency of aortic wall layers.

Iatrogenic aortic dissection is usually associated with invasive retrograde catheter interventions, or occurs during, or much later after, valve or aortic surgery (34,36,41). Given the substantial morbidity and mortality of iatrogenic aortic dissection (Table 2), careful assessment is strongly encouraged in patients with unexplained hemodynamic instability or malperfusion syndromes following invasive vascular procedures or aortic surgery (Table 2).

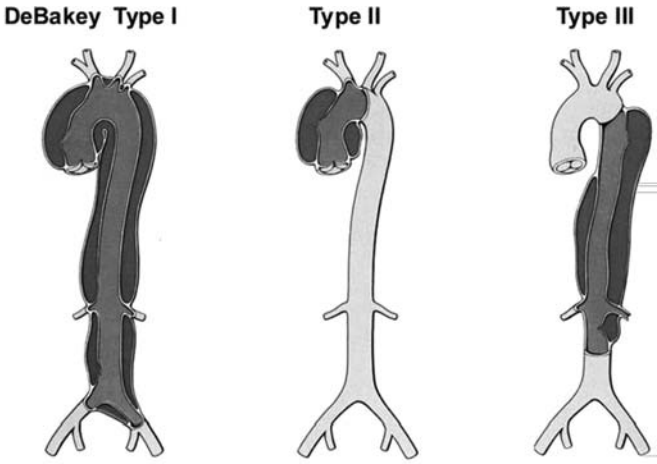
Pregnancy

Finally, pregnancy related aortic dissection is extremely rare, as long as the patient is not affected by connective tissue disease. The putative association of pregnancy and acute dissection may largely be an artifact of selective reporting. Pregnancy is a common condition, and aortic dissection may occur coincidentally only with the concomitant existence of other risk factors such as hypertension and MFS. Preliminary data from the International Registry of Acute Aortic Dissection (IRAD) show that even in female MFS, dissection also occurs outside the setting of pregnancy, further supporting a coincidental association with pregnancy. Even in MFS, pregnancy is not associated with aortic tears, unless root size exceeds 40 mm (33,42).

CLASSIFICATION WITH RESPECT TO PATHOANATOMY

DeBakey Classification

While the pathologic description of acute aortic syndromes has been enhanced by modern tomographic imaging (7,10), historically developed classifications of dissection are still being used (Fig. 1) (1,2). The surgically oriented DeBakey classification highlights the anatomic involvement and the extent of aortic dissection (43). In the DeBakey terminology, Type I represents extension of dissection from the ascending aorta, through the transverse arch, into the descending segments. Type II involves only the ascending aorta. Type III extends from the left subclavian artery to the descending thoracic diaphragmatic (IIIa) or upper abdominal region (IIIb). Types I and II require urgent surgical repair with an interposition graft, a conduit, or even associated hemi-arch or arch reconstruction. Conversely, Type III DeBakey dissection appears less life threatening and may be followed conservatively, or subjected to nonsurgical stent-graft repair (40).



DeBakey

Type I	Originates in the ascending aorta, propagates at least to the aortic arch and often beyond it distally
Type II	Originates in and is confined to the ascending aorta
Type III	Originates in the descending aorta and extends distally down the aorta or, rarely, retrograde into the aortic arch and ascending aorta

Stanford

Type A	All dissections involving the ascending aorta, regardless of the site of origin
Type B	All dissections not involving the ascending aorta

Figure 1 The most common classification systems of thoracic aortic dissection—the Stanford and DeBakey classifications.

Stanford Classification

The original Stanford classification described by Daily et al. (44) stratified dissection into two different groups with respect to management and prognosis, with type A involving the ascending aorta and type B involving all other dissections beyond the left subclavian artery. Notably, there is contemporary consensus that aortic arch dissection without involvement of the ascending aorta qualifies as type B, although previously considered proximal dissection (2). The Stanford classification, by distinguishing between proximal and distal dissections, is of direct clinical utility. Proximal dissections are associated with poor outcome if not subjected to urgent surgical repair, while distal dissections are known to have a wide spectrum of outcomes.

Various attempts to further subdivide both DeBakey and Stanford classification systems have not been fully adopted in the medical community (45,46), although the arch region desperately deserves integration into a modern classification system. Moreover, recent observations highlight the importance of precursors of typical aortic dissection, such as intramural hematoma (IMH), penetrating aortic ulcers, or localized intimal tears as variants of a wall dissecting process (47–51). Early outcomes of acute aortic dissection are summarized in Figure 2.

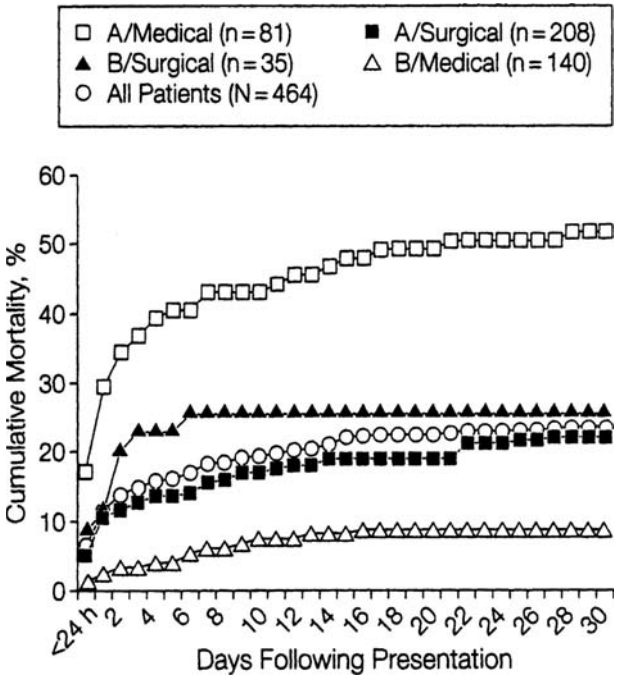


Figure 2 30-day mortality in 464 patients from the International Registry of Acute Aortic Dissection stratified by medical and surgical treatment in both type A and type B aortic dissection. *Source*: From Ref. 73.

Lansman's Classification

In an attempt to improve existing classifications from a surgical perspective, Lansman et al. defined subtypes of acute type A and type B dissection by incorporating dynamic information such as progression or propagation of dissection to the classification (Fig. 3). The two fundamental anatomic features of acute aortic dissection pertain to origin (site of entry) and propagation (dissected segments) of the false lumen in the thoracic aorta. Nevertheless, both classics, the DeBakey and the Stanford classification, are also based on these pathoanatomic variables.

The DeBakey classification (43), which involves both variables, specifies site of intimal tear and associated false lumen propagation. However, the system is limited by making the variables dependent, linking a given tear with a given direction and extent of propagation. Some resulting categories have marginal clinical significance, such as type II dissection, while many possible anatomic variations are omitted. Although straightforward, the Stanford classification (44), based only on the presence (type A) or absence (type B) of false lumen propagation in the ascending aorta, is limited by its simplicity (Fig. 1). Frequent clinically relevant variations in the site of intimal tear cannot be accommodated by these schemes. Often, it is assumed that the intimal tear is above the commissura in type A dissection and in proximity to the subclavian artery in type B dissection; but other clinical patterns are common.

Interestingly, both the DeBakey and Stanford classifications ignore dissections originating from intimal tears in the aortic arch. While the DeBakey classification has no category for a tear in the arch, the Stanford scheme is independent of intimal tears. Moreover, more than a third of type A dissections

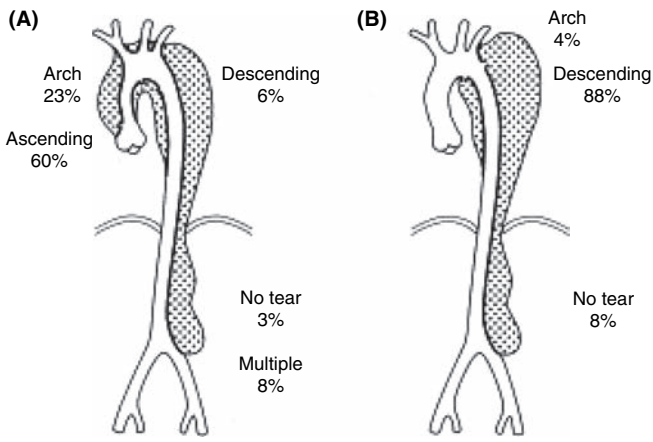


Figure 3 Incidence of subtypes of acute type A and type B aortic dissection. Lansman's classification takes into account both the propagation of the dissection and the site of the inciting tear (shown in text beside the schematic drawings). *Source*: From Ref. 45.

Table 3 Subtypes of Acute Aortic Dissection

Type A	Type B
Ascending	Arch
Arch	Descending
Descending	Multiple tears
Multiple tears	No tear
No tear	

Source: From Ref. 45.

are not characterized by a single tear in the ascending aorta, but by several tears located more distally. The refined Lansman classification scheme describes both site of entry and propagation of dissection independently (Table 3) (45).

Classification according to Lansman's proposal makes sense, since the scheme combines the clinical relevance of the Stanford classification with a precise description of all anatomic combinations of entry site location and propagation. Moreover, it does not require a new alphanumeric nomenclature and conveys clinically useful incremental information (Fig. 3).

For example, compared to patients with type A–ascending dissection, patients with type A–arch dissection are more likely to present with both anterior and posterior chest pain, but not severe hypertension (52); they tend to be older, are less likely to be male or to present with aortic regurgitation, are more likely to present with rupture, and may have diminished survival (Table 4). Lastly, comparing literature reports would be less confusing if acute dissections were subcategorized; Lansman's system groups patients with similar anatomic lesions.

In Lansman's classification, for specific subtypes of type A dissection, systematic resection of the primary tear yielded similar hospital mortality, five-year survival, and aorta-related event-free survival rates. Ten-year survival for type A–arch dissection was lower than other type A subtypes, perhaps reflecting the older age of these patients. A selective approach to type B dissection (53), including surgical therapy for patients presenting with aortic dilatation, resulted in

Table 4 Clinical Characteristics of Lansman's Classification

	Type A subtypes				
Variable	Asc	Arch	Desc	Mult	None
Patients (n)	83	31	8	11	4
Age (yrs)	57.3	61.3	58.6	69.4	68.5
M/F	2.61	1.58	1.67	1.75	0.33
Ao reg (%)	63.9	38.7	37.5	63.6	25.0
Rupture (%)	41.0	32.3	37.5	54.6	25.0
Mortality (%)	14.5	18.8	0.0	0.0	0.0

Abbreviations: M/F, male/female; Asc, ascending; Desc, descending; Mult, multiple entries; Ao reg, aortic regurgitation.

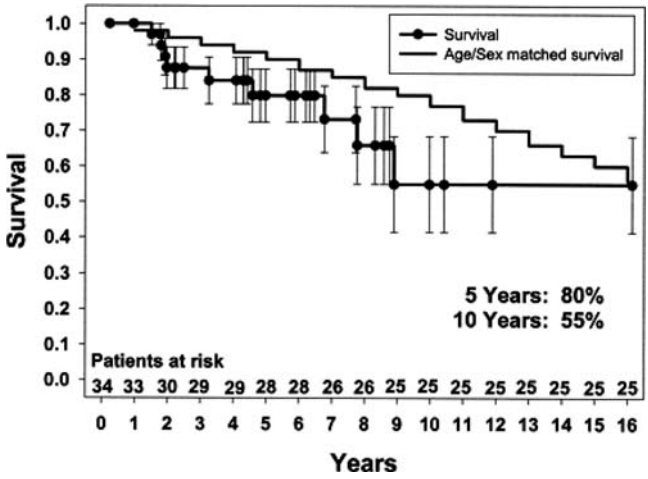


Figure 4 Curves showing Kaplan-Meier survival for 34 patients after urgent surgery for acute type B aortic dissection and survival for an age- and gender-matched population. *Source*: From Ref. 45.

no hospital mortality, 3.4% paraplegia, an 18% incidence of false lumen patency, and excellent long-term survival (Table 4 and Fig. 4). The ability to formulate such precise estimates of clinical course reflects the increased anatomic precision of the subgroupings in Lansman's scheme.

European Working Group Classification

New studies demonstrated that intramural hemorrhage, IMH, and aortic ulcers may be signs of evolving dissections or dissection subtypes. Consequently, a new differentiation has been proposed by the European Working Group (Fig. 5) (54,55):

1. class 1: classical aortic dissection, with an intimal flap between true and false lumen
2. class 2: medial disruption with formation of IMH/hemorrhage
3. class 3: discrete/subtle dissection without hematoma, eccentric bulge at tear site
4. class 4: plaque rupture leading to aortic ulceration, penetrating aortic atherosclerotic ulcer with surrounding hematoma, usually subadventitial
5. class 5: iatrogenic and traumatic dissection

Classic Aortic Dissection (Class 1)

Classic acute aortic dissection is characterized by the rapid development of an intimal flap separating the true and false lumen (56). Due to the pressure difference, the true lumen is usually smaller than the false lumen. Intimal flap tears characterize communicating dissections. However, tears are not always found, and

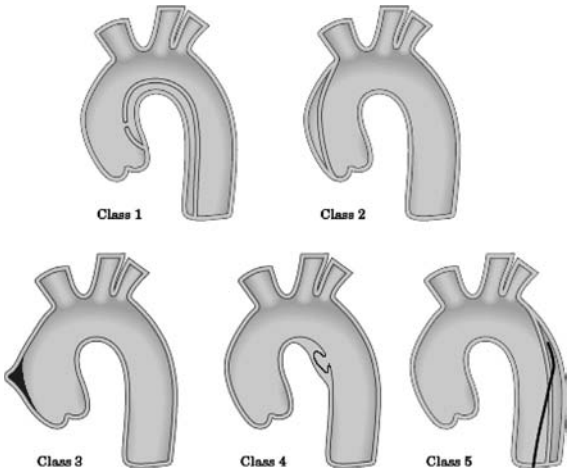


Figure 5 Differentiation of classes one to five of aortic dissection. (Class 1) classic aortic dissection with true and false lumen without communication of the two lumina; (Class 2) intramural hemorrhage or hematoma; (Class 3) ulceration of aortic plaque following plaque rupture; (Class 4) subtle or discrete aortic dissection with bulging of the aortic wall; (Class 5) iatrogenic or traumatic aortic dissection, illustrated by a catheter-induced separation of the intima. *Source*: From Ref. 55.

noncommunicating dissections are not uncommon (45–51,57). In an autopsy study, dissecting aneurysms without tears were found in up to 12% of 311 autopsies (58). Others have reported an incidence of 4% in 505 cases (59). In a series of sudden deaths, 67% of patients with dissections did not have tears (60). The dissection can spread from diseased segments of the aortic wall in an antegrade or retrograde fashion, involving side branches and causing other complications.

IMH (Class 2)

An IMH is probably the initial lesion in the majority of cases of cystic medial degeneration. This leads to localized aortic dissection, in which the intimal tear seems to be secondary to preceding intramural hemorrhage (45–48). IMH may be the result of ruptured normal-appearing vasa vasorum, which are inadequately supported by the surrounding aortic media or the result of rupture of diseased vasa vasorum. As a dissection, the hematoma can extend longitudinally along the aorta. The weakened inner wall is subjected to the elongating force of the diastolic recoil, which can result in intimal tears only visible at surgery or autopsy. Differences in elasticity between the aortic fibrous adventitia and the inner more elastic media may play an additional role (59). The prevalence of IMH in patients with suspected aortic dissection, as observed by various new imaging techniques, is reported in the range of 10% to 30% (45–50). There are two distinct types of IMH: type I shows a smooth inner aortic lumen, the aortic diameter is usually less than 3.5 cm, and the wall thickness greater than 0.5 cm. Echo-free spaces are found in only

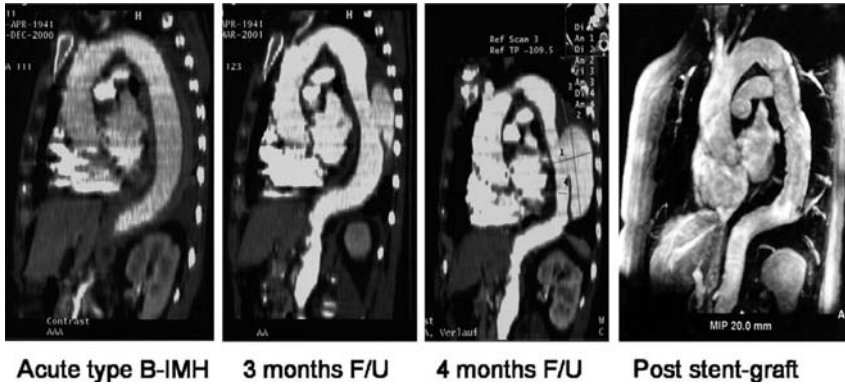


Figure 6 Evolutions of acute IMH of the descending aorta (*left*) to growing local dissection, and formation of an aneurysm on spiral contrast-enhanced completed axial tomography (CAT) scans within four months; reconstruction of the dissected aorta and exclusion of aneurysm after interventional stent-graft placement. *Abbreviation*: IMH, intramural hematoma. *Source*: From Ref. 40.

one-third of these patients; the echo-free spaces show no signs of flow. Type II occurs in aortic atherosclerosis with characteristic severe aortic sclerosis; the aorta is dilated to more than 3.5 cm and calcium deposits are frequently found; echo-free spaces are present in 70%. IMH is diagnosed more frequently in the descending than in the ascending aorta. The evolution of IMH to aortic dissection has been demonstrated in follow-up studies (45–51,62). Acute aortic dissection as a consequence of IMH develops in 28% to 47% of the patients. IMH is associated with aortic rupture in 21% to 47%, and regression is seen in about 10% of patients. Potential treatment options range from conservative (antihypertensive medication) to interventional placement of stent-grafts (Fig. 6).

Subtle-Discrete Aortic Dissection (Class 3)

The structural weakness of the aortic wall can, in certain cases, lead to minor forms of aortic dissection, which may be clinically inapparent. Such subtle dissection has been described (55) as a partial stellate or linear tear of the vessel wall, covered by thrombus. When the partial tear forms a scar, this constellation is called an abortive, discrete dissection. Partial ruptures of the inner layer of the aorta allow blood to enter the already damaged media and thus cause dissection of the aortic wall, eventually leading to a second lumen within the wall, which may, on the one hand, rupture, or, on the other hand, heal completely during follow-up.

Plaque Rupture/Ulceration (Class 4)

Ulceration of atherosclerotic aortic plaques can lead to aortic dissection or aortic perforation (62–65). This was first observed by computed tomography (62,63). New imaging techniques—such as intravascular ultrasound, spiral computed

tomography, and magnetic resonance imaging—provide increased ability to diagnose aortic ulcers and novel insights into the pathophysiology of this condition (66). The ulcers seem to affect the descending thoracic aorta, as well as the abdominal aorta, and are not usually associated with extensive longitudinal propagation or branch vessel compromise. Valvular, pericardial, or other vascular complications appear rarely. The ulcer may penetrate beyond the intimal border, often with a nipple-like projection with subjacent type II IMH formation. The continuous erosion of the atherosclerotic plaque may eventually violate the internal elastic membrane (63). False aneurysms, aortic rupture, or dissections may occur (67).

Traumatic/Iatrogenic Aortic Dissection (Class 5)

Blunt chest trauma usually causes dissection located in the ascending aorta and/or the region of the ligamentum botalli at the aortic isthmus. Iatrogenic dissection of the aorta occurs rarely during heart catheterization. Iatrogenic dissection is regularly seen following angioplasty of an aortic coarctation (in adults) but can also be observed after intra-aortic balloon pumping or as a consequence of clamping the aorta during cardiac surgery (26–29). Most catheter-induced dissections are retrograde dissections from the femoral arterial puncture. They will usually decrease in size as false lumen thromboses. In the case of iatrogenic dissection of coronary arteries, these can progress retrograde proximally to involve the ascending aorta.

CLASSIFICATION RELATED TO ACUITY

Acute aortic dissection is characterized by the rapid development of an intimal flap, separating true from false aortic lumen. In the majority of cases (~90%) intimal tears are identified, as sites of communication between true and false lumen. The dissection can spread from diseased segments of the aortic wall in an antegrade or retrograde fashion, involving side branches and causing complications such as malperfusion, tamponade, or aortic insufficiency (61,68–72).

The arbitrary classification of acute, subacute, or chronic dissection appears neither helpful for didactic nor for differential therapeutic considerations, but may rather be used to describe the individual situation and timespan of survival of a given patient. From a pathophysiological point of view, progression of dissection is difficult to predict once a patient with dissection has survived the initial two weeks after its inception, although false lumen expansion is likely to develop over time. Several clinical features may be used to roughly estimate late risk, including spontaneous false lumen thrombosis, evidence of persistent communication, patent false channel, and others (39,47,68).

Acute Phase

By convention, the initial 14 days after the clinical onset of aortic dissection is coined the "acute phase," regardless of a stable or unstable clinical course. For type A

dissection, surgical care should be instituted as early as possible during this acute phase, because mortality of type A dissection can reach up to 2% per hour in the initial 24 hours and seems to level off gradually with time thereafter; it makes little sense to wait and waste time to reach a subacute stage in this precarious situation. Any type A scenario will benefit from swift transfer to a surgical center for definitive care.

Subacute Phase

Again, by convention, the so-called "subacute phase" is an arbitrarily chosen interval between 14 days after clinical onset and one month. Few patients with type A or proximal dissection reach that subacute phase without urgent surgical repair (Fig. 7). Conversely, distal dissections of the Stanford type B scenario often reach the subacute phase of the dissection process. All-cause mortality of type B dissection within one month of clinical impact is ~10% according to the IRAD data (Fig. 2). Many cases of type B dissection actually reveal a stable clinical course once the acute phase has passed, under conservative management (including

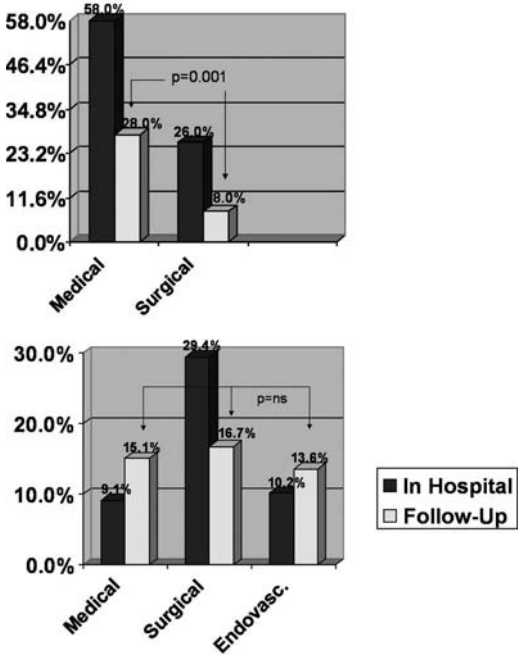


Figure 7 Statistics from the International Registry of Acute Aortic Dissection show that mortality of medical treatment of type A dissection is extremely high both in-hospital and during follow-up and clearly surpasses mortality of type B dissection during a median follow-up of 357 days. Swift surgical repair is much more rewarding for patients with type A dissection than for type B dissection in whom the most beneficial therapy is still unresolved and under debate.

monitoring, careful blood pressure lowering, and mild sedation in selected cases). This subacute phase is indeed a sensitive time window to screen for potentially emerging subacute or late complications, such as malperfusion syndrome, impending rupture, repetitive pain, or extra-aortic blood collection. Under such conditions even asymptomatic patients qualify for open surgery or endovascular strategies such as stent-grafts.

Chronic Phase

The chronic phase of dissection is arbitrarily defined as the time window beyond one month of the acute onset of dissection. The chronic state pertains rarely to type A (for the reasons discussed earlier), but commonly for type B dissection. Once distal or type B dissections reach the chronic phase, without complications, they usually enjoy a clinically stable course for months or years. However, from careful observational evidence, it is obvious that with time late aneurysmal expansion does develop—usually at the proximal segment of the descending thoracic aorta near the subclavian artery. This chronic dilatation confers an increasing risk of late rupture as a function of an expanding false lumen. Other complications in the chronic phase include compression of vital structures in the vicinity of an expanding false lumen aneurysm, late malperfusion syndrome, and peripheral emboli. The scientific community is currently interested to identify those patients at high risk to develop late complications in the chronic phase. It is hoped that appropriate ways to prevent these complications will be found—by timely interventions in the acute or subacute phase. Interestingly, there is mounting evidence that successful remodeling of a dissected aorta by means of stent-grafts early in the course of the disease may prevent those difficult to treat late complications (40).

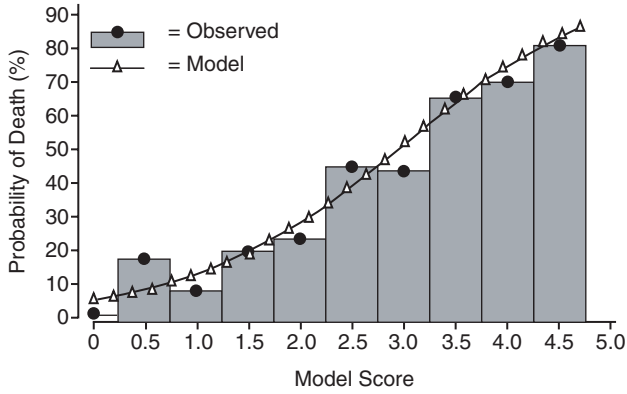
CLASSIFICATION WITH PROGNOSTIC IMPACT

Proximal vs. Distal Dissection

Anatomic classification is important for both therapy and prognostic assessment. The involvement of the proximal or ascending aorta in the dissection process may be accompanied by complications such as new onset of aortic valve regurgitation, pericardial effusion, hypotension, shock, syncope, or a widening mediastinum. These clinical features prior to surgery are associated with a significantly elevated in-hospital death rate (Fig. 8). Best surgical results are obtained with swift surgical repair in a stable hemodynamic setting without any evidence of neurological compromise or side branch obstruction; absent such adverse developments, an in-hospital mortality around 10% can be attained. By comparison, the 30-day mortality in all patients with proximal dissection, regardless of preoperative state and type of surgical technique, averages around 25%, even in experienced centers in different parts of the world (73).

Type B dissection usually portends a more benign early clinical course (Fig. 7). The subset of patients at greater risk is characterized by malperfusion,

(A)



(B)

	Score	p	Death OR (95 % CI)
Age ≥ 70 a	**0.5**	0.03	1.70 (1.05–2.77)
female	**0.3**	0.20	1.38 (0.85–2.27)
sudden chest pain	**1.0**	0.01	2.60 (1.22–5.54)
pathological ECG	**0.6**	0.03	1.77 (1.06–2.95)
pulse deficit	**0.7**	0.004	2.03 (1.25–3.29)
ARF	**1.6**	0.002	4.77 (1.80–12.6)
Hypotension Shock/ Tamponade	**1.1**	< 0.0001	2.97 (1.83–4.81)

Figure 8 Observed versus predicted mortality for acute type A aortic dissection based on a risk score; each risk factor was statistically extracted from retrospective analysis in International Registry of Acute Aortic Dissection (IRAD) and then prospectively confirmed. Both predicted and observed mortality rates in IRAD increase with increasing number and weight of risk factors. *Abbreviations*: ARF, acute renal failure; CI, confidence interval; ECG, electrocardiogram. *Source*: From Ref. 40.

a pulse differential, sudden onset of renal failure or abdominal pain (Fig. 9). These patients have a 3.5 times higher risk of death than patients without these features. Overall, in distal dissection, the in-hospital mortality averages around 13%, with most fatalities occurring within the first week after onset. Additional factors associated with increased in-hospital mortality include hypotension and shock, a widened mediastinum, periaortic hematoma, an excessively dilated descending aorta (≥6 cm), and need for surgical management (all $P < 0.05$). A risk prediction model controlling for age and gender showed hypotension/shock [odds ratio (OR) 23.8; $P < 0.0001$], absence of chest/back pain on presentation (OR 3.5; $P = 0.01$), and branch vessel involvement (OR 2.9; $P = 0.02$), collectively named "the deadly triad," to be independent predictors of in-hospital death even in distal aortic dissection (74). These factors associated with increased in-hospital mortality

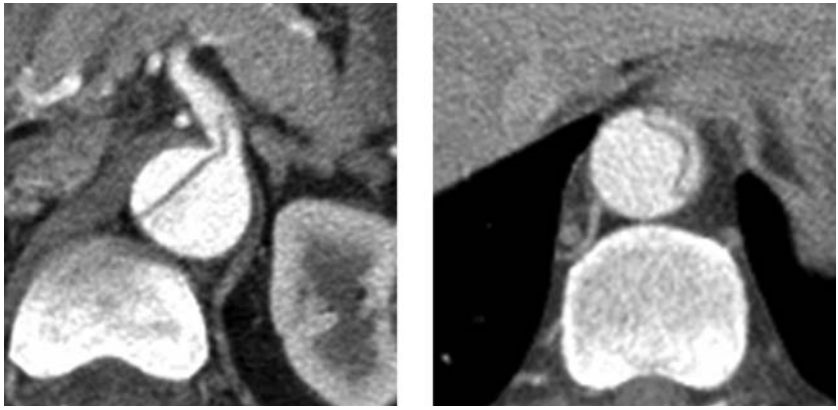


Figure 9 Imminent malperfusion syndrome in an initially stable patient emerging as complicated type B dissection with invagination of the dissecting lamella into celiac trunk (*left*) and true lumen collapse from systemic pressure in the false lumen (*right*).

("the deadly triad") should be taken into consideration for risk assessment and decision-making (40,41,74).

Complicated vs. Noncomplicated Dissection

Another clinically useful way to stratify is to differentiate between complicated and uncomplicated dissection, regardless of both the time elapsed since onset of dissection and proximity of the dissected segments of the aorta. Any proximal aortic dissection deserves an ultimate effort to save the life of the patient. An assessment of impending risk regardless of swift surgery is possible by use of the IRAD risk prediction model as illustrated in Figure 8. The clinical features listed in Figure 8 are associated with scoring points and add up to a risk prediction score that allows a realistic assessment of individual prognosis in proximal dissection (75). The modelled probability of death is closely reflected in the observed in-hospital mortality of proximal dissection cases.

Even more clinically applicable is the distinction between complicated and uncomplicated type B dissections. A recent analysis from the IRAD group identified variables in type B dissection associated with increased risk of in-hospital mortality that may help clinicians in risk stratification and decision-making (Table 5). Type B dissection is generally associated with a more favourable outcome (short- and mid-term) than type A lesions, but decision-making may be more complex due to an emerging variety of treatment options. In contrast to type A dissection, which requires surgical attention even in uncomplicated cases, medical management with antihypertensive and cardiac output suppressing drugs is currently the preferred strategy in uncomplicated type B dissection. Complicated type B lesions (contained rupture, malperfusion from compromised side branches, rapid enlargement) have traditionally required open surgical repair,

Table 5 Risk Prediction Model for Type B Dissection

Variable	OR	95% CI	*P*-value
Age ≥70 yrs	1.56	0.67–3.61	0.3
Male gender	0.96	0.39–2.36	0.92
Branch vessel involvement	2.92	1.21–6.99	0.02
Lack of chest/back pain	3.51	1.3–9.52	0.01
Hypotension/shock	23.8	10.31–54.94	<0.0001

Abbreviations: OR, odds ratio; CI, confidence interval.

but will most likely qualify for endovascular surgery in the near future (Fig. 9). Percutaneous interventional techniques are already being used successfully today for complicated type B scenarios (Fig. 10). Percutaneously performed interventions are likely to replace open surgical repair in complicated type B dissection (74).

The IRAD Classification (Combining Anatomic and Prognostic Information)

Neither of the established classifications utilizes the full diagnostic capabilities of modern tomographic imaging technology (74,76). With current computed tomography, magnetic resonance imaging, and transesophageal echocardiography technology, excellent pathoanatomic mapping of the dissecting process is readily available, allowing precise definition of entry sites and communications between the lumina. This modern imaging provides viable information never before integrated into individual risk assessment (73,74,77). IRAD, using current modern

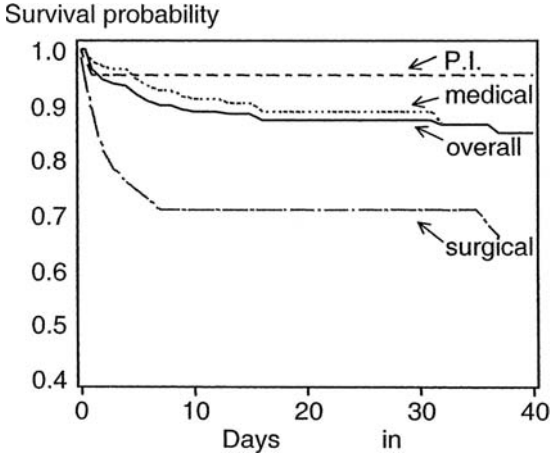


Figure 10 Survival curves due to acute type B aortic dissection for all patients and by management group based on Kaplan-Meier analysis of 40-day mortality. *Abbreviation*: PI, percutaneous intervention.

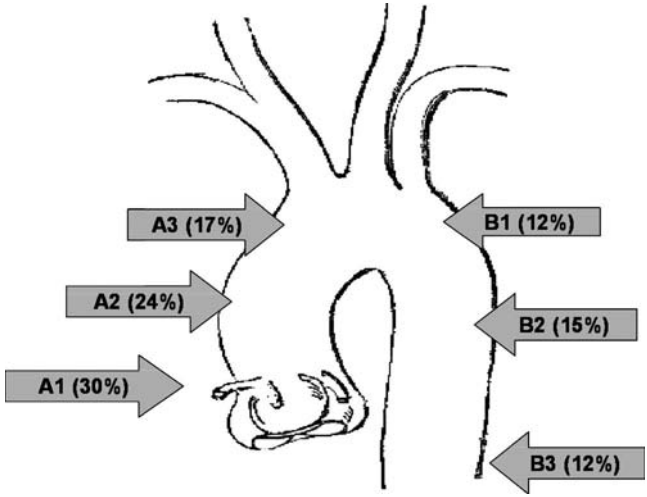


Figure 11 Graphical display of International Registry of Acute Aortic Dissection-code of entry site locations in relation to 30-day-mortality. The more proximal the entry site location the higher the in-hospital mortality in percent.

imaging technology, differentiates type A dissections, based on location of the most proximal entry site, into subgroups with distinct prognoses. Moreover, by defining dissection according to proximity to the aortic valve, we found a declining death rate with increasing distance between entry site and aortic valve. Not surprisingly, IRAD had previously identified shock and tamponade as significant predictors of death (40,74,75,78,79), supporting the concept of a correlation of entry site and prognosis (Fig. 11).

Through incorporation of diagnostic imaging information from modern technology, the IRAD classification system ideally connects anatomic detail with prognostic information. The knowledge of entry location, thus, may help to estimate the individual risk in proximal dissection better than either the Stanford or DeBakey classification. Prognosis in proximal dissection is diverse considering differences of 30-day-mortality related to entry location. Patients may be classified according to the IRAD-code as A1, A2, and A3. Type B dissection is prognostically the same, regardless of entry site, and the IRAD subclassification, B1 to B3, is useful only from a descriptive perspective.

Various mechanisms may explain the inverse relationship between the anatomic proximity of the entry site and the outcome in patients with acute dissection. First, the more proximal the origin of the dissected aortic layer, the more likely is a mechanical obstruction of coronary ostia, rupture within the pericardial sac (79), and/or new aortic regurgitation. Second, loss of elasticity in proximal aortic segments may predispose to aortic wall disintegrity preferentially adjacent to the sinuses of valsalva (80). Third, cyclic changes of aortic radius and distensibility (pressure strain elastic modulus) are most compromised at the level

of the predilated sinus junction, according to the law of Laplace (81). In addition, the proximal segment of the aortic wall is known to lose distensibility with hypertension or increasing age. In this context, aortic regurgitation and the fluid dynamics of a bicuspid aortic valve may relate to these pathophysiologic mechanisms.

CONCLUSION

With the historic evolution of different classifications of aortic dissection, various prognostic mechanisms and management strategies have eventually emerged. The medical community faces the responsibility to integrate the clinical complexity of the disorder, improving classification algorithms and eventually understanding aortic dissection better via improved classification.

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DISCUSSION AND COMMENTARY

Question for the Authors

In discussing classification by acuity of presentation, Dr. Nienaber mentions that some dissections are discovered incidentally at the time of imaging for other purposes. Does Dr. Nienaber have any hints for surmising the age of these dissections? How can we be sure that they are not acute? This question has medico-legal implications as well—for fear that one of these lesions, interpreted as incidental and non-acute—may rupture soon after detection.

It can indeed be difficult to determine whether an incidentally discovered dissection is acute or chronic. The absence of acute symptoms argues for chronicity. At times, the dissection flap appears thick and fibrotic, again arguing for chronicity. If in doubt, we admit the patient for 48 hours of observation, on the off-chance that an acute aortic dissection may have been "caught in the making" by the incidental radiographic imaging study.

Editor's Counterpoint

Utility of Stanford Classification

The Editor differs respectfully with the chapter authors (whom he respects immensely) with regards to the utility of the Stanford classification of aortic dissection (type A and type B). The editor has found this simple classification extremely useful clinically. This classification is simple, easily understood, easily communicated, and very meaningful in terms of clinical implications: type A—surgery, type B—"anti-impulse" therapy. Yes, there are nuances that are not fully accommodated by this simple schema, but they are uncommon and not of overwhelming clinical significance. The alternate, more complex classification schemas are useful for extreme experts, like the chapter author, and for research, but perhaps a bit too cumbersome for every day applications in the emergency department, the diagnostic imaging suite, and the clinical wards.

Categorization of Dissections with Arch Tear Propagating Distally

The author is pleased to learn that Dr. Nienaber, in his immense wisdom and experience, groups dissections starting in the aortic arch (around and between the head vessels) with the Type B category. This has been the Editor's policy at his own institution. We prefer to treat these dissections non-operatively, and they do well. We remain alert for proximal propagation, which would mandate surgery, but this does not eventuate frequently.

Dissection Variants—Penetrating Aortic Ulcer and Intramural Hematoma

We use a very simple schema for distinguishing between typical dissection, on the one hand, and the variant entities penetrating aortic ulcer (PAU) and intramural

hematoma (IMH). This is our schema: "No flap, no dissection." Please see Figure 1 in Chapter 12, which makes this point schematically.

We believe that PAU and IMH are not the same as typical dissection, and the simple distinguishing criterion encompassed in that one phrase has proved useful for us from an educational and communication standpoint.

We have a somewhat different approach to descending PAU and IMH than some centers, certainly vis-à-vis centers in Japan. We believe these are serious lesions that behave malignantly. Yes, we understand that descending PAU and IMH can be controlled medically and that patients can usually leave the hospital alive. However, we operate on these lesions at about three to four weeks, if the patient is not too old or frail. [PAU, especially, is a disease of old age (Fig. A)]. We changed our management—from non-operative to operative—when we accomplished medium-term follow-up on these patients (1). We found that (1) Many of the PAU/IMH patients died in only mid-term follow-up, of causes compatible with an aortic etiology, and (2) Many of the IMH and PAU went on to manifest as typical dissections. We feel that a non-operative policy permits fairly frequent death of these patients (1,2).

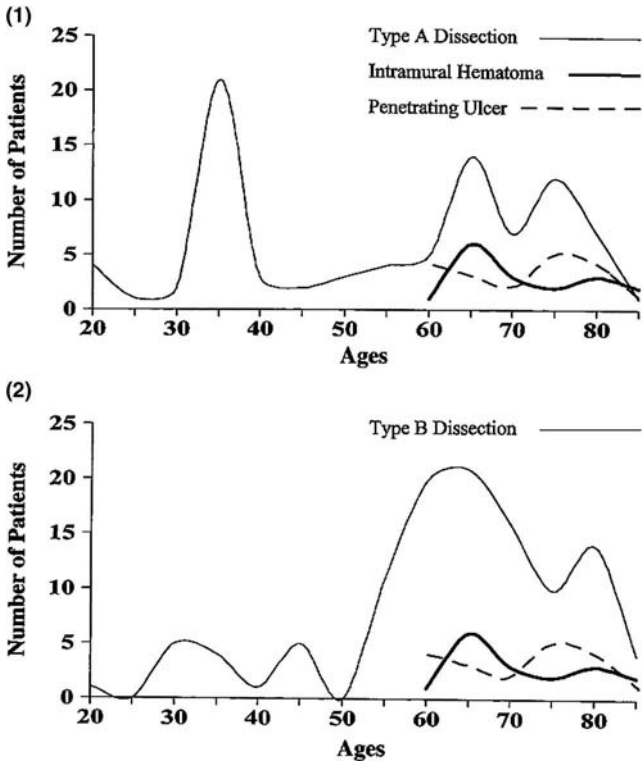

Figure A Note advanced age of IMH and, especially, PAU patients, compared to those with typical ascending (**1**) or descending (**2**) dissection. *Abbreviations*: IMH, intramural hematoma; PAU, penetrating aortic ulcer.

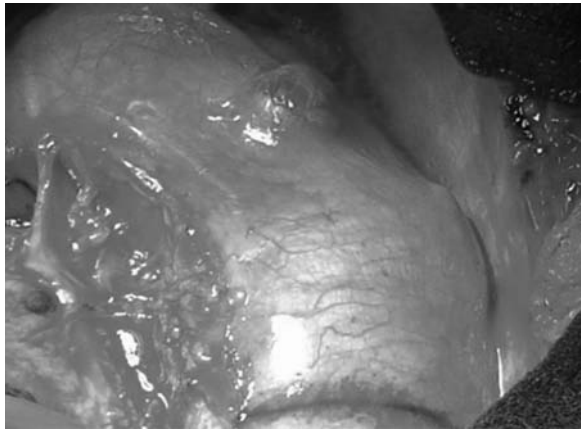

Figure B (*See color insert*) Note multiple penetrating aortic ulcers, although only one was suspected radiographically.

Furthermore, we find at surgery that the PAU patients, despite radiologic detection of a single penetrating ulcer, often harbor many such ulcers over a wide segment of aorta. In the operating room, these appear "ready to burst" (Fig. B). We feel this factor also argues in favor of an aggressive surgical approach.

For ascending IMH and PAU, we have an aggressive posture, like most centers. We operate on these lesions acutely, like for type A dissection.

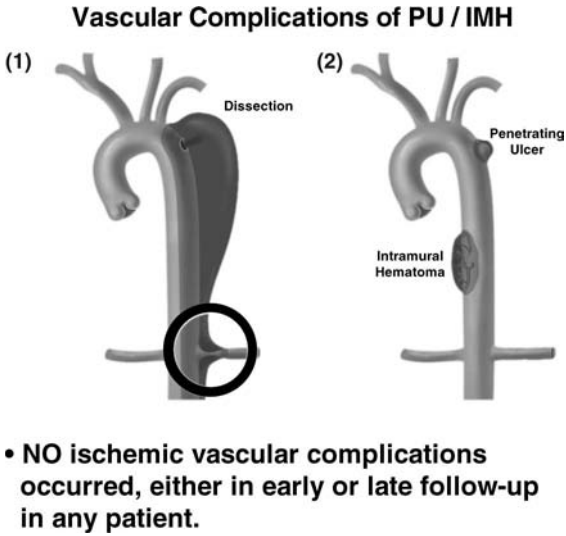

Figure C (*See color insert*) Note from schematic depictions that typical dissection (**1**) often impairs branch vessel flow, but this never happens with IMH and PAU (**2**). *Abbreviations*: IMH, intramural hematoma; PAU, penetrating aortic ulcer.

One good feature regarding IMH and PAU, on which Dr. Nienaber touches briefly, which we wish to emphasize, is the following: IMH and PAU, in sharp contradistinction to typical aortic dissection, never produce branch vessel occlusion (Fig. C). We have not encountered a single violation of this principle; colleagues from around the world have similar impressions.

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2

The Symptoms and Signs of Acute Aortic Dissection: Clinical Diagnosis of "The Great Masquerader"

Eric M. Isselbacher

Department of Medicine, Harvard Medical School and Thoracic Aortic Center, Massachusetts General Hospital, Boston, Massachusetts, U.S.A.

INTRODUCTION

There is a "classic" constellation of symptoms and signs of acute aortic dissection that is commonly taught in medical school. One classic example would be a 72 year-old man with a history of longstanding hypertension, who presents with the acute onset of severe stabbing, interscapular back pain; on arrival he is diaphoretic and restless, with a blood pressure of 195/110 mmHg. A second example would be a 35-year-old woman, who is tall and thin, presenting with the acute onset of severe tearing chest pain that radiates to her neck and then moves to her back as well; her blood pressure is 20 mmHg lower in the right arm than in the left, and on physical examination she has a loud decrescendo diastolic murmur at the left sternal border. Offered these clinical vignettes, most medical students would readily propose aortic dissection as the most likely diagnosis.

Indeed, if all of the patients with aortic dissection presented in such a "classic" fashion, aortic dissection could be easily distinguished from other acute syndromes and thus be more promptly diagnosed. Unfortunately, in reality, only a minority of patients with aortic dissection actually present with fully classic symptoms and signs; rather, the majority present with less typical symptoms and often few, if any, of the classic signs. Moreover, the mix of symptoms and signs are often quite varied, so that even experienced clinicians find diagnosing aortic dissection consistently challenging.

SYMPTOMS

Pain

Experience of Pain

One feature of aortic dissection present in almost all cases is pain. In the International Registry of Acute Aortic Dissection (IRAD), which initially reported on a series of 464 consecutive patients with acute aortic dissection from 12 international referral centers, 96% of those with dissection presented with pain (Table 1) (1). Three-quarters of patients will experience pain in the chest, either anterior, interscapular, or both, and sometimes the pain will extend to the neck as well. Half will experience back pain, and a third will experience abdominal pain. Sometimes patients will experience leg pain as well, although this symptom is sometimes transient.

Table 1 Symptoms of Aortic Dissection

Symptom	Comment
Experience of pain	Almost ubiquitous—96% of patients report pain
Location of pain	Anterior characterizes ascending dissection; posterior characterizes descending dissection
Severity of pain	"10 out of 10"
Onset of pain	Abrupt (distinguishes from MI)
Quality of pain	"Tearing" quality
Variability of pain	Classical patterns common, but not invariable; 4% of patients experience no pain
Waxing and waning of pain	Variability in severity of pain reflects physiological (decrease in aortic wall tension with rx of BP) and anatomic events (spontaneous re-entry).
Pleuritic component	Reflects pericardial and pleural inflammation
Cardiac ischemia	True anginal/infarction symptoms may occur from involvement of RCA
Abdominal pain	Vigilant search for intestinal ischemia essential (lethal phenomenon)
Renal ischemia	Usually asymptomatic, except in case of infarction
Leg pain	From involvement of iliac artery by dissection process
Paralysis of legs (paraplegia)	From spinal cord ischemia or peripheral nerve ischemia
Syncope	From either: Involvement of head vessels Tamponade Acute aortic insufficiency Vaso-vagal response to pain
Dyspnea	Acute aortic insufficiency poorly tolerated

Abbreviations: MI, myocardial infarction; RCA, right coronary artery; BP, blood pressure.

Location of Pain

Not surprisingly, the location of the pain often corresponds to the underlying segment of the dissected aorta; anterior chest or neck pain tends to be associated with dissection of the ascending thoracic aorta, whereas interscapular, lower back pain, or abdominal pain are typical of dissection of the descending thoracic aorta (2). The pain sometimes radiates or frankly migrates from one location to another, such as from the front of the chest to between the shoulder blades, or from the back to the abdomen.

Severity of Pain

The pain is usually severe and often the worst pain a patient has ever experienced; not uncommonly, the pain is rated as a 10 on a scale of 1 to 10. Indeed, the pain may be so severe and unrelenting that patients appear restless or writhe around the examination room or on the stretcher, and sometimes even drop to their knees when standing. This is in contrast to the chest pain associated with angina or acute myocardial infarction, which is rarely rated 10 out of 10.

Abrupt Onset of Pain

In addition, the pain of aortic dissection is typically abrupt in onset and described as at its most severe, right at the outset. In fact, given the abruptness of the onset, patients will often recount exactly what they were doing the moment the pain began. This abrupt pattern distinguishes the pain of aortic dissection from the pain of myocardial infarction or angina, which is typically mild at the outset and crescendos.

Tearing Quality of Pain

Classically, the quality of aortic dissection pain is described as "tearing" or "ripping." Indeed, according to the IRAD study, 51% of patients confirmed that these adjectives were fitting descriptors of their pain (1). However, whereas many will confirm these descriptors if asked, in reality, patients do not often offer these particular adjectives spontaneously. Instead, they are more likely to describe the pain as "sharp" or "stabbing," which are the adjectives used by 64% of patients in the IRAD population.

Variability of Pain

Once again, the qualities of the pain described in the previous section are typical, and not all patients with aortic dissection experience symptoms in the typical fashion. For example, in 15% of those with aortic dissection the pain is gradual in onset rather than abrupt, and in 10% the pain is not severe. A minority will describe the pain as tightness or pressure, which can be easily mistaken for anginal pain. Finally, 4% will present without any symptoms of pain at all.

Waxing and Waning of Pain

Most physicians assume that the pain of aortic dissection must be constant and unrelenting, and in some cases it is. However, in other instances the pain may wax

and wane in severity. Often, lowering a patient's blood pressure will reduce the intensity of the pain, probably by reducing mechanical tension on the torn aortic tissues. Sometimes patients will even become pain free spontaneously, particularly if there has been a spontaneous change in the anatomy of the aortic dissection (e.g., the occurrence of a new distal reentry site that decompresses a distended false lumen).

Pleuritic Component of Pain

Sometimes aortic dissection is accompanied by pleuritic pain, which may even become the dominant pain symptom at presentation. The etiology of the pleuritic pain is uncertain, but, based on the settings in which it occurs, there are likely two potential causes. When dissections involve the ascending thoracic aorta, a small volume of blood will sometimes leak into the pericardial sac, even in the absence of frank rupture. The presence of blood may induce pericardial inflammation, thereby producing symptoms typical of pericarditis, such as chest pain that is relieved by sitting up and exacerbated by deep inspiration. Interestingly, even though these pleuritic symptoms may be similar to pericarditis, rarely are they accompanied by an audible pericardial friction rub or electrocardiographic findings of pericarditis. On the other hand, dissections that involve the descending thoracic aorta often produce marked inflammation of the adventitial layer of the aorta, which may in turn result in an exudative left pleural effusion. During inspiration, as the left lung rubs across the surface of the inflamed descending aorta, patients may experience pleuritic pain. In this case, however, the pleuritic pain tends to be in the back rather than in the anterior chest.

True Cardiac Ischemia

In rare cases, a dissection flap in the ascending thoracic aorta may involve the coronary arteries, which may result in a secondary coronary occlusion and myocardial infarction. In IRAD, myocardial infarction was reported in 2% of the dissection population. The right coronary artery is affected much more often than the left main coronary artery, so inferior myocardial infarctions occur most often. Those affected may have pain from the myocardial infarction that sounds more typical of angina and therefore may obscure the other symptoms related to the primary aortic dissection, such as neck pain or back pain. Moreover, clinically, it may be difficult to distinguish this from a typical myocardial infarction due to plaque rupture, as the electrocardiographic findings are the same. A careful history and physical examination, looking for symptoms and signs more consistent with aortic dissection than an acute coronary syndrome, is essential, if one is to recognize that dissection is the primary diagnosis.

Abdominal Pain

Abdominal pain occurs in one-third of aortic dissection cases, usually together with chest pain or back pain, but occasionally without other pain. In most cases, the abdominal pain results from the dissection process itself, rather than from

compromise of organ perfusion. Indeed, with control of hypertension, abdominal pain often improves. On the other hand, abdominal pain may also arise as a consequence of mesenteric ischemia, which occurs in 5% of all aortic dissection cases. Compromise of branch artery perfusion occurs either from direct involvement of the branch arteries by the dissection flap, or by compression of the true aortic lumen by a distended false lumen. Patients will typically experience pain that is out of proportion to findings on physical examination of the abdomen. When persistent, mesenteric ischemia progresses to infarction, with patients developing bloody diarrhea and acidemia, usually followed by death. On the other hand, when mesenteric ischemia is less severe, patients may complain of postprandial abdominal pain (often referred to "abdominal angina") or perhaps only a feeling of anorexia (no interest in eating). Mesenteric ischemia is the leading cause of death among those with type B aortic dissection, so it is critical to remain vigilant for these symptoms, throughout the patient's hospital course.

Renal Ischemia

Aortic dissection can lead to compromise of flow to one or both kidneys in 5% to 8% of cases. Acute renal ischemia may result in oliguria and acute renal insufficiency, but it typically does not cause pain. Frank renal infarction, however, usually does cause a pain that is typically localized to the flank.

Leg Pain

Leg pain occurs in only a small minority of cases. Most often this is associated with a cold and pulseless extremity and is thus indicative of acute compromise of the ipsilateral common iliac artery. This can result from extension of the dissection process itself into the common iliac artery or, less often, from thromboembolism (the mechanism of which is not well understood).

Peripheral Neurologic Symptoms

Other peripheral symptoms of aortic dissection include acute unilateral lower extremity numbness and/or weakness. The symptom is often transient. The mechanism of the symptom is not entirely clear, but likely reflects an acute peripheral ischemic neuropathy. Compromise of the spinal arteries can produce spinal cord ischemia resulting in paraplegia, but thankfully, and inexplicably, this complication occurs in less than 1% of cases. In some cases, the paraplegia can be transient.

Other Symptoms

Syncope

Whereas pain is by far the most common symptom of aortic dissection, patients may present with other less common symptoms, as well. Patients can present with a variety of neurologic symptoms. Syncope occurs in 13% (3), and on occasion syncope occurs in the absence of pain. Among type A dissections the prevalence of syncope at presentation is 19%, versus only 3% among type B dissections (3).

The mechanisms are uncertain, but a number of possible causes include acute hemopericardium from a contained rupture, abrupt onset of severe aortic insufficiency, transient impairment of cerebral flow, and an acute vagal response from severe pain. Patients may also present with cerebrovascular accidents (6%) or transient ischemic attacks.

Dyspnea

Finally, when a type A aortic dissection results in acute moderate or severe aortic insufficiency, patients may present with the symptoms of pulmonary edema, such as dyspnea and orthopnea, as discussed later in this chapter.

SIGNS (TABLE 2)

Abnormal Blood Pressure

One half of patients with acute aortic dissection have significant hypertension (systolic blood pressure ≥ 150 mmHg) on presentation, making this the most common diagnostic sign (1). When present, the hypertension may be moderate or even severe, with systolic blood pressures in the range of 180–200 mmHg. The prevalence of hypertension differs significantly by dissection type: Among those with type B aortic dissection, hypertension is particularly prevalent, found in 70% on presentation, compared with only 36% among those with type A aortic dissection (1). Conversely, those with type A aortic dissection often present with hypotension rather than with hypertension. Indeed, among those with type A dissection, 12% present with hypotension (systolic blood pressure 81 to 99 mmHg), and another 13% present with shock (systolic blood pressure ≤ 80 mmHg), compared with only 2% and 2%, respectively, among those with type B aortic dissection. Thus, the presence of an abnormal blood pressure, either high or low, is a clue to

Table 2 Signs of Aortic Dissection

Sign	Comment
Hypertension (or hypotension)	Hypertension more common in descending dissection
	Hypotension may signify tamponade
Aortic insufficiency	AI murmur may hide
	Wide pulse pressure may be helpful sign
Pulse deficits	Most common in an arm: "pseudo-hypotension"
Fever	Intense inflammatory response to dissection
Local signs in mediastinum	Hoarseness (stretch of recurrent laryngeal nerve)
	Tracheal obstruction (by aorta)
	Hemoptysis (pulmonary rupture)
	Hematemesis (esophageal rupture)
	Continuous murmur (rupture into RA, RV, LA)

Abbreviations: AI, aortic insufficiency; LA, left atrium; RA, right atrium; RV, right ventricle.

the presence of aortic dissection. Nevertheless, the remaining 35% of aortic dissection patients present with a blood pressure in a normal range, so hemodynamic stability does not in any way rule out dissection.

Aortic Insufficiency

When the dissection involves the aortic root or ascending thoracic aorta, it often results in acute aortic insufficiency. Mild aortic insufficiency will often go unrecognized on cardiac auscultation, but when the aortic insufficiency is moderate or severe, a decrescendo diastolic murmur is usually audible. Of those in IRAD with type A aortic dissection, 44% had a murmur of aortic insufficiency detected on presentation (1). Interestingly, a murmur of aortic insufficiency is also detected in 12% of IRAD subjects with type B aortic dissection; however, such murmurs must be unrelated and incidental, as the lack of involvement of the ascending thoracic aorta precludes dissection as the cause of the aortic insufficiency in this group.

Detecting a decrescendo diastolic murmur in a patient not known to have the murmur or not known to have aortic insufficiency should lead one to assume that there is acute aortic insufficiency. The differential for acute, moderate, or severe aortic insufficiency is limited primarily to aortic dissection and aortic valve endocarditis, and clinically one should be able to distinguish readily these two diagnoses.

When acute aortic insufficiency results in acute pulmonary edema, patients may present with tachypnea, hypoxemia, low oxygen saturation, and tachycardia. Indeed, when the patient has rales from pulmonary edema and is working hard to breathe, the diastolic murmur of aortic insufficiency may be obscured, even though it is severe. Similarly, the murmur may be obscured by the sounds of a ventilator or even the loud ambient noise of an emergency department. Therefore, when present, a wide pulse pressure or hyperdynamic peripheral pulses may be the best clues to the presence of underlying severe aortic insufficiency. However, a wide pulse pressure is sometimes not evident in the acute setting.

Overall congestive heart failure occurs in approximately 6% of patients with acute aortic dissection. The large majority (80%) of dissection patients with congestive heart failure have a type A aortic dissection, as one would expect mechanistically. Nevertheless, the other 20% presenting with heart failure have only a type B aortic dissection, so the aortic valve is not compromised; in such patients the congestive heart failure is likely due to associated significant hypertension, precipitating acute diastolic dysfunction. Interestingly, compared with others with aortic dissection, those who present with congestive heart failure are more likely to describe their pain as only mild in severity (29% vs. 7%) and less likely to describe it as abrupt in onset (70% vs. 88%) (4).

Pulse Deficits

When aortic dissection compromises arterial flow to one of the extremities, a differential in blood pressure may occur, often referred to as a "pulse deficit." Pulse

deficits are most commonly detected in the arms, and since most type B aortic dissections arise just distal to the subclavian artery, they are less likely to compromise arterial flow to the arms. Not surprisingly, pulse deficits occur twice as often among those with type A aortic dissection than type B, at 30% versus 15%, respectively (5). It goes without saying that in order to detect a blood pressure differential, one must check blood pressure readings in both arms. However, quite often in emergency departments blood pressure readings are performed in one arm only. If one checks the blood pressure in only the arm that has a pulse deficit, one will obtain a falsely low blood pressure reading; this has often been referred to as "pseudohypotension," and it sometimes leads to incorrect diagnosis or therapy. In order to avoid being misled in this way, and in order to identify pulse deficits as valuable clinical clues, blood pressure readings should be taken in both arms in all patients presenting with chest pain syndromes.

In rare cases arterial supply to both arms is compromised, in which case comparing the blood pressure readings in the two arms will fail to reveal a difference, and yet both readings will be falsely low. One should suspect bilateral pseudohypotension if a patient appears to be well perfused despite low blood pressure readings in both arms. In such a case, one should check bilateral thigh blood pressure readings to detect evidence of a higher true arterial pressure.

Even when a subclavian artery is completely occluded, in most cases there is still adequate perfusion to the arm to prevent any overt arm symptoms or signs at rest. However, occlusion of one of the common iliac arteries will typically result in a cold and pulseless lower extremity, which is readily evident on physical examination.

It should also be noted that in some cases pulse deficits can be transient, as a result of acute decompression of the false lumen by distal reentry into the true lumen or movement of the intimal flap away from the occluded orifice.

Other Signs

Patients with aortic dissection may present with a fever, often accompanied by leukocytosis and an elevated erythrocyte sedimentation rate; the etiology of the fever is uncertain. Rarely, aortic dissection may produce hoarseness, upper airway obstruction, hemoptysis (due to rupture into the tracheobronchial tree), hematemesis (due to rupture into the esophagus), a pulsating neck mass, or a continuous murmur (due to rupture of the aorta into the right atrium, the right ventricle, or the left atrium).

THE GREAT MASQUERADER

Many more patients present with symptoms of chest, back, or abdominal pain than have aortic dissection, and there is significant overlap among the symptoms and signs of aortic dissection and other acute syndromes. Indeed, most patients with aortic dissection do not present in a "classic fashion," but rather with only a

handful of the known symptoms or signs. Nevertheless, although aortic dissection is uncommon, it is so life threatening that prompt diagnosis is essential if patients are to survive.

It is therefore critical that clinicians be vigilant and have a low threshold for adding aortic dissection to the differential diagnosis. Indeed, if one does not always at least consider the possibility of aortic dissection when even just one of the typical findings is present, one may miss the diagnosis. Moreover, when any combination of cardiac, neurologic, abdominal, or vascular abnormalities cannot be otherwise explained, one must consider aortic dissection as a possible unifying diagnosis, and have a low threshold to obtain an appropriate diagnostic imaging study. Indeed, as the great aortic surgeon Dr. Michael DeBakey once stated, "No physician can diagnose a condition he never thinks about."

EDITOR'S COMMENT

The editor wishes to emphasize the following clinical pearls from Dr. Isselbacher's chapter, which are consonant with the Editor's clinical experience as well.

- *Aortic dissection is "the Great Masquerader."*
- *Patient's often describe their pain as the most severe pain a human being can have.*
- *It is remarkable that patients describe the pain of dissection with anatomically precise descriptors such as "tearing" and "ripping."*
- *The abrupt onset of pain distinguishes dissection from myocardial infarction.*
- *Anterior chest pain suggests ascending dissection, and posterior interscapular pain suggests descending dissection.*
- *"No physician can diagnose a condition he never thinks about." (c/o Dr. Michael DeBakey)*
- *The inflammation that accompanies dissection can cause fever.*
- *One must consider aortic dissection in any patient with unexplained cardiac, neurologic, abdominal, or vascular symptoms and signs.*
- *One must remember to check blood pressure in both arms, to detect the "pulse deficit" of acute aortic dissection.*
- *Acute aortic insufficiency (in contradistinction to chronic aortic insufficiency) is very poorly tolerated, possibly leading to acute pulmonary edema or even cardiogenic shock in patients with acute ascending dissection.*

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3

Imaging of Aneurysms and Dissections: Chest X-Ray, Echo, Computed Tomography, Magnetic Resonance Imaging

Peter G. Danias

Department of Medicine, Tufts University Medical School, Boston, Massachusetts, U.S.A., and Cardiac MR Center, Hygeia Hospital, Maroussi, Athens, Greece

INTRODUCTION

Acute aortic pathology may not be a very common presentation of cardiovascular disease, but, if undetected, it carries a significant mortality (1). As symptoms are frequently vague, more than one-third of acute thoracic aortic dissection cases go undiagnosed, while in approximately one-quarter of cases the diagnosis is first established at the post mortem examination (2). Even when a timely diagnosis is made, optimal therapy may differ depending on the extent and characteristics of the underlying pathology. Thus appropriate management requires both a high clinical index of suspicion to make the diagnosis and a precise knowledge of the aortic anatomy to guide appropriate therapy. Aortic imaging is probably the most important tool that the clinician has in hand when evaluating patients with known or suspected aortic disease.

Imaging of the thoracic aorta has many objectives: The location and size of the aorta must be assessed. Knowledge of the anatomic relationships with other intrathoracic organs is of great importance, particularly for preoperative planning. Similarly, the origin of branch vessels (arch vessels, intercostals, and

spinal arteries) and the possible extension of the aortic pathology into these arteries need to be evaluated to guide appropriate therapy. In certain aortic diseases (e.g., dissections, aneurysms, etc.) the vessel wall may become thicker, as part of the lumen may be occupied by a dissection flap, thrombus, atherosclerotic plaque, or debris. Thus both the outer and inner (luminal) diameters of the aorta need to be measured, and the integrity and consistency of the vessel wall need to be examined. In cases of dissection, the possibility of early or concealed aortic rupture needs to be definitively ruled out. When vessel wall pathology is identified, characterization of the histologic structure is helpful for further management. Assessment of blood flow in the aorta provides clinically pertinent information in patients with aortic valve involvement related to the aortic pathology. The degree of the valvular pathology is usually related to the aortic disease itself, and may thus offer additional prognostic information. In patients with aortic dissection and false lumen formation, evaluation of blood flow in the true and false lumens is needed, particularly when branching vessels originate from the false aortic lumen. Finally, though rarely clinically used to establish the diagnosis of aortic disease, knowledge of the physiology of the aortic wall and its elastic properties may be a useful predictor of future outcome, or may serve as a surrogate marker of other cardiovascular disease.

Among the noninvasive imaging modalities used to assess thoracic aortic diseases, chest X-ray (CXR), transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), computed tomography (CT), magnetic resonance imaging (MRI), and magnetic resonance angiography (MRA) are the most commonly used. Invasive evaluation with conventional aortography carries a considerable risk of exacerbating pre-existing pathology. Particularly in patients with aortic dissection, manipulation of guidewires and catheters in the aorta may extend the dissection and even precipitate aortic rupture. Moreover, invasive aortography offers no advantages over modern noninvasive imaging techniques, as will become evident in the discussion that follows. Accordingly, diagnosis and follow-up of aortic disease relies on noninvasive imaging modalities.

CHEST X-RAY

CXR is a simple and easily accessible diagnostic procedure that may assist in the diagnosis of thoracic aortic disease. Though CXR rarely establishes conclusively the diagnosis of aortic disease, it can suggest acute or chronic aortic pathology and lead to subsequent testing for more definitive diagnosis and anatomic delineation. Other times CXR may be helpful in the initial assessment of patients and contribute to the differential diagnosis by ruling in or out certain common pulmonary or chest wall pathologies (e.g., pneumonia, rib fracture, etc.) whose symptoms may overlap with those of aortic diseases. In general, the radiographic findings of aortic disease on the plain chest films are not pathognomonic, and, thus, despite common use, the actual value of CXR for specific diagnosis of aortic pathology is limited.

Aortic aneurysms can be suspected on the CXR by broadening of the mediastinum in the anteroposterior view. In the lateral views the dilated aorta can

Table 1 Radiographic Findings Suggestive of/Consistent with Thoracic Aortic Dissection

Widened mediastinum (wide ascending aorta, wide aortic knob, wide descending aorta)
Blurred aortic knob
Wide paraspinal shadow
Pleural effusion (ipsilateral to the aorta)
Tracheal shift or distortion of the (left) main bronchus
Displaced intimal calcification

also be visualized, particularly if the vessel wall is calcified. The differential diagnosis of radiographic mediastinal widening also includes lymphadenopathy, hilar vascular engorgement, mediastinal masses, and congenital cardiac or vascular abnormalities. However, enlargement of the ascending, descending, and arch portions of the aorta provide specific contours with which the front-line evaluator must become familiar. An ascending aneurysm bulges just to the right of the mid-mediastinal contour. A descending aortic aneurysm produces a widened paravertebral stripe. An arch aneurysm produces an enlarged aortic knob.

Aortic dissection may be challenging to diagnose from plain chest radiography. Table 1 lists the most common radiographic findings suggestive of aortic dissection. Among these findings, displaced intimal calcification has been suggested as the most specific for aortic dissection, but only occurs in approximately 14% of patients. Widened mediastinum (Fig. 1) and abnormal aortic contour (Fig. 2)

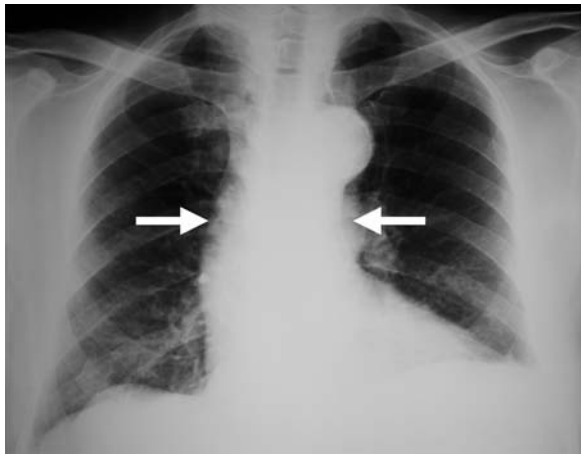

Figure 1 Anteroposterior chest X-ray of a patient with a type A dissection. There is mediastinal widening (*arrows*) consistent with the diagnosis. However, the diagnosis in this patient was delayed because the patient's presenting symptoms were rather atypical for aortic dissection, and the mediastinal widening was considered to be due to aortic ecstasia related to his advanced age. The diagnosis was established with chest computed tomography imaging several days later.

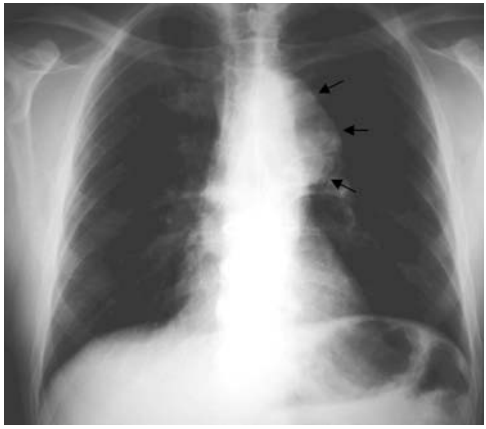

Figure 2 Anteroposterior CXR of a patient with post-traumatic pseudoaneurysm of the aorta, years after a motor-vehicle accident. There is distortion of the aortic knob, with protuberance of the aortic contour to the left.

occur in more than half of patients with dissection, but these findings are not pathognomonic. Typically, the mediastinum bulges to the right with dissection of the ascending thoracic aorta, and to the left with dissection of the descending aorta (3,4). At least 10% of patients with dissection have a normal CXR (1).

Therefore, the utility of CXR alone for confirmation or exclusion of thoracic aortic dissection is rather limited and may even delay appropriate diagnosis. Luker et al. (5) evaluated the effect of prospective chest radiographic diagnosis on the delay of definitive diagnosis of aortic dissection. The authors reviewed the records and CXRs of 75 patients who were subsequently proven to have aortic dissection. The original reports suggested that aortic dissection was likely or that additional imaging was necessary in only one-quarter of patients with dissection. In the retrospective review of the chest radiographs, only about one-half of patients had sufficient findings to suggest the diagnosis. Notably in five patients there was a delay to diagnose aortic dissection due to failure of CXR to prospectively suggest the diagnosis.

Other studies have also reported a low diagnostic yield of chest radiography for diagnosis of aortic dissection. Spittell et al. (2) reported an initial radiographic diagnosis of possible aortic dissection in only 9% of cases proven to have dissection. The most common finding in this series was aortic dilation (noted in over three-quarters of cases); however this is considered a nonspecific finding and frequently difficult to differentiate from the aortic ectasia encountered with aging and hypertension. In the study by Luker et al. (5), widening of the aortic contour was also seen in three-quarters of patients with dissection, but only in half of these cases was it felt to be sufficiently abnormal to suggest the diagnosis in the retrospective evaluation. In the International Registry of Acute Aortic Dissection,

widening of the mediastinum and abnormal aortic contour were noted in 60% and 50% of patients with aortic dissection, respectively (1).

Other authors have reported a higher sensitivity, specificity, and accuracy of CXR for assessment for aortic dissection. Jagannath et al. (4) evaluated the utility of CXR to differentiate aortic dissection from normal aortas in age-matched controls, and reported a sensitivity, specificity, and accuracy of 81% to 85%, but associated with a rather low interobserver agreement. These investigators noted that the radiologist's impression was a better predictor of the presence of dissection than any single radiographic finding alone. Hartnell et al. (6) also reported that plain radiographic evaluation had an accuracy of 81% in differentiating between aortic dissection and myocardial infarction. However, both these studies involved a focused comparison between aortic dissection and a specific other disease, condition, or patient population. Therefore, findings from these studies might not be applicable to patients first presenting with symptoms suggestive of aortic dissection, a population closer to that evaluated by Luker et al. (5).

ECHOCARDIOGRAPHY

Echocardiography relies on the reflection of ultrasound waves that are transmitted from an appropriate transducer to the organ of interest. The amplitude, phase, and time delay of the reflected echoes due to their relative distance from the imaging transducer, and differences in acoustic properties between adjacent structures are decoded to provide images in one dimension (M-mode) or 2-dimensions (2D-echo), thereby providing time-resolved anatomic information. More recently, 3D-echo has been developed by combining several 2D images that are acquired simultaneously or in rapid succession to cover an entire volume-of-interest. Taking advantage of the Doppler effect, blood flow can also be assessed and characterized as laminar or turbulent, while the direction of flow and blood flow velocity can be quantified. Depending on the mode of acquisition, the ultrasound Doppler beam may be pulsed or continuous, providing spatial flow information versus measurement of high velocity flows, respectively. If pulsed Doppler is color-coded and combined with the anatomic 2D information, color images are obtained and can easily demonstrate normal and abnormal intracardiac and intravascular flow patterns. With a combination of M-mode, 2D- and 3D-echo, Doppler, and color Doppler techniques, imaging of the anatomy and function of the cardiovascular system, including the thoracic aorta, may be obtained.

Due to limitations of acoustic penetration, TTE can usually visualize only a few segments of the aorta. The proximal ascending aorta can usually be examined using the parasternal (and occasionally the suprasternal) approach. The more distal ascending aorta can sometimes be visualized from the suprasternal window, which is also typically used to assess the aortic arch. The descending thoracic aorta is usually seen from the suprasternal, parasternal, and subcostal views.

However, due to the distance of the aorta from the anterior chest wall and the imaging transducer and intervening lung tissue, the TTE image quality is usually suboptimal, except for the proximal ascending aorta. Diagnostic images of extended segments of the aorta can only be obtained in slender subjects with good acoustic windows, while adequate imaging of the entire thoracic aorta becomes impossible in patients with emphysema or other lung disease, obesity, and chest wall abnormalities. Nevertheless, TTE frequently initiates the work-up of patients with aortic pathology by demonstrating some abnormal finding during evaluation for another indication.

Aortic aneurysms can be easily detected with TTE when the ascending aorta is involved (Fig. 3). Particularly in patients with Marfan's syndrome, their slender body habitus and usual confinement of aortic dilation to the sinuses of Valsalva and aortic root make TTE a valuable method for initial and subsequent evaluation.

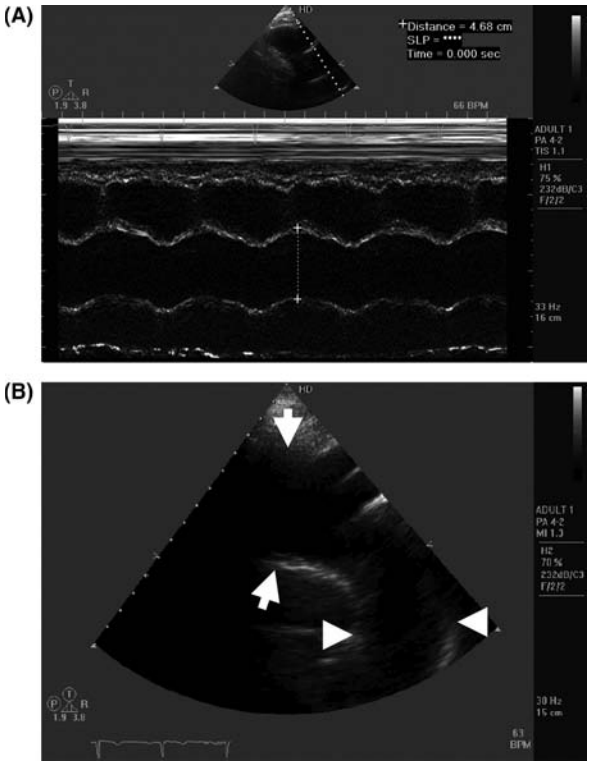

Figure 3 Transthoracic echocardiogram of a patient with dilated thoracic aorta. The M-mode echocardiogram from the parasternal long axis view (**A**) demonstrates dilation of the ascending aorta. The two-dimensional image of the arch from the suprasternal approach (**B**) demonstrates dilation of the aortic arch (*arrows*) and descending thoracic aorta (*arrowheads*).

TTE has significant added value in patients in whom the aortic pathology also involves the aortic valve. The degree of aortic regurgitation is a major determinant of the surgical planning, as degree of aortic insufficiency enters into the equation, in addition to the goal of preventing rupture and/or dissection. Aortic aneurysms and pseudoaneurysms in more distal segments of the aorta may be harder to diagnose, due to limited visibility. Even when the diagnosis can be made by TTE, additional imaging is usually required to define the exact aortic anatomy, to obtain a more precise diameter measurement, and to visualize adequately the length of the abnormality.

For the reasons described, mainly the incomplete vessel visualization and large distance from the transducer, TTE is not highly accurate for diagnosis of thoracic aortic dissection. Sensitivity of TTE for detection of aortic dissection is best in the ascending aorta, with reported values 78% to 100% and corresponding specificities 87% to 96%. Accuracy is substantially lower in cases with type B dissections, with much lower sensitivities (7–9). Even when detected, TTE is rarely able to fully describe the length of the dissection, and to clarify the entry and exit points. The proposed echocardiographic criteria for diagnosis of aortic dissection are listed in Table 2. These criteria are applicable for both TTE and TEE.

Specificity of TTE for detection of acute aortic dissection is better than the corresponding sensitivity but also suboptimal (7–9). False positive findings are frequently the result of echo reverberations, occurring usually when the ultrasound beam is directed perpendicularly to an interface of tissues with greatly different acoustic impedance (10). Therefore, a positive TTE study may not automatically establish the diagnosis, and confirmation may be sought with a more definitive imaging modality. Similarly, when there is a strong clinical suspicion for dissection, failure of echocardiography to detect the abnormality should not be interpreted as absence of the disease. Instead, additional imaging should be obtained, so that the entire aorta can be adequately imaged.

TTE can be particularly helpful in assessing patients with acute aortic dissection when the dissection involves the aortic valve with subsequent aortic regurgitation. This may occur in as many as 50% of patients with ascending aortic dissection (11). In cases where hemopericardium develops from rupture of the aorta into the pericardial sac, TTE can demonstrate the pathology, although the acuity of this condition rarely allows for elective or very detailed assessment.

Table 2 Proposed Echocardiographic Criteria for Aortic Dissection

Aortic root dilation (type A dissections)
Widening of the aortic wall
Identification of the dissection flap
Detection of two separate flows in the aorta (true and false lumens)
Visualization of complications of dissection (aortic regurgitation, left pleural effusion, and hemopericardium)

TEE is highly sensitive for detection of acute aortic pathology. Compared to TTE, TEE has the advantage of unobscured images, courtesy of the immediate proximity of the esophagus to the heart and the aorta. The descending thoracic aorta lies immediately behind the esophagus and therefore the entire descending aorta can be visualized in transverse, longitudinal, and oblique planes from the upper and lower esophagus. Imaging of the ascending aorta can be obtained from the upper esophagus, along with a thorough evaluation of the aortic valve. Finally, as the probe is pulled further back, a good view of the aortic arch and the takeoff of the large arch vessels can be obtained.

Aortic aneurysms can be thoroughly imaged and precise measurements can be obtained in all directions. The thickness and texture of the aortic wall can also provide information regarding the underlying pathology. For example, in patients with atherosclerotic aneurysms, the presence of calcium, plaque, and intramural thrombus can be easily detected. Regarding assessment of aortic dissection, the sensitivity of TEE is much higher than TTE, and almost the entire thoracic aorta can be adequately imaged. The same diagnostic criteria as those previously described for TTE (Table 2) are used for detection of aortic dissection. The typical diagnostic finding is the identification of the intimal flap inside the aortic lumen (Fig. 4). Blood flow is usually slower in the false lumen compared to the true lumen, and thrombosis of the false lumen is not uncommon. The lumen diameter may be increased in patients with dissecting aneurysm and, in cases with aortic valve involvement, aortic insufficiency can be clearly visualized. TEE can usually identify the entry and exit points (12) but identification of multiple entry and exit sites may be challenging. Compared to TTE, TEE has enhanced sensitivity due to improved visualization. However, the incremental increase in specificity is not similar.

Reverberation and linear artifacts are a common source of erroneous interpretation in TEE (13). These artifacts in the ascending aorta occur in as many as one-quarter of patients. Linear artifacts are less common in the descending thoracic aorta and account for <10% of cases (14). Vignon et al. (14) evaluated retrospectively 351 patients at high risk for aortic dissection or traumatic rupture, all of whom underwent TEE, to quantify the occurrence of linear artifacts and to formulate criteria for their correct categorization. Subsequently, the authors applied these criteria prospectively to a cohort of 121 consecutive patients, demonstrating an increase in the specificity of TEE for detection of aortic dissection. The criteria used to identify artifacts were: displacement of the line in a pattern parallel to the aortic wall, and superimposition of blood flow and similar blood flow velocities in both sides of the line within the aorta (i.e., blood flow does not "respect" the reverberation line). The presence of an anomalous inferior vena cava may also be misinterpreted as an aortic dissection. Extensive, chronic, and complicated dissections may be misinterpreted for other aortic pathology.

A major advantage of both TTE and TEE is that both tests can be performed quickly at the bedside or en route to the operating room, even in hemodynamically unstable patients. It is important that appropriate sedation be used for TEE in patients with suspected aortic aneurysm and/or dissection, to avoid an abrupt

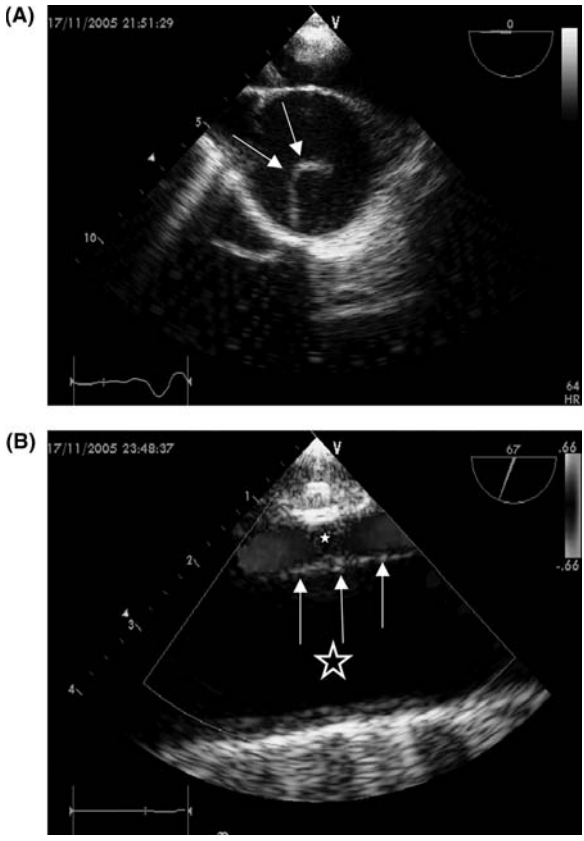

Figure 4 Transesophageal echocardiogram of the descending thoracic aorta of a young patient with Marfan's syndrome. The dissection flap is clearly identified within the aortic lumen (*arrows,* panels **A** and **B**), establishing the diagnosis. Mapping demonstrates different flow velocities in the smaller true lumen (*small star,* panel **B**) and the larger false lumen (*large open star,* panel **B**). *Source*: Courtesy of Drs. Kiaffas and Kirvasilis, Onasseio Cardiac Surgery Center, Athens, Greece.

increase in blood pressure that may worsen a dissection or precipitate rupture. Moreover, because of the semi-invasive nature of TEE, this is usually not the best alternative for pathology that requires sequential follow-up evaluations, for example, in patients with aortic aneurysms for whom repeat imaging is warranted to determine the optimal timing for surgical correction.

COMPUTED TOMOGRAPHY

Even at early stages of development, CT proved to have great value for assessment of aortic disease. As CT evolved from conventional to helical to multislice, with evergrowing number of radiation detectors, the examinations became considerably

faster, with higher resolution and fewer artifacts, and thus more accurate and user-friendly. With modern scanners the entire thoracic aortic volume can be imaged with submillimeter in-plane resolution within the timespan of a single breath-hold of a few seconds' duration.

The inherently high resolution of CT, combined with the fact that images are obtained in the transverse orientation while the aorta is positioned vertically in the body, make cross-sectional evaluation of the vessel possible with high degrees of accuracy. The very high time-efficiency of CT is another major advantage, allowing for even the sickest patients to be imaged quickly, without compromise of their medical status. Moreover, the relatively low cost of CT and its widespread applications in all other areas of diagnostic imaging, along with the simplicity of image acquisition, have made CT one of the most easily available tests in virtually every medical facility. Accordingly, CT is the most frequently used initial test for patients suspected to have acute aortic pathology (15).

CT is not free of drawbacks. The examination involves exposure to ionizing radiation, making it a suboptimal test for younger patients and, particularly, women of reproductive age. There is a considerable radiation exposure from a single chest CT (16), which is even higher for the newer multi-detector CT ECG-gated cardiac studies (17). More importantly, the organ-specific absorbed dose for the breast is rather high, potentially increasing the risk for malignancies in the subsequent years of life. The issue of radiation exposure becomes pertinent for patients who need to have frequent repeat evaluations (e.g., those with aneurysms), as there is an additive effect of ionizing radiation on biologic tissues. Another limitation of CT is the use of contrast media, which are usually necessary for assessment of suspected aortic pathology. Although imaging of aortic aneurysms may be performed without contrast enhancement, imaging for suspected aortic dissection requires administration of intravenous iodinated contrast. X-ray contrast media are potentially nephrotoxic, particularly in diabetics, hypertensives, and patients with pre-existing renal disease. These subgroups are also the ones more likely to develop aortic pathology and to be referred for CT imaging. Thus, the risk to develop contrast-induced renal complications in patients with suspected acute aortic pathology is not negligible.

Aortic aneurysms can be readily diagnosed with CT imaging. The dimensions of all segments of the vessel can be accurately measured in the transverse orientation, and this has become the standard of quantification of aortic diameter (Fig. 5). Following contrast administration, a 3D representation of the aorta can be created, and the cross-sectional area perpendicular to the vessel can be obtained through post-processing. CT can also identify mural thrombus by demonstrating differential attenuation within the aortic lumen. When using a standardized protocol, the reproducibility of thoracic aortic diameter measurements has been shown to be high (18), allowing for reliable sequential examinations.

Typical CT findings in patients with aortic dissection are listed in Table 3. Identification of the intimal flap in the contrast-enhanced scan is diagnostic for aortic dissection (Fig. 6). The findings from nonenhanced scans are usually

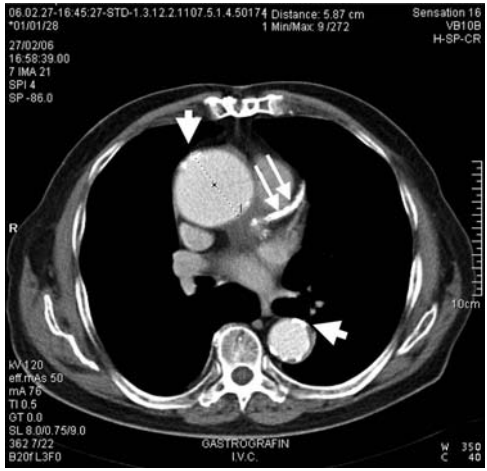

Figure 5 Contrast enhanced computed tomography (CT) in a patient with aneurysm of the ascending thoracic aorta. The patient was previously operated on for aortic dissection, and developed the aneurysm several years after the initial operation. The ascending aorta diameter is 59 mm. There are calcifications on both the ascending and descending thoracic aortic wall (*thick white arrows*). The left anterior descending coronary artery is also heavily calcified (*thin white arrows*).

suggestive but not diagnostic, and can be used when the intimal flap is not visible. The displacement of intimal calcification (Fig. 7) may be difficult to discern in small dissections and in patients with highly tortuous aortas. A thrombosed false lumen usually presents as hyperattenuating region of the vessel wall. Similar imaging characteristics are found in cases of periaortic hematomas, the difference being that the hyperenhanced region is now outside the vessel wall.

In aortic dissections, CT can usually identify the true and false lumens. The true lumen is usually smaller and, because blood flow velocity is higher than in the false lumen, there is differential attenuation in the contrast-enhanced scan (Fig. 8). On cross-sectional imaging, the dissection flap and the outer vessel wall of the false lumen form an acute angle, giving the impression of a bird's beak (the so-called "beak sign") (19). Cobwebs (thin filamentous fibrous strands) are also frequently seen in the

Table 3 Computed Tomography Findings in Aortic Dissection

Nonenhanced scans
Displacement of intimal calcification from the vessel wall
Thrombosed false lumen (differential attenuation)
Periaortic hematoma
Distortion of aortic contour
Enhanced scans
Intimal flap

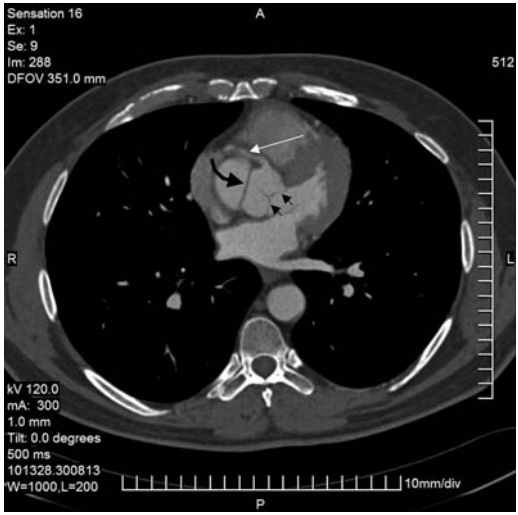

Figure 6 Transverse slice from a contrast-enhanced CT scan at the base of the heart in a patient with type A dissection. The right and noncoronary cusps of the aortic valve are visualized (*black straight arrows*). The dissection flap (*curved black arrow*) is visualized just above the aortic valve, but does not involve the origin of the right coronary artery (*white arrow*). *Abbreviation*: CT, computed tomography.

contrast-filled false lumen. LePage et al. (20) evaluated the clinical utility of indicators of true and false lumen in 51 patients with aortic dissection. The two most reliable signs to identify the false lumen were the "beak sign" and the larger area.

CT can define the entry point in the majority of cases with confirmed aortic dissection. In a study of 57 patients with aortic dissection or intramural

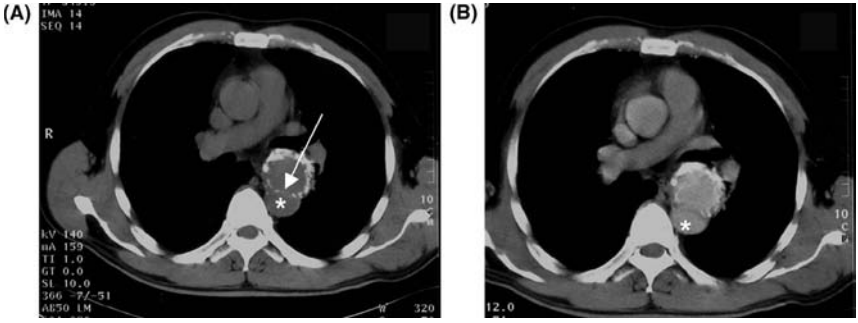

Figure 7 Non-enhanced (**A**) and contrast-enhanced (**B**) CT of a patient with post-traumatic pseudoaneurysm of the aorta, years after a motor-vehicle accident (the patient's CXR is shown in Fig. 2). The nonenhanced scan demonstrates intraluminal calcification (*arrow*). The contrast-enhanced scan demonstrates homogenous signal enhancement in both the aortic lumen and pseudoaneurysm (∗). *Abbreviations*: CT, computed tomography; CXR, chest X-ray.

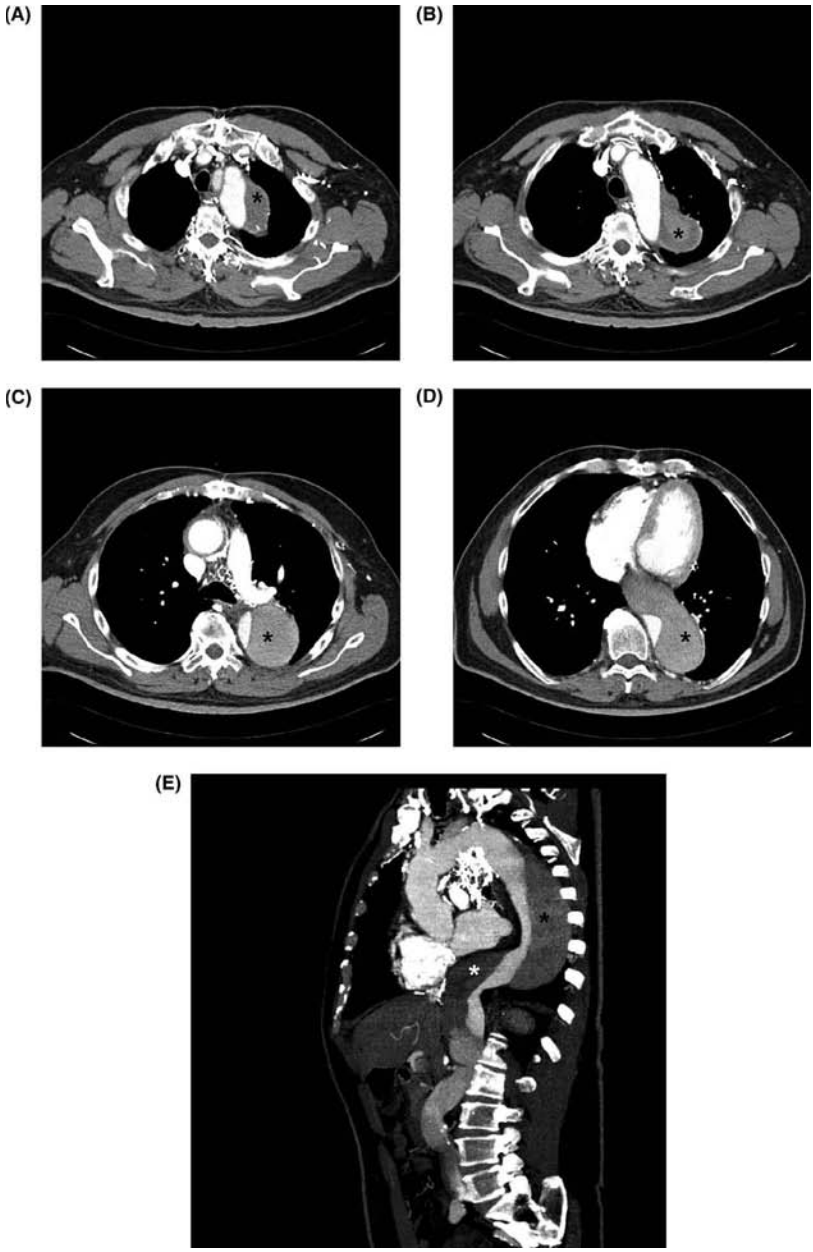

Figure 8 Extensive type B aortic dissection extending from the distal aortic arch to the abdominal aorta. The transverse images of the contrast-enhanced CT at various levels (**A**–**D**) clearly demonstrate the thrombosed false aortic lumen (∗) as an area of lower signal intensity. The 3-dimensional reconstruction at an oblique saggital plane (**E**) provides an easier appreciation of the extent of the dissection.

hematoma, CT was reported to identify the entry point with a sensitivity of 82%, specificity of 100%, and overall accuracy of 84% against surgical findings (21). In certain cases, however, and particularly in those where the dissection involves the aortic root, CT may not adequately visualize the entry point. CT is very good to image hemopericardium if the dissection extends into the pericardial sac, but may fail to demonstrate involvement of the aortic valve and resulting aortic regurgitation.

A variety of pitfalls have been described with CT imaging of aortic dissection that may be responsible for false positive interpretations and corresponding lower specificity. These pitfalls were attributable to technical factors (e.g., improper timing of contrast material administration relative to image acquisition); streak artifacts generated by high-attenuation material, high-contrast interfaces, or cardiac motion; periaortic structures (e.g., aortic arch branches, mediastinal veins, pericardial recess, thymus, atelectasis, pleural thickening, or effusion adjacent to the aorta); aortic wall motion and normal aortic sinuses; aortic variations such as congenital ductus diverticulum and acquired aortic aneurysm with thrombus; and penetrating atherosclerotic ulcer (22). It is thus important for the radiologist to be very familiar both with normal intrathoracic anatomy and these potential pitfalls, to minimize false positive interpretations.

ANEURYSMS AND DISSECTIONS: ROLE OF MAGNETIC RESONANCE IMAGING

MRI offers unique advantages for imaging of the aorta (Table 4). Importantly, MRI is entirely noninvasive, has no associated ionizing radiation exposure, and can be performed without use of potentially nephrotoxic contrast media. Comorbidities, such as hypertension and diabetes, are more common in patients with aortic pathology, and in these patients, the potential avoidance of nephrotoxic agents is of paramount importance.

Despite its several advantages, MRI is subject to a number of shortcomings. Patients with claustrophobia (approximately 5% of the general population) are not

Table 4 Advantages of Magnetic Resonance Imaging for Imaging of the Aorta

Noninvasive
No exposure to ionizing radiation
Three-dimensional
Unrestricted image orientation
Large field-of-view
High contrast resolution (tissue contrast)
High spatial resolution
No need for iodinated or potentially nephrotoxic contrast
Ability to evaluate multiple aspects of cardiovascular structure and function

good candidates for MRI and may require sedation. Patients with pacemakers, automatic implantable defibrillators, and many metallic implants are also not MRI candidates. Finally, MRI is not suitable for restless or hemodynamically unstable patients because data for MRI are acquired over relatively long time periods, and physical communication with the patient is hindered during the examination. Although there are no conclusive data that patients with acute aortic syndromes who undergo MRI have increased morbidity or mortality rates, the longer examination time of MRI compared with competing technologies (e.g., CT or TEE) has to be factored into the decision, regarding the diagnostic evaluation of such patients.

MRI offers extremely high (submillimeter) in-plane resolution and has inherently high contrast resolution. Accordingly, adjacent tissues can be imaged as having a big difference in signal intensity, depending on their magnetic properties and the technical characteristics of the imaging sequence. Although the physics underlying various image acquisition techniques is beyond the scope of this review, the selection of the optimal diagnostic protocol and image interpretation requires a good knowledge of the advantages and limitations of each approach.

With black-blood MRI techniques, the normally flowing blood appears black. These techniques are typically used to assess anatomy and also have value for tissue characterization. The components of the atherosclerotic plaque can be separated based on their appearance in T1-, T2-, and proton-density weighted images, and on differential enhancement following administration of paramagnetic contrast media (such as gadolinium chelates). With black blood images, precise measurements of the aortic lumen diameter and wall thickness can be readily obtained (Fig. 9). Thus, black blood images are clinically used to assess aortic aneurysm size and to evaluate whether there is mural thrombus lining the vessel wall. In patients with aortic dissection, the intimal flap can be readily identified, thus establishing the diagnosis. Because of the relative ease of identification, even in early studies, conventional black blood techniques were shown to have very high sensitivity for acute aortic dissection (9). However, image quality can be adversely affected by several factors. Motion artifacts may occur from excessive respiratory and whole body bulk displacement. Blood pool signal suppression may be incomplete, making vessel border definition difficult, particularly in areas of decreased blood flow (for example inside an aneurysm or at the false lumen of an aortic dissection). The differential blood signal suppression inside the true and false lumens may be helpful to identify the pathology (Figs. 10 and 11).

With white blood MRI techniques, the normally flowing blood appears white. As image acquisition is rapid (20–30 ms), these techniques are typically obtained for acquisition of cine images with a high temporal resolution. Early sequences for white-blood imaging (fast gradient-echo sequences) relied on the inflow of blood to the slice of interest. Newer image acquisition schemes (steady-state free-precession sequences) rely more on the difference of magnetic properties between the blood and surrounding tissues (a combination of T1 and T2 weighing), allowing for excellent border definition even with slower flow rates. Besides obtaining anatomic measurements, bright blood images can also be used

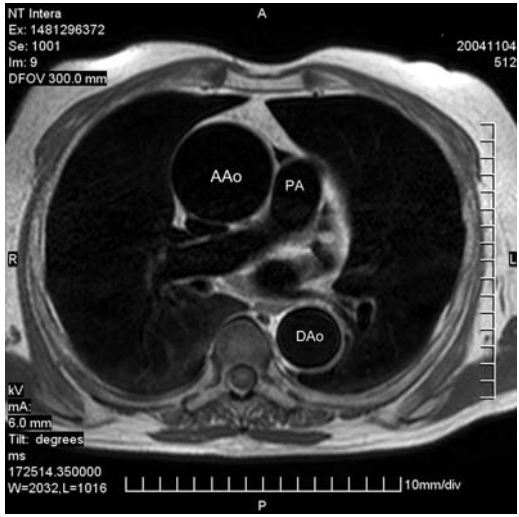

Figure 9 Transverse black blood MR image at the bifurcation of the pulmonary artery (PA) in a patient with aneurysm of the ascending aorta (AAo), with a 60 mm vessel diameter. There is excellent contrast between the vessel wall and blood pool in the AAo, PA and descending thoracic aorta (DAo).

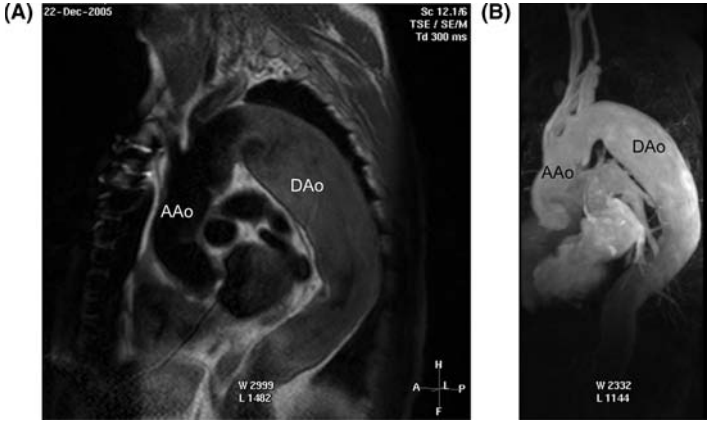

Figure 10 Black blood oblique sagittal image including the entire thoracic aorta (**A**) and similar view from the 3-dimensional maximal intensity projection reconstruction from the gadolinium (Gd)-enhanced aortic MRA (**B**), in a patient with aortic aneurysm following surgical replacement of the ascending aorta (AAo) with a gortex graft. The descending thoracic aorta (DAo) is aneurysmal. In the black blood image (**A**) signal suppression is good in the AAo because of rapid blood flow, while in the DAo blood signal suppression is not adequate due to slower flow. This may not be appreciated with the Gd-enhanced aortic MRA (**B**).

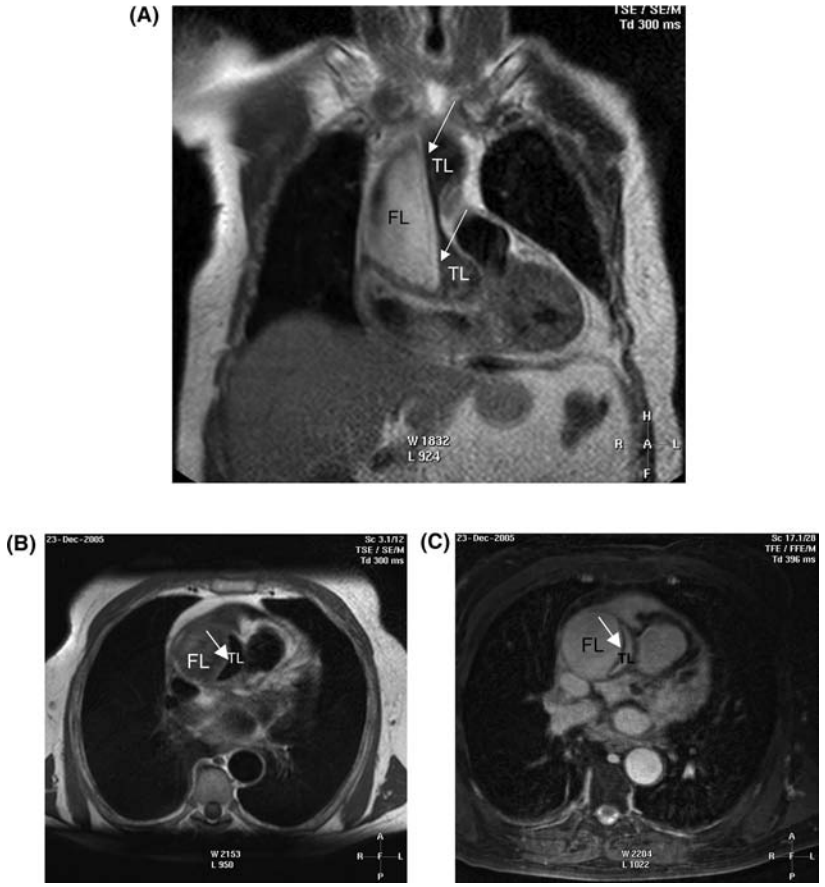

Figure 11 MR images of a patient with type A dissecting aneurysm (DeBakey type II). The coronal black blood image (**A**) demonstrates the dissecting flap (*arrow*) extending straight up from the aortic root to the arch. The dissection flap (*arrow*) is also easily identified in transverse black blood (**B**) and white blood (**C**) images. The smaller true lumen (TL) has good blood suppression due to faster blood flow (**A,B**), while the larger false lumen (FL) is easily identified as having slower blood flow (**A,B**). With high resolution white blood imaging (**C**) the difference in flow velocity between true and false lumens is not apparent.

to assess the change of the aortic diameter during the cardiac cycle. Changes in cross-sectional area throughout the cardiac cycle, combined with measurement of the systemic aortic blood pressure, can be used for evaluation of the elastic properties of the aorta, a marker of atherosclerosis and coronary artery disease.

With MRI, the blood flow in the aorta and other large vessels can be accurately measured using phase contrast techniques. These techniques have clear value in cases in which the aortic pathology (aneurysm or dissection) also involves the aortic valve, causing valvular insufficiency. Quantitation of the degree

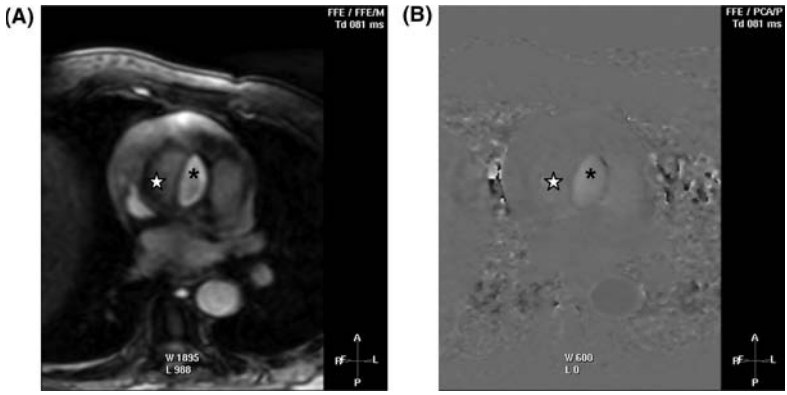

Figure 12 Single phase-contrast MR image at the base of the heart, perpendicular to the aortic root. Both the magnitude (**A**) and phase (**B**) images clearly demonstrate the difference in blood flow in the true (∗) and false (☆) lumens of the ascending aorta. Aortic blood flow can be quantified from the phase image.

of valvular regurgitation is particularly important when surgical correction is contemplated and may determine the type of operation that will be performed (valve sparing surgery vs. valve replacement with or without aortic graft). Moreover, in cases of aortic dissection with true and false lumen formation, the demonstration of different flow rates in the two parts of the lumen can help establish the diagnosis and identify the false lumen as the one having the slower flow (Fig. 12).

MRA with intravenous contrast media is yet another technique to visualize the aorta in its entire length and assess for aortic pathology. Paramagnetic contrast media (such as gadolinium chelates) dramatically change the magnetic properties (decrease the T1). MRA images are typically obtained as the bolus of contrast goes through the aorta during the first pass. Therefore, all the contrast is in the intravascular compartment during image acquisition, yielding a very high target-to-background signal ratio. Even small abnormalities, such as atherosclerotic aortic wall ulcerations, can be easily detected (Fig. 13). The source images from MRA can be used to create 3D reconstructions, as previously described for CT angiography. Although the 3D images do not convey additional information, compared to source images, visualization of the 3D structure makes the understanding and appreciation of pathology easier.

A typical MRI examination of the aorta includes a combination of the techniques described previously to fully delineate aortic pathology. For example, in cases of aortic aneurysms, black blood techniques are used to assess the length of the aneurysm and the luminal diameter, and to image the anatomic relationships with surrounding structures. Bright blood and phase contrast sequences may also be helpful, particularly if the black blood images suffer artifacts from incomplete blood signal suppression, motion, or other factors. Gadolinium (Gd)-enhanced MRA can also describe the aneurysm and provide the source images for

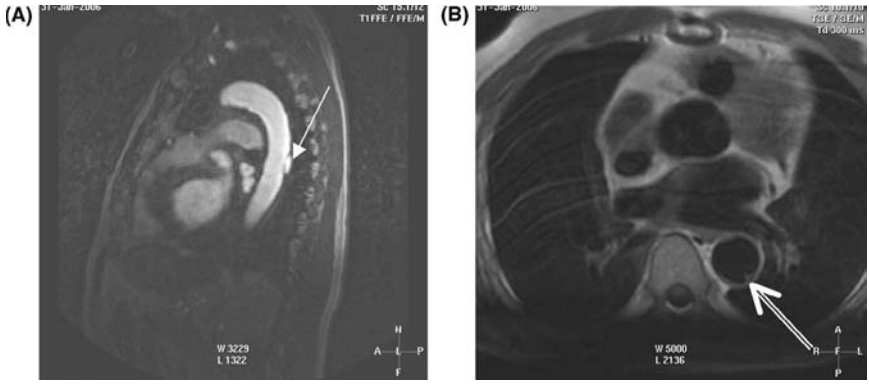

Figure 13 Aortic ulcer of the descending thoracic aorta, best visualized in the Gd-enhanced MRA (**A**) (*arrow*). The ulcer is depicted as a discontinuity of the aortic contour and resembles a limited dissection. Cross-sectional black blood image at the same level (**B**) demonstrates the ulcerated atherosclerotic plaque that is responsible for the angiographic appearance (*open arrow*).

three-dimensional reconstructions. Evaluation of pseudoaneurysms (the etiology of which is usually post-traumatic or postsurgical) is very similar to that described for true aneurysms (Fig. 14).

MRI and MRA offer significant advantages for imaging of acute and chronic aortic dissections. The typical characteristic—including the dissection flap, true and false lumen, aortic dilation, and complications such as hemopericardium, pleural effusion, and rupture—can all be assessed with a combination of white blood and black blood techniques. In potentially unstable patients, the examination should be

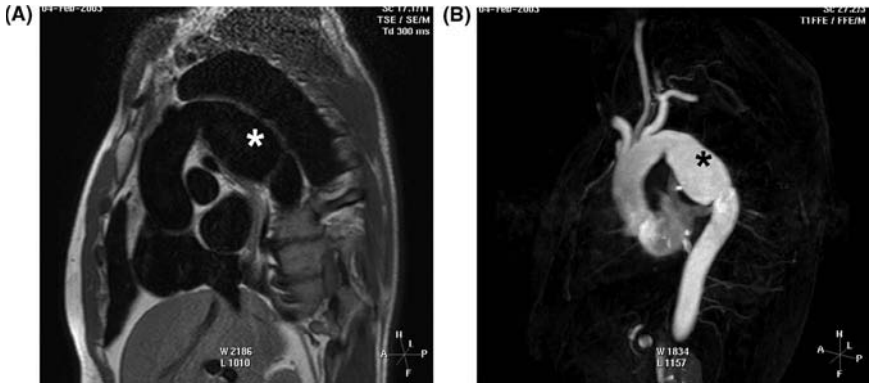

Figure 14 Black blood oblique sagittal image of the thoracic aorta (**A**) and similar view from the 3-dimensional maximal intensity projection reconstruction from the Gd-enhanced aortic MRA (**B**), of a patient with post-traumatic pseudoaneurysm of the aorta, years after a motor-vehicle accident (the patient's CXR is shown in Fig. 2, CT is shown in Fig. 8).

restricted to the absolute minimum necessary to establish the diagnosis and provide answers to questions that may modify treatment and prognosis (e.g., aortic valve involvement, dissection entry and exit points, etc.) MRI is the most appropriate test for patients who require frequent repeat imaging—for example, patients with aneurysms or chronic aortic dissection—because it is noninvasive, it has no ionizing radiation, and it provides anatomic detail of the abnormality and its extent.

COMPARISON BETWEEN TECHNOLOGIES AND CLINICAL IMPLICATIONS

CXR and TTE are very commonly obtained tests that may provide clues regarding the presence of acute or chronic aortic pathology. However, the sensitivity and specificity of both these imaging modalities are too low to reliably establish a diagnosis or reliably exclude aortic pathology. Additional testing should usually be performed when either CXR or TTE are suggestive of aortic pathology. Similarly, when there is high clinical suspicion, additional imaging should be obtained even if CXR and TTE are negative. In patients with high clinical likelihood of acute aortic dissection, it may be prudent to proceed directly to more definitive imaging tests, as the initial CXR and TTE may introduce undue delays without significantly altering the subsequent management.

Barbant et al. (23) calculated the predictive value and accuracy of CT, MRI, TEE, and invasive aortography, using the Bayes' theorem. For patients with a high index of clinical suspicion (pretest likelihood >50%) all tests had positive predictive values >85%. For intermediate risk patients, (pretest likelihood ~10%) all noninvasive tests performed very well, with positive predictive value >90%, while aortography was inferior (positive predictive value ~65%). For low risk patients (disease prevalence 1%), only the MRI had high positive predictive value (close to 100%), while all other imaging modalities had positive predictive values in the order of 50%.

In a landmark study by Nienaber et al. (9), TTE was compared against CT, TEE, and MRI in 110 patients with suspected acute thoracic aortic dissection. The Gold standards for comparison were findings at surgery, at postmortem examination, or on contrast angiography. In this population TTE was found to be only moderately sensitive, specific, and accurate for this diagnosis. CT, MRI, and TEE had all very high sensitivity for detection of aortic dissection, but specificity was suboptimal. The technology used for this study was at that time considered state-of-the-art, but compared to what is currently available, there is a considerable difference for all imaging modalities. TTE did not use harmonic or contrast-enhanced imaging, TEE was monoplane instead of omniplane, CT was single-slice helical instead of the modern multidetector CT scanners, and MRI was confined to conventional spin echo imaging without the added value of Gd-enhanced MRA, bright blood or phase contrast imaging. In a subsequent study with contemporary technology, Sommer et al. (24) compared CT, TEE, and MRI in patients with suspected acute aortic dissection and found that all tests had very high sensitivity, specificity, and diagnostic accuracy for detection of aortic dissection.

Table 5 Relative Clinical Values of Noninvasive Imaging Modalities for Assessment of Known or Suspected Aortic Pathology

	CXR	TTE	TEE	CT	MRI
Aortic size, location	+	++	+++	++++	++++
Blood flow	–	+++	++++	–	+++
Vessel wall integrity	+	+	++++	++++	++++
Tissue characterization	–	–	+++	++	++++

Abbreviations: CT, computed tomography; CXR, chest X-ray; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

TEE, contrast-enhanced spiral CT, and MRI/MRA are all equally good tests for diagnosis of thoracic aortic pathology. Although CT is most commonly the first test used, the majority of patients will require multiple imaging tests to establish the diagnosis (1). All tests contribute information on aortic pathology and can help assess known or suspected aortic disease (Table 5). In this context, the various noninvasive imaging modalities should be considered complimentary and not antagonistic.

The selection of which test will be used first depends on several factors:

1. The acuity of the situation. TTE and CT are usually preferred for more acute presentations, because imaging can be completed rather quickly, with close monitoring of the patient being possible. In chronic presentations patient comfort and safety becomes a primary determinant of the imaging modality selection, and TEE becomes a less preferred test due to its semi-invasive nature. In a young patient with Marfan syndrome or post-traumatic aneurysm where sequential imaging may be required for follow-up, MRI/MRA would be the preferred approach, while for repeat CT there is a concern from frequent, repeated radiation exposure. In contrast, for an 80-year old patient with newly diagnosed thoracic aortic aneurysm for whom monitoring of the size of the aneurysm is indicated, CT would be the faster and more convenient test, while risks from radiation exposure are of lesser concern.
2. The availability of imaging modality. TEE and CT are more widely available on a round-the-clock basis, even in smaller hospitals. Thus MRI/MRA is usually reserved for cases where initial imaging has remained inconclusive. Competence in interpreting the corresponding imaging modalities is also mandatory. All approaches may suffer artifacts, the knowledge and appreciation of which is of paramount importance for correct diagnosis.
3. The presence of comorbidities. The presence of renal failure or allergy to iodinated contrast media may preclude the use of contrast-enhanced CT as the primary diagnostic tool. The presence of pacemakers, defibrillators, or metallic implants precludes the use of MRI/MRA as a diagnostic tool. Finally, patients with esophageal strictures, varices, or bleeding disorders may not be good candidates for TEE for fear of procedure-related complications.

In conclusion, in the right hands, TEE, contrast-enhanced CT, and MRI/MRA can all accurately diagnose aortic pathology—of both acute and chronic presentation. CXR and TTE may provide clues but usually do not suffice to establish the diagnosis and optimal guide management. Considering the individual peculiarities of each case, a patient-driven approach should be used to image the aorta when clinically indicated.

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DISCUSSION AND COMMENTARY

Questions for the Author

The ordering of aortic imaging studies can be confusing. How do we know when to order contrast or non-contrast studies (or both), CT scan or CT angiogram, MR scan, or MR angiogram? When should we order 3-D reconstructions? Can these always be regenerated from the basic study, if required? Does the creation of 3-D formulations still require major input from the technician, or is this fully automated now?

Ordering of aortic imaging studies can be quite confusing. Even more complicated is the ordering situation with MRI, because the terminology of the various sequences and the imaging characteristics differ among vendors and users.

However, some general principles may be kept in mind when ordering imaging aortic studies. The three major factors that determine which test should be ordered, and when, for a particular suspected aortic pathology are: (*i*) the acuity of the situation (*ii*) the availability of each modality, and (*iii*) the presence of comorbidities. In general, for known or suspected aneurysms, noncontrast CT or MRI studies are usually adequate. For suspected or known dissections or vessel wall ulcerations, TEE or contrast enhanced CTA or MRA are indicated. If vessel wall rupture is suspected, contrast enhanced CT or MRI would be the preferred modalities.

It is important to recognize that the inherent tissue contrast in non-contrast enhanced studies is not high enough to allow for digital (post-processing) separation of the aorta from the surrounding structures. Thus 3-D reconstructions can only be obtained with contrast-enhanced studies (be they CTA or MRA). It generally takes a short time (a few minutes) for a trained technician to create a 3-D model of the aorta and its main branches. Operator skill is important because it is easy artifactually to eliminate useful information and also to introduce artifacts by excessive subtraction of background tissues. This is why clinical interpretations should never be based on 3-D reconstructions alone. In general 3-D reconstructions do not add diagnostic value to a CTA or MRA. The main value of these representations is to more effectively transfer information to the nonimaging specialist, because 3-D reconstructions obviate the need to mentally integrate the 2-D information into a volume image. Thus, the 3-D images help the clinician to better appreciate the anatomic relationships of the aorta with other adjacent structures. In this context, it is frequently helpful to ask for 3-D reconstructions, although the focus should never be on just a pretty image.

As a final note, personal contact and discussion with the imaging specialist regarding the value of each modality for any particular patient should be encouraged. The clinical history is very helpful in guiding the imager. Also, intermediate or equivocal findings may be better assessed in the context of the clinical presentation via discussion between radiologist and clinician.

Are there prospects for increasing beyond the 64-slice CT scanning machines currently coming into widespread use? Can we expect 128- or 256-slice machines and studies?

Imaging technology advances at a rapid pace. Over the last few years, CT technology has evolved from single slice to spiral to multislice technology, and the number of detectors in multislice scanners has increased from 4 to 16 to 64. One hundred and eight- and 256-slice scanners are in development and likely to be in clinical practice soon. With the increasing number of detectors, one issue of concern is that radiation exposure increases proportionately. With the 64 detectors, the absorbed radiation dose for a cardiac study is ~11 mSv, almost double that of a 16-slice scanner (Reference 18, above). This may in fact become a limiting factor in the widespread applicability of scanners with higher number of radiation detectors.

A different approach to conventional CT imaging is represented in the so-called flat-panel technology. This approach does not use rotating detectors but rather a flat detecting surface that allows for volumetric high-resolution imaging. Preliminary application of this technology has been reported for imaging of the coronary arteries in an excised swine heart (1). At the present time, the computing power needed for in vivo cardiovascular imaging is not practical, although in the future computer technology may surpass this frontier.

Do you anticipate that in the future interventional vascular procedures can be performed under "CT fluoro," obviating the need for angiographic control of these procedures?

Currently, interventional vascular procedures are performed under fluoroscopy. One drawback of this approach is the considerable radiation exposure. CT fluoroscopy, at least with current technology, could potentially facilitate the three-dimensional appreciation of the inter-relationships of the anatomic structures visualized during interventional procedures. CT guidance, however, would not eliminate the radiation exposure, and in fact the radiation dose would likely be higher than the current projection angiographic approach. On the other hand, real-time MR guidance would be a significant advance, as this would eliminate ionizing radiation exposure. Catheters equipped with receiver coils at tip have been developed and shown to be adequately imaged at a rate of a few frames per second. MR advancement of catheters in the aorta of experimental animals has been shown to be possible (2), and even feasibility data in peripheral arterial interventions in humans have been described (3). Because of the minimal biologic cost that this approach offers, it is likely that this technology will become a clinical tool in the not too distant future.

Are there any totally new imaging modalities on the horizon, different from CT or MR?

Technology advances at a rapid pace. Over the last decade we have witnessed a shift from macro-anatomical imaging to micro-molecular and cellular imaging. Developments have focused more on coronary atherosclerosis, as this is the major cause of morbidity and mortality in humans. These developments, however, can be applied to the entire vascular tree, where atherosclerosis can develop.

Newer technologies that attempt to assess the atherosclerotic plaque include thermography, angioscopy, spectroscopy, elastography, and optical coherence

tomography, among others. Excellent reviews of these new technologies have recently been published (4,5). Positron-emission-tomography (PET) has also been reported to visualize atherosclerotic plaque by way of selective FDG uptake at the vessel wall. This may be an indicator of increased metabolic activity at the plaque, and may carry additional prognostic information (6,7).

Finally combination technologies are now being developed, whereby anatomic information is merged to functional-metabolic data. The most commonly used such technology is PET-CT, although PET-MRI, ultrasound-MRI and X-ray-MRI systems have been or are being developed. It is certain not only that the technological developments in the years to come will allow us to accurately evaluate the anatomic macroscopic appearance of the cardiovascular system, but also to get insights into the pathophysiologic mechanisms of cardiovascular disease that can lead to more targeted therapeutic approaches.

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Editor's Counterpoint

Dr. Danias, in his superlative review of diagnostic imaging in aortic diseases, gently impugns the utility of the plain chest x-ray in thoracic aortic aneurysm and dissection. The Editor respectfully takes issue with this, believing that the plain film contributes immensely to the early diagnosis of aneurysm and dissection.

The plain chest x-ray shows the contours of the thoracic aorta quite well, given the contrast between the air-filled lungs and the fluid-filled aorta. The normal contours of the aorta are quite familiar and generally very well seen (Figs. A and B). The ascending aorta, if substantially enlarged, will appear outside the upper right

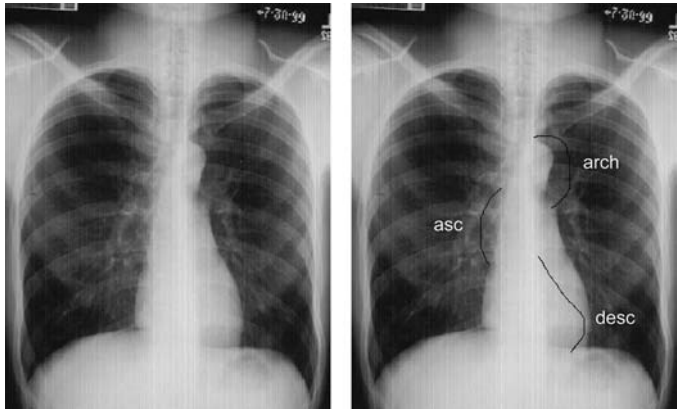

Figure A (**1**) Normal chest x-ray. (**2**) Same chest x-ray, with areas where ascending, arch, and descending aortic aneurysm shadows may appear.

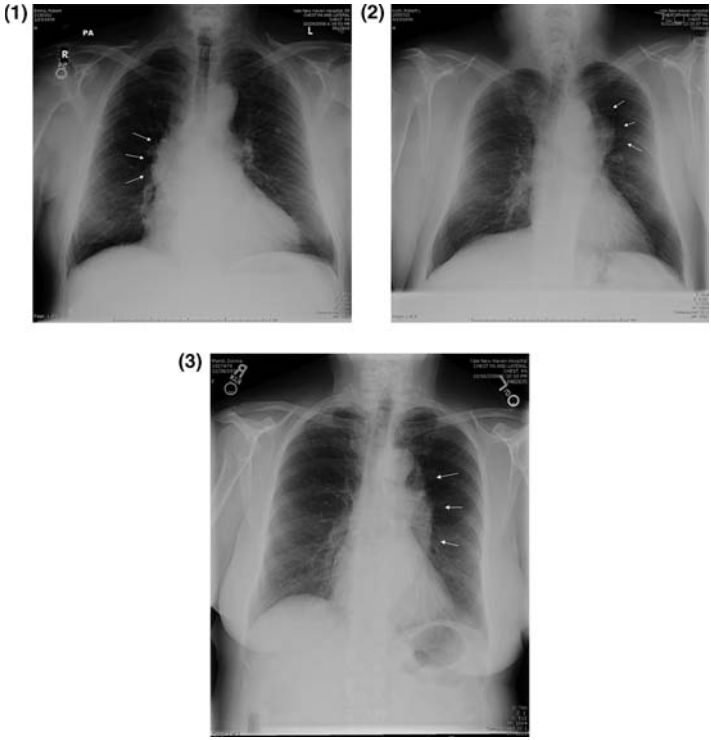

Figure B Aneurysms diagnosed by CXR. (**1**) Ascending; (**2**) arch; (**3**) descending.

cardiac silhouette. The aortic knob should normally be small and distinct. This knob will enlarge in case of arch aneurysm and become indistinct in patients with aortic dissection. The descending aorta normally makes a clean, crisp stripe to the left of the vertebral column. Aneurysmal dilatation of the descending aorta will be clearly seen, with bulging of this stripe to the right.

Of course, Dr. Danias' erudite comments are very well taken. In the current era, three-dimensional imaging with echocardiography, CT scanning, or MRI imaging will provide precise anatomic information about an aneurysm suspected on chest x-ray. On the Editor's aortic service, however, we strive hard to encourage residents trained entirely in the CT/MR era not to ignore the chest x-ray; the plain film can, upon careful reading, not only raise the suspicion of aortic disease, but also predict, with surprising accuracy, the findings that will obtain on more advanced imaging modalities.

4

Putting It All Together: Symptoms, Signs, and Images

Arun Raghupathy and Kim Eagle

Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan, U.S.A.

Pain attending the splitting of the aortic wall is usually excruciating and extensive, radiating from midthorax front or back through the chest, down the back, and even into the thighs or up into the neck. The pain in the thorax or back comes suddenly at its maximum and is often prostrating, inducing a state of shock or even death.

—Paul Dudley White, 1944

INTRODUCTION

Acute aortic dissection is a cardiovascular emergency associated with high mortality, and successful outcomes depend on the rapid recognition of the clinical symptoms and signs associated with this condition (1–5). Modern imaging modalities can precisely define a spectrum of aortic pathologies, but they are clinically useful only when patients are accurately identified in a timely fashion so that treatment can be delivered promptly. Therefore, the astute clinician must know how to quickly incorporate key elements from the symptoms, signs, and images in order to confirm the diagnosis and initiate appropriate therapy for this life-threatening disease.

Keeping this in mind, this review will discuss our current understanding of the clinical presentation of this complex yet fascinating disease. Compared to other cardiovascular emergencies, such as stroke and acute myocardial infarction,

the incidence of aortic dissection is quite rare, with an estimated range of 5 to 30 cases per million persons per year (1). As such, clinical observations pertaining to acute aortic conditions, although valuable, are often limited by the naturally smaller sample sizes found in single-center case series. In contrast, much of our current and expanding body of knowledge derives from our experience with the International Registry of Aortic Dissection (IRAD). Since its inception in 1996, this ongoing, worldwide multi-institution research collaboration among specialized aortic referral centers has collected important clinical data on over 1350 consecutive patients to gain insight into the clinical presentation, management, and outcomes of acute aortic conditions.

This chapter is designed to equip the triaging clinician with the essential information required to develop a practical and efficient diagnostic approach to the patient with an acute aortic condition. Speed in appropriately suspecting and confirming the diagnosis is a recurring theme echoed throughout this discussion, as severe, often catastrophic complications tend to develop quickly. From the time of symptom onset, mortality in untreated (or undiagnosed) acute dissection rises rapidly with each passing hour, approaching 50% in the first 24 hours (6,7). Early mortality is usually the result of a ruptured aorta, manifesting clinically as cardiac tamponade or frank exsanguination. Serious morbidity, including multisystem organ failure, may result from occlusion of the aortic branches, with resultant malperfusion to vital organs such as brain, kidney, spinal cord, and limbs. Therefore, the importance of prompt action and maintaining a high index of suspicion to minimize diagnostic delays cannot be overemphasized.

PREDISPOSING FACTORS

The initial approach to evaluating the patient suspected of having an acute aortic condition begins with recognizing the constellation of high-risk conditions that are associated with the disease. A summary of such predisposing conditions is listed in Table 1. Hypertension exists in up to 72% of patients and is by far the most common feature. Advanced age is another common characteristic, with a mean age of dissection occurring in the seventh decade of life (1,8). Among younger patients (age <40), hereditary connective tissue disorders, such as the Marfan's syndrome or bicuspid aortic valve, play a larger role than long-standing hypertension (5,9). Men are twice as likely as women to suffer an acute aortic dissection. However, women tend to present with dissection at older ages, with nearly half of women presenting at age >70 years old. Contrary to previous reports from case studies, our experience with IRAD suggests that pregnancy is only rarely associated with acute dissection, unless it co-exists with the Marfan's syndrome and an aortic root diameter >40 mm (1,10). Prior cardiovascular intervention, including surgical or catheter instrumentation of the aorta, is an important feature found in 4% to 5% of patients with Type A or Type B dissection. An even greater association is seen in patients presenting with Type A dissection, where a history of recent or prior cardiac surgery is present in approximately one of every six patients (11,12).

Table 1 Predisposing Factors for Acute Aortic Conditions

Hypertension
Advanced age
Atherosclerosis
Smoking
Cocaine or amphetamine use
Male gender
Connective tissue disorders
Marfan's syndrome
Ehler's Danlos syndrome
Aortic coarctation
Bicuspid aortic valve
Vascular inflammation
Giant cell arteritis
Takayasu arteritis
Syphilis
Iatrogeni
Catheter instrumentation of aorta
Prior or recent cardiac surgery
Aortic cross clamping/aortotomy

SYMPTOMS

Typical Symptoms

Because dissection may present with a broad range of symptoms, it is essential for the clinician to maintain a high index of suspicion for acute aortic syndrome when evaluating any patient who carries the usual predisposing risk factors (Table 1). From our experience with IRAD, the single most reliable presenting symptom in patients with acute dissection is the sudden onset of severe pain localized to the anterior chest or back, and less often, the abdomen. Contrary to classic teaching, patients are more likely to describe the quality of pain as sharp, as opposed to tearing or ripping. Moreover, the abrupt onset of pain seems to be the most frequent and consistent characteristic, as it is reported in 85% of both Type A and Type B aortic dissections (1). The sudden onset of severe pain is typically dramatic enough that patients often describe the details of the inciting event with a pinpoint or "freeze-frame" accuracy (13). A pattern of recurrent or stuttering pain should alert the clinician to the potential progression of an unstable aortic lesion such as penetrating aortic ulcer or intramural hematoma into overt dissection (Fig. 1) (4,14–21). The location of pain may sometimes be helpful in distinguishing Type A from Type B aortic dissection, but this type of assessment should be regarded as nonspecific. In general, pain localized to the back or abdomen is more consistent with Type B dissection, whereas patients with Type A dissection usually localize pain to the anterior chest (Table 2) (1,22,23).

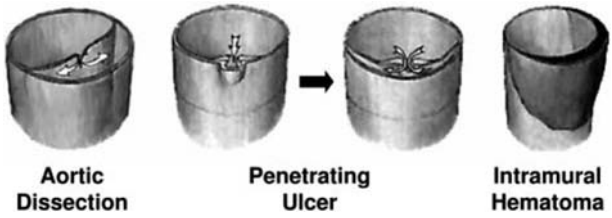

Figure 1 Spectrum of acute aortic conditions. *Source*: From Ref. 47.

Syncope occurs in 5% to 10% of patients with dissection, and is nearly always unique to Type A dissection. In this setting, it may herald serious hemodynamic compromise, as seen in cardiac tamponade and stroke. Mechanisms for syncope in dissection are diverse and vary based on the location and extent of the dissection. For example, rupture into the pericardium may produce tamponade physiology or dissection of the carotid arteries may lead to stroke with cerebral hypoperfusion. Severe pain, hypovolemia, or an exaggerated aortic baroreceptor response due to stretching of the aortic wall are other possible mechanisms (2,3,13,24). A small percentage (up to 3%) of patients with dissection will have syncope without prior back or chest pain (24), highlighting the importance of recognizing atypical presentations, as discussed in the following section.

Atypical Symptoms

Although the abrupt onset of thoracic pain is not difficult to elicit by history, not all patients with an acute aortic condition will present in this classic manner (Table 3). Atypical clinical symptoms, with asymptomatic or nonlocalizing pain, are most often seen in female patients, the elderly, and those with prior cardiovascular surgery (8,10,12). When compared to men, women are less likely to have pain on presentation (10). The elderly tend to present with unexplained syncope and neurological deficits (8). Such challenging variations in symptoms may in part explain why the diagnosis of acute dissection is only suspected in as few as 15% to 43% of patients presenting acutely (6,25). Furthermore, the subset of patients

Table 2 Typical Symptoms of Acute Aortic Dissection

	All (%)	Type A (%)	Type B (%)	*P*-value
Pain	92.9	91.5	95.2	0.001
Abrupt	85.1	84.8	85.5	NS
Anterior	65.9	72.2	55.7	<0.001
Back	52.8	44.2	66.7	<0.001
Abdominal	28.0	23.1	36.0	<0.001
Sharp	80.4	78.9	82.7	NS
Tearing	72.8	71.6	74.6	NS
Syncope	13.1	18.8	3.9	<0.001

Table 3 Atypical Symptoms inAcute Aortic Conditions in Different Patients

Patients at risk for presenting with atypical symptoms	Atypical symptoms of acute aortic conditions
Elderly (age >70)	Painless acute aortic condition
Female	Abdominal pain
Diabetic	Syncope
Existing aortic aneurysm	Altered mental status
Prior cardiovascular surgery	Stuttering, recurrent pain

with atypical presentations will often present later in the natural course of dissection and are at high risk for hemodynamic derangement, malperfusion, and death if the diagnosis is missed or further delayed (2,23).

Therefore, it is imperative for the clinician to recognize patients who are more likely to present atypically and aggressively pursue the diagnosis of an acute aortic condition in any patient who presents with unexplained hypoperfusion to an end organ or extremity. Symptoms consistent with end-organ malperfusion may include abdominal pain, neurological deficit due to ischemia of the spinal cord, limb ischemia, and renal failure. The specific symptom complex may help localize the anatomic extent of the dissection along the aorta and its major branches.

In IRAD, up to 6.4% of patients denied any pain on presentation, consistent with the 5% to 15% incidence, reported in the literature. When compared to patients who describe pain on presentation, these patients are significantly more likely to have syncope, congestive heart failure, stroke, and in-hospital death. Alarmingly, patients presenting without pain had a median time of 29 hours for diagnosis versus 10 hours in those who presented with typical pain. Painless aortic dissection is more common in the elderly patients with existing aortic aneurysms, prior cardiovascular surgery, and diabetics (8,10,12,26). Women are more likely than men to have painless aortic dissection (10). Mechanisms of painless aortic dissection are poorly understood, but may be related to conditions in which the aorta dissects gradually or in some manner spares the richly innervated adventitia. Prior cardiovascular surgery and surgical aortic manipulation may also alter the patient's perception of aortic pain, and diabetics may be vulnerable to painless dissection due to denervation of perioaortic pain receptors (12,26,27).

Another atypical presentation is that of acute aortic dissection manifesting in a patient who presents with a primary or isolated complaint of abdominal pain. This challenging presentation was reported in approximately 5% of patients in IRAD, and each patient was ultimately diagnosed with acute Type B aortic dissection. Although relatively rare, patients presenting in this manner had significantly higher rates of in-hospital death when compared to patients with more typical symptoms.

SIGNS

A thorough understanding of the typical signs of aortic dissection is necessary to aid in confirming the diagnosis and to assess for anticipated complications (Table 4). When the proximal aorta is involved, lethal complications develop quickly, requiring a rapid assessment using a focused physical exam to guide clinical decision-making. In performing the bedside assessment, the clinician must work quickly to stabilize the patient while seeking out important clues from the physical exam. Unfortunately, the physical examination findings are often unremarkable or nonspecific; nevertheless, certain characteristic signs, when present, may help to predict prognosis and contribute to the development of an optimal treatment strategy (3,28–31).

Perhaps the most obvious and ominous clinical sign signaling hemodynamically significant acute aortic dissection is hypotension (systolic blood pressure <90), which occurs in up to 40% of patients with dissection (2,29). Moreover, hypotension is present on the first hospital blood pressure recording in nearly half of these patients. In this setting, hypotension as a presenting clinical sign is independently associated with a number of serious complications, including syncope and new neurological deficit. In patients with acute dissection who develop hypotension, in-hospital mortality exceeds 50%, with cause of death, when known, due to aortic rupture, neurological complications, visceral ischemia, and cardiac tamponade (2,5,29).

Although only documented in a minority of patients, special attention should be paid to the presence or absence of pulse deficits, defined by the physical exam finding of weak or absent carotid, brachial, or femoral pulses. In patients with Type A dissection, pulse deficits were significantly associated with an increased frequency of neurological deficit, coma, hypotension, and renal failure (31). Furthermore, the presence of any pulse deficit has been reported as an independent predictor of mortality, with the number of pulse deficits being directly proportional to rate of in-hospital death (Fig. 2) (2,31). Importantly, pulse deficits may only be an intermittent finding, caused by the transient obstruction of arterial flow by a mobile dissection flap (13).

As outlined in Table 4, the serious complications of shock and tamponade, aortic insufficiency, and stroke are significantly more likely to be observed in patients with acute Type A dissection. Although part of classic teaching, the

Table 4 Typical Signs of Aortic Dissection

	All (%)	Type A (%)	Type B (%)	*P*-value
Hypertension	45.0	31.1	67.1	<0.001
Hypotension	11.0	16.0	2.9	<0.001
Shock/tamponade	11.6	17.6	1.8	<0.001
AI murmur	31.2	42.1	14.2	<0.001
Pulse deficit	24.8	28.9	18.2	<0.001
Stroke	5.5	7.5	2.2	<0.001

Abbreviation: AI, aortic insufficiency.

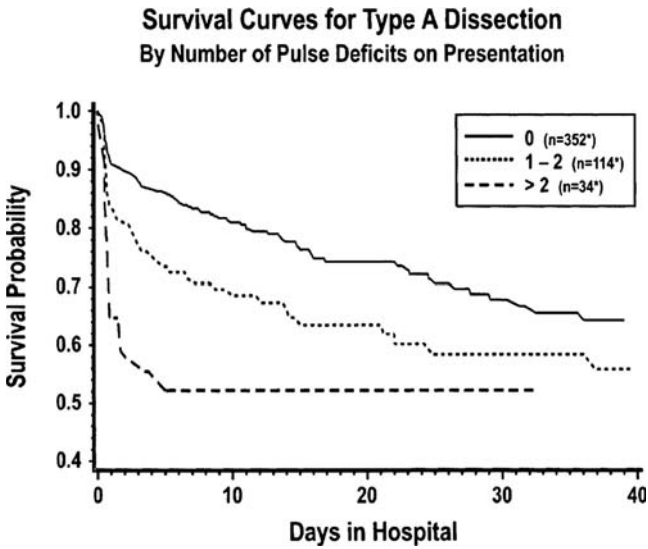

Figure 2 Pulse deficits as a clinical predictor of mortality in acute aortic dissection. *Source*: From Ref. 31.

expected diastolic murmur of aortic regurgitation is often brief and hard to hear, and is only documented in less than half of patients with acute Type A dissection. Cardiac tamponade may be suspected at the bedside and rapidly confirmed with bedside echocardiography (2,13,24,32). If cardiac tamponade occurs in the setting of acute aortic dissection, bedside pericardiocentesis is relatively contraindicated and should be deferred until emergency cardiac surgery can be performed (33).

ELECTROCARDIOGRAM AND CHEST X-RAY

A 12-lead electrocardiogram (ECG) should be obtained to document the presence of ischemia in every patient presenting with chest pain or suspected aortic dissection (5,30,34). The ECG may imply useful prognostic information, as observational studies in patients with acute dissection have found that an abnormal ECG is an independent predictor of in-hospital death (2). A challenging dilemma exists in differentiating acute coronary syndrome from acute aortic syndrome, as patients with both conditions will often carry overlapping risk factors and will have similar clinical presentations. Most importantly, establishing the correct diagnosis is essential, as treatment for acute coronary syndrome (anticoagulation and cardiac catheterization) may have catastrophic consequences in the presence of aortic dissection (34). In this setting, a normal ECG may persuade the clinician to pursue the diagnosis of aortic dissection over acute coronary syndrome. However, nonspecific repolarization abnormalities (ST and T-wave segments) are the most common finding in patients with acute dissection. Also, a small percentage of

patients may present with aortic dissection complicated by concomitant acute coronary insufficiency, thus further limiting the differential diagnostic utility of the ECG (13,34,35).

Although easily available and commonly ordered as part of the emergency room evaluation, the chest x-ray has limited value in confirming the diagnosis of aortic dissection. In studies performed on patients with high (>50%) pretest probability for acute aortic syndrome, the sensitivity and specificity of chest radiography was only 64% and 86%, respectively (36). Although the classic radiographic finding of widened mediastinum or abnormal aortic contour is seen in up to 75% of subjects with acute dissection, it is important to realize that the chest x-ray is completely normal in up to 15% of these patients. Associated clues to the presence of aortic dissection may include pleural or suspected pericardial effusion and rightward tracheal deviation, but these findings are nonspecific (1,36,37). Therefore, an unremarkable chest x-ray should never dissuade the clinician from pursuing confirmatory testing in any patient suspected of having acute aortic syndrome. Given that the utmost priority is to obtain a rapid and accurate diagnosis, the routine chest x-ray should probably be replaced by a first-line, more highly sensitive modern aortic imaging modality (36).

Given the complex mixture of typical and atypical clinical presentations seen in the acute aortic syndromes, it may be helpful to highlight the most common "red-flag" features that are known to affect mortality. In Type A dissection, the clinical characteristics and symptoms that independently predict in-hospital death include advanced age, female gender, and abrupt onset of pain on presentation. Similarly, the key signs predicting early mortality include abnormal presenting ECG, any pulse deficit, renal failure, and hypotension, shock, or tamponade (Figs. 3A and B). Such modeling of risk may have clinical utility in stratifying highest risk patients and for assessing prognosis for patients and their families (2).

MODERN AORTIC IMAGING

With the advent of modern imaging techniques, a number of highly sensitive modalities have emerged that can provide accurate and detailed assessment of acute aortic pathologies (38,39). Regardless of which modality is utilized, the identification of an aortic intimal flap that separates the true from false lumen is the defining hallmark of acute aortic dissection. Additionally, the superb image quality, produced by the current generation of ultrasound and tomographic studies, has allowed for the discovery of previously unrecognized variants of acute aortic dissection such as intramural hematoma and penetrating aortic ulcer. Penetrating aortic ulcer is an ulceration of atheromatous plaque that disrupts the internal elastic lamina and burrows deeply into the aortic media. Intramural hematoma of the aorta is a concentric collection of blood in the wall of the aorta, thought possibly due to a localized rupture of the vasa vasorum into the medial aortic wall. Patients with either of these variants present similarly to those with acute aortic dissection, and therefore the diagnosis is usually made solely on the basis of

(A)

Overall Model Variables	Overall Type A, %	% Among Survivors	% Among Deaths	Parameter Coefficient	Score Assigned	*P*	Death, OR (95% CI)
Age ≥70 y	35.2	30.0	46.1	0.53	0.5	0.03	1.70 (1.05–2.77)
Female	34.5	30.7	42.7	0.32	0.3	0.20	1.38 (0.85–2.27)
Abrupt onset pain*	84.5	82.3	89.0	0.96	1.0	0.01	2.60 (1.22, 5.54)
Abnormal ECG*	69.6	65.2	79.5	0.57	0.6	0.03	1.77 (1.06, 2.95)
Any pulse deficit*	30.1	24.7	41.1	0.71	0.7	0.004	2.03 (1.25, 3.29)
Kidney failure†	5.6	2.9	11.9	1.56	1.6	0.002	4.77 (1.80, 12.6)
Hypotension/shock/tamponade*	29.0	20.1	47.1	1.09	1.1	<0.0001	2.97 (1.83, 4.81)

*On presentation; †on presentation and before surgery.

(B) Observed vs. Model Probabilities of Death by Score

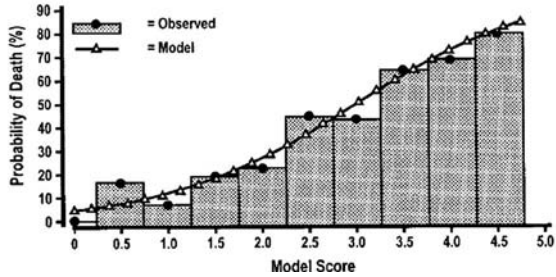

Figure 3 (**A**) and (**B**) Signs and symptoms predicting death in acute Type A aortic dissection. Advanced age, female sex, abrupt onset of pain, abnormal EKG, and especially pulse deficit, kidney failure, and shock all have adverse impact on outcome. *Abbreviation*: ECG, electrocardiogram. *Source*: From Ref. 2.

advanced imaging. Thus, the acute aortic conditions consist of a spectrum of clinically indistinguishable and inter-related high-risk lesions that may, ultimately, manifest as overt acute aortic dissection (15,18,21,40,41).

In the setting of presumed acute aortic condition, the purpose of diagnostic imaging is to confirm the diagnosis, identify key characteristics, and assess cardiac and valvular function (Table 5) (13). The choice of imaging modality depends on several factors, including the clinical condition of the patient as well as institution-specific variables such as cost, availability of equipment, and local expertise. As all modern modalities [computed tomography (CT) scan, magnetic resonance imaging (MRI), transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE)] have suitably high accuracy and sensitivity, the most readily available and rapidly accessible noninvasive test should be selected first. Because of the potential for false negative findings, all patients with at least moderate pre-test suspicion for acute aortic syndrome should undergo a second test if the initial imaging study is negative or only "suggestive" of acute aortic pathology (5,39,42). From our experience with IRAD, the majority of patients with acute dissection require two imaging tests to confirm the diagnosis and provide essential supporting data. The most common combination of imaging modalities is CT and echocardiography (Figs. 4A and B). Aortography and MRI are more

Table 5 Diagnostic Imaging, Identification, and Assessment of Acute Aortic Patients

Goals of imaging in acute aortic conditions
Confirmation
Diagnosis: acute dissection, intramural hematoma, penetrating aortic ulcer
Anatomy
Location and origin
Extent
Intimal tear/communication
Identification
Location and origin false lumen patency (partial vs. complete thrombosis)
Branch vessel involvement
Extra-aortic extension
Pericardial effusion
Functional assessment
Aortic valve insufficiency
Left ventricular function

commonly selected as third-line and fourth-line tests (Figs. 4C and D) (39). A summary of the major strengths and limitations of CT, TTE, TEE, MRI, and aortography is listed in Table 6.

Computed Tomography

The current generation of CT offers excellent contrast imaging of the aorta in the setting of acute aortic syndrome with a sensitivity greater than 95%. CT is also useful for visualizing the extent of aortic and branch vessel involvement, the presence of hemopericardium, pleural effusion, penetrating aortic ulcer, and intramural hematoma (Figs. 5–8). Another advantage of CT is its convenient, 24-hour access to most emergency room facilities. For these reasons, CT is most often selected as the initial imaging study for acute aortic dissection (Figs. 4A and B). Limitations of CT include its inability to completely assess cardiac and valvular function, potential nephrotoxicity of intravenous contrast agents, and limited ability to identify very small intimal tears (1,5,39,41,43).

Echocardiography

Although its use is confined to evaluating the heart and proximal ascending aorta, TTE may identify aortic dissection in this segment and offers the clinician a rapid bedside assessment of potential complications, such as acute aortic regurgitation, pericardial tamponade, and compromised left ventricular function (1,32,39,42). Given its limited ability to scan the entire aorta, TTE may be best reserved to screen for dissection in patients presenting with unexplained shock or syncope (13,24,29).

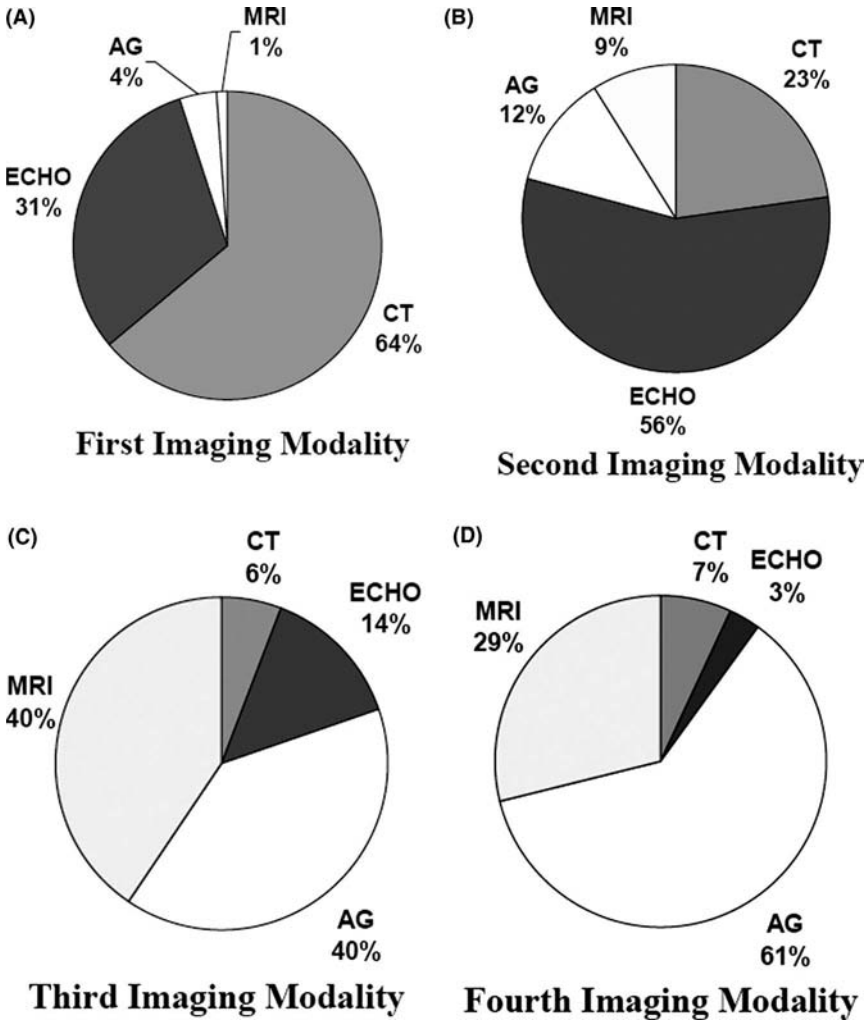

Figure 4 (**A–D**) Choice of imaging modality in diagnosing acute aortic syndrome. *Abbreviations*: AG, aortography; CT, computed tomography; ECHO, echocardiogram; MRI, magnetic resonance imaging.

Alternatively, TEE offers excellent views of the aorta from the root to the distal descending aorta. Additionally, color flow Doppler, can assess the pattern of blood flow within and between true and false lumens (Fig. 9). The sensitivity and specificity of TEE for diagnosing acute aortic dissection approach 99% and 89%, respectively. The intimal tear may be found in up to 60% of patients, and TEE can be used to identify false lumen patency, focal aortic wall thickening, and variants of dissection such as intramural hematoma or penetrating aortic ulcer. The primary advantages of TEE include its safe use at the bedside in the hemodynamically

Table 6 A Summary of the Major Strengths and Limitations of CT, TTE, TEE, MRI, and Aortography

	Strengths	Limitations
Aortography	Historical "gold standard" Superior detection of localized tears Excellent assessment of branch vessels Can measure false lumen hemodynamics Access for endovascular stenting or fenestration	Invasive, requires arteriotomy Time-consuming High-contrast exposure Limited detection of intramural hematoma
TTE	Rapid/portable bedside use Can assess for AI, LV function, pericardial effusion and/or tamponade May identify dissection of aortic root/proximal aorta	Limited spatial resolution Anatomic window limited to aortic root and heart, cannot assess extent of dissection beyond aortic root
TEE	Portable Excellent spatial resolution Safe in hemodynamically unstable patient Fast diagnosis (complete study in <30 minutes) May be used intraoperatively Assessment of cardiac anatomy/function	Limited view of distal ascending aorta ("blind spot") Cannot assess distal abdominal aorta Potential false positive from reverberation artifact
CT	Rapid exam Offers excellent resolution of aorta, including aortic arch and branch vessels Shows extent of dissection into branch vessels	May miss small tears or entry site Cannot assess cardiac or valvular function Moderate contrast exposure/risk nephrotoxicity Limited use in hemodynamically unstable patient
MRI	Highest accuracy, sensitivity, and specificity Can identify even very small aortic tears Safer contrast media Excellent depiction of arch and branch vessels	Limited availability Expensive Limited use in hemodynamically unstable patient Incompatible with implanted metal devices or prostheses Rarely used as initial test (<2%)

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

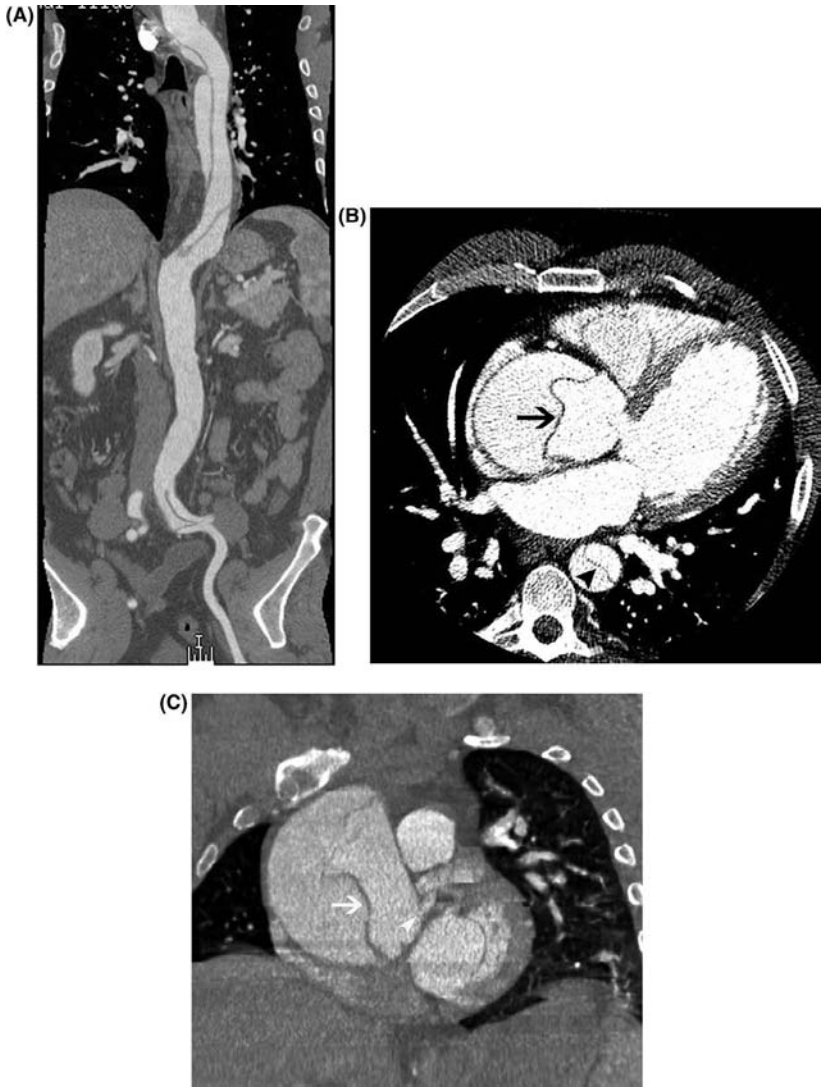

Figure 5 (**A–C**) Contrast-enhanced electrocardiogram-gated computed tomography in a 49 year-old male presenting with acute chest pain and aortic dissection. (**A**) Reformatted image of the thoracoabdominal aorta shows Type A dissection extending from the aortic valve to the bifurcation and extending into the left common iliac artery. In this view, the dissection flap is not identified within the abdominal aorta (only the false lumen is visualized), because the dissection flap lies coronally over the origins of the celiac axis, superior mesenteric artery (SMA) and inferior mesenteric artery (IMA), which may cause dynamic obstruction. (**B**) Axial image at the level of the aortic root confirms Type A dissection with a dissection flap in the aortic root (*arrow*) and a dissection flap within the descending aorta (*arrowhead*). (**C**) Coronal-oblique image of the aortic root shows the dissection flap (*arrow*), and the left coronary artery arising from the true lumen (*arrowhead*). *Source*: Courtesy of Dr. Paul Cronin, University of Michigan, Ann Arbor.

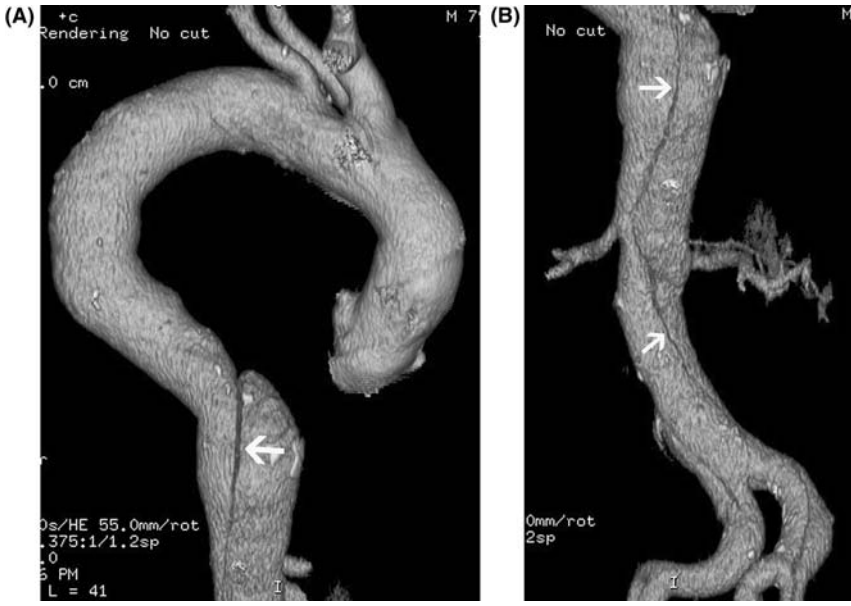

Figure 6 (**A** and **B**). Contrast-enhanced electrocardiogram-gated computed tomography in a 74 year-old male presenting with Type B dissection. (**A**) Three dimensional reformatted image of the thoracoabdominal aorta shows previous repair of the descending thoracic aorta, with a Type B dissection seen at the distal anastamosis (*arrow*). (**B**) The dissection flap extends through the abdominal aorta (*arrows*) to the bifurcation, and into the common iliac arteries bilaterally and external iliac on the left. *Source*: Courtesy of Dr. Paul Cronin, University of Michigan, Ann Arbor.

unstable patient and its rapid accessibility (a complete study and diagnosis can usually be made in less than 30 minutes). Because of its portability, TEE offers the distinct advantage of intraoperative use in patients requiring emergency surgery. Limitations of TEE include difficulty imaging the distal ascending aorta, where an echocardiographic "blind spot" typically exists, as well as the inability to visualize the distal abdominal aorta (5,13,32,37,44).

Aortography

Long considered the "gold-standard" in diagnosing acute aortic dissection, the utilization of invasive aortography has largely been supplanted in favor of more practical, noninvasive imaging modalities such as CT and echocardiography. Although of adequate sensitivity to diagnose aortic dissection, angiography requires arterial puncture, exposes the patient to significant amounts of intravascular contrast, and has limited ability to diagnose intramural hematoma. Aortography does offer a few advantages, including the opportunity to measure hemodynamics between true and false lumen and, when indicated, to perform endovascular

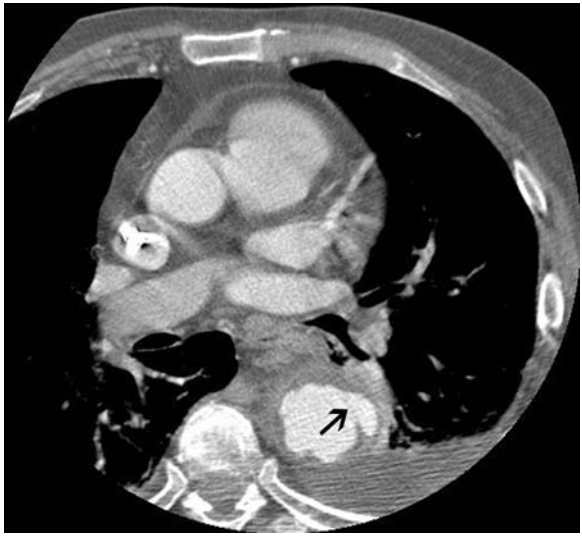

Figure 7 Contrast-enhanced electrocardiogram-gated computed tomography in a 68 year-old male presenting with acute onset severe chest and back pain. Axial CT at the level of the pulmonary arteries shows evidence of atherosclerotic disease within the descending thoracic aorta with intraluminal thrombus. In addition, there is a collection of contrast lying outside the aortic true lumen, in the aortic wall but confined by aortic adventitia, and with a gaping communicating with the aortic true lumen, that is, a penetrating ulcer (*arrow*). *Abbreviations*: CT, computed tomography. *Source*: Courtesy of Dr. Paul Cronin, University of Michigan, Ann Arbor.

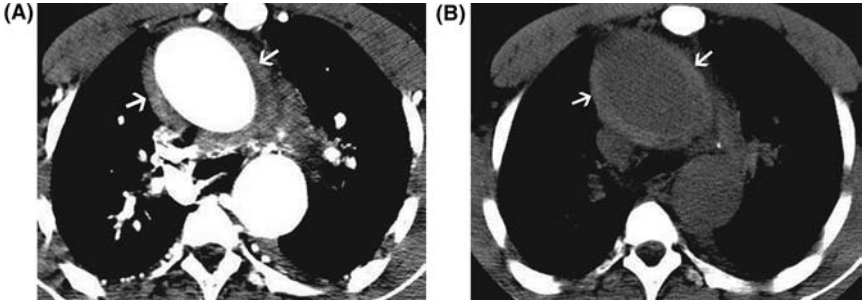

Figure 8 (**A** and **B**) Contrast-enhanced electrocardiogram-gated computed tomography in a 73 year-old female presenting with acute onset severe back pain. (**A**) Axial CT just below the aortic arch shows aneurysmal dilatation of the ascending and descending thoracic aorta. No dissection flap is present. In addition, there is thickening of the wall of the ascending aorta, which is of high attenuation compatible with intramural hematoma (*arrow*). (**B**) This is best appreciated on the non contrast-enhanced images. *Abbreviation*: CT, computed tomography. *Source*: Courtesy of Dr. Aine Kelly, University of Michigan, Ann Arbor.

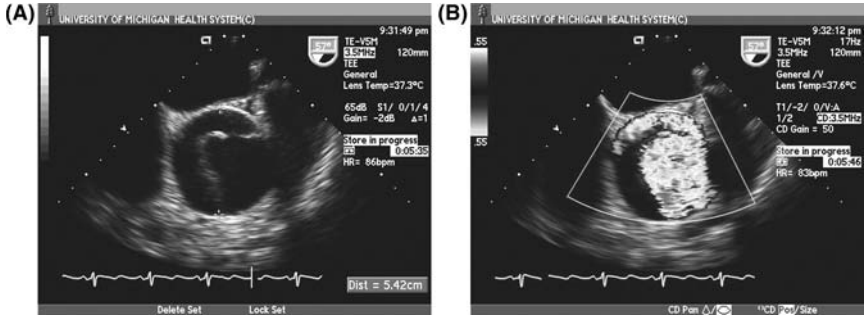

Figure 9 (**A** and **B**) Transesophageal echocardiogram performed in patient presenting with acute Type A aortic dissection. (**A**) Short axis view at approximately 60 degrees demonstrating a mobile dissection flap in the ascending aorta. (**B**) Flow Doppler showing flow pattern in true and false lumen. *Source*: Courtesy of Dr. William F. Armstrong, University of Michigan, Ann Arbor.

interventions such as aortic stenting and fenestration, even during the same procedure. Invasive intravascular ultrasound may also be used during the procedure, improving the sensitivity of aortography alone to nearly 100%. Still, aortography is best reserved for use as a third or fourth line test (Figs. 4C and D), or in appropriately selected cases that require endovascular repair (25,37,39,45).

Magnetic Resonance Imaging

Although it offers superior image resolution and perhaps the highest sensitivity and specificity for diagnosing acute aortic conditions, MRI is not often selected as the initial imaging study. In IRAD, MRI was a selected imaging modality in 19% of patients, but was chosen as the initial study in only 1% (Fig. 4A) (39,41,42–46). Practical issues such as the inability to monitor an unstable patient, limited availability of equipment, and the incompatibility with implanted devices or prostheses may in part explain the underutilization of this modality. When it is used, however, MRI can visualize even very small tears as well as precisely characterize branch vessel involvement. It is ideally applied to the stable patient for whom a second imaging study is required (5,13,39).

PUTTING IT ALL TOGETHER

With the inherent diagnostic challenges and extreme urgency surrounding the patient presenting with acute aortic condition, a decisive and efficient approach should be consistently applied using a high index of suspicion (Fig. 10). Aortic dissection or its variants must be considered in any patient with thoracic pain, particularly of a sudden onset, or in any patient with unexplained heart failure, syncope, or neurological deficit. Once the diagnosis is suspected, the emergency

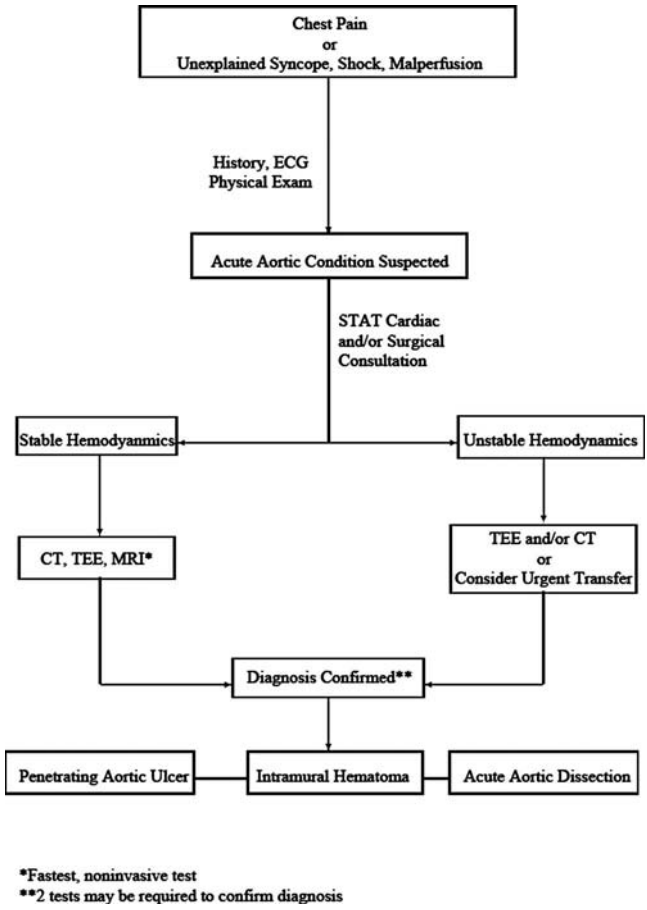

Figure 10 Suggested approach to diagnosing acute aortic conditions. *Abbreviations*: CT, computed tomography; ECG, electrocardiogram; MRI, magnetic resonance imaging; TEE, transesophageal echocardiograph.

room physician should promptly alert surgical and cardiovascular services to the potential scenario while confirmatory testing is pursued. In general, a relatively stable patient may undergo whichever imaging test is most readily available, keeping in mind that serious complications may develop quickly and continuous monitoring for change in status is necessary. In the hemodynamically unstable patient, TEE is the preferred initial test, provided that qualified personnel are readily available to rapidly perform and interpret the test. If emergency TEE is not an option, CT, aortography, or MRI may be pursued to confirm the diagnosis. If imaging tests are unavailable, the unstable patient should be emergently transferred to a tertiary referral center, preferably one with aortic expertise, for definitive diagnosis and therapy.

EDITOR'S COMMENT

Aortic dissection can be an easy diagnosis, in the presence of typical symptoms, signs, and radiographic findings. As aortic specialists, we see patients already screened and imaged; we see them through the always accurate "retrospectoscope." Our plea to those on the front lines, especially in the Emergency Department, is that aortic dissection be part of the mindset, in the differential diagnosis of a wide variety of presentations. If aortic dissection is even remotely entertained, please image the patient. Once a CT scan, TEE, or MRI scan has been performed, the correct diagnosis sis all but assured. We respect our colleagues in the Emergency Department for the great job they do "sifting out" the few aortic dissection cases from the hundreds of patients they see with chest or abdominal symptoms. (See also Section 5: Litigation in Aortic Disease.)

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DISCUSSION AND COMMENTARY

Questions for the Authors

How does a frontline physician practically separate out the rare patient with an aortic dissection from the multitudes of patients with myocardial infarction, or other causes of chest symptoms?

When patients with acute aortic syndromes present in the classic manner with typical symptoms and signs, making the correct diagnosis is not difficult. Recall that the pain of aortic dissection is typically of sudden and dramatic onset, as opposed to the crescendo or stuttering course seen in myocardial infarction. Evidence of end-organ malperfusion should alert the clinician to consider acute aortic dissection. The real challenge for the front-line physician is in suspecting an acute aortic syndrome in the patient who presents with atypical features. Recall that women, the elderly, diabetics, and those with prior cardiac or aortic surgery are more likely to present with atypical features, including nonspecific chest pain or synocope. An even higher index of suspicion is required when evaluating symptoms in these patients, especially when more common diagnoses (e.g., myocardial infarction) have been ruled out.

How much can fairly be expected of the frontline physicians in recognizing aortic dissection in a patient presenting solely with abdominal symptoms? Aortic dissection must be very low down in the differential diagnosis among the myriad of patients seen in an emergency room with abdominal pain or nausea.

A high index of suspicion for aortic dissection is necessary whenever evaluating abdominal pain in patients at risk for this type of atypical presentation, especially when a more obvious diagnosis has not been made. Patients predisposed to presenting with abdominal pain include the elderly patient with hypertension or known aortic aneurysm or patients who have had prior aortic surgery. The physical exam should always include careful palpation and auscultation of the abdomen for pulsatile mass or bruit and a thorough examination of the peripheral vasculature for pulse deficits should be documented. Laboratory testing may confirm evidence of end-organ malperfusion, including acute renal insufficiency or mesenteric ischemia. Appropriate aortic imaging tests should be obtained for any patient with unexplained abdominal pain that has these risk factors or physical signs.

Do you feel that there is ever a role for going directly to the operating room in a critically ill patient with suspected aortic dissection even without an imaging study (e.g., in a hypotnesive patient with a unilateral pulse deficit)?

When the pretest probability of acute dissection is intermediate or less, the most easily obtained aortic imaging test should be sought to confirm the diagnosis. However, acute aortic dissection causing hemodynamic instability is a surgical emergency that requires rapid surgical intervention. In these patients, withholding surgery until confirmatory imaging studies are obtained may create an unacceptable delay in delivering life-saving treatment. When the diagnosis of acute dissection

is highly likely based on presenting characteristics and physical signs, the cardiac and surgical consultants should be notified immediately, and an operating room should be emergently prepared to minimize logistical delays. When available, the ideal imaging study in this situation is a portable transesophageal echocardiogram (TEE), which can follow the patient into the operating room and rapidly confirm the diagnosis just prior to surgery.

How does one identify the "reverberation artifact" that can cause a false appearance of an aortic flap on echocardiography (TTE or TEE)? What are the distinguishing characteristics?

Reverberation artifact usually mirrors an adjacent structure (i.e., a calcified segment of aortic wall) and "moves" in parallel to this reference structure. In contrast, a true aortic dissection flap moves independently of surrounding structures, often undulating in more than one plane. To better distinguish artifact from an actual dissection flap, one should examine the structure, utilizing multiple viewing angles, to ensure the abnormality makes sense anatomically.

5

Epidemiology: Incidence, Prevalence, and Trends

John A. Elefteriades

Section of Cardiothoracic Surgery, Yale University, New Haven, Connecticut, U.S.A.

John A. Rizzo

Department of Epidemiology, State University of New York at Stony Brook, Stony Brook, New York, U.S.A.

INTRODUCTION

For multiple reasons, it is a challenge to assess the epidemiology (incidence and prevalence) of aortic aneurysms and their corresponding acute aortic diseases. The methodological challenges include the following:

1. *Referral center bias*. Tertiary referral centers that specialize in treatment of aortic diseases receive patients from a broad geographic territory. The number of patients treated at such centers does not, therefore, directly reflect the incidence or prevalence of aortic diseases in the hospital environs.
2. *Unknown presence of aneurysm*. Unlike many other cardiac and pulmonary diseases, aneurysms produce no specific symptoms in over 95% of affected patients. Thus, large pools of patients go undiagnosed unless they have undergone screening imaging studies—almost always for other purposes.
3. *Misdiagnosis as myocardial infarction*. Frequently, patients who enter an emergency room with aortic rupture or dissection and promptly die are misdiagnosed as "heart attack" (1). This is understandable. The patient presents with chest pain, he often loses consciousness, instability of vital signs ensues, and the patient dies in electromechanical dissociation. Thus, routine autopsies on patients dying in the emergency room are

required to ascertain the true incidence of death from aortic rupture and dissection. Anagnostopoulos has said, "Acute aortic dissection is the most common catastrophe involving the aorta" (1). This statement is based on the recognition that autopsy studies disclose that many patients thought to have died from myocardial infarction have actually succumbed from aortic dissection (1,2).

4. *Confusion in terminology*. It is common for three related but distinct entities—acute aortic transection, rupture of aortic aneurysm, and aortic dissection—to be confused, both in substance and in terminology (Fig. 1). Acute aortic transaction is a traumatic phenomenon, with circumferential tearing of the wall of the aorta, without propagating dissection. The aortic wall is intrinsically normal and resistant to the dissection process. Rupture of aortic aneurysm is self-explanatory; however, confusion in terminology may arise if an acute aortic transaction or an acute aortic dissection happens to rupture—a common eventuality. Acute aortic dissection refers to the very specific process of separation of layers of the aortic wall discussed fully in other portions of this book. For dissection to occur, the aortic wall must nearly always be affected by structural disease of the media. These three conditions—acute aortic transaction, ruptured aortic aneurysm, and acute aortic dissection—are frequently confused, leading to difficulties in categorization for epidemiologic purposes.
5. *Limitations of administrative databases*. Administrative data bases—such as those maintained by state and Federal governments, by insurers, and by hospitals and hospital systems—rarely are so detailed as to accommodate the subtleties of the factors enumerated here. Thus, data on incidence and prevalence arising from such databases are inherently flawed.

Despite these considerable methodological limitations, multiple studies have assessed the epidemiology of abdominal and thoracic aortic aneurysm (3–17). Relatively self-contained populations in Olmstead County (Minnesota) and Upsalla

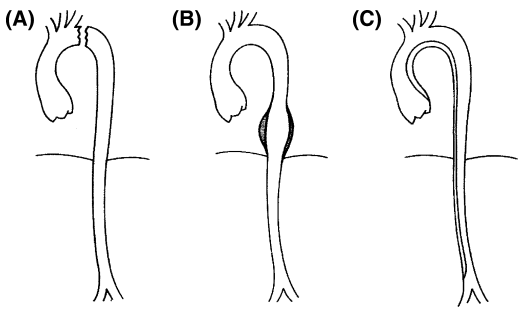

Figure 1 Three commonly confused disorders. (**A**) Acute aortic transaction. (**B**) Degenerative aneurysm of the descending aorta. (**C**) Acute aortic dissection. Confusion in terminology wreaks havoc with epidemiologic studies. *Source*: From Ref. 20.

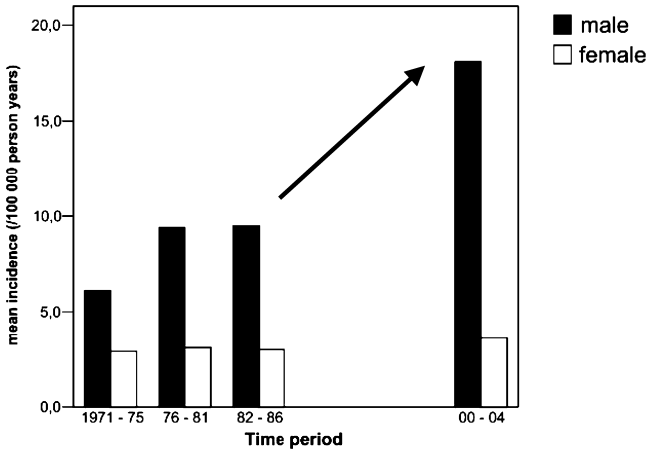

Figure 2 Note increased incidence of ruptured abdominal aortic aneurysm in total population of Malmo, Sweden, between 1971 and 2004. *Source*: From Ref. 7.

(Sweden) (Fig. 2) have contributed immensely to our understanding of the epidemiology of aneurysm disease. Nonetheless, given the methodological issues discussed earlier, the incidence and prevalence figures for aortic aneurysms should best be viewed as rough approximations of the true rates. The most important findings are summarized by category in the accompanying Table 1.

PREVALENCE

The most recent data available from the Centers for Disease Control indicates that aneurysm disease (abdominal and thoracic) is the 17th most common cause of death in all individuals and the 15th most common in individuals aged over 65, accounting for 14,810 and 12,040 deaths annually in these two groups, respectively (3) (Table 2). Note that aneurysm causes more deaths than Human Immunodeficieny Virus (HIV) disease. These figures almost certainly represent underestimates, not only for the reasons enumerated earlier in this chapter, but also because many aneurysm-related deaths (especially for the ascending aorta) are likely included in the group classified as "cardiac" and not tabulated in the aneurysm figures. In fact, experts have suggested that 30,000 to even 60,000 aneurysm related deaths per year in the United States per year represent a more reasonable estimate (1).

Abdominal aortic aneurysm (AAA) affects about 5% of individuals over 65 years of age. The prevalence is considerably higher in men than in women (4–6).

INCIDENCE

The incidence of ruptured AAA is about 10 per 100,000 patient years (7). For men in their 60s, this rate rises to about 50 per 100,000 patient years. For men in their

Table 1 Summary of Available Information on Incidence of Aneurysm Disease

AAA	TAA
Prevalence	
Prevalence of AAA in individuals 65–89 yrs old Overall: 5.5% (4) Men: 5–7% (5,6) Women: 1.5% (5,7)	Aneurysm disease is 17th most common cause of death overall, 15th most common in patients over 65 yrs (3)
Aneurysm disease is 17th most common cause of death overall, 15th most common in patients over 65 yrs (3)	
Incidence	
Incidence of ruptured AAA (rAAA) is 10.6/100,000 patient-yrs (7)	Incidence of TAA is 10.4/100,000 patient yrs (equally divided between M and F) (8)
For men (7)	
60–69 yrs old, the incidence of rAAA is 46/100,000 patient-yrs	—F older than M at diagnosis (75 vs. 63 yrs)
70–79 yrs old, the incidence of rAAA is 117/100.000 patient-yrs	
Rate of acute complications	
Yearly risk of rupture is about 1% for AAA 4.0–5.4 cm (4)	Incidence of AAD is 3.5/100,000 (11,12) Incidence of rTAA is 3.5–5/100,000 (10,11) Thus total incidence of acute thoracic phenomena is 7/100,000 (11) 79% of ruptures of TAA occur in F (8)

Benefit of screening programs (all re: AAA)

Screening for AAA significantly reduces AAA-related mortality in men 65 to 80 yrs old (OR 0.57). (No significant reduction in all-cause mortality) (4).

Cigarette smoking is the most significant risk factor distinguishing populations at higher risk for AAA (OR 5.07) (4).

Prevalence of AAA 5.1% in smokers
1.5% in nonsmokers

89% of AAA-related deaths occur in smokers

To prevent one AAA-related death, only 500 smokers need to be screened, compared to 1783 smokers

Other risk factors for AAA included (4)

Family history (OR 1.94)
CAD (OR 1.52)
Age (OR 1.71/7 Yr interval)
Hypercholesterolemia (OR 1.44)
Cerebrovascular disease (OR 1.28)

Protective risk factors were: female gender (OR 0.17), DM (OR 0.52), black race (OR 0.53).

(*Continued*)

Table 1 Summary of Available Information on Incidence of Aneurysm Disease (*Continued*)

Benefit of screening programs (all re: AAA)

Cost per life saved is approximately $10,000 (10).

A single negative ultrasound screening at 65 yrs suffices, as this virtually excludes future risk of AAA rupture or AAA-related death (4).

Decision-making (all re: AAA) (see chapter 12 for TAA)

HSTAT meta-analysis of surgical intervention criteria for AAA leads to the following conclusions:

3.0–3.9 cm AAA	Very low risk of rupture	Periodic surveillance
4.0–5.4 cm AAA	Yearly rupture rate ~1%	Surgery or surveillance
5.5 cm or larger AAA	Substantial rupture risk	Surgery advised

Trends

The incidence of rAAA is increasing dramatically (7)	The incidence of TAA is increasing dramatically (8)
1971–1986: 4.9/100,000 patient-Yr	Increased three times over 15 yrs
Current: 10.6/100,000 patient-Yr	

Abbreviations: AAA, abdominal aortic aneurysm; AAD, acute aortic dissection; CAD, coronary artery disease; HSTAT, health services/technology assessment text; TAA, thoracic aortic aneurysm.

Table 2 Leading Causes of Death

Ages 65+		All ages	
Heart disease	563,390	Heart disease	685,089
Cancer	388,911	Cancer	556,902
Stroke	138,134	Stroke	157,689
COPD	109,139	COPD	126,382
Alzheimer's	62,814	Trauma	106,277
Influenza	57,670	Diabetes	74,219
Diabetes	54,919	Influenza	65,183
Kidney disease	35,254	Alzheimer's	63,457
Trauma	34,335	Kidney failure	42,453
Septicemia	26,445	Septicemia	34,069
Hypertension	18,657	Suicide	31,484
Parkinson's	17,566	Liver disease	27,503
Pneumonia	15,850	Hypertension	21,940
Arteriosclerosis	12,336	Parkinson's	17,997
Aortic aneurysm	12,040	Homicide	17,732
Benign neoplasm	10,838	Pneumonia	17,335
Liver disease	10,210	Aortic aneurysm	14,810
Suicide	5,248	Perinatal	14,378
Anemia	3,539	HIV	13,658
Peptic ulcer	3,110	Benign neoplasm	13,563

Abbreviation: COPD, chronic obstructive pulmonary disease.
Source: From Ref. 3.

70s, this rate rises to over 100 per 100,000 patient years. (This corresponds to one out of every thousand men in their 70s suffering rupture of AAA each year.)

The incidence of thoracic aortic aneurysm is also about 10 per 100,000 patient years (8). Women and men have a similar incidence, but the age at diagnosis is a decade higher in women (70s) than in men (60s).

RATE OF ACUTE COMPLICATIONS OF CHRONIC AORTIC CONDITIONS

This book is about acute aortic diseases, so we are especially interested in the rates at which aneurysms, abdominal and thoracic, rupture or dissect.

For patients with abdominal aortic aneurysms about 1% of those with moderate-sized aneurysms (4.0–5.4 cm) will suffer rupture each year. The rate rises, of course, for larger aneurysms. For abdominal aortic aneurysms larger than 5.5 cm, the rupture risk exceeds the surgical risk, and pre-emptive surgical extirpation is recommended (4).

Among patients with thoracic aortic aneurysms, the rate of rupture, dissection, or death rises to 14.1% per year for aneurysms 6 cm or more in diameter (9). This is a huge number, representing a virulence beyond that of most other diseases. The behavior of thoracic aortic aneurysms is covered fully in Chapter 12.

The total yearly incidence of rupture or dissection of thoracic aortic aneurysm is about 7% per year, equally divided between rupture and dissection (10,11,12). A curious and as yet unexplained finding is that 79% of thoracic aortic aneurysm ruptures occur in women (2,11,12).

Benefits of Screening Programs

The epidemiological implications of screening programs have been studied quite extensively for abdominal aortic aneurysms (but not for thoracic) (4,13).

Screening programs based on abdominal ultrasound clearly detect aneurysms effectively and reduce the number of aneurysm-related deaths. The medical care cost per single aneurysm-related death prevented is about $10,000 USD (13).

One very important benefit of screening is that a single negative ultrasound at age 65 suffices: patients without an aneurysm at this age will simply not die of aneurysm rupture (4).

Efforts have been expended to define populations at risk whose routine screening would be more cost-effective than screening the general population. Family history, age, male sex, coronary artery disease, cerebrovascular disease, and hypercholesterolemia all represent incremental risk factors for aneurysm disease, and, thus, constitute potential criteria for opportunistic population screening. However, one other characteristic dwarfs the statistical significance of those other risk factors: cigarette smoking (4). AAA is five times more common in smokers, and 89% of all aneurysm ruptures occur in smokers. So, screening smokers is a cost-effective way to look for abdominal aortic aneurysm disease. In fact, one need screen only 500 smokers (compared to 1700 nonsmokers) to prevent one aneurysm-related death.

TRENDS

There is little doubt that the diagnosis of aortic aneurysm and its acute complications are being made with greater frequency. The Swedish group found a doubling in the rate of ruptured AAA over several decades (7). The Mayo group found a tripling in the diagnosis of thoracic aortic aneurysm over 15 years (8).

This trend toward increased incidence of aneurysm disease over the last three decades has been confirmed also for the United States as a whole by the Centers for Disease Control (14), for Scotland (15), for the Netherlands (16), and for England and Wales (17).

So, the diseases of interest to this book are definitely being diagnosed more frequently than ever before.

It is unclear how much of this increased incidence is due to several important factors:

Improved Diagnosis in This Era of Common Application of Three-Dimensional Imaging (Computed Tomography Scan, Magnetic Resonance Imaging, and Echocardiography)

This seems quite likely an important factor in the increased incidence, as so many of our aneurysm patients have the first diagnosis made on a 3D image done for entirely unrelated reasons.

The Aging of Our Population

This is certainly an important factor, as aneurysm disease increases with age.

True Increase in Disease Incidence, Independent of Diagnosis and Population Age

This possibility is intriguing. Best et al. feel that, in addition to improved diagnosis of existing cases and aging of the population, a "genuine and persistent rise in the incidence of AAA has probably occurred" (15). They find this increase especially interesting in terms of its contrast with the general decrease in arteriosclerotic vascular disease realized through the vigorous preventive efforts of the last several decades. If we are living in an era of true increase in the incidence of aneurysm disease, the relevant causes are obscure.

Genetics

There is an important observation regarding the impact of genetic syndromes on the epidemiology of thoracic aortic aneurysms. This concerns the relative contributions of Marfan's disease and bicuspid aortic valve disease to the incidence of aortic aneurysm.

Marfan's disease is more widely recognized as a cause of aneurysm and dissection. Nonetheless, Marfan's disease is relatively uncommon, affecting only 1 in 10,000 live births. A patient with Marfan's disease has a 40% likelihood over a lifetime of developing an aortic dissection.

Table 3 Comparison of Epidemiology of Marfan's Disease and Bicuspid Aortic Valve, with Special Reference to Number of Cases of Aortic Dissection Brought on by Disease

	Incidence	AAD likelihood (lifetime)	AADs caused (as % of population)
Marfan's disease	1/10,000 (0.01%)	40%	0.004%
Bicuspid aortic valve	2/100 (2%)	5%	0.1%
			BAV = 25 × MFD

Note: BAV causes 25 times more acute aortic dissections than MFD.
Abbreviations: AAD, acute aortic dissection; BAV, bicuspid aortic valve; MFD, Marfan's disease.

While a patient with bicuspid aortic valve has only a 5% chance over a lifetime of developing an aortic dissection, this disease is very common—in fact, this is the most common congenital condition affecting the human heart. Bicuspid valve disease affects 2% of the overall population. It has been estimated that bicuspid valve disease accounts for more morbidity and mortality than all other congenital heart diseases combined (18,19).

In Table 3, we perform the relative calculations, and, it turns out, bicuspid valve disease accounts for an order of magnitude more aortic dissections than the better-appreciated Marfan's disease.

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DISCUSSION AND COMMENTARY

Question for the Authors

Do you feel that routine screening for aortic aneurysm will become standard practice?

We feel that this is happening already and is appropriate. Elderly males with risk factors for arterial disease are already being commonly screened by their primary physicians using ultrasound exams for abdominal aortic aneurysm.

The word is getting out that abdominal and thoracic aortic aneurysm are genetically transmitted, so family members are increasingly being screened. For the abdomen, an ultrasound exam suffices. For the thorax, we use a transthoracic echo for young individuals (< 40) and a transthoracic echo supplemented by a CT scan or MRI exam for those family members who are older.

Screening of the general population is occurring incidentally by virtue of the huge number of CT exams being done for other reasons (trauma, pulmonary symptoms, chronic smoking, etc.) Many, thoracic aortic aneurysms are picked up in this way.

In terms of a useful clinical vignette, we use the "thumb-palm" sign to screen for inherited connective tissue disease (Fig. A). The thumb should not be able to cross beyond the edge of the palm in a normal individual. In connective tissue disease, the digits are excessive in length, and the ligaments are lax, allowing the thumb to cross beyond the edge of the palm. This screening test, remarkably, is free.

Figure A A positive "thumb-palm" sign. This young woman has nonMarfan's familial thoracic aortic aneurysm. Note the excessive length of the digits and the hypermobility of the thumb joint, permitting the thumb to extend beyond the edge of the palm. We recommend screening for such patients.

6

Genetic Basis of Thoracic Aortic Aneurysms and Dissections

Dianna M. Milewicz, Hariyadarshi Pannu, Nili Avidan, Dong-chuan Guo, and Van Tran-Fadulu

Division of Medical Genetics, Department of Internal Medicine, University of Texas Medical School, Houston, Texas, U.S.A.

INTRODUCTION

The natural of aneurysms involving the ascending aorta is to progressively enlarge over time, leading to an ascending aortic dissection in the absence of prophylactic repair of the diseased segment of the aorta. Therefore, thoracic aortic aneurysms and ascending aortic dissections are related conditions, termed thoracic aortic aneurysms and dissections (TAAD) for this chapter. It is well established that known genetic syndromes predispose to TAAD, such as Marfan syndrome (MFS). This chapter will review genetic syndromes that are associated with TAAD, including MFS and Loeys-Dietz aortic syndrome (LDAS).

The majority of patients with TAAD do not have a named genetic syndrome. Up to 20% of patients referred for surgical repair have a family history of TAAD, suggesting a significant genetic component to this disease. Families characterized with multiple affected members have demonstrated that the condition is typically inherited in an autosomal dominant manner with decreased penetrance and variable expression. This chapter will also review the mapping and identification of genes causing nonsyndromic, familial forms of TAAD.

KNOWN GENETIC SYNDROMES ASSOCIATED WITH THORACIC AORTIC ANEURYSMS AND DISSECTIONS (TABLE 1)

MFS is an inherited connective tissue disorder characterized by cardiovascular, skeletal, and ocular complications. MFS is inherited in an autosomal dominant manner; one-quarter of patients do not have a family history and result from new mutations (1). The predominant cardiovascular complication associated with MFS is dilatation of the ascending aorta, typically beginning at the sinuses of Valsalva. Other cardiovascular complications include both ascending and descending aortic dissections, along with mitral valve prolapse and regurgitation. The specific ocular manifestation of MFS is lens dislocation, which is present in approximately 60% of patients. The skeletal features of MFS include dolichostenomelia (long, thin extremities), arachnodactyly (long, slender, curved fingers, like a spider's legs), scoliosis, joint laxity and pectus deformities. The diagnosis of MFS is currently primarily a clinical diagnosis that is based on Ghent nosology, which requires two major manifestations and involvement of third system in an index case (Table 2) (2). The cardiovascular complications, primarily progressive dilation of the aortic root leading to an ascending aortic dissection, are the major cause of morbidity and mortality in MFS (3–6).

Aortic dilation observed in MFS patients is caused by defects in a specific component of the elastic fiber, fibrillin-1. The elastic fiber is biochemically and histologically composed of a core of elastin protein surrounded by a peripheral mantle of 10 nm micro fibrils (7). Microfibrils contain several proteins, with the major and best-characterized components being the fibrillin proteins, termed fibrillin-1 and fibrillin-2. Two homologous genes encode the fibrillin proteins,

Table 1 Documented Genetic Causes of Thoracic Aortic Aneurysm

Syndrome	Abnormal protein	Genetic mutation
MFS	Fibrillin-1	*FBN1* (>600 mutations) on chromosome 15 (15q15-32)
		MFS2 on chromosome 3 (3p24.2-p25)
		MFS2 (*TGFBR2*)
Lowys-Dietz syndrome		*TGFBR1*
		TGFBR2
Beals' syndrome (congenital contractural arachnodactyly)	Fibrillin-2	*FBN2*
Turner's syndrome		*45, XO*
Noonan's syndrome		
Ehlers-Danlos vascular type	Type III Collagen	*COL3A1*
Ehlers-Danlos kyphoscoliotic form	Procollagen lysine hydroxylase	*POLD 1*

Abbreviations: FBN, fibrillin; MFS, Marfan's syndrome; TGFBR, transforming growth factor β receptor.

Table 2 Quick Guide to Diagnosis of Marfan's Disease

	Cardiovascular system	Skeletal system	Ocular system	Pulmonary system	Skin and integument	Dura	Family history/genetics
Major criteria	One required: Dilatation of Asc Ao (± AI), involving sinuses of Valsalva AAD	Four required: Pectus carinatum Pectus excavatum (requiring surgery) Reduced upper to lower segment ratio or I increased arm span to height ratio Positive wrist and thumb signs Elbow extension reduced below 170° Pes planus Protrusion acetabulae	Ectopia lentis	None	None	Dural ectasia	Parent, child, or sibling with Marfan's disease *FBN1* mutation
Minor criteria	MVP (± prolapse) Dilatation main PA (patients less than 40 yo)	Pectus excavatum (mod) Hypermobile joints Crowding of teeth or highly arched palate	Flat cornaes Increased axial length of globe Hypoplastic iris or ciliary muscles, causing decreased meiosis	Spontaneous pneumothorax Apical blebs hernias	Striae Recurrent or incisional	None	None

(*Continued*)

Table 2 Quick Guide to Diagnosis of Marfan's Disease (*Continued*)

	Cardiovascular system	Skeletal system	Ocular system	Pulmonary system	Skin and integument	Dura	Family history/genetics
Involvement (req'd to say organ system involved)	One major or one minor criterion	Two major or one major and one minor criteria	One major or two minor criteria	One minor criterion	One minor criterion	Major criterion	Major criterion

Note: Diagnosis requires

For an index case (w/o documented mutation)	Major criteria in two organ systems, plus Involvement of another organ system
For an index case (w/ documented mutation)	Major criterion in one organ system, plus Involvement of another organ system
For a relative of a known case	Major criterion in the family history, plus Major criterion in one organ system, plus Involvement of another organ system

Definitions and normals:
Upper to lower segment ratio = distance from top of head to symphisis pubis / distance symphisis pubis to floor (normal 0.89–0.95).
Arm span to height ratio (normal <1.05).
Wrist sign = positive if a person's thumb and little finger overlap when gripping own wrist.
Thumb sign = positive if the entire nail of a person's thumb projects beyond the border of the hand when their fist is closed around their thumb.
Abbreviations: AAD, ascending aortic dissection; AI, aortic insufficiency; Ao, aorta; Asc, ascending; MVP, mitral valve prolapse; PA, pulmonary artery.
Source: From Refs. 60, 61.

FBN1 on chromosome 15 (15q15-32) and *FBN2* on chromosome 5 (5q23-31) (8). These genes encode large, cysteine-rich glycoproteins (approximately 350 kDa) with a similar repetitive domain structure (9–11). Mutations in *FBN1* are the cause of MFS. Numerous *FBN1* mutations have been identified in MFS patients and over 600 mutations have been entered in the international Marfan database (http://www.umd.be: 2030/). The majority of them are missense mutations, many of which involve the most repeated domain in the molecule, the calcium binding epidermal growth factor life (cbEGF) domains (Fig. 1) (12).

FBN1 mutations have been identified in individuals and families with isolated features of the MFS who do not fulfill the diagnostic criteria of the MFS, including isolated skeletal features and lens dislocation (13,14). TAAD in the absence of other manifestations to fulfill the criteria can occur in individuals due to *FBN1* mutations. Two mutations, D1155N in *FBN1* exon 28 and P1837S in *FBN1* exon 44, were identified in two unrelated patients with TAAD and without typical MFS skeletal and ocular complication (15). The mutation G1127S in *FBN1* exon 27 was found in 9 of the 10 members of a family in whom the

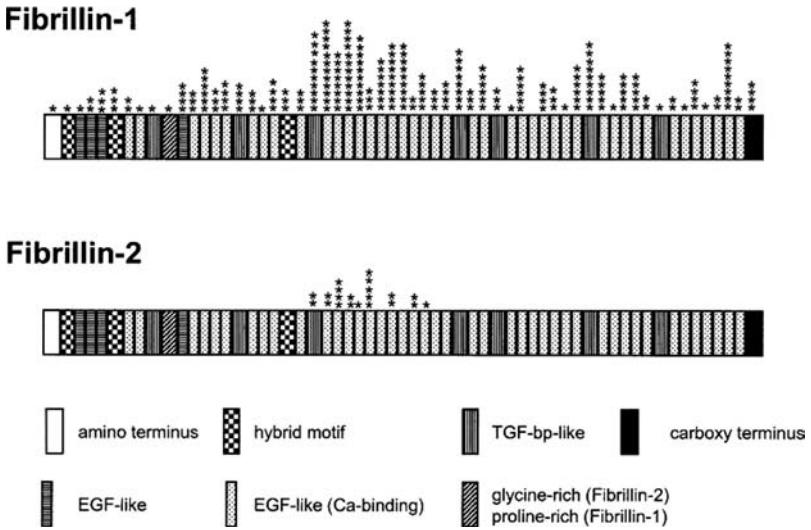

Figure 1 Domain organization of fibrillin-1 and fibrillin-2. Boxes designate the structural domains of the fibrillin proteins and are indicated as follows: calcium-binding epidermal growth factor-like domains (cbEGF, *dotted*); EGF-like domains that do not bind calcium (*horizontal lines*); novel domain containing eight cysteines that is also found in transforming growth factor beta-binding protein (TGF-bp-like, *vertical lines*); hybrid domains that are combinations of the cbEGF and TGF-bp-like domain (*checkered*); unique amino terminus (*white*); glycine-rich and proline-rich motif (*diagonal lines*); and carboxyl terminus (*black*). The domain indicated by diagonal lines is proline-rich in fibrillin-1 and glycine-rich in fibrillin-2. Each asterisk appearing above the schematic indicates the domain location of a characterized mutation in fibrillin-1 and fibrillin-2. *Source*: From Ref. 57.

ascending aortic disease had been identified. None of the individuals had typical MFS features (16,17). These studies indicate that although *FBN1* mutations can cause TAAD in individuals who do not have MFS, this is a rare cause of this disorder.

A second locus for MFS was identified at 3p24.2-p25 (*MFS2*) based on linkage analysis of a large French family in whom the diagnosis of MFS has been controversial (18,19). Although affected members of this family did not meet the diagnostic criteria for classical MFS, the condition was characterized by skeletal and cardiovascular complications similar to MFS. Recently, mutations in the gene for transforming growth factor β receptor Type II (*TGFBR2*) have been identified as the cause of disease at the *MFS2* locus (20). The *TGFBR2* mutations in patients with MFS were three missense mutations (L308P, S449F, and R537C) and a splicing error of exon 6. These *TGFBR2* mutations in MFS patients all involved the serine-threonine kinase domain, and have been determined to diminish receptor signaling induced by TGF-β when co-expressed with a TGF-β responsive promoter in an in vitro assay system.

Heterozygous mutations in both *TGFBR2* and *TGFBR1* were reported in ten families with a newly described syndrome associated with disruption in cardiovascular, craniofacial, neurocognitive, and skeletal development (21). The syndrome was originally described as Furlong syndrome but has been more recently termed Loey-Dietz syndrome (LDS) (22–24). Clinical features of the syndrome include vascular disease involving initially dilatation, and then dissections, of the ascending aorta but also aneurysms and dissections of peripheral arteries associated with generalized arterial tortuousity. The craniofacial abnormalities include widely spaced eyes (hypertelorism), bifid uvula and/or cleft palate. The skeletal abnormalities are similar to those observed with MFS and include arachnodactyly, pectus deformities, camptodactyly (fixed flexing of the 5th digit), scoliosis, and joint laxity (Fig. 2). The described mutations largely occurred in the intracellular kinase domains of these receptors (Fig. 3). Therefore, it was surprising when fibroblast cells explanted from individuals heterozygous for these mutations did not demonstrate altered TGF-β signaling. Tissues from affected individuals showed increased expression of both collagen and connective tissue growth factor, as well as nuclear enrichment of phosphorylated Smad2, suggesting increased TGF-β signaling in these tissues.

Mutations in the gene for fibrillin-2, *FBN2*, cause congenital contractural arachnodactyly or Beals syndrome (CCA), a syndrome that is closely related to MFS (25). CCA patients have the skeletal features of MFS, along with congenital contractures and a crumpled appearance to the helix of the ear, but lack the ocular complications. Although CCA patients were initially thought not to have aortic root dilatation, recently it has been shown that a subset of CCA patients with characterized *FBN2* mutations have aortic dilation that can progress over time (26–28). It has not been determined if the aortic root dilatation observed in CCA patients will progress to aortic dissection or rupture, as it does in MFS. The *FBN2* mutations leading to CCA all cluster in a limited region of the fibrillin-2 protein (Fig. 1).

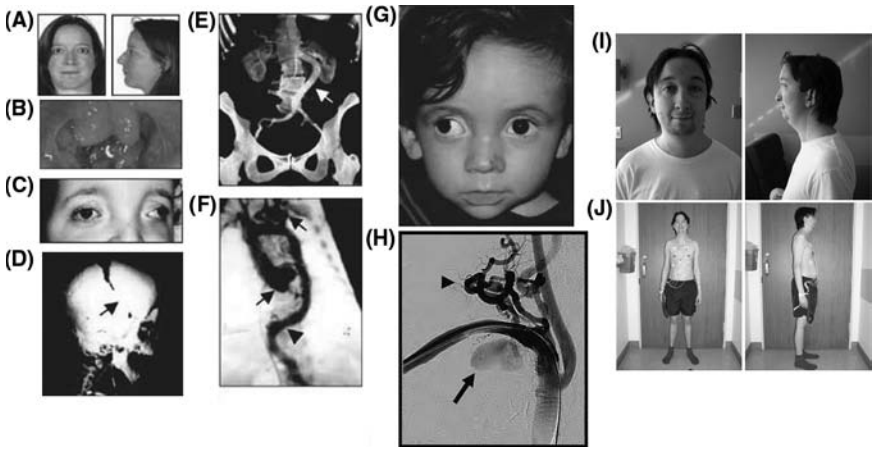

Figure 2 (*See color insert*) Variable clinical presentation of individuals with transforming growth factor β receptor (*TGFBR1* or *TGFBR2)* mutations. Individuals may present with hypertelorism and malar flattening (**A**); bifid uvula (**B**); marked hypertelorism with exotropia (**C**); premature fusion of the coronal suture of the skull (*arrow*, **D**); marked tortuosity of the aorta (*arrow head*), aortic root and subclavian artery aneurysms (*arrows*) or tortuous abdominal aorta (*arrow*) (**E,F,H**); micrognathia, retrognathia, downslanting palpebral fissures, and skeletal features including pectus excavatum, scoliosis, and pes planus (**G,I,J**). *Source*: From Refs. 21, 51.

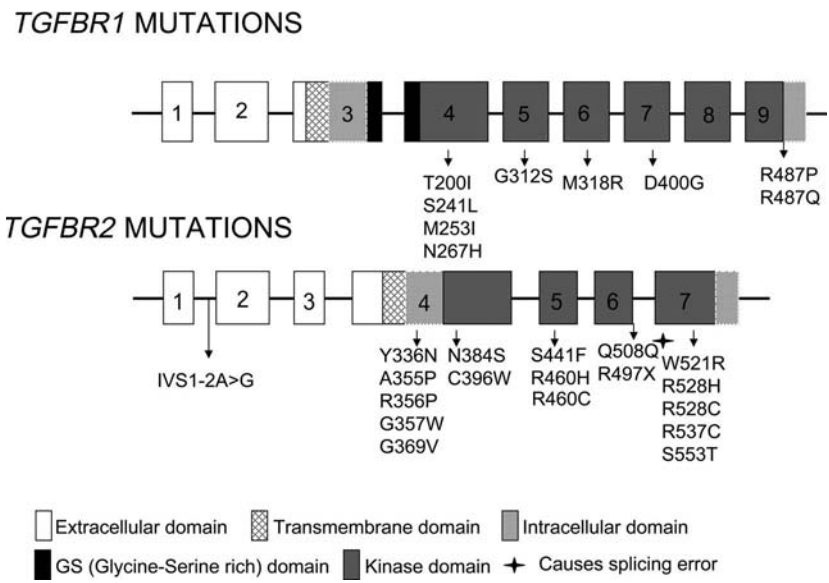

Figure 3 Heterozygous germline transforming growth factor β receptor *TGFBR1* and *TGFBR2* mutations in syndromic and nonsyndromic aortic disease. Genomic and protein structure of the *TGFBR1* and *TGFBR2* genes showing known mutations previously identified in MFS, LDS, Furlong syndrome, and TAAD. *Source*: From Ref. 58.

Turner syndrome is a sex aneuploidy syndrome in which the most frequent chromosome constitution is 45, X (also written 45, XO to indicate the loss of one of the two X chromosomes). A significant number of patients with Turner syndrome have other karyotypes that involve mosaicism or abnormalities of the second X chromosome. The incidence of Turner syndrome is approximately 1 in 5000 live female births. The typical features of Turner syndrome include short stature, gonadal dysgenesis, unusual facial appearance, neck webbing, low posterior hairline, broad chest with widely spaced nipples, and an increased frequency of renal and cardiovascular abnormalities. The cardiovascular problems include bicuspid aortic valve (BAV), coarctation of the aorta, hypertension, and TAAD (29,30). Aortic root dilatation is present in approximately 40% of women with Turner syndrome. It has recently been suggested that the risk of aortic dissection in patients with Turner syndrome is increased with growth hormone treatment (31). Routine surveillance of the aortic root diameter is currently recommended for women with Turner syndrome.

Noonan syndrome is an autosomal dominant condition that shares many phenotypic features with Turner syndrome. Congenital heart abnormalities, including pulmonary valve stenosis, hypertrophic cardiomyopathy, and other structural defects are present in 50% to 80% of patients. TAAD is a rare finding in patients with Noonan syndrome (32,33).

Ehlers-Danlos syndrome Type IV "or the vascular form" is a disorder characterized by thin, translucent skin, spontaneous bowel rupture, and arterial fragility (34). The vascular fragility includes aneurysm with rupture and dissection. Although the aorta can be involved, it is typically the smaller arteries that rupture or dissect in this syndrome. This condition results from mutations in the *COL3A1* gene, which encodes a polypeptide of Type III collagen. The vascular complications of this syndrome are difficulty to manage, leading to premature death at a median age of 48 years.

A few other genetic conditions predispose individuals to TAAD. Polycystic kidney disease is an autosomal dominant, late onset disorder characterized by progressive cyst development and bilaterally enlarged polycystic kidneys. Although this disease is primarily associated with intracranial aneurysms, a rare patient will have TAAD (35). Ehlers-Danlos syndrome Type VI (kyphoscoliotic form) is characterized by kyphoscoliosis, joint laxity, and muscle hypotonia and is caused by deficient activity of the enzyme procollagen lysine hydroxylase (36). Vascular rupture is a life-threatening feature of this disorder, and both aortic dilatation/dissection and rupture of medium-sized arteries may occur.

FAMILIAL THORACIC AORTIC ANEURYSMS AND DISSECTIONS

The initial studies to determine if there was a genetic contribution to nonsyndromic TAAD were familial aggregation studies. Family histories were obtained on patients with ascending aortic aneurysms or dissections to determine if they had first-degree relatives with similar aortic disease. These studies have indicated that between 13% and 19% of individuals referred for repair of a TAAD have a

first-degree relative with similar aortic disease (37,38). Initial characterization of TAAD families with multiple affected members typically demonstrated autosomal dominant inheritance with decreased penetrance and variable expression (39,40).

We have identified and characterized over 350 families with multiple family members with thoracic aortic aneurysms and/or dissections. In these families, primarily males are affected (two-thirds were men and one-third were women). There is a wide range in age of initial diagnosis of aortic disease, ranging from 1 to 87 years of age. Even within a single family, the age of diagnosis can range from 14 to 83 years of age (Fig. 4) (41). The average age of affected individuals is approximately 50 years, with no difference in the affected ages of men and women. The inheritance of the aortic disease in 155 of these families was determined by visual inspection of pedigrees. The majority of the families demonstrate autosomal dominant inheritance. Within the families, there are multiple examples of decreased penetrance in women, that is, the woman has inherited the defective gene causing TAAD but does not exhibit any evidence of aortic disease, and had at least one offspring with TAAD.

The majority of TAAD families have one or more family members with vascular disease extending beyond the ascending aorta, including aneurysm or

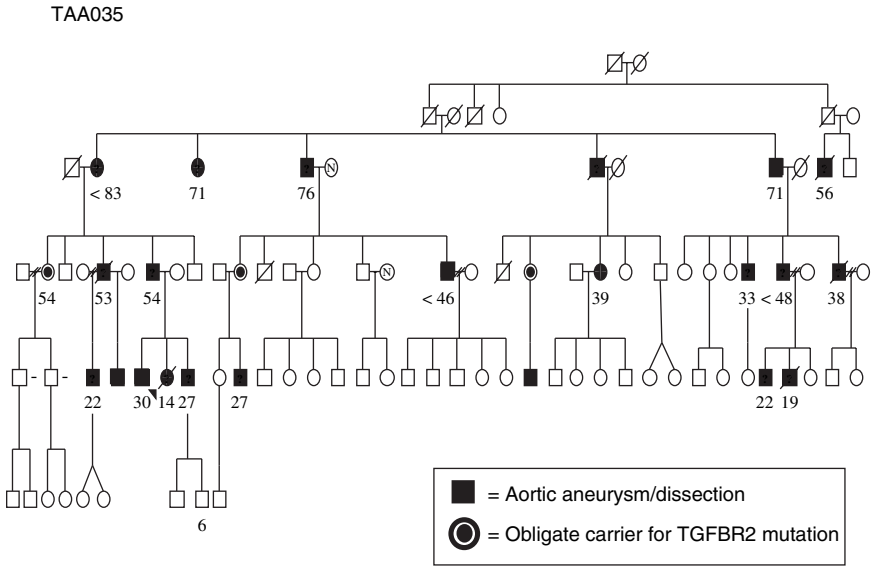

Figure 4 Pedigree of TAAD-family demonstrating autosomal dominant inheritance, decreased penetrance in women, and variable age of onset of disease. Aortic disease affected status is indicated as filled square (male) or circle (female), and obligate carriers (all female in this example) of the disease predisposition are indicated by a dot within the circle. Deceased individuals are indicated by a line across the symbol. Age at disease onset (where known) is indicated below the individual symbols. *Abbreviation*: TAAD, thoracic aortic aneurysms and dissection.

dissection in the descending aorta, abdominal aorta, cerebral vasculature, carotid arteries, and peripheral arteries. Many of the TAAD families have congenital cardiac features in one or more members as documented by echocardiogram or surgical repair, including bicuspid aortic valve (BAV), patent ductus arteriosus (PDA), and septal defects (ASD or VSD) (42,43).

Analysis of the inheritance of TAAD in the families collected indicates that the predisposition to develop TAADs is inherited in these families as mutations in a single gene and the phenotype has a variable age of onset and clinical presentation. In addition, decreased penetrance is evident, especially in the women in these families, that is, inheritance of the defective gene did not always result in aortic disease. Genetic mapping is an approach used to determine the location of the gene responsible for an inherited single-gene disorder in the human genome. Linkage describes the phenomenon that genetic markers, which are located near the defective gene causing the disease, will segregate with the disease phenotype in a family. Microsatellites and single nucleotide polymorphisms (SNPs) are the two most common genetic markers used for genetic mapping. A microsatellite marker is a short tandem repeat polymorphism and each repeat unit contains two to four nucleotides or bases. SNP represents an alteration in DNA sequence at a single nucleotide position. Microsatellite markers have higher variability or heterozygosity compared to the biallelic SNP markers. On the other hand, SNP markers are more abundant in human genomes, averaging one SNP per 500 to 1000 nucleotides compared to one microsatellite per 30,000 nucleotides. Recently, techniques have been developed that are extremely powerful for multiplexing biallelic SNP assays, which offer the possibility of simultaneously testing thousands of SNP loci in genome.

Linkage analysis involves studying the segregation of disease in large families with disease phenotype. If genetic markers are identified to cosegregate with a disease phenotype more often than expected by chance, this suggests that the defective gene is located close to these markers. Statistical analysis is used to compare the likelihood that two loci are linked to the phenotype to the likelihood that two loci are not linked. The common logarithm of ratio of these two likelihoods is the log-of odds ratio, which is called the LOD score. A maximum LOD score of 3.0 or greater is used as the criterion that two autosomal loci are linked, because the odds in favor of linkage with this LOD are 1000 to 1 or greater. A LOD score of −2.0 or less is considered to be sufficient to exclude linkage between two loci, because the chance that these loci are linked is only 1 to 100 or less.

One aspect critical to determining the gene involved in a disease is the identification of families with multiple affected members. We initially identified families with multiple members with TAAD. The DNA was collected from these families for genetic studies. In addition, we determined that the disease in these families was not due to mutations in the *FBN1* gene, the defective gene that causes the MFS.

For our gene mapping studies for familial TAAD, we have primarily used a large family to map the chromosomal location of the defective gene causing the

disease in the family. This approach is used in an attempt to avoid problems in mapping the gene due to genetic heterogeneity; that is, many different genes can cause disease in unrelated families. To map the first locus for familial TAAD, a genome-wide scan for the genetic defect causing the aortic disease was done using DNA from affected members from families TAA002 and TAA003. Genome-wide scan was performed using ABI Prism Linkage mapping sets-MD-10, which contains 382 microsattelite markers spaced approximately 10 cM apart throughout the genome. The marker data were analyzed using the affected-pedigree-member method of linkage analysis because of the decreased penetrance of the disorder. This analysis revealed three loci with multiple linked markers showing highly statistically significant regions of linkage for the TAAD gene in these families. Three candidate loci, a 38 cM region of chromosome 3q, a 52 cM region of chromosome 5q, and a 26 cM of region chromosome 16q, showed multiple linked markers significantly associated with the disease. Fine mapping was performed to verify the observed linkage using more microsatellite markers located on three candidate loci. Fine mapping used DNA from five TAAD families that included 18 affected, 33 unknown, and 14 unaffected individuals. The result of this analysis excluded the 3q and 16q loci as the location of the defective gene causing TAAD. However, three of the five families studied showed evidence of linkage to 5q markers.

Further fine mapping was performed on 15 TAAD families using 21 microsatellite markers to confirm the 5q loci and identify the critical interval. Linkage analysis confirmed that markers on 5q were linked to TAAD. Pairwise and multipoint LOD scores were calculated using MLINK and LINKMAP programs of the computer software FASTLINK version 3.P. Allele frequencies for each marker were obtained using the founders in the pedigrees. Based on the proportion of affected individuals in the pedigrees, the penetrance for the homozygous and heterozygous carriers of the disease allele was deduced as 10% for individuals under the age of 30 years, 30% between ages 30 and 40, 70% between ages 40 and 60, and 90% for individuals older than 60 years.

Linkage analysis showed that some of the families had significant positive LOD scores, whereas some of the families had significant negative LOD scores. Therefore, a heterogeneity test was performed to determine if the families with positive LOD scores are linked to the marker locus, while the families with negative LOD scores are unlinked to the marker locus (18). This analysis was done for the marker D5S2029 since this marker demonstrated the highest LOD score in some families. This analysis supported genetic heterogeneity for the condition ($p = 0.004$). The estimate of alpha, the proportion of families that are linked, was found to be 0.45. Nine families with the highest conditional probability of being linked to 5q13–14 were used for the multipoint analyses. A maximum LOD score (Z_{max}) of 4.74 at no recombination ($\theta = 0$) was obtained for the marker D5S2029. Family TAA002 has the highest LOD score of 1.75 for this marker (Fig. 5). Pairwise and multipoint LOD scores were tested in 38 TAAD families and 13 families showed a positive LOD score at *TAAD1* locus with maximum LOD score 6.5 for marker D5S2029. This result indicates that the *TAAD1* locus is a major locus for TAADs.

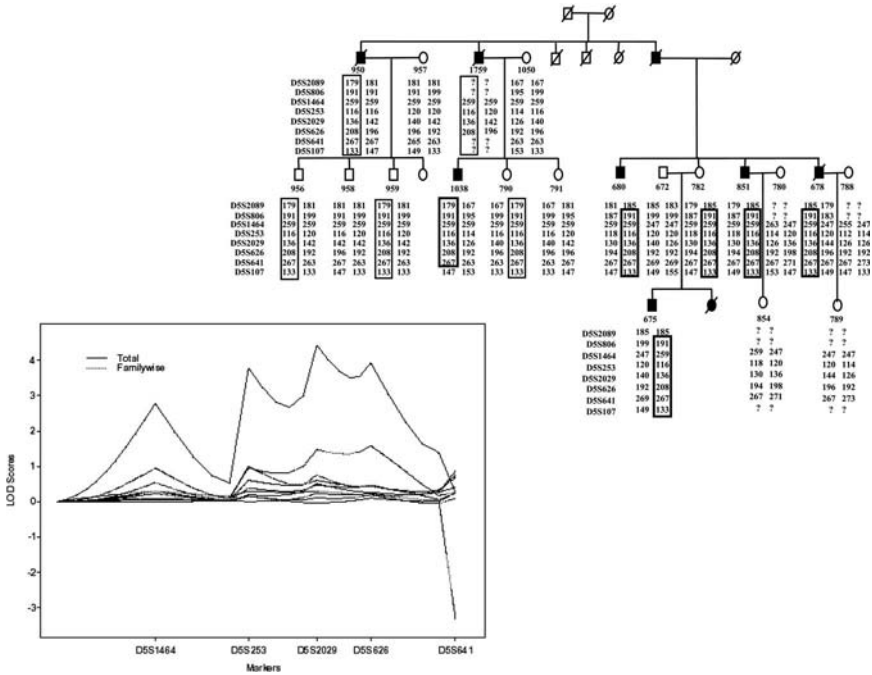

Figure 5 Haplotypes constructed with chromosome 5q13–14 microsatellite markers in family TAA002. The boxes indicate the 5q marker haplotype segregating with the disease. The bold boxes show the recombination events occurring at proximal or distal markers. The physical distance between markers D5S2089 and D5S107 is approximately 17 Mb. Inset shows three-point linkage analysis of marker data of TAA/dissection pedigrees. The Y-axis shows calculated LOD score; X-axis shows markers based on their relative distance along chromosome 5q. A maximum LOD score of 4.76 is obtained for marker D5S2029. The solid line shows total multipoint LOD score for all families; dotted lines show multipoint LOD score of all 13 individual families linked to the locus. *Source*: From Ref. 44.

Subsequently, the *TAAD1* locus was confirmed by studying 11 Finnish TAAD families with 115 members. Markers at the *TAAD1* locus were found to be linked to the disease in five of the families with nonparametric LOD score 3.0. Therefore, these studies confirmed mapping of the first locus for familial TAAD, and also determined that there was genetic heterogeneity for the condition, that is, more that one gene can lead to this familial disease (44).

Haplotypes of 5q markers were constructed based on the chromosomal order of the markers. A haplotype is a particular combination of genetic markers presented on a single chromosome. The chromosomal recombination can be identified through haplotype study that enables to determine the critical interval where the defective gene is located in chromosome. Chromosome 5q haplotypes were constructed on the TAAD families that were linked to 5q locus. The segregation of haplotype with the disease phenotype is verified for each family. Some unaffected

individuals also have the 5q haplotype, but this is consistent with the decreased penetrance of the disorder. Using both TAA002 and TAA012, along with microsatellite markers found in the BACs located between D5S1962 and D5S1501, the critical interval between BACs CTC-310F2 and CTD-2038E6 is approximately 4.5 Mb. The defective gene at the *TAAD1* locus has yet to be identified but studies continue to sequence the genes in the critical interval.

Another locus for familial aortic aneurysms mapped to 11q23.3–q24, termed the *FAA1* locus, using a single large family (45). The disease in this family was fully penetrant and associated with both TAAs and abdominal aortic aneurysms. This locus appears to be a rare cause of disease and the defective gene at this locus has not been identified.

TAAD1 is a major locus for familial TAAD and in approximately 20% to 30% of families the phenotype is linked to this locus. DNA samples collected from another large TAAD family were used to identify other loci that are responsible for this condition; specifically family TAA035 (Fig. 6). Family TAA035 had 89 members in four generations and the phenotype was not linked to *TAAD1*, *FAA1*, or *FBN1*. Fifty-one members contributed the DNA samples for this study, including 15 affected members. The large family size and structure indicated that TAA035 could be used to map another TAAD locus.

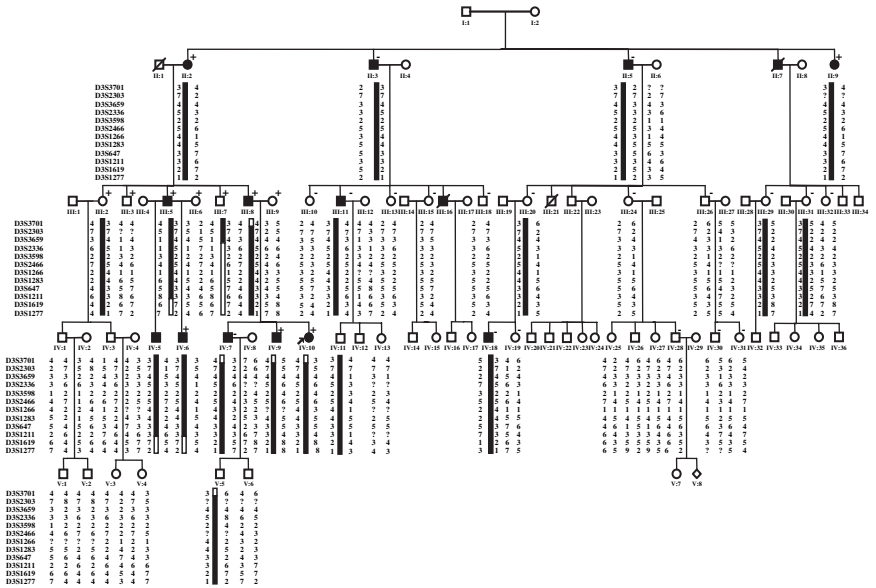

Figure 6 Pedigree of the TAA035 family and segregation of the 3p24–25 haplotype at TAAD2. Filled symbols indicate affected individuals; open symbols, unknown disease status in family members and normal in spouses. Plus symbols indicate samples used for the genome-wide scan; minus symbols, family members included for linkage confirmation. Blackened bar indicates markers associated with the disease. *Source*: From Ref. 46.

A genome wide survey using 382 highly polymorphic microsatellite markers and DNA from individuals in the TAA035 family was done to identify the chromosomal location of the defective gene. LOD scores were obtained using the MLINK program assuming an autosomal dominant model with age dependent penetrance. Eighteen markers on chromosome 3p demonstrated a suggestive LOD score greater than 0.6 ($p = 0.05$). Fine linkage analysis was carried out at these positive markers using all samples collected and confirmed the defective gene causing the aortic disease in the family was located at 3p with a maximum multipoint LOD score of 3.68 with marker D3S2336 (Fig. 7) (46). Interestingly, this 3p locus, termed *TAAD2*, encompassed the *MFS2* locus previously mapped using a large French family (19).

The gene for *TGFBR2* gene, mapped into the critical interval at the *TAAD2* locus, and therefore this gene was sequenced. *TGFBR2* mutations were found in four out of 80 unrelated families with familial TAAD, including family TAA035. These results indicated that *TGFBR2* mutations are a relatively rare cause of

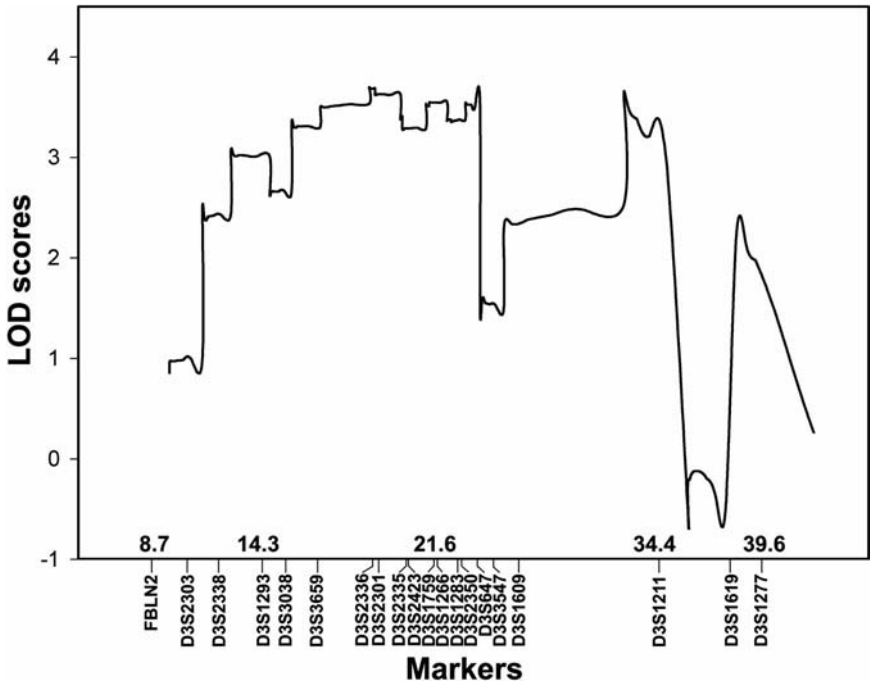

Figure 7 Three-point linkage analysis of marker data at the *TAAD2* locus on chromosome 3p. Y-axis, LOD score; X-axis, position of the markers on chromosome 3p, based on their relative chromosomal distance. Position of the markers is indicated in centimorgans (cM). A maximum multipoint LOD score of 3.68 is obtained with D3S2336. *Source*: From Ref. 46.

familial TAAD, accounting for approximately 5% of familial TAAD (95% CI: 1.4–12.3%) (46,47). Although the majority of vascular disease in families with *TGFBR2* mutations involved ascending aortic aneurysms (leading to type A dissections), affected family members also had descending aortic disease and aneurysms of arteries in other vascular beds, including cerebral, carotid, and popliteal aneurysms (Fig. 8).

A striking finding in the mutational analysis was that all four families carried mutations that affected arginine at amino acid 460 in the intracellular domain of *TGFBR2*, suggesting a mutation "hot-spot" or familial TAAD and establishing a strong genotype–phenotype correlation between familial TAAD and mutations at this location. Polymorphic markers flanking the *TGFBR2* mutation indicated that the families do not share a common haplotype, an observation consistent with these mutations occurring independently and providing further evidence for a "hot spot" for mutations causing this disease.

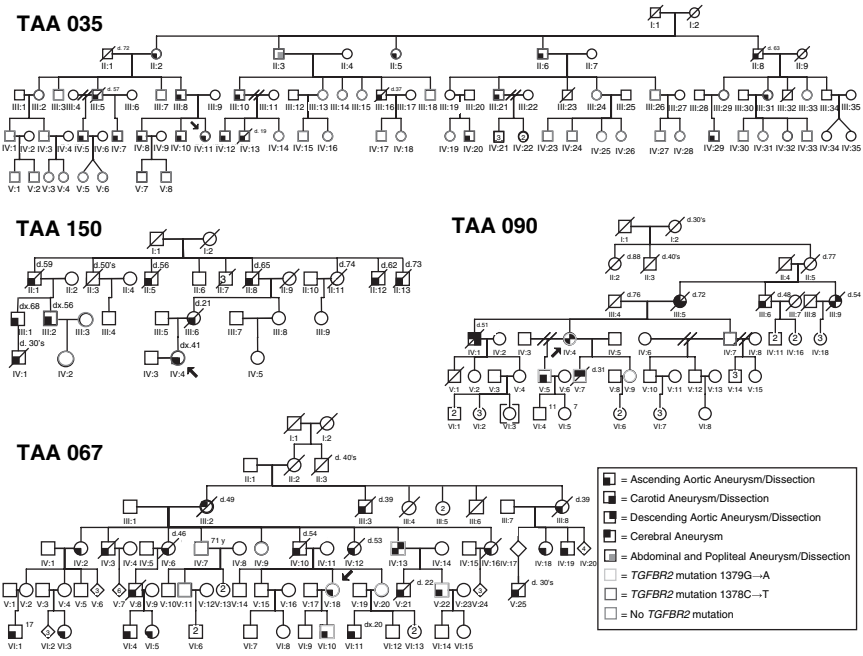

Figure 8 Pedigrees of thoracic aortic aneurysm and dissection families with *TGFBR2* mutations. Vascular disease status is indicated as filled quadrant, with legend indicating vascular disease associated with quadrant. Aneurysms of arteries in various vascular beds are observed in affected individuals, along with descending aortic disease. *TGFBR2* was sequenced from all family members providing samples for these studies. Dark gray symbols indicate individuals heterozygous for *TGFBR2* mutation 1378C→T (R460C). Light gray symbols indicate individuals heterozygous for *TGFBR2* mutation 1379G→A (R460H). Medium gray symbols indicate individuals whose DNA was sequenced and who were found not to have *TGFBR2* mutation. *Source*: From Ref. 47.

Structural analysis of the functionally critical *TGFBR2* serine/threonine kinase domain revealed that R460 is strategically located within a highly conserved region of this domain and that the amino acid substitutions resulting from these mutations will interfere with the receptor's ability to transduce signals and lead to a diminished response to TGF-β. An intriguing observation in these families was the lack of evidence for an increased susceptibility to cancer in families with germline *TGFBR2* mutations, despite considerable evidence in the literature that somatic *TGFBR2* mutations occur in a variety of cancers (47,48).

Heterozygous mutations in the intracellular glycine-serine rich and kinase domains of another key receptor for TGF-β, *TGFBR1,* have been reported in a subset of patients with severe congenital anomalies that include aortic root aneurysms (21). We have sequenced *TGFBR1* using genomic DNA from 100 affected individuals with familial TAAD and have identified no mutations to date (unpublished data). Thus, we find no evidence that *TGFBR1* mutations are a cause of familial TAAD.

Recently, a fourth locus for familial TAAD was mapped at 16p12.2-13.13 in a large French family, in whom the TAAD was associated with patent ductus anteriosus (PDA) (49). The defective gene at this locus was identified as the *MYH11* gene encoding for smooth muscle myosin heavy chain, a specific contractile protein found in smooth muscle cells (50). Causative mutations were identified in two families with TAAD associated with PDA. We have identified unique *MYH11* mutations in two unrelated families with TAAD associated with PDA but have not identified any mutations in familial TAAD not associated with PDA (unpublished data). Therefore, mutations in *MYH11* appear to be specific for the phenotype of TAAD associated PDA and not commonly found in families with TAAD not associated with PDA.

The mapping and identification of defective genes at the mapped loci have illustrated a number of features of familial TAAD. First, the phenotype demonstrates significant genetic heterogeneity. Currently, there are five loci for this disease, including *FBN1*, *TAAD1*, *FAA1*, *TAAD2 (TGFBR2)*, and *TAAD/PDA (MYH11)*. The chromosomal location of these loci is summarized in Figure 9. Further genetic heterogeneity is evident by the fact that we have recently mapped another locus for the condition to 15q (distal to the *FBN1* gene), termed the *TAAD3* locus (unpublished data). Based on linkage data in the families that we have recruited with familial TAAD, there are families that are not linked to any of the known loci. The significant genetic heterogeneity is typical for adult onset inherited cardiovascular disorders. For example, 20 loci have been mapped to date for familial dilated cardiomyopathy and 10 loci have been mapped for hypertrophic cardiomyopathy.

Mapping of genes for familial TAAD has also illustrated that specific phenotypic features are associated with mutations in specific genes. For example, *MYH11* mutations causing TAAD are associated with PDA. In contrast, *TGFBR2* mutations lead to a wide range of phenotypes that includes the spectrum of LDS to MFS to familial TAAD. In addition to TAAD, patients with *TGFBR2* mutations are at risk for aneurysms and dissections of other arteries and need to be routinely surveyed for disease involving other vascular beds, including the cerebral circulation (51). Therefore, the identification of specific genes causing familial TAAD

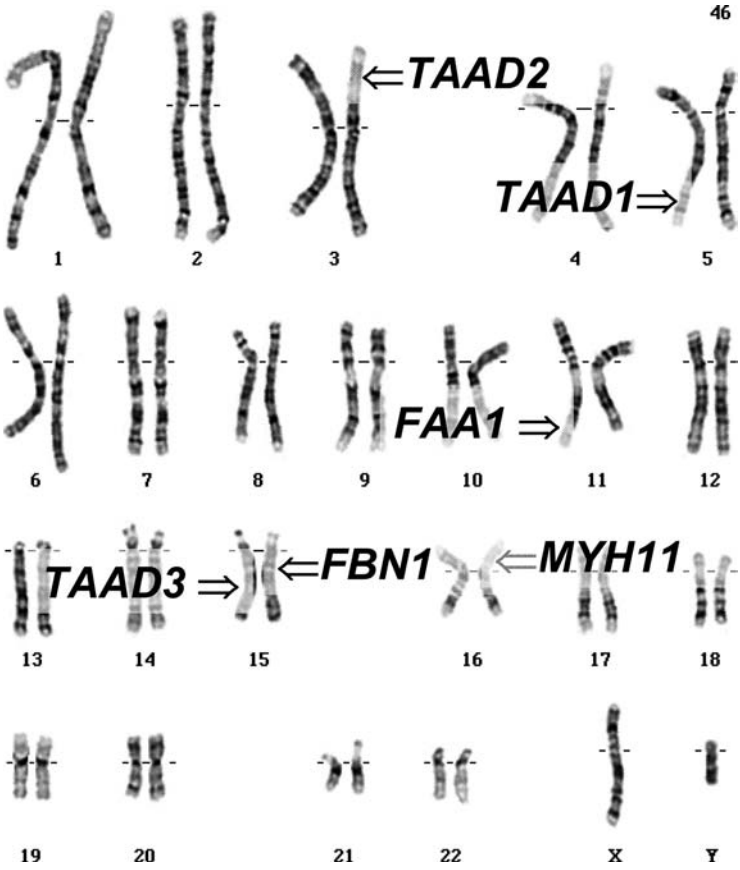

Figure 9 Genetic heterogeneity of TAAD. The six loci that are known to cause familial TAAD to date are shown on a 46,XY karyotype.

will allow for gene-specific management of the vascular disease in individuals and their family members.

Finally, identification of defective genes has provided some insight into molecular pathways leading to disease. Specifically, *FBN1* and *TGFBR2* mutations have highlighted a role of the TGF-β pathway in the pathogenesis of TAAD, which is discussed further in this chapter. The pathways altered with *MYH11* mutations causing familial TAAD/PDA have yet to be determined.

TGF-β PATHWAY INVOLVEMENT IN GENETIC FORMS OF THORACIC AORTIC ANEURYSMS AND DISSECTIONS

TGF-β superfamily members signal through heteromeric complexes of Type II and Type I transmembrane serine-threonine kinase receptors (52). TGF-β induces

assembly of a heteromeric receptor complex of Type I and Type II receptors, within which the TGF-β receptor II transphosphorylates and activates the Type I receptor. Cellular signaling after TGF-β binding and receptor activation is regulated through several pathways, of which the most thoroughly investigated pathway is the Smad pathway. The TGF-β Type I receptor signals through Smad2 and Smad3. Phosphorylation of Smad2 and Smad3 by the TGF-β Type I receptor increases the affinity of these for Smad4, leading to the translocation of the heteromeric Smad complex from the cytoplasm into the nucleus and the subsequent transcription of downstream effector genes (Fig. 10).

Current research suggests a broad role for dysregulated TGF-β signaling in aortic disease pathogenesis, either via inappropriate release of bioactive TGF-β, as observed in MFS, or by disruptions in signaling due to mutations in the receptors for TGF-β observed in familial TAAD, LDS, as well as a subset of MFS. Analysis of the hypomorphic *FBN1* mouse model of MFS first provided a connecting pathway between decreased formation of microfibrils, TGF-β, and the manifestations of MFS. The bioavailability of active TGF-β ligand is tightly regulated and dependent on its release from a large latent complex to which TGF-β is noncovalently associated with its propeptide fragment, the latency-associated peptide, and covalently linked to latent TGF-β-binding protein 1 (LTBP-1) (Fig. 10). This complex associates with fibrillin-1-containing extracellular microfibrils and mutations in fibrillin-1 lead to diminished amounts of microfibrils in the extracellular matrix. Studies of fibrillin-1 deficient mice demonstrated increased active TGF-β in tissues when compared with wild type mice, suggesting diminished microfibrils increased the bioavailability of active TGF-β in tissues (53). Furthermore, antagonism of active TGF-β prevented the pulmonary parenchymal and mitral valve abnormalities observed in these mice, suggesting a cause and effect relationship (53,54). Interestingly, a recent study has also shown that aortic aneurysm in a mouse model of MFS is indeed associated with increased TGF-β signaling and can be ameliorated by the angiotensin II Type 1 receptor (AT1) blocker, losartan (55). Prior evidence suggests crosstalk between the TGF-β and angiotensin II signaling pathways; however, the mechanism by which losartan acts to prevent aortic aneurysms remains to be elucidated.

The mechanism of enhanced TGF-β signaling implicated in MFS manifestations caused by *FBN1* mutations, while difficult to reconcile with the putatively kinase-inactivating *TGFBR1* and *TGFBR2* mutations identified in LDS, appears to be the basis of aortic disease in both these syndromes (21). Surprisingly, tissues from these affected individuals with *TGFBR2* mutations showed increased expression of both collagen and connective tissue growth factor, as well as nuclear enrichment of phosphorylated Smad2, suggesting increased TGF-β signaling in these tissues.

This theme of activation of TGF-β signaling is also observed in familial TAAD. Transient transfection experiments to measure cellular responsiveness to TGF-β mediated by wild type or mutant (R460C and R460H) *TGFBR2* confirmed our structural modeling studies indicating that both the R460C and R460H mutations diminish downstream signaling in response to TGF-β. This was followed

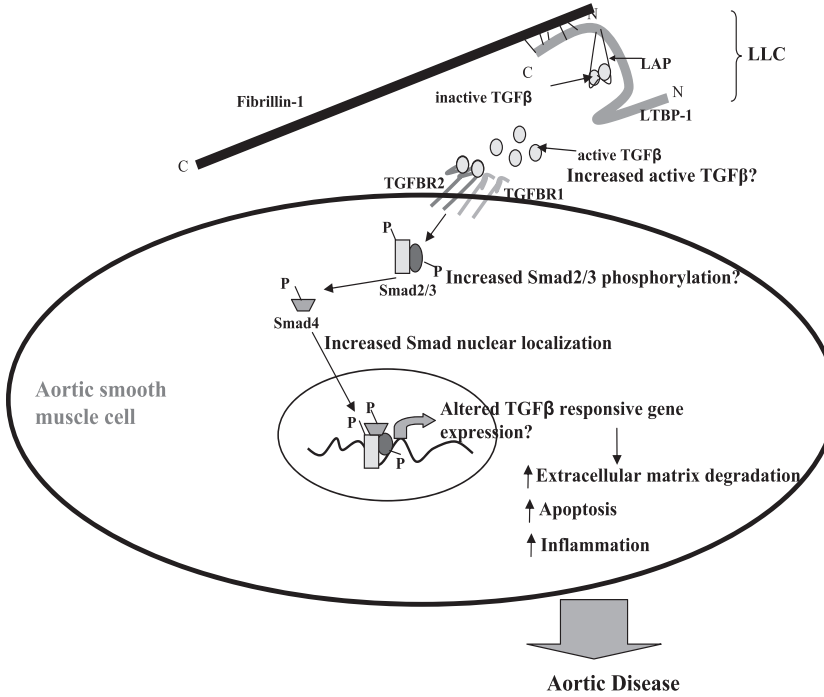

Figure 10 (*See color insert*) A potential molecular pathway of dysregulation of transforming growth factor (TGF)-β leading to aneurysms and dissections. TGF-β is secreted in a biologically inactive form and stored in the extracellular matrix in a complex termed as the large latent TGF-β complex, consisting of a TGF-β homodimer associated with the latency-associated peptide, and the latent TGF-β binding protein-1. Dysregulated TGF-β signaling results from mutations in *FBN1*, *TGFBR1*, or *TGFBR2*, leading to altered transcription of TGF-β responsive genes, and ultimately resulting in degenerative changes in the vessel wall leading to aneurysms and dissections. *Abbreviations*: LAP, latency-associated peptide; TGF, transforming growth factor; TGFBR, transforming growth β-receptor. *Source*: From Ref. 59.

by evaluation of the consequence of R460C and R460H *TGFBR2* mutations identified in familial TAAD on propagating TGF-β signal in primary cell culture by assessing immediate Smad2 phosphorylation, in response to the addition of exogenous TGF-β, using both dermal fibroblasts and aortic smooth muscle cells (SMCs) explanted from two unrelated patients heterozygous for the R460C *TGFBR2* mutation and compared with controls. Smad2 phosphorylation in response to recombinant TGF-β1 was preserved in both dermal fibroblasts and aortic SMCs and comparable to the response in control cells.

However, phosphorylation of Smad2 and Smad3 in serum-deprived cells in the absence of TGF-β1 stimulation was observed to be present only in the aortic SMCs from the patients. Furthermore, phosphorylated Smad2 was present

in the nuclei of the patients' aortic SMCs in the absence of TGF-β stimulation, and expression array as well as quantitative reverse transcription analysis of specific transcripts confirmed altered expression of TGF-β targeted genes in these cells. The picture emerging from these studies indicates that aortic disease results from a complex pathogenetic sequence that includes loss of tissue integrity and perturbed TGF-β signaling that may affect smooth muscle cell morphology and survival in the aortic media.

GENES PREDISPOSING TO NONFAMILIAL FORMS OF DISEASE

TAAD is a complex human disease that results from the inputs of both genetic and environmental factors. The molecular basis of complex disease is different from the Mendelian inheritance because it introduces only a subtle alteration in the protein functions or the levels of gene expression. The functional polymorphic variants predisposed in genes involved in the pathogenesis are suggested to be the underlying genotypes that are associated with the disease phenotypes. A functional polymorphic variant can be an SNP, a short nucleotide polymorphic repeat, or a short DNA insertion or deletion, which can be located in the promoter region, introns, or exons of a susceptibility gene. Functional variants result in subtle functional alteration of genes, and some of them may contribute to an increased risk of developing complex human diseases. A functional variant may be found in the genes that cause TAAD inherited in a Mendelian manner, as well as genes that do not.

To identify a functional variant is very difficult because millions of genomic polymorphic variants exist in the human genome. However, using an association study of genomic polymorphic markers with the affected phenotype, susceptibility genes can be identified because functional variants tend to demonstrate linkage disequilibrium with nearby polymorphic markers, even when they do not manifest detectable linkage disequilibrium in the general population. When frequencies of marker genotypes or alleles are significantly different between cases and controls, it suggests that a susceptibility gene is located at or near these markers. Currently SNPs are widely used as genetic markers for case-control association study of complex diseases because SNP markers are stable and are the most abundant polymorphic markers in the human genome. Using this approach, the matrix metalloproteinase-9 gene has been shown to be associated with TAAD (56). Further studies are needed to identify genetic variants that predispose to TAAD in the absence of a family history of disease.

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DISCUSSION AND COMMENTARY

Questions for the Authors

Are you sometimes unsure, on clinical grounds, whether a given patient actually has Marfan disease, despite the Ghent criteria? Doesn't it sometimes seem that not all the systems are yet manifesting the Marfan disorders, but that they will in time? How do you classify these patients?

The current diagnostic criteria (Ghent criteria) are complicated by a number of factors. First, younger children may not fill the diagnostic criteria and may require repeat evaluations to be certain that the diagnostic features for MFS do not emerge as the child grows older. Second, some individuals have skeletal features of MFS, aortic root dilation, and mitral valve prolapse, but may not meet the diagnostic criteria of the MFS. A separate diagnosis for these individuals has been suggested in the past (MASS for *m*itral valve prolapse, *a*ortic root dilatation, skeletal features of MFS, and *s*triae atrophicae) (1). It was subsequently determined that some of these patients had *FBN1* mutations and represented the phenotypic spectrum of MFS (2). Whether or not a diagnosis of MASS is made, the clinical management focuses on routine imaging of the ascending aorta and recommendation of prophylactic repair when the aorta enlarges to 5.0 cm. and as needed management of the skeletal features.

Finally, we now know that individuals who do or do not fill the diagnostic criteria for MFS may have mutations in *TGFBR1* and *TGFBR2*. Since the aortic disease in patients with *TGFBR1/2* mutations requires aggressive management and can extend beyond the ascending aorta, it is important to differentiate these patients from classic MFS. The diagnostic criteria for MFS need to be revised and criteria established for the spectrum of disease cause by *TGFBR1/2* mutations.

In the practical assessment of a patient with suspected Marfan's syndrome, is there currently any role for genetic studies on the patient's DNA—or are genetic studies just a research tool at this stage?

Sequencing of the *FBN1* gene should be considered if the patient narrowly misses the diagnostic criteria of MFS. Please note that if the patient has features of Loeys-Dietz syndrome, sequencing of the *TGFBR1/2* genes should be considered. Another clinical scenario where *FBN1* mutational analysis should be considered is when an individual does not want to transmit the defective gene to their offspring. Identification of the mutation causing the disease will allow for reproductive options to prevent passing the defective gene to offspring.

In the practical assessment of a patient with non-Marfan's aneurysm disease, is there currently any role for genetic studies on the patient's DNA—or are genetic studies just a research tool at this stage?

TGFBR2 mutations are found in approximately 5% of patients with a familial history of thoracic aortic aneurysms and dissections in the absence of features of MFS and Loeys Dietz syndrome. We have also determined that a rare family will have *TGFBR1* mutations as the cause of disease (unpublished data). Therefore, we recommend that all patients with a family history of aortic aneurysms and

dissections have *TGFBR1/2* mutational analysis to screen for mutations in these genes as a cause of disease because finding such a mutation has significant implications for the subsequent management of the patient and their family. We hope that in the future, more genes will be identified that can be screened for mutations in families with thoracic aortic aneurysms and dissections.

Do you think that the ARB drugs will prove to be a panacea for aneurysm disease? Does this possibility seem almost too good to be true?

It will be determined if the success of losartan in blocking the progressive aortic disease in a mouse model of MFS will also apply to humans with MFS, in a clinical trial comparing beta adrenergic blocking agents to losartan. The clinical trial, funded by NHLBI and using the Pediatric Heart Network, will recruit patients under the age of 26 years with MFS and randomize them to either drug. A similar trial of adults with MFS is in the planning stage.

It is not certain if the success of losartan in the animal model of MFS will translate to humans with MFS. In addition, we do not know the role of TGF beta signaling in aortic disease in patients who do not have MFS. Further studies are needed to determine if ARB drugs will prove to be a panacea for aneurysm disease.

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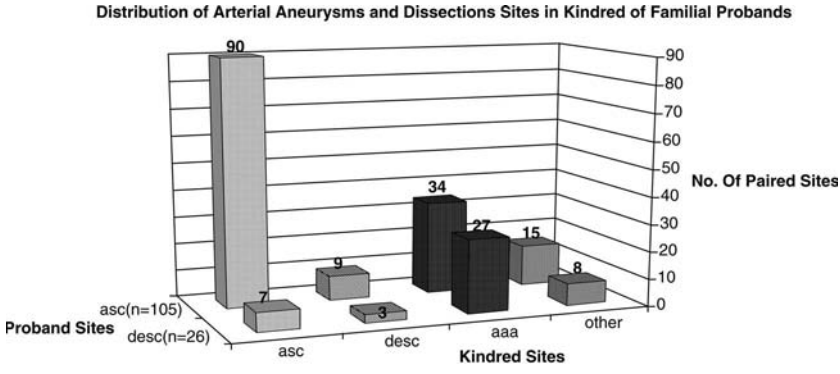
Editor's Comments

Dr. Milewicz et al. have made extraordinary contributions to the fundamental genetic understanding of aortic diseases, which they enumerate clearly in this chapter. Their work reflects tremendous industry, acumen, and insight. The entire vascular community respects and is grateful for it.

Our own team is working with molecular geneticists at Celera Diagnostics in California to explore the automated SNP avenue of investigation that Dr. Milewicz describes. Our preliminary findings have shown that (1) aneurysm disease has a unique "RNA signature" in the peripheral blood. (2) This signature, if confirmed in further investigations, promises to facilitate clinical diagnosis of aneurysm disease on a molecular genetic basis. Our separate investigations on 30,000 DNA SNPs is ongoing. We hope to identify specific alterations in the genome of aneurysm patients. The DNA studies look at the blueprint which programs the body is to be made. The RNA studies look at which proteins are actually upregulated or downregulated in terms of active manufacture at the time of sampling.

In terms of clinical genetic patterns, our most recent examination of 520 family pedigrees of patients with thoracic aortic aneurysms indicates that there are distinct patterns of inheritance among family members. (3) Family members



		Kindred sites				
Probandsites		asc	desc	AAA	other	Total paired sites
asc	106	90	9	34	15	148
desc	25	7	3	27	8	45
						193

Figure A Distribution of aneurysm sites among family of probands with thoracic aortic aneurysms.

of patients with ascending aortic aneurysms are very likely to manifest their aneurysms in the ascending aorta as well. However, family members of patients with descending aortic aneurysms are more likely to manifest their aneurysms in the descending aorta (Fig. A).

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7

Mechanical Properties of the Aorta—6 cm Is "Special"

John A. Elefteriades

Section of Cardiothoracic Surgery, Yale University, New Haven, Connecticut, U.S.A.

George Koullias

Department of Thoracic and Cardiovascular Surgery, AHEPA University Hospital, Aristotle University Medical School, Thessaloniki, Greece

As emphasized throughout this book, the dimension of the aorta can predict the onset of acute aortic events—rupture or dissection—with reasonable accuracy. By and large, bad events occur very frequently as the aortic diameter approaches 6 cm. However, we recognize that dimensional predictive criteria fall short of ideal. For this reason, we have begun to examine the ascending aorta from an engineering standpoint, with an eye toward using measurement of mechanical properties of the aorta as another potential criterion for appropriate timing of surgical intervention. This chapter reviews our very interesting findings. It is intriguing how closely our engineering findings correlate with the clinical behavior of the aorta in patients.

Our technique involves examining the aorta by epi-aortic echocardiography in the operating room during surgery for replacement of the aorta for aneurysm disease (Fig. 1) (1). Patients being operated for nonaneurysmal disease constituted our controls.

As it turns out, the major mechanical parameters of the aorta can be calculated by measuring the following six easily assessed parameters (Fig. 2):

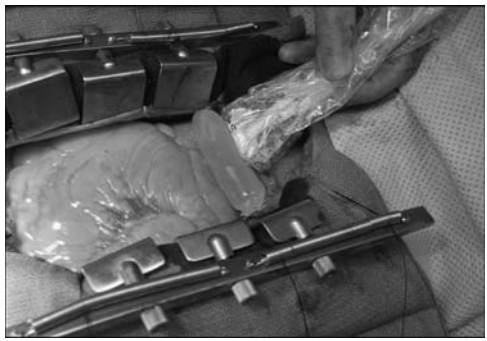

Figure 1 (*See color insert*) The technique of epi-aortic echocardiography. Note the fluid-filled interface between the probe and the aortic wall.

1. The diameter of the aorta, in systole and diastole.
2. The thickness of the aortic wall, in systole and diastole. (The aortic wall thins in systole, under the increased stretch of the higher pressure. This measurement of subtle differences in a small dimension has a significant learning curve attached to it.)
3. The blood pressure, in systole and diastole. (In our experiments, the blood pressure was determined very accurately using intraoperative direct arterial line monitoring.)

What we found was that the distensibility of the aorta essentially vanishes as the dimension of the aorta increased (Fig. 3). The normally distensible aorta became essentially a rigid tube at about 6 cm in diameter.

Likewise, wall stress shows dramatic and serious aberrations as the aorta grows, again reaching critical levels by about 6 cm aortic diameter (Fig. 4). The maximal strength of the aortic wall is known by prior investigations done directly

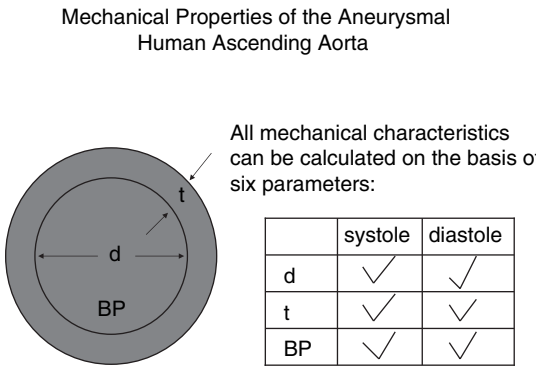

Figure 2 The parameters that need to be measured for calculation of mechanical properties of the aorta.

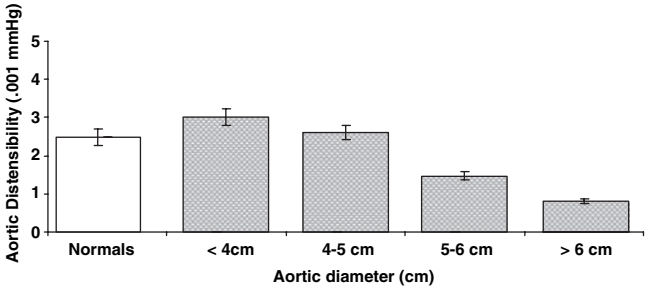

Figure 3 Distensibility of the aorta at various dimensions. Note that the aorta becomes essentially a rigid tube by a dimension of 6 cm.

on aortic aneurysm tissue by Vorp et al. (2). In the figure, wall stress at an ambient blood pressure of 100 mmHg is shown in dark gray and at 200 mmHg in light gray. The dotted line represents the known maximum strength of the aortic wall. Note that at an aortic dimension of 6 cm and an ambient blood pressure of 200 mmHg, the wall stress "flirts" dangerously close to the ultimate strength of the aortic wall.

It is, thus, no wonder that patients with aortic enlargement approaching 6 cm are vulnerable to aortic rupture and dissection. This is exactly what we found in clinical investigations from our database (3–5).

This investigation of the mechanical properties of the aneurysmal aorta shows that clinical events occur exactly at the same dimensions at which mechanical

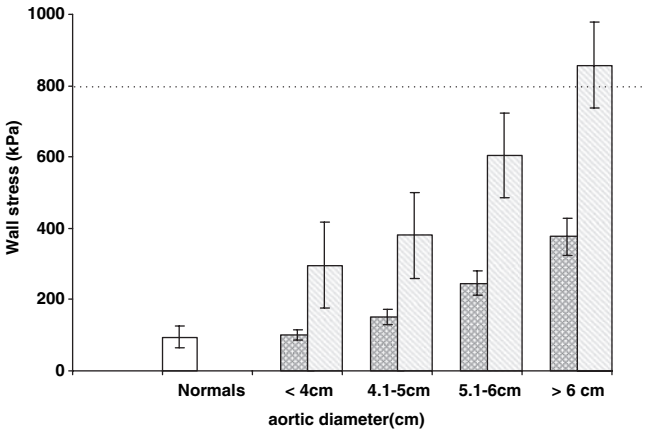

Figure 4 Wall stress of the aorta at various dimensions. The dotted line shows the known maximal tensile strength of the aortic wall. The dark gray bars reflect an ambient blood pressure of 100 mmHg. The light gray bars reflect an ambient blood pressure of 200 mmHg. Note that at a dimension of 6 cm and an ambient blood pressure of 200 mmHg, the wall stress approaches the maximal strength of the aortic wall.

properties deteriorate severely. This represents a dramatic convergence of experimental findings with clinical behavior. These findings lend further credence to the dimensional criteria for pre-emptive surgical intervention discussed in the clinical chapters of this book.

Of course, epi-aortic echocardiography is not workable as a clinical monitoring tool, as the patient is already undergoing operation at the time of the test. We are now transitioning our studies in the direction of transesophageal echocardiography (TEE). Specifically, at the same time that we perform the epi-aortic echocardiography on surgical patients, we are also performing the same measurements by TEE. Our initial experience seems favorable—that is, it appears that the TEE measurements will be possible, will be accurate, and will correlate with the epi-aortic calculations.

If we can validate TEE as a means of assessing the mechanical properties of the aorta, then it becomes reasonable to postulate that direct measurement of distensibility, wall stress, or other biomechanical variables may be applied to predict rupture or dissection—and, thus, to guide optimal timing of pre-emptive surgical intervention. The potential exists to measure mechanical properties by computed tomography scan or by magnetic resonance angiography as well.

We are hopeful that serial measurement of aortic distensibility and aortic wall stress may become part and parcel of clinical follow-up of aneurysm patients, augmenting clinical assessment and aortic diameter as tools for predicting aortic behavior and timing surgical intervention.

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DISCUSSION AND COMMENTARY

Question for the Authors

The six data points for calculation of mechanical properties of the aorta include aortic diameter in systole and diastole, blood pressure in systole and diastole, and aortic wall thickness in systole and diastole. I understand how you can measure aortic diameter in systole and diastole. Blood pressure in systole and diastole is also easy to retrieve from the arterial line. However, how can you measure the thickness of the aorta in systole and diastole? Can this be done accurately?

Yes, this can be done. The shadow of the aortic wall is magnified, and multiple measurements are taken and averaged. Please note, in Figure A, how clearly the aorta thins at the beginning of systole (under increased pressure) and thins in diastole (with relief of pressure).

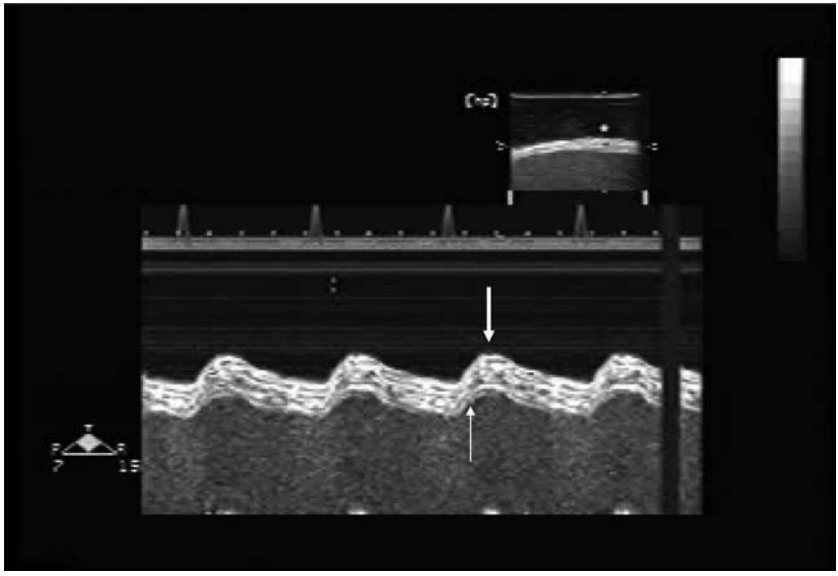


Figure A Magnified view of aortic wall by epiaortic echocardiography. Aorta thins in systole (*thin arrow*) and thickens in diastole (*thick arrow*).

8

Matrix Metalloproteinases in Aortic Aneurysm and Dissection

Donald M. Botta, Jr. and John A. Elefteriades

Section of Cardiothoracic Surgery, Yale University, New Haven, Connecticut, U.S.A.

George Koullias

Department of Thoracic and Cardiovascular Surgery, AHEPA University Hospital, Aristotle University Medical School, Thessaloniki, Greece

Thoracic aortic aneurysms (TAAs) (Fig. 1) have an annual incidence in population-based studies of as high as 10.4 per 100,000 persons (1). The population based annual rate of thoracic aneurysmal rupture or dissection was 7.0 per 100,000 (2) in one study, and the rate of rupture was 5.0 per 100,000 in another (3). The gravity of these occurrences is illustrated by the median survival of three days after aneurysmal dissection in the former study (2), and the 97% to 100% mortality after rupture in the latter (3). The public health impact of this disease can be brought into focus by comparing these rates to the 5.0 per hundred thousand mortality rate from Human Immunodeficiency Virus infection in the United States (4). Operative repair of TAAs is effective in improving survival (5). However, elective surgical repair for asymptomatic aneurysms remains a clinical decision, which must be based on the patient's operative risk, and the risk that a given TAA will progress, dissect, or rupture. In order to consider the risks of these complications, a thorough understanding of both the natural history and the pathophysiology of TAAs are required.

To understand the natural history of TAAs, we at the Yale Center for zThoracic Aortic Disease have been compiling an ongoing, cumulative database since 1995, including data and imaging studies on all patients whom we evaluate for thoracic aortic disease. The database currently contains information on nearly

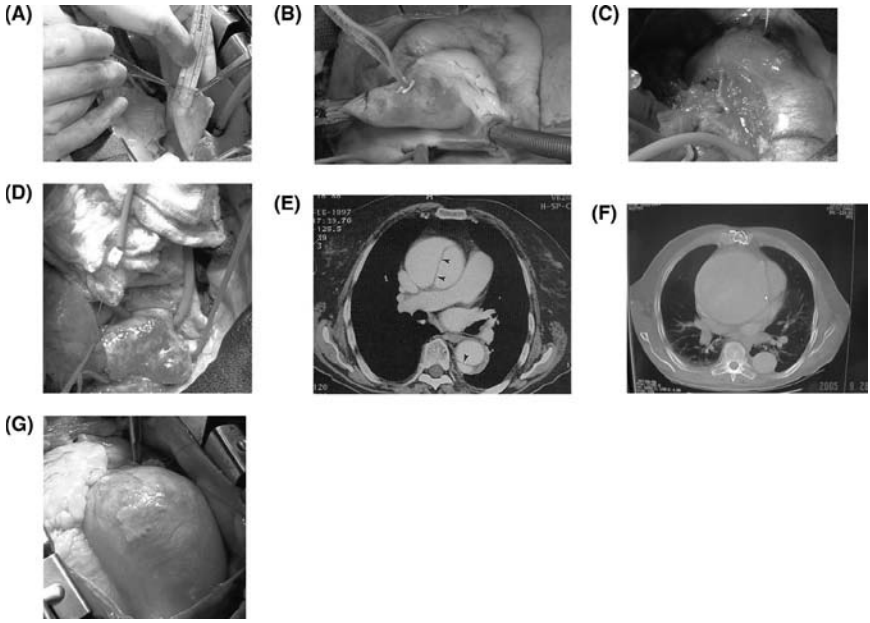


Figure 1 (*See color insert*) Dramatic clinical examples of aortic destruction, likely at least in part at the hands of excess lytic activity of matrix metalloproteinase. Clockwise, from upper left hand corner: (**A**) An ascending aorta rendered so thin that the markings on a ruler can be read right through the aortic wall. (**B**) Severe annulo-aortic ectasia. Note aneurysm partially hiding under right ventricular outflow tract. (**C**) Descending aortic aneurysm, with penetrating ulcer, appearing "ready to burst." (**D**) Massive descending aortic penetrating ulcer/saccular aneurysm-precarious in appearance. (**E**) Ascending aortic dissection, with descending aortic intramural hematoma. (**F**) Massive ascending aortic aneurysm on computed tomography scan. (**G**) Massive ascending aortic aneurysm at operation. (Head of patient is to right and below).

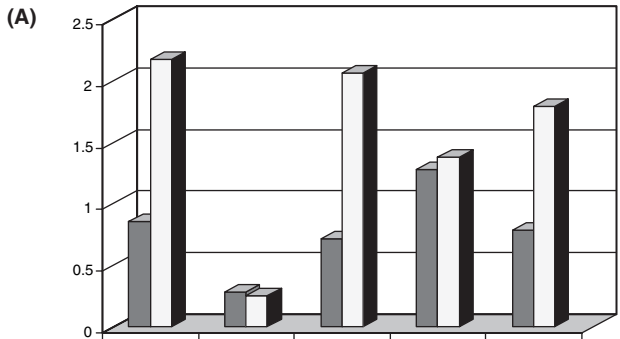
3000 patients, with 9000 patients years of follow-up and 9000 computerized imaging studies. Analysis of these data with specialized statistical methods developed and validated at our institution (6–8) has permitted us to quantify yearly rupture rates based on the diameter of the aneurysm, as well as annual aneurysmal expansion rates, and to describe the natural history of thoracic aortic aneurysms (9). We have developed a formula for predicting aneurysm rupture based on an index of aneurysm diameter to body surface area (10). Additionally, we have described the mechanical properties of the aneurysmal thoracic aorta (11) and identified familial patterns of aneurysms that were once considered sporadic (12).

Despite these advances, more accurate prediction of aneurysmal growth and rupture in individual patients is needed (13,14). With that in mind, we have begun to focus on the pathophysiologic processes involved in thoracic aneurysm development, progression, and complications.

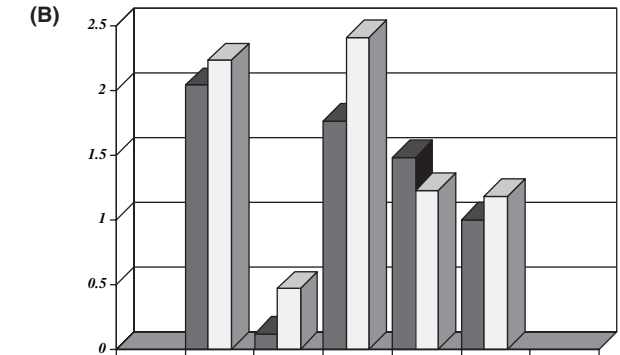
There is a paucity of literature relating specifically to the pathogenesis of thoracic aneurysmal disease at the molecular level, likely because there has not been an adequate animal model of TAA until recently (15). In contrast, a large body of data exists with regard to the pathogenesis of abdominal aortic aneurysms (AAAs), beginning with the first report of upregulated matrix metalloproteinases (MMP) activity in aneurysm tissue (16), and proceeding with ongoing work supported by the National Heart Lung and Blood Institute (17). This work, and that of others, has shown that aortic expansion and rupture is related to proteolytic degradation within the wall of the aorta (18). The group of enzymes that has shown the most promise as the etiologic factor of this proteolysis, leading to the formation (18,19), expansion (20), and rupture (21–23) of AAAs is the MMPs, and imbalance of these enzymes with their tissue inhibitors (TIMPs).

The MMPs are a group of zinc dependent enzymes whose chief role, in both physiologic and pathophysiologic states, is to degrade the extracellular matrix (24). They were first discovered when it was noticed that the tail of a tadpole digested collagen on a laboratory plate (24) (Fig. 2). They are active in a wide array of disease processes, which range from periodontal disease (25) to congestive heart failure (26–28). Experimentally, MMPs have been pharmacologically inhibited, resulting in improvement in disease processes, both in animal (29–33) and human models (34–37). MMP activity in AAA disease is evident from animal studies, which have shown that MMP inhibition, either through targeted gene deletion (38–40) or pharmacologic inhibition (41–43), results in decreased expansion of experimental AAAs. In humans, pharmacologic inhibition of MMPs has been shown to decrease their expression within the aortic wall (44). The importance of MMP activity in AAA disease has been reviewed by Kadoglou and Liapis (45), and the rationale for their pharmacologic inhibition in a clinical trial has been outlined by Thompson and Baxter (46). Other work by the latter group has demonstrated that circulating levels of MMP-9 correlate directly to aortic wall levels of MMP-9 (47). MMP-9 levels have been demonstrated to be 20 times higher in the wall of AAAs than in normal aorta (48). Thus, it appears that the MMPs play an important role in aneurysm formation, that measurement of MMP levels may shed light on aneurysm behavior, and that pharmacologic modification of MMP levels may influence aneurysm progression.

While there is considerable evidence that MMPs play a pivotal role in the pathogenesis of AAAs, the thoracic aorta and the abdominal aorta have different embryologic origins (neural crest ectoderm and mesoderm, respectively) (49), are exposed to different physical forces (50), and have different ultrastructural morphologies (51,52). TAAs and AAAs have another important distinction. Asymptomatic AAAs tend to have thick rinds of laminated thrombus within their walls that is biologically active but relatively isolated from the circulation. This may render them less amenable to pharmacologic MMP inhibition than TAAs, which are more commonly classic, true aneurysms, and, especially in the case of ascending TAAs, lack laminated thrombus. Each layer of the TAA aneurismal wall should be perfused at least as well as it is during the nonaneurismal state.



	MMP-1	MMP-2	MMP-9	TIMP-1	TIMP-2
Controls n=7	0.857	0.285	0.714	1.28	0.79
Patients n=47	2.18	0.255	2.067	1.38	1.79
P-Value	p<0.05	NS	p<0.05	NS	p<0.05



-	MMP-1	MMP-2	MMP-9	TIMP-1	TIMP-2
Aneurysms n=30	2.04	0.12	1.76	1.48	1
Dissections n=17	2.23	0.47	2.41	1.23	1.18
p-value	NS	p <0.05	p <0.05	NS	NS

Figure 2 Increased matrix metalloproteinase levels in aneurysm patients compared to controls (**A**) and in dissectors compared to nondissecting thoracic aneurysm patients (**B**).

Indeed, aneurysm walls that lack a layer of laminated thrombus tend to have a higher level of MMP expression than those with inner layers of thrombus (53). This may render TAAs more amenable to pharmacologic intervention than AAAs. Given these differences, it cannot be assumed that TAAs and AAAs behave similarly with regard to their pathogenesis, or their response to pharmacologic MMP inhibition.

Now that TAAs are being investigated on a molecular level, it appears that there is some homology in the pathophysiology of AAAs and TAAs. A recent complementary DNA-based micro-array study has identified some genes whose overexpression TAAs and AAAs share. These genes include those coding for intracellular adhesion molecule 1, v-yes-1 oncogene, mitogen activated protein kinase-9, and MMP-9 (54). In agreement with this, recent work at our center (55) has noted an increased level of MMP-1 and MMP-9 in the walls of thoracic aortas that were either aneurismal or dissected compared to controls (Fig. 3).

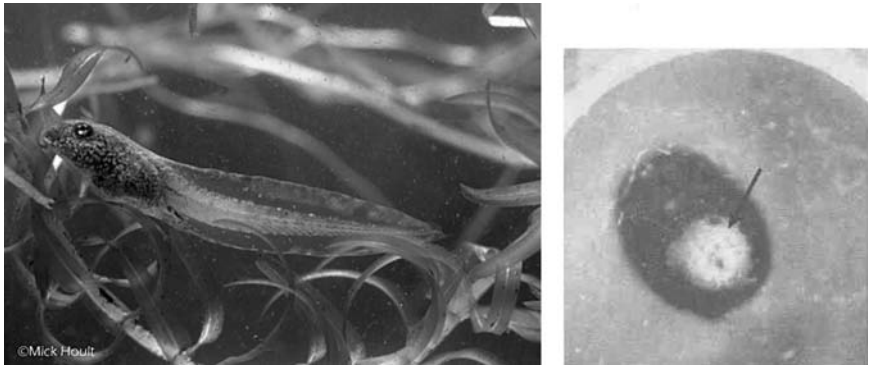


Figure 3 (*See color insert*) Matrix metalloproteinases were discovered when it was noticed that a piece of tadpole tail digested the collagen on a laboratory plate. *Source*: From Ref. 24.

MMP levels were even higher in dissection patients than in aneurysm patients. In this study, we also noted an increase in the MMP-9 to TIMP-1 ratio, which has been shown to favor proteolysis within the aortic wall (56), during AAAs. Thus, it appears that the MMPs have a pivotal role in the pathophysiology of TAAs.

In recent years this role has become increasingly clear (54,55,57–61). Table 1 lists the investigations that have been published to date examining the role of MMPs in human TAAs. To summarize, increased aortic wall gene expression and/or protein expression levels of MMP-1, 2, 3, and 9 are associated with TAAs.

This association raises several important questions (Table 2). First, are the increased MMP levels simply the result of systemic inflammation, or do they

Table 1 The Role of Matrix Metalloproteinases in Human Thoracic Aortic Aneurysms

Study	Setting	MMP related findings
Ref. 104	Patients with TAA associated with Marfan's syndrome	Increased immunoreactivity for MMP 1,2,3, and 9 in smooth muscle cells and areas of elastin degradation.
Ref. 105	Patients with TAA associated with Marfan's syndrome or bicuspid aortic valves	MMP 2 upregulated in Marfan's associated aneurysm tissue. Not assessed in BAV tissue.
Ref. 106	Patients with non-Marfans syndrome associated TAAs and dissections	MMP 1 and 9 increased by immuno-histochemical microarray in thoracic aortae with either aneurysm or dissection. TIMP 2 increased in all patients. MMP 2 and 9 levels higher in dissection tissue than aneurysm tissue. MMP 9 to TIMP 1 ratio higher in tissue with aneurysm or dissection.

Abbreviations: BAV, bicuspid aortic valve; MMP, matrix metalloproteinase; TAA, thoracic aortic aneurysms; TIMP, tissue inactivators of metalloproteinases.

Table 2 Important Questions Regarding Matrix Metalloproteinases and Aneurysm Disease

MMP's are elevated in the wall of thoracic and abdominal aneurysms, but
Are these MMPs locally generated in the aortic wall, or systemically circulating, due to general inflammation?
Are MMPs elevated only in the aneurysmal segment, or throughout the aorta?
Do circulating levels of MMPs correlate with tissue levels?
Can high circulating MMP levels serve as biomarkers of disease activity or progression?
Can aneurysm expansion, dissection, or rupture be modified by pharmacologic MMP manipulation?

Abbreviation: MMP, matrix metalloproteinase.

reflect a local pathologic process? Second, are the MMP levels elevated in the aneurismal segment only or is the elevation measurable throughout the aorta? Third, do circulating levels of MMPs reflect the tissue levels of MMPs? Fourth, if circulating levels of MMPs reflect tissue levels, do higher MMP levels portend more rapid expansion, and/or more frequent complications from TAAs? Finally, can the expansion or complication rate of TAAs be modified by pharmacologic MMP manipulation?

Systemic or local? To answer the first question, one must assess gene expression at the tissue level of MMPs. If MMP levels were elevated without locally increased gene expression, then the increased levels could simply be a reflection of high systemic MMP levels. Conversely, if both the MMP levels and the gene expression for these proteins are elevated, a localized process is more likely. Indeed, we were able to demonstrate increased levels of MMP-1 and MMP-9, at an RNA expression level (55). These findings are consonant with a cDNA based micro-array study carried out by Taketani et al. with regard to MMP-9 gene expression (61). They found elevated gene expression for MMP-1 and MMP-9 in aneurismal aorta compared to adjacent, nonaneurysmal aorta. Thus, it certainly appears that the MMPs are elevated at the aortic level, and this elevation is the result of local production.

Localized or pan-aortic? To answer the second question as to whether this MMP elevation is localized to the aneurismal segment or if a pan-aortic rise in MMPs occurs, an elegant study was recently published by Sinha et al. which measured MMP expression in descending thoracic aneurysms. They were able to show increased MMP-9 expression in the more rapidly expanding anterior wall of the aneurismal segment of the aorta compared to the more slowly growing posterior wall at the same level, and compared to controls (57). Thus, the association between local production of MMP-9 and aneurysm growth seems very clear.

Circulating levels reflective of tissue levels? The third question is whether levels of MMPs are concordant between the aneurismal aortic tissue and the circulation. If this correlation exists, it would allow us to gauge the pathologic process involved with aneurysm expansion by means of a simple blood test.

Hovespian et al. (47) were able to demonstrate concordance between circulating and tissue levels of MMPs in AAA disease. For human TAA, recent work at our center has demonstrated, for the first time, that there is a correlation between tissue levels of MMP-9 and circulating levels of this enzyme. This pilot study involved ten patients with thoracic aneurysms who underwent elective operative repair of ascending TAAs. We noted an extremely strong (R squared = .913) correlation between tissue and circulating MMP-9 levels (Fig. 4). We are currently continuing our work in this area, and if this correlation holds true, it could represent an advance in the way patients with early TAAs are monitored.

MMPs as "biomarkers"? The fourth question is whether circulating MMPs are reflective of overall expansion and complication rates of TAAs. For AAAs, McMillan et al. demonstrated a relationship between circulating MMP 9 levels and abdominal aortic diameter (56). For TAAs, no published study to date has addressed this issue, but it is one on which work is progressing at our institution.

Benefit from pharmacologic inhibition? The answer to the fifth question as to whether pharmacologic manipulation of MMPs can result in a beneficial change in aneurysm behavior is slowly beginning to become clear. The idea of medical therapy for TAAs is not new. For patients with early or inoperable TAAs, decreased growth rate with "anti-impulse therapy"—limiting the heart rate, blood pressure, and pressure up-slope in systole (Dp/Dt)—is a standard and well-accepted practice, both for AAAs and TAAs, which has met with varied success since its introduction in 1965 (62–64), mostly in limiting progression of aortic dissections. This therapy is based on the premise that if the forces on the aortic wall, most importantly the wall stress, can be limited, aortic expansion will also be ameliorated. The mainstay of anti-impulse therapy is currently beta-adrenergic receptor blockade. However, enthusiasm for aneurysm treatment with beta blockade should be tempered by the results of a randomized trial of propranolol for aneurysm

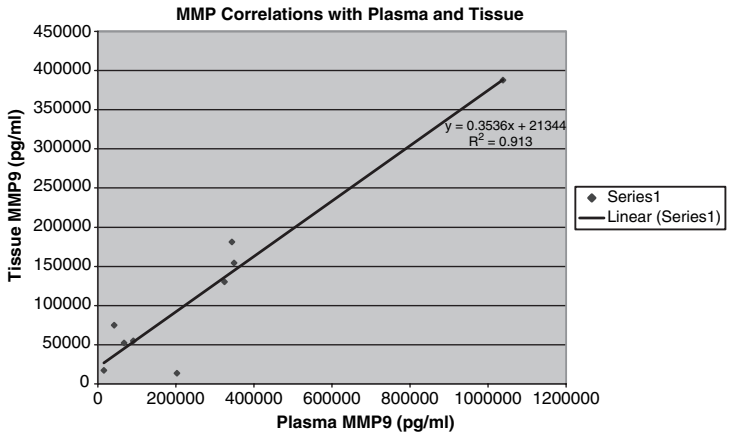


Figure 4 Correlation between serum and tissue matrix metalloproteinase levels in thoracic aortic aneurysms. (Unpublished Yale data.)

management that was terminated early due to poor tolerability and increased mortality in the study group, although the aneurysm expansion rate was lessened (65).

The beneficial effects of beta blockers on aneurysm expansion, however, may not be solely attributable to mechanical forces. Similar changes in heart rate, blood pressure, and Dp/Dt can be achieved with calcium channel blocking medications (66), but these medications have been shown to be independently associated with increased risk of AAA development, with an odds ratio of 2:6 over those who do not take this class of drugs (67). It is probably no coincidence that amlodipine, a calcium channel blocker, potentiates MMP activity and elastin degradation (68). It is also probably not coincidental that beta-adrenergic blockade is associated with decreased tumor necrosis factor alpha expression, which leads to decreased MMP production (69,70).

Specific inhibition of MMPs may become the mainstay of pharmacologic therapy for TAAs. The literature is replete with reports of animal models demonstrating decreased formation or progression of aneurysms through either MMP inhibition or targeted MMP gene deletion. Mosorin et al. (71) published a randomized controlled trial, which demonstrated a decreased expansion rate in human AAAs after administration of doxycycline, an antibiotic with known MMP inhibitory properties. Further investigations of MMP inhibition using doxycycline and other MMP inhibitors in AAAs are ongoing. For TAAs in humans, this question has not been directly addressed, although reports of animal models of TAAs are yielding encouraging results.

Recently, great interest has been focused on an article by Habashi et al. in which losartan, an angiotensin receptor type I (ATI) antagonist, was used in a murine model of Marfan's syndrome to prevent aortic root aneurysms and pulmonary alveolar septation defects (72). Alhough the mechanism of beneficial effects of ATI blockade with losartan is not clearly elucidated, the authors postulated several possible explanations. These included decreased mechanical stress on the aorta, which the authors state is unlikely because the control group was treated with beta blockade to achieve similar blood pressure control to the study groups, direct inhibition of transforming growth factor beta (TGFB) expression, indirect inhibition of TGFB expression through inhibition of thrombospondin production, decreased proliferation of vascular smooth muscle cells (VSMCs) and subsequent vessel wall fibrosis, and decreased Smad-2 dependent signaling and fibrosis.

If one carefully examines each of the postulated mechanisms, however, the downstream effect of each mechanism can lead to MMP inhibition. With regard to TGFB inhibition, TGFB has been shown to enhance MMP expression in sites of inflammation (73,74). VSMCs, whose proliferation is inhibited by losartan, are an abundant source of MMPs in TAAs (60). These findings, as well as preservation of VSMC density in early ascending thoracic aneurysms, were also demonstrated in our laboratory (75). Thrombospondin has also been shown to modulate MMP-2 activity in VSMCs (76). Concerning decreased Smad-2 dependent signaling, a study by Dixon et al. (77) demonstrated that chronic ATl receptor blockade abrogated this process, and led to decreased MMP1 and 2 production. When one carefully

considers the pathways of cellular responses to ATI blockade, each of the proposed beneficial mechanisms of losartan can be linked to decreased MMP production. Thus, it appears that the MMPs may represent a final common pathway in aneurysm progression and complications, and that losartan exerts its beneficial effects through inhibition of certain MMPs. In fact, numerous studies have demonstrated the salutary effect on aneurysm formation of antagonism of the angiotensin system in general (78–80), the ATI receptor specifically (81), and the use of losartan (82–84) precisely on MMP production. One possible additional benefit of angiotensin system inhibition relates to increased type III collagen synthesis (85).

Other pharmacologic agents that have shown promise in limiting aneurysm formation or progression in animal models include the hydroxymethylglutaryl coenzyme-A inhibitors, commonly referred to as the statins (86,87), the cyclooxygenase inhibitors (88–90), nitric oxide inhibitors (88,91), hydroxamate based compounds (92–94), an nuclear factor-Kappa B inhibitor (95), broad spectrum MMP inhibitor, BB94 (96), trapidil, a CD40/CD40 ligand system inhibitor (97), macrolide antibiotics (98), sulfonamide antibiotics (99,100), and rapamycin (101). It is likely that in the future patients with early or inoperable aneurysms, or those at high risk for aneurysm occurrence, may be placed on a combination of these agents at a low dose, in order to maximize the MMP inhibition while minimizing the side effects of each individual agent.

If levels of MMPs and their tissue inhibitors can be minimally invasively followed to yield information about the pathogenic activity of TAA and the prognosis of the affected patients, the surgical decision-making process will be significantly improved. If the role of MMP inhibition in TAAs can be firmly established, the medical management of TAAs will be rendered much more effective. At the Yale Center for Thoracic Aortic Disease, we will continue to investigate the mechanism of TAA formation and progression, with the goals of precise prediction of those TAAs that will expand or become complicated, defining the optimal medical therapy for early, inoperable, or stable aneurysms. We will also work toward the best therapy of all, prevention of TAAs in those whom we identify to be at greatest risk. To that end, we are clarifying the genetics of thoracic aneurysms (102,103). We predict that MMP monitoring and modulation will become valuable tools in the armamentarium of those who treat aortic diseases, but these tools will not replace careful clinical follow-up, effective clinical judgment, and timely operative intervention.

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DISCUSSION AND COMMENTARY

Questions for the Authors

Are MMP levels followed clinically, or does assessment of levels of these important enzymes remain a research tool?

At the time being, these levels are followed as part of research efforts. We are not aware of a laboratory that offers MMP assay as a clinical test. If a predictive utility for disease progression should be developed, there would then be impetus for conversion to a clinically available testing modality.

Doxycycline has been shown to inhibit MMPs. Why is doxycycline-based treatment not applied more widely?

First, benefit from doxycycline has not been conclusively demonstrated, even for abdominal aortic aneurysm. Second, the MMPs are a complex system of several dozen discrete enzymes. We need to determine which ones need to be inhibited in aneurysm disease, as well as which MMPs are inhibited by specific antibiotics or other drugs. Vast efforts are being expended in this regard by drug companies, not so much with aneurysm in mind, but with an aim of modifying post-myocardial infarction remodeling. We need to keep in mind as well that there can conceivably be dramatic adverse effects from inhibiting MMP activity too broadly or severely. For example, MMPs play a role in eliminating arterial atheromas as they form.

9

Inflammation and Remodeling in the Thoracic Aorta

Donald M. Botta, Jr., Paul C. Y. Tang, John A. Elefteriades, and George Tellides

Section of Cardiothoracic Surgery, Yale University, New Haven, Connecticut, U.S.A.

INTRODUCTION

Acute thoracic aortic conditions do not occur by accident. They represent a culmination of a process that begins oftentimes at the conception of the individual and progresses throughout the lifetime of the individual to result in the acute condition. Many factors in this process are measurable and to some degree may be modifiable. This chapter will explore the events that occur at the cellular and the extracellular matrix levels that, in concert with mechanical forces and over a period of time, lead to the acute conditions of the thoracic aorta that are addressed in the remainder of this book.

To cover this topic, we will begin with a discussion of the changes in inflammatory cell types and activity that occur in the aneurismal thoracic aorta, and then proceed with a summation of the events that occur in the extracellular matrix as a result of these cellular events. We will then explore how these events lead to changes in thoracic aortic morphology that act synergistically with mechanical forces to cause aneurysm progression and complications. Finally, we will discuss how these events can be measured, and how they may be modified in the future to treat, or even prevent, thoracic aneurysms.

INFLAMMATORY CELL TYPES AND ACTIVITY

Normal Thoracic Aortic Histology (Fig. 1)

In order to relate the pathophysiology of the thoracic aorta, we must first briefly describe its normal architecture, histology and function. The normal human thoracic aorta is more than a simple tube that conveys blood downstream for use by other organs (Fig. 1) (1). It is a complex structure that plays an active role in systemic inflammation and blood pressure regulation, from both an endocrine and a mechanical standpoint. It has been stated that the aorta "plays a game of catch" with blood, absorbing some of the force of the fluid column in systole and transmitting this stored energy back to the blood during diastole (2–4). To perform this function, the thoracic aorta has a complex architecture that nature has designed for this purpose.

Like all arteries, the normal thoracic aortic wall can be divided into three basic layers, namely the intima, media, and adventitia.

The intima is composed of endothelial cells, which can express a wide array of adhesion molecules and chemotactic factors and can secrete a number of substances to orchestrate local thrombotic, thrombolytic, or inflammatory processes. It also possesses a subendothelial collection of vascular associated lymphoid tissue (VALT), which may serve a function in immune surveillance. The normal aortic intima and inner media are bereft of vasa vasorum, being supplied with oxygen and nutrients by diffusion from the aortic lumen (5).

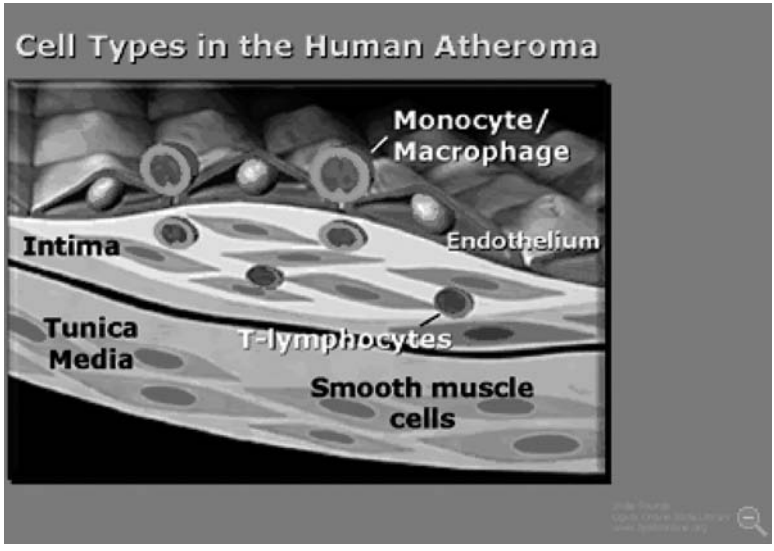

Figure 1 (*See color insert*) Histology of aortic wall, emphasizing the three layers of the aortic wall (intima, media, adventitia). Note the depiction of the vascular associated lymphoid tissue and vascular smooth muscle cells, which are so important in the inflammatory and lytic processes underlying the pathophysiology of aneurysm development. Note the lamellar architecture of the media (collagen and elastin) and the matrix.

The aortic media is composed of multiple elastic lamellae, which are concentric, well organized layers, or lamellae of elastin that impart the ability to expand and contract in response to applied force (6). The area between these lamellae, the extracellular matrix, is filled with collagen, proteoglycans, and glycosaminoglycans, which impart strength to the aortic media, vasa vasorum, which nourish the outer media, and vascular smooth muscle cells (VSMCs), which can serve either a motile or a secretory function, depending on the situation (7). The extracellular matrix is in a constant state of flux, with a homeostatic balance between production and destruction of matrix substances, largely orchestrated by VSMCs (8–11). Interestingly, the normal thoracic aortic media has very little VALT (12,13). The adventitia also contains vasa vasorum, VALT, as well as collagenous connective tissue that significantly enhance the strength of the aortic wall.

As we will discuss later in this chapter, as an aneurysm forms, each component of the complex make-up of the aortic wall behaves differently.

Vascular Associated Lymphoid Tissue in Thoracic Aneurysms

In contrast to aneurysms in other locations, thoracic aortic aneurysms (TAAs) tend to exhibit greater variability in the level of inflammation within their walls (14). This inflammation, evidenced by an upregulation in the amount of VALT, and its level of activity can range from "bland," especially in the ascending aorta, to exuberant, which is more common in the descending aorta [similar to the level of inflammation present in abdominal aortic aneurysms (AAAs)]. These differences are evident even on gross inspection in the operating room.

When inflammation does occur, the media is usually spared from leukocytic infiltration, leading some to conclude that it is an "immunoprivileged" region (15). This paucity of inflammatory cells is likely a consequence of the many lamellae of elastin, which can serve as a barrier to leukocyte migration, and the lack of vasa vasorum (which can serve as a conduit for leukocyte delivery) in the inner media, at least early on in aneurysm formation. This immunoprivilege may, to some extent, preserve the structural integrity of the media and delay aneurysm expansion. In a large subgroup of aneurysms, which we have dubbed "inflammatory," the immunologic privilege of the media is breached, and medial inflammation by inflammatory cells develops (16) (Fig. 2).

The intima is a place where active inflammation more commonly occurs in TAAs. The subendothelial VALT exhibits increases in the number and activity of leukocytes. Using cytokine profiling, we have been able to demonstrate an increased production of interferon gamma (IFNG), interferon-gamma-inducible 10 kD protein (IP-10), and monokine induced by gamma interferon, all of which are evidence of orchestration of this inflammatory response by T helper type 1 (Th1) lymphocytes (16). This finding is in contradistinction to arterial inflammatory mediation in other sites, where Th2 lymphocytes are associated with aneurismal dilation, and Th1 cells are associated with stenotic lesions (17,18). Under T cell direction, monocytes become transformed to macrophages that

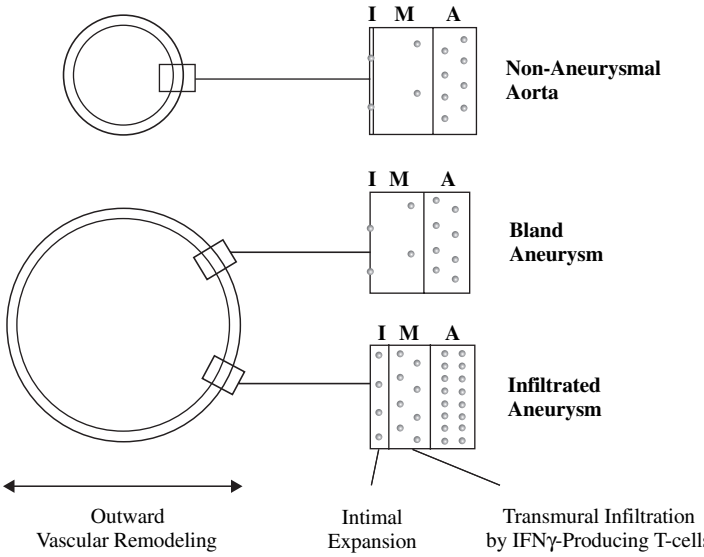

Figure 2 We found on immunohistochemical analysis that our ascending aortic aneurysms fell into two categories: "bland" and "infiltrated." This schematic indicates results of our staining for interferon-γ producing T cells. Vessel diameter and wall layer thickness are drawn to scale based on data means. The intima (I), media (M), and adventitia (A) are drawn at 10-times magnification. Infiltrating leukocytes are represented as shaded circles. Inflammatory infiltration of the inner media is a simple pathological marker that differentiates infiltrated from bland aneuirysms, as compared with normal aortas. *Abbreviation*: IFNγ, inteferon gamma.

are capable of releasing a wide variety of inflammatory, proteolytic, and reactive oxidative substances.

The increase in inflammation leads to increased production of pro-angiogenic factors like vascular endothelial growth factor, resulting in an increase in the number of vasa vasorum, and migration of these vessels into areas where they are absent in the normal state, like the inner media. These new vessels are fragile and prone to rupture, and they are excellent conduits for leukocyte transmigration, perpetuating the inflammatory process (19–21).

VAMCs in the media can also become active participants in the inflammatory process (22,23). In animal aneurysm models, a number of factors, including mechanical stress, angiotensin II, tumor necrosis factor alpha, interleukin-6, and IFNG can induce the activity of c-Jun N-terminal kinase, a protein kinase in VSMCs whose activity results in the production of neutrophil elastase, also known as matrix metalloproteinase-9 (MMP-9), an enzyme that breaks down elastin (24).

The media is also home to mast cells, which become activated in TAAs and contribute oxidases to the milieu (25), as well as chymase, which has been shown to convert angiotensin I to angiotensin II, as well as pro-MMP-9 to MMP-9, resulting in increased proteolytic activity (26).

The thoracic aortic adventitia, in the aneurismal state, has a pronounced accumulation of B lymphocytes (27) (Fig. 3). Other studies have echoed these findings, and demonstrated a B lymphocyte/T lymphocyte costimulation in aneurysm tissue (28).

CELLULAR AND MATRIX REMODELING

Hyperplastic Cellular Remodeling

In contrast to AAAs, where programmed cell death or apoptosis of the VSMCs in the media is a ubiquitous and probably contributory factor in expansion (29,30), TAAs have a preservation of the density of VSMCs. Considering the greater laminar volume associated with outward remodeling, a net hyperplasia of these VSMCs exists. These cells can produce an array of substances that contribute to inflammation and break down the extracellular matrix (31,32).

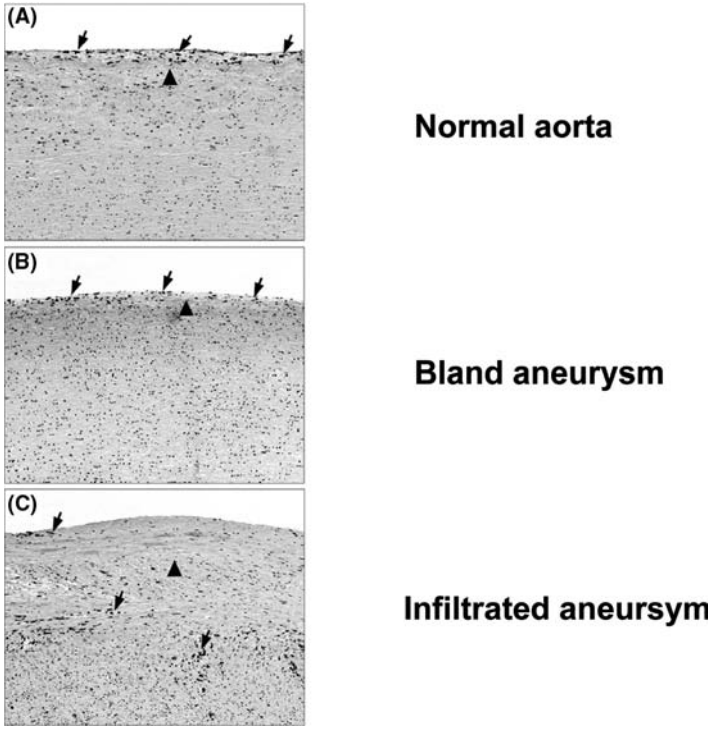

Figure 3 (*See color insert*) Stain for leukocytes in aortic wall (by immunohistochemistry using an antibody to the pan-leukocyte marker CD-45). Note relative paucity of leukocytes in normal aorta and "bland" ascending aortic aneurysm. Note marked leukocytic infiltration in "inflammatory" aneurysm. Arrows denote leukocytes. Arrowhead indicated border between media and adventitia.

The Role of *Fibrillin I*

It is impossible to have a discussion about thoracic aneurysms without mentioning aneurysms in patients with Marfan's syndrome, and it is impossible to discuss Marfan's syndrome associated aneurysms without mentioning the role of *fibrillin I.*

Fibrillin I is a gene that is defective in patients with Marfan's syndrome. Defects in this gene cause abnormalities in microfibril production (33). If one cannot effectively produce microfibrils, the strength of structural proteins will be significantly affected. In addition, a domain of this gene codes for products that have a regulatory roles (34). In animal models, defects of this gene cause increased synthesis of transforming growth factor beta (TGFB). Overproduction of TGFB can increase the level of proteolytic activity within the aortic wall, as well as within the lungs, another location of pathology in patients and animal models of Marfan's syndrome (35). The results of increased proteolysis are seen in Figure 4, from our immunohistochemical studies (16).

Matrix Degradation Within the Aortic Wall

As stated before, a homeostatic balance exists between production and breakdown of the substances in the extracellular matrix of the aortic wall. In patients with

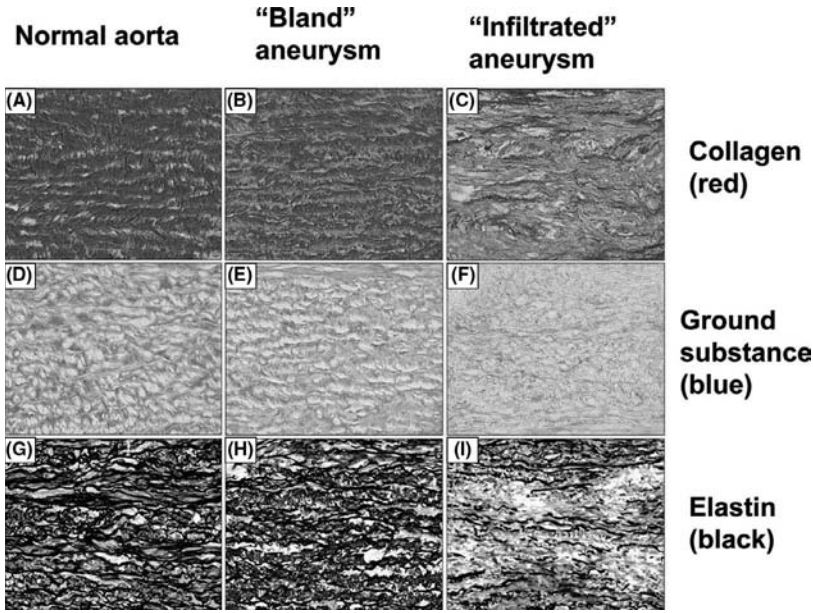

Figure 4 (*See color insert*) Demonstration of destruction of matrix proteins, progressively more severe in bland and then in inflammatory aneurysms. These figures depict the media of the aorta of the indicated categories. Sirius red is used to stain collagen. Alcian blue is used to label ground substance. EVG (black) is used to label elastin. Note marked degradation of collagen, ground substance, and elastin in inflammatory aneurysms. *Abbreviation*: EVG, Elasfica-van Gieson.

TAAs, protein production continues to occur, but this production becomes overwhelmed by protein destruction (36). The chief culprits in the breakdown of the matrix structure are the matrix metalloproteinases (MMPs).

The MMPs are a group of zinc dependent enzymes whose role, in both physiologic and pathologic states, is to break down the extracellular matrix (37). Without the MMPs, normal growth and angiogenesis could not occur (38). These enzymes are active in a wide array of disease processes, from periodontal disease (39) to congestive heart failure (40–42). The activity of the MMPs is normally held in check by their natural inhibitors, known as the tissue inhibitors of metalloproteinases (TIMPs). When an imbalance between the MMPs and TIMPs exists, tissue destruction can ensue.

In no disease process is the role of MMPs more clear than aneurysm disease, and thoracic aneurysms are no exception to this rule. A number of studies, including those in our laboratory, have noted increased expression of MMPs at the DNA, RNA, and protein level in TAAs. In particular, overexpression of MMP1, MMP2, MMP3, and MMP9 have been noted (43). In addition, we have noted an increase in the MMP to TIMP ratio in thoracic aneurysms, resulting in a condition that favors proteolysis (36). These enzymes serve to break down the building blocks of the thoracic aortic media, most importantly collagen and elastin. In animal models of TAA, inhibiting the production of these enzymes limits aneurysm formation and progression.

Interplay Between Mechanical Forces and Remodeling

Once the aneurysm process begins, its progress is usually assured. This is likely because the changes that occur in the thoracic aortic wall lead to increased wall stress, which leads to greater inflammation, which leads to further remodeling, perpetuating a vicious cycle.

The components of wall stress include pressure, lumen diameter, and wall thickness. As the aneurismal aorta remodels, the lumen diameter increases, and the wall thins. Both of these conditions lead to increased wall stress. Increased wall stress leads to greater inflammatory and proteolytic activity within the aortic wall, and more outward remodeling. Once a critical diameter is reached, the aorta loses its elastic properties, and the energy transmitted during systole cannot be effectively absorbed. Once the tensile strength of the aorta is matched by the stress applied (usually at about six centimeters diameter at a pressure of 200 mmHg for the ascending aorta) aortic rupture or dissection ensues (44) (Fig. 5).

WHAT IS MEASURABLE AND WHAT IS MODIFIABLE?

A number of studies have recently been completed or are ongoing to answer these questions. Currently available imaging technology, coupled with a comprehensive database, has already allowed us to develop predictive models of thoracic aortic expansion and complications (45–50). While these models work well on a population based sample, further investigations are required to predict which patients with aneurysm require more urgent intervention. Targets of these investigations begin

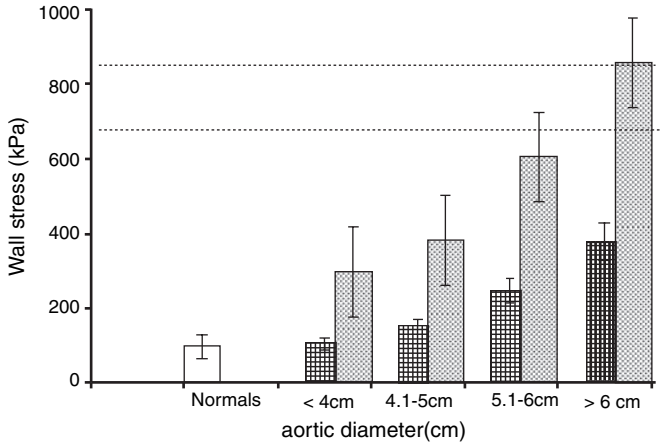

Figure 5 From our mechanical studies on the aneurysmal ascending aorta. Note the exponential relationship between wall stress and aneurysm size in ascending aortic aneurysms. Dark bars represent blood pressure of 100 mmHg; light bars represent blood pressure of 200 mmHg. Lines at 800 to 1000 kPa represent range of maximum tensile strength of human aorta. It is no wonder that the aneurysmal aorta ruptures or dissects, especially under stress or exertion.

at the DNA level in tissues, and proceed through the RNA and protein expression level (51–54). To assess risk without aortic tissue requirement, circulating biomarkers are beginning to be assessed.

We have recently completed work that has identified a group of single nucleotide polymorphisms from peripheral blood samples that are reflective of aneurysm risk (55). Work is now underway to harness these data and develop a micro-array chip that would be broadly applicable as a predictive test for aneurysm propensity.

We have also begun to investigate the correlation between tissue levels and circulating levels of MMP-9, which is responsible for the breakdown of elastin in TAAs. We have identified a correlation in MMP-9 levels between these two locations (blood and tissue) (56). Study is ongoing to determine if MMP-9, among other biomarkers is predictive of aneurysm expansion or complications. If so, measurement of serum MMP-9 levels would greatly enhance the decision-making process in those who are being evaluated for thoracic aneurysm disease.

For aortic dissection, evaluation of circulating levels of d-dimers, which are products of cross-linked fibrin degradation, has emerged as an extremely sensitive tool for diagnosis (57,58). If the D-dimers are not elevated, an acute aortic dissection can almost certainly be excluded.

Is it possible to prevent, arrest, or reverse the process of aortic remodeling? In animal models, the answer is affirmative (59–64), and limited data in humans seem to concur (65–68). A number of agents or modalities have been shown to

limit production of MMPs, and in so doing limit aneurysm formation or expansion. These agents include inhibitors of the angiotensin system, tetracyclines, sulfa antibiotics, hydroxymethylglutaryl coenzyme-A inhibitors, commonly referred to as the statins (69,70), nitric oxide inhibitors (71) the cyclo-oxygenase inhibitors (71–73), hydroxamate based compounds (74), a NFKB inhibitor (75), broad specrum MMP inhibitor, BB94 (76), trapidil, a CD40/CD40 ligand system inhibitor (77), macrolide antibiotics (78,79), sulfonamide antibiotics (80), and rapamycin (81). In addition, inhibition of the angiotensin pathway has been shown to limit aneurysm formation both through an MMP dependent means (81–87), and through a TGF-B mediated mechanism (88,89). It is most likely that a combination of these medications will be used in the future to limit aneurysm progression and to prevent aneurysm formation in those who are at high risk.

CONCLUSION

The behavior of TAAs is beginning to be understood at a cellular level. Much of this behavior is based on a combination of inflammation, proteolysis, and mechanical forces. We are now beginning to understand how to noninvasively measure the activity of these factors, and noninvasive modification of each of these forces is on the horizon.

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10

Weight Lifting and Aortic Dissection

John A. Elefteriades

Section of Cardiothoracic Surgery, Yale University,
New Haven, Connecticut, U.S.A.

INTRODUCTION

On rounds in 2002, we noted that our team had cared for a number of young men who suffered an acute aortic dissection while lifting weights. In 2003, we reported in the Journal of the American Medical Association on a connection between weight lifting and aortic dissection in five young men (1). We found some precedent in the literature supporting such a connection (2). We also found evidence in the literature that high-intensity weight lifting can produce extreme levels of systemic hypertension (3).

Since our original report, additional cases of aortic dissection related to weight lifting (or other severe exertion) have been brought to our attention. These cases often represent tragic, lethal outcomes in otherwise healthy young people. We recently reported on 31 patients in whom weight lifting or other severe exertion was associated with the onset of acute aortic dissection (4).

Thirteen of these 31 cases were treated at Yale University. The other 18 cases were relayed to us by patients or family members expressly for the purpose of enhancing our research into exercise-related aortic dissection. In all cases, all available records—including hospital charts, X-ray reports, pathology reports, and operative notes—were reviewed and tabulated (Table 1).

Over 50 cases had been identified or submitted to our attention, but only the 31 included in our tabulations met criteria for inclusion as weight lifting or extreme exertion related. We required documentation of severe lifting-type exertion immediately preceding the onset of symptoms of dissection, concrete

Table 1 Relationship Between Weight Lifting and Extreme Exertion with Aortic Dissection

	Occupation	Age	Sex	Rx'd	Family Hx	Activity	Ao size (cm)	Type of Dissection (Asc or Desc)	Surgery	Outcome
1	Student	24	M	Yale	Yes	Weight lifting	5.5	Asc	Yes	Alive
2	Student	19	M		No	Weight lifting	5	Asc	No	Dead[a]
3	Salesman	53	M	Yale	No	Weight lifting	4.0	Asc	Yes	Alive
4	Policeman	37	M	Yale	No	Push-ups	5	Asc	Yes	Alive
5	Security	52	M		No	Push-ups		Asc	No	Dead[b]
6	Attorney	68	M		No	Weight lifting (175 lbs)	"Dilated"	Asc	Yes	Dead
7	Signalman	55	M		No	Lifting generator (80 lbs)	3	Asc	Yes	Dead
8	Repairman	44	M		No	Lifting tank (400 lbs)	7.8	Asc	Yes	Alive
9	Professor	49	M		No	Weight lifting	6.3	Asc	Yes	Alive
10	Writer	43	M		No	Weight lifting (300 lbs)		Asc	No	Dead[b]
11	Social worker	42	M		No	Weight lifting	4.0	Asc	Yes	Alive
12	Surgeon	63	M		Yes	Weight lifting	3.8	Desc	Yes	Alive
13	Mason	34	M		No	Lifting concrete blocks (150 lbs)	4.0	Desc	No	Alive
14	Priest	56	M		No	Weight lifting (250 lbs)	3	Asc	Yes	Alive
15	Businessman	40	M		No	Weight lifting	6.9	Asc	Yes	Alive
16	Journalist	50	M		No	Weight lifting (500 lbs)		Asc	Yes	Alive

17	Surgeon	43	M		No	Intense swimming	4.0	Asc	Yes	Alive
18	Mason	75	M	Yale	No	Intense swimming	6.0	Asc	Yes	Alive
19	Clerk	49	F	Yale	No	Pulling hard against lg. dog	4.3	Asc	Yes	Alive
20	Professor	74	M	Yale	No	Intense tennis	4.0	Desc	Yes	Alive
21	Mailman-ret	76	M	Yale	No	Moving heavy boxes	4.3	Desc	Yes	Alive
22	Unemployed	35	M	Yale	No	Exercising	3.1	Asc	Yes	Alive
23	Computers	50	M	Yale	No	Changing storm windows	6.0	Asc	Yes	Dead
24	Security guard	48	M	Yale	No	Intense swimming	4.9	Asc	Yes	Alive
25	Businessman	35	M	Yale	No	Intense racketball	4.1	Asc	Yes	Alive
26	Machinist	50	M	Yale	No	Shoveling snow		Asc	Yes	Alive[c]
27	Mechanic	51	M	Yale	Yes	Weight lifting	6	Asc	Yes	Alive[c]
28		37	M		No	Weight lifting		Asc	No	Dead[b]
29	Construction	35	M		No	Lifted power washer from truck	4.1	Asc	No	Dead[b]
30	Mover	38	M		No	Carried freezer 2 flights (700 lbs)	4.3	Asc	No	Dead[b]
31	Engineer	43	M		No	Weight lifting	4	Asc	Yes	Dead

[a]Diagnosis made by imaging (echocardiography or computed tomography), but patient not transferred in time for surgery.
[b]Diagnosis not made during life. Postmorten confirmatory.
[c]Prior Type B dissection.

confirmation (radiographic, surgical, or autopsy) of the diagnosis of dissection, and documentation that pain symptoms came on during or immediately after the extreme exertion. All patients sought attention promptly after onset of symptoms. We also included in our tabulation five patients who were engaged in severe nonlifting type exercise.

Interesting and illuminating patterns emerged in the evaluation of the clinical spectrum of these cases.

PATIENT CHARACTERISTICS

All individuals were male except for one female (30 M, 1 F). Ages ranged from 19 to 76 (mean 47.3 years). Twenty-one of the 31 cases were 50 years of age or less. Three patients (9.7%) had a history of aortic disease in a family member. In only two cases was the affected patient in this study group aware of a pre-existing aortic abnormality.

The activity leading to aortic dissection was weight lifting (or push-ups) for strength training in 16 cases, and lifting of heavy weights in nonexercise settings in nine cases. The heavy weights being lifted included a gasoline-powered generator, an oil tank, concrete blocks, a large dog, heavy boxes, storm windows, snow (shoveling), a power washer, and a freezer. In five cases, the inciting exertion was very heavy nonlifting exercise [including swimming (3), tennis, and racquetball].

Twenty-seven patients (87.1%) had ascending dissection (Type A) and four (12.9%) had descending (Type B).

In 26 of the cases, an aortic diameter was available from premortem imaging studies (echocardiography or and computed tomography) or from postmortem examination. In all but four cases, the aorta was abnormally enlarged (>4 cm). Aortic size ranged from 3 to 7.8 cm (mean 4.63 cm). In 17 of the 26 patients (65%), whose aortic size was available, the aorta was only moderately enlarged (≤5 cm). Our prior experimental observations have shown that aortic diameter does not increase dramatically at the time of aortic dissection (5), so we interpret these dimensions as generally characteristic of the predissection aortic size.

TREATMENT AND OUTCOMES

In 26 cases, the diagnosis of acute aortic dissection was made clinically. In the remaining five cases, the diagnosis of acute aortic dissection was not made clinically, and aortic dissection was not detected until postmortem examination.

Twenty-four patients underwent surgical correction and aortic grafting [23 operatively and one (descending dissection) by an endovascular approach]. Six patients (four descending and two ascending) were treated exclusively medically (with an “anti-impulse” regimen of beta-blockers and afterload reducers). One patient, correctly diagnosed but treated without an operation, died waiting for a helicopter to transport him to a tertiary care facility. One patient with descending aortic dissection was treated exclusively medically (with an “anti-impulse” regimen of beta-blockers and afterload reducers).

Ten of the 31 (32.3%) patients died, all with ascending dissections. Five patients died undiagnosed (one during catheterization for presumed myocardial infarction). One aforementioned patient died awaiting transportation. Four patients died during or after surgical correction. The remaining patients survived the acute episode.

IMPLICATIONS

We feel that the identification of these 31 cases in which acute aortic dissection occurred during heavy weight lifting or other extreme exertion strengthens the causative association between these events. These cases represented situations in which heavy weights were being lifted as part of athletic strength training, as well as a few instances in which heavy objects were lifted in nonexercise settings and a few instances of nonlifting extreme exertion. In most cases, the individuals affected were relatively young (mean age 47.3 years) and had no prior history of cardiac disease.

In the vast majority of cases, the aortic dissection affected the ascending aorta (Type A).

We feel that pre-existing enlargement of the aorta is a prerequisite for the phenomenon of weight lifting related aortic dissection to occur. This is seen in the fact that most aortas for which a dimension was available were mildly to moderately enlarged (mean size 4.63 cm). This observation dovetails with our recent analysis of the mechanical properties of the human aorta (6). We found that wall stress in the aorta increases to dangerously high levels as the aorta enlarges. We feel that individuals without aortic enlargement appear to be largely spared from the weight lifting related dissection phenomenon.

Based on our blood pressure studies during weight lifting (7) and the evidence available in the exercise literature, we are convinced that dramatic elevation in blood pressure occurs with heavy weight lifting or other strenous exertion (Fig. 1). Blood pressures easily exceed 300 mmHg. Pressures as high as 380 mmHg have been recorded in competitive weight lifters. These pressures exceed considerably those seen in the process of daily intensive care in Cardiac Care Units or postoperative Cardiothoracic Intensive Care Units. Our mechanical studies (5) demonstrated that increased blood pressure in an enlarged aorta yields extremely dangerous levels of wall stress—in fact exceeding the previously known ultimate wall strength of human aortic tissue (800 to 1000 kPa).

Our conclusion is that increased blood pressure due to heavy weight lifting raises aortic wall stress to a level that produces aortic dissection in individuals susceptible by virtue of pre-existing mild to moderate aortic enlargement.

Certain considerations must temper our observation of this weight lifting-to-aortic dissection association. First, the causative relationship between the extreme exertion and the advent of aortic dissection is surmised based on the close temporal association of the activity and the onset of pain. This association is not proven conclusively by our observations. Such proof would be very difficult to come by in the real world. Second, the denominator of patients lifting weights

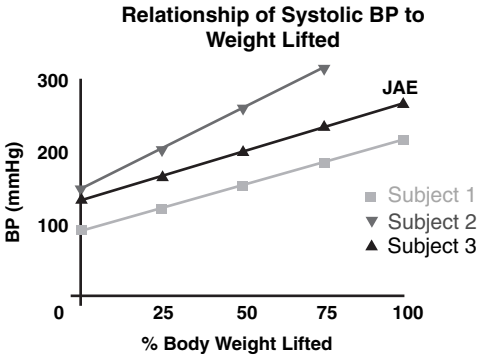

Figure 1 We performed the investigation on ourselves, using an apparatus developed by our anesthesia team that permitted determination of instantaneous blood pressure without placement of an arterial line. Blood pressure during lifting was related to percent of body weight lifted in the bench press exercise. Subject 1 was a healthy 16-year-old athlete; he reached a blood pressure exceeding 200 mmHg at 100% body weight lifted. Subject 2 was a prior athlete, now sedentary; his lifting was stopped when he attained a blood pressure of 320 mmHg at 75% of his body weight. Subject 3, the author, an experienced weight lifter, reached a blood pressure of 250 mmHg at 100% of body weight lifted. In professional weight lifters, blood pressures as high as 380 mmHg have been recorded.

(or experiencing other extreme physical strain) is very large and unmeasurable by our data. This study examines only the clinical characteristics of certain patients treated by or made known to us who fall in the numerator of the ratio of dissection to weight lifting activity.

We believe strongly in the value of weight training. We feel that, especially in middle age and beyond, such strength training is essential to preserving muscle mass and bone strength. We feel that such exercise training appears to be safe, from an aortic standpoint, as long as the individual does not harbor unknown aortic enlargement. As an initial rule of thumb, it appears that lifting up to one half the individual's body weight is relatively safe, not exceeding a blood pressure of 200 mmHg, even during the effort cycle of the lifting exercise.

We feel that better systems need to be developed for monitoring of blood pressure during weight lifting and other strenous exercise. Such efforts are underway at our institution.

We urge that individuals with known aortic enlargement be strongly counseled to avoid or limit weight lifting or other activities that involve extreme exertion or straining.

Also, we suggest that individuals pursuing or embarking on serious weight training undergo transthoracic echocardiography to confirm that they harbor no undetected aortic enlargement. We recognize that this recommendation affects a huge number of individuals. We realize as well that consideration of such a policy involves

important social, economic, and political factors, which fall beyond the scope of purely clinical considerations. However, the alternative to routine screening appears to be accepting that certain otherwise healthy young people will remain susceptible to, and that some will tragically succumb to, weight lifting related aortic dissection.

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DISCUSSION AND COMMENTARY

Questions for the Author

How much weight is OK for someone with a small aneurysm, say 4.5 cm?

We have done limited testing, and it appears that if the weight lifted is less than 50% of body weight, in the bench press, blood pressure will not exceed 200 mmHg. Thus, we usually recommend that such an individual lift no more than 50% of his body weight in the bench press.

How about other lifts?

We simply have not tested other exercises. These tests are currently under way, in our Medical School gymnasium.

How about aerobic activity?

Tremendous elevation of blood pressure more commonly characterizes resistance training rather than aerobic training. It is known from the exercise literature that the degree of blood pressure elevation during even intense aerobic exercise is modest; thus, we have not forbidden aerobic exercise. Also, of course, regular aerobic exercise produces a beneficial drop in ambient blood pressure at rest, with likely benefit to the aorta. That said, we must emphasize that a small number of the patients listed in the table in this chapter did suffer their dissections during intense aerobic exercise.

11

Timing of Acute Aortic Events: How Does Dissection Pick a Date, Time, and Moment to Occur?

John A. Elefteriades

Section of Cardiothoracic Surgery, Yale University, New Haven, Connecticut, U.S.A.

Why did Mr. Smith's aortic dissection occur at 7 AM on a Monday in December? Until very recently, the timing of an acute aortic event was totally obscure.

We have seen from the chapters in this section that there is a genetic predisposition for aortic aneurysm and dissection. We have seen that the occurrence of these events can be predicted with a fair degree of accuracy based on the size of the aorta. We have reviewed biomechanical studies of the aorta, which indicate that the enlarged aorta experiences severe wall stress. We have also seen that extreme exertion can be associated with onset of aortic dissection-acting, we believe, via the mechanism of increased blood pressure. These findings permit an emerging understanding of the timing of acute aortic events. That is, these observations permit us to understand how dissection picks a date, time, and moment to occur.

After the observations regarding weight lifting or other extreme exertion discussed in some detail in Chapter 10, our team became intrigued with the issue of what our patients were doing at the precise time of onset of acute dissection pain. Accordingly, we conducted large-scale interviews of our patients with aortic dissection. In case the patient had died or lost consciousness at the time of the acute event, we also interviewed family members. The findings were quite interesting.

We found that in 26.6% of cases, the patients or families were able to recall a specific severe physical exertion at the time of onset of the dissection pain (Fig. 1). We found that in 45.6% of cases, the patients or families were

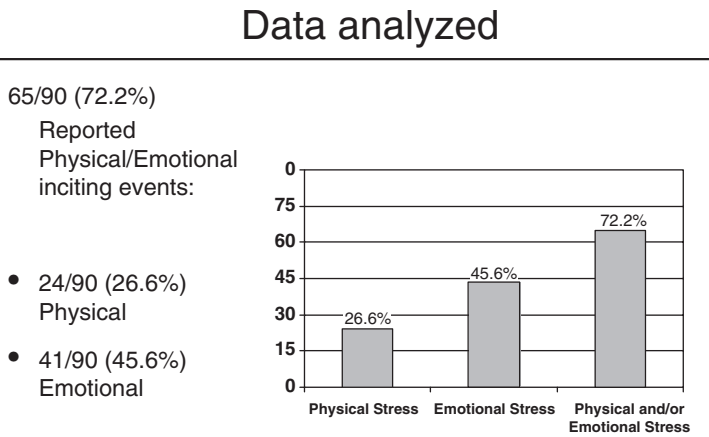

Figure 1 Antecedent physical or emotional events at the time of acute onset of acute dissection pain. Note that exertions or emotions were extremely prevalent inciting factors.

able to recall a specific severe emotional event at the time of onset of the dissection pain. Some examples of specific negative emotional events recalled include the following. One woman was just informed of a diagnosis of lung cancer. Another reported receiving some "very upsetting news." One patient had just completed a "bad business lunch." Another had suffered "big losses at the casino." One gentleman reported extreme stress while on a business trip. Taking into account both the reports of severe physical and those of severe emotional events, this adds up to 72.2% of cases in which either a severe exertion or a severe emotion appeared to trigger the dissection process. We can postulate the following mechanism for the timing of acute aortic events (Fig. 2):

1. A genetic diathesis sets the stage for development of aneurysm or dissection disease.
2. Through the mechanisms elaborated in the chapters of this book on pathophysiology of aneurysm disease—including inflammation and matrix injury, as well as smooth muscle cell loss and action of cytokines—the aortic wall is injured.
3. The injured aortic wall dilates.
4. The dilatation, as we saw in the chapter on biomechanics, causes excess mechanical stress on the aortic wall.
5. At a moment of extreme exertion or emotion, a spike in blood pressure causes the aortic wall stress to exceed the tensile strength of the aortic tissue.
6. Rupture or dissection eventuates.

We feel this overall schema best fits with the insights obtained from genetic studies, from pathophysiologic studies, from investigations of the natural history

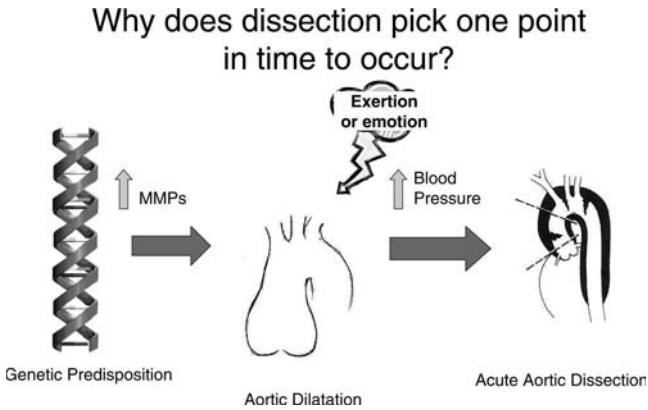

Figure 2 (*See color insert*) Proposed schema for the occurence of an acute aortic condition at one particular moment in time. *Abbreviation*: MMPs, matrix metalloproteinases.

of aortic aneurysms, from biomechanical studies, and from clinical interviews of dissection survivors and relatives.

This schema suggests that interventions to interrupt this process leading to catastrophic aortic events may be entertained for each point in this continuous process. For example, activities may be restricted, as we propose regarding weight lifting, for individuals with substantive aortic enlargement. Similarly, for susceptible individuals, the emotional milieu in which the patient lives his life may be altered by lifestyle changes, therapy, or medication aimed at avoiding peaks of negative emotion. These possibilities will be explored more fully in the chapter on novel therapeutic strategies near the end of this book.

DISCUSSION AND COMMENTARY

Question for the Author

Is not your schema speculative?

Of course, you are correct, the schema we present for the causation and timing of aortic dissection is an oversimplification, at least partially speculative. However, we believe that this schema best represents the available evidence.

Specifically, there is no longer room for doubt about the genetic origin of many, if not most, thoracic and abdominal aneurysms. While pointing to the MMPs as the effector of the genetically-programmed aortic destruction is an oversimplification (see Chapter 17), the MMPs clearly play a major role. We have little doubt about the importance of physical stress in bringing on an aortic dissection—as evidenced in our reports of exercise-induced aortic dissection. Acute hypertension makes great sense as the culprit in cases of extreme physical exertion. That blood pressure rises astronomically with weight lifting is not disputable. We were surprised to see just how large a proportion of patients and families interviewed reported extreme emotional stress at the moment of onset of dissection pain. We believe it is reasonable to speculate that severe hypertension accompanied these episodes of extreme emotional stress.

12

The Natural History of Thoracic Aortic Aneurysms: Etiology, Pathogenesis, and Evidence-Based Decision Making for Surgical Intervention

Michael A. Coady
Harvard University, Landmark Hospital, Boston, Massachusetts, U.S.A.

John A. Elefteriades
Section of Cardiothoracic Surgery, Yale University, New Haven, Connecticut, U.S.A.

INTRODUCTION

Many clinicians hold a utilitarian view of the aorta, considering it merely a large conduit through which blood travels to the vital organs of the body. For this reason, the thoracic aorta may not capture the full attention that more elaborate functional organs receive. Nevertheless, aneurysmal disease of the aorta is the thirteenth most common cause of death in the United States (1).

With gradual dilation, the aortic wall becomes increasingly weakened, leading to possible dissection, rupture, and even death. The incidence of thoracic aortic aneurysm (TAA) is estimated to be 5.9 cases per 100,000 person-years (2). TAAs have a mean age at the time of diagnosis between 59 and 69, with men predominating over women with a ratio of 2–4 to 1. Affected individuals often have concomitant medical conditions including hypertension, coronary artery disease, chronic obstructive pulmonary disease (COPD), and congestive heart failure.

The prevalence of aortic aneurysms appears to be increasing, which may reflect improvements in imaging techniques as well as heightened clinical awareness of the disease (3). At the Center for Thoracic Aortic Disease at the

Yale University School of Medicine, we have examined the natural behavior of the thoracic aorta both at the molecular level and in a robust clinical statistical analysis in an effort to better understand the biological basis and natural history of this disease process. It is hoped that these efforts may one day enable disease prevention and refine current management. A further understanding of factors influencing aortic growth, rupture, and dissection analyzed in a vigorous statistical model enables us to develop strong, evidence-based indications for surgical intervention.

In this chapter, the etiology of TAA will be explored in detail. Second, we will explore the pathogenesis and risk factors for development and expansion of TAAs. Finally, we will review a sparsely studied area, namely, the appropriate aortic diameters which necessitate surgical intervention. The current recommendations for surgical intervention are based largely on clinical judgment, with a paucity of hard scientific and statistical data regarding the appropriate size criterion for surgical treatment. A recent MEDLINE search identified nearly 1000 articles addressing the surgical treatment of TAAs, but less than 10 specifically examining the natural risk of rupture or dissection in aneurysms not treated surgically. In deciding whether or not to operate on the basis of the clinical characteristics of patients, there has been little hard scientific guidance.

All patients discussed in this work were seen at Yale-New Haven Hospital from October 1985 to May 2006. The insights into the behavior of the thoracic aorta have been gleaned from our large, computerized database on thoracic aortic diseases, which currently includes over 3000 total patients and over 9000 patient-years of follow-up and 9000 catalogued imaging studies.

ETIOLOGY

Aneurysms of the ascending aorta are most commonly related to degenerative changes in the medial layer of the aortic wall (Fig. 1A and B). These changes within the muscular layers of the aorta may be associated with connective tissue, disease acquired defects in the aortic media, annuloaortic ectasia, or idiopathic causes (4). Atherosclerosis is less commonly seen in the ascending aorta, as opposed to its frequency in descending and abdominal aortic aneurysms. Chronic type A dissections are another potential cause of ascending aortic aneurysms. Other more rare causes include poststenotic dilatation from aortic stenosis, trauma, infections, mycotic aneurysms, and syphilitic aneurysms. Approximately 25% of aortic aneurysms occur in the ascending aorta (5).

Annuloaortic ectasia, progressive dilatation of the sinuses of Valsalva and the aortic annulus, is frequently associated with cystic medial necrosis (Fig. 2) (6). As the media undergoes progressive degeneration, the aortic diameter undergoes gradual fusiform widening. Progressively, the aortic root becomes widened, and the annulus dilated, with resultant loss of coaptation of the valve leaflets and regurgitation. Annuloaortic ectasia is commonly seen in individuals with Marfan's syndrome and true cystic medial necrosis. Cystic medial necrosis is, indeed, a rare disease and should be differentiated from aortic medical degeneration, which is

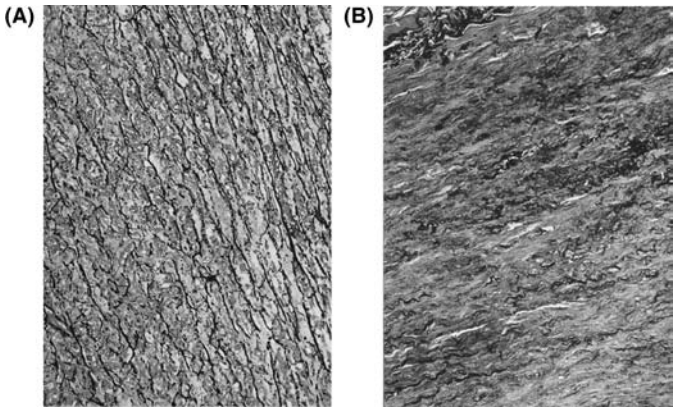

Figure 1 (**A**) Elastic van-geison stained section of a normal ascending aorta (×40). Note the uniform elastin fibers in the aortic media. (**B**) Hematoxylin and eosin stained section of an ascending aortic aneurysm (×40). Note the disrupted elastin fibers in the media.

seen in elderly patients (2). Aortic medial degeneration has been shown to occur in most aneurysms regardless of cause or location (7).

Patients with Marfan's syndrome and annuloaortic ectasia develop severe aortic regurgitation. Patients without Marfan's syndrome may also have annuloaortic ectasia, however, those individuals with aortic regurgitation and annuloaortic ectasia usually have some stigmata of Marfan's syndrome (8).

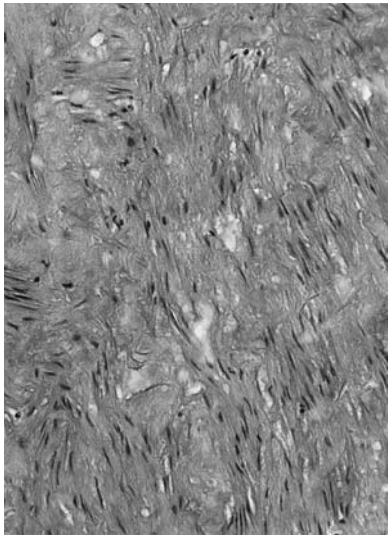

Figure 2 Hematoxylin- and eosin-stained section of an ascending aortic aneurysm (×40). Cystic medial degeneration is seen here with focal degeneration of the elastic tissue in the media and the presence of mucoid material in the media.

Aneurysms of the descending aorta most commonly arise at the level of the left subclavian artery. Approximately 50% of TAAs are located in the descending thoracic aorta (9). Historically, atherosclerosis has been linked to the development of descending TAAs. Whether this represents a "cause and effect" is debatable. Other causes of descending TAA may include chronic dissections, cystic medial necrosis, aortitis, and traumatic transections.

Genetic Basis for Thoracic Aortic Aneurysms Formation

Marfan's syndrome has been quite well characterized, and the gene has now been isolated on the long arm of chromosome 15 (10). Any of a host of mutations on the *fibrillin* gene can produce this phenotype, with its well-known skeletal, ocular, cardiac, and aortic manifestations. However, Marfan's syndrome is just the tip of the aortic genetic iceberg, accounting for only 5% to 10% of TAAs.

NonMarfan's related TAA and dissections are genetic diseases as well. Our group has documented that TAAs run strongly in families (Fig. 3) (11). In fact, the likelihood that a proband with aortic aneurysm has a first-order family member with an aneurysm somewhere in the body is 21.5% (12). This percentage has remained quite consistent as we have expanded our data to over 500 completed pedigree charts. The predominant mode of inheritance appears to be autosomal dominant (76.9%), but recessive and sex-linked patterns have been identified as well. We have also demonstrated that probands with aneurysms in the thorax can have family members with aneurysms in other locations as well, including the abdomen and brain (12). Aortic growth rate is highest for nonMarfan's patients who have family members with aneurysms (0.21 cm/yr), as opposed to sporadic aneurysms (0.16 cm/yr) and patients with Marfan's symdrome (0.1 cm/yr) ($p<0.01$) (12). This suggests that familial patients harbor a more aggressive clinical entity and that familial incidence represents an added risk factor for associated complications. Relative to their sporadic TAA cohorts, familial TAA patients also tend to be younger at presentation—again implying a more aggressive clinical entity.

PATHOGENESIS

The Aortic Wall and Aneurysm Formation

Aneurysm formation involves alterations in structural proteins of the aorta in addition to modifications in other extracellular matrix proteins, such as laminin, glycosaminoglycans, proteoglycans, and fibronectin. These are regulated in part by alterations in matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs).

Collagen and elastin are the major structural proteins of the aorta. Decreases in aortic content of these structural proteins were initially reported by Sumner et al. (13) in 1970. Decreased elastin content has been confirmed by a number of groups (14–16); however, collagen content appears to be more variable, with some groups reporting elevated levels (17). Cells of the connective tissue matrix have potential for synthesis of new collagen after injury; however, the capacity for generation of

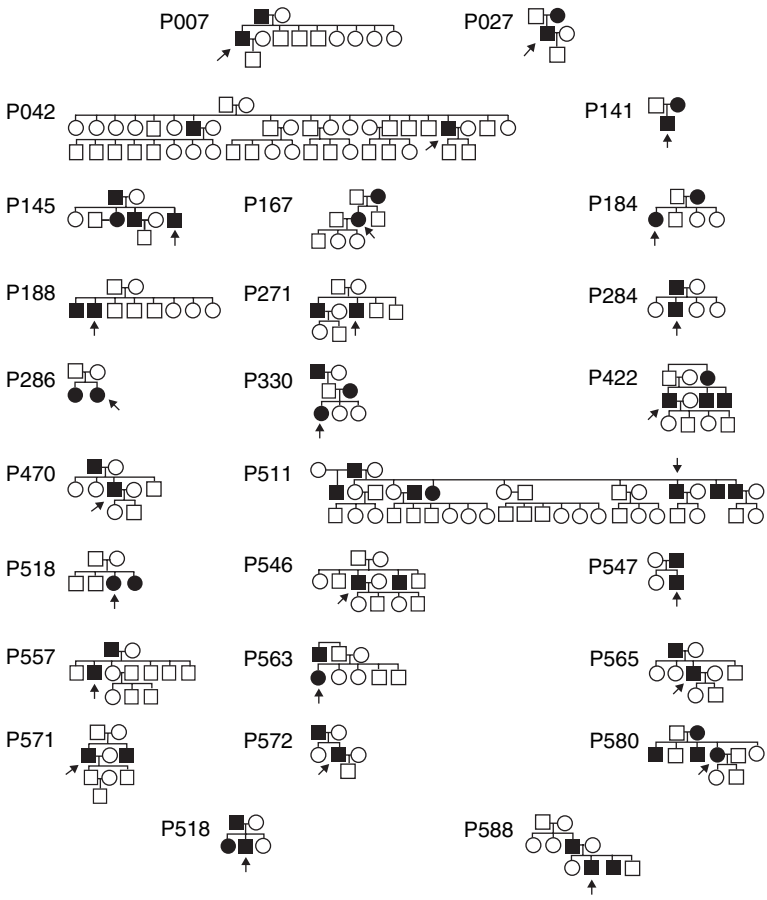

Figure 3 Thoracic aortic aneurysm (TAA) family pedigrees selected from over 500 family pedigrees. Squares represent men and circles, women. An arrow indicates the proband with a TAA. Blackened circles or squares represent affected patients with aortic aneurysms.

new elastin is limited. In the aortic wall, collagen is responsible for the tensile strength of the vessel, whereas elastin is responsible for its recoil capacity.

Fibrillin is another structural protein that contributes to the microfibrillar organization of the extracellular matrix. The microfibrillar construction functions as scaffolding for the deposition of elastin during elastogenesis. A mutation in fibrillin has been demonstrated in patients with Marfan's syndrome.

The aorta is categorized as an elastic artery with three defined layers—the intima, media, and adventitia. The intima consists of single layer of endothelial cells that rest on a basal lamina. The intimal cells rest on a subendothelial tissue comprised of collagen and elastin fibers, fibroblasts, and a mucoid ground substance.

The internal elastic lamina separates the intimal layer from the media. The internal elastic lamina, composed primarily of elastin, has fenestrae that allow substances from the lumen to diffuse to nourish cells within the aortic wall.

The media is composed of smooth muscle cells within a matrix of elastin, collagen, and ground substance. The elastic fibers in the aortic wall are arranged in the media as circumferential lamellae. The thoracic aorta consists of 45 to 56 lamellar units (concentric elastic lamellae with smooth muscle cells, collagen, and ground substance); the abdominal aorta contains only 28 units (18). The number of lamallar units is preserved throughout the mammalian species, with the exception of the human abdominal aorta, which consists of fewer units than expected given the load it bears. This may be a contributing factor in the prevalence of abdominal aorta aneurysm (AAA) compared to aneurysms in the thoracic aorta.

The lamallar units provide a structural framework for the media. These elastic lamellae serve to maintain the forward flow of blood during diastole: during systole, the diameter of these lamellae increases; the elastic fibers recoil during diastole (19). Smooth muscle cells within the medial layer maintain vascular resistance, serve a macrophage-like function, and are capable of collagen synthesis when stimulated (20). Humans lose the ability to produce elastic fibers in early life, and little elastin synthesis can be detected within the aortic wall beyond infancy (21).

In most patients with aortic aneurysm, histology examination reveals loss of elastic fibers—so called "medial degenerative disease." The mechanisms for this degeneration are not known, but fragmentation and retrogression of elastic fibers within the aortic media are clearly evident. More advanced medial degeneration (as in Marfan patients) leads to loss of smooth muscle cells. Histologic examination reveals significant reduction in the number of smooth muscle cells within the tunica media, and multiple interspersed lakes of mucopolysaccharide ("cystic medial necrosis").

White et al. (22) however, emphasize that loss of smooth muscle cells of the media should not directly affect the maximal outer diameter of the aorta. They and other others believe that loss of smooth muscle cells may play an important role in the formation of aortic aneurysm and growth through their degradative and synthetic functions but not through loss of contractile function (23). Loss of structural integrity of the adventitia, not the media, is required for aneurysm formation (24). The biomechanical function of the adventitia is the maintenance of the maximal aortic outer diameter (23). Destruction of elastin within the aortic wall results in pathologic dilation of the vessel, whereas destruction of the collagen within the vessel has been shown to cause rupture (23). Therefore, at least in AAA, it is presently believed that maintenance of adventitial elastin is critical for sustaining the integrity of the aortic wall.

Since it is well recognized clinically that it is unusual for aneurysm formation to occur after an endarterectomy if the adventitia remains intact, White et al. (24) believe that aneurysmal disease must be a disorder of the adventitia. The integrity of this layer is critical for maintenance of aortic wall integrity under wall stress

and high intraluminal pressure. Elastin degradation of the aortic wall manifests first in the intima and media (medial degenerative disease), causing deterioration of these layers (23). Disruption of the medial architecture does not directly result in the loss of biomechanical function of the aortic wall or in clinically detectable aortic dilation.

Elastin disruption and depletion is complete at the stage of relatively small aneurysms, implying that loss or reorganization of the additional structural components is important (24). Ultimately, the forces that lead to medial elastin degradation also cause degradation of the elastic lamellae within the inner third of the adventitia. This allows for damage to the collagen within the adventitial layer, resulting in aneurysm formation. Since the strength of collagen is significantly greater than elastin, degeneration, synthesis, and redeposition of poorly organized collagen may account for the maintenance of collagen content in aneurysms despite the significant elastin degradation.

Recent investigations at our own and other institutions have shed light on certain additional cellular mechanisms that underlie aneurysm formation and expansion. It has become clear in both the abdomen and the thorax that MMPs participate in the destruction of the structural components of the aortic wall. These proteolytic enzymes were discovered in tadpole tails, where they play a role in the regenerative capacity of that organism.

MMPs initiate tissue remodeling by degradation of existing extra-cellular macromolecules such as collagens and proteoglycans. Over 20 different MMPs have been identified, with additional identifications occurring with regularity. There is considerable consistency between species in the importance of these enzymes. The MMPs are held in check in a homeostatic balance by the tissue inhibitors of MMPs, or TIMPs.

Our group has demonstrated that in both aortic aneurysm and dissection patients, the levels of certain key MMPs, including MMP-1 (collagenase) and MMP-9 (gelatinase B), are elevated in the aortic wall, compared to control aortas (25). In addition, the ratio of MMPs to TIMPs, a measure of the proteolytic state, is also elevated. Those patients who had an aortic dissection had even higher levels of MMPs than the aneurysm patients. In patients with bi-leaflet aortic valves, these levels are also elevated compared to tri-leaflet aortic valves—perhaps explaining the close relationship between bi-leaflet aortic valve and aortic dissection (26).

In our laboratories, we have also been analyzing the molecular biologic events occurring during aneurysm formation and expansion (27–29). Specimens of aortic aneurysms from various thoracic locations were harvested. These investigations have shown that: (*i*) Although the aortic media becomes thinner, the total amount of aortic medial tissue increases, due to the much larger diameter that the aorta attains. (*ii*) An intense inflammatory process is involved in aneurysm formation. There is prominent infiltration by interferon-γ-producing T-cells. (*iii*) Programmed cell death, with apoptosis of vascular smooth muscle cells is not seen, in contradistinction to findings in abdominal aortic aneurysms. This fundamental difference in the biological response in thoracic compared to abdominal

aneurysms may be reflective of the difference in embryologic origin between the ascending aorta, originating from ectoderm, as opposed to the abdominal aorta, arising from mesoderm.

Risk Factors for Aneurysm Growth

Size

The natural history of TAA, as in any aneurysm, is related to size. Since the initial studies in 1966 by Szilagyi et al. (30), size has been shown to be a significant risk factor for aortic rupture. Survival expectancy in untreated small abdominal aortic aneurysms (<6 cm) was shown to be better than for larger aneurysms (>6 cm). For nonsurgical aneurysms over a 10-year period, the risk of rupture was 19.5% for small aneurysms and 43% for larger aneurysms. Removal of the aortic aneurysm was shown to double the patient's survival expectancy (31).

Size has also been considered a major risk factor for complications (dissection and rupture) and is perhaps the single most important factor in the decision to intervene surgically on a nonemergent basis. The empirical evidence on the influence of size on rate of growth, however, is mixed. Dapunt et al. (32) note, for example, that a higher rate of expansion was found in those patients with a larger aortic diameter (>5 cm) at diagnosis. In contrast, Hirose et al. (33) find no significant effect of size on aortic growth.

Table 1 shows the estimated aneurysm growth rates from our own institutional data in relation to initial aneurysm size, chronic dissection, and location. Annual growth varied from 0.10 cm/yr for small (4.0 cm) aneurysms to 0.19 cm/yr for large (8.0 cm) aneurysms. This relationship is depicted graphically in Figure 4. Also seen in Table 1, dissected aortas grow more rapidly than nondissected aortas, and descending aneurysms grow more rapidly than ascending aneurysms physicians must remember to compare to the patient's earliest study—not the most recent prior study—in order to asses growth rate properly in a particular patient (34).

Females are at higher risk than males at relatively similar aortic sizes for the combined endpoint of rupture or dissection (35). We hypothesize that this may be due in part to differences in mean body size between males and females, with a given aortic size representing a proportionally greater diameter in smaller women. In a recent manuscript, we demonstrated that, at any given aortic size, lower body surface area (BSA) is associated with a higher incidence of complications—including rupture, dissection, and death. In order to more accurately assess the risk of aneurysm complications, we developed a new measurement, aortic size index (ASI), which takes into account both aortic diameter and BSA. ASI is simply aortic diameter divided by BSA. Throughout all methods of analysis, ASI was a better predictor of complications than maximal aortic diameter.

In particular, we found that using ASI, patients could be stratified into three categories of risk (Fig. 5). Those with ASI <2.75 cm/m^2 are at low risk for rupture or dissection, with a yearly incidence of approximately 2.5%. Those with ASI between 2.75 and 4.25 cm/m^2 are at moderate risk, with yearly incidence of

Table 1 Multivariable Estimates of Aneurysm Growth Rates—Annual Growth Rates According to Intial Aneurysm Size[a]

Patient category	<4.0 cm (n=84)	4.0–4.9 cm (n=220)	5.0–5.9 cm (n=106)	6.0–6.9 cm (n=42)	7.0–7.9 cm (n=19)	>8.0 cm (n=7)	5.0 cm (sample mean)
All (n=478)	0.12 cm/yr (0.09–0.14)	0.16 cm/yr (0.13–0.18)	0.19 cm/yr (0.15–0.24)	0.21 cm/yr (0.10–0.32)	0.24 cm/yr (–0.06–0.55)	0.40 cm/yr (–0.18–1.02)	0.16 cm/yr (0.15–0.18)
Dissection status							
Chronic dissection (n=123)	0.12 cm/yr (0.07–0.17)	0.20 cm/yr (0.14–0.27)	0.25 cm/yr (0.10–0.43)	0.83 cm/yr (0.57–1.10)	0.08 cm/yr (–0.16–0.34)	N/A	0.21 cm/yr (0.17–0.25)
No dissection (n=355)	0.11 cm/yr (0.08 –0.15)	0.14 cm/yr (0.11–0.17)	0.18 cm/yr (0.14–0.23)	0.15 cm/yr (0.04–0.27)	0.71 cm/yr (–0.04–1.55)	0.39 cm/yr (–0.13–0.94)	0.15 cm/yr (0.13–0.17)
Location of aneurysm							
Ascending or Arch (n=358)	0.12 cm/yr (0.08–0.14)	0.14 cm/yr (0.11–0.17)	0.18 cm/yr (0.12–0.22)	0.52 cm/yr (0.33–0.73)	0.18 cm/yr (–0.19–0.57)	N/A	0.15 cm/yr (0.13–0.17)
Descending or TA (n=120)	0.10 cm/yr (0.00–0.21)	0.20 cm/yr (0.13–0.27)	0.24 cm/yr (0.14–0.34)	0.13 cm/yr (–0.02–0.28)	0.98 cm/yr (0.24–1.78)	0.41 cm/yr (–0.32–1.20)	0.21 cm/yr (0.16–0.26)

[a]95% Confidence intervals in parentheses.

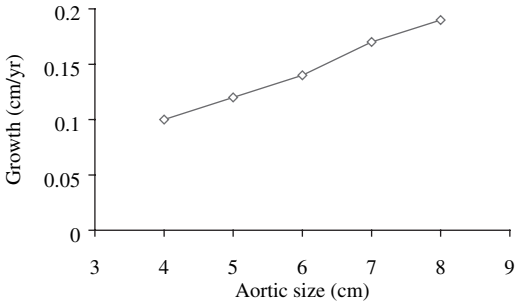

Figure 4 Absolute change in growth as a function of aortic size.

approximately 10%. And, those with ASI above 4.25 cm/m^2 have yearly rates of rupture, dissection, or death as high as 30% to 40% (35).

This data is summarized in Table 2. These differences in yearly rates were reflected in the Cox proportional hazards regression, where the odds ratio for rupture was more than 11-fold higher in patients with aortic size index >4.25 cm/m^2.

Hypertension

Small abdominal aneurysms have been shown to rupture, with one study demonstrating a 39% rupture rate during long-term nonoperative management of aneurysms <6 cm in diameter (36). Cronenwett et al. (37) sought other factors important in predicting rupture in small abdominal aortic aneurysms. Of the potential risk factors studied, only diastolic blood pressure >100 mmHg, initial anteroposterior diameter greater than 5 cm, and degree of COPD (FEV1 <50% of predicted) were independently predictive of rupture. This study recognized the fact that small aneurysms can rupture, that aneurysm expansion rate is not well correlated with rupture, and that risk factors other than initial size may be of important prognostic

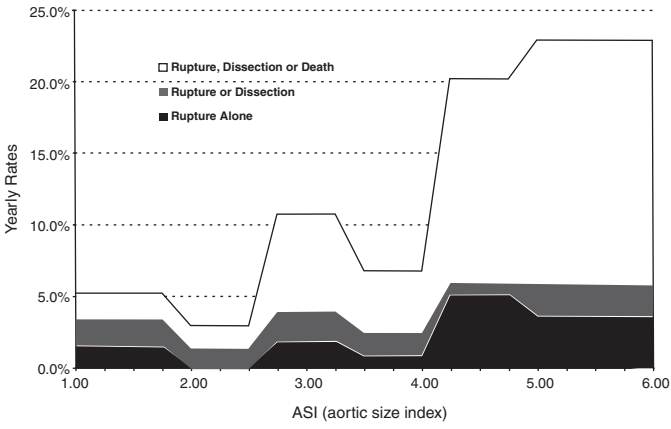

Figure 5 Average yearly rates of negative outcomes (rupture, dissection and death). These estimates represent the average rate during the first five years after presentation.

Table 2 Risk of Complications by Aortic Diameter and Body Surface Area with Aortic Size Index Given Within Chart

	Aortic size (cm)									
BSA	3.5	4.0	4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.0
1.30	2.69	3.08	3.46	3.85	4.23	4.62	5.00	5.38	5.77	6.15
1.40	2.50	2.86	3.21	3.57	3.93	4.29	4.64	5.00	5.36	5.71
1.50	2.33	2.67	3.00	3.33	3.67	4.00	4.33	4.67	5.00	5.33
1.60	2.19	2.50	2.80	3.13	3.44	3.75	4.06	4.38	4.69	5.00
1.70	2.05	2.35	2.65	2.94	3.24	3.53	3.82	4.12	4.41	4.71
1.80	1.94	2.22	2.50	2.78	3.06	3.33	3.61	3.89	4.17	4.44
1.90	1.84	2.11	2.37	2.63	2.89	3.16	3.42	3.68	3.95	4.22
2.00	1.75	2.00	2.25	2.50	2.75	3.00	3.25	3.50	3.75	4.00
2.10	1.67	1.90	2.14	2.38	2.62	2.86	3.10	3.33	3.57	3.80
2.20	1.59	1.82	2.05	2.27	2.50	2.72	2.95	3.18	3.41	3.64
2.30	1.52	1.74	1.96	2.17	2.39	2.61	2.83	3.04	3.26	3.48
2.40	1.46	1.67	1.88	2.08	2.29	2.50	2.71	2.92	3.13	3.33
2.50	1.40	1.60	1.80	2.00	2.20	2.40	2.60	2.80	3.00	3.20

□ = Low risk (~2.5% per yr); □ = Moderate risk (~10% per yr); □ = Severe risk (~35% per yr).
Abbreviation: BSA, body surface area.
Source: From Ref. 35.

value. Predicted five-year rupture rates varied from 2%, when these risk factors were absent to 100%, when all three risk factors were significant.

The law of Laplace states that as a cylinder increases in size, the wall tension also increases. Therefore, when hypertension is associated with larger aortic diameters, it has been considered a risk factor for the development of aneurysm rupture based on this law. Foster et al. (38) showed that rupture occurred in 72% of patients with diastolic hypertension but in only 38% of the entire group. Szilagyi et al. (31) found hypertension (>150/100 mmHg) to be present in 67% of patients who experienced aneurysm rupture, but in only 23% of those without rupture. For TAAs, Dapunt et al. (32) reported that a history of hypertension correlated with a greater thoracic aortic diameter at diagnosis, but did not significantly affect the rate of enlargement. Masuda et al. (39) reported a positive association between diastolic blood pressure and rate of expansion of TAA, which was statistically significant in univariate but not in multivariate analysis.

Acute rupture and aortic dissection can also be linked to hypertension in younger patients. In 2003, our group reported the occurrence of acute ascending aortic dissection in five previously healthy young athletes who were lifting weights at the time of onset of their aortic pain (40). We have now expanded this series to 31 young athletes (41). These are all tragic cases, often fatal if diagnosis is delayed or immediate access to a major cardiac center is not effected.

We found that all these young athletes harbored unsuspected, moderate dilatation of the aorta, in the range of 4 to 5 cm. Also, we found that weight training produces dramatic rises in arterial blood pressure, up to 320 mmHg in our studies (42).

Smoking

In 1991, Strachan (43) published the Whitehall study, which examined 19,403 male civil servants, and found 99 deaths attributed to aortic aneurysm during 18 years of follow-up. Their results showed that fatal aneurysms were substantially increased in current smokers, particularly in those who smoked hand-rolled cigarettes. Dapunt et al. (32) in 1994, found smoking to be a significant risk for aneurysm expansion.

Presence of a Chronic Dissection

In our present series, we have demonstrated that the presence of a chronic dissection was a significant predictor for more rapid aneurysmal growth (Fig. 6) (44).

Collagenase Activity

Busuttil et al. (45) reported increased collagenase activity in human aortic aneurysm walls, particularly in larger or ruptured aneurysms. Collagenase functions to break down collagen, thus weakening the arterial wall. Individuals with COPD have been shown to have increased elastolytic activity in polymorphonuclear leukocytes of patients with aortic aneurysmal but not occlusive disease (46). Not all smokers develop elevated proteolytic activity after smoking, and the exact mechanism of aneurysm formation is still being investigated (38).

Syphilis

The early studies by Boyd (47) in 1924, Colt (48) in 1927, Kampmeier (49) in 1938, and Cranley (50) in 1954, detailed the influence of syphilis in generating aortic aneurysms, with little information on aneurysms of arteriosclerotic origin. Before antibiotics became prevalent, syphilis accounted for approximately 75% of abdominal aortic aneurysms. Since the discovery of appropriate antibiotic treatment for syphilis, the incidence of syphilitic aneurysms has dropped dramatically.

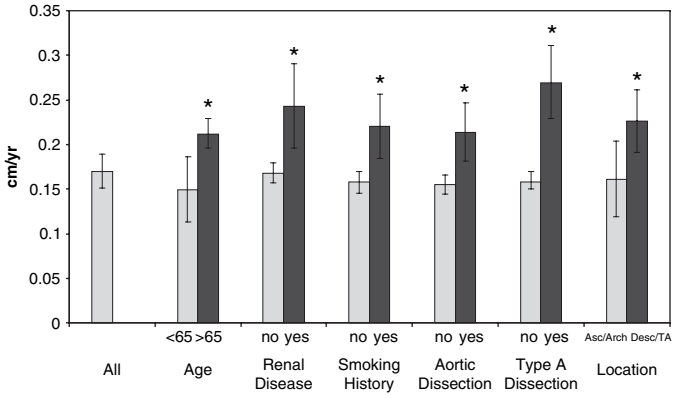

Figure 6 Risk factors for aneurysm growth rates. Bars shown in each group represent the mean growth rate of each patient population ± the standard error. *Note*: *P<0.04.

Arteriosclerosis

Joyce et al. (51) in 1964 studied 107 patients who had nondissecting, nonsurgically treated TAAs. Approximately 73% were considered "arteriosclerotic" in origin, and the incidence of syphilitic aneurysms at that time had fallen to 20%.

One of the reasons that the natural history of aortic aneurysms has been difficult to record is the fact that arteriosclerosis is so prevalent in this population. Joyce et al. (51) attributed the most deleterious effects on survival to the presence of associated coronary, cerebral, or other peripheral arterial occlusive or aneurysmal disease. In their study, approximately 50% of patients with aortic aneurysms were not alive at five years after diagnosis. Whether arteriosclerosis is a cause of aortic aneurysm formation, or simply a coexisting disease process, is still a matter of debate.

EVIDENCE-BASED CLINICAL DECISION-MAKING FOR THORACIC AORTIC ANEURYSM

TAAs are serious conditions that frequently require surgical intervention due to the threat of dissection or rupture. The natural history of aortic aneurysm is often related to the specific location and the primary cause of the disease. The decision-making process is further complicated by the greater risks of thoracic aortic replacement compared to abdominal aortic replacement.

In developing management protocols for appropriate patient selection for surgery, it is essential to study risk factors that may influence the natural history of the disease. The specific objective is to select patients for whom the operative risks are justified.

Our team at the Yale Center for Thoracic Aortic Disease has developed and maintained a robust clinical database to:

1. Further define the natural history of TAAs in terms of thoracic aortic growth, incidence of complications (dissection and rupture), and survival;
2. determine risk factors for thoracic aortic growth, dissection, and rupture; and
3. define scientific criteria for surgical intervention based on the natural history available from these patients.

The Yale observations confirm that TAA is, over the long term, a lethal disease. Figure 7A illustrates that patients with TAA do, indeed, have a dramatically poorer natural outlook than an age and sex-matched general population. Figure 7B illustrates that patients with descending aneurysms do have a poorer outlook than those with ascending aneurysm. Figure 7C illustrates that patients with dissection fare more poorly than patients free of dissection. And, Figure 7D shows that prognosis depends on size of the aortic aneurysm: patients with larger aneurysms do more poorly. Careful scrutiny of Figure 7D reveals that that TAA is

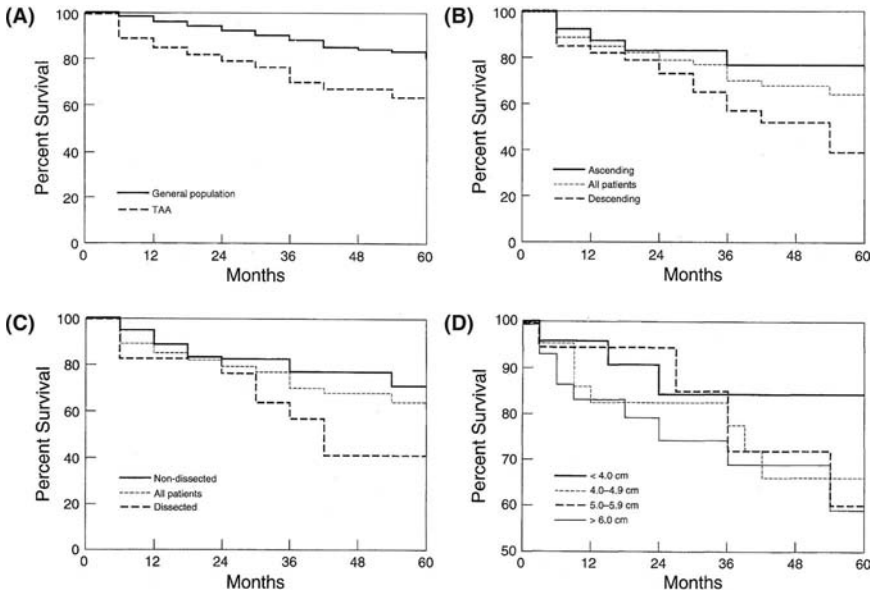

Figure 7 Key natural history graphs from the Yale database. (**A**) Survival of patients with unrepaired thoracic aortic aneurysm compared to that of the age and sex-matched general population. (**B**) Poorer outlook of patients with descending compared to ascending thoracic aortic aneruysm. (**C**) Adverse impact of aortic dissection on outlook. (**D**) Larger aneurysms do more poorly in the long run. (**E**) Elective surgical therapy is very safe, and restores excellent long-term prognosis. *Source*: From Ref. 1.

indeed a lethal disease, but that it takes years for this lethality to express itself. Please note that it is not until after three years of follow-up, even in the largest aneurysms, that the survival curve drops significantly. Figure 7E demonstrates the excellent survival after elective surgical therapy for TAA. Note that emergent surgical therapy leads to much poorer long-term survival.

These graphs argue strongly for elective, prophylactic surgical extirpation of the aneurysmal thoracic aortic aorta, before rupture or dissection—which either result in death or require emergent surgery—have a chance to occur.

Aortic Growth

Our team has found that calculation of growth rate is more complicated than simply subtracting original size from current size and dividing by time. Rizzo (52), from the Yale School of Public Health, has developed exponential equations that permit rigorous calculation of growth rates for large populations of TAA patients.

Growth rate estimates were obtained for our entire population and for subgroups with specific risk factors by means of a multivariable regression analysis in which aneurysm growth followed an exponential path. In particular, the natural logarithm of the difference between the last measured size and the first measured

size was related to the time interval between the two tests and interactions between this time variable and risk factors. This statistical method was previously described in detail by our team (52).

The growth rates for TAA are displayed in Table 3. The overall growth rate is approximately at 0.17 cm/yr (range 0.136 and 0.306 cm/yr). Risk factors that increase aortic growth include advancing age, smoking, and progressive aortic size.

The slowest mean growth rate represents patients younger than 45 years and the fastest estimated growth rate is seen in patients with initial aortic size greater than 7.5 cm (Table 3) (44).

Table 3 Analysis of the Relationship of Different Variables on Thoracic Aortic Aneurysm Growth

Variable	Number (%)	Growth rate (cm/yr)	95% CI	*P* value
Overall	493	0.170	0.151–0.189	
Gender				
Male	317 (64.3)	0.170	0.093–0.247	0.9688
Female	176 (35.7)	0.170	0.135–0.206	
Age				
<65	252 (51.1)	0.149	0.078–0.222	0.0020[a]
≥65	241 (48.9)	0.212	0.180–0.245	
Non-Marfan family history				
(–)	290 (83.6)	0.177	0.153–0.201	0.8074
(+)	57 (16.4)	0.170	0.087–0.253	
Marfan syndrome				
(–)	453 (91.9)	0.174	0.153–0.195	0.4395
(+)	40 (8.1)	0.156	0.089–0.223	
Hypertension				
(–)	149 (32.9)	0.186	0.117–0.255	0.1272
(+)	303 (67.0)	0.155	0.126–0.183	
Renal disease				
(–)	375 (87.0)	0.168	0.146–0.190	0.0348[a]
(+)	56 (13.0)	0.243	0.151–0.337	
Pulmonary disease				
(–)	334 (75.9)	0.173	0.150–0.196	0.8245
(+)	106 (24.1)	0.179	0.103–0.256	
Smoking history				
(–)	264 (61.8)	0.158	0.133–0.183	0.0079[a]
(+)	163 (38.2)	0.220	0.148–0.292	
Initial aortic size (cm)				
<4.5	204 (41.9)	0.171	0.100–0.243	0.9402
4.5–5.4	187 (38.4)	0.179	0.111–0.243	0.6986
5.5–6.4	54 (11.1)	0.137	0.049–0.227	0.2991
6.5–7.4	28 (5.8)	0.219	–0.003–0.452	0.6420

(*Continued*)

Table 3 Analysis of the Relationship of Different Variables on Thoracic Aortic Aneurysm Growth (*Continued*)

Variable	Number (%)	Growth rate (cm/yr)	95% CI	*P* value
≥7.5	14 (2.9)	0.306	–0.088–0.733	0.4887
Aneurysm location				
Ascending/arch	369 (74.9)	0.161	0.078–0.246	0.0898
Descending/TA	124 (25.2)	0.226	0.158–0.296	0.0041[a]
Chronic aortic dissection				
(–)	362 (73.4)	0.155	0.134–0.177	0.0081[a]
(+)	131 (26.6)	0.214	0.149–0.279	
Type A dissection				
(–)	433 (87.8)	0.158	0.139–0.178	0.0003[a]
(+)	60 (12.2)	0.269	0.189–0.352	
Type B dissection				
(–)	406 (82.4)	0.163	0.142–0.184	0.1520
(+)	87 (17.7)	0.197	0.130–0.265	

Source: From Ref. 44.

The presence of a chronic aortic dissection was associated with a faster growth rate, as was the presence of TAAs in the descending thoracic and thoracoabdominal aortas compared to ascending aneurysms and aneurysms of the aortic.

Complications: Rupture and Dissection

The incidence of adverse events (rupture and dissection) increases with faster growth rates, as illustrated in Figure 8. When the growth rate was less than 0.05 cm/yr the incidence of a negative event was 24% compared to 45% with a growth rate above 0.20 cm/yr (44).

Figure 9 illustrates the estimated increase in the probability of incurring a dissection or rupture as a function of ascending aneurysm size. On the y-axis is displayed the likelihood of natural complications of the aortic aneurysm, namely rupture or dissection. On the x-axis is the size of the aneurysm. These curves present the cumulative risk, over the patient's lifetime in achieving a certain current aortic size, of rupture or dissection. It can be seen that there are discrete "hinge points" in the behavior curves for the ascending and the descending aortas. For the ascending aorta, the hinge point occurs at 6 cm. Relative to the 4.0 to 4.9 cm cohort, the probability of incurring a dissection or rupture is 32.1 percentage points higher in the 6.0 to 6.9 cm cohort ($p<0.01$). This is a sobering statistic, expressing once again the virulence of this disease over time.

Similarly, Figure 10 shows that the rate of dissection or rupture increases by 43.0% points in descending aneurysms ≥7 cm in diameter ($p<0.01$). For the descending aorta, the hinge point occurs at 7cm.

Note that the descending aorta does not rupture or dissect until a somewhat larger size is attained. This is not an intuitive finding, as the descending aorta has

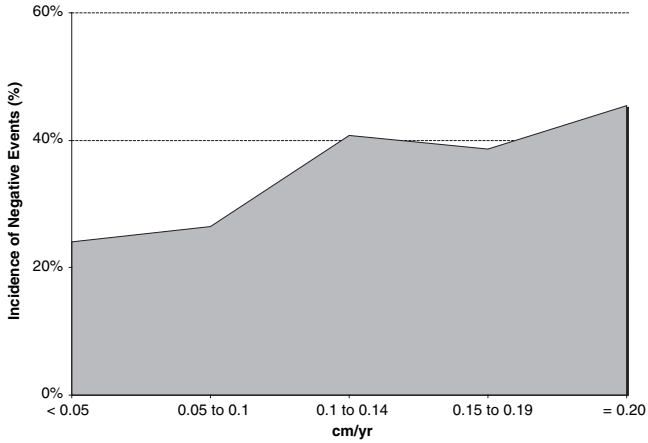

Figure 8 The incidence of negative events (rupture, acute dissection, and death) as a function of growth rate. *Source*: From Ref. 44.

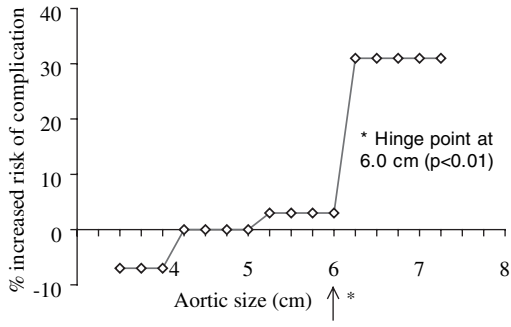

Figure 9 Regression analysis for the ascending aorta.

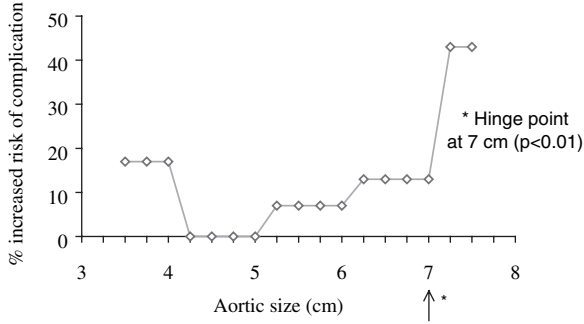

Figure 10 Regression analysis for the descending aorta.

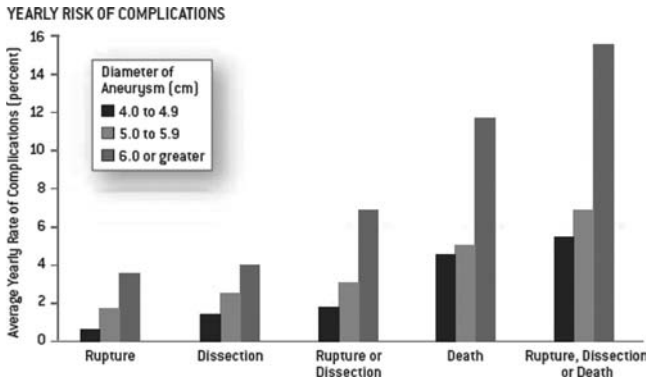

Figure 11 Probabilities that rupture or dissection will occur have been calculated for aortic aneurysms in the chest. There is a dramatic surge in danger when aneurysms reach 6 cm. Based on this information, we conclude that many patients with aneurysms in the range of5.5 cm should undergo elective, pre-emptive aortic replacement to prevent aortic rupture. Such a criterion spares most patients from naturally occurring rupture, dissection, or death, P. *Source*: From Ref. 42.

fewer lamellae than the ascending and is normally smaller in the preaneurysmal state (53). We would expect the descending aorta to rupture earlier, but this does not appear to be the case. Fluid dynamics, flow patterns, wall stress, and the like may underlie this observation.

A "Holy Grail" has been to make predictions of specific yearly dissection, rupture, and mortality rates for each size of the thoracic aorta. We were not able to do this until relatively recently, as this requires extremely robust data, with many "hard end-points" for each aortic size. Our database has recently reached a size where such calculations have become possible. As can be seen in Figure 11, the risks of rupture, dissection, and death increase in stepwise fashion as the aorta grows, with high risk being seen at the vital aortic dimension of 6 cm. At that 6 cm dimension, yearly risk of rupture is about 4%, dissection is about 4%, death is about 10%, and risk of rupture, dissection, or death is about 14%.

Surgical Decision Making for Prophylactic Resection of the Thoracic Aorta

We believe that these observations permit evidence-based conclusions regarding when the asymptomatic aneurysmal thoracic aorta should be resected, to prevent rupture, dissection, and death. Recommendations are indicated in Figure 12 (54). This data indicates that replacement of the ascending aorta at about 5.5 cm will preclude most ruptures and dissections, while not exposing affected patients unduly early to the risks and discomforts of surgery. For the descending aorta, surgery at about 6.5 cm will, similarly, pre-empt most adverse aortic-related events. We apply more stringent criteria for patients with Marfan's disease, whose disease is more aggressive. We intervene prophylactically at 5.0 cm for the ascending

1. Rupture
2. Symptomatic states

    a. Pain consistent with rupture and unexplained by other causes.
    b. Compression of adjacent organs, especially trachea, esophagus, and left main stem bronchus.
    c. Significant aortic insufficiency in conjunction with ascending aortic aneurysm

3. Absolute size

	Marfan's syndrome patients[a]	NonMarfan's syndrome patients
Ascending	5.0 cm	5.5 cm
Descending	6.0 cm	6.5 cm

4. Documented enlargement

    a. Growth ≥ 1 cm/yr or substantial growth, and aneurysm is rapidly approaching criteria in number 3 above.

5. Acute aortic dissection
    a. Ascending requires urgent operation
    b. Descending requires "complication-specific approach"[116]

Figure 12 Recommended surgical intervention criteria for thoracic aortic aneurysms. [a]The Marfan's intervention criteria should also apply if there exists a family history of aortic disease other than Marfan's syndrome.

aorta and 6.0 cm for the descending aorta in Marfan's patients. We, and others, have observed that even for patients without a recognizable connective tissue syndrome like Marfan's disease, aortic aneurysm and dissection the run in families (11). We found that these familial aortas grow relatively rapidly. We tend to intervene at the Marfan's criteria, namely 5.0 cm for the ascending and 6.0 cm for the descending aorta, in patients with this type of familial (non-Marfan's) aortic aneurysm or dissection. If there is a family history of aortic dissection or aortic-related death, we are especially inclined to move at these "early" criteria. Similarly, because bicuspid aortic valves are also virulent in inducing aortic dissection, we tend to operate sooner than in other patients.

It cannot be emphasized too strongly that these size criteria apply for the asymptomatic TAA. Any symptomatic aneurysm must be resected, regardless of size. It is an unfortunate characteristic of this disease that only a small proportion of patients are symptomatic—with pain, tracheal or esophageal compression, or vocal cord paralysis. For most patients, their first symptom is an acute aortic event. However, if a patient is symptomatic, his aorta must be resected, even if it does not meet traditional size criteria.

It is, of course, a matter of clinical judgment whether the pain symptoms experienced by an individual patient are of aortic origin. Unless we can demonstrate

another cause—angina, esophageal spasm, lumbosacral spine disease or the like—we presume that the pain is of aortic origin. We know of no other way to protect the patient from aortic rupture than to draw this conclusion.

It is taken as self-evident that age and coexisting disease may well render aggressive surgical intervention inappropriate for some patients. Thus, each patient must be evaluated independently, and anticipated risks of operation (especially paraplegia with descending aortic aneurysms) weighed against the anticipated risks of rupture and dissection. Moreover, the level of experience at the treating medical center with these major surgical procedures must be taken into account. The size criteria presented in this chapter are proposed for otherwise healthy patients cared for at experienced centers.

CONCLUSION

The natural behavior of the thoracic aorta is increasingly being clarified, strengthening the physician's and surgeon's position in the treatment of patients harboring this virulent disease.

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DISCUSSION AND COMMENTARY

Questions for the Authors

How often should the aorta be imaged in a patient in follow-up for a thoracic aortic aneurysm?

We tend to image rather infrequently, as the aneurysmal thoracic aorta grows slowly—at just over 1 mm (0.1 cm) per year. So, because of this indolent growth, frequent scans will not show any changes—just like a parent does not notice the growth of his children, whom he sees every day.

What is most important is to compare your current study, not with the last prior study, but with the earliest study on record for your patient. This is how growth can be appropriately noted and appreciated. This takes more work and may mean digging deep into a computerized registry of CT scans or pulling old hard copies of imaging studies. We recently published a plea to radiologists to do this extra work of comparing with the earliest study on record, to prevent missing substantive overall growth by comparing only with the most recent study (1).

When seeing a patient for the first time, we usually re-image in 6 to 12 months, so as to identify a quick second point on the size or growth curve for that patient. Thereafter, it is rare for us to image more frequently than every one to two years. We must be cognizant also of the radiation danger of CT scanning.

Does the aorta ever grow very rapidly?

With rare exceptions, sudden, rapid growth of the aorta is usually spurious, involving measurement at noncorresponding segments of the aorta on different scans. Another common source of error has to do with measuring across oblique segments of the aorta (such as the aortic arch on an axial study); obliquity will give an oblong cross-section, which overestimates true diameter.

A sudden true increase in caliber of the thoracic aorta can be caused by intercurrent aortic dissection. If the aorta has truly grown, please be sure to check for presence of a dissection flap, which may have developed in the interim between studies.

What imaging study should I use in follow-up?

Our studies have shown a high concordance between dimensions on echocardiography, CT scanning, and MRI imaging. For acutely ill patients, we usually prefer ECHO and CT, which are immediately available. For chronic follow-up, we usually prefer ECHO for young patients, especially women of childbearing age. Of course, the (transthoracic) ECHO shows mainly the proximal ascending aorta, so for older patients, we combine with either CT or MRI, which shows very well the entirely of the aorta—ascending, arch, descending, and abdominal.

How about family members?

There is no longer any question that thoracic aortic aneurysm is a hereditary disease, and abdominal aneurysm as well. We recommend imaging all first-order

family members. We believe this represents the current standard of care. We image parents, grandparents, siblings, children, and grandchildren. We image even more widely if, as in so many families, there has been devastation by premature dissection or death.

What size criteria should be applied for aneurysms of the aortic arch?

Arch aneurysms are far less common than ascending and descending aneurysms, and, in fact, many arch aneurysms represent extensions from ascending or descending aneurysms. We do not have criteria specific for the arch. We apply the ascending or descending size criteria, depending on whether the arch aneurysm is most closely related anatomically to the ascending or descending aorta in a particular patient.

What size criteria should be applied for saccular aneurysms?

We have not analyzed saccular aneurysms separately. However, we measure the maximum diameter across both the saccular aneurysm and the adjacent aortic lumen. If this dimension exceeds criteria, we operate. We also recommend surgery for anatomically concerning saccular aneurysms—those with abrupt contours, rapid growth, or thin walls.

What about intramural hematoma and penetrating aortic ulcers?

Intramural hematoma and penetrating ulcer of the aorta are variants on the aortic dissection theme. These are what we call "no flap" acute aortic phenomena (Fig. A). We use the dictum: "No flap, no dissection." That is to say, an aortic dissection is characterized by a flap running obliquely across the aortic lumen.

In intramural hematoma, there is no such oblique flap. In such cases, there is often no intimal tear visible radiographically (by CT scan, MRI, or echocardiography). Rather one sees only a crescentic rim of hemorrhage in the aortic wall. The rim of hemorrhage is concentric with, not oblique to, the aortic circumference. Some authorities feel these lesions are due to rupture of the vasa vasorum, leading to bleeding within the aortic wall.

Penetrating aortic ulcers look like the name implies. In fact, if blinded as to organ of origin, one would be hard-pressed to distinguish these from peptic ulcers in the duodenum (Fig. B). It is thought that these ulcers represent leaking of blood through an intimal defect deep into the layers of the aortic wall, creating an ulcer crater.

Most authorities would agree that acutely symptomatic intramural hematomas or penetrating ulcers of the ascending aorta should be treated by prompt, if not immediate, surgical aortic resection—much like a typical ascending aortic dissection. There is difference of opinion regarding intramural hematoma and penetrating aortic ulcer in the descending aorta. Many authorities recommend medical therapy with anti-impulse drugs. Especially in the Far East, where the disease may be less virulent for some reason, conservative management is encouraged (1). Indeed, it is clear that anti-impulse therapy will allow many of these patients to be discharge alive from the hospital.

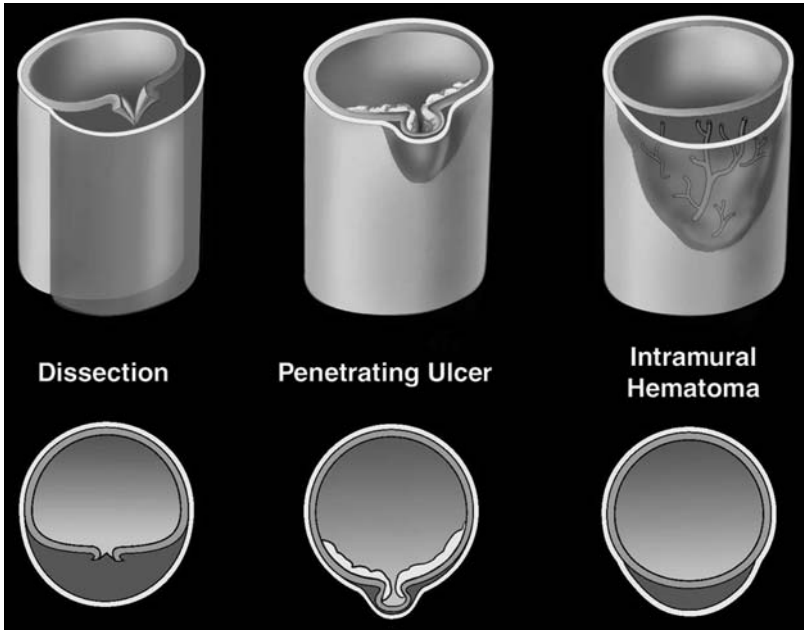

Figure A (*See color insert*) Artist's schematic of variant forms of aortic dissection: typical dissection, penetrating ulcer, and intramural hematoma.

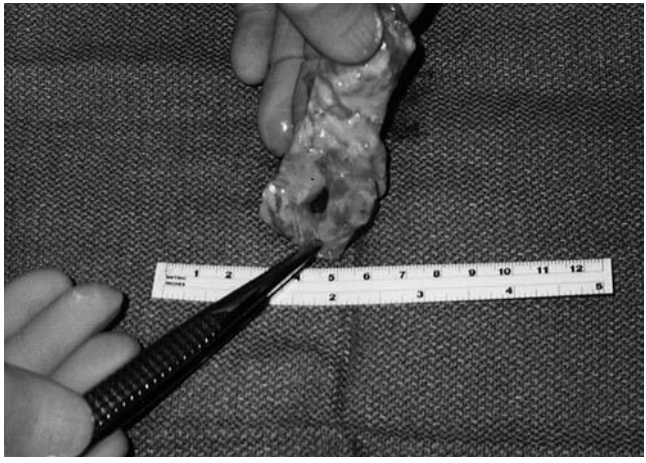

Figure B (*See color insert*) Excised aortic specimen bearing penetrating ulcer of aorta. Note similarity in appearance to duodenal ulcer, for which this photo could easily be mistaken.

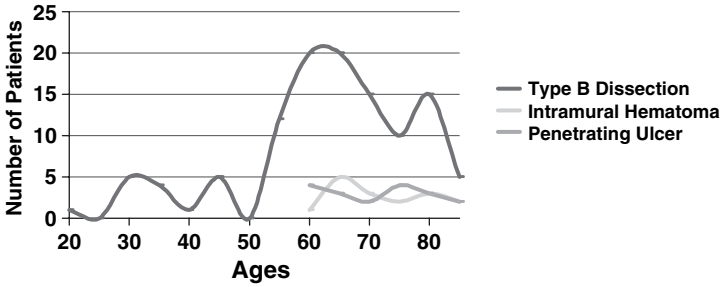

Figure C (*See color insert*) Age distribution of variant forms of aortic dissection, compared to typical descending dissection. Note that intramural hematoma and penetrating ulcer are diseases of advanced age.

At our center, however, we have been discouraged by poor outcome with medical management detected upon following these patients to midterm. In mean follow-up of three years, we found that many patients died from rupture (2). Many more progressed to typical, flap-type, aortic dissection. For this reason, we recommend routine surgical extirpation of the descending aorta in case of intramural hematoma or penetrating aortic ulcer. We usually wait two to three weeks, to permit fibrosis of the affected aortic wall, and then we proceed with resection. In penetrating ulcer patients, it is not uncommon to find many more ulcers than were identified on preoperative scans. These other smaller ulcers often appear as if they are about to "pop," like a pimple or boil. These are resected in addition to the radiographically identified lesion.

This recommendation for aggressive surgical intervention must be tempered by the recognition that patients with intramural hematoma or penetrating aortic ulcer are almost invariably elderly (Fig. C) (3). If serious comorbidities independently limit life-expectancy or quality of life, we may confine our care to exclusively medical management.

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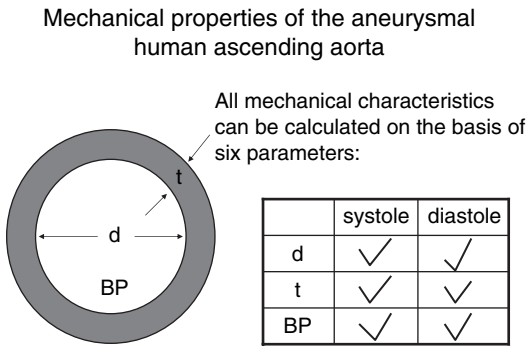

Figure D The six measured parameters that are required for calculation of engineering aspects of consequences of aortic dilatation. *Abbreviation*: BP, blood pressure.

Are there any totally new parameters on the horizon (besides aortic size) that promise to predict aortic rupture and dissection more accurately in the future?

We are excited about the possibility of predicting aortic events—and, thus, the proper timing of surgical intervention—based on the engineering properties of the aorta. We have recently analyzed the mechanical properties of the aorta by epi-aortic echocardiography (1). The intrinsic mechanical properties of the aorta can be calculated by measuring six parameters—blood pressure in systole and diastole, aortic diameter in systole and diastole, and aortic wall thickness in systole and diastole (Fig. D). (The aorta thins during systole, being stretched by the rise in aortic pressure.)

These investigations have shown that by a diameter of 6 cm, the aorta loses all distensibility (Fig. E) becoming, essentially, a rigid tube. This means that, instead of expanding the aorta cylindrically, thus dissipating the mechanical forces, the rush of blood in systole is translated to increased wall stress in the rigid aortic wall (Fig. F). In fact, the dotted line in Figure 6 represents the previously known maximal tensile strength of the human aortic wall (2). It can be seen that,

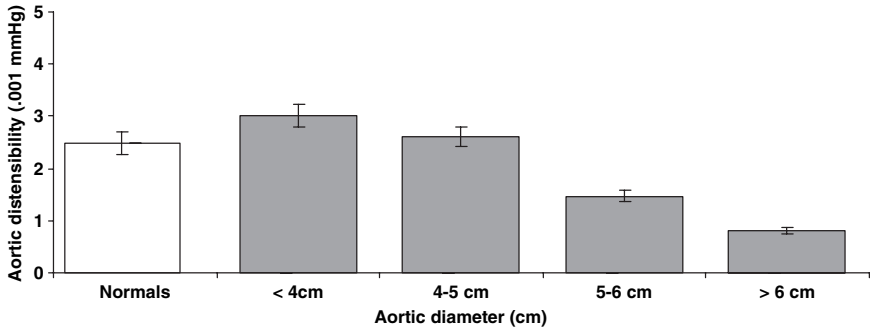

Figure E Aortic distensibility vanishes as the aorta enlarges.

for 6 cm aortas, the ultimate tensile strength of the aortic wall is easily exceeded. It is thus not at all surprising that rupture and dissection occur at these dimensions. The clinical data presented in this chapter, showing that bad clinical events occur at 6 cm, and this engineering data "dovetail" nicely. This engineering data helps to understand why the aorta ruptures at this critical dimension of 6 cm (Fig. G).

We are in the process of measuring the same engineering data by transesophageal echocardiography (TEE), instead of epi-aortic echocardiography. This would take this method of investigation from a research tool to one of clinical utility. We look forward to reporting on this avenue further in the next one or two years. Measuring aortic wall stress, in addition to diameter, by this means may amplify our ability properly to time surgery so as to preclude the devastating complications of dissection and rupture.

We are just beginning to investigate various biomarkers, such as the MMP serum levels and the RNA profile of the blood as possible markers or aortic biology or predictors of aortic events. Further work needs to be done before clinical application (3).

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What medical management is appropriate for aneurysm patients under medical follow-up?

One well-known study from Johns Hopkins University has driven the standard of care in medical management of thoracic aortic aneurysm. In this study, a relatively small number of Marfans patients did better on beta-blocking medications than those treated without beta-blockers (1). Use of beta-blockers has, on the strength of this article, become standard of care. We believe that this issue needs to be revisited. These findings need to be replicated and extended to nonMarfan patients. In fact, the appropriateness of beta-blockade has been questioned, based on experimental studies suggesting that beta-blockers have deleterious mechanical effects on the aorta (2). Also, randomized studies of beta-blockers in abdominal aortic aneurysm have yielded equivocal results (3–4).

Some very recent, very preliminary data suggests that angiotensin receptor blocking medications (ARBs) have a marked beneficial effect on growth of aortic aneurysms in a small animal model (5). This intriguing finding deserves further study. Benefit has been shown in an experimental model also for ACE inhibitiors (6).

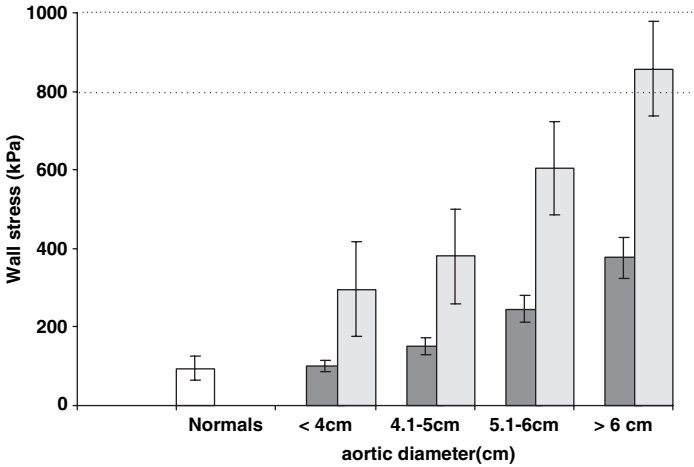

Figure F Impact of increasing diameter on aortic wall stress. Dark bars indicate stress at an ambient blood pressure of 100 mmHg systolic; light bars, an ambient blood pressure of 200 mmHg. The dotted line represents the known ultimate tensile strength (breaking point) of aortic tissue. For enlarged aortas, in a hypertensive situation, the wall stress approaches or exceeds the ultimate tensile strength of the aortic tissue; it is no wonder, then, that rupture or dissection occur at these dimensions.

Figure G (*See color insert*) A large thoracoabdominal aortic aneurysm. The head is to the top and the feet to the bottom of the picture. The chest and abdomen have been opened widely, revealing a large, extensive aneurysm of the thoracoabdominal aorta. A soda can is about 6 cm in diameter. If a patient's aorta is approaching this dimension, the aorta should be extirpated surgically to prevent rupture or dissection.

There is theoretical and limited clinical evidence that statin drugs, above and beyond their lipid-lowering properties, have a beneficial effect on the aortic wall, suppressing inflammation. It is possible that these drugs may have a role in the treatment of thoracic aortic aneurysm. Further studies are warranted.

We and others have demonstrated a role for matrix metalloproteinases (MMPs) in the pathogenesis of thoracic aortic aneurysm (7,8). It is clear that MMP expression is elevated in patients with thoracic aortic aneurysm and dissection, and that some of the tissue inhibitors of MMPs (TIMPs) are not upregulated, in patients with thoracic aortic aneurysm. This raises the possibility of applying drugs that inhibit MMPs in the treatment of thoracic aortic aneurysms. Doxycycline is an antibiotic that is used very widely in the treatment of gingivitis. Preliminary studies of doxycycline in randomized trials for abdominal aortic aneurysm have been equivocal. Many inhibitors of specific MMPs are in the drug pipelines at several manufacturers.

All of these promising avenues will be explored in the next decade. There is hope for viable medical treatments for thoracic aortic aneurysm, which may delay or preclude aortic expansion, rupture, and dissection. At this time, no medications can be said to be of proven benefit.

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Many cardiac specialists are aware of individual patients who have suffered dissection of the aorta at a relatively small dimension, in the range of 4 cm. These patients would not be selected for surgery based on the criteria enumerated in this chapter. What response do the authors have to this point?

We have seen an abstract on this topic, but not a subsequent paper. There is no question that dissection can occur at small sizes. In our studies of weight lifters suffering aortic dissection (see Chapter 10), most young men dissected at a dimension between 4 and 5 cm. We feel these individuals imposed an extreme blood pressure stress (likely above 300 mmHg) on their aortas. We know (see Chapter 7) that wall stress depends on both aortic size and blood pressure. Aortic dissection at small sizes does, additionally, occur in nonweight lifters. Here one must keep in mind how huge is the denominator of patients with aortas in this size range. If aortic dimension follows a bell curve, like most physical traits, the number of patients must increase immensely as one comes back from the tails of the curve. Our feeling is that there are so many (probably millions) of patients with aortas of size 4 cm or more that the observed cases of dissection at these sizes represent a very low percentage. This is certainly the case in our careful follow-up of patients with known aortic size, whose percentage likelihood of dissection is represented in the figures and tables in this chapter. The likelihood of dissection in this population under direct observation is very low. In fact, once a patient has entered our system, and a decision made for medical management because of lack of symptoms and small aortic size, we are not aware of any instances of aortic dissection under such observation. We are now looking at this phenomenon from a heuristic, decision-making standpoint, to determine precisely how many patients may dissect when our recommended algorithms are applied. In short, we are not aware of a means to apply clinically the observation that some patients dissect at very small sizes. To operate prophylactic on all patients with minor enlargement of the aorta (say those with aortas between 4 and 5 cm) would probably cause more harm (surgical) than good.

13

Treatment of Ruptured Aortic Aneurysms

Ali Shahriari and Emily A. Farkas

Section of Cardiothoracic Surgery, Yale University, New Haven, Connecticut, U.S.A.

INTRODUCTION

Despite advances in diagnostics, aortic surgical techniques, technology, and perioperative medicine, ruptured aortic aneurysm remains one of the most lethal conditions with which aortic surgeons are challenged. The perioperative mortality of these conditions has remained unchanged over the past 20 years (1). In fact, mortality from acute aortic syndromes, including ruptured aneurysms, ranks among the top 13 causes of death according to the National Center for Health Statistics (2). Since the prevalence of aneurysmal disease increases with age, we can expect to encounter this problem at an advancing rate as we face an expanded aging population.

The sobering statistics for ruptured aneurysm emphasize the importance of rigorous screening programs for patients at risk for degenerative and hereditary aneurysms. Such programs may translate into decreased incidence of rupture and improved survival (3,4). Understanding the inheritance patterns and the molecular biology (5) of this disease will be imperative for the development of genetic and pharmacologic interventions to slow the progression to rupture.

PATHOLOGY

The most common pathology involving aortic aneurysms is degenerative atherosclerotic disease. The two most important protein fibers in the normal human aorta are elastin and collagen, Types I and III. Elastin contributes to the viscoelastic

properties of the aorta, whereas collagen provides tensile strength. Histologic examination of human aneurysmal aortic tissue has documented fragmentation and decreased concentration of elastin. While this compromise in the quality and quantity of the elastin contributes to the dilatation of the aorta (6–8), it does not markedly decrease the tensile strength. As demonstrated in rodent experiments, transgenic animals that do not produce elastin will form aortic aneurysms, yet will not succumb to rupture. If there is degradation of the collagen in the same elastin-deficient animal, however, susceptibility to rupture is demonstrated. The loss of the elastic properties in the aortic wall seems to be compensated by an increase in collagen synthesis during the early stages of aneurysm formation (9). Later in the disease process, collagen degradation exceeds its synthesis and this culminates in rupture (10).

Over the last decade, much research has been focused on the enzymes involved in the degradation of elastin and collagen. The imbalance between proteases such as matrix metalloproteinases (MMPs) and their inhibitors [e.g., tissue inhibitors of metalloproteinases-2, Plasminogen activator inhibitor (PAI)] (11) has been suggested as a possible mechanism (12–14). New insight into immunologic mechanisms underlying aneurysm formation and rupture has resulted in emerging hypotheses regarding the interactions between Th1/Th2 cytokines (15–18). Understanding these complex relationships may assist in altering the natural history of aortic aneurysmal disease in the future.

EPIDEMIOLOGY

Thoracic Aortic Aneurysms

According to a Swedish study (19), the prevalence of asymptomatic thoracic aortic aneurysms (TAAs) is highest in males 75 to 79 years of age, with a peak incidence occurring 10 years later in females. Thirty-nine percent of the males and 27% of the females have coexisting abdominal aortic aneurysms (AAA) or iliac artery aneurysms. Bickersatff et al. (20) estimated the prevalence of TAA to be 5.9/100,000 population per year. The incidence of rupture was calculated to be 5.0/100,000 population per year (21). Our own institutional database outlining the characteristics of over 1600 patients with TAA has previously shown (22) a growth rate of 0.19 cm per year, and a mean annual rate of rupture or dissection of 3% for aneurysms measuring 5.0 to 5.9 cm, and 7.0% for aneurysms greater than 6.0 cm (Fig. 1) (23).

Risk factors for rupture include vascular disease, female gender, pulmonary disease, hypertension, size of the aneurysm, chronic obstructive pulmonary disease, the presence of symptoms, and dissection within the aneurysm (21–23). In one series (24) 12% of thoracic aortic ruptures were associated with dissection in aortas less than 5.0 cm. Our institution addressed the impact of relative aortic size by developing the "aortic size index," which incorporates the patient's body surface area in the measurement (25). Increasing aortic size index was found to

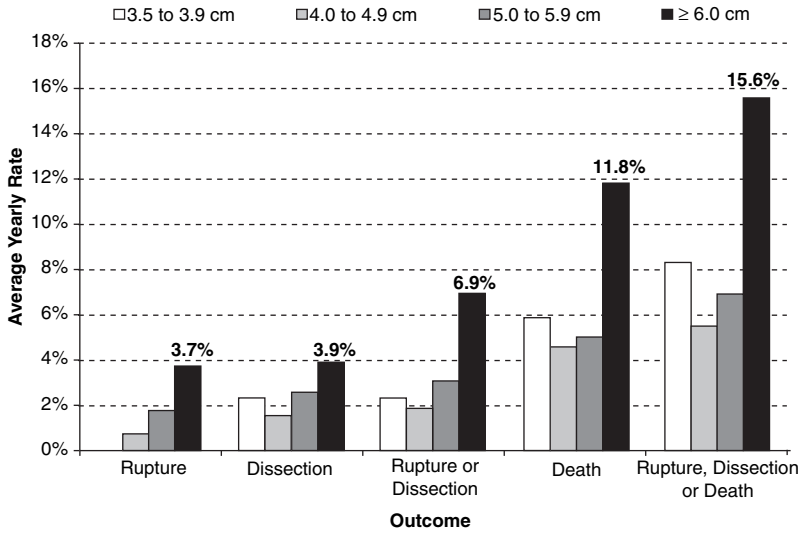

Figure 1 Average yearly rates of negative outcomes (rupture, dissection, and death). *Source*: From Ref. 23.

be a significant predictor of increasing rates of rupture ($P = 0.0014$) as well as the combined endpoint of rupture, death, or dissection ($P = 0.0001$). Using this measurement, patients were able to be stratified into three risk groups: less than 2.75 cm/m^2 were at low risk (~4% per year), 2.75 to 4.24 cm/m^2 were at moderate risk (~8% per year), and those above 4.25 cm/m^2 were at high risk (~20% per year).

Thoracoabdominal aortic aneurysms (TAAA) tend to follow the natural history of their respective thoracic and abdominal components. Ruptured TAAA represent approximately 15% of surgically treated TAAA in the United States, and postoperative mortality for this condition ranges between 40% and 70% (26,27). Crawford et al. (28) followed 94 patients who were poor surgical candidates or refused surgical intervention. The two-year survival was 24%, with 50% of the mortality related to rupture.

Abdominal Aortic Aneurysms

The most frequently ruptured segment of aorta involves the infrarenal location. Rupture of AAA accounts for 1% to 3% of deaths in males between 65 to 85 years. Bickerstaff et al. (29) found the incidence of AAA to be 36.5/100,000 population per year, with 12% having ruptured aneurysms. The mortality for ruptured AAA approaches 65% to 85% (30,31) and is responsible for 15,000 deaths annually in the United States.

Estimated Rupture Risk

AAA diameter (cm)	Rupture risk (%/y)
<4	0
4.5	0.5.5
5.6	1–15
6.7	10–20
7.8	20–40
>8	30–50

Figure 2 Estimated risk of rupture for abdominal aortic aneurysms. *Source*: From Ref. 34.

The average yearly growth rate has been estimated to be 0.28 cm per year (32). The incidence of rupture is 8/100,000 population per year, with an annual risk of rupture that increases to 8% per year for aneurysms >5.0 cm (Fig. 2) (33,34). The majority of patients who die from ruptured AAAs are asymptomatic prior to their catastrophic event.

Familial Aneurysms

Familial aneurysms account for approximately 15% to 20% of all aneurysms, both in the descending thoracic and abdominal aorta. Our knowledge and understanding of the genetic etiology responsible for the presence of these aneurysms continues to expand, as evidenced by the recent identification and investigation of several loci responsible for their development. Familial TAAs are inherited through Mendelian autosominal dominant traits with variable expressivity and incomplete penetrance (35,36). Loci discovered to date include thoracic aortic aneurysms and dissections 1 (TAAD1) (5q13-14), TAAD2 (3p24-25), and familial aortic aneurysms (FAA) (11q) (37–42). A recent nationwide Swedish study (40) revealed a biphasic distribution in the incidence of familial aortic aneurysms, with an early peak between the ages of 20 and 40 and a late peak after the age of 60 (Fig. 3). There are also data to suggest that patients with familial aneurysms rupture at a younger age than those with degenerative pathology (39,40). Recommendations regarding the optimal timing of surgical intervention specific to familial aortic aneurysms in the abdomen lack robust data in the current literature. Our institution's risk/benefit analysis following review of 3000 serial images and 3000 patient-years of follow up for TAAs suggests preemptive extirpation in asymptomatic familial disease at 6.0 cm for the descending aorta. Close follow up of patients and their family members with clinical evaluations and serial imaging is mandatory.

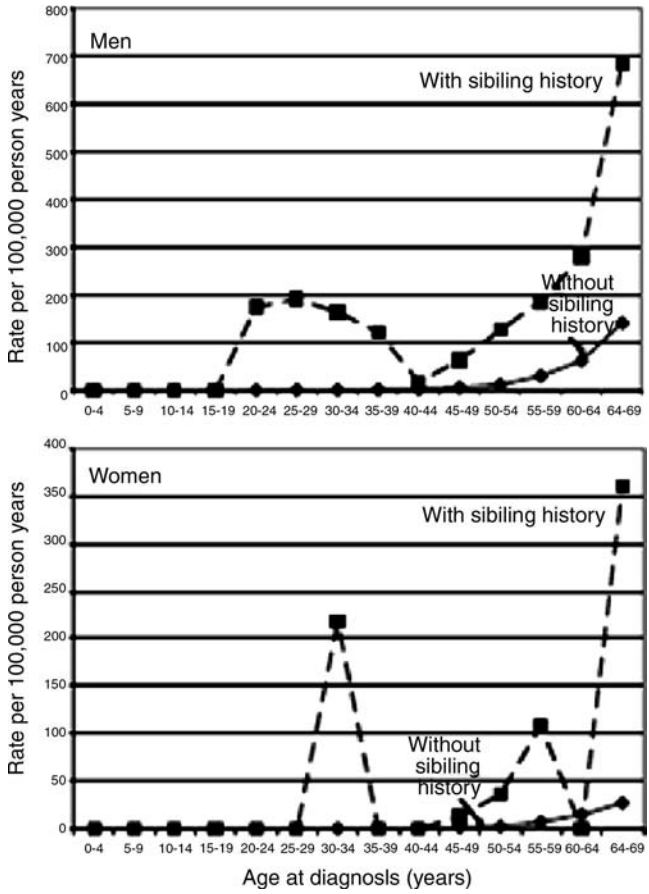

Figure 3 Age-specific incidence rates for familial (with sibling history) and sporadic (without sibling history) aneurysms. The difference between the two curves gives an approximation of the familial risk. *Source*: From Ref. 40.

PRESENTATION, DECISION-MAKING, AND RESUSCITATIVE MANAGEMENT

True demographics of ruptured aortic aneurysms are speculative, since the majority of patients do not survive long enough to pursue medical care. Most patients with ruptured thoracic aortic aneurysm present with hypotension and sharp pain in the back or interscapular region. A symptomatic thoracic aortic aneurysm may be confused with many alternative disease processes including acute coronary syndrome, acute pulmonary embolism, esophageal perforation, and pneumothorax. It is often a chest radiograph and computed tomography (CT) of the chest and abdomen that will enable the diagnosis of the ruptured aneurysm (Fig. 4).

Less than 15% of patients who present with ruptured AAAs carry a previous diagnosis of aneurysm. The most common presentation associated with this condition is abdominal and lower back pain associated with a tender and pulsatile mass. Only one-third of patients present with the "classic triad" of pain, hypotension, and pulsatile mass. Plain abdominal radiographs will reveal the calcified contour of the aneurysm wall in approximately 75% of cases.

There has been much debate about the optimal preoperative management of these patients. In particular regard to resuscitation, no randomized studies exist evaluating different strategies. Crawford (43) published a series of 87 patients with ruptured AAA with a 77% survival. Based on this experience, he recommended the utilization of blood for resuscitation until surgery, while keeping the systolic blood pressure less than 70 mmHg. Aggressive resuscitation with blood and fresh frozen plasma was not recommended until after application of the aortic cross clamp, and extensive evidence in the literature reinforces the danger of overvigorous volume resuscitation, which can exacerbate coagulopathy in patients with ruptured AAA (44–49). However, this strategy has been criticized by other authors who suggest that permissive hypotension may itself cause hypoperfusion and multisystem organ failure leading to death (50).

The role of CT scans in the diagnosis of ruptured aortic aneurysms has been discussed in the literature, and some authors have questioned its value in the management of the patient. It is speculated that obtaining a CT scan may contribute to mortality by delaying the surgical therapy. For TAAs, most surgeons would be reluctant to operate on a patient based only on suspicion. For abdominal aortic aneurysm, because of the ability of the surgeon to diagnose the malady based on the clinical presentation and the physical exam, some authors argue that time should not be spent in the radiology department, but is better spent in the Operating Room (OR). However over 40% of normotensive patients with known AAA and

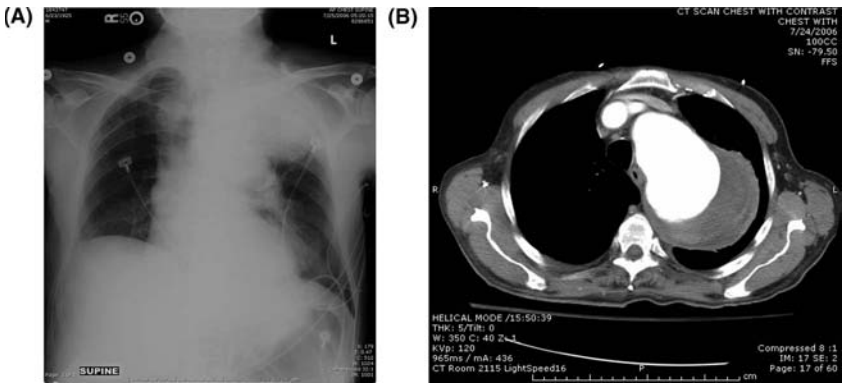

Figure 4 Computed tomography image of a patient with contained rupture of the descending thoracic aneurysm.

abdominal pain do not suffer from ruptured AAA. In these situations CT scans can be of utmost help in avoiding a negative laparotomy. The sensitivity and specificity of CT scans for ruptured AAA have been estimated to be 79% and 78%, respectively (51). Despite this there appears to be clinical advantage in judgmental use of CT scanners for diagnosis. Kvilekval et al. (52) studied 65 hemodynamically stable patients with AAA and abdominal and back pain. There were no deaths related to the delay caused by obtaining the CT scan. The study provided useful anatomic information in 28% of patients, and in 70% of patients, emergency surgery was avoided.

Thus we recommend CT scans of the chest and abdomen with intravenous contrast for all hemodynamically stable patients in whom there is a suspicion for symptomatic or ruptured thoracic aortic aneurysm.

The CT scan should be obtained with and without intravenous contrast. The noncontrast scans allow for detection of fresh hematomas, and the contrast images permit accurate identification of the anatomy of the aneurysm. CT findings suggestive of ruptured abdominal aortic aneurysm include obscuration of the retroperitoneum and displacement of the aneurysm by an irregular high-density collection. The kidneys may also be displaced anteriorly by a perinephric fluid collection. Other signs include enlargement of the psoas muscle contour and a crescent shaped area of high attenuation within the wall or mural thrombus of the aneurysm (53–55). Rapid opacification of the inferior vena cava suggests an aortocaval fistula.

MANAGEMENT OF RUPTURED AORTIC ANEURYSMS

General Considerations

While hemodynamic stability affords the opportunity to obtain imaging, the converse requires expeditious transfer to the OR for emergency surgery. Successful management of the unstable patient with ruptured aortic aneurysm requires a high index of suspicion, an experienced surgical team, and a clear plan and pathway for treatment.

Patients with ruptured aortic aneurysms should not be denied therapy on the basis of any specific set of preoperative factors. According to Halpern et al. (56) there is no correlation between preexisting medical comorbidities in ruptured aortic abdominal aneurysm patients and the immediate perioperative outcome. However, that series did find that hemoglobin level less than 10 mg/mL, loss of consciousness, and creatinine >1.5 mg/mL were predictive of death.

Ruptured Thoracic Aortic Aneurysm and Thoracoabdominal Aortic Aneurysm—Open Repair

Distal Arch/Proximal Descending Aortic Rupture

Efficient transfer of the patient to the operating suite is of paramount importance. While there is no absolute requirement for selective ventilation, this may be

helpful if the clinical situation allows time for placement of a double-lumen endotracheal tube.

The patient is positioned in the right lateral decubitus position, with the shoulders at a 90º angle to the operating table and the left groin exposed for TAAs and the abdomen rotated to 45º for ruptured Thoracoabdominal Aortic Aneurysms (TAAAs). In cases of ruptured TAAAs, we recommend dealing with the ruptured segment emergently and repairing the rest of the diseased aorta electively at a later time.

A standard posterolateral thoracotomy is performed, and the chest is entered through the fourth intercostal space for disease in the distal aortic arch or proximal descending aorta. The fifth, sixth, and seventh intercostal spaces are best used for the mid to distal descending aorta. In cases of ruptured TAAs, depending on the extent of the lesion, the sixth intercostal space may be entered and the costal arch divided for improved exposure. At this point the diaphragm is divided radially and the retroperitoneum exposed. A selfretaining, multibladed, ring-type abdominal retractor is of the utmost importance.

Clamp and sew technique: As soon as the chest is entered, the aorta is cross clamped proximal to the rupture site and fluid resuscitation with blood products and colloids or crystalloids begun. If the site of rupture is at the distal aortic arch or proximal descending aorta, then the clamp should be placed proximal to the left subclavian artery, and the subclavian artery controlled by a bulldog clamp. The aorta distal to the aneurysm is controlled with another aortic clamp. If the patient is in extremis, with severe shock and acidosis, despite aggressive resuscitation, the operation should be kept to a minimum even if segments of mildly to moderately diseased aorta are left behind. In these situations we recommend the clamp and sew technique—where the aneurysm between the clamps is opened, the intercostal vessels are oversewn, and an interposition tube graft is anastomozed to the two cut ends of the aorta (without perfusion adjuncts) (Fig. 5A). These two suture lines initially do not need to be completely hemostatic. The main objective is to remove the cross clamps as quickly as possible. This is a situation where technical precision may be sacrificed to some extent in favor of alacrity. Data has shown that the incidence of paraplegia increases after 30 min of aortic cross clamping in normothermia (57). Fine hemostasis of the suture lines can be dealt with after the clamps are removed.

Left atrial to femoral artery bypass: If hemodynamic stability is achieved initially in the operating room, atriofemoral bypass may be used to perfuse the spinal cord and the lower body and a more extensive resection may be accomplished, if needed (Fig. 5B). In these situations the femoral artery or the descending aorta may be used for arterial cannulation and the left inferior pulmonary vein may be used for venous return. Using atriofemoral bypass, the distal aortic clamp may be positioned proximal to T8 and the proximal anastomosis created while the lower body and the spinal cord are being supplied with oxygenated blood. After the completion of the proximal anastomosis, the proximal clamp is moved on to the body of the graft. This is very important, especially if the aorta has been controlled proximal to the left subclavian artery. In this way, the vertebral artery is

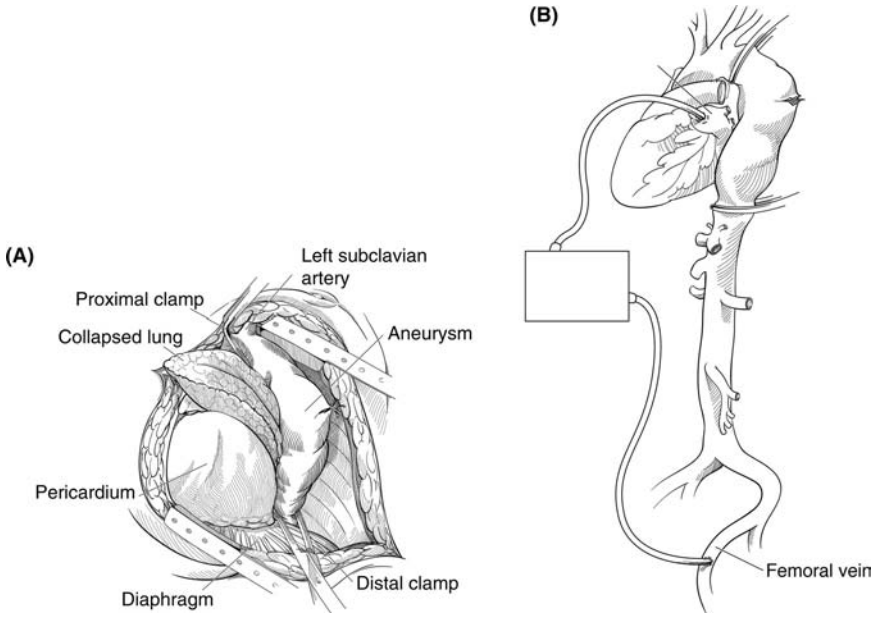

Figure 5 (**A**) Clamp and sew technique for ruptured thoracic aortic aneurysm. (**B**) Left atrial to femoral artery bypass.

re-recruited, supplying the basilar artery to the spinal cord. The lower clamp is now moved beyond the distal end of the aneurysm and the distal anastomosis is created. Appropriate intercostal vessels are attached to the graft using the island inclusion or "Cobrahead" technique (58). The distal clamp is removed, the patient is rewarmed, and the chest is closed after decannulation and placements of chest tubes.

Aortic Arch Rupture

Full cardiopulmonary bypass and deep hypothermic circulatory arrest: For ruptures proximal to the subclavian artery, clamping proximal to the injury is rarely feasible and full cardiopulmonary bypass with deep hypothermic arrest is required (Fig. 6).

The site may be controlled manually, and systemic perfusion can be accomplished by femoral or direct aortic cannulation. Venous return is provided by cannulating the femoral vein or main or left pulmonary artery. Cardiopulmonary bypass is instituted and the patient is cooled to 18ºC. A left ventricular vent is optional. The heart may be arrested by systemically administering 40 to 60 mEq KCl for better myocardial protection. This is optional, as the deep hypothermic arrest itself usually suffices for myocardial protection (Direct delivery of cardioplegic solution to the heart is difficult or impossible in this circumstance). Under deep

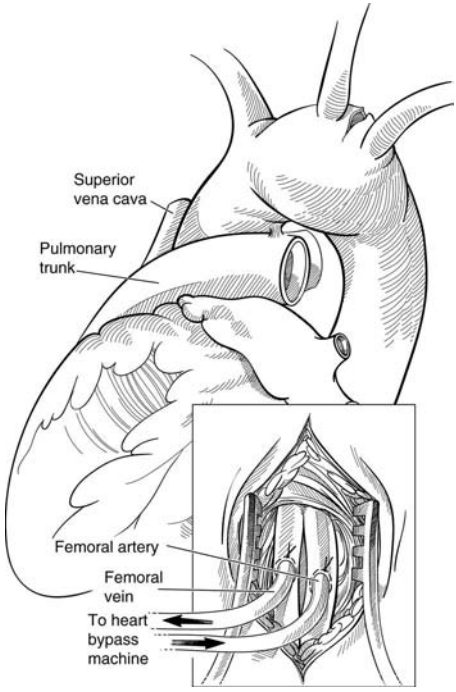

Figure 6 Aortic arch rupture treated using deep hypothermic circulatory arrest.

hypothermic circulatory arrest, the proximal anastomosis is constructed using a graft with a sewn-in 10 mm side arm. If the anastomosis is created proximal to the left subclavian artery, an interposition graft is created between the graft and the left subclavian artery either during rewarming or at the end of the case. After completion of the proximal anastomosis, the patient is placed in Trendelenberg, and the arch and the graft are deaired. A clamp is applied on to the graft distal to the side arm and perfusion of the ascending aorta and the aortic arch is resumed with a rate of about 30 cc/kg/min flow to the lower body can also be resumed through the femoral cannula, with the distal aorta clamped. At this point the patient may be slowly rewarmed and the distal anastomosis created. All appropriate intercostals vessels between T8 and L2 should be implanted. The distal cross clamp is now removed and the left subclavian interposition graft is created, if indicated.

Ruptured Thoracoabdominal Aneurysm

Ruptured suprarenal and Crawford level III and IV TAAs are best approached via a left thoracoabdominal incision as previously described (Fig. 7). For Crawford level III aneurysms we use the sixth, seventh, or eighth intercostal space for chest entry and proximal control. For Crawford level IV and suprarenal aneurysms we use the ninth or tenth intercostals space for entry. The remainder of the exposure

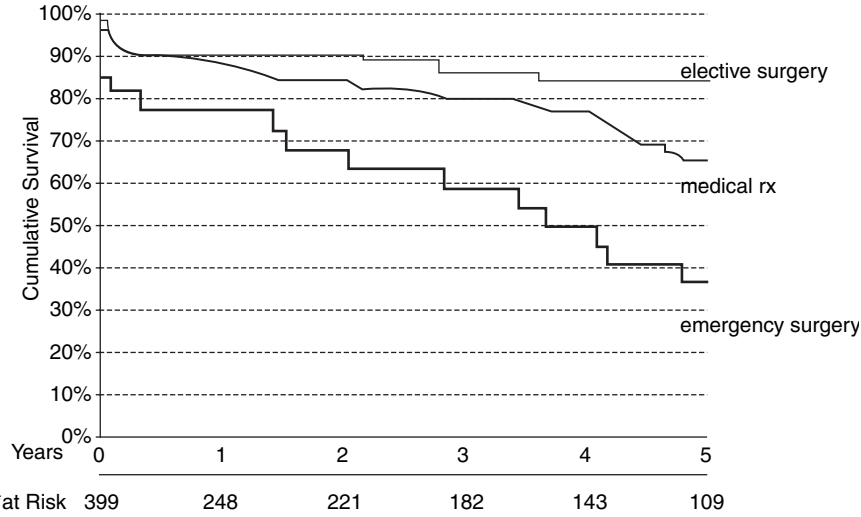

Figure 7 Kaplan–Meier cumulative survival. Five-year survival estimates are illustrated for patients as a function of presentation ($P = +0.002$). (rx = treatment). *Source*: From Ref. 23.

is carried out as described previously. Again, based on the hemodynamic status of the patient and the experience of the surgical team, the techniques most frequently used are clamp and sew or atriofemoral bypass with selective visceral perfusion.

Ruptured Myocotic Aneurysm

Ruptured mycotic aneurysms pose a difficult problem. If the rupture has occurred in the thoracic aorta, and the patient is hemodynamically stable, then the aneurysm can be excised and the proximal and distal aortic stumps closed and covered with healthy muscle flaps or omentum. The patient can then be turned and a median sternotomy created. Using a tube graft an extra-anatomical bypass between the ascending aorta and the supravisceral abdominal aorta is created (59). The graft should be brought from the lateral aspect of the ascending aorta, within the pericardium, behind the inferior vena cava (IVC) and through the diaphragm to the abdominal aorta within the aortic hiatus of the diaphragm. If the patient is hemodynamically unstable, an aortic cryopreserved homograft wrapped by omentum (60–63), or a tube graft (64) wrapped by omentum may be used in situ, instead of the extra-anatomic bypass. These patients should receive chronic antibiotic therapy tailored to the intraoperative culture results.

Surgical Results

With advances in surgical treatment for elective TAA repair, a perioperative mortality or neurological injury less than 5% can be expected (65–67). However, the mortality for repair of ruptured TAA is three to five times higher than that for elective repair (68–70). In one study, the mean size of the TAAs at the time of rupture was 8.1 cm

(68). Many had previous aortic surgery or chronic Stanford type B dissection, and were not followed by serial imaging. This again emphasizes the importance of longitudinal follow-up by teams experienced in aortic surgery and preemptive, prophylactic repair of the aneurysm to prevent rupture. As shown by Davies et al. (23) the long-term prognosis for patients surviving ruptured thoracic or TAA is markedly worse than for patients who electively undergo repair of TAA (Fig. 7).

Ruptured Thoracic Aortic Aneurysm and Thoracoabdominal Aortic Aneurysm—Endovascular Treatment

Although experience with use of endografts in thoracic aortic pathology is growing, it is still quite limited with regards to its use for ruptured aneurysms. The only FDA approved device in the United States is the Gore-Thoracic aortic aneurysm (TAG) (W.L. Gore, Arizona, U.S.A.), however other manufacturers are conducting trials in preparation for FDA approval. Several institutions outside the United State are using homemade devices.

From a technical point, once the diagnosis of ruptured TAA has been established, the patient is rapidly transferred to the OR. The chest, abdomen, and both groins are prepared as the patient is being anesthetized. If the patient is unstable, percutaneous femoral arterial access is quickly obtained and a balloon occlusion catheter is passed over a guidewire proximal to the site of the rupture, and the aortic lumen is occluded (Fig. 8). After anesthetic induction, percutaneous arterial

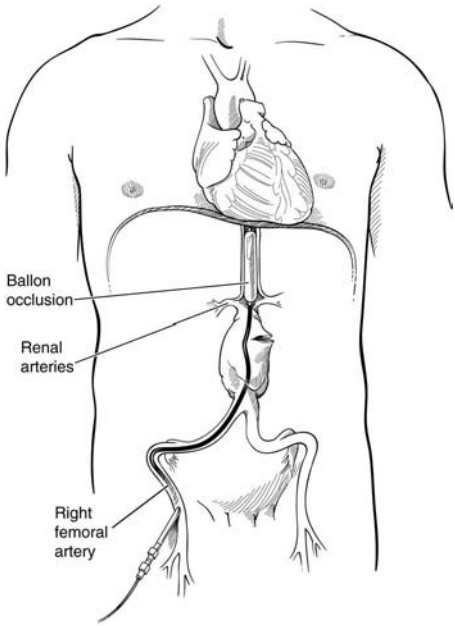

Figure 8 Balloon occlusion proximal to the rupture site as the first step in endovascular treatment of thoracic aortic rupture.

access is gained in one groin while a femoral cutdown is performed in the other groin. An aortogram is performed and the final measurements are carried out in preparation for the introduction of the endovascular device. The endograft chosen should be 10% to 20% larger than the measured diameter of the landing zones. Proximal and distal control of the common femoral artery is obtained and an arteriotomy created. The delivery sheath is introduced into the aorta through the arteriotomy. Once the delivery device is in the desired location, the graft is deployed. A completion aortogram is performed. Any type I endoleaks should be obliterated by deployment of Gianturco Z-stents (Cook Corporation, Bloomington, Indiana, U.S.A.).

Morishita et al. (71) have reported on 29 patients treated for acute rupture of the descending thoracic aorta. The in-hospital mortality was 17%, but these patients were not immune to pulmonary complications, renal failure requiring dialysis, or paraplegia (one patient). In another report by Kato et al. (72), 13 patients were treated for ruptured descending TAA. The in-hospital mortality was 38%. The endografts were also used in five patients with mycotic aneurysms or aortoesophageal fistulas. Four of these patients died of infections, three of them directly related to the aortic pathology. Semba et al. (73) reported a survival rate of 80% in 11 patients treated endovascularly for contained rupture of the descending thoracic aorta. However, these results reflect a selection bias toward patients with contained ruptures and potentially more stable pathology, as reflected by some of the patients undergoing treatment as late as 28 days after the onset of symptoms.

These short-term results are encouraging. As our experience with endografting is growing, we are also learning more about the complications and the durability of this treatment. A detailed discussion of these complications and durability concerns are beyond the scope of this chapter. However, one must not lose sight of our primary goal in treating these patients—that is, helping the patient to survive the acute insult. Thus durability concerns in the ruptured settings are of less importance than the immediate results. As our experience grows, these devices may offer a temporary stabilizing solution to a life-threatening problem. Close follow-up is warranted to permit offering the patient elective, definitive repair if late complications such as migration, pseudoaneurysm formation, or aneurysm recurrence occurs. Also, we must not forget that a well-performed open procedure is better than a poorly performed endovascular option, offered by inexperienced care providers.

Ruptured Abdominal Aortic Aneurysm—Open Repair

For decades open repair of ruptured abdominal aortic aneurysm (RAAA) via laparotomy has been the mainstay of treatment. The published mortality has remained between 30% and 70%. Approximately 80% of ruptured aortic aneurysms occur in the infrarenal region. These may rupture into the retroperitoneum (80%), into the free peritoneal cavity, or present as aorto-caval fistulae. Experience has shown that to achieve successful outcomes in this complex clinical situation, an organized system needs to be in place. Several institutions (74–76) have

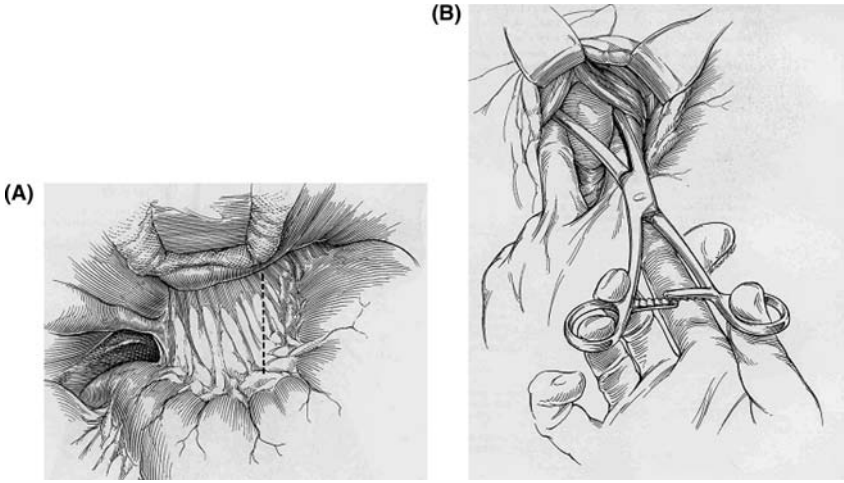

Figure 9 High control of aorta for ruptured abdominal aortic aneurysm. (**A**) Division of gastrohepatic ligament. (**B**) Clamping of aorta at diaphragm. Note proximity of esophagus, which must be protected.

suggested that improved results can be expected from such dedicated pathways. As with all aortic pathology, a high index of suspicion is required for rapid diagnosis and triage to appropriate treatment.

Upon diagnosis the patient is quickly transferred to the OR suite. The patient's chest, abdomen, and bilateral thighs are prepared as anesthesia is being induced. A midline laparotomy is performed form the xiphoid process to the pubic symphysis, and upon entry into the abdominal cavity, the gastrohepatic ligament is divided and the aortic hiatus identified. Using blunt finger dissection the aorta is isolated and cross clamped. Care is taken not to injure the esophagus adjacent to the aorta (Fig. 9). Resuscitation with blood products and intravenous fluids is commenced. A retractor is positioned such that the small bowel is packed in moist towels and gently retracted to the right of the abdomen to expose the peritoneum overlying the aorta. This is incised and the proximal neck of the aneurysm is identified and clamped. Iatrogenic injury to the left renal vein, renal artery, iliac veins, inferior vena cava, mesenteric artery and vein, spleen, and duodenum during this dissection is almost uniformly fatal (Fig. 10) (56).

At this point the supra-celiac clamp can be removed to minimize the visceral ischemic time. Once the proximal neck of the aneurysm has been clamped, the aneurysm is cut open and back bleeding from the iliac arteries is controlled with balloon occlusion catheters. The lumbar arteries are oversewn, and an appropriate sized graft is chosen and the proximal and distal anastomoses are created. If the aneurysm involves both iliac arteries, a bifurcated graft is chosen and an aorto-bi-iliac anastomosis is created.

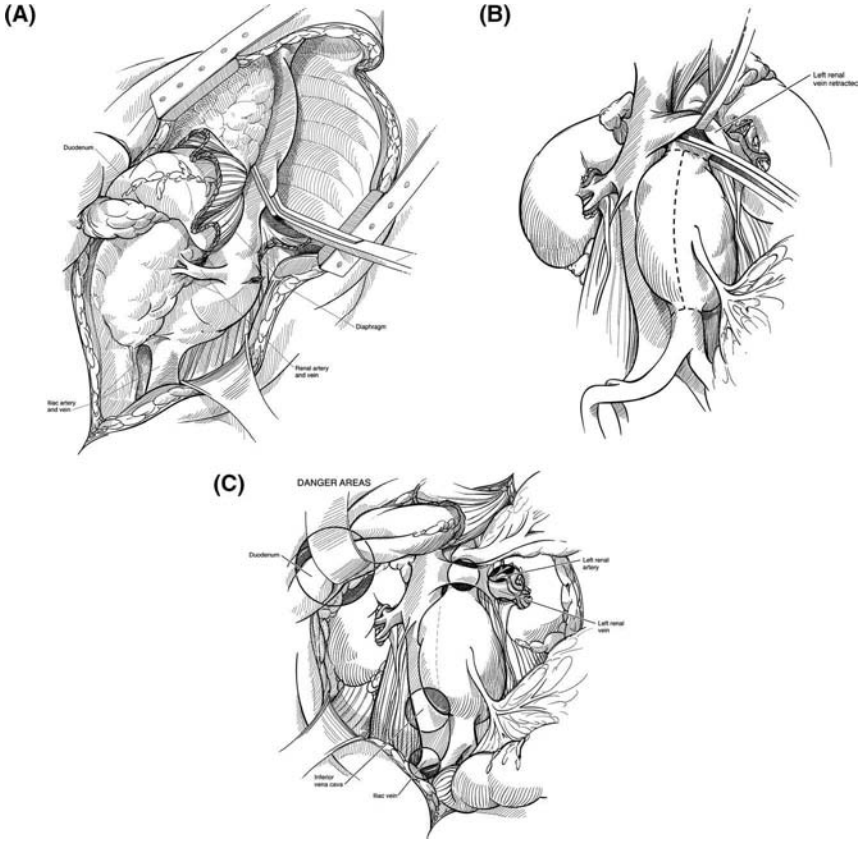

Figure 10 Switching clamp to just above the ruptured abdominal aortic aneurysm, thus reperfusing the abdominal viscera. (**A**) Viscera are rotated to the right of the abdomen to expose the abdominal aorta. (**B**) Clamp is applied just proximal to neck of aneurysm. (**C**) Note proximity of the following structures, whose injury must be avoided: left renal vein, renal arteries, liliac veins, inferior vena cava, superior mesenteric artery and vein, spleen, and duodenum.

For juxtarenal aneurysms, we maintain the supra-celiac clamp while creating the proximal anastomosis just distal to the origin of the renal arteries, including the lower lip of the renal artery orifice in the anastomosis if warranted. Once the proximal anastomosis is created, the clamp is moved onto the body of the graft in order to perfuse the visceral vessels. The rest of the operation is conducted as described earlier. Hemostasis is achieved, the incision reapproximated, and the patient transferred to the intensive care unit.

When an aorto-caval fistula is suspected on the CT scan or identified intraoperatively, severe hemorrhage may result from venous bleeding through the fistula upon opening the aneurysm. In this situation, the assistant uses two sponge sticks to compress the IVC proximal and distal to the fistula. The orifice of the

fistula is closed with pledgeted nonabsorbable monofilament sutures from within the aneurysm sac. No attempts should be made to separate the IVC from the aorta at the fistula, as this maneuver may result in lethal hemorrhage.

Ruptured mycotic aneurysms are rare causes of intra-abdominal aortic rupture. They are usually secondary to infectious endocarditis or Staphylococcal bacteremia in the presence of severe atherosclerotic disease. Depending on the degree of contamination of the aneurysm bed, we recommend complete resection of the aneurysm, aggressive debridement of the aneurysm bed, and either the use of a cryo-preserved homograft or the performance of an extra-anatomical axillo-bi-femoral bypass. Autografting using the patient's bilateral femoral veins has also been described and is favored in some institutions. Intraoperatively, the aneurysm and its bed should be sampled for culture and microbiologic analysis. We recommend buttressing the retroperitoneal area with omentum to lessen the risk of aortic stump blowout, anastomotic rupture, or pseudoaneurysm formation.

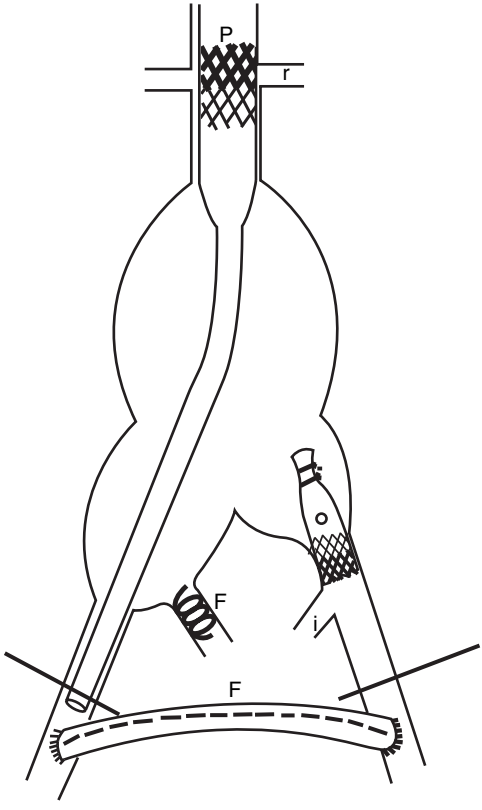

Figure 11 Endovascular repair of ruptured abdominal aortic aneurysm (Montefiore technique). See text.

Ruptured Abdominal Aortic Aneurysm—Endovascular Repair

Since its introduction in the early 1990s, endovascular abdominal aortic aneurysm repair (EVAR) has become an accepted treatment for elective AAA repair and has reduced the associated mortality in appropriately selected patients. Recently EVAR has also been introduced into the armamentarium for treatment of ruptured abdominal aortic aneurysm (eEVAR) by institutions highly experienced with this treatment modality.

There are several designs of aorto-uni-iliac systems, but none of these devices are FDA approved. One system that has received some attention in this country is the Montefiore endovascular grafting system (MEGS) designed by the Montefiore group (77). This system allows rapid deployment of the endograft to exclude the aneurysm and the site of rupture. The authors suggest a clinical pathway that includes rapid transfer of patients with ruptured AAAs to the OR. Prior to induction of anesthesia, a 5Fr sheath is introduced into the brachial artery and an aortogram is performed. If the patient is hemodynamically unstable, the 5Fr sheath is exchanged for a 14Fr sheath. A 40 mm compliant balloon catheter is introduced into the supra-celiac aorta and inflated to achieve proximal control. Once the aortogram is performed, if the anatomy is suitable for eEVAR, the

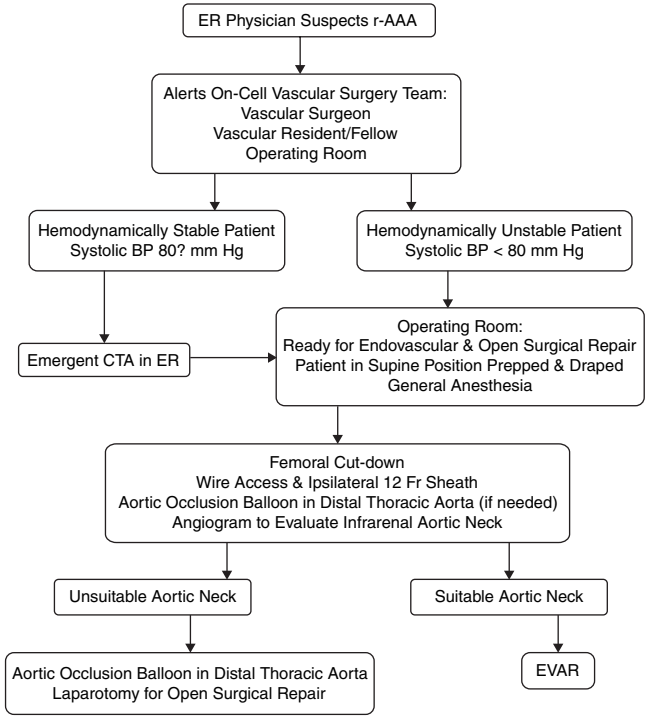

Figure 12 Algorithm for treatment of abdominal aortic aneurysm. *Source*: From Ref. 75.

MEGS is deployed in position, the ipsilateral hypogastric artery is coil embolized, and an occluder device is used to permanently occlude the contralateral common iliac artery. To complete the procedure, a femoro-femoral bypass graft is created (Fig. 11). If the patient does not meet criteria for eEVAR, an open procedure is performed. Using this system, the authors have reduced their operative mortality for RAAAs to 10%.

Results achieved by other groups have not been so outstanding.

Using the Talent aorto-uni-iliac system (Medtronic, Minnesota, U.S.A.) in the New ERA study (76), the investigators achieved 40% mortality in patients treated with the Talent device versus 42% mortality in the open repair group. Also, the group from Eindhoven (78) treating 24 patients with RAAAs achieved a 24% 30-day mortality with eEVAR.

Based on these feasibility studies, Mehta et al. (75) have established a protocol to facilitate endovascular treatment of patients with RAAA. They treated 40 patients, using a variety of commercially available modular aorto-bi-iliac grafts, with a mortality of 18% (Fig. 12).

Thus, eEVAR appears to be a promising treatment modality that may reduce mortality in this difficult patient group. Although selected institutions have had great success with eEVAR, the results have not been reproducible by others. Lacking a well-designed prospective randomized trial, it is difficult to draw solid conclusions for comparison of results between open and endovascular repair. We should also keep in mind that the impressive results by the Montefiore group (77) and Albany Medical Center (78) are also reflective of large clinical experience with elective EVAR and a well-organized system that rapidly establishes a clinical pathway for treatment of the patient with ruptured abdominal aortic aneurysm. Until most centers that offer treatment to patients with RAAA have developed such organized multidisciplinary systems, open repair for ruptured abdominal aneurysm remains the gold standard.

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DISCUSSION AND COMMENTARY

Questions for the Authors

Do you think that endovascular repair of ruptured abdominal aortic aneurysm will replace open repair in the setting of acute ruputure?

It is too early to tell. Traditional open repair can be extremely rewarding, but the risk in the setting of acute rupture remains considerable. A few specialized centers have reported excellent results with catheter-based management. The key advantage is the potential to obtain near-immediate control of the rupture by passage of a proximal occlusion balloon catheter. This controls the hemorrhage and sets the stage for controlled stent-based aneurysm exclusion. However, the excellent results in the small number of institutions with a special interest in interventional treatment of ruptured AAA have not yet been widely duplicated. The next five to ten years will probably show the proper place for endovascular therapy in the setting of ruptured AAA.

Is it worthwhile to operate on ruptured thoracoabdominal aortic aneurysms?

The risk of mortality in ruptured thoracoabdominal aortic aneurysm is truly daunting (73% in a recent series from Great Britain). We have a policy at our institution that we operate for all ruptured aneurysms except thoracoabdominal aneurysms, because of the very high acute risk (as well as a very poor long-term survival for this particular group of patients). If the rupture is not frank, and the patient is reasonably stable hemodynamically, then we do go forward with surgery. Thoracoabdominal aneurysms can be operated quite safely electively, again making the point that planned, pre-emptive surgical extirpation of these aneurysms is optimal, preventing the difficult circumstance of a patient with a ruptured thoracoabdominal aneurysm.

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14

Acute Aortic Dissection: Anti-impulse Therapy

Javier Sanz, Andrew J. Einstein, and Valentin Fuster

The Zena and Michael A. Wiener Cardiovascular Institute and Marie-Josee and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai School of Medicine, New York, New York, U.S.A.

INTRODUCTION

Acute aortic dissection is associated with extremely high mortality and morbidity. Death rates are on the order of 1% to 2% per hour during the first 24 to 48 hours after the onset of symptoms (1,2). Although today approximately 70% of those receiving appropriate care survive the acute episode (3), it is important to realize that up to 20% of subjects die before reaching the hospital (2).

Regardless of the definitive therapeutic option, most of these patients will require intensive medical treatment at the time of presentation. In many instances, the goal will be temporary clinical stabilization before surgical or percutaneous repair is attempted. In other cases, depending on the location of the pathologic process, the clinical course, and the presence of comorbidities, medical therapy may be the preferred choice for long-term management.

In this chapter, we will review the most important principles of medical therapy in the setting of acute aortic dissection. We will start with a brief overview of the components of the aortic wall, focusing on their role in maintenance of aortic structure and function. We will subsequently review those biomechanical forces that trigger or contribute to the loss of integrity of the aortic wall, which constitute the basis for the use of specific medications in this context. Finally, we

will summarize current recommendations for the medical management in subjects with acute aortic dissection, with special emphasis on drug therapy.

AORTIC WALL STRUCTURE

The aortic wall is composed of three layers: the intima, the media, and the adventitia (Fig. 1). The intima consists of a thin monolayer of endothelial cells resting on a basal membrane and a variable amount of subendothelial space that contains fibroblasts and connective tissue. The contribution of the endothelial layer to modulation of wall tension is considered negligible (4).

The media is constituted by cellular elements (mostly smooth muscle cells) and extracellular matrix that contains a variety of structural proteins, of which collagen and elastin are the most important. Elastin forms fibers that organize in circumferential layers with interspersed cells and collagen, a structure known as a

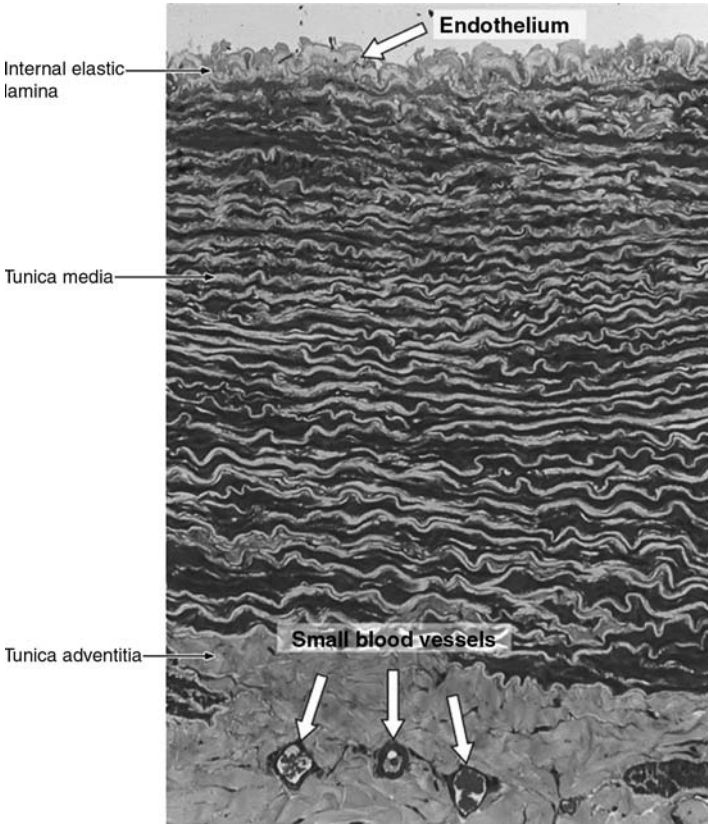

Figure 1 Transverse section of the wall of a large elastic artery demonstrating the well-developed tunica media containing elastic lamellae (pararosaniline–toluidine blue stain; medium magnification). *Source*: From Ref. 97.

lamellar unit (5). The number of lamellar units in a particular species is proportional to the ambient arterial pressure and is similar among mammals, although it is unexpectedly low in the infrarenal abdominal aorta in humans (6,7). Out of the three aortic wall layers, the media plays the predominant role in bearing mechanical stress (6). Elastin is very distensible and, under physiological conditions, supports most of the tension derived from the arterial pulse, absorbs the systolic impact of blood, and is responsible for the diastolic recoil of the arterial wall that contributes to maintaining forward flow. On the other hand, collagen has very little distensibility but provides most of the aortic wall's mechanical resistance to rupture or deformation (tensile strength). The distribution of elastic fibers and collagen is such that, at low levels of dilatation, elastin will be stretched and deformation is possible. When the vessel enlarges, nondistensible collagen fibers become stretched and support most of the wall tension, preventing rupture and further dilatation (4,8). In addition, elastic and collagen fibers have many interconnections that ensure uniform distribution of tensile stress even in the presence of minor inhomogeneities of the aortic wall which may occur, for example, with aging (6). Nonetheless, there is a transmural gradient of mechanical stress, more prominent in the inner portions of the media (8). Smooth muscle cells regulate vascular tone and stiffness through changes in their contraction status (9) and additionally have significant metabolic functions that include the synthesis of collagen. Conversely, the capability to synthesize elastin is lost early in life in humans (7).

The outer portion of the arterial wall, the adventitia, is composed of collagen, elastin and few cells (mainly fibroblasts). Integrity of this layer seems to be an important determinant of the maintenance of aortic diameter, and elastin degeneration involving its inner portion may be necessary for aneurysmal dilatation to occur (8,10). The adventitia is classically thought of by surgeons as the layer that has strength for suturing and holds stitches well.

CONTRIBUTORS TO AORTIC WALL DISRUPTION

Structural Factors

The multiple abnormalities at the molecular and histological levels that occur in conditions predisposing to aortic aneurysms or dissection are extensively reviewed in other sections of this textbook. In brief, one of the common pathologic findings is medial degeneration, characterized by the fragmentation of the lamellae and loss of elastin fibers. In advanced cases, this is accompanied by reductions in the numbers of smooth muscle cells and multifocal accumulation of basophilic mucoid material. Such medial degeneration is seen with aging, atherosclerotic disease, arterial hypertension, and genetic diseases such as Marfan's syndrome (11–13). The loss of elastin fibers results in decreased arterial distensibility, leading to increases in pulse pressure and systolic hypertension (14,15). Reduced distensibility by itself may not influence the risk of rupture, independently of blood pressure and aortic diameter; however, changes associated with medial degeneration

also decrease wall strength, thus favoring rupture (16–18). Reductions in the number of smooth muscle cells appear to favor aortic dilatation due to loss of their metabolic function rather than because of diminished contractile capacity (7). Collagen abnormalities, such as those seen in Ehlers–Danlos syndrome, are similarly associated with increased risk of arterial dilatation and dissection (19). Although conflicting results have been reported, collagen amount seems to be increased in pathologic aortas, perhaps in an attempt to repair or maintain structural integrity, although newly synthesized collagen may be defective (20–23). Elastin and collagen crosslinks, which play a role in filament stabilization, are also abnormally reduced in aneurysms (23,24).

Other structural proteins may also be involved in aneurysm formation and predisposition for dissection (7). Fibrillin, abnormal in Marfans's syndrome, contributes to the extracellular microfibrillar ultrastructure that serves as the support for elastin deposition and plays a role in the distribution of shear stress (7,25) Fibulin-5 participates in the regulation of elastic fiber assembly. Its expression is reduced in subjects with proximal aortic dissection and correlates with the degree of elastin degeneration (26). Also, peptidases, such as matrix metalloproteinases and elastase, play a role in elastin and collagen degeneration and aneurysm formation (27–29).

Mural ischemia is probably a significant contributor to the development of aortic dissection. Whereas the intima and inner media nourish mainly by passive diffusion from the lumen, the outer layers of large arteries receive their nutrients through the vasa vasorum (30). Interestingly, the common plane of dissection of the vessel wall is the outer third of the media, the limit between the two zones (30,31). Intimal thickening characteristic of atherosclerotic disease may compromise the nourishment of the inner media. Similarly, a decrease in number or function of the vasa vasorum results in ischemic medial necrosis, morphologic changes in collagen and elastin fibers of the outer media, increases in collagen content, and enhanced aortic stiffness at various levels of mechanical stress (32,33). Ischemia promotes inhomogeneity in the transmural mechanical properties, resulting in increased interlayer shear stress that may favor dissection (33). Alterations in vasa vasorum functionality take place, for example, in arterial hypertension (34).

Hemodynamic Factors

In a cylindrical tube, circumferential stress is determined by Laplace's law (35):

$$T \approx P_t \times R/\mu,$$

where T is the circumferential wall tension, P_t the transmural wall pressure (intravascular minus extravascular wall pressure), R the radius of the vessel, and μ the wall thickness. Although there are ethnic and interindividual differences in aortic wall thickness that may influence wall tension (36), transmural pressure and the vessel diameter are considered the most important determinants. It is clear from Laplace's law that stress will increase proportionally to the arterial diameter, which explains why aneurysms rupture more frequently than nondilated segments.

P_t is usually simplified to the intravascular distending force, that is, the arterial pressure. Indeed, arterial hypertension has been often associated with the propensity to develop aortic dissection and aneurysms, and constitutes a common clinical finding in acute aortic syndromes (3,37–39). An increment in systolic blood pressure of 26 mmHg has been found equivalent to an increase in aortic diameter of 1 cm in terms of generated wall stress (16).

However, wall stress prediction is actually much more complex, particularly in the presence of aneurismal dilatations where the assumption of a cylindrical shape of Laplace's law does not hold. Stress distribution in aneurysms is in fact largely heterogeneous—depending on the shape of the dilatation, local differences in the wall characteristics, or presence of mural thrombosis (17). Apart from circumferential stress (perpendicular to the arterial wall), there is probably considerable shear stress among lamellae, as there is slight motion of the different layers of the media along the plane of the vessel wall. This shear stress also increases significantly in the presence of aortic dilatation (31). As mentioned earlier, uniformity in stress distribution is an important protective characteristic of the arterial wall. Homogeneity of the media is lost in the presence of focal fibrosis, calcification, islets of mucoid material, or intramural hemorrhage that can occur with conditions associated with medial degeneration (13,31,40). This results in nonuniform distribution of stress that can trigger dissection (31).

Although it is clear that wall stress is directly proportional to blood pressure, observations made in the 1960s suggested that pressure itself is not the main determinant of aortic disruption. Interestingly, both normal and diseased aortas were found to be highly resistant to rupture from static forces, indicating the importance of pulsatility as a contributor to wall rupture (41). This led to the hypothesis that the morphology of the arterial pulse wave might have a stronger influence than the actual pressure level (42,43).

In this regard, the contractile status of the myocardium plays an important pathophysiological role. Impulse is defined as the product of force and time. The term cardiac impulse has been employed to define the net force exerted by the contracting myocardium during ejection. During systole, the maximum rate of myocardial shortening occurs at the beginning of contraction, when load is minimal, and the velocity of shortening decreases as load grows. This results in maximal velocity of ejected blood early in systole, which coincides with the maximal rate of pressure change within the ventricle (or dp/dt_{max}). Information regarding ventricular impulse and dp/dt_{max} can be derived from the upslope of the initial portion of the aortic pressure curve (Fig. 2) (44,45).

Sympathetic stimulation results in increases in cardiac impulse, whereas reductions in sympathetic tone lead to diminished force of contraction and decreased dp/dt_{max} (44). The impact of dp/dt_{max} and pulsatility is most prominent in the ascending aorta and the aortic isthmus—areas where intimal tears often develop (46). The maximal rate of pressure rise (dp/dt_{max}) appears to be the most important determinant of aortic rupture and the progression of dissection. It is important to realize that regardless of the initial mechanism leading to wall

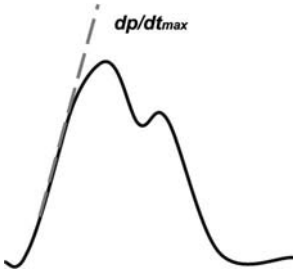

Figure 2 In the aortic pressure curve, the tangent (*dashed line*) of the steepest point in the ascending portion indicates the maximum pressure change (dp/dt_{max}).

disruption (intimal tear or intramural bleeding), it is the progression of the dissection that leads to clinical complications (47).

In an important experiment, Prokop et al. (48) evaluated the effects of stepwise increases in flow, pressure, or dp/dt_{max} on the rate of dissection progression using prosthetic as well as explanted dog aortas in which an artificial tear was produced. Neither high nonpulsatile flows nor elevated intra-aortic pressures caused dissection extension. However, pulsatile flow led to progression of dissection both proximal and especially distal to the intimal tear. Importantly, the rate of dissection was not dependent on the mean or peak pressure. When dp/dt_{max} was gradually increased, the rate of dissection progressed in parallel. Moreover, a threshold value of dp/dt_{max} was identified below which no progression of dissection occurred (Fig. 3). In the animal aortas, some of the dissections progressed to complete wall rupture, whereas, in others, the false cavity recanalized into the true lumen, a behavior similar to that observed in spontaneous human dissections.

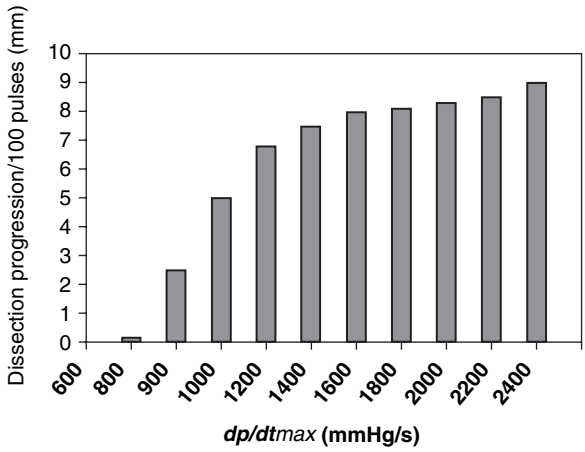

Figure 3 Enhanced progression of aortic dissection in relation with increasing levels of dp/dt_{max}. It can be noted that, at least in the experimental setting, no progression occurs below a threshold of dp/dt_{max}. *Source*: From Ref. 48.

From these experiments, it was shown that static forces and/or laminar flow do not appear to promote extension of the dissection, as there is no pressure gradient between the torn intima and the adjacent tissue. However, in the presence of pulsatile flow, such a gradient, proportional to dp/dt_{max}, develops and leads to rapid progression of the dissection. Elastic pulsation of the wall with each heartbeat or shear stress caused by flowing blood could additionally contribute to the evolution of the dissection, although these forces appear to play minor roles (48).

Anti-impulse Therapy and Blood Pressure Control for Acute Aortic Dissection

The pathophysiological considerations we have described provide the rationale for using drugs with anti-impulse properties as the cornerstone of medical therapy in acute aortic dissection. Although blood pressure control is also fundamental, it is crucial to realize that drugs with arterial vasodilator properties, very effective in decreasing arterial pressure, often result in increments in dp/dt_{max} and may paradoxically increase the risk of wall rupture (Fig.4) (46,49). This is due to reflex sympathetic responses mediated by arterial baroreceptors when blood pressure drops, leading to increased cardiac chronotropy and inotropy.

Additional evidence supporting the use of anti-impulse therapy came from experimental studies evaluating the effects of chronic administration of various drugs on the risk of aortic ruptures. These studies were performed in turkeys with medial degeneration induced by β-aminopropionitrile, an inhibitor of lysyl oxidase, which interferes with the formation of elastin and collagen crosslinks (50).

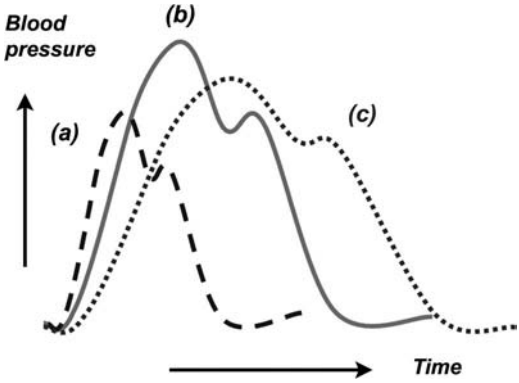

Figure 4 Diagram of aortic pressure curves under various conditions. The continuous line (*b*) represents the baseline state. Administration of a vasodilator agent such as nitroprusside is represented by the dashed curve (*a*). There is significant decrease in pressure levels and acceleration in heart rate, but this is accompanied by a steepest slope of the ascending portion of the curve (increased dp/dt_{max}). Beta blockade administration is represented by the dotted line (*c*). Although the degree of pressure lowering is usually smaller, the drug negative inotropic and chronotropic effects result in decreased impulse and dp/dt_{max}.

Hydralazin, a direct arterial vasodilator, increased the risk of aortic rupture due to its inability to reduce dp/dt_{max} and also probably because of direct toxic effects on elastin ultrastructure (50,51). Drugs with sympathicomimetic activity also favored rupture (52). On the other hand, propranolol, a nonselective β-1 and β-2 receptor blocker, increased aortic tensile strength and reduced contractility and dp/dt_{max}, conferring the greatest protection (50,53). The cardioselective β-1 receptor antagonists sotalol and practolol also lowered dp/dt_{max} with little change in the aortic tensile strength, resulting in partial protection from aortic rupture (50,53). Similar partial protection was observed with reserpine, a drug that depletes catecholamine stores and causes increases in aortic tensile strength, but increments in dp/dt_{max} (50,52). Interestingly, propranolol demonstrated protective actions at doses without significant hemodynamic effects, suggesting direct effects on the arterial wall. Subsequently, it was shown that propranolol enhances the formation and maturation elastin crosslinks in the aorta, probably by stimulating of lysil-oxidase (54). In one study, in patients with Marfan's syndrome, intravenous propranolol failed acutely to reduce dp/dt_{max}, suggesting that it might be less effective in the presence of a dilated aortic root (55).

Despite the important beneficial effects derived from decreasing dp/dt_{max}, the role of arterial pressure must not be underestimated. In a study involving dogs with surgically produced dissection, progression in one hour was evaluated under different pharmacological treatments. In agreement with prior considerations, nitroprusside was effective in controlling arterial hypertension but not dissection progression. However, the control of dp/dt_{max} with propranolol alone was also insufficient. The best results were reached with the combination of nitroprusside and propranolol or with trimethaphan, an autonomic ganglion blocker with effects in contractility and vascular resistance (56). Therefore, both aggressive reductions in both blood pressure and dp/dt_{max} constitute the basis for contemporary medical therapy of acute aortic syndromes.

MEDICAL TREATMENT OF ACUTE AORTIC DISSECTION

General Considerations

An overview of the management of acute aortic dissection is shown in Figure 5. Current recommendations, particularly with respect to medical treatment, are largely based on noncontrolled experience and studies with limited numbers of patients. As pointed out elsewhere, evidence-based medicine principles are difficult to apply in a relatively uncommon and life-threatening condition (57). Initial series suggested that medical therapy was a potential alternative to surgical intervention in aortic dissection and that untreated patients fared worse than those treated either medically or surgically (58–62).

In uncomplicated type B dissection, surgery does not improve survival (63,64) and therefore these patients are managed medically in most instances. Surgery (or percutaneous intervention) is usually reserved for those cases with

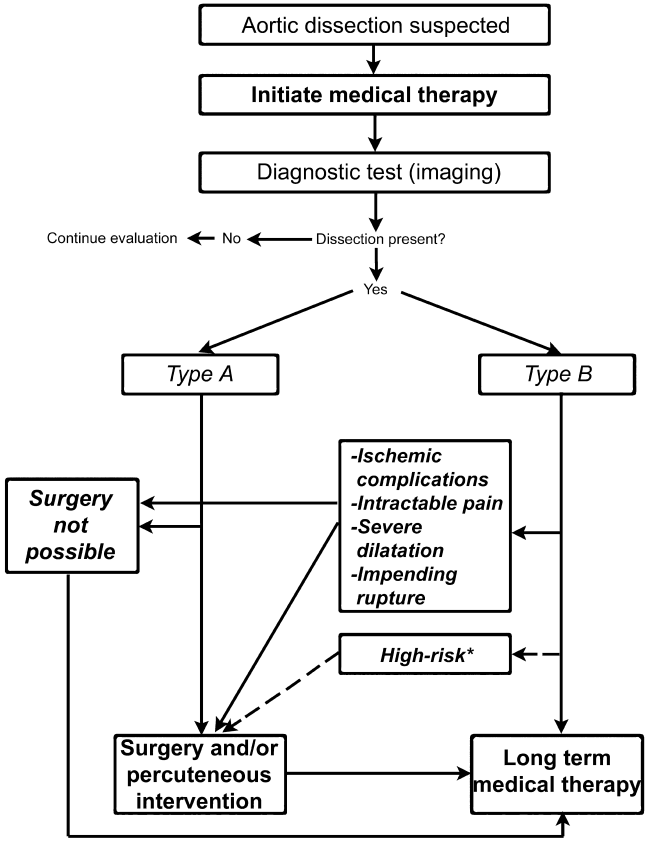

Figure 5 Flow diagram of the global approach to the patient with suspected acute dissection of the aorta. The dashed line indicates a less well-accepted alternative.

ischemic complications, impending rupture, severe aortic dilatation, or intractable pain (37,65). However, due to the reductions in surgical morbidity-mortality achieved during the last decades, early operation may be considered in good surgical candidates (i.e., younger subjects) or in cases of estimated higher risk (such as Marfan's syndrome, residual patency of the false lumen, or poor response to drug therapy) (46,66,67). Recently, the absence of pain has also been associated with higher mortality in type B dissection (68).

In type A dissection, immediate surgery is the treatment of choice, because survival is largely improved when compared with the dismal natural history of the disease (37,65,69–71). However, if surgery is not possible due to significant comorbidities or patient's refusal, intensive medical therapy may be associated with acceptable short-term survival, particularly in those diagnosed after the initial phase (72).

The patient in whom acute aortic dissection/rupture is suspected requires early and aggressive medical management (Fig. 6), while urgent imaging and surgical

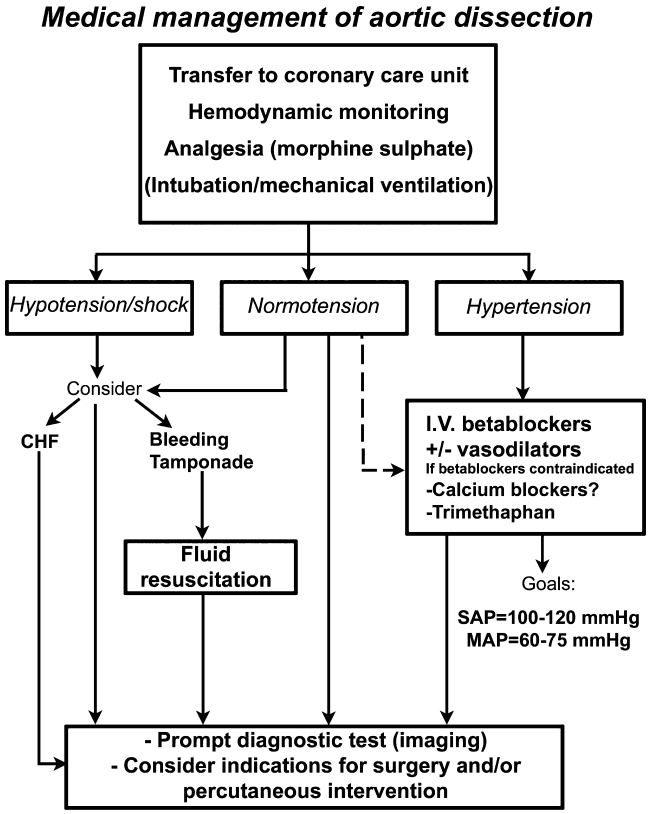

Figure 6 Schematic diagram of the medical management of patients with suspected or confirmed acute dissection of the aorta. Subjects with normal blood pressure may still require medication to reach the desired hemodynamic goals. *Abbreviations*: CHF, congestive heart failure; IV, intravenous; MAP, mean arterial pressure; SAP, systolic arterial pressure.

evaluation occur. Whereas the decision to proceed with surgery is individualized (depending on the aforementioned considerations and institutional expertise and approach), all patients should be managed medically in the meantime. The goals of medical therapy are both clinical and hemodynamic stabilization.

The patient should be admitted to an intensive care unit, where vital signs, cardiac rhythm, urine output, and neurologic status can be closely monitored for any change due to aortic complications (73). Blood pressure should initially be quantified in both arms, as there may be involvement of the arch vessels by the dissection with falsely low measurements unilaterally. Subsequently, it is preferable to monitor blood pressure with an arterial line, enabling optimal choice and titration of medical therapy, especially in the presence of hemodynamic instability. The arterial line should typically be placed in the right radial artery, because the right brachiocephalic artery is less often affected by the dissection. If there is

concern about involvement of the brachiocephalic trunk, or significantly higher blood pressure measurements from the left arm, then a left radial arterial line should be placed (37). Because hemodynamic deterioration may occur abruptly, an intravenous access different from that used for drug infusions should be readily available. Antithrombotic medications (e.g., heparin and fibrinolytics), commonly used in other chest pain syndromes, should be withheld until the diagnosis of dissection is ruled out, as their administration may have catastrophic consequences. Pain contributes to a hyperadrenergic state with worsening of tachycardia and hypertension, and should be eliminated promptly by the intravenous administration of morphine sulfate, a drug with additional blood pressure lowering effects.

Medical management largely varies depending on the patient's hemodynamic status (Fig. 6). A normotensive or hypotensive patient requires close evaluation for heart failure (due to concomitant aortic insufficiency or myocardial ischemia), blood loss, and pericardial tamponade, prior to the administration of volume. Hypotension or shock constitute signs of ominous prognosis (74) and should usually be treated with volume resuscitation. A patient with significant hemodynamic instability may require intubation and mechanical ventilation. In the case of tamponade, pericardiocentesis appears to be contraindicated, based on a small series in which three of four patients completing the procedure successfully subsequently developed electromechanical dissociation and death within 40 minutes (75). This may be due to acute rebound of arterial pressure or increase in the pressure gradient between the false lumen and the intrapericardial space, favoring new bleeding, after correction of the tamponade. Immediate bedside sternotomy for surgical access to the ascending aorta has been suggested in some cases of tamponade, but remains controversial (65). Cornerstones in the medical management of hypertensive and most normotensive patients with suspected acute aortic dissection are anti-impulse therapy and blood pressure control, with a target systolic blood pressure of 100–120 mmHg or mean arterial pressure of 60–75 mmHg (37,46).

Pharmacological Therapy

Short-acting intravenous agents are preferred to facilitate titration to blood pressure goals, both in the intensive care unit and the operating room. In patients who are normotensive and clinically stable (at presentation or after intravenous therapy) and who are not undergoing intervention, oral drugs can be started as a preliminary step before discharge. Table 1 summarizes pharmacologic properties of intravenous drugs commonly used in the management of acute aortic dissection and Table 2 is a summary of advantages and disadvantages of the different drugs.

Beta Blockers

The initial agent of choice in most cases should be an intravenous beta blocker. Beta blockers have the dual advantage of decreasing dp/dt_{max} as well as lowering blood pressure. They are contraindicated in patients with significant bradycardia

Table 1 Pharmacologic Properties of Intravenous Agents for the Management of Acute Aortic Dissection

Drug	Initial bolus	Initial maintenance dose	Maximum dose	Mechanism of action	Onset of action	Duration of effect
Anti-impulse agents						
Beta blockers						
Esmolol	500 μg/kg	10–50 μg/kg/min	300 μg/kg/min	β1-antagonist	2 min	20 min
Metoprolol	5 mg q5min × 3	5 mg q2–3hr	5 mg q2–3h	β1-antagonist	2 min	3–6 hr
Propranolol	1–2 mg	1 mg/hr gtt or 2 mg q3–4hr	2 mg/hr gtt or 4 mg q3–4hr	β1-, β2-antagonist	5 min	3–6 hr
Labetalol	20 mg	2 mg/min gtt or 20–80 mg boluses	300 mg in 24 hr	β1-, β2-, β1-antagonist	2–5 min	2–4 hr
Calcium blockers						
Verapamil	5–10 mg	5 mg/hr	5 mg/hr	Negative inotrope/ chronotrope	3–5 min	not available
Ganglionic blocker						
Trimethaphan		0.5 mg/min	15 mg/min	Ganglionic blocker	1–5 min	10 min
Vasodilator agents						
Nitroprusside		0.25 μg/kg/min	2 μg/kg/min	Arterial and venous dilator	seconds	3 min
Enalaprilat	0.625–1.25 mg	0.625–1.25 mg q6hr	5 mg q6hr	ACE inhibitor	15 min	12–24 hr
Fenoldopam		0.1 μg/kg/min	1.6 μg/kg/min	Dopamine1-agonist	15 min	15 min
Calcium blockers						
Nicardipine		5 mg/hr	15 mg/hr	Vasodilator	5–15 min	4–6 hr
Diltiazem	5 mg q5min × 3	5 mg/hr	15 mg/hr	Vasodilator, negative chronotrope	2–7 min	not available

Note: Table and doses are for reference only and should be individualized for the management of actual patients.
Abbreviations: ACE, angiotensin converting enzyme; gtt, drip.
Source: From Refs. 37, 73, 81, and 94.

Table 2 Advantages and Disadvantages of Intravenous Agents for the Management of Acute Aortic Dissection

Drug	Advantages	Disadvantages
Anti-impulse agents		
Beta blockers	Decrease dp/dt_{max} and blood pressure	Contraindicated in bradycardia, bronchospasm
Esmolol	Rapid onset, short duration	High fluid volume, drug levels increased by morphine
Metoprolol	Inexpensive, widely available	Longer duration of action
Labetalol	Alpha and beta blockade, maintains cardiac output	Longer duration of action
Propranolol	Inexpensive, widely available	Longer duration of action
Calcium blockers	Decrease blood pressure and maybe dp/dt_{max}	Contraindicated in bradycardia
Verapamil	Can be used in setting of bronchospasm	Constipation, limited evidence
Ganglionic blocker		
Trimethaphan	Can be used when beta blockers contraindicated	Unpredictable hemodynamics, anticholinergic, tachyphylaxis
Vasodilator agents	Decrease blood pressure	Increase force of left ventricular ejection, reflex tachycardia
Nitroprusside	Most rapid onset and shortest duration	Thiocyanate toxicity
Enalaprilat	Useful in high renin states	Very long duration of action
Fenoldopam	Intermediate onset and duration	Tachyphylaxis, contraindicated in glaucoma
Calcium blockers		
Nicardipine	Can be used in the setting of bronchospasm	Long elimination half life; interaction with anesthetic agents
Diltiazem	Can use in bronchospasm, some negative inotropic effect	Peripheral edema, gastrointestinal side effects, limited evidence

Source: From Refs. 37, 73, 81, and 94.

or high-grade heart block, and should be used with caution if there is a history of congestive heart failure or bronchospasm.

Esmolol hydrochloride has the advantages of rapid onset on action, short half-life of distribution (two minutes) and elimination (nine minutes), and brief duration of action. Serum drug levels are undetectable 20 to 30 minutes after cessation of infusion. Esmolol is hydrolyzed by erythrocyte cytosol esterases into methanol and an acid metabolite with a low affinity for beta receptors. Therefore, its pharmacokinetic properties are not significantly altered in the setting of renal insufficiency or liver disease (76).

Esmolol interacts with several commonly used drugs, including those that play a role in the medical and surgical management of patients with aortic

dissection, although these interactions are of minimal clinical significance. Administered concurrently with morphine, serum esmolol levels were found in an open-label study to be 46% higher than in esmolol infusion alone; morphine levels were unchanged (77). This effect can be compensated for simply by prudent dose titration. In another study, esmolol was found to delay recovery from succinylcholine-induced neuromuscular blockade by less than three minutes (78). Similarly, in rabbits, esmolol decreased the neuromuscular blocking potency of mivacurium and prolonged its effect by 30% (79).

Side effects from esmolol are typical of those for beta blockers, although, due to its short duration of action, this drug is the best choice in its class for a trial in patients for whom there is concern about bronchospasm. Caution should be used in patients with a history of congestive heart failure, as esmolol may be responsible for a large fluid load with the current 10 mg/mL formulation, especially at high doses. A double-strength, 20 mg/mL preparation is available. In sum, esmolol has been called an "ideal" beta blocker for critically ill patients due to its favorable pharmacokinetic, hemodynamic, and metabolic properties (80).

Alternative beta-blocking agents include metoprolol tartrate, which is inexpensive and widely available, as well as propranolol and labetalol. The latter is both an alpha and nonspecific beta blocker, with an alpha to beta-blocking ratio of 1:7. It has been shown to be safe and effective in the management of hypertensive emergencies, and it maintains cardiac output (81).

Calcium Channel Blockers

For patients for whom beta blockade is contraindicated or not tolerated, calcium channel blockers are commonly used for the management of acute aortic dissection. The use of calcium channel blockers in this setting is based on an understanding of their pharmacology, but no data exists supporting this practice (37). Verapamil, in particular, has been shown to decrease contractility and dp/dt_{max} in some studies (82,83), although not all (84,85). Impulse appears to be unchanged by diltiazem, whereas dp/dt_{max} was increased by nifedipine in a canine model (86). Thus, for patients not receiving beta blockers, verapamil might be a reasonable alternative, although conclusive evidence for its use is lacking. For patients already receiving intravenous beta-blocker therapy, calcium channel blockers are not typically used. Infact, concomitant use of intravenous beta blockers and calcium channel antagonists is generally considered contraindicated, due to potential for severe toxicity (brady cardia and hypotension). Nicardipine is a 1,4-dihydropyridine with potent vasodilatory and blood pressure lowering effects. It may cause reflex sympathetic activity, and thus patients receiving this drug should be monitored closely (87). It also potentiates neuromuscular blockade from vecuronium (88), and its effects are modified by flurane inhalational anesthetics (89).

Trimethaphan Camsylate

Trimethaphan is an older, uncommonly used agent with a significant side effect profile, but one that may be particularly effective for patients with acute aortic

dissection. It depletes norepinephrine from sympathetic ganglia, thereby reducing contractility and blunting the sharpness of the pulse wave generated by myocardial contraction, and consequently dp/dt_{max}. It also decreases peripheral vascular resistance, and it is recommended to place the patient in reverse Trendelenburg position to optimize trimethaphan's hypotensive action. The side effects of this drug are related to its mechanism of action. It can cause depletion of neurotransmitters in cholinergic ganglia and severe anticholinergic effects, including urinary retention, ileus, and mydriasis. Neuromuscular blockade and respiratory muscle paralysis leading to acute respiratory failure have been reported. Tachyphylaxis occurs commonly (87). For patients with strong contraindications to beta blockade, trimethaphan may represent the most effective anti-impulse therapy, but this needs to be weighed against the downside of ganglionic blockade.

Other Vasodilators

When intravenous beta blockade is inadequate to lower blood pressure to the desired target in a timely manner, a second agent may be considered, typically one with vasodilatory effects. Sodium nitroprusside is widely used due to its effectiveness, ease of administration, rapid onset of effect, and brief duration of action. It is an arterial and venous vasodilator that decreases both preload and afterload and increases intracranial pressure. Patients, particularly those with renal or hepatic dysfunction, should be monitored for cyanide toxicity, which may manifest as encephalopathy, convulsions, focal neurologic deficits, or coma. Coronary steal may occur with nitroprusside in patients with coronary artery disease (81). Nitroprusside, like other vasodilators, should not be used in suspected aortic dissection in the absence of anti-impulse therapy, for it can increase dp/dt_{max} via reflex-mediated increased inotropy and chronotropy.

An alternative to nitroprusside is intravenous enalaprilat. The blood pressure lowering effects of this angiotensin converting enzyme inhibitor have been shown to be directly related to pretreatment concentrations of angiotensin-II and plasma renin activity (90). Enalaprilat will be particularly effective in situations in which the dissection extends into a renal artery, where elevated plasma renin activity is characteristic (91). Enalaprilat should be used only with extreme caution in patients in whom there is a realistic possibility of acute myocardial infarction, a setting in which a trend toward increased mortality has been noted in CONSENSUS II, a large randomized controlled trial (92).

The newest vasodilator used in acute aortic dissection is fenoldopam. This agent is a short-acting, dopamine-1 agonist that acts as a peripheral arterial vasodilator. It also has multiple effects on the kidneys, including increasing blood flow, diuresis, natriuresis, and renin release. As such, it is another agent particularly suited for aortic dissection complicated by renal impairment. One study in patients undergoing elective thoracoabdominal aortic aneurysm repair showed fenoldopam to be associated with a reduction in mortality, dialysis, and length of stay (93). Side effects include headache, flushing, dizziness, tachycardia, bradycardia, and increases in intraocular pressure. Tachyphylaxis occurs after 48 hours of infusion (94).

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DISSCUSSION AND COMMENTARY

Questions for the Authors

Should aggressive vasodilator treatment be initiated as the first line of therapy in hypertensive patients with acute aortic dissection?

No, as discussed in the text, vasodilator therapy should only be initiated after aggressive intravenous beta blockade has been completed, to prevent rebound tachycardia and increases in dp/dtmax.

Should a patient with normal blood pressure and heart rate still receive medical therapy?

Yes, because, at least in experimental models, there is a threshold of dp/dt_{max} below which dissection does not progress, so one of the goals of therapy should be to reduce cardiac impulse even in normotensive, nontachycardic patients. In addition, adequate beta blockade may help prevent normal daily variations in heart rate and blood pressure that may be unnoticed but still potentially harmful.

Should complications of acute aortic dissection be managed for other critically ill cardiac patients?

No. In the event of tamponade, pericardiocentesis appears to be contraindicated, based on a small series (75). This study found that most aortic dissection patients with tamponade successfully undergoing pericardiocentesis subsequently died in less than an hour, presumably due to acute rebound of arterial pressure or increase in the pressure gradient between the false lumen and the pericardial space.

In a patient with acute dissection and tamponade, should "partial" pericardiocentesis be attempted?

This is a controversial issue. As discussed in the text, pericardiocentesis has been associated with sudden hemodynamic deterioration and death, probably because of recurrent intra-pericardial bleeding. However, if the tamponade is so severe as to cause organ hypoperfusion, a reasonable compromise may be to attempt drainage of the minimum amount of fluid necessary to increase blood pressure to a tolerable level, without excessively decompressing the intrapericardial cavity (75). It is important to acknowledge that the possibility of hemodynamic collapse still remains.

Should a Swan–Ganz catheter be placed?

Monitoring left ventricular filling pressures may be useful to guide therapy, particularly in patients developing congestive heart failure (e.g., in the setting of acute aortic regurgitation) or in whom large amounts of fluid are administered. Although evidence in the particular context of aortic dissection is lacking, we may extrapolate from recent randomized trials in heart failure or the intensive care unit that systematic use of Swan–Ganz catheters is neither useful nor detrimental (95,96). Placement of a pulmonary catheter should not be allowed to delay implementation of urgent medical therapy or prompt imaging or other vital testing.

15

Surgical Procedures: A Primer

John A. Elefteriades

Section of Cardiothoracic Surgery, Yale University, New Haven, Connecticut, U.S.A.

Randall Griepp

Department of Surgery, Mt. Sinai School of Medicine, New York, New York, U.S.A.

INTRODUCTION

This chapter addresses the surgical management of acute aortic dissection. It is intended not only for surgeons, but also for all readers with an interest in acute aortic diseases. The decisions that must be made—as to which patient needs an operation and what operation should be done—are of general relevance in achieving an understanding of acute aortic dissection.

The questions that will be addressed include:

1. When is operation necessary?
2. Which operation should be done?
3. Should the operation be done with deep hypothermic circulatory arrest (DHCA) and an "open" distal anastomosis?
4. Does the aortic arch need to be resected?
5. How does surgical treatment differ for the variant dissection phenomena of penetrating aortic ulcer (PAU) and intramural hematoma (IMH)?
6. What is the appropriate management of retrograde dissection from the descending to the ascending aorta?
7. How is ascending aortic dissection treated after antecedent remote cardiac surgery (prior coronary bypass or aortic valve replacement)?

ACUTE ASCENDING AORTIC DISSECTION

When to Operate

As is well known, the natural history of acute ascending (type A) aortic dissection is poor, with high early mortality in patients not treated surgically. For this reason, acute ascending aortic dissection is generally regarded as a surgical emergency. All acute ascending aortic dissections are operated urgently unless the patient's general condition is inappropriate for major cardiac surgery. This could be the case from overwhelming comorbidities, such as extremely advanced age, uncontrolled malignancy, or end-stage lung disease. A recent publication demonstrates the relative safety of surgery, even in patients of advanced age (1). Nonoperative management might also be appropriate if the patient presents with realized stroke due to the dissection itself. In such cases, if the stroke is already established, operation is usually withheld. If the cerebral event more closely resembles a transient ischemic attack, urgent operation is required, not only for cardiac, but also for brain reasons, as an effective aortic operation will restore brain perfusion. It may be difficult to distinguish between ischemia and realized brain infarction. Certainly, if the patient is unconscious and the computed tomography (CT) scan shows a discernible lesion, the brain injury is already realized, and surgery is inappropriate. Surgery under these circumstances can precipitate a major intracranial bleed, with devastating consequences. If the degree of realized cerebral injury is uncertain, we often obtain an urgent neurologic or neurosurgical consultation to help with the distinction.

In the minority of patients who are treated nonsurgically, about a 10% to 20% early survival can be expected, with modern medical management—mainly "anti-impulse" therapy with β-blockers and afterload reducers. Aortic surgery can be performed late, after recovery from stroke or resolution of other comorbid problems.

A situation often arises in which the diagnosis of aortic dissection is not made until some days after the acute presentation. It is not uncommon to receive patients in the evening hours who had presented to the transferring institution several days earlier, until someone stumbled on the diagnosis of aortic dissection, usually via a CT scan done for another reason. We looked at such patients specifically in a recent report (2). We found that if more than 48 to 72 hours have elapsed since the onset of symptoms, one can safely delay operation until the next semi-elective operating room slot. Thus, despite the general urgency of operation for acute ascending aortic dissection, in cases presenting after two or three days from symptom onset, "the eye of the storm has passed." Recognition of the ability to wait in these cases can preclude the dreaded middle-of-the-night aortic arch replacement.

Descending Aortic Dissection with Retrograde Extension to the Aortic Arch

Often, a patient presents with interscapular pain and is found to have a descending aortic dissection with some involvement proximal to the origin of the

subclavian artery, that is, involvement of the distal aortic arch. The radiologist, reading defensively, may emphasize that, technically speaking, the aortic arch is involved (Fig. 1). The majority of these patients have the dissection process confined to the very distal aortic arch, in the vicinity of the left subclavian artery. We have found that these patients rarely extend their dissection more proximally or go on to occlude the cerebral arteries. At our institution, we treat these patients like ordinary descending aortic dissections, with "anti-impulse" medical therapy. If brain ischemia should develop, we proceed to surgery. Also, if the initial dissection process extends retrograde proximal to the innominate artery, we proceed to operate, as the ascending aorta has become involved, and the patient is thus rendered vulnerable to all the attendant complications, including intrapericardial rupture, acute aortic valvular insufficiency, and coronary artery dissection.

Variants of Typical Aortic Dissection: IMH/PAU

IMH of the aorta differs from typical dissection in that there is no flap defining a true and a false lumen, and the hematoma is located circumferentially around the aortic lumen, rather than obliquely oriented across the aortic lumen. Penetrating ulcer of the aorta (PAU) involves a local penetration deep into the wall of the aorta, resembling a penetrating ulcer of the stomach (Figs. 2 and 3).

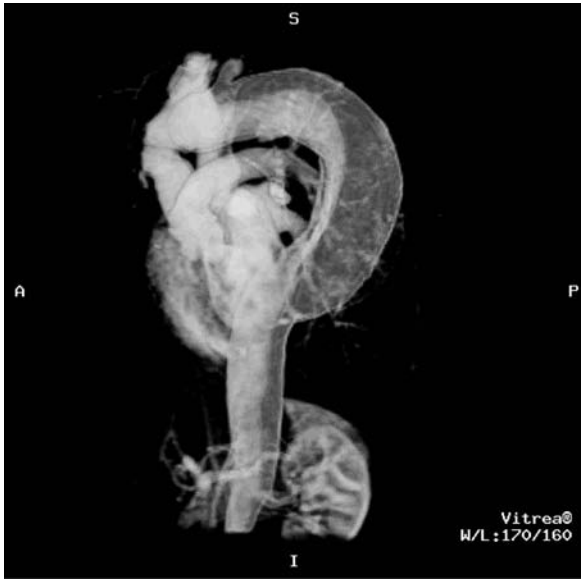

Figure 1 Computed tomography scan showing involvement of the distal aortic arch, in the vicinity of the subclavian artery, in a predominantly Type B aortic dissection. This is treated as a Type B aortic dissection.

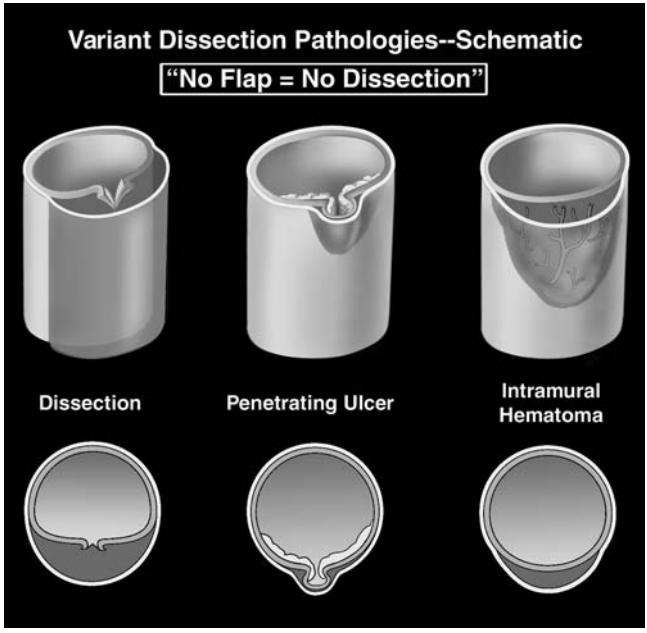

Figure 2 Schematic representation of typical aortic dissection and the variant forms of aortic dissection—intramural hematoma of the aorta and penetrating aortic ulcer.

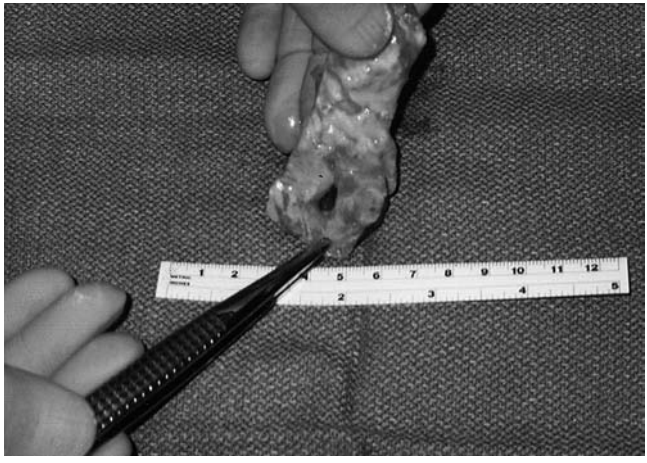

Figure 3 Photograph of penetrating ulcer of the thoracic aorta. Note resemblance to duodenal ulcer in overall appearance.

The general management of these lesions is still a matter of debate. Most authorities believe that descending aortic IMH and PAU can be managed medically, with "anti-impulse" therapy. We take a more aggressive stance at our institution, operating within the initial hospital admission on all except the very old and infirm. Our reason for this posture resides in our mid-term follow-up of unoperated patients (3). We found that, although one can often achieve a hospital survival with solely medical management, many of these patients die of rupture in the first year or two after discharge. We prefer to preempt this rupture by early (but not immediate) surgical intervention. Some of the discrepancy in recommendations also has to do with regional differences: in Japan, IMH behaves in a more benign fashion than in the Western world, perhaps reflecting fundamental genetic differences in the aortic wall, or differences in body size and aortic dimension.

For ascending variant dissections, IMH and PAU, most authorities agree on aggressive immediate surgical intervention, although one recent paper from Japan challenges the need for routine surgery, even in this anatomic location (4). The consensus opinion, however, is in favor of surgery for ascending IMH and PAU. Figure 4 shows a dramatic case in which the ascending aorta has ruptured through the posterior wall of the ascending aorta. The surgical team was called to relieve a "cryptogenic" pericardial effusion.

Very little direct information is available for IMH and PAU in the aortic arch itself. For IMH, the aortic arch may or may not be involved, as these lesions

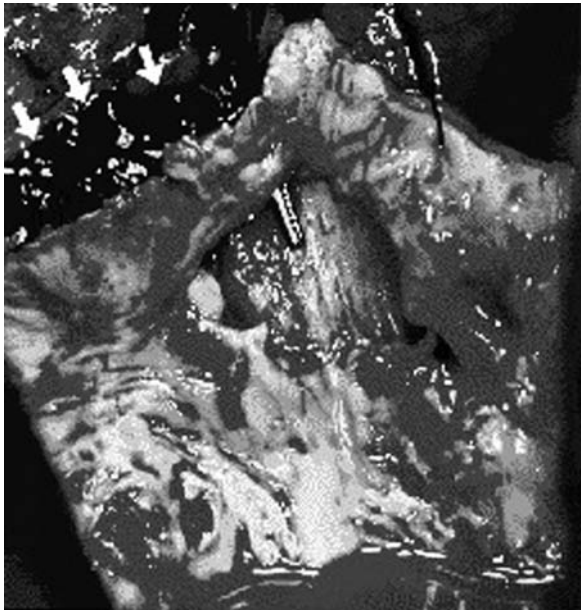

Figure 4 A dramatic case of a ruptured posterior penetrating ulcer of the ascending aorta. The opening in the back wall of the aorta is a transmural rupture of the aortic wall. The patient survived aortic replacement. *Source*: Courtesy of Dr. C. Russell.

sometimes confine themselves to the ascending portion of the aorta. If the arch is involved, the patient is managed as for a typical aortic dissection. If a PAU happens to be located in the aortic arch itself, arch replacement is performed using one of the standard techniques enumerated later in this chapter.

What Operation for Acute Aortic Dissection?

The most important fundamental questions regarding surgical decisions in the management of acute type A dissection relate to the extent of the operation (5). Regarding the proximal aorta, does the aortic root need to be replaced? In which patients will a supracoronary tube graft suffice, and in which patients is a more complex resection including the segment of aorta between the valve and coronary arteries required? Does the aortic valve need to be replaced? Regarding the distal aorta, should the anastomosis be done closed or open? Should the aortic arch be resected, or will it suffice to stay proximal to the origin of the innominate artery?

We have to remember that acute type A aortic dissection is an inherently lethal condition. Our first job is to produce a live patient. If the patient survives the acute episode, this constitutes a success, regardless of later onset of further aortic problems. The early mortality for urgent operation for acute aortic dissection ranges from 15% to 25%, depending largely on institutional experience. While such results represent a dramatic improvement from earlier eras, clearly surgical science still has room for progress in the treatment of this challenging disorder. Critical to achieving patient survival are complete hemostasis, prevention of intrapericardial bleeding, prevention of coronary artery dissection, prevention or correction of major aortic insufficiency, and restoration of flow to compromised branch vessels.

Certain technical truths regarding the surgical management of acute type A dissection are nearly self-evident. One is that performance of a composite graft replacement on an acutely dissected aorta is a dangerous procedure, best avoided if possible. Mobilization and connection of acutely dissected coronary artery buttons is potentially dangerous and problematic. For this reason a supracoronary tube graft is preferred whenever feasible and appropriate. A second technical truth is that an open distal anastomosis permits a more satisfactory technical result. A closed anastomosis always results in a cramped, distorted region at the posterior tip of the clamp, which is a frequent source of bleeding. Also, the mere application of a clamp forces the anastomosis considerably more proximally on the aorta, resulting in a less complete resection of the ascending aorta (Fig. 5).

A pertinent physiologic truth is that mild to moderate aortic insufficiency is well tolerated. It is widely known that onset of left ventricular dilatation and heart failure may take many years to become manifest in a general cardiologic patient with aortic insufficiency. Many patients are left with mild to moderate aortic insufficiency after type A aortic dissection repair and do well for years thereafter, if not indefinitely. Such a scenario of survival, albeit with mild aortic insufficiency, represents a successful outcome, even if further surgical attention should be required many years later.

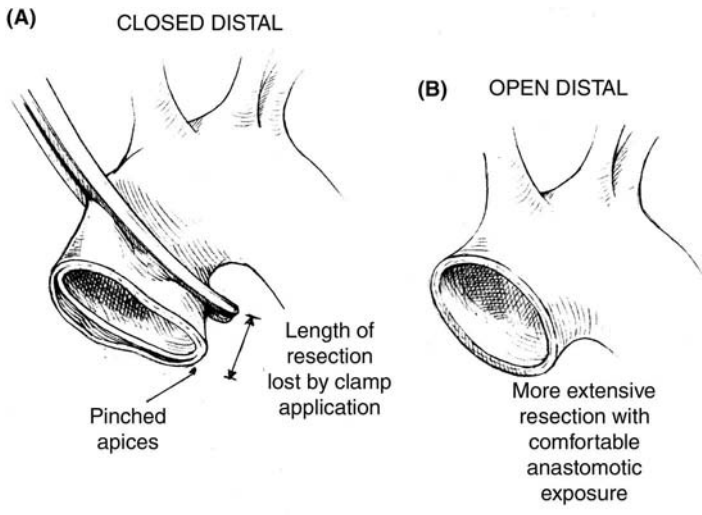

Figure 5 Comparison of (**A**) closed (clamp) and (**B**) open (no clamp) techniques for distal anastomosis in acute Type aortic dissection. Note how clamp application forces the anastomosis closer to the aortic valve and results in a "cramped" exposure for anastomotic construction. Note technical superiority of open anastomosis, with more complete resection of damaged tissue and excellent operative exposure for anastomosis.

The technical approach to acute type A aortic dissection that we follow at our institution is generally supported by a considerable body of recent literature that has examined many of these important issues (6–19). We recommend the following approaches to the issues listed previously.

Extent of Proximal Resection

A simple tube graft suffices in most cases. This does not suffice if the patient has Marfan's syndrome, other known severe connective tissue disorder, or frank annuloaortic ectasia. In such cases, composite graft replacement with coronary button implantation is mandatory. In these situations, the increased complexity of replacement of the aortic root must be borne. Sewing to an ectatic proximal aortic cuff is likely to result in subsequent further dilatation or rupture. Furthermore, technical problems at the time of the acute operation related to sewing to this dilated, weakened tissue are quite common and often lethal. In such instances not only is the patient better served in the long run, but the secure proximal anastomosis to the aortic anulus, which is always strong, is expedient. However, the vast majority of patients with acute type A aortic dissection do not have frank annuloaortic ectasia or Marfan's syndrome and can be treated appropriately with a simple supracoronary tube graft. We classify the morphology of the aortic root into three categories, illustrated in Figure 6. Supracoronary tube graft replacement is applied in the case of supracoronary aortic aneurysm. Composite graft replacement is

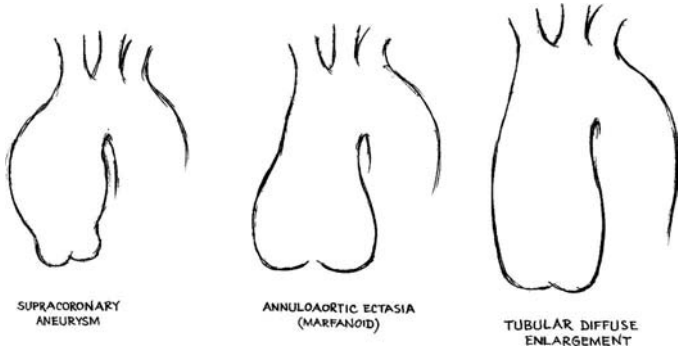

Figure 6 The three common patterns of chronic ascending aortic aneurysm: supracoronary, annuloaortic ectasia, and tubular. Supracoronary aneurysms are adequately addressed by a supracoronary tube graft. Annuloaortic ectasia requires composite graft replacement (or valve-sparing root replacement). Tubular lesions can be treated either by tube graft or composite graft, usually depending of the patient's age.

applied in the case of frank annulo-aortic ectasia. For the intermediate condition of tubular enlargement of the ascending aortic and aortic root, either tube grafting or composite graft replacement may be applied. In a younger patient, we would favor composite grafting, whereas in an older individual, we would consider that a supracoronary tube graft would suffice. The relatively new valve-sparing techniques for root replacement developed by David et al. (20) and by Yacoub et al. (21) are just beginning to be applied to acute type A dissection. It is too early to speculate on the appropriate role of these operations in this condition.

Management of the Aortic Valve

In most cases the aortic valve can be left alone, or the commissures can be resuspended. Only if the aortic insufficiency is 3+ or more does the operation need to be prolonged by concomitant aortic valve replacement. Intraoperative transesophageal echocardiography provides an accurate assessment of the severity of the aortic insufficiency before initiation of cardiopulmonary bypass. The severity of aortic insufficiency usually improves even from simple tube graft replacement of the aorta, which brings the aortic valve leaflets closer to coaptation.

Open or Closed Distal Anastomosis?

An open distal anastomosis is preferable for the technical reasons stipulated previously. There appears to be a near consensus on this point at experienced aortic centers. The required brief period of circulatory arrest is uniformly well tolerated.

Does the Arch Need to Be Resected in a Typical Type A Aortic Dissection?

In the vast majority of acute type A aortic dissections, the intimal tear is located circumferentially above and lateral to the right coronary artery. While the

dissection usually extends longitudinally all the way around the aortic arch, to the descending and abdominal aortas, the inciting tear is rarely located in the aortic arch itself. A beveled, hemiarch replacement can usually be easily incorporated into the open distal technique of tube grafting and results in a low rate of subsequent arch aneurysm formation. This should be the standard operation in the vast majority of patients.

What About Intimal Tears in the Aortic Arch Itself?

The question of whether to "chase" an inciting intimal tear that is located not in the ascending aorta (as is overwhelmingly usual) but in the aortic arch proper has not been conclusively answered. This would require a full arch replacement in the face of an acute aortic dissection, an extremely challenging procedure. In such a case, although a full aortic arch resection encompassing the arch tear might be strictly preferable for the long-term benefits that could accrue, a tube graft will probably suffice. If the operator feels that full arch replacement is too formidable an undertaking in these urgent circumstances, a tube graft can be performed, keeping in mind the all-important goal of producing a live patient at the conclusion of the operation.

Technical Options for Handling Dissected Aortic Tissue

At both the proximal and distal ends of an acute type A aortic dissection, the separated layers of the aortic wall (the "intima" and the "adventitia") need to be reapproximated prior to anastomosis to the prosthetic graft. The pertinent options are illustrated in Figure 7. Some surgeons merely place a circumferential running suture to approximate the layers. Others use biological glue (either the "French" GRF glue or the commercially available BioGlue) to strengthen and bind the layers prior to anastomosis. We prefer the "sandwich" technique, in which we place strips of Teflon felt inside and outside the aortic wall, often supplementing with glue. The felt adds considerably to the strength of the reconstituted aortic wall. We secure the two strips to the reconstituted wall by radially oriented horizontal mattress sutures prior to anastomosis to the main graft.

Technical Options for Formal Aortic Arch Replacement

Should one decide in favor of formal aortic arch replacement, multiple technical options are available for intraoperative management.

Carrel patch of head vessels (Fig. 8A): The aorta can be opened longitudinally along its anterior surface, exposing the origins of the head vessels. These vessels can be mobilized as a Carrel patch. Because this is a dissection case, the layers of the head vessel patch have often been dissected, partially or completely. Care must be taken to reapproximate the layers in the dissected portions, often with a Teflon felt external reinforcement or with a felt inner and outer "sandwich," as described earlier for the proximal and distal aortic anastomoses.

Modified carrel patch (Fig 8B): At our institution (and at certain centers in Japan) we frequently modify our technique for arch replacement from the standard

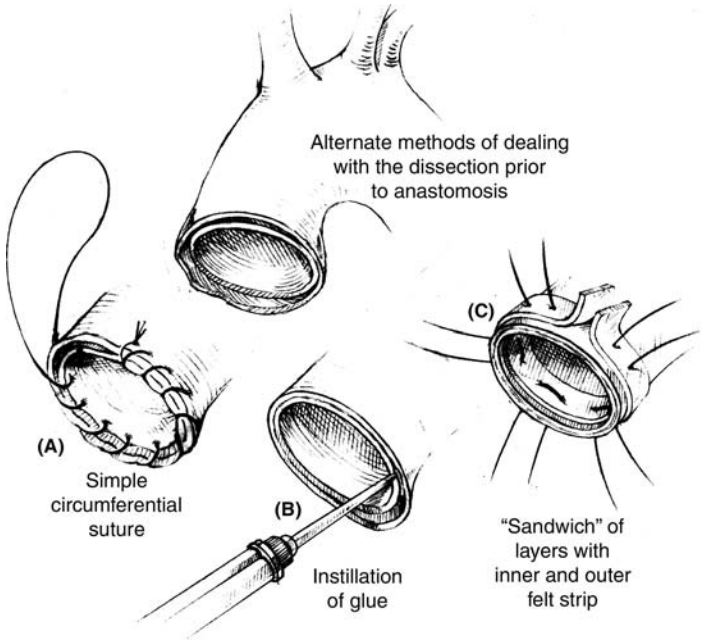

Figure 7 Technical options for preparing debrided ends of the dissected aorta for anastomosis.

mentioned earlier. We do this by confining the Carrel patch to the innominate and left carotid arteries. This makes a more manageable patch, located close to the operator and fully accessible for subsequent hemostasis. This factor of accessibility becomes even more important in the case of acute dissection of the aortic arch, as the dissected aorta is friable, and bleeding can frequently ensue, requiring tension-free exposure and placement of additional sutures. The smaller two-vessel patch meets all of these requirements for accessibility and ease of addition of hemostatic sutures. Also, this smaller patch can be anastomosed in relatively short order, thus decreasing the length of cerebral ischemia and DHCA. After the patient is weaned from bypass, we place a side-arm graft to the subclavian artery, almost as an afterthought. In case of patient instability, the subclavian artery can be simply ligated; ischemic problems would be rare with such a proximal ligation of the subclavian artery, as there are extensive collaterals via the thyrocervical trunk, internal mammary artery, and other routes.

Prefabricated arch grafts (Fig. 8C): In all geographic regions, including Europe, Asia, and North America, prefabricated aortic grafts are now available, with three branches for separate, direct anastomosis of the innominate artery, left carotid artery, and the left subclavian artery. A fourth preformed arm is also available for reinstitution of cardiopulmonary bypass after the distal and arch anastomoses have been completed. These prefabricated grafts can be especially

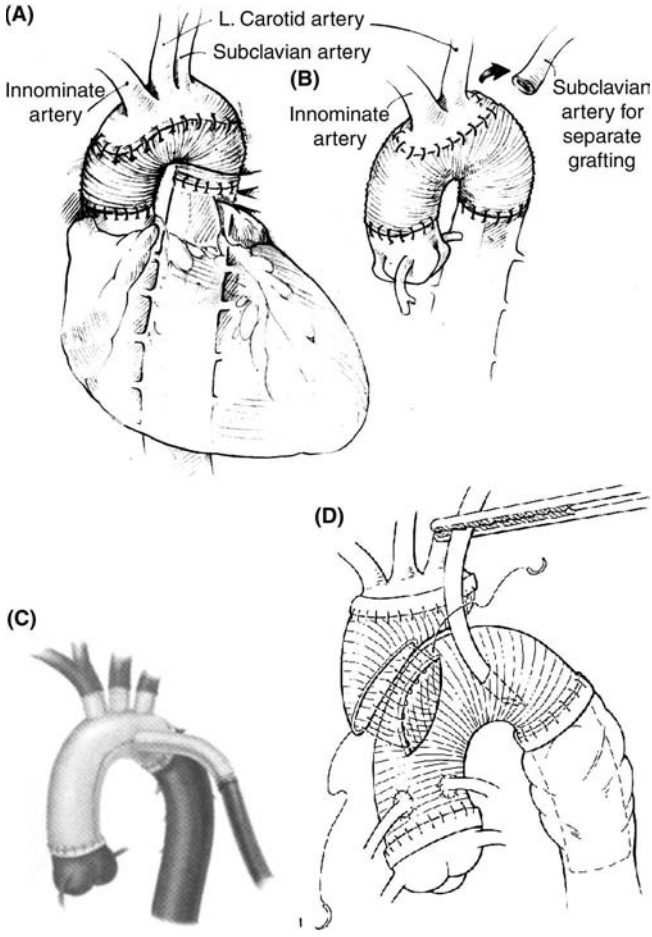

Figure 8 Techniques for arch anastomosis. (**A**) Classic Carrel patch of head vessels (innominate, left carotid, and left subclavian in a single patch). (**B**) Modified carrel patch (only innominate and left carotid in patch, with left subclavian omitted for later, separate grafting). (**C**) Prefabricated arch technique. (**D**) Griepp "arch first" technique.

useful in arch dissection, as the resulting individual branch anastomoses are small, with low tension and quite excellent hemostasis. Also, at the level of the individual arch branches, at least some vessels will be found nondissected, facilitating anastomosis and increasing security. These prefabricated grafts represent a valuable option for the surgeon's armamentarium, in cases of arch dissection.

Nonanatomic grafts (Fig. 7D): The Mt. Sinai team has developed and published a variety of imaginative nonanatomic methods for reconstruction of the aortic arch, based generally on the theme of anastomosis of the head vessels

to a separate vertically oriented graft, which is then secured to the main graft traversing from the ascending aorta to the descending aorta (22). Griepp even constructs the nonanatomic graft first in some cases, to permit brain perfusion via a side-arm from the arterial line. These techniques represent another valuable tool for the surgeon's armamentarium in acute dissections involving the aortic arch.

By applying one of these multiple techniques, the experienced aortic surgeon can accomplish formal arch replacement for the minority of patients who are not adequately served by the hemiarch technique. This minority of patients is usually distinguished by origin of the dissection at an inciting intimal tear in the aortic arch itself. It goes without saying that the surgeon would not even be aware of this situation without the unique opportunity for visualization afforded by the open distal technique.

Chronic Arch Dissection

One more vitally important technical point deserves to be emphasized. It is generally agreed that in acute type A aortic dissection, the two dissected layers should be approximated to obliterate the false lumen. In contrast, for chronic aortic dissection, the two layers should not be approximated, because to do so would risk depriving the vital organs of circulation that has been flowing through the false lumen (Fig. 9). The author has witnessed from other centers the devastating cerebral results consequent upon ignoring this important caveat for chronic arch dissections.

ACUTE DESCENDING AORTIC DISSECTION

We recently reviewed the outcome of 100 consecutive patients with acute descending (type B) aortic dissection treated at our institution (23). This experience provides a useful "snapshot" of the "nature of the beast" of acute descending aortic dissection (Fig. 10). The upshot is that, in most cases, descending aortic dissection is much less morbid than its ascending counterpart. In fact, as can be seen in Figure 10, 91% of patients were discharged from hospital alive after treatment for acute descending aortic dissection.

At our institution, we follow what we call the "complication-specific approach" to acute descending aortic dissection. The cornerstone of this approach is that, absent specific complications, no surgical treatment is required. We simply apply "anti-impulse" therapy, as described earlier in this textbook. Most patients are relieved of their pain and continue to an uneventful recovery and hospital discharge in a week to ten days, after at least one follow-up aortic imaging study demonstrates stability of the dissection.

The development of various complications of acute descending aortic dissection mandates that operation be performed. We predicate the specific operation on the specific complication at hand: Rupture requires traditional

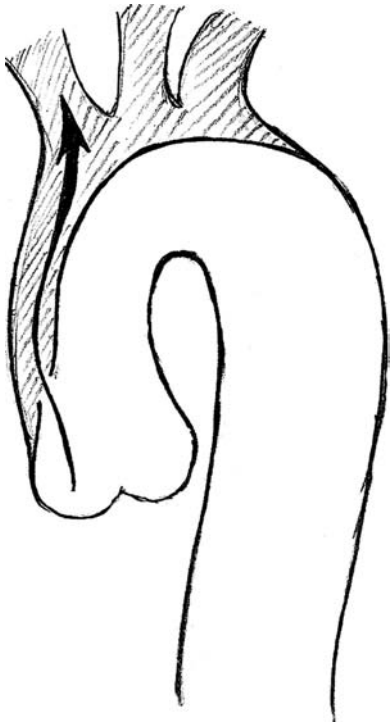

Figure 9 Schematic showing danger of obliterating false lumen in chronic aortic dissection—to do so may obliterate flow to vital organs dependent on the false lumen, including the brain.

replacement of the descending aorta, as described in the chapter on "Rupture" earlier in this textbook. (We often identify a state of "impending rupture," preferring to operate before the patient bleeds internally. This is usually a matter of clinical judgment and experience—with warning signs such as persistent pain, bloody pleural effusion, or small amounts of extravasated contrast on CT scan. Treatment is as for realized rupture.) Uncontrolled pain and rapid expansion of the aorta (on repeat imaging studies) also require operation, which once again should be formal aortic replacement. Organ ischemia is the most common complication, and this also requires operation—urgent operation, in fact, so as to save organs and/or limbs. Here, we prefer an operation different from aortic replacement—namely, the "fenestration" procedure (Fig. 11). Although developed many decades ago, this operation is predicated on the still valid concept that taking the pressure off the false lumen (by creating a wide communication—or "fenestra," Latin for "window"—to drain the false lumen into the true lumen) can restore blood flow to the affected organ (Fig. 12). We have found this procedure, performed quickly and effectively through a retroperitoneal approach, to be extremely effective in

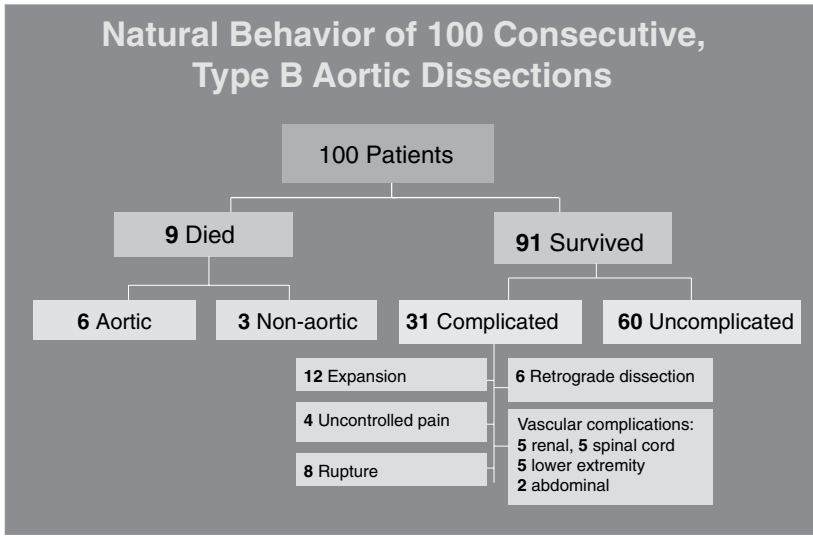

Figure 10 Outcome of 100 acute descending aortic dissections. Note relative benignity of outcome compared to ascending dissection. *Source*: From Ref. 23.

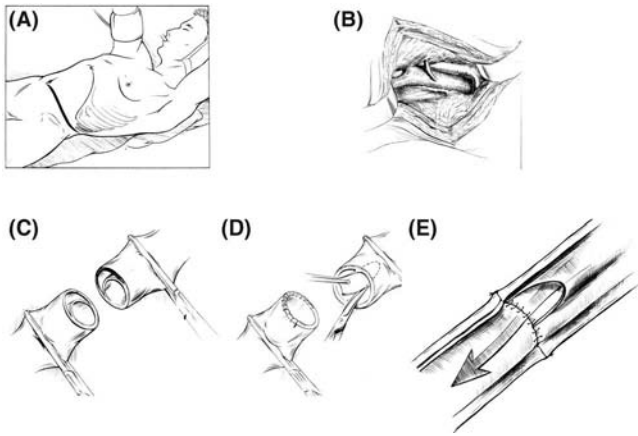

Figure 11 The fenestration operation. A retroperitoneal approach is made (**A**). The infrarenal aorta is exposed (**B**). The aorta is transected (**C**). A large flap is removed from the upper portion (fenestration) (**D**). The distal aorta is reconstituted by reapproximating the dissected layers by simple suture. The two ends of the transected aorta—the upper fenestrated end and the lower reconstituted end—are reattached by running suture (**E**). No graft material is required. No perfusion adjuncts are required.

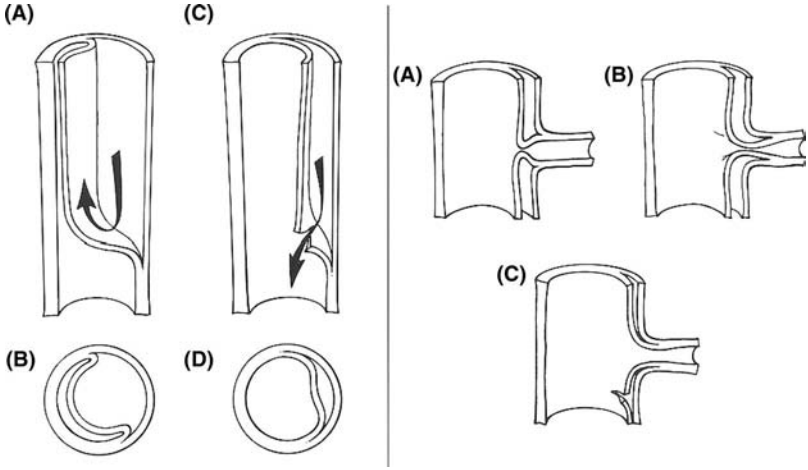

Figure 12 Schematic diagram of mode of benefit from fenestration.

restoring blood flow to affected organs (24,25). This procedure is extremely well tolerated by these very critically ill patients.

Fenestration is especially attractive an option, as early operation on the acutely dissected aorta has traditionally been fraught with high mortality and morbidity. One must remember that the descending aorta has only half the lamellar units of the ascending. In acute dissection, the outer, adventitial, layer has only a small number of lamellae to hold the surgeon's sutures. We found, in examining microscopically many dozens of resected aortic dissection specimens, that within about two weeks, significant fibrosis develops in the dissection plane; we believe this fibrotic process is the reason that surgery after three to four weeks following acute descending aortic dissection is much, much safer—if surgery can possibly be delayed [A very recent publication by the Mt. Sinai group is the first to show improved, in fact excellent, results with early direct operation on the descending aorta (26)]. In many cases, the fenestration may be performed percutaneously by catheter in the present era. We have no objection to such an approach. In fact, there may be a larger role for interventional management of acute descending aortic dissection. The INSTEAD trial is looking at the impact of routine stenting of subacute descending aortic dissections, with the thesis that obliterating the false lumen at the time of occurrence of dissection may have beneficial effects later on—perhaps decreasing the rate of growth of the dissected descending aorta or the onset of late complications (27). Such interventional treatments are covered fully elsewhere in this textbook.

As with chronic ascending aortic dissections, one must never obliterate the false lumen in chronic descending aortic dissections, as organs will be chronically dependent on flow through the false lumen.

CONCLUSION

Acute descending aortic dissection is less lethal than its aortic counterpart, and "anti-impulse" therapy is effective in preserving life. When surgery is necessary, a "complication-specific" approach yields satisfactory results.

Although acute type A aortic dissection remains a serious condition, the safety of operation for this pathologic entity has certainly improved. At experienced aortic centers, mortality for acute type A aortic dissection has dropped to the lowest double digits, approaching the single figures (5). Improvements in surgical experience and technique have certainly been important factors in achieving these excellent results. Other factors include the widespread availability of impregnated grafts, use of activated clotting time nomograms for calculation of protamine doses, advent of effective antifibrinolytic drugs (Amicar and Trasylol), and commercial availability of biologic glues (Bioglue).

Acute aortic dissection remains an extremely serious foe, with wiles that will test even the most experienced operator, especially when the aortic arch is involved. This condition continues to prove the veracity of Osler's pronouncement some 100 years ago (courtesy of Dr. Vincent Gott), "There is no condition more conducive to clinical humility than aneurysm of the aorta."

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DISCUSSION AND COMMENTARY

Questions for the Authors

When selecting an aortic prosthesis in the setting of acute type A dissection, do the usual tenets apply, or is a particular valve more suitable for the acute dissection patient? Similarly, is it valuable, or unnecessary, to avoid the need for anticoagulation in these patients?

Patient survival from the operation and the acute illness is Job #1. So, long-term considerations are secondary.

It is helpful to avoid anticoagulation in patients with acute dissection, although anticoagulation is not entirely contra-indicated. A biological valve certainly has advantages in this regard. However, a biological valve, by virtue of its higher profile, may be more cumbersome to seat in the proximal aorta that has been or will be reconstructed with a Teflon "sandwich." A low-profile mechanical valve has an advantage in this regard. The bottom line, then, is for the surgeon to choose the valve that will make his operation the most expedient and secure.

If a composite graft is required, the choice will usually be for a pre-fabricated mechanical valved conduit. In the acute setting, there will usually not be time to make a biological valved conduit on the field. No pre-fabricated biological valved conduits are currently available commercially in the United States.

Is it safe to use biological glue in the distal aortic sandwich, near the head vessels?

This question is very well taken. We use extreme care in application of glue inside the aorta. However, in the case of the sandwich, the glue is separated from the lumen by the inner layer of the dissection. Also, a huge clinical experience, both in Europe and in the United States, supports the safety of construction of a Teflon "sandwich" with a biological glue for layer reapproximation and aortic wall reconstitution.

16

Endovascular Thoracic Aortic Stent Grafting in Acute Aortic Catastrophes

Derek R. Brinster

Division of Cardiothoracic Surgery, Virginia Commonwealth University Medical Center/Medical College of Virginia, Richmond, Virginia, U.S.A.

Wilson Y. Szeto and Joseph E. Bavaria

Division of Cardiac Surgery, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania, U.S.A.

INTRODUCTION

Thoracic aortic endovascular repair (TEVAR) has been shown to be an effective treatment for many thoracic aortic conditions over the past few years. Although there is no long-term data about the effectiveness of this radical and revolutionary new therapy, the intermediate results have been promising. Interestingly, while the initial applications of TEVAR have been in the elective treatment of thoracic aortic conditions, TEVAR may have its most profound benefit in the catastrophic presentations associated with acute aortic conditions. It is in the acute aortic condition that standard operative treatment has the highest mortality and morbidity rates.

It may be difficult to prove that TEVAR is actually superior to elective open surgery for aneurismal disease because elective open surgery in the modern era is quite successful. The same dilemma is true when comparing endovascular repair of the abdominal aorta (EVAR) to standard open abdominal aortic aneurysm (AAA) repair, as vascular surgeons have perfected open AAA repair with overall mortality rates between 2% and 4% in most large published series.

TEVAR utilized in acute aortic presentations most probably will not suffer from this ambiguity, as most acute thoracic aortic conditions, such as ruptured

thoracic aneurysm, ruptured thoracic aortic dissection, branch artery malperfusion in the setting of acute aortic dissection, and acute traumatic transection, have such high medical and surgical morbidity and mortality rates that a minimally invasive and anatomically successful treatment will be obviously beneficial.

ANATOMICAL REQUIREMENTS FOR STENTS/TECHNICAL ASPECTS

Anatomical requirements and key technical considerations for successful TEVAR revolve around answering the question: What makes a patient a suitable anatomical candidate for a thoracic aortic stent graft? The most important considerations are listed in Table 1.

The initial assessment of a stent graft candidate begins with the preoperative workup and evaluation. Key points of the history and physical exam should include a detailed neurological and cardiovascular exam. Distal vascular pulses and preoperative neurological deficiencies must be documented. Any previous abdominal, pelvic, and inguinal surgeries should be noted. Previous surgery may demand an alternate access route.

Extensive preoperative planning with appropriate imaging is mandatory. The "gold standard" for preoperative evaluation is a computed tomography (CT) angiogram, which includes the thorax, abdomen, pelvis, and femoral arteries. Fine cut helical CT scanning with minimum of 3 mm slices is ideal. Medical metrix systems (MMS, Lebanon, NH) reconstruction into a 3-D image allows accurate assessment of the thoracic aorta and iliofemoral access. In those patients who cannot receive a CT with contrast, magnetic resonance angiography is an acceptable substitution.

Access

Safe access for thoracic aortic device deployment is the key to thoracic aortic stent grafting. The majority of morbidity and mortality is a direct result of arterial access complications (1). All thoracic endovascular devices are long (so as to reach the

Table 1 Important Anatomical Considerations When Considering Thoracic Endovascular Aortic Repair

Iliofemoral and peripheral access
Suitability of the proximal and distal landing zones
Diameter
Intramural thrombus considerations
Tapering
Calcification
Aortic wall integrity e.g., Marfan's, IMH, acute dissection
Distal aortic arch angulation (radius of curvature)
Thoracic aortic tortuosity
Branch vessel considerations
Left subclavian artery bypass

descending aorta), of large caliber (to contain the thoracic aortic endoluminal graft), and relatively stiff (to allow "pushability" through the ileo-femoral access points and through the abdominal aorta). The management of delivery of the thoracic aortic stent graft is often the most challenging aspect of the case.

Delivery systems of the current FDA approved Gore TAG (W. L. Gore Flagstaff, A2) graft require sheaths ranging in size from 22 Fr to 24 Fr outer diameter. Other devices, which have not been FDA approved, have similar size requirements for arterial access, either with or without sheaths. Therefore, arterial access size must be 7.5–8.0 mm ID to be considered as a conduit.

Not only the size of the arterial vessels but the anatomy of the ileo-femoral and abdominal aorta must be considered when planning the access route. Excessive tortuosity and atherosclerosis with occlusive disease may provide barriers to safe delivery of the endograft. In approximately 20% of patients, retroperitoneal access to the common iliac arteries will be required due to issues of femoral or external iliac artery size and/or tortuosity (2,3).

Careful review of preoperative studies will indicate which patients will have difficult access. Patients with atherosclerotic occlusive iliac disease may be treated with standard endovascular balloon angioplasty techniques to reduce the obstruction. Iliac stents should be avoided due to the potential interference of these stents with the thoracic aortic access devices. These procedures on the access vessels should be carried out at least six weeks before thoracic aortic stent grafting to allow healing of the iliac postangioplasty and manipulation. At the completion of thoracic aortic endografting, iliac stents may be placed if appropriate.

Access to the retroperitoneum allows several options for safe device deployment. The common iliac artery may be used for device deployment. An open surgical conduit can be constructed via an end-to-end anastomosis or a side-to-side anastomosis. A 10 mm Dacron conduit is commonly used and allows ample size for insertion of all necessary devices. The conduit may be brought through a separate counter-incision in the groin to allow better angulation of the relatively long and stiff deployment devices. At the conclusion of the procedure, these conduits may be used to revascularize distal obstructions if needed (Fig. 1A) (4).

Alternatively, the retroperitoneal iliac vessels or even the distal aorta may be accessed using direct sheath insertion. A double pursestring of 4–0 Tycron is used to secure the vessel and provide hemostasis with the application of two sets of tourniquets. Direct needle puncture of the artery is followed by dilation and insertion of the device. At completion, the device is removed and the pursestring sutures are tied down (Fig. 1B) (4). Excessive tortuosity of the ilio-femoral arteries requires adaptive strategies. The use of external manual manipulation provides a simple method of straightening some of the tortuosity of the aorta and iliac arteries. During fluoroscopy the operator's hand can provide gentle force to the tortuous arterial segment to allow straightening and subsequent endovascular access.

In cases of iliac artery tortuosity, advanced endovascular techniques may aid in straightening these segments. The use of stiff wires or buddy wire techniques can provide some degree of straightening of the diseased arteries. In severe cases

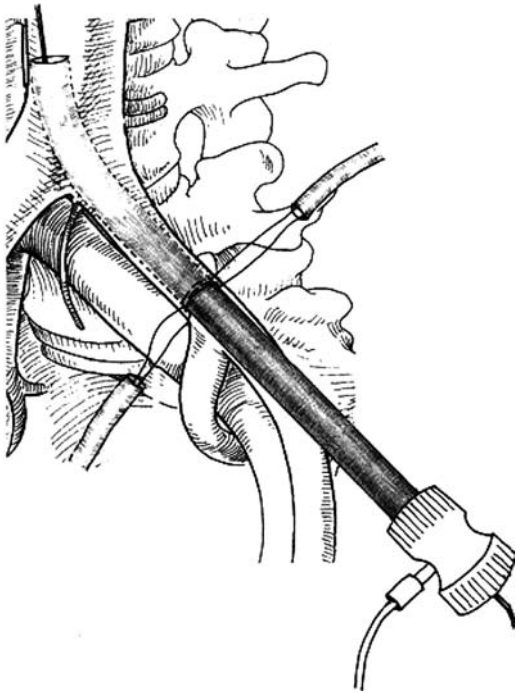

Figure 1 Retroperitoneal access of common internal iliac using double pursestring and Seldinger technique. *Source*: From Ref. 127.

of tortousity, brachiofemoral access may be required to perform "body-flossing" with an appropriately stiff wire. Typically, a 5 Fr sheath with a long catheter is placed into the aortic arch and then into the descending aorta. A long stiff wire, such as a 450 cm SS Guidewire (Boston Scientific), is guided from the brachial and retrieved through the femoral artery. Gentle traction on both the brachial and femoral sites will straighten out the tortuosity. Of note, a long catheter must be placed through the brachial artery into the aorta to prevent excessive trauma by the stiff wire along the arch and innominate vessels.

At the completion of the deployment and ballooning of the thoracic stent graft, the entire route of access must be carefully examined to ensure that there has been no injury. The stiff guidewire used to position the thoracic endograft, should be left in place as the sheaths and remaining endovascular materials are removed. A smaller sheath should be reinserted and the iliac vessels should be retrogradely injected to check for thrombus, dissection, or complete avulsion.

The removal of the large sheath, especially when inserted with some force and manipulation, is a particularly dangerous period when injury may occur. There have been numerous reports of successful thoracic endografting with a sheath removed having a complete iliac artery avulsed on the sheath (Fig. 2). At the time

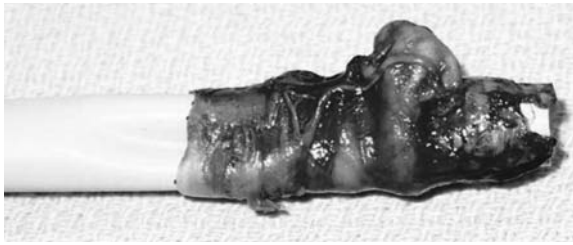

Figure 2 "Iliac on a stick." Figure of large sheath with avulsed external iliac which occurred after successful stent deployment.

of recognition, a stiff wire through this injured artery may be life saving, allowing insertion of an occluding balloon proximally to control potentially life threatening bleeding. In addition, both the blood pressure and heart rate should be carefully monitored during removal and completion of the endovascular procedure for signs of an occult injury.

Landing Zones

The proximal aorta is divided into landing zones as illustrated in Figure 3. Proximal landing in Z0 and Z1 are unacceptable due to the necessary occlusion of the left common carotid artery in Z1 and the innominate artery in Z0. Proximal landing in Z2 is commonly used with either partial or total occlusion of the left subclavian

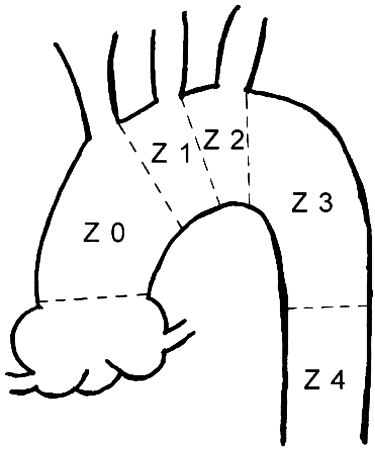

Figure 3 Proximal landing zones of the aorta. Z0: ascending aorta to the distal aspect of the innominate artery origin. Z1: distal to the innominate artery origin including the left common carotid artery origin. Z2: distal to the left common carotid artery origin including the left subclavian artery origin. Z3: proximal third of the descending thoracic aorta distal to the left subclavian artery origin. Z4: remainder of the supradiaphragmatic descending thoracic aorta. *Source*: From Ref. 67.

artery. Z3 landing is dependent on the exact anatomical neck at the arch. Proximal landing in Z3 can lead to angulation of the graft, which provides inadequate sealing of the proximal graft along the lesser arch and "bird beaking" or "stove piping" graft placement, with resultant high incidence of type II endoleaks (Fig. 4). Z4 landing is usually straightforward due to the lack of angulation and distance from the arch vessels.

Presently, the proximal and distal landing zones must be of an appropriate diameter to allow for stent grafting with available devices. The safe aortic diameter at the time of this writing is between 19 mm and 43 mm depending on the different devices available. Generally, devices can be oversized (compared to the diameter of the landing zone) between 5% and 18%, depending on presenting aortic pathology.

As discussed, the proximal landing zone of the aorta must be carefully examined on preoperative imaging workup. The goal is to create a good seal of 15–20 mm length between the graft and the aortic wall on a disease-free, nontapered, nonangulated portion of the aorta. There should be adequate length of the proximal landing zone, minimal angulation, minimal tortuosity, and minimal calcification (Fig. 5). Angulation of the aortic arch is acceptable if the inner radius is >35 mm and the outer radius is >70 mm (Fig. 6). These parameters allow adequate conformation of the aortic stent graft to the arch.

Since Z2 is often the site of best proximal landing to avoid excessive angulation and tortuosity, the management of the left subclavian artery requires preoperative planning. Possible complications of covering the left subclavian artery include verterbrobasilar artery insufficiency or stroke, left arm ischemia,

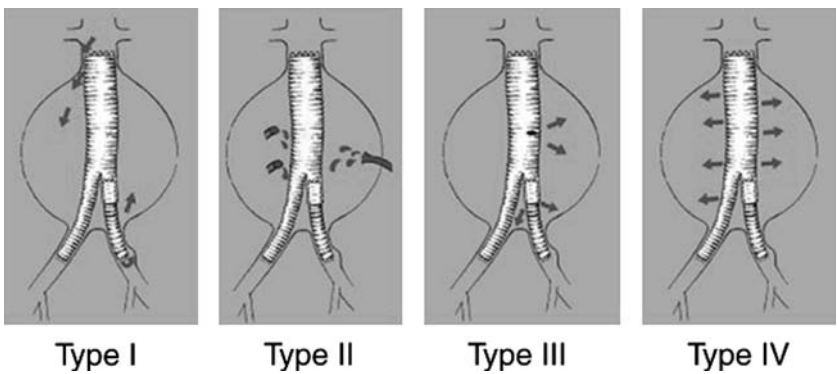

Figure 4 Type I endoleak (periprosthetic) occurs at the proximal and/or distal attachment zones. Type II endoleak is caused by retrograde flow from patent lumbar or inferior mesenteric arteries. Type III endoleak arises from a defect in the graft fabric, inadequate seal, or disconnection of modular graft components. Type IV endoleak is due to graft fabric porosity, often resulting in a generalized mild blush of contrast within the aneurysm sac. *Source*: From Ref. 128.

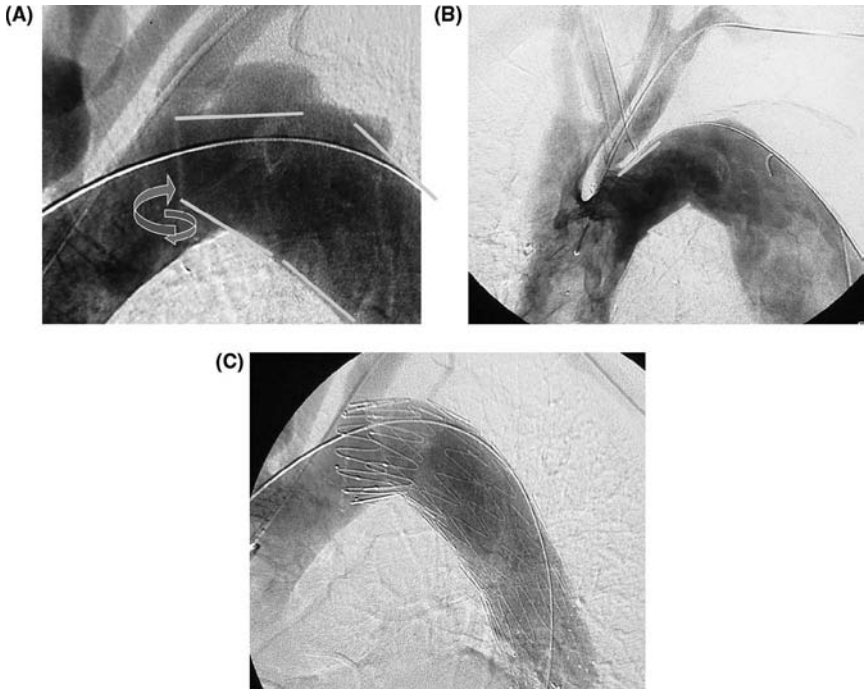

Figure 5 (**A**) Angiogram and diagram of angulated arch without suitable proximal landing zone with high risk of Type I endoleak from "stove piping" of the graft (*arrows*). (**B**) Angiogram, which demonstrates a longer proximal landing zone without excessive angulation. (**C**) Successful stent graft placement in proximal landing zone with no endoleak.

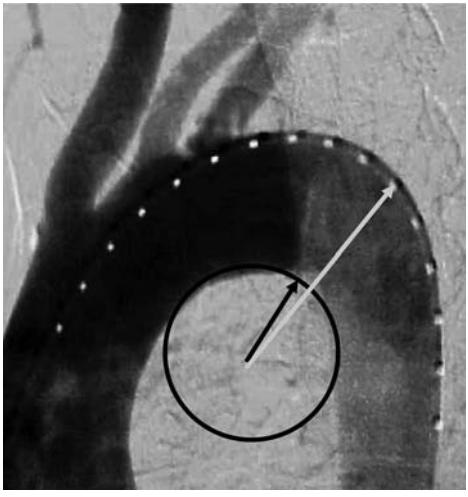

Figure 6 Inner radius should be <35 mm and outer radius >70 mm.

or ischemia of the heart in patients with a previous left internal mammary artery to left anterior descending coronary artery bypass graft.

An evaluation of the right vertebral artery and the adequacy of the circle of Willis are crucial when planning to cover the left subclavian artery. In those patients with inadequate collaterals through the circle of Willis, a stenotic right vertebral artery, or a dominant left vertebral artery, strong consideration should be made to bypass the left subclavian artery prior to covering. One option is to transpose the left subclavian artery to the left common carotid artery with oversewing of the proximal left subclavian artery. Another option is to bypass from the left common carotid artery to the left subclavian artery with an 8 mm Dacron graft. Either surgical ligation of the proximal left subclavian at the time of bypass or staged coil embolization of the proximal left subclavian artery at the time of graft delivery may be used. Bypass of the left subclavian may be preferable because it avoids any mediastinal dissection and there is no interruption of antegrade flow to the vertebral artery or internal mammary artery branch vessels (Fig. 7).

Evaluation of the distal landing zone also requires careful preoperative workup. The distal landing zone should again have 15–20 mm of normal aorta with minimal calcification, angulation, and tapering. The celiac artery is the first distal branch vessel that must be avoided. Therefore, the length of the aortic graft must be correctly planned. Enough graft length should cover the aortic pathology while avoiding excessive coverage of the descending thoracic aorta. The goal is to preserve the distal intercostal arteries and perfusion to the spinal cord. When planning the length of the graft, the outer curvature of the aorta is assumed to be the correct area to measure (Fig. 8). However, the graft may lie along the lesser curvature instead. Therefore, a strategy must be developed to select a graft, which will be able to work in either the greater curvature or lesser curvature.

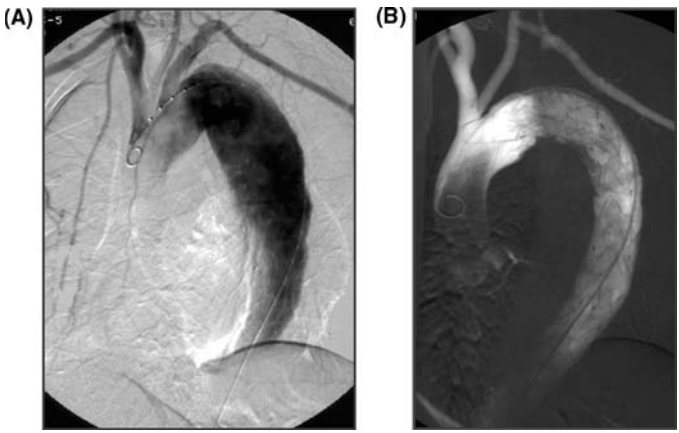

Figure 7 (**A**) Image prior to translocation of left subclavian artery. Note the inadequate length of proximal landing zone. (**B**) Same patient after translocation of left subclavian artery to the left common carotid artery and status post successful stent graft placement.

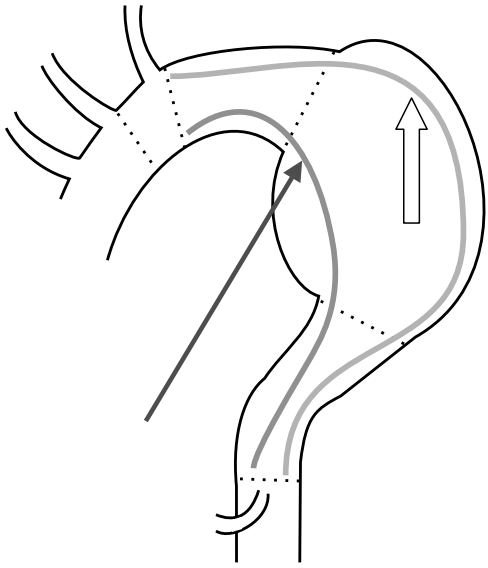

Figure 8 Demonstration of the possible maximum (*hollow arrow*) and minimum (*long solid arrow*) course that stent graft may be positioned.

RESULTS OF TEVAR IN DESCENDING THORACIC AORTIC ANEURYSMS

Three United States clinical trials have examined the use of endovascular aortic stent graft technology in the treatment of descending thoracic aortic aneurysms. The three devices (Medtronic Talent, Gore TAG, and Cook Zenith TX2) have also been used extensively worldwide. Results from the U.S. clinical trials as well as results from the worldwide experience have been encouraging, prompting investigators to expand the role of TEVAR to acute thoracic aortic pathologies. The three U.S. trials will briefly be discussed.

VALOR Trial

The Medtronic VALOR trial is a prospective, multicenter, nonrandomized, observational trial evaluating the use of the Medtronic Talent thoracic stent graft system in the treatment of thoracic aortic pathology. One-year data for the VALOR trial is expected soon. The trial consists of three groups: (*i*) the test arm, (*ii*) the registry arm, and (*iii*) the high-risk arm. The test arm consists of patients with the diagnosis of thoracic aortic aneurysms who are considered surgical candidates for traditional open repair with low to moderate risk [based on society of vascular surgery (SVS)/ international society of cardiovascular surgery (ISCVS) criteria]. At least 20 mm of normal aortic neck at the proximal and distal landing zone is required. Enrollment of 195 patients is complete, and one-year follow-up data (rate of mortality and successful aneurysm treatment) is awaiting accrual prior to FDA disclosure. The

registry arm (27 patients) included patients considered to be open surgical candidates with low to moderate risk but either proximal or distal neck less than 20 mm in degenerative aneurysm, chronic pseudoaneurysm, or chronic dissection.

The results of the high-risk arm were recently presented at the SVS annual meeting (June 2005, Chicago, U.S.A). This arm consists of SVS group 3, or nonsurgical, candidates with thoracic aortic pathology including degenerative aneurysms (82%), chronic dissection with aneursymal formation (9%), pseudoaneursym (9%), traumatic injury (6%), and complicated type B dissection (4%). A total of 150 patients were accrued in this arm with a mean age of 73. Procedural success rate was 98%, with a 30-day mortality of 8.4%. The incidence of neurologic complication was 8% for stroke and 5.5% for paraplegia. At one and six months, the endoleak rate was 12% and 10% respectively, with a secondary reintervention rate of 2.8% at six months. In this arm, 15% of patients required surgical placement of a conduit for arterial access for device deployment. The clinical experience with the Talent device worldwide as well as in the VALOR trial has been summarized in Table 2.

TAG Trial

The Gore TAG 99-01 trial is a Phase II, U.S. multicenter investigation comparing the Gore TAG endoprosthesis (W.L. Gore, Flagstaff, Arizona, U.S.A.) in the treatment of descending thoracic aortic aneurysms to an open surgical control group. Between September 1999 and May 2001, 140 patients with descending thoracic aortic aneurysms were enrolled from 17 sites in the United States. All patients were required to have at least 2 cm length of nonaneurysmal aorta distal to the left carotid and proximal to the celiac axis. At the same centers, the open surgical control cohort enrolled 94 patients. Forty-four patients were concurrent controls and 50 were historically and retrospectively acquired by selecting the most recent surgical patients in reverse chronological order.

The results are summarized in Table 3. Thirty-day mortality was 2.1% and 11.7% in the Gore TAG group and the open surgical control group, respectively. Spinal cord ischemia was 2.9% in the Gore TAG group versus 13.8% in the control group. The mean length of intensive care unit stay and total length of hospital stay were significantly shorter in the Gore TAG group (5).

STARZ-TX2

The study of thoracic aortic aneurysm repair with the Zenith-TX2 (STARZ-TX2) trial is a nonrandomized, open label, efficacy study evaluating the safety and effectiveness of the Cook Zenith TX2 (Bloomington, Indiana, Massachusetts, U.S.A.) endoprosthesis in the treatment of thoracic aortic aneurysms. The primary outcome of the study is 30-day survival. Enrollment began in March 2004 with an expected enrollment of 275 patients. The trial is currently ongoing. The study is near completion with closure of the trial expected soon.

In summary, TEVAR is an evolving technology for the treatment of thoracic aortic pathology. Preliminary data demonstrate that the short- and mid-term outcomes

Table 2 Summary of Medtronic Talent Experience

Author	Total patients	Mean follow up (months)	Patients with TALENT	Procedural success rate (%)	Paraplegia (%)	Endoleak	Reintervention	30-Day mortality (%)	Survival
VALOR (high-risk group)	150	12	150	98	5.5	10% at 6 mos	2.8% at 6 mos	8.4	—
TTR	457	24	457	98	1.7	9.6%	8% at 1 yr, 19% at 3 yrs, 30 at 5 yrs	5	91% at 1yr, 85% at 3 yrs, 77%at 5 yrs
Zipfel (2006)	172	—	123	92	1	—	—	9.7	—
Appoo (2005)	99	—	63	100	2	23%	10%	5	85% at 1yr, 71% at 3 yrs, 52% at 5 yrs
Criado (2005)	186	40	186	96.7	4.3	15% at 30 days	15%	4.7	62.5% at 40 mos
Farber (2005)	22	12.5	19	100	9	4%	—	4.5	—
Riesenman (2005)	50	9	45	96	0	20%	14%	8	79.4% at 3 yrs
Scheinhert (2004)	31	15	29	100	0	0%	0%	9.7	90% at 17 mos
Fattori (2003)	70	25	67	97	0	7%	4%	8	91% at 25mos
Ellozy (2003)	84	15	62	90	4	5%	—	6	67% at 40 mos
Herold (2002)	34	8	33	100	0	0%	—	2.9	88.7% at 8 mos

Table 3 Early Postoperative Outcomes (Gore TAG 99–01)

	Endovascular (%)	Open surgical	*P*-value
Mortality–30-day or in hospital	2.1% ($n=3$)	11.7% ($n=11$)	<0.001
Respiratory failure[a]	4%	20%	<0.001
Post op MI	0%	1%	0.40
Renal failure[b]	1%	13%	<0.04
Wound infection/dehiscence	4%	11%	0.07
GI complication (ileus, bowel ischemia, or bowel obstruction)	2%	6%	0.16
Peripheral vascular complications[c]	14%	4%	0.015
Neurologic complications			
CVA	4% ($n=5$)	4% ($n=4$)	1.00
Paraplegia/paraparesis	3% ($n=4$)	14% ($n=13$)	<0.003
Mean ICU length of stay (days)	2.6±14.6	5.2±7.2	<0.001
Mean length of hospital stay (days)	7.4±17.7	14.4±12.8	<0.001

[a]Mechanical ventilation >24 hrs post op or need for reintubation.
[b]≥30% rise in base line creatinine level.
[c]Includes embolism, thrombosis, and vascular trauma.
Source: From Ref. 5.

with both the Medtronic Talent and Gore TAG endoprosthesis compare favorably with the conventional open repair for the treatment of descending thoracic aortic aneurysm. The results of the STARZ-TX2 trial are not available yet. However, worldwide experience with the Zenith TX2 endoprosthesis has been equally encouraging. The durability of TEVAR remains unclear. Further investigation with long-term followup comparing TEVAR and conventional surgical repair is needed before definitive conclusions can be made.

ACUTE AORTIC SYNDROME

Although TEVAR for elective repair of descending thoracic aortic aneurysm has been performed worldwide with increasing frequency, it is the potential role of TEVAR in acute thoracic aortic pathologies that has gathered increasing interest and fits most closely with the subject matter of this book. Through recent surgical advances, morbidity and mortality with elective conventional surgical repair of thoracic aortic aneurysms has been reduced to acceptable levels. However, mortality for emergent thoracic aortic pathologies remains substantial. The minimally invasive nature of TEVAR renders this a potentially attractive surgery for this high-risk group of patients. The emerging role of TEVAR for acute aortic diseases is discussed in the following section.

Type A Dissection

Ascending aortic dissection (Stanford type A), is the most common lethal aortic condition requiring emergent surgical management (6–9). The estimated worldwide

prevalence is 0.5 and 2.95 per 100,000 per year. In the United States, it is estimated that the prevalence is between 0.2 and 0.8 per 100,000 per year, resulting in approximately 2000 new cases per year (10). These estimates may be low, with one autopsy series demonstrating the antemortem diagnosis was made in only 15% of patients (11). Analysis that takes this factor into account results in an estimate of approximately 6000 new cases per year in the United States.

The standard of care for the treatment of type A aortic dissection is surgical therapy. The present surgical strategy is designed to prevent (*i*) rupture, (*ii*) heart failure related to acute aortic valve insufficiency, (*iii*) coronary malperfusion, and (*iv*) cerebral malperfusion, or stroke. Recent advances in surgical management of acute type A dissection have resulted in significantly lower morbidity and mortality. Recent series demonstrated mortality rates ranging from 9% to 25% (12–19). Five-year survival following type A dissection repair ranges from 71% to 89% (13,17,20).

Proximal operative strategy (i.e., the choice of surgical technique for managing the proximal end of the dissection) does not appear to have significant impact on morbidity and mortality. Driever et al. (17) noted no difference in survival or stroke rate when comparing aortic valve replacement (AVR) with supracoronary ascending aortic replacement and valve resuspension with supracoronary aortic replacement at five and 10 years. Lai et al. (16) similarly reported no difference in six year survival between patients treated with composite valve conduit (65%), AVR and supracoronary replacement (45%), and valve resuspension and supracoronary aortic replacement (69%). In the largest reported single-center experience (295 patients treated between 1990 and 2003 for acute type A aortic dissection), Kallenbach et al. (13) showed no difference in outcome with respect to mortality, neurological complications, and five year survival when comparing composite valve conduit, supracommissural replacement, and valve-sparing aortic root replacement.

Due to the improved surgical outcome and the inherent complexity of proximal repair, the application of endovascular aortic stent graft therapy has been limited in acute type A dissection. A few case reports have demonstrated feasibility of endovascular repair of type A dissection in a very small number of patients (22–24). The role of endovascular stent graft therapy in the treatment of acute type A dissection remains unclear.

In an adjunctive role, investigators have reported the concomitant use of an aortic stent graft in the descending thoracic aorta during conventional open type A dissection repair—in an effort to obliterate the distal thoracic dissection and prevent chronic aneurysmal dilatation. The long-term results of these "hybrid" procedures remain to be determined.

Type B Dissection

Although there is consensus that ascending aortic dissections should be managed by urgent surgical repair, controversy currently exists regarding the optimal therapeutic strategy for descending thoracic aortic dissections (Stanford type B).

According to the International registry of acute aortic dissection (IRA) (25), uncomplicated type B dissection treated with medical therapy is associated with a mortality rate of 10.7%. However, up to 20% of patients with type B dissection develop complications (i.e., rupture, malperfusion) requiring surgical intervention (25). Surgical management of acute type B dissection is associated with significant mortality rates, ranging from 30% to 50% (13,25,26). The management of complicated and uncomplicated type B dissection and the potential role of endovascular therapy will be discussed separately.

Uncomplicated Acute Type B Dissection

The majority of patients with acute type B dissections present without complications (i.e., rupture, malperfusion, or hemodynamic instability). Uncomplicated type B dissections have traditionally been managed successfully with anti-impulse medical therapy, demonstrating low morbidity and mortality rates. In contrast, emergent open surgical repair of acute type B dissections has historically been associated with significant morbidity and mortality.

Although medical therapy of type B dissections is associated with good early outcomes, long-term outcome and survival of patients with type B dissection remain disappointing. Umana and coworkers recently reported a retrospective study of 189 patients with type B dissections followed over a 36-year period. Acutuarial survival for all patients was 71%, 60%, 35%, and 17%, at 1,5,10, and 15 years, respectively, regardless of medical versus surgical therapy. There was also no difference in the freedom from reoperation and freedom from aortic-related complications between the two groups. Other series comparing long-term outcomes between medical and surgical management of patients with type B dissections have demonstrating similar results (27–30).

The poor long-term outcome of uncomplicated type B dissection is a result of the predisposition of these patients to develop aneurysmal dilatation of the thoracoabdominal aorta (31). Contemporary series have reported the incidence of aneurysmal dilatation to be upwards of 80% over a five-year period (32,33). Persistent patency of the false lumen has also been shown to be a strong predictor of both the formation of distal aneurysmal dilatation (31) and mortality (34,35). The reported rate of aneurysmal degeneration of residual dissections in the thoracic aorta with a patent false lumen averages 4.1 mm per year (36), and its risk of rupture becomes significant at 6 cm in diameter (37). The absence of a false lumen in the descending aorta decreases the incidence of aneurysmal formation and the need for distal operation, with an increase in late survival rate (31).

Surgical intervention to address the resulting chronic aneurysmal type B dissection is equally unsatisfactory and is associated with significant morbidity and mortality. The morbidity and mortality associated with the standard open repair of all thoracoabdominal aneurysms, including nondissecting aneurysms, approach 8% to 15% in an age dependent manner (37–42). Recent series have reported significant perioperative morbidity, including stroke, spinal cord injury, renal dysfunction, and pulmonary insufficiency, and mortality rates as high as 20% to

25% (37,39–43). In our own institutional experience, complications of surgical repairs of chronic aneurysmal type B dissections are much higher when compared to nondissecting aneurysms, with mortality rate approaching 30% (44,45).

Given the disappointing long-term results of both medical and conventional open surgical repair of type B dissection, there has been interest in the use of TEVAR in the treatment of uncomplicated acute type B dissection. The rationale for the use of TEVAR in type B dissections is based on the concept that that obliteration, or thrombosis, of the false lumen may result in improvement in long-term outcome and survival (31). Closure of the primary tear site of a type B dissection may promote decompression of the false lumen, with subsequent reestablishment and stabilization of the true lumen of the aorta, a process of so called "aortic remodeling" (Fig. 9).

The first reported use of TEVAR in type B dissections was in 1999. Dake and coworkers reported a series of 19 patients undergoing TEVAR for acute aortic dissections. Fifteen patients had acute type B aortic dissections. Complete thrombosis of the thoracic aortic false lumen was achieved in 15 patients (79%), with a 30-day mortality of 16%. In the followup period of 13 months, there was no death (46).

Many other investigators have reported favorable short-term results, with complete and partial obliteration of the false lumen in type B dissections, demonstrating stabilization of the descending aorta in up to 75% of patients (20,47–52). Kusagawa et al. (47) reported a series of 49 patients with type B dissections (32, acute; 17, chronic). The mean followup period ranged from four months to six years. In the acute dissection group, the false lumen decreased from an average of 16 to 3 mm at two years after treatment. In 76% of the patients, the false lumen of the thoracic aorta completely disappeared after two years. The results were less dramatic in the chronic group.

Dialetto et al. (48) reported a series of 56 patients with type B dissections treated either medically ($n = 28$) or with aortic stent grafts ($n = 28$). Follow-up

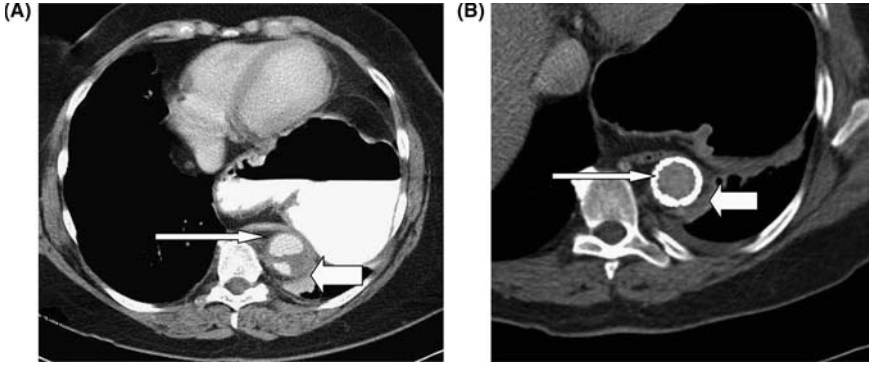

Figure 9 Remodeling of type B dissection. (**A**) True lumen with narrow arrow and false lumen with wide arrow. (**B**) After thoracic endovascular aortic repair on followup visit demonstrating resolution of false lumen.

ranged from 1 to 61 months with 100% followup. In-hospital mortality was 10.7% with no incidence of spinal cord ischemia. Followup CT scans demonstrated complete thrombosis of the false lumen in 75% of patients treated with TEVAR, as compared to only 10.7% of patients in the medically treated group. Aneurysmal dilatation of the descending aorta was seen in only 3.5% of patients treated with TEVAR, as compared to 28.5% of patients in the medically treated group.

Eggebrecht and coworkers recently reported a meta-analysis of TEVAR for patients with type B dissections (Table 4). Thirty-nine studies were included, with a total of 609 patients. The mean follow-up period was 19.5 months. The mean procedural success rate was 98.2% with a complication rate of 11.1%. Neurologic complication was 2.9%, with stroke at 1.9% and paraplegia at 0.8%. Overall, complications were statistically higher in patients with acute type B dissection (21.7%) when compared to chronic type B dissection (9.1%). The 30-day mortality in the acute and chronic dissection groups were 9.8% and 3.2%, respectively. False lumen thrombosis was seen in 75.5% of patients. Late surgical conversion was required in 2.5% of patients. Endovascular reintervention with TEVAR was necessary in 4.6% of patients. Overall survival by Kaplan–Meier analysis was 90.6%, 89.9%, and 88.8% at six months, one, and two years, respectively (49).

In summary, short-term results of TEVAR for the treatment of type B dissection are promising, demonstrating early evidence of false lumen thrombosis and aortic remodeling. However, longer followup with more definitive evidence will be needed before conclusions can be drawn. The current INSTEAD trial will further characterize the role of TEVAR in acute type B dissections (53). Designed as a multicenter, randomized trial in Europe, the purpose of the study is to compare the outcomes of uncomplicated type B dissections treated by: (*i*) TEVAR (Medtronic Talent device) adjunctive to anti-impulse therapy, or (*ii*) anti-impulse therapy alone. The study period is two years with the primary outcome measure as all-cause mortality. Secondary outcomes include conversions to TEVAR or surgery, false lumen thrombosis, cardiovascular morbidity, rate of aortic dilatation, quality of life, and length of ICU and hospital stay. One hundred twenty five patients were enrolled and randomized by December of 2004, with a target of 136 patients in the study design. Final results of the trial are expected soon.

Complicated Acute Type B Dissection

Complicated acute type B dissections (with rupture, malperfusion, refractory pain, or rapid aortic expansion) represent only approximately 20% of patients with acute descending aortic dissection (25). However, surgical management of this specific population of patients has been challenging, with significant mortality rates ranging from 30% to 50% (13,25,26). The early success of TEVAR for aneurysmal disease has prompted investigators to examine the role of this new technology for complicated acute type B dissections.

There are a few small series reporting the role of TEVAR in the treatment of type B dissections in the acute setting (within 48 hours). Duebener et al. (54)

Table 4 Meta-Analysis of Tevar for Patients with Type B Dissections

Author	Year	Patients with AD (*n*)	Proc. success (*n*)	Emergency conversion (*n*)	Overall complications (*n*)	Major complications (*n*)	Overall neurologic complications (*n*)	Paraplegia (*n*)	30-day mortality (*n*)	Late surgical conversion (*n*)	Aortic rupture during follow-up (*n*)	Late mortality during follow-up (*n*)
Dake (5)	1999	19	19/19	0	4	3	0	0	3	0	0	0
Nienaber (6)	1999	12	12/12	0	0	0	0	0	0	0	0	0
Czermak (10)	2000	7	6/7	0	2	2	0	0	0	1	0	1
Hausegger (11)	2001	5	5/5	0	1	0	0	0	0	0	0	0
Kang (12)	2001	6	6/6	0	0	0	0	0	0	0	0	0
Sailer (13)	2001	7	7/7	0	n.a.	n.a.	0	0	0	0	0	0
Taylor (14)	2001	6	6/6	0	1	1	n.a.	0	1	0	0	n.a.
Tiesenhausen (15)	2001	4	4/4	0	0	0	0	0	0	0	0	0
White (16)	2001	9	9/9	0	0	0	0	0	0	0	0	1
Won (17)	2001	12	10/12	0	n.a.	n.a.	0	0	0	0	0	n.a.
Bortone (18)	2002	12	12/12	0	1	1	0	0	1	0	0	0
Cambria (18)	2002	4	4/4	0	n.a.	n.a.	0	0	0	0	0	n.a.
Duda (20)	2002	5	5/5	1	1	1	0	0	0	0	0	n.a.
Haulon (21)	2002	4	4/4	0	2	2	1	0	2	0	0	0
Herold (22)	2002	18	18/18	0	3	1	0	0	1	0	2	2
Hutschala (23)	2002	9	9/9	0	1	1	1	1	0	0	0	0
Kato (24)	2002	38	38/38	0	9	7	1	0	2	2	1	0
Nienaber (25)	2002	127	127/127	0	4	3	2	1	2	n.a.	3	2
Palma (26)	2002	58	n.a.	2	n.a.	n.a.	n.a.	0	n.a.	3	2	n.a.
Pamler (27)	2002	14	14/14	2	4	3	1	1	0	0	0	1
Quinn (28)	2002	15	15/15	0	3	2	0	0	4	0	0	1
Rousseau (29)	2002	20	20/20	1	2	2	1	0	2	1	1	0

(Continued)

Table 4 Meta-Analysis of Tevar for Patients with Type B Dissections *(Continued)*

Author	Year	Patients with AD (*n*)	Proc. success (*n*)	Emergency conversion (*n*)	Overall complications (*n*)	Major complications (*n*)	Overall neurologic complications (*n*)	Paraplegia (*n*)	30-day mortality (*n*)	Late surgical conversion (*n*)	Aortic rupture during follow-up (*n*)	Late mortality during follow-up (*n*)
Saccani (30)	2002	3	3/3	0	1	1	0	0	0	0	0	1
Shim (31)	2002	15	14/15	0	0	0	0	0	1	2	0	1
Totaro (32)	2002	25	25/25	1	n.a.	n.a.	0	0	0	0	0	0
Balzer (33)	2003	8	7/8	0	n.a.	n.a.	0	0	0	0	0	0
Beregi (34)	2003	12	11/12	0	4	2	1	0	2	0	1	1
Fattori (35)	2003	22	22/22	0	1	1	0	0	1	2	1	0
Gerber (36)	2003	3	3/3	0	1	1	0	0	1	0	0	0
Grabenwöger (37)	2003	11	11/11	0	2	2	1	1	0	0	0	0
Krogh-Sorensen (38)	2003	3	3/3	0	0	0	0	0	0	0	0	0
Lambrechts (39)	2003	11	11/11	0	n.a.	n.a.	0	0	0	0	0	2
Lonn (40)	2003	20	20/20	0	10	10	5	1	3	0	0	0
Lopera (41)	2003	10	9/10	0	2	2	1	0	0	0	2	1
Matravers (42)	2003	9	8/9	0	1	1	0	0	2	0	1	0
Nienaber (43)	2003	11	11/11	0	1	1	0	0	0	0	0	0
Ramaiah (44)	2003	20	20/20	0	n.a.	n.a.	n.a.	0	n.a.	0	0	n.a.
Ianelli (45)	2004	8	8/8	0	n.a.	n.a.	0	0	0	0	0	0
Scheinert (46)	2004	7	7/7	0	n.a.	n.g.	n.a.	0	n.a.	1	0	0
All (%)		609	543/551 (98.5)	7/609 (1.2)	61/449 (13.6)	50/449 (11.1)	15/518 (2.9)	5/609 (0.8)	28/524 (5.3)	12/482 (2.5)	14/609 (2.3)	14/504 (2.8)

Source: From Ref. 49.

reported a series of 10 patients with complicated acute type B dissections treated with TEVAR. The mean interval to treatment from the time of diagnosis was 11 hours. Indications for TEVAR were rupture ($n=2$), malperfusion ($n=5$), rapid aortic expansion ($n=1$), and refractory pain ($n=2$). The primary tear site was covered in 90% of patients, and the early mortality was 20% ($n=2$). The causes of death in the two patients were aortic disruption distal to the stent graft and hemorrhagic shock after surgical fenestration of the abdominal aorta for persistent malperfusion. The duration of followup ranged from 1 to 38 months.

Doss et al. (55) reported their experience of 54 patients undergoing emergent surgical management of thoracic aortic diseases, with 28 patients undergoing conventional open surgical technique and 26 patients undergoing TEVAR. The mean age of the patients ranged from 28 to 83 years. Of the 54 patients, the indication for intervention was perforated type B dissection in 14 patients. The mortality was 17.8% in the conventional surgical group versus 3.8 in the TEVAR group. Paraplegia occurred 3.6% and 0% in the conventional surgical and the TEVAR group, respectively. The same investigators reported their more recent experience with emergent endovascular treatment of acutely perforated type B dissections. In a series of 11 patients over a 10-month period, seven patients were treated for ruptured aortic aneurysms and four for acutely perforated type B dissections. The average interval from diagnosis to treatment was 28 hours. Technical failure (i.e., access failure) occurred in two patients. With a mean follow-up of 12 months, there were no cases of paraplegia, stent migration, or endoleaks (56).

Nienaber and coworkers reported their experience of 11 patients undergoing emergency TEVAR for acute type B dissections complicated by contained rupture. Emergency TEVAR was successful, with no morbidity or stent-graft related complications. At a mean followup of 15 months, there was no mortality. This was a statistically significant improvement when compared to a historic-matched control group of patients undergoing conventional surgical therapy (death, $n=4$) (57).

For acute type B dissections complicated by malperfusion, definitive evidence for the role of TEVAR is equally lacking. Historically, surgical fenestration has been reported with durable success (58–60). Percutaneous aortic fenestration was first described by Williams and coworkers in 1990 (61) in the setting of mesenteric ischemia. Although reperfusion was achieved, the dissected aorta demonstrated aneurysmal dilatation requiring surgical repair. Other current endovascular strategies for visceral/renal and lower extremity malperfusion include bare metal stent deployment in the mesenteric and ilio-femoral system, respectively. Long-term results comparing these new endovascular techniques versus conventional open surgical extra-anatomic bypass techniques are lacking. The concept of deploying endovascular stent graft (covered stents) in the descending thoracic aorta at the primary tear site to remodel and to redirect flow in the distal aorta is appealing. However, more evidence is needed before definitive conclusions can be made.

In summary, the role of emergent endovascular therapy for complicated acute type B dissection remains unclear. However, early evidence from short-term small studies suggests a potential role for TEVAR. Given the poor results with emergent

conventional open surgical repair, TEVAR in centers with expertise provides a surgical alternative for patients typically associated with poor outcome.

Penetrating Atherosclerotic Ulcer/Intramural Hematoma

Historically, penetrating atherosclerotic ulcer (PAU) with intramural hematoma (IMH) in the descending thoracic aorta have been managed medically. The behavior and optimal clinical management of PAU and IMH in the descending thoracic aorta are not well defined and remain a clinical challenge. Furthermore, the natural history of PAU and IMH remains unclear (62–64). Cho et al. (65) recently reviewed the Mayo Clinic experience with PAU of the descending thoracic aorta over a 25-year period. From 1977 to 2002, 105 patients with PAU of the descending thoracic aorta with ($n=85$) and without ($n=20$) IMH were included in the study. The medical group included 76 patients and the surgical group included 29 patients. Thirty-day mortality in the medical group was 4% versus 21% in the surgery group ($P<0.5$). Defined as conversion to surgery or death, failure of medical therapy was predicted by presence of rupture at presentation and the era of treatment (before 1990). Aortic diameter, ulcer, or extent of hematoma were not risk factors for medical therapy failure or death.

The introduction of TEVAR has prompted investigators to examined the role of this new technology in descending thoracic aortic PAU and IMH. Jin et al. (66) reported their experience with TEVAR for PAU in the descending thoracic aorta. In their series of 14 patients, the majority of patients were symptomatic and were treated emergently. Endoleaks were present in two patients at completion angiography. With a mean follow-up period of 17.2 months, coverage of PAU was achieved in all patients with complete reabsorption of IMH in two patients. One patient died of rupture of psuedoaneurysm at one month after surgery. Other investigators have also reported small series of endovascular aortic stent graft therapy for PAU and IMH (67,68,133). Technical success with good short-term followup has been demonstrated with no mortality.

In summary, TEVAR for PAU and IMH in the descending thoracic aorta is promising. Endovascular therapy for complicated or symptomatic PAU appears to be indicated. However, more evidence and long-term follow-up is needed for definitive conclusion.

Traumatic Transection

Traumatic aortic injury resulting from blunt trauma is often associated with high morbidity and mortality, with the majority of patients dying at the scene (69). Rarely is traumatic transection an isolated injury, as the majority of patients sustain other concomitant orthopedic, neurosurgical, and abdomen injuries. Mortality rates in most recent surgical series range from 11% to 40% (69–71). Paraplegia rate ranges from 0% to 20% (70,72,73), depending on the operative technique and circulatory management employed. Often, concomitant nonaortic injuries may preclude immediate surgical repair of the aorta. This may be due to issues regarding

positioning, single lung ventilation for thoracotomy, or injuries precluding systemic heparinization.

Due to the significant morbidity and mortality associated with surgical repair of traumatic aortic injury in this group of severely injured patients, there has been a growing interest in the emergent treatment of traumatic aortic transection with TEVAR (Fig. 10). The minimally invasive approach of TEVAR offers these often severely injured patients a less morbid intervention.

Reed and coworkers recently reviewed their experience with traumatic transections over a 5-year period from 2000–2005. A total of 51 patients presented with the diagnosis of traumatic transection. Twenty-seven (52%) patients died before intervention. Of the remaining 24 patients, nine patients underwent emergent conventional open repair. Thirteen patients underwent delayed TEVAR, with the mean duration from diagnosis to treatment of 6 days. Technical success with complete exclusion of the transection was achieved in all 13 patients. Thirty-day mortality was 23% ($n=3$) (74).

Multiple small series have demonstrated that TEVAR in the acute setting for traumatic transections can be performed with excellent technical success and acceptable perioperative morbidity and mortality, when compared to conventional open repair. Tehrani et al. (75) reported their experience of 30 patients with traumatic aortic and severe concomitant nonaortic injuries treated with TEVAR. Technical success was 100% with angiographic evidence of complete exclusion of the disruption. There were two peri-procedural deaths and no incidence of paraplegia. With a mean follow-up of 11.6 months, there was no evidence of endoleak, stent migration, or late pseudoaneurysm formation. Other smaller series have demonstrated similar findings, with a mean follow-up period up to 21 months (21,67,76,77,100). Peri-procedural mortality rates range from 0% to 11%, with no incidence of paraplegia. All endovascular stent graft deployment was performed

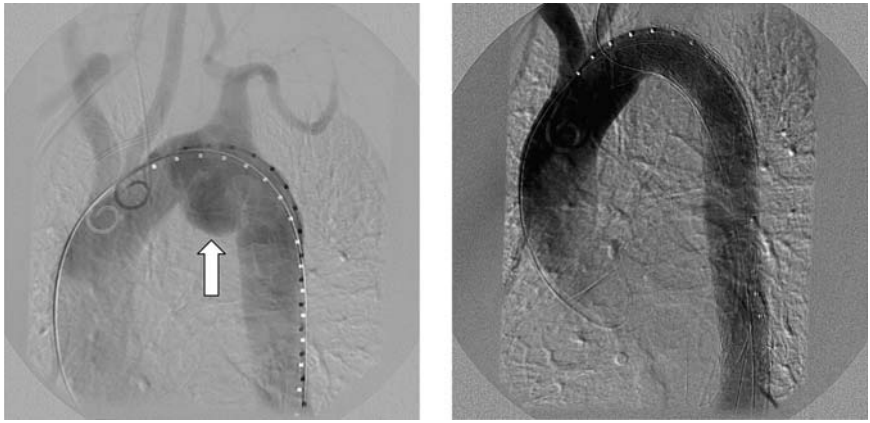

Figure 10 Thoracic endovascular aortic repair of traumatic transection (*white arrow*).

using no (or low dose) heparin. Stroke was rare with only one series reporting a single patient suffering a cerebrovascular accident (76).

In summary, TEVAR for traumatic transection appears to be a surgical alternative with morbidity and mortality rates similar to conventional open surgical repair. The most useful application of endovascular technology appears to be for patients with concomitant severe nonaortic blunt injuries who would otherwise be denied surgical repair of the aortic injury. However, TEVAR in this group of severely injured patients may not significantly improve overall survival, as these patients may eventually succumb to their associated nonaortic traumatic injuries. More evidence and long-term follow-up will be needed before definitive conclusions can be drawn.

Rupture (Aneurysmal)

Although ruptured descending thoracic aortic aneurysm is relatively uncommon compared to ruptured AAA, the complication and mortality rates are equally devastating. Mortality rates for emergent open repair of descending thoracic aortic aneurysms approach 70% and the associated paraplegia rates are about 20% (55,78,79).

TEVAR offers several potential advantages over conventional surgical repair. These advantages include the avoidance of thoracotomy and single lung ventilation, avoidance of aortic cross clamping, decreased blood loss, shorter operative time, and the avoidance of systemic heparinization and cardiopulmonary bypass (CPB). Recent reports confirm an emerging role for TEVAR in this population of patients (Fig. 11).

Recently, Leurs and coworkers reported the European experience (EUROSTAR Registry) with TEVAR for thoracic aortic aneurysms and dissections. From 1997 to 2003, 443 patients underwent TEVAR for thoracic aortic diseases.

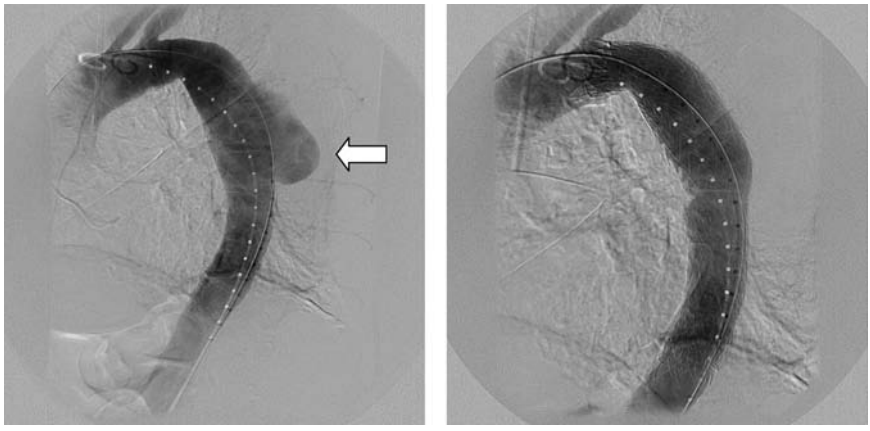

Figure 11 Successful stenting of ruptured aneurysm (*white arrow*).

Degenerative aneurysms comprised the majority of the patients (n=249). Of the total 443 patients, 35% required emergency treatment. In the degenerative aneurysm group, 24% were treated emergently with TEVAR. Over half (58%) of the patients in this group were classified as high risk (ASA class 3 or 4). Technical success was 87% in the entire group. Thirty-day mortality in the emergent group was 28%, compared to 5.3% in the elective group ($P<0.0001$). Among all patients with degenerative aneurysms, paraplegia occurred in 4.0% of patients. The mortality in the entire degenerative aneurysm group at 12 months was 10% (79).

Other smaller series have confirmed the potential role of TEVAR in the emergent treatment of ruptured degenerative thoracic aortic aneurysms. Scheinert and coworkers (80) reported a series of 31 consecutive patients undergoing TEVAR for perforating lesions of the descending aorta. Twenty-one patients were treated for aortic perforation secondary to rupture of a descending thoracic aneurysm or dissection, with a 30-day mortality of 4.3%. Complications, including renal failure ($n=4$) and stroke ($n=2$), occurred in 28.6% of patients, with no incidence of paraplegia. Farber and coworkers reported their experience of 184 TEVAR over a 3-year period. Of the 22 patients undergoing emergent TEVAR for nontraumatic etiology, 11 patients had ruptured thoracic aneurysms. The average age was 66.5. Average aneurysm diameter was 73.1 mm. Technical success in aneurysm exclusion was achieved in 100% of patients. Thirty-day mortality was 27.3%, with major complications occurring in 54.5% of patients. Cerebrovascular accidents occurred in two patients, and spinal cord ischemia in two. There was one late cardiac death in a mean follow-up period of 12.5 months. Other investigators, including Doss and Morishita (81–83), reported their experiences with emergent TEVAR. Their respective mortality rates were 3.8% and 17.8%. Both investigators demonstrated 100% technical success with no incidence of paraplegia.

In summary, emergency TEVAR has emerged as a potential surgical alternative for ruptured descending thoracic aortic aneurysms. Patients presenting with ruptured thoracic aortic aneurysms face very significant surgical morbidity and mortality rates. Early results with TEVAR in this group of patients are encouraging, with morbidity and mortality rates at least equivalent to conventional open repair. However, long-term durability of the stent grafts remains to be determined. Larger studies with longer follow-up will be needed to make definitive conclusion.

COMPLICATIONS

Neurological Complications

Neurological complications associated with endoluminal thoracic aortic stent grafting fall within two major areas: stroke and spinal cord ischemia. Endovascular stent graft repair of isolated descending thoracic aortic aneurysms has a reported spinal cord ischemia frequency that ranges from 3.6% to 12.0% with approximately two-thirds of these cases resulting in permanent deficits (Table 5) (84).

Table 5 Risk Factors for Spinal Chord Ischemia After Endovascular Stent Repair of Descending Thoracic Aortic Aneurysm

Report	*n*	Spinal cord ischemia (%)	Recovery	Risk factors
Gravereaux et al. (87)	53	3 (5.7)	1/3	AAA repair, Long graft
Mitchell et al. (88)	108	4 (3.7)	0/4	AAA repair, Aortic occlusion
Moon et al. (89)	18	1 (5.6)	0/1	AAA repair
Ellozy SH *J Vasc Surg 2003*	84	3 (3.6)	1/3	Not described
Greenberg et al. (90)	25	3 (12.0)	2/3	Long graft
Cheung et al. (84)	75	5 (6.5)	3/5	AAA repair, Mobile atheroma Vascular injury, Hemorrhage Hypotension
Total	363	19 (5.2)	7/19 (37%)	

In contrast, open repair of isolated descending thoracic aneurysms, in the modern era, has been associated with a 2.6% and 2.7% incidence of neurologic deficits in two recent studies from major centers (85,86).

Stent grafting offers several potential advantages in reducing the risk of spinal cord ischemia (SCI). These advantages include the avoidance of an aortic cross clamp, fewer episodes of hypotension, less bleeding, and an earlier emergence from general anesthesia to allow detection and treatment of a neurological deficit. Conversely, stent grafting may have the following disadvantages: requiring more extensive aortic coverage to allow adequate sealing between endoluminal graft and aorta, inability to reimplant intercostal arteries, and injury to ileofemoral vessels that may provice flow to the anterior spinal artery through the hypogastric and pelvic vascular plexus.

Identified risk factors for SCI following thoracic aortic stent grafting include: previous AAA repair, long segment of thoracic aortic stent graft, mobile atheroma, iatrogenic vascular injury, hemorrhage, and hypotension (84,87–90). The mechanisms which contribute to post-procedural SCI after TEVAR are multifactorial. The risk of SCI in patients with previous AAA repair may be explained by the destruction of pelvic and hypogastric arterial collateral to the anterior spinal artery. Extended graft coverage, especially in the levels of T6 to T12, compromises the vertebral levels that are known statistically to supply the anterior spinal artery. Hypotension and hemorrhage contribute by decreasing the perfusion pressure to the spinal cord.

Techniques to reduce the risk of SCI from TEVAR include using lumbar CSF drains and applying neurocerebral monitoring. The use of a lumbar CSF drain has been shown in numerous studies to decrease the risk of SCI in open surgical thoracoabdominal aortic aneurysm repairs and endovascular thoracic aortic aneurysm and dissection stent graft repair (91–93). The use of neurophysiological monitoring has been traditionally applied to detect intraoperative spinal cord ischemic changes and allow immediate alterations in perfusion management to reverse insults. The

use of neurophysiological monitoring in endovascular treatment of the thoracic aorta has been reported to also allow early detection and intervention to augment spinal cord perfusion pressure to decrease the risk (94). A proposed algorithm to manage the risk of spinal cord ischemia is demonstrated in Figure 12.

The risk of stroke in endovascular repair is approximately 3% to 9%, which is similar to open repair (95). Therefore, stroke rates are 2–3 × higher than paraplegia rates for thoracic endografting. There are several possible reasons for this high stroke risk. Endovascular placement of thoracic aortic stent grafts requires multiple

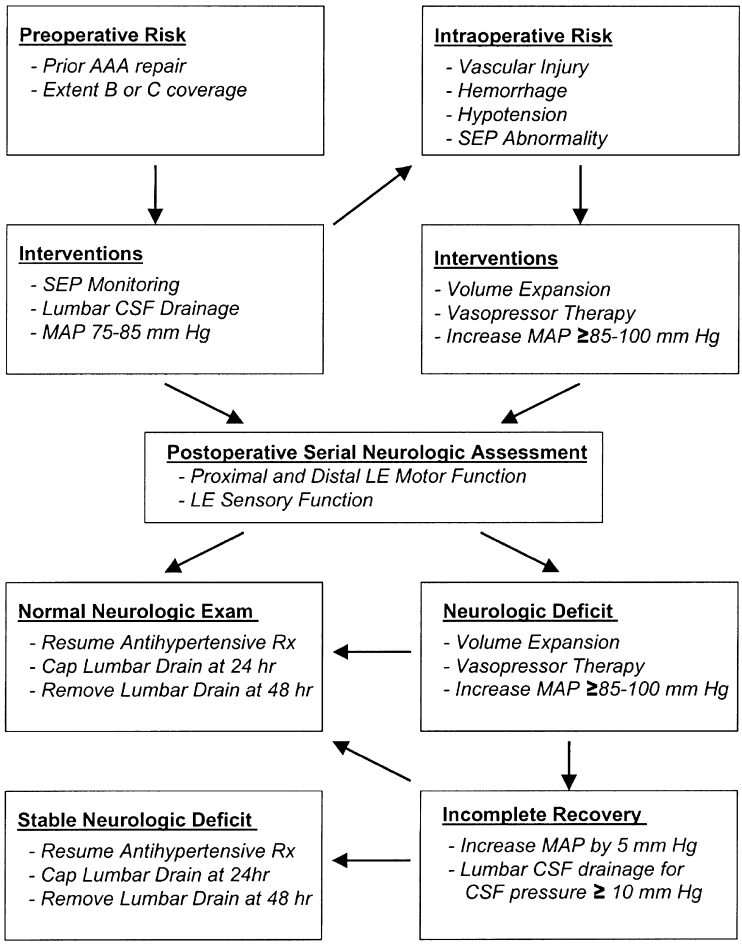

Figure 12 Proposed algorithm to manage the risk of spinal cord ischemia in patients undergoing endovascular stent repair of descending thoracic aortic aneurysms. *Abbreviations*: AAA, abdominal aortic aneurysm; CSF, cerebrospinal fluid; LE, lower extremity; MAP, mean arterial pressure; Rx, drug therapy; SEP, somatosensory evoked potential. *Source*: From Ref. 84.

wire manipulations in the aortic arch. These manipulations may contribute to stoke risk by producing emboli. Other risk factors for stroke include history of previous stroke and grade V atheroma of the aortic arch (129).

Stent Migration

In most series, stent migration has been relatively rare (ranging from 1% to 3%). Early stent migration is usually a result of inadequate proximal or distal landing zone length. If the landing zone is inadequate, the stent can be displaced into the aneurismal sac, resulting in migration. Additionally, persistent type I endoleaks can cause aneurismal sac enlargement, which then may displace the stent from its apposition to the proximal or distal landing zone. Late stent migration is usually related to either continued tortuous lengthening of the native aorta, resulting in stent component separation, or continuous increases in native aortic landing zone diameter, which eventually results in a "free floating" stent within the enlarging aorta.

FUTURE DIRECTIONS

Early reports have suggested the possible beneficial use of TEVAR in a number of acute aortic syndromes involving the ascending aorta and arch. A very likely and appropriate application of ascending aortic TEVAR has been the treatment of isolated saccular aneurysms and pseudoaneurysms of the ascending aorta. These successful ascending aortic TEVAR applications have been characterized by limited coverage distances, normal aortic diameters proximal and distal to the psuedoaneurysm, and a corresponding high predicted mortality rate from standard redo open surgery. The present limitation of this therapy is the fact that thoracic endovascular devices have been designed for descending aortic diameters and lengths. Examples of treated catastrophic ascending aortic conditions have been cannulation site pseudoaneurysms and ascending aortic suture line disruptions.

An acute proximal aortic presentation treated with adjunctive thoracic aortic stent grafting has been acute type A dissection. Most reports utilizing TEVAR in the setting of acute type A dissection revolve around the hybrid deployment of a descending stent anchored at the distal aortic arch after standard open type A dissection repair. The theoretical rationale for this TEVAR application is the knowledge that standard acute type A dissection repair is associated with an 80% to 100% rate of residual descending aorta dissection. Therefore, an adjunctive stent procedure on the distal arch and proximal descending aorta may allow improved "remodeling" of the residual dissected thoracoabdominal aorta compared to standard acute type A repair. Multiple investigators have reported on the adjunctive use of an aortic stent graft in the descending thoracic aorta during repair of acute type A dissection and its effect on aortic remodeling. Early reports by Fleck et al. (96) and Kato et al. (97) described preliminary results using home-grown stent grafts. The largest series, by Liu et al. (98), reported 36 consecutive patients with acute type A dissection treated with total arch repair with a simultaneous antegrade deployment of a "stented elephant trunk." They demonstrated an obliteration rate of the false lumen in the

distal thoracoabdominal aorta approaching 92%. Panos and coworkers (99) reported on five patients undergoing similar surgical strategy using the Endofit endoluminal stent graft (Endomed Inc., Phoenix, Arizona, U.S.A.) with complete obliteration in two patients and partial obliteration in three patients.

At the University of Pennsylvania, we have attempted to alter the prognosis and natural history of the residual type B dissection following acute type A dissection repair by stenting the distal aortic arch and descending thoracic aorta. We have presented a method for simultaneous open repair of the aortic dissection and antegrade "stented elephant trunk" stabilization of the descending aorta using thoracic aortic stent grafts (Fig. 4) (101). To date, nine patients have been treated with this technique, with five patients (56%) demonstrating complete thrombosis and stabilization of the false lumen in the entire aorta (Fig. 5). Two patients (22%) had stabilization of the descending thoracic aorta with persistence of the false lumen in the aorta beginning at the level of the celiac axis. Two patients (22%) had persistent false lumen in the descending thoracic aorta. Paraplegia did not develop in any of the nine patients. Other reports of similar combined open and aortic stent graft repair of acute type A dissection demonstrated comparable results of false lumen obliteration and prevention of distal aortic aneursymal remodeling (96–99).

Arch Hybrids

Conventional repair of atherosclerotic aortic arch aneurysm is technically demanding, requiring CPB and deep hypothermic circulatory arrest. Despite recent improvements in surgical technique, total arch repairs of large atherosclerotic arch aneurysms still have significant morbidity and mortality (102–105). In contrast to nonatherosclerotic aortic arches, large atherosclerotic saccular aneurysms of the arch are extremely high risk for perioperative stroke, as this disease is a grave marker of extensive arch and brachiocephalic atheromatous disease. In this subset of high risk patients, even the most recent series indicate in-hospital mortality rates ranging from 6.3% to 20%, with stroke rates up to 12% (43,106–111).

Beginning with descending thoracic aortic aneurysms, endovascular stent graft technology has evolved as a safe and effective treatment for various thoracic aortic diseases (20,46,50,112–115). Because of the anatomical features of the aortic arch, endovascular therapy of arch aneurysms remains a technical challenge (130,131). Maintaining cerebral perfusion and eliminating embolic events during deployment are crucial for optimal neurologic outcome. Limited to Europe and Japan due to the availability of stent graft devices, small series of combined extra-anatomical bypass of the great vessels with endovascular deployment of a stent graft in the arch have been reported with promising results (102,116–121). With FDA approval in 2005, the Gore TAG (W.L. Gore, Flagstaff, Arizona, U.S.A.) thoracic endoprosthesis became available commercially in the United States. Previously, these patients have been considered prohibitively high risk for conventional open arch repair due to their comorbidities, including the atherosclerotic burden in the arch and the associated high stroke risk.

Thoracoabdominal Aneurysms

Thoracic aortic stent grafting has now been utilized in the treatment of elective thoracoabdominal aneurysms (122,123). Although this advance has not been applicable in acute catastrophic presentations such as rupture or secondary dissection, thoracoabdominal aortic applications will undoubtedly be utilized in the future. These are complex procedures requiring branch artery revascularization.

Postoperative Pseudoaneurysms

Psueodaneurysms of the thoracic aorta are an excellent indication for TEVAR. Most general series report a small subset of patients treated with TEVAR for pseudoaneurysms of previous thoracic aortic suture lines. Technically, this urgent aortic condition is eminently suitable for stent grafting, as either the proximal or distal landing zone is usually within a previously placed Dacron graft, which is ideal for stent deployment (132).

Mycotic Aneurysms

TEVAR has been applied to a broad range of thoracic aortic diseases with mycotic or septic characteristics. These have included isolated mycotic aneurysms, broncho-aortic fistulas, aorto-esophageal communications, and infected grafts and stent grafts (124–126). In general, the effectiveness of TEVAR for "mycotic" type indications has been poor in the long-term. However, there maybe a role for thoracic aortic stent grafting in the setting of mycotic or infected thoracic aortic diseases as a "bridge," to "defuse" the potentially catastrophic situation, while allowing the patient to recover sufficiently for a definitive procedure.

CONCLUSION

In summary, it is precisely in acute aortic events that application of TEVAR may be most beneficial. Since traditional open surgical procedures for acute aortic conditions have historically had a high morbidity and mortality, the application of TEVAR to these pathologies may offer significant survival benefits. As device technology improves and clinical experience expands, TEVAR applications are also likely to expand.

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DISCUSSION AND COMMENTARY

Editor's Counterpoint

(Based on Elefteriades J. "Endograft Therapy for Thoracic Aortic Aneurysms: Wave of the Future or The Emperor's New Clothes," an invited editorial in press in the Journal of Thoracic and Cardiovascular Surgery, by permission.)

As a profession, cardiothoracic surgeons owe a debt of gratitude to Dr. Bavaria and colleagues for spearheading these exciting clinical investigations into novel endovascular therapies for aneurysm disease.

It is important for medical science to evaluate endografting of aneurysms with enthusiasm for this new modality, but, at the same time, a grain of skepticism, or at least realism. Multiple reasons to be cautious can be cited.

Conceptual issues. First, some authorities question the very concept of repair of an expanding cylindrical structure by means of a graft placed within its lumen. Stents, it is pointed out, were developed to keep arteries from closing in (as in coronary angioplasty), not to keep them from expanding outward. How can a graft placed inside an enlarging aorta—and not attached to the aorta—prevent the inexorable expansion of that aorta? Some say the graft would have to go outside, not inside, the aorta—a concept that was tried and failed many years ago. To control a herd of cattle, the analogy goes, the wooden pen has to go outside the cows; an internal endograft is like putting the pen inside the herd. The concern is that the inexorable expansion of the aorta will ultimately leave the endograft behind, "ignoring" it, so to speak. Another conceptual issue concerns continued pressurization of the aneurysm sac by intercostal or lumbar vessels. Yet another conceptual issue concerns the surgeon's understanding that the strength of the aorta resides in the adventitia, which is not incorporated in any way by the endograft.

Short duration of follow-up of an indolent disease. This line of reasoning leads to the second major concern: Thoracic aortic aneurysm, though ultimately lethal, is an indolent disease. Many years are generally required from the time of diagnosis to the time of aneurysm-related death, especially with small to moderate size aneurysms (Fig. A) (2). To have patients alive at one or two years is not at all reassuring. These patients would probably still be alive absent any directed therapy whatsoever. As longer term follow-up becomes available through the EUROSTAR investigation of endografting for abdominal aortic aneurysm, this concern literally comes to life, with mortality and rupture rearing their ugly heads as the aneurysm disease expresses its natural history, even after "successful" endografting. The EUROSTAR study of endografting for abdominal aortic aneurysms is much more "mature" than corresponding studies of thoracic aortic aneurysm. In Figure B, it can be noted that endoleak becomes increasingly common as duration of follow-up is extended (3). It appears that nearly half of patients will suffer diagnosed endoleak as follow-up becomes extended toward the five-year point. In this context, we need to keep in mind that the word "endoleak" is itself a euphemism for failure of treatment. It has been demonstrated

Figure A Indolent nature of thoracic aortic aneurysm. Survival prior to operative repair is shown, for different size classes. Note that years generally pass before the mortality risk expresses itself, even for large aneurysms. Source: From Ref. 2.

that endoleak predicts need for surgical conversion, rupture, and death, which in one EUROSTAR publication affected respectively 14%, 13%, and 27% of patients by five years post-procedure in patients presenting originally with large aneurysms—sobering statistics after endograft therapy (4). Also concerning is the emergence of substantial rates of aneurysm-related death after endograft therapy,

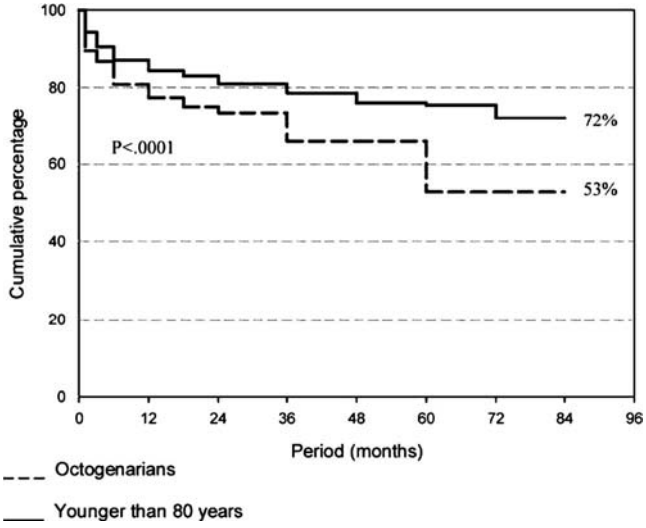

Figure B Kaplan-Meier graph represents cumulative freedom from any endoleak in patients operated for abdominal aortic aneurysm with endovascular aneurysm repair. Source: From Ref. 3.

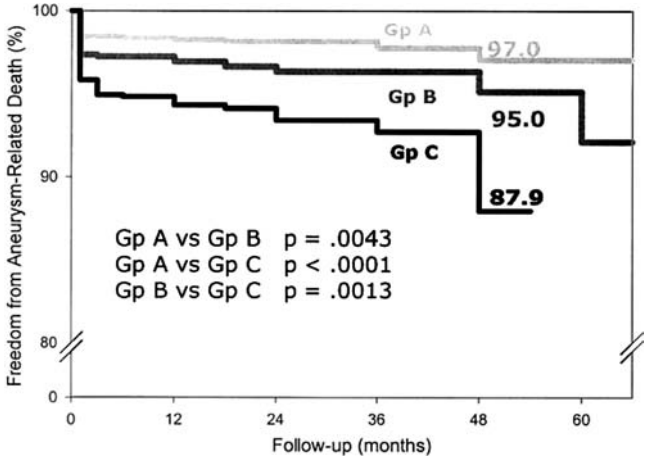

Figure C Cumulative freedom from aneurysm-related death. Note low attrition of survival in first three years of follow-up and rapid attrition in fourth year. Gp, Group. Groups represent increasing initial aneurysm size: Gp A = 4.0–5.4 cm, Gp B = 5.5–6.4, Gp C > 6.5 cm. Source: From Ref. 5.

when follow-up extends to four years, especially for large aneurysms (5). This is shown vividly in Figure C; this figure suggests, in fact, that the aneurysm is indeed "ignoring" the endograft and merely expressing its natural tendency to rupture. In recognition of these sobering statistics, several major EUROSTAR publications end with serious cautions about endograft therapy, calling attention to concerns about the long-term effectiveness and safety:

- "The high incidence of late secondary interventions is a cause for concern with regard to broad application of endovascular AAA repair, and emphasizes the need for lifelong surveillance" (6).
- "Continuing need for surveillance for device related complications remains necessary" (7).
- "… the durability of this technique is currently unknown, and continued use of registries should provide data from long-term follow-up…. Only long-duration studies can tell us whether this type of therapy really works—whether it prevents aneurysm growth and rupture and patient death (8).
- The midterm outcome of large aneurysms after EVAR was associated with increased rates of aneurysm related death, unrelated death, and rupture…. This finding may justify reappraisal of currently accepted management strategies (5).

The encyclopedic Health Services Technology Assessment Text of the Guide to Clinical Preventive Services, 3rd Edition, issued the following concluding statement on endografting.

- "Long-term complications, including AAA rupture … may result in significant long-term morbidity and mortality" (9).

The pioneering investigations presented in this chapter should be viewed as extended short-term evaluations of endograft therapy.

Despite these multiple concerns regarding endograft therapy, the work described in this chapter represents a bold venture into new territory with a promising, albeit unproven; less invasive modality of therapy. We are indebted to the investigators for this work. As the authors rightly point out, it is essential that each patient who has received endograft therapy be followed vigilantly for possible deterioration or complications as time passes. Moreover, it is incumbent on our profession not only to follow individual patients closely, but also to evaluate the durability of endograft therapy in general with a vigilant eye. We look forward to longer and more complete follow-up of these specific patients and to randomized studies in the future.

The authors of this chapter have done groundbreaking clinical work, forging a very important initial foray into endograft treatment of thoracic aortic aneurysms and the evaluation of its early efficacy.

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Long-Term Suppressive Therapy: Clinical Reality and Future Prospects

Amy E. Hackmann and Robert W. Thompson

Departments of Surgery (Section of Vascular Surgery), Radiology, and Cell Biology and Physiology, Washington University School of Medicine, St. Louis, Missouri, U.S.A.

Scott A. LeMaire

Division of Cardiothoracic Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, and Cardiovascular Surgery Service, The Texas Heart Institute at St. Luke's Episcopal Hospital, Houston, Texas, U.S.A.

INTRODUCTION

Progressive aortic dilatation and rupture are the inevitable consequences of untreated aortic aneurysms and dissections. The only treatments that effectively eliminate the risk of aortic rupture are surgical replacement of the diseased aortic segment with a graft and intraluminal exclusion of the segment with an endovascular stent graft. Because of the associated risks, aortic repair procedures are performed only in patients who are at significant risk of aortic rupture. The decision of when to repair an aneurysm is based primarily on the severity of aneurysmal disease—as indicated by symptoms, aortic diameter, and aortic expansion rate—in the context of other factors that increase the likelihood of rupture, such as connective tissue disorders or a family history of ruptured aneurysm. Patients who have not reached the clinical threshold for aortic repair receive nonoperative treatment and careful surveillance with imaging studies.

Current nonoperative treatment is rather unsophisticated and comprises smoking cessation, avoidance of strenuous activity, and pharmacologic reduction of hemodynamic stress. Although this regimen successfully halts aortic expansion in some patients, aneurysms continue to enlarge and rupture in many patients, despite

treatment. New treatments are needed to stop aneurysm expansion and prevent rupture. Recent experimental work has focused on improving our understanding of the pathobiology of aortic aneurysms in hope of identifying new strategies for long-term suppressive therapy.

PATHOBIOLOGY OF AORTIC ANEURYSMS

Over the last two decades, research on the pathobiology of aortic aneurysms has greatly improved our understanding of the cellular and molecular mechanisms involved in progressive aortic dilatation. Most studies have focused on abdominal aortic aneurysm (AAA) formation. Until recently, most of the research regarding thoracic aortic aneurysms (TAAs) has concentrated on those related to connective tissue disorders, particularly Marfan syndrome (MFS). Relatively little is known about the pathobiology of TAAs related to chronic medial degeneration or dissection in patients without MFS. Studies in animals and human aortic tissue have shown that the development of aneurysms results from a cascade of interacting cellular and molecular processes, including matrix degeneration by elastin- and collagen-degrading proteases, chronic inflammation, cytokine activity, and loss of smooth muscle cells (SMCs) (Fig. 1) (1). Together, these processes undermine the mechanical properties of the aortic wall, and lead to aneurysm expansion and rupture (2).

Matrix Proteolysis

The two proteins responsible for maintaining structural integrity of the aortic wall are elastin and collagen, which respectively confer elasticity and tensile strength.

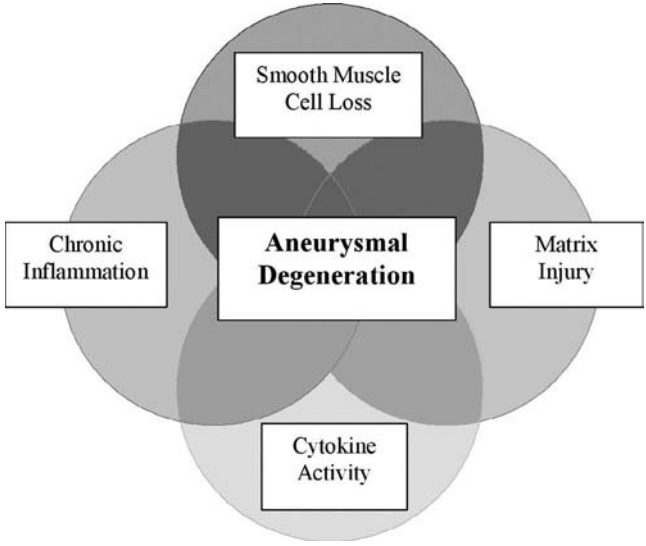

Figure 1 Diagram illustrating the overlapping cellular and molecular processes that contribute to aortic aneurysm formation.

Medial destruction of the aortic wall by enzymes—especially matrix metalloproteinases (MMPs)—that degrade elastin and collagen is a critical component of aneurysmal degeneration (3). Although each enzyme in the MMP family has some specificity for certain substrates, all MMPs have several similarities, including a zinc-binding active site, a propeptide domain at the amino terminus, and additional variable domains (4). MMP production is regulated through gene transcription, and each enzyme in this family is secreted as a zymogen (pro-MMP) that must be activated. This activation step may be promoted by certain chemicals, decreased pH, increased temperature, plasmin, nitric oxide, urokinase-type plasminogen activator, or other activated MMPs (5–8). Activated MMPs are regulated by tissue inhibitors of metalloproteinases (TIMPs).

MMP-9 has been a target of intense study because of its ability to degrade insoluble elastin and because of increasing evidence that supports its role in aneurysmal disease and other inflammatory conditions (9–11). Also known as 92-kDa type IV collagenase or gelatinase B, MMP-9 is produced by mononuclear phagocytes and vascular SMCs after stimulation by inflammatory cytokines or other factors (12,13). In addition to its elastolytic properties, MMP-9 promotes the inflammatory response (14–17). For example, after being cleaved by MMP-9, interleukin-8 potency as a neutrophil activator increases more than 10 times (18).

Several other members of the MMP family, including MMP-1, 2, 3, 12 (macrophage elastase), and MMP-13, as well as TIMPs, have been implicated in the development of aneurysms. MMP-2 shares several properties with MMP-9, including the ability to degrade elastin, and is secreted by vascular endothelium, SMCs, fibroblasts, lymphocytes, and macrophages. Inflammation increases the expression of MMP-2 in the aortic wall (13). Adding to its role in matrix degradation, MMP-2 helps activate other proteinases along the cell surface (5). Furthermore, MMP-2 promotes the migration of SMCs and inflammatory cells through elastin-rich matrices (19). MMP-3 can activate MMP-9 in the extracellular matrix (20).

The contribution of MMPs to aneurysm formation has been studied in animal models. In a mouse model of MFS, immunohistochemical studies showed an inverse relationship between MMP-9 expression and elastic fiber number and integrity (21). Genetically modified mice deficient in MMP-9 or MMP-2 do not develop AAAs in either the elastase-induced or calcium chloride model, but "normal" aneurysms develop in MMP-9 knockout mice transplanted with wild-type macrophages (22,23). Doxycycline, a broad MMP inhibitor, prevents aneurysm formation in animal models (22,24–26). These studies strongly support the idea that MMP-9, probably secreted by activated macrophages, contributes to an early critical step in aneurysm formation. The incidence of TAAs is increased in TIMP-1 deficient mice but decreased in MMP-3 deficiency (27,28).

Several human studies indicate roles for MMP-1, 2, 3, 9, 12, and 13, and TIMP-1 and 2 in aneurysm formation (29–33). Minimal, if any, MMP-9 is found in normal aortic tissues; however, large quantities are secreted by macrophages in AAAs (34). Levels of MMP-9 are significantly higher in organ cultures of AAA

tissue than in atherosclerotic and normal aortas (35), and plasma levels of MMP-9 are increased in patients with AAAs (11,35–37). Moreover, MMP-9 levels decrease by more than 90% after aneurysm repair (35,37–39). Some investigators have suggested that MMP-9 levels correlate with the size and rate of expansion of the aneurysm, but this association remains unclear (35,37,39–41). MMP-2 may contribute to the initial dilatation of small aortic aneurysms (42). Two small studies of acute dissection have shown MMP-2 and 9 at the site of the initial tear in the intima (43,44). cDNA analysis indicates that inflammatory and proteolytic genes are upregulated in acute dissections (45). Significantly higher than normal levels of MMP-12 have been reported in patients with aneurysms (46), especially smokers, which suggests a possible mechanism linking tobacco use and AAAs (47–49). In summary, the MMP family plays an important role in both aortic dissections and aneurysms, but the complex interplay between these enzymes is not well understood.

Inflammation and Cytokines

Histologic studies of aneurysmal degeneration have shown a transmural infiltration of inflammatory cells in the aortic wall in both AAAs and TAAs (50). Monocytes, macrophages, plasma cells, B lymphocytes, and T lymphocytes have been identified in AAA tissues. Proinflammatory products released by these cells in the aortic wall are responsible for degradation of the extracellular matrix. T helper 2 lymphocytes invade the medial layer and, combined with nonspecific immune responses, destroy the structural proteins (51). T helper 1 immune responses have also been correlated with vascular remodeling during TAA formation (50). Several antigens have been associated with inflammatory responses in aneurysms. In one study of men with AAAs, 83% had high immunoglobulin A titers (>20:1) against *Chlamydia pneumoniae*, which was considered a marker of rupture risk (52–54); however, the relationship between *Chlamydia* infection and aortic inflammation, MMP-9 production, and aneurysm formation remains unclear (55,56). Although inflammatory infiltration is an important component of aneurysmal degeneration, the specific roles of the different inflammatory cell types need to be further defined.

Levels of inflammatory cytokines are elevated in aortic aneurysms. Interleukin (IL)-1 beta, IL-6, and IL-8 are increased in the circulation and aortic tissue in patients with aneurysms (57–62). Although not consistently increased in AAAs, interferon-gamma (IFN-γ) may be involved in the rapid expansion of aneurysms (51,58,63). Expression of mRNA for tumor necrosis factor-alpha (TNF-α) is up-regulated in AAAs (63). In addition, TNF-α-binding protein, given perioperatively, prevents the development of experimental aneurysms in rats (64).

In addition to their central role in inflammation, cytokines have many other functions that can affect the integrity of the aortic wall, including the regulation of cell proliferation, extracellular matrix deposition, and protease activity. Therefore, alterations in cytokine activity also affect the development of aortic aneurysms.

Transforming growth factor-β (TGF-β) has many functions, including production of extracellular matrix. Mutations in the TGF-β receptors have been identified in patients with familial TAAs and dissection, MFS, and Loeys-Dietz syndrome (65–70). Fibrillin-rich microfibrils are believed to interact with inactive TGF-β binding proteins. As a result, these microfibrils affect how TGF-β is concentrated and regulated before activation and control its release to intended targets (71). Abnormalities in TGF-β signaling weaken connective tissue structures by causing abnormal matrix deposition (65). Current studies investigating TGF-β antagonists may have profound clinical implications (72).

Loss of Medial Smooth Muscle Cells

Elastin and collagen destruction is clearly involved in aneurysm formation; however, impaired damage repair may also be a key factor. The fact that some aneurysms remain the same size for many years and others rapidly enlarge in a few months indicates great variability in the ability of the aortic wall to compensate for the proteolytic processes. One obstacle to matrix repair is loss of SMCs, which is a characteristic of some aneurysms, particularly AAAs. Although atherosclerotic disease does not affect the density of SMCs in the aortic wall, patients with AAAs have a 75% loss in SMCs (73). Two factors have been identified as a cause of this SMC deficiency. Cytokines and other mediators released from the inflammatory cell infiltrate may initiate programmed SMC death. The rate of SMC apoptosis is up to 300% higher in AAAs than in normal aortas (74–76). Increased SMC apoptosis has also been identified in patients with TAAs related to congenital bicuspid aortic valve or MFS (30). Secondly, cell culture studies indicate that the growth capacity of SMCs from AAAs is less than that from adjacent normal vessels (77). The loss of SMCs impairs the repair process, further handicapping healing from matrix degradation and compounding aortic damage.

CURRENT PHARMACOLOGIC TREATMENT

Current pharmacologic treatment of patients with aortic aneurysms and aortic dissection focuses on reduction of hemodynamic stress (Table 1). The goal of treatment is to slow or halt aortic dilatation to prevent the aneurysm from becoming large enough to rupture or need operative repair. No available pharmacologic treatments cause regression of aneurysmal degeneration.

Hypertension is extremely common in patients with aortic aneurysms and dissections. Strict control of hypertension is a standard treatment goal in the long-term management of these patients. Patients without hypertension are also treated with antihypertensive agents because of the beneficial effect of minimizing the force of left ventricular ejection (dP/dT). Therefore, long-term "anti-impulse" therapy is prescribed for patients with small aneurysms, chronic dissections, and connective tissue disorders; medications are adjusted to keep blood pressure below 130/80 mmHg (78–80). In patients with aortic dissection,

Table 1 Pharmacologic Agents Currently Used Clinically or Under Investigation for Long-Term Treatment of Aortic Aneurysms and Dissection

Currently used
Beta-receptor antagonists
Calcium channel blockers
Angiotensin converting enzyme inhibitors
Under investigation
Anti-hyperlipidemic agents
Anti-inflammatory agents
Immunosuppressants
Tetracycline derivatives (doxycycline)
Nuclear factor-kappa B inhibitors
Transforming growth factor-beta antagonists (losartan)

control of blood pressure contributes to prolonged, event-free survival (81). Classes of drugs used to minimize hemodynamic stress on the diseased aortic wall include beta-receptor antagonists, calcium channel blockers, and angiotensin converting enzyme (ACE) inhibitors.

Beta-Receptor Antagonists

Beta-blockers, traditionally thought to be the most effective medical therapy, are used to treat acute and chronic aortic dissection and aortic aneurysms (82). The mechanism of beta-blocker therapy involves lowering both blood pressure and pulsatile or contractile force applied to the aorta (83,84). However, the increase in peripheral vascular resistance associated with long-term use of beta-blockers may negate some of the beneficial effects (82).

As the most studied medical therapy, beta-blockers have been assessed in many different trials, but results have been conflicting. In studies of patients with MFS, long-term treatment with beta-blockers reduced the rate of aneurysm expansion and decreased aortic root dilatation (85,86). In a study of patients with chronic descending aortic dissections, beta-blocker therapy decreased the need for operative intervention three-fold; most of the patients who required surgery did so because of an increase in aortic diameter (87). However, other studies have shown that long-term treatment with beta-blockers in patients with MFS increased aortic stiffness and decreased aortic distensibility (88,89). Progressive aortic dilatation and aortic dissection can occur despite prophylactic beta-blocker therapy in patients with MFS (86,90).

Long-term use of beta-blockers is associated with significant side effects that can limit treatment by reducing patient compliance. In a Canadian study on the use of propranolol for treating small (3–5 cm) AAAs, 42% of patients in the beta-blocker group withdrew from the study because of adverse effects, and no significant difference was seen in AAA expansion among the remaining patients (91,92).

In a similar European trial in patients with small AAAs, 60% of patients quit taking propranolol because of side effects, and mortality was significantly higher in the treatment group (16.7%) than in the placebo group (4.2%) (92). Thus, the benefits of beta-blockers in aortic diseases need to be clarified.

Calcium Channel Blockers

Limited data are available on the use of calcium channel blockers for suppression of aneurysms or dissections. These agents can be useful as an adjunct to beta-blockade in patients who remain tachycardic despite maximal beta-blocker therapy and in patients who need a vasodilator to counteract the associated vasoconstriction of long-term therapy with beta-blockers (66,82).

Angiotensin Converting Enzyme Inhibitors

ACE inhibitors are emerging as a viable treatment option in the suppression of aortic diseases. In a rat model of elastase-induced AAA, captopril, enalapril, and lisinopril prevented aneurysm formation (93). In a three-year study in patients with MFS, the amount of aortic expansion was less in patients treated with enalapril than in those treated with atenolol or propanolol (94). In addition, patients treated with enalapril showed reduced aortic stiffness and increased distensibility. The mechanism of this benefit relates to the inhibition of angiotensin II, which normally promotes apoptosis of vascular SMCs (95), one of the histologic hallmarks of aortic dilatation and dissection in MFS. Thus, ACE inhibitors may preserve aortic distensibility (96,97). Another important characteristic of ACE inhibitors is that they are associated with fewer side effects than beta-blockers (94).

POTENTIAL FUTURE TREATMENT OPTIONS

While current pharmacologic treatment of aneurysms focuses on reducing hemodynamic stress on the aortic wall, new options under investigation involve stabilizing the mechanical integrity of the aortic wall by targeting the molecular and cellular mechanisms of aneurysmal degeneration, including matrix proteolysis, inflammatory infiltration, cytokine activity, and SMC loss. Medications that have the potential to suppress aneurysm formation include anti-hyperlipidemic agents, anti-inflammatory drugs, immunosuppressants, tetracycline derivatives, and TGF-β antagonists (Table 1).

Anti-hyperlipidemic Agents

Although the American Heart Association recommends that all patients with aneurysms be treated with an HMG CoA reductase inhibitor because of the prevalence of coronary artery disease in this population, these agents are not currently used to suppress aneurysm formation (98). Experimental evidence, however, suggests that anti-hyperlipidemic medications may be useful as treatment for aneurysms.

Some anti-hyperlipidemic agents block inflammatory signaling cascades, an effect that is separate from their lipid-lowering properties (8). Statins can inhibit MMP-9 production by preventing the activation of neutrophils and macrophages (95). In addition, statins inhibit expression of MMP-9 and inducible nitric oxide synthase from SMCs and macrophages (99) and prevent the activation of nuclear factor-kappa B (NF-κB) (100). NF-κB suppression is associated with decreased aneurysm expansion (101). Statins usually offset the activation of upstream signaling pathways in the inflammatory cascade (102).

In animal studies, treatment of AAAs with simvastatin decreased aneurysm size and reduced MMP-9 and NF-κB levels by more than 50% (103). However, simvastatin did not significantly reduce elastin destruction or inflammatory cell infiltration. This finding suggests an alternative mechanism of action for simvastatin. In the same study, gene array analysis showed downregulation of more than 300 genes, most of which are involved in inflammation, immune function, synthesis or remodeling of extracellular matrix, and oxidative stress pathways (103).

Anti-inflammatory Agents

To suppress the inflammatory component of aneurysmal degeneration, investigators initially used nonsteroidal anti-inflammatory agents to prevent the aortic damage caused by macrophages and neutrophils (104–106). Studies have shown that indomethacin suppresses elastase-induced aneurysms through several mechanisms (24). In animal studies, indomethacin inhibited cyclooxygenase-2 (COX-2), and subsequently decreased prostaglandin E2 (PGE-2), IL-6, and MMP-9 levels (24,107). Histology demonstrated that indomethacin preserved elastin within the aortic media, even though infiltration of inflammatory cells was not decreased (24). In addition, indomethacin inhibited the release of inflammatory mediators from human AAA cultures (106).

More recent studies have shown that COX-2 and PGE-2 increase both the release and activation of pro-MMP-2 and pro-MMP-9 (108,109). Furthermore, PGE-2 increases the production of IL-6, one of the principal inflammatory cytokines in aneurysms (110). Soon after macrophage activation, COX-2 stimulates the release of TNF-α (111). The activation of macrophage proteinases leads to increased COX-2 expression and synthesis of PGE-2, creating a self-activating pathway (112). Studies of macrophage cultures have shown that COX-2 regulates chronic inflammatory diseases by affecting the degradation of extracellular matrix and tissue remodeling (112). Moreover, COX-2 inhibition prevents atherosclerotic plaques and decreases MMP-9 expression (111,112).

Immunosuppressants

Because of the significant inflammatory component of aneurysmal disease, immunosuppressants have been used in pharmacologic suppression of aneurysms. However, AAAs have developed in patients who were receiving long-term steroid treatment for diseases such as systemic lupus erythematosis and sarcoidosis.

In animal studies, glucocorticoids decrease the incidence and severity of elastase-induced aneurysms and reduce the degree of inflammation in the aortic wall (113,114). Histologic examination in the same studies showed preservation of the elastic lamellae of the aorta, due to decreased MMP-9 production by the inflammatory cells. Cyclosporine produces a similar effect (113). The success of drug-eluting coronary stents has led to the study of rapamycin in the treatment of aneurysmal disease. When administered systemically, rapamycin reduces aortic expansion (115); further studies are ongoing in this area.

Doxycycline

In addition to their antimicrobial actions, doxycycline and other tetracycline derivatives broadly inhibit MMPs, but the specific mechanism is unclear. Some investigators have proposed that doxycycline may accelerate the degradation of pro-MMPs before they are fully activated (116). Others have suggested that tetracycline may eliminate subclinical infection of the aorta, thereby decreasing inflammation and thus MMP-9 activity (117,118); however, this explanation seems unlikely because modified tetracyclines without antibiotic activity also inhibit experimental AAAs (119–122). Another possibility is that doxycycline decreases MMP-9 production by inhibiting transcription factors (119). Regardless of the mechanism, patients receiving doxycycline treatment have lower MMP-9 levels in plasma and the aortic wall (24,25,46,123).

In vitro studies of AAA explants have shown that doxycycline decreases MMP-9 secretion (121). Animal studies in multiple aneurysm models have shown that doxycycline inhibits tissue expression of MMP-9 and aneurysm development (24,25). In an elastase-induced AAA model, doxycycline decreased the size and incidence of aneurysms and the levels of MMP-9 (but not MMP-2) in a dose-dependent fashion (123). Furthermore, doxycycline reduced the incidence (35% vs. 85%) and degree of dilatation in an angiotensin II-induced aneurysm model (26).

Doxycycline has shown therapeutic benefits in human trials. Patients treated with doxycycline for two weeks before open aneurysm repair had a 400% decrease in the expression of MMP-9 in the aortic wall at the time of operation when compared with untreated patients (22). Six months of doxycycline suppression therapy in patients with small AAAs resulted in decreased MMP-9 levels and no significant progression of aortic dilatation, and the therapy was well tolerated with only a few patients experiencing minor, easily treated side effects (123). Randomized, placebo-controlled clinical trials of doxycycline are ongoing.

Nuclear Factor-Kappa B Inhibitors

NF-κB is a proinflammatory transcription factor that promotes expression of MMPs in macrophages. Several classes of drugs suppress aneurysmal degeneration and aortic dilatation through the NF-κB pathway. Salicylates, statins, NSAIDs, glucocorticoids, proteosome inhibitors, antioxidants, and selective peptide antagonists block this proinflammatory transcription factor (124,125). High-dose aspirin

inhibits NF-κB (104,105). In a recent study in mice, pyrrolidine dithiocarbamate, an experimental NF-κB inhibitor, prevented aortic dilatation after elastase perfusion, preserved elastin in the aortic wall, and significantly reduced levels of MMP-9, IL-1β, and IL-6 (126).

Losartan

Losartan, an angiotensin II type 1 receptor antagonist, has recently received substantial attention because of studies in a mouse model of MFS (72). Losartan prevented aneurysm formation in these mice; the proposed mechanism of action was inhibition of TGF-β, which led to preservation of the mechanical properties of the aortic wall. Because of these compelling results in animals, a clinical trial is being initiated to assess the efficacy of prophylactic losartan administration in patients with MFS. Of note, losartan did not prevent AAA formation in elastase-perfused mice (93). If losartan proves effective in patients with MFS, determining which other patient groups will benefit from this agent will be an important area of investigation.

POTENTIAL BENEFICIARIES OF EFFECTIVE SUPPRESSIVE THERAPY

The development of effective long-term suppressive therapy could affect treatment of aortic disease in several settings, including patients with small, asymptomatic aneurysms; patients unable to undergo aortic repair due to comorbidities; patients with chronic aortic dissection who are managed nonoperatively; patients with conditions that predispose them to the development of aortic aneurysms or dissections; patients with unrepaired aneurysms who are undergoing other operations; and patients who have undergone open or endovascular aortic repairs, but are at risk for repair failure due to disease progression (Table 2).

Patients with Small Aneurysms

The number of patients diagnosed each year with aortic aneurysms is increasing because of the aging population and the increased use of imaging studies. With the

Table 2 Potential Indications for Long-Term Suppressive Therapy

Patient group	Reason
Small, asymptomatic aneurysm that does not warrant surgical intervention	Prevent expansion and rupture
Not surgical candidates (comorbidities, age)	Prevent expansion and rupture
Chronic descending aortic dissection	Prevent expansion and rupture
Predisposed to aneurysm and dissecton: Marfan syndrome, Loeys–Dietz syndrome, Ehlers–Danlos syndrome, bicuspid aortic valve, familial aortic disease	Prophylaxis
Undergoing nonaortic surgery	Prevent perioperative rupture
Prior aneurysm repair	Prevent pseudoaneurysm and endoleak

initiation of screening programs in high-risk patients, more patients will be put on the "watchful waiting" list, with a potential catastrophic outcome. The management of patients with small, asymptomatic aneurysms is challenging. The size of an aneurysm is used to determine whether repair is indicated. Intervention is usually recommended for AAAs of at least 5.5 cm in anterior–posterior diameter or greater than twice the diameter of nonaneurysmal aorta. In the U.K. small aneurysm trial, open repair of AAAs smaller than 5.5 cm conferred no survival advantage (127). With the advent of endovascular procedures, however, smaller aneurysms are being repaired. Despite being minimally invasive, endovascular repair of AAAs is not without risks; mortality can be up to 9%, and 35% of patients have complications (128). Suppressive therapy might delay intervention permanently for many patients because their life expectancy is often shorter than the time necessary for the benefits of surgery to outweigh the risks (123). Even a 50% effective therapy could delay intervention for nearly a decade (Fig. 2) (123).

Patients Who Are Poor Surgical Candidates

Some patients face the diagnosis of aneurysm without the option for surgery because of comorbid illnesses. Open repairs require considerable physiologic reserve. Although endovascular repairs can be performed in many patients who are not candidates for open surgery, anatomical issues may preclude stent graft placement. The possibility of pharmacologic suppression of aneurysm expansion may be a lifesaving option in which patients may delay or avoid operations that carry the risk of significant morbidity and death.

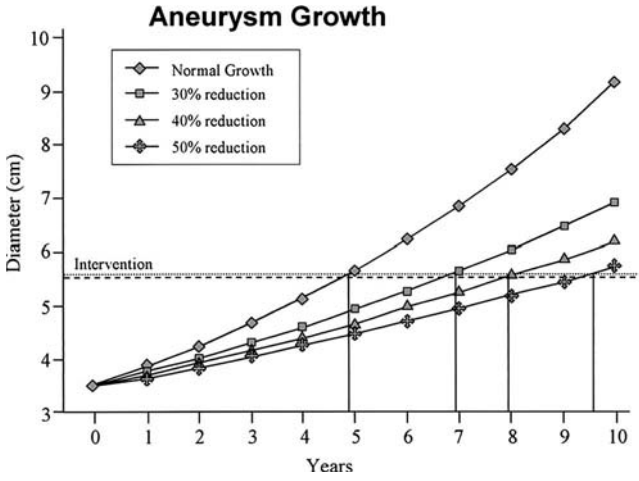

Figure 2 Diagram illustrating how even moderate suppression of aneurysm growth can substantially forestall the need for surgical intervention. *Source*: From Ref. 123.

Patients with Chronic Aortic Dissection

Similar to patients with small asymptomatic aneurysms, patients with chronic descending aortic dissection receive nonoperative management (i.e., anti-impulse therapy and imaging surveillance) until symptoms or significant aortic expansion occur. Unfortunately, the current pharmacologic approach has limited efficacy. Aneurysm expansion occurs in 43% to 81% of patients receiving nonoperative management of chronic descending aortic dissection, and fatal rupture occurs in up to 23% (87,129–132). Patients who ultimately require surgical treatment undergo extensive aortic replacement, an operation that carries substantial morbidity and mortality. Enhancements in pharmacologic treatment could improve the prognosis of chronic dissection.

Patients with Predisposing Conditions

Many patients are born with disorders that predispose them to aortic dilatation and aortic dissection. Patients with these conditions, including MFS, Ehlers–Danlos syndrome type IV, Loeys-Dietz syndrome, and congenital bicuspid aortic valve, often develop aortic complications at an early age (4,70,133). In addition, the rates of rupture are higher in patients with these syndromes. Suppressive medical therapy before aneurysm formation might dramatically alter the course for patients with known matrix defects.

Similarly, the risk for developing aortic aneurysms and dissections is high in some families. About 15% of patients diagnosed with AAAs have a first-degree relative who had an AAA (134). Mutations causing familial predisposition to TAAs and dissection have been described in several families (69,135,136). Young patients with a known family history of aortic aneurysms or dissection are screened aggressively so that aneurysms can be detected and treated before rupture. Long-term suppressive therapy may reduce the incidence of aneurysms and decrease the risk of dissection or rupture in these families.

Patients Undergoing Nonaortic Operations

Patients with aortic aneurysms who undergo nonaortic operations, such as cardiac, abdominal, and orthopedic procedures, are at risk of postoperative aneurysm rupture (137). Several retrospective or autopsy studies have suggested a 2% to 3% risk of aneurysm rupture in the months after any major surgery. Postoperative suppressive therapy may decrease this risk.

Patients Who Have Had Open or Endovascular Aortic Repair

Both open and endovascular repairs have limited durability. During open repair, the prosthetic graft is sutured to aorta that is prone to continued deterioration, resulting in new adjacent aneurysms or anastomotic pseudoaneurysms. The durability of endovascular repair relies on the ability of the stent graft to maintain an

effective seal against the aortic wall at the proximal and distal attachment sites. Dilatation of the aorta at the landing zones can lead to endoleaks and stent migration, complications that require reintervention to prevent the catastrophic consequences of aneurysm repressurization. Preliminary studies suggest that doxycycline therapy administered after endovascular repair may more rapidly decrease the size of the aneurysm sac in certain patients (unpublished data, John A. Curci). Suppressive pharmacologic therapy could become an important strategy for improving the durability of aortic repairs.

FUTURE DIRECTIONS

As our understanding of the pathobiology of aortic dilatation continues to expand, new potential treatment options will emerge. Determining the relationships of various molecular and cellular events during disease progression may allow for the identification of biomarkers. Reliable biomarkers that indicate the presence and severity of aortic dilatation could serve several important roles in the diagnosis and treatment of aortic aneurysms and dissection. In theory, changes in the relative circulating levels of various MMPs, cytokines, and products of matrix degradation could be used to follow progression through the stages of disease (Fig. 3). Using this type of biomarker profile, physicians might be able to detect aneurysm growth in patients undergoing nonoperative management or discover endoleaks in patients who have had endovascular aortic repairs. The ability to administer long-term suppressive therapy while using reliable biomarkers to assess efficacy would represent a major advance in the treatment of aortic aneurysms and dissection.

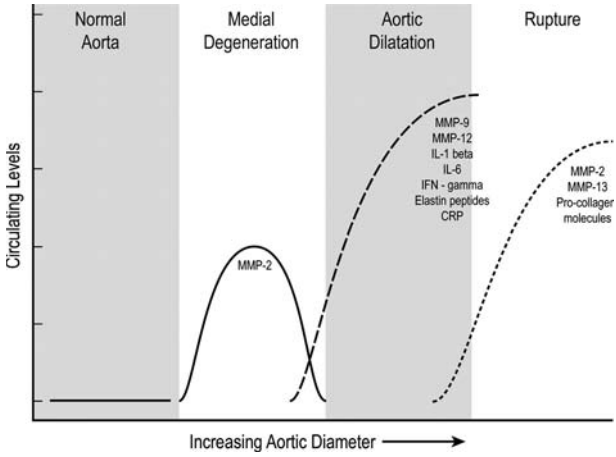

Figure 3 Diagram illustrating how relative changes in biomarker levels might be useful in following disease progression throughout the development of an aneurysm. *Abbreviations*: CRP, C-reactive protein; IFN, interferon; IL, interleukin; MMP, matrix metalloproteinase.

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DISCUSSION AND COMMENTARY

Questions for the Authors

What are the key pathobiologic features of abdominal aortic aneurysm formation?

Extracellular matrix proteolysis, chronic inflammation, cytokine activity, and smooth muscle cell loss all play a role in the development of abdominal aortic aneurysms.

What is the goal of currently available pharmacologic treatment options?

Current options focus entirely on reducing hemodynamic stress on the aortic wall.

What is the goal of the potential pharmacologic treatment options currently under investigation?

Future treatment options will address the cellular and molecular aspects of aortic degeneration in order to stabilize the mechanical properties of the aortic wall.

Why is doxycycline being studied as a potential treatment for abdominal aortic aneurysms?

Doxycycline broadly inhibits matrix metalloproteinases and prevents aneurysm formation in several animal models.

Why is losartan being studied as a potential prophylactic treatment for patients with Marfan syndrome?

Losartan is an angiotensin II type 1 receptor antagonist that also inhibits transforming growth factor-beta, an important mediator in aortic matrix degeneration. Losartan effectively prevents aneurysm formation in a mouse model of Marfan syndrome.

How important is it that a new treatment completely halts aneurysm expansion?

Although stopping aortic dilatation would be ideal, even modest reductions in the rate of aneurysm expansion would substantially delay the need for surgical intervention in many patients.

Is long-term suppressive therapy needed after aneurysm repair?

Yes. Patients who have had aneurysm repair remain at risk for degeneration of adjacent segments of aorta, which can cause the repair to fail. Long-term suppressive therapy may improve the durability of both open and endovascular aortic repairs.

18

Legal Considerations in Acute Aortic Diseases†

John A. Elefteriades

Section of Cardiothoracic Surgery, Yale University, New Haven, Connecticut, U.S.A.

INTRODUCTION

Most of this book concentrates on pathogenesis, imaging, diagnosis, and treatment of acute aortic diseases. There is, however, another major dimension to the care of patients with acute aortic diseases that it behooves us not to ignore—the medical-legal dimension.

As is well known, we in the United States find ourselves in the midst of a worsening crisis of medical malpractice litigation. This crisis is said to contribute to cost of healthcare through increased liability insurance expenses and through excess "defensive" patient testing (1,2). This crisis is said to be driving physicians out of high-cost states and high-risk specialties (3). Malpractice-related psychological forces are said to cause major emotional stress to physicians, manifest both at work and at home (1,4–7). Residency training is affected markedly by medico-legal concerns (4). Liability concerns and related expenses are thought to be among the major factors affecting choice of specialty for physicians in training (4,8). This is thought to be a factor in the alarming fall in applicants for residencies in Cardiothoracic Surgery. Among the six medical disciplines that face the highest frequencies of litigation and the highest malpractice rates (1,3,8), four are involved intimately in the assessment and treatment of acute presentation of aortic diseases: surgical specialties (cardiothoracic), radiology, emergency medicine, and anesthesiology.

†Adapted from an article in press in the journal *Cardiology*, with permission.

Diseases of the thoracic aorta are highly morbid conditions. Chronic aneurysms frequently produce death within several years of diagnosis. Acutely presenting aortic aneurysms and aortic dissections are often lethal within hours or days of onset. These conditions leave little room for error in diagnosis. Once diagnosed, thoracic aortic aneurysms require major surgery for correction. Although thoracic aortic operations are becoming progressively safer, reflecting improvements in hemostasis, graft materials, and surgical techniques, risks remain substantial and complications, when they do occur, can be devastating. Death, stroke, and paraplegia are the cardinal complications feared by thoracic surgeons. These are complications that can either take patients' lives or destroy their quality of life.

It is not surprising, with these high stakes, that diseases of the thoracic aorta are highly charged medico-legally and are frequently fodder for litigation.

Extensive attention has been placed in the past on litigation issues involving traumatic aortic transection—among the most highly litigated situations in cardiothoracic surgery and medicine in general. Mattox has addressed legal issues in traumatic aortic transection dissection insightfully and eloquently (9,10). Nontraumatic aneurysms and dissections, despite being much more common than traumatic aortic transections, have not received the same kind of direct attention to litigation-related issues. In fact, diseases of the thoracic aorta are responsible for more deaths in the United States than AIDS. This chapter study focuses specifically on nontraumatic aortic diseases and litigation surrounding their care.

In this chapter, we examine patterns of litigation in a relatively large number of legal cases revolving around diseases of the thoracic aorta. The author has published extensively on the scientific basis, natural history, and optimal treatment patterns of thoracic aortic aneurysm and dissection (11). For this reason, he is often asked to review patient files where suspicion exists that clinical evaluation and/or management fell below the standard of care. This chapter examines these cases for patterns of adverse events and resulting litigation.

It is hoped that focusing on litigation in nontraumatic aortic diseases may provide benefit in two forms. First, such examination may disclose pertinent, bona fide medical shortcomings, whose correction may enhance patient care and safety. Second, from concerted examination of legal case materials, suggestions for means to prevent litigation may be feasible—based on corollaries that can be drawn from the clinical patterns of the litigated cases. Thus, we hope that clinical and legal benefit may ensue from this examination of litigated cases.

CASE MATERIALS

In the last several years, the author has reviewed 30 legal cases involving thoracic aortic disease (Table 1). Among the 30 involved patients, there were 22 males and eight females. Ages range from 19 to 74 (mean 48.7).

Eight cases involved nondissecting aneurysms (three ascending, two descending, and three thoracoabdominal), 20 involved dissections [18 Type A

(*Text continues on pg. 337*)

Table 1 Individual Nontraumatic Thoracic Aortic Cases Reviewed

Patient no.	Age (decile)/sex	Aneurysm or dissection (plus location)	Onset of symptoms	Malpractice claim	Alive (A) or dead (D)	Meritorious (Yes/No)
1	50s/M	Type A dissection	Lifting heavy device on job	Failure to exclude from hazardous duty	D	N
2	71/F	Thoracoabdominal aneurysm	Ruptured in OR holding area, after case cancellation	Delay in surgery	D	N
3	50s/M	Type A dissection	Doing arm push-ups	Failure to diagnose (not until postmortem)	D	Y
4	40s/F	Type A dissection	Developed abdominal symptoms (nausea, vomiting, pain, anorexia)	Failure to diagnose on 2 ER visits (not until post-mortem) (CXR misread)	D	Y
5	50s/M	Type A dissection	Stress at work. Chest and abdominal symptoms	Delay in diagnosis (CT scan eventually demonstrated dissection, but patient died upon transfer to tertiary facility)	D	N
6	60s/M	Descending aneurysm (9 cm)	Surgery performed	Failure to prevent paraplegia	A	N
7	40s/M	Type B dissection	Subacute presentation (thoracic back pain)	Delay in diagnosis	D	Y
8	50s/M	Aortic rupture (descending)	Iatrogenic perforation during IABP placement	Surgical error. IABP placed during cardiac arrest resuscitative efforts	D	N

(*Continued*)

Table 1 Individual Nontraumatic Thoracic Aortic Cases Reviewed (*Continued*)

Patient no.	Age (decile)/sex	Aneurysm or dissection (plus location)	Onset of symptoms	Malpractice claim	Alive (A) or dead (D)	Meritorious (Yes/No)
9	60s/M	Aortic rupture (descending)	Weeks of chest and back pain	Delay in diagnosis (missed on CT scan)	D	Y
10	20s/M	Type A dissection	One week back pain, abdominal pain, bloody diarrhea	Failure to diagnose (not until postmortem)	D	Y
11	Teens/M	Type A dissection	Chest pain after training	Delay in diagnosis (died before transfer to tertiary facility)	D	Y
12	30s/F	Coarctation	Presented with CHF	Failure to prevent paraplegia	A	N
13	50s/M	Type B dissection (prior Type A repair)	Sudden onset chest pain	Delay in surgery. Ruptured awaiting catheterization	D	N
14	50s/F	Type A dissection	Pain on watching TV	Failure to diagnose (CXR misread)	D	Y
15	50s/M	Type A dissection	Pain on job	Failure to diagnose (arrested during cardiac catheterization)	D	Y
16	70s/M	Type A Dissection	Atypical chest pain	Delay in surgery for symptomatic aneurysm. 6.8 cm aorta ruptured	D	Y
17	70s/M	Thoracoabdominal aneurysm	Abdominal pain	Delay in surgery. Aneurysm diagnosed. Repeated CT scans looking for "signs of rupture." Patient's 7 cm aneurysm ruptured after being heparinized for atrial fibrillation	D	Y

18	70s/M	Ascending aneurysm (?iatrogenic dissection)	Operated urgently—aortic replacement	Improper postoperative care	D	Y
19	40s/M	Type A Dissection (s/p AVR X 2)	Abdominal symptoms (nausea, vomiting). Pancreatitis by enzymes	Failure to diagnose (not until post-mortem)	D	Y
20	30s/F	Type A Dissection	Chest pain 6 days post-partum. Bicuspid aortic valve	Failure to diagnose (not until post-mortem). Repeated r/o pulmonary embolism. Unaware of phenomenom of peri-pregnancy dissection	D	Y
21	60s/M	Thoracoabdominal aneurysm	Gut ischemia after difficult operation (atheroembolism)	Improper conduct of operation	D	N
22	30s/M	Type A Dissection	Acute GI symptoms	Failure to diagnose	D	Y
23	40s/M	Type A Dissection	Syncope, chest pain, bradycardia	Failure to diagnose (not until post-mortem)	D	Y
24	Teens/M	Type A Dissection (following prior aortic root operation)	Chest pain upon exertion	Inadequate pre-operative care. Died on OR table	D	N
25	20s/F	Type A Dissection	Chest pain two days after delivery of child	Failure to diagnose (not until postmortem). Rx'd for flu	D	Y
26	50s/M	Type A Dissection	Iatrogenic dissection during coronary angioplasty	Improper surgical conduct (ligated innominate artery)	A (Severe CVA)	Y

(*Continued*)

Table 1 Individual Nontraumatic Thoracic Aortic Cases Reviewed (*Continued*)

Patient no.	Age (decile)/sex	Aneurysm or dissection (plus location)	Onset of symptoms	Malpractice claim	Alive (A) or dead (D)	Meritorious (Yes/No)
27	70s/F	Ascending aneurysm	Postoperative AI, requiring early re-operation. Subsequent death	Improper surgical conduct (causing early AI)	D	Y
28	30s/M	Ascending aneurysm	Months of feeling unwell, with heartburn	Two month delay in cardiology consultation to f/u on diastolic murmur. Died of apparent rupture between echo/cath and surgical consultation.	D	Y
29	20s/M	Type A Dissection	Two weeks nausea, vomiting, feeling ill. No chest pain	Delay in diagnosis (repeated ER visits, diagnosed as "asthma, bronchitis"). Massive cardiomegaly when CXR ultimately done. Dissection of 10 cm aorta and massive AI found. Died of pulmonary edema	D	Y
30	40s/F	Type A Dissection	Sudden onset of abdominal pain/nausea/vomiting	Failure to make diagnosis (until post-mortem). CT scan mis-read.	D	Y

Abbreviations: AVR, aortic valve replacement; CHF, congestive heart failure; CXR, chest X-ray; CT, computed tomography; ER, emergency room; IABP, intro-aortic balloon pump; OR, operating room.

(ascending) and two Type B (descending)], and two involved miscellaneous other phenomena (one coarctation and one iatrogenic descending aortic rupture).

It is noteworthy that two cases involved peripartum aortic dissection in young, childbearing women.

Of the 30 patients, 27 had died at the time the suit was filed, and of the remaining three, two had paraplegia and one had a major cerebrovascular accident.

The allegations centered around the following issues:

1. Failure to make a diagnosis or delayed diagnosis in 17
   a. eleven failure to make antemortem diagnosis and
   b. six delay in diagnosis,
2. Delay in surgical therapy in four,
3. Error in surgical technique in four,
4. Failure to prevent paraplegia in two, and
5. Miscellaneous in three (failure to restrict activities, improper preoperative care, improper postoperative care).

The physicians being sued were often multiple and included emergency physicians, radiologists, cardiac surgeons, vascular surgeons, cardiologists, internists, and obstetrician–gynecologists.

FINDINGS

The reviewing physicians felt that medical care delivered was suboptimal in 21 cases and satisfactory in nine. This designation was not based on legal definitions of standard of care, but rather on whether or not retrospective case review revealed substantive diagnostic or therapeutic instances where care could have been improved.

In this review, it was found that litigation for nontraumatic thoracic aortic diseases involved the following categories of alleged malpractice, in decreasing order of frequency: failure-to-diagnose (or delay in diagnosis), delay in surgical therapy, error in surgical technique, failure to prevent paraplegia, and miscellaneous.

The seriousness of these cases is apparent in the sobering fact that, of the 30 patients, 27 were dead at the time of the lawsuits and the remaining three were permanently impaired by paralysis or stroke. This statistic underscores the highly lethal nature of thoracic aortic aneurysm and dissection. Mistakes, delays, and failure to include aortic diseases in the differential diagnosis can easily result in patient mortality or devastating debility.

Of all types of aortic disease resulting in lawsuits, Type A dissection predominates by a wide margin, accounting for 60% of our reviewed cases.

Helpful corollaries can be drawn from the observation in this study of the existence of several major patterns—both clinical and legal—for these aortic-related lawsuits. These patterns will be examined individually, category by category.

Failure to Diagnose (or Delay in Diagnosis)

Relative Infrequency of Aortic Dissection

Aortic dissection is relatively uncommon compared to other causes of chest pain, especially myocardial infarction. It is not surprising that this less common etiology of chest pain is not always paramount in the consciousness of emergency and primary care physicians responsible for screening the enormous numbers of patients who present with chest complaints. In fact, it has been estimated that, on the front lines, a physician will, on average, see 80 patients with acute coronary syndrome before encountering one with aortic dissection (12). In fact, over one and one-half million patients are admitted to hospital per year in the United States with chest pain. The emergency physician carries the burden of sifting out among this massive group of patients those with the relatively uncommon phenomenon of acute aortic dissection (13).

The "Great Masquerader"

Aortic dissection is known as "the great masquerader"—for good reason. Aortic dissection commonly extends from the top of the chest to the bottom of the abdomen—thus, gaining the capability to produce pain in the chest, the back, the flanks, the abdomen, and even the pelvis. Aortic dissection can also, by virtue of a false lumen bulging into the main arterial channel, occlude virtually each and every branch of the aorta—from the coronary arteries to the brain and arm vessels, to the spinal arteries to the visceral arteries to the leg vessels (Fig. 1). In view of its protean manifestations it is not surprising that aortic dissection has come to be known as the great masquerader—not only capable of producing chest symptoms, but also stroke, paralysis, abdominal pain, nausea and vomiting, and limb ischemia, among other symptoms and signs.

The difficulty of diagnosis of aortic dissection has been well documented in the scientific literature. Nearly 20% of affected patients present without typical signs and symptoms (i.e., without chest pain, malperfusion phenomena, cerebral disturbances, or signs of cardiac compromise) (14–16). Furthermore, clinical studies have documented that the diagnosis of aortic dissection is frequently missed on initial evaluation and not made until postmortem examination in 27% to 55% of patients (12,16–19). In fact, the diagnosis of aortic dissection is often made incidentally on an imaging study done for another reason (17). Thus, in a context where atypical presentation and failure to diagnose are common, the concept of "malpractice" in failing to diagnose aortic dissection becomes intrinsically suspect—especially, if one considers the common definition of malpractice based on what can be expected of a physician of average ability and training. The evidence cited in this paragraph argues for a high degree of leniency in the physician's favor in determining departure from the standards of care in thoracic aortic diseases. In fact, difficulty in diagnosis, delayed diagnosis, or failure to diagnose are so common as to approach the "norm" for this disease, even in the best hands, rather than the exception.

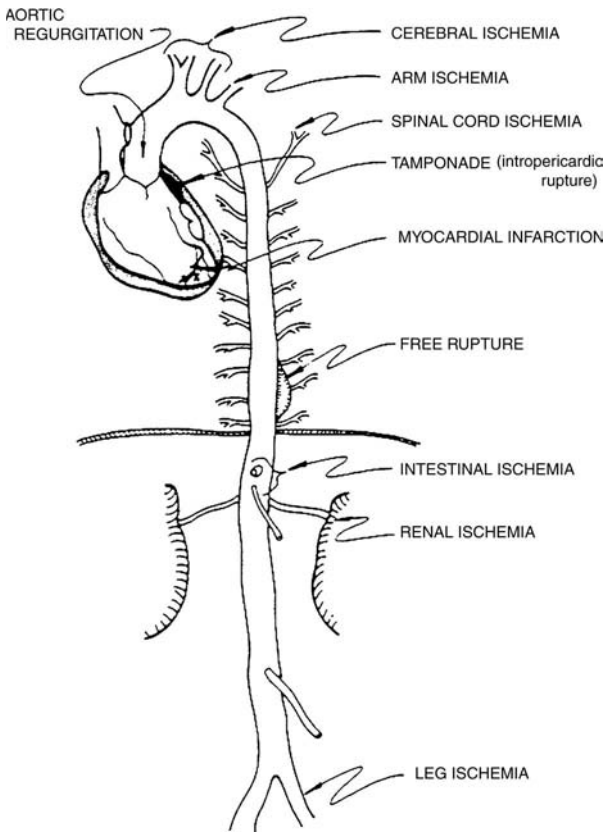

Figure 1 Aortic dissection can affect virtually any branch or any organ of the body, leading to potentially protean manifestations, and justifying the reputation as "the great masquerader."

Some quotations from the literature are in order to bring home the inherent difficulty in diagnosing aortic dissection. Spittel (17) indicates that "with such diverse clinical manifestations, the diagnosis of aortic dissection can be challenging, and misdiagnosis commonly occurs." Aortic dissection can be mis-diagnosed as, among other entities, myocardial infarction, pericarditis, congestive heart failure, pulmonary embolism, pneumothorax, lymphoma, and cholecystitis. Fradet (19) indicates that "acute aortic dissection remains a challenge for the physician."

For all these reasons, it is not surprising that failure to reach a diagnosis of aortic aneurysm or dissection (or delay in diagnosis) was by far the most frequent reason for aortic-related litigation in this series.

We have the following discrete suggestions to make, which promise not only to decrease the likelihood of lawsuits, but also to enhance patient care and save lives:

1. *Include aneurysm and dissection in the differential diagnosis.* Aortic aneurysm and dissection must have a prominent place in the consciousness

of physicians on the front lines of chest pain evaluation—especially emergency physicians and primary care doctors. The very process of including these diseases in the differential diagnosis of chest or abdominal symptoms will suggest that studies be done to rule these diseases in or out—the first step in preventing catastrophic oversight.

2. *Perform simple pertinent blood tests, including a D-dimer*. Creatine phosphokinase isoenzyme and troponin levels are useful in ruling in or out myocardial infarction. If these enzymes are negative, aortic disease must rise in the differential diagnosis of acute chest pain (this is especially true if the electrocardiogram (EKG) fails to show suspicious ST or T-wave changes of ischemia or infarction). The D-dimer is another useful test. D-dimer is a degradation product of fibrin crosslinking in clot. This test is sensitive for detecting on-going intravascular thrombosis. Emergency physicians are familiar with ordering this test to rule out pulmonary embolism. This test has a high sensitivity for that purpose. Less well known is the fact that D-dimer is nearly invariably elevated in acute aortic dissection. The sensitivity of this test is 99% (16). If the D-dimer is negative, acute aortic dissection is essentially ruled out. This is probably true because significant amounts of clot form quite quickly in the false lumen of any dissection, liberating D-dimer. In fact, the degree of elevation of D-dimer correlates with the longitudinal extent of the dissection, suggesting that surface area for contact of the bloodstream with the dissection plane determines D-dimer release. A large body of knowledge has now accumulated supporting the application of D-dimer in aortic dissection (20–23). In fact, bedside kits are now available (24). A recent paper has shown an extremely high sensitivity and specificity (90% and 97%, respectively) for aortic dissection of a test called smooth muscle myosin heavy chain assay (25). However, this test is not widely and immediately available in the clinical setting.
3. *Image freely, including the "Triple Rule-Out."* In many of the cases we studied, no imaging studies whatsoever were done, not even a chest X-ray. Had imaging been done, the lawsuit would have been prevented and, quite possibly, the patient's life saved.
    a. *Chest X-ray*. The chest X-ray can certainly provide useful clues—such as prominence of the ascending aorta to the right of the upper mediastinal contour, indistinctness of the aortic knob, and widening or distortion of the descending aortic stripe. Also, pulmonary congestion can be a helpful indicator of cardiac issues. We suggest this test as a minimum in patients with chest, or even abdominal, symptoms.
    b. *Echocardiogram.* The transthoracic echocardiogram is available on an urgent basis in nearly all emergency rooms. This test is highly sensitive for ascending dissection. It may show enlargement of the ascending aorta, a dissection flap, or aortic insufficiency—all clues to the existence of an aortic dissection.

c. *Computed tomography (CT) scan*. In nearly all cases, had a CT scan been done, the diagnosis would have been made and prompt, appropriate therapy begun. The CT scan is available in nearly all emergency rooms on an immediate basis. For patients with unexplained chest or abdominal symptoms, the CT scan can be remarkably pertinent and helpful. We use the CT scan for a "Triple Rule-Out." The three conditions most threatening to the patient with unexplained chest pain are aortic dissection, pulmonary embolism, and myocardial infarction (Fig. 2). In the current era of 64-slice CT scanners, all three diagnoses can effectively be ruled out within just a few minutes by a chest CT scan (13). The CT scan is sensitive for detection of dissection, pulmonary embolism, and coronary artery calcification. Absent any of these phenomena, the patient is unlikely to be in acute jeopardy from his symptoms. Another advantage of the Triple Rule-Out CT scan is that treatment with thrombolytic agents for presumed myocardial infarction can be disastrous in a patient who really has an aortic dissection (this occurred in one of the cases in this series, contributing to a lethal outcome). Such inappropriate thrombolysis can be prevented by the Triple Rule-Out CT scan.

4. *Read the imaging studies correctly*. In most of the cases with delay in diagnosis, the chest X-ray, echocardiogram, and/or CT scan were read incorrectly—because aortic dissection was not in the consciousness of the reader (Fig. 3). It was not until another individual reviewed the

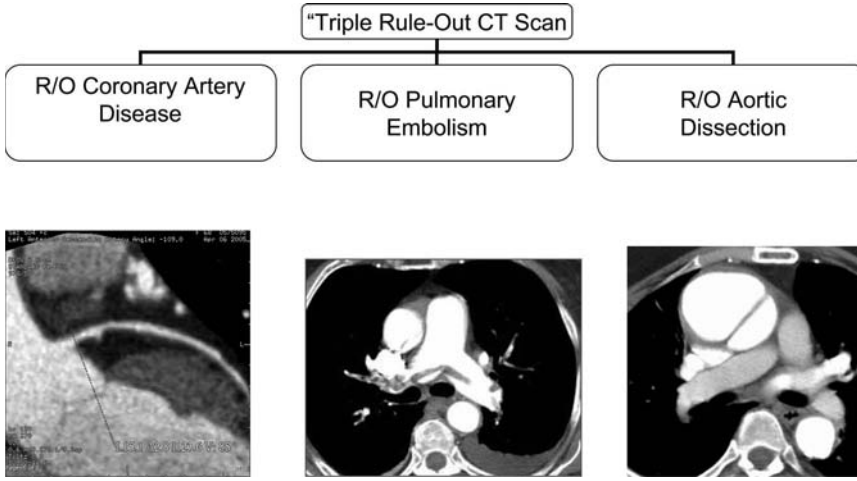

Figure 2 The "Triple Rule-Out" computed tomography scan that can be so useful in diagnosing or ruling out the "big three" conditions that threaten the life of the chest pain patient: coronary artery disease, pulmonary embolism, and aortic dissection. We strongly recommend its use.

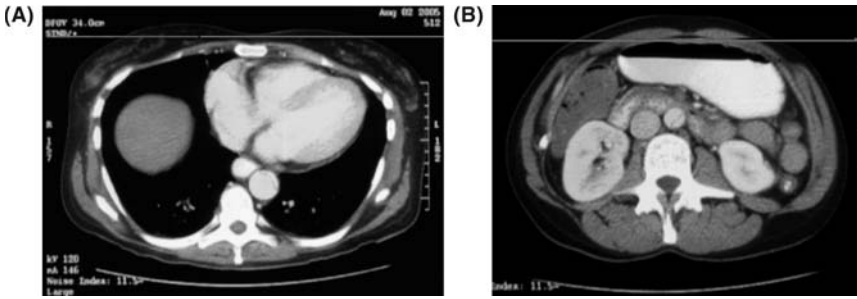

Figure 3 Computed tomography scan of patient with abdominal pain. A relatively subtle, but definite, aortic dissection was missed on these images. Note flap at thoracic (**A**) and (**B**) abdominal levels.

images that an initial negative reading was corrected—often with devastating results. We encourage radiologists to save an important place in their consciousness for aortic dissection. Remember to look at the aorta, even in a patient with abdominal pain. Look closely, as the flap of dissection may be subtle.

Delay in Surgical Therapy

In fairness, it must be recognized that the exact behavior of thoracic aneurysms and dissections cannot be predicted, even by the most highly trained, experienced, skilled, attentive, and intuitive physicians and surgeons. Four of the cases in this series involved a delay in treatment before surgery. It is appropriate for the medicolegal system to acknowledge the whimsical nature of aortic diseases. Not every patient presenting with radiographic or symptomatic aortic disease should be taken to the operating room immediately. In fact, we have outlined certain categories of acute dissection that can wait fairly safely to be operated in daytime hours, when many technical and personnel advantages accrue (26). This is especially true for patients whose onset of pain was more than 48 to 72 hours before referral to the tertiary center; these patients seem to have weathered the "eye of the storm" and can safely wait till morning for surgery.

Some of the lawsuits for delay in surgery had to do with the cardiologist's or surgeon's scheduling of catheterization or operation (Fig. 4). These temporally-based lawsuits, we feel, usually have little merit, as in the overwhelming majority of cases cared for, timing will prove adequate. The unpredictability of this disease makes it understandable that some minority of cases will rupture before the scheduled operating room time. By pure statistics alone, any major aortic center will be vulnerable each year, as some one of the hundreds of aortic cases cared for will likely rupture during workup, scheduling, or optimal patient preparation. We suggest that the legal system recognize this capricious nature of aortic diseases and show leniency in this regard.

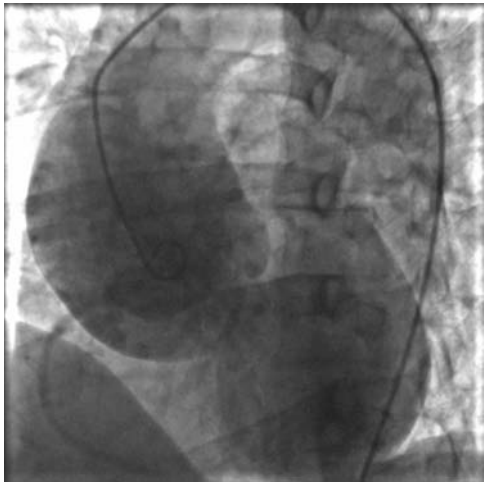

Figure 4 Ascending aortogram of a patient who died in the interval between diagnosis and surgical therapy. Note massive dilatation of ascending aorta, with wide-open aortic insufficiency.

Also, it must be recognized that the patient who suffers an aortic dissection presents with a medical problem of the highest magnitude. Even with optimal diagnosis and treatment, 15% to 25% of such patients will die with the presenting illness, and, even in the case of survival, their long-term prognosis will be less than the normal population (27,28).

In some of our cases, the scheduled operating room time was pre-empted at the decision of operating room administrators, because the surgeons booked the case as urgent but not emergent. Because the surgeon described his aortic case as "stable," other cases were given priority. We decry this type of administrative rescheduling and suggest that it be kept to an absolute minimum.

Failure to Prevent Paraplegia

It must also, in fairness, be recognized that, in the current state of the art, paraplegia cannot be fully prevented. Current paraplegia rates still run from 5% to 15%, depending on the location and extent of the thoracic or thoracoabdominal aneurysm to be resected. If a surgeon follows accepted practice guidelines (including distal perfusion, spinal drainage, and meticulous control of blood pressure), it is unfair to hold the surgeon accountable for paraplegia. Every aortic surgeon would be thus accountable nearly every year if that were the case. We suggest that the legal system recognize this limitation in surgical science, which we have tried for decades to ameliorate.

Family Patterns

It is becoming increasingly apparent that aortic aneurysm and dissection are familial diseases (29–31). We anticipate that, as this understanding disseminates, physicians will become vulnerable to lawsuits for not advising or screening at least first order relatives. Although this issue did not surface in the series of cases

reviewed over the last few years, we anticipate this will occur soon. We suggest that physicians begin immediately to counsel and/or screen close family members of patients with aortic aneurysm or dissection.

The recommendations made in this chapter do not take into account the economic burden of the clinical application of liberal aneurysm screening by CT scan, magnetic resonance imaging, or transesophageal echocardiography that we have recommended. Liberal screening will obviously take a financial toll. Such considerations exceed the limited scope of this investigation.

CONCLUSION

In the current medico-legal climate, if there is a bad outcome in an aortic case, it is quite likely that a lawsuit will eventuate. As Mattox (9) has indicated, a bad outcome in so virulent a disease does not necessarily imply malpractice. It is hoped that the observations in this series of aortic-related litigations—along with the corollaries that can be drawn from their analysis—will permit enhancement of patient care, with consequent reduction in the substrate for lawsuits. This chapter indicates, based on this analysis of a large number of aortic-related litigations, specific areas for improvement both for the medical profession (in the clinical care of patients) and for the legal profession (in the understanding that not all patients with aortic disease can have a good outcome). The virulence of thoracic aortic disease is indicated in a quotation from the great Canadian 19th century physician, Sir William Osler: "There is no disease more conducive to clinical humility than aneurysm of the aorta" (32). Although medical science has improved remarkably since Osler's era, we have far from conquered aneurysm disease. This manuscript, based on cases with unfortunate outcome, suggests ways to improve our diagnostic and therapeutic regimens further. Current scientific investigations, especially in the genetics, mechanics, and biologic assessment of thoracic aortic aneurysm, promise substantive advances in the near future (11).

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DISCUSSION AND COMMENTARY

Questions for the Authors

The potential for molecular genetic diagnosis of the aneurysm diathesis poses many ethical issues. In reference to children, how early in life will we want to have this diagnosis?

It is absolutely true that the advancement of genetic diagnosis in medicine, and the corresponding potential and actual molecular therapies, pose profound ethical issues. Many of these issues are eloquently and insightfully examined in a recent book by Gregory Stock (1). In terms of diagnosing the aneurysm diathesis in children, we hope that this will not place an undue emotional burden on the child or his parents. Acute aortic events are extremely uncommon until the teenage years. In the large Yale registry, we have just one pre-teen patient who suffered a Type A dissection (a 10-year-old girl, who died of this disorder). We currently recommend conventional echocardiographic screening in the early to mid-teen years. If the genetic tests advance as we hope, we see no reason not to screen from a blood sample or buccal swab in early childhood.

Do you predict that the RNA-signature gene chip will be used in Emergency Rooms for screening, in a fashion similar to the use of d-Dimer for pulmonary embolism?

We would be delighted if further in-the-field testing confirmed a sensitivity adequate for use of the RNA-signature gene chip for screening purposes. This remains to be determined. Another use we hopefully envision would involve screening of family members of affected individuals. Ultimately, screening of the general population, as in the use of the PSA for prostate cancer, can be envisioned as well. All of these applications are at this time potential, but as yet unrealized or proven, avenues for diagnosis.

Stress is a factor in precipitating acute aortic dissection. Could the molecular confirmation of the aneurysm diathesis in a particular patient contribute to stress and, thus, help to precipitate an aortic dissection?

This is certainly possible. A similar potential exists for conventional imaging studies like echo, CT, and MRI scanning.

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19

Future Prospects: Molecular Diagnosis, Enhanced Imaging, Molecular-Based Conventional Drugs, and Gene Therapy

John A. Elefteriades

Section of Cardiothoracic Surgery, Yale University, New Haven, Connecticut, U.S.A.

INTRODUCTION

The great vascular surgeon Dr. John Chang asked the author to give a lecture on the present and future of medical care for aneurysm disease. This provided an opportunity to look forward into the future and speculate as to what advances would occur in the next decade or so. These possibilities are depicted in Figure 1.

MOLECULAR DIAGNOSIS OF ANEURYSM DISEASE ON A GENETIC BASIS

First and foremost, we stand on the cusp of molecular diagnosis of the aneurysm diathesis. The molecular genetics of Marfan's disease have been known for some time. Marfan's disease, as we know, is just the tip of the iceberg, accounting for only 5% to 10% of patients with thoracic aortic aneurysm and dissection. Medical science is now homing in on the remainder. The pioneering work of Dr. Diana Milewicz, presented in her own words in Chapter 6, has made great strides toward elucidating the genetics of thoracic aortic aneurysm. She has made this progress through the application of linkage analysis to large families with aortic aneurysm

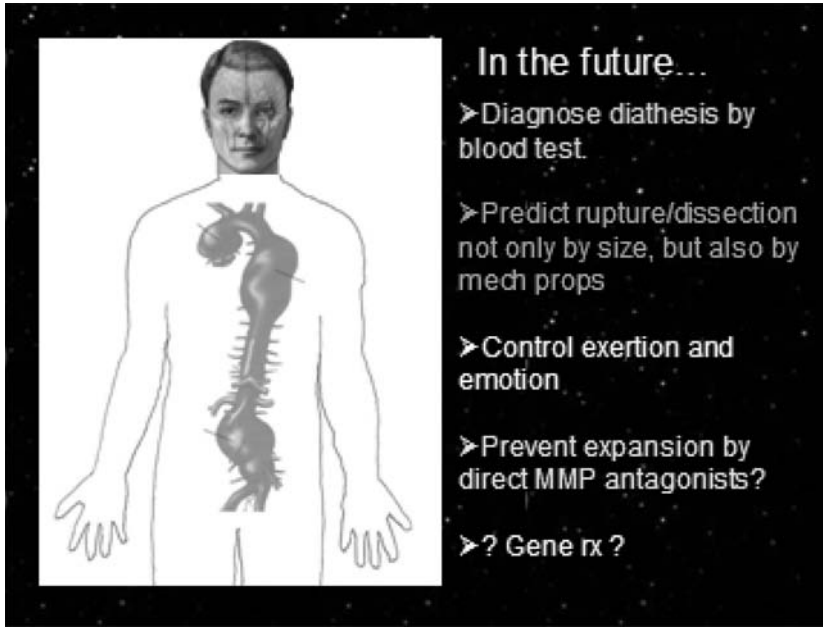

Figure 1 (*See color insert*) Future prospects in care of aneurysm disease.

disease. She has enumerated various categories of mutations, which comprise considerable portions of the population with thoracic aortic aneurysm. Our own laboratory, in conjunction with colleagues at Celera Diagnostics and Applied Biosystems, has been performing genome-wide scanning of large libraries of specific single nucleotide polymorphisms in hundreds of patients affected by thoracic aortic aneurysm. We are hopeful that DNA patterns will be uncovered that can diagnose a genetic aneurysm diathesis. At the RNA level, we have already achieved some success, with identification of upregulated and downregulated RNAs that distinguish patients with thoracic aortic aneurysm from controls (1–3). We are in the process of reducing this testing to a clinically applicable 41-RNA gene chip that can be used at the bedside (Fig. 2). If this "RNA Signature" profile is borne out in more extensive clinical testing, it may be possible to test a chest pain patient on presentation to the emergency department for the aneurysm diathesis. The diagnosis of aneurysm disease on a molecular, genetic basis is becoming a reality. This means of diagnosis is virtually assured of advancing dramatically in the near-term future.

FURTHER ADVANCEMENTS IN DIAGNOSTIC IMAGING OF THE AORTA

Diagnostic imaging has undergone tremendous advancement in the last decade. Three-dimensional imaging techniques [computed tomography (CT), magnetic resonance imaging (MRI), transesophageal echocardiography (TEE)] have virtually supplanted angiography in imaging of aortic aneurysms and dissections and,

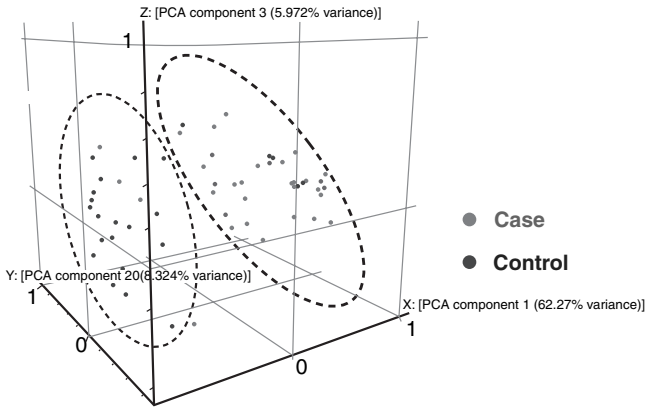

Figure 2 (*See color insert*) RNA "Signature" analysis allows effective discrimination (in three-dimensional space) of aneurysm patients ("cases") from controls, on the basis of examination of peripheral blood alone.

evidence suggest, this is only the beginning (4,5). Predictions are that CT scanners will become so compact that they will be carried by paramedics in the field and on ambulances, relaying images to the emergency department from the moment of arrival on the scene. Diagnosis will be expedited dramatically. Catheters may be replaced by "remote-controlled electronic devices that … like microscopic missiles, travel through vessels to reach organs or tissues"(4). These devices are powered by the energy of an MRI field. Tissue imaging and molecular imaging are on the horizon. Improved imaging has been the cornerstone of advancement in the diagnosis and treatment of aneurysms and dissections. More of the same appears to be in store.

BIOMARKERS FOR CLINICAL FOLLOWUP, EVENT PREDICTION, AND SURGICAL DECISION MAKING

As we have seen in Chapter 12, on the natural history of thoracic aortic aneurysms, the diameter of the aorta is key in determining the patient's future and in our making the decision for pre-emptive surgical extirpation of the aneurysmal aorta. However, dimensional criteria, while very helpful, are far from ideal. The potential to use biomarkers to study the progression of aortic disease is very real. It is now becoming clear that serum levels of matrix metalloproteinases (MMPs) are quite reflective of tissue levels for both abdominal and thoracic aortic aneurysms (see Chapters 8 and 17). This raises the potential to follow the aneurysm state by serial assessment of serum MMPs. One study (6) already shows that MMP serum levels rise as aneurysms increase in size. Another (7) suggests that MMP rise may precede or accompany acute aortic dissection. Our "RNA Signature" profile may also change over time. It may be that a "blip" in one or more of these potential biomarkers may herald the onset of the acute aortic events

that are the subject of this textbook. Such a "blip" may alert us that pre-emptive surgery should be carried out.

MECHANICAL PROPERTIES AS MONITORS AND PREDICTORS

As explained in Chapter 7, on mechanical properties of the aorta, we have accumulated evidence that aortic distensibility and wall stress can be measured by epiaortic echocardiography. If we can make similar measurements by TEE, then this can become a clinical tool. We may, in the future, monitor not only size on a yearly basis, but also aortic distensibility and aortic wall stress. We may be able to develop criterion levels of these biomechanical parameters that signal looming adverse events and mandate surgical intervention.

CONTROL OF ENVIRONMENTAL FACTORS

As detailed in Chapters 10 and 11, it is becoming clear that physical exertion and extreme emotion are often the triggers that cause aortic dissection in an individual who is susceptible on the basis of genetic predisposition and underlying aortic enlargement. We are already beginning to limit physical activity in patients with known aortic enlargement. Although we cannot live our lives without stress, it is possible that altering a patient's life milieu (e.g., job change) may decrease episodes of stress. Also, medications may be applied to limit emotional stress in extremely vulnerable individuals. We have also recommended widespread screening of individuals engaging in extreme physical training, to uncover occult aortic enlargement and prevent tragic deaths. We hope that this recommendation will see application, despite societal and economic restraints.

MATRIX METALLOPROTEINASE ANTAGONISTS TO PREVENT ANEURYSM GROWTH

We are on the cusp of effective treatment for aneurysm disease. The role of beta blockers, which have emerged as standard of care therapy despite a paucity of evidence, has been controversial for decades. New evidence, presented in Chapters 8 and 17, suggests that direct MMP inhibitors may slow the process of aneurysmal degeneration. Although the antibiotic doxycycline has been used most widely, in the pioneering efforts of Dr. Thompson, many specific MMP inhibitors are under development and hold great promise for the future. Medical science has been excited by the work of Dietz et al., with the angiotensin receptor blocker Losartan in preventing aneurysm growth in an animal model of Marfan's disease. As Dr. Botta explains in Chapter 7, this drug as well may work through a final MMP-related pathway. The future is bright for drug therapy based on breakthroughs in understanding the molecular pathophysiology of aneurysm disease.

GENE-DIRECTED CONVENTIONAL DRUG DEVELOPMENT

As we identify the aberrant genes responsible for aneurysm development, we will be able to pinpoint the corresponding errant proteins coded by those genes. Such understanding can suggest specific avenues for development of conventional drugs to strengthen those proteins.

GENE THERAPY

The overall status of gene therapy is reviewed beautifully in a book by Stock (8). As we understand the genetics of aneurysm disease, direct gene therapy will certainly become a consideration.

All of this points toward a bright future for the therapy of acute aortic diseases and for our affected patients.

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20

The Key Lessons of This Book—In a Nutshell

John A. Elefteriades

Section of Cardiothoracic Surgery, Yale University, New Haven, Connecticut, U.S.A.

The various chapters of this textbook have provided up-to-the minute information from authorities in a wide variety of disciplines impacting on acute aortic diseases—from genetics to pathophysiology to imaging to clinical presentation and diagnosis to surgical treatment and future prospects. It is hoped that this information will benefit a multidisciplinary group of medical professionals interested in and involved with these disorders and, ultimately, contribute to the clinical care of affected patients.

Every chapter likely includes some information not previously familiar to each of us, even those of as intimately involved in the scientific investigation and/or clinical care of acute aortic diseases.

For purposes of review and ease of assimilation, the key points from each chapter are summarized in Table 1.

Osler said a hundred years ago that "there is no disease more conducive to clinical humility than aneurysm of the aorta." Although this is still true, through our combined efforts in many related disciplines, we are definitely gaining ground against this disease—in favor of our patients.

Table 1 A Summary of the Key Points of Each Chapter

Chapters	Title	Author names	Key points
1	Terminology and Classification	Nienaber	Dr. Nienaber classifies aortic dissections based on: Etiology Anatomy Acuity Clinical predictive patterns. The Stanford classification (Type A = ascending, Type B = descending) has been most widely adopted. Alternate classifications (e.g., Lansman's) are more detailed anatomically and accommodate more of the precise information now available from three-dimensional imaging.
2	Symptoms and Signs	Isselbacher	Aortic dissection is "the great masquerader," with protean potential manifestations. Abrupt onset of pain distinguishes dissection from myocardial infarction. "One cannot make a diagnosis that one does not consider."
3	Imaging	Danias	CT, MRI, and TEE are all acceptable imaging modalities for the diagnosis of aneurysm and dissection. In ambiguous cases, dual modalities should be employed.
4	Putting It All Together	Eagle	The most reliable presenting symptom characteristic of aortic dissection is sudden onset of severe pain in the anterior chest or back. Anterior chest pain suggests ascending dissection. Interscapular back pain suggests descending dissection. Painless aortic dissection can occur (6% of cases), especially in the elderly and in diabetics. Hypotension on presentation with aortic dissection portends poor prognosis (mortality >50%). Differentiation from MI is essential, as anticoagulation may have disastrous consequences in case of aortic dissection. Diagnosis of aortic dissection requires a flap: "No flap, no dissection." IMH and PU are nonflap variants of dissection-type disease.

5	Epidemiology: Incidence, Prevalence, and Trends	Elefteriades/Rizzo	Aneurysm causes more deaths in the U.S. than HIV disease Aneurysm and dissection are truly increasing in frequency (not just being diagnosed more effectively). Ruptured AAA affects about 10/100,000 patients per year. Ruptured AAA or AAD affect about 7/100,000 patients per year. If a screening abdominal ultrasound exam is negative at 65 years of age, that patient will never die of ruptured AAA.
6	Genetics of Aortic Aneurysm and Dissection	Milewicz	Marfan's disease is autosomal dominant. Three-fourth of Marfan's cases are transmitted from parents, but one-fourth represent new mutations. Over 600 specific mutations have been registered, producing the Marfan's abnormality in fibrillin-1. A second Marfan's locus has recently been identified. Loeys–Dietz is a newly described genetic syndrome associated with aneurysm disease. Familial thoracic aneurysm disease occurs frequently, in the absence of named genetic syndromes like Marfan's disease. Dr. Milewicz's ground-breaking work has identified the following loci for familial aortic aneurysm: TAAD1 (20–30% of cases) FAA1 TGFBR2 (5% of cases) MYH11. Much attention is currently being focused on the TGF-β pathway and its potential blocking by Losartan.
7	Mechanical Properties	Elefteriades/Koullias	Biomechanical properties of the aorta can be calculated from echocardiographic measurements. Distensibility becomes seriously impaired and wall stress increases dangerously at an aortic diameter of 6 cm. Monitoring of mechanical properties of the aorta may become feasible in the near future.

(*Continued*)

Table 1 A Summary of the Key Points of Each Chapter (*Continued*)

Chapters	Title	Author names	Key points
8	MMPs in Aortic Disease	Botta/Elefteriades	MMPs are definitely involved in the pathogenesis of aortic aneurysm and dissection. MMP levels are elevated in abdominal and thoracic aneurysms. Blood levels mirror tissue levels of MMPs. Inhibition of MMPs makes physiologic sense for impeding aneurysm growth. The ARBs (Losartan) have shown promise in very preliminary studies
9	Molecular Biology of Aortic Destruction	Botta/Tang/Tellides/ Elefteriades	The aorta "plays a game of catch" with the stroke volume, absorbing some of the force in systole and transmitting this stored energy back in diastole. Thus, the aorta is "much more than a tube." VSMCs serve both a motile and a secretory function. The balance between production and destruction of matrix proteins is largely orchestrated by the VSMCs. MMPs are excessively active in aneurysm disease, leading to excess proteolsis in the aortic wall. Aneurysm formation proceeds through a combination of inflammation, inflammation-induced proteolysis, and mechanical forces. Once the aneurysm process begins, its progress is assured.
10	Weight Lifting and Aortic Dissection	Elefteriades	Evidence is mounting that weight lifting brings on acute dissection via extreme elevation of BP during the effort cycle. Aneurysm patients should be cautioned against heavy lifting or straining. Individuals embarking on strenuous exercise programs should be screened for occult aortic dilation.
11	Timing of Acute Aortic Events	Elefteriades	Extreme emotion or exertion bring on dissection in an aorta susceptible by virtue of pre-existing enlargement.
12	Natural History of Aortic Aneurysm	Coady/Elefteriades	Aortic aneurysm is lethal, but indolent, growing at about 0.1 cm/yr for the ascending aorta. Acute aortic events (rupture and dissection) begin to occur with frequency at 5.5–6 cm diameter of the ascending aorta. Pre-emptive surgical intervention before those sizes are reached is prudent.

13	Ruptured Aneurysm: Abdominal and Thoracic	Ashirari/Farkas/ Elefteriades	For ruptured AAA, caution in fluid resuscitation is warranted, even at the expense of moderate hypotension, so as to prevent free rupture prior to clamp application. For AAA, initial supraceliac clamping is often essential. For AAA, catheter-based therapy for rupture is growing in popularity. For TAA, the "clamp and sew" technique (without perfusion adjuncts) is appropriate when free rupture has occurred. Surgical techniques are depicted in chapter figures.
14	Acute Aortic Dissection: Anti-Impulse Therapy	Fuster	Death rate is 1–2%/hr early after acute aortic dissection. Elastin (distensible) absorbs the force of cardiac contraction, but collagen (inelastic) supplies the tensile strength of the aorta. The adventitia is the "strength" layer of the aorta. By Laplace's law, thickness of the arterial wall decreases wall stress. The maximal rate of pressure rise (dp/dt_{max}) appears to be the most important determinant of aortic rupture and the progression of dissection. IV esmolol is a nearly ideal agent for initial lowering of dp/dt for acute aortic dissection, because of its: Rapid onset of action Short half-life of distribution Rapid elimination Suitability in renal/hepatic disease (hydrolyzed by erythrocytes). When β-blockers are contraindicated, calcium channel blockers are the next line agents, although conclusive evidence of a beneficial action on dp/dt is lacking. Nitroprusside should not be used without β-blockade, as alone it can increase dp/dt. Pericardiocentesis appears to be contraindicated for tamponade from acute Type A aortic dissection, even as an interim measure before the OR.

(*Continued*)

Table 1 A Summary of the Key Points of Each Chapter (*Continued*)

Chapters	Title	Author names	Key points
15	Surgical Therapy: A Primer	Elefteriades/Griepp	First job is to achieve patient survival: Discretion should be used in replacing the aortic arch. Discretion should be used in replacing the aortic root. An open distal anastomosis, under DHCA, is preferable. Descending dissections can achieve a survival of 80–90% with "anti-impulse" therapy alone. Operation for descending dissection is required in case of rupture, uncontrolled symptoms or rapid enlargement, or organ ischemia. Surgical techniques are depicted in chapter figures.
16	Stent Therapy	Bavaria	Complications of stent therapy arise most commonly from accessing the central aorta from the femoral or iliac arteries. Stent therapy appears to have a role in treatment of: Aortic transection Certain descending dissections IMH and PAU Ruptured descending aneurysms. Stent therapy has no current role in ascending dissections. Longer term f/u is required to determine the durability and appropriate role of stent therapy. Paraplegia, stroke, and renal failure still occur, even with stent therapy.
17	Long-Term Suppressive Therapy	LeMaire/Thompson	Aneurysm formation involves: Extracellular matrix proteolysis Chronic inflammation Cytokine activity SMC loss.

			The benefit of β-blockers for long-term prevention of aneurysm expansion and rupture is far from proven. Potential future treatment options include: Statin medications Anti-inflammatory agents (COX-2 inhibitors) Immunosuppressants (rapamycin) Antibiotics (doxycycline) ARBs (Losartan). Suppressive therapy may have a role in treatment of patients with predisposing conditions, patients with small aneurysms, patients who are poor surgical candidates, patients with chronic aortic dissection, patients who have already undergone open or endovascular repair (to protect the remaining aorta), and patients with aneurysms undergoing nonaortic operations (to prevent aneurysm "activation" and early rupture).
18	Litigation	Elefteriades	Consider aortic dissection. Check D-dimer (100% sensitive). Image liberally. Consider the "Triple Rule-Out CT scan" (PE, CAD, dissection).
19	Future Prospects	Elefteriades	DNA diagnosis of aneurysm diathesis. RNA diagnosis of acute dissection. Biomarkers for clinical followup. Genetic-guided conventional drug development. Control of physical and emotional stress.
20	Key Lessons	Elefteriades	See this Table.

Abbreviatons: AAA, abdominal aortic aneurysm; ARBs, angiotensin receptor blockers; BP, blood pressure; CAD, coronary artery disease; CT, computed tomography; DHCA, deep hypothermic circulatory arrest; IMH, intramural hematoma (of aorta); IV, intravenous; MI, myocardial infarction; MMPs, matrix metalloproteinases; MRI, magnetic resonance imaging; OR, operating room; PE, pulmonary embolism; PAU, penetrating ulcer (of aorta); SMC, smooth muscle cells; TAA, thoracic aortic aneurysm; TEE, transesophageal echocardiography; VSMC, vascular smooth muscle cells.

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Figure 2 (*from Preface—see text page x*) Albert Einstein, Lucille Ball, Jonathan Larson (author of "Rent"), Flo Hyman (Olympic volleyball player), George C. Scott, and John Ritter are just a few among scores of brilliant people whose lives were cut short by acute aortic diseases.

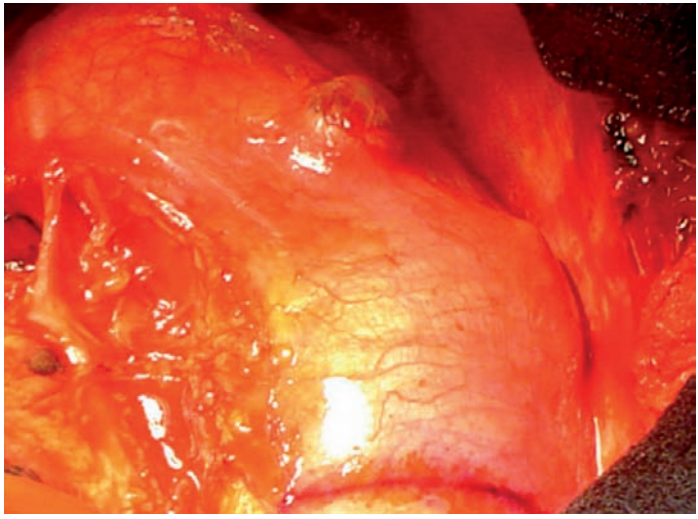

Figure 1.B Note multiple penetrating aortic ulcers, although only one was suspected radiographically.

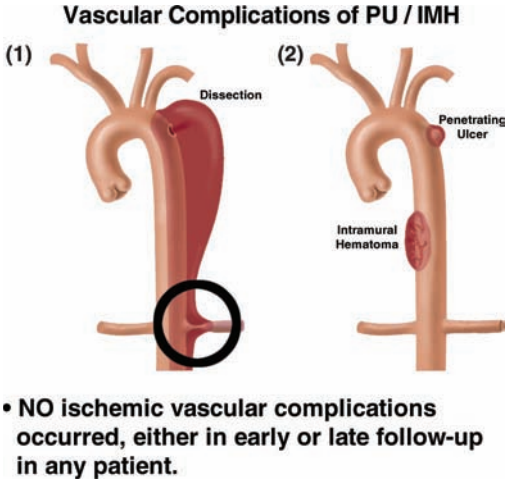

Figure 1.C Note from schematic depictions that typical dissection (**1**) often impairs branch vessel flow, but this never happens with IMH and PAU (**2**). *Abbreviations*: IMH, intramural hematoma; PAU, penetrating aortic ulcer.

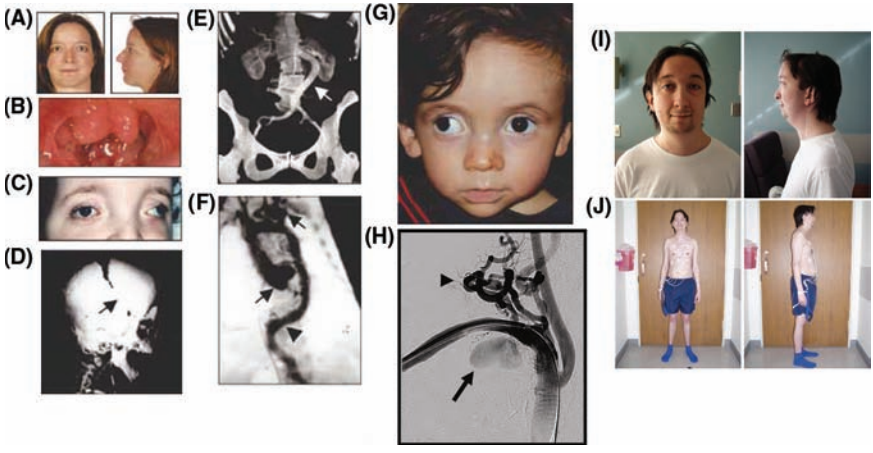

Figure 6.2 Variable clinical presentation of individuals with transforming growth factor β receptor (*TGFBR1* or *TGFBR2)* mutations. Individuals may present with hypertelorism and malar flattening (**A**); bifid uvula (**B**); marked hypertelorism with exotropia (**C**); premature fusion of the coronal suture of the skull (*arrow*, **D**); marked tortuosity of the aorta (*arrow head*), aortic root and subclavian artery aneurysms (*arrows*) or tortuous abdominal aorta (*arrow*) (**E,F,H**); micrognathia, retrognathia, downslanting palpebral fissures, and skeletal features including pectus excavatum, scoliosis, and pes planus (**G,I,J**). *Source*: From Refs. 21, 51.

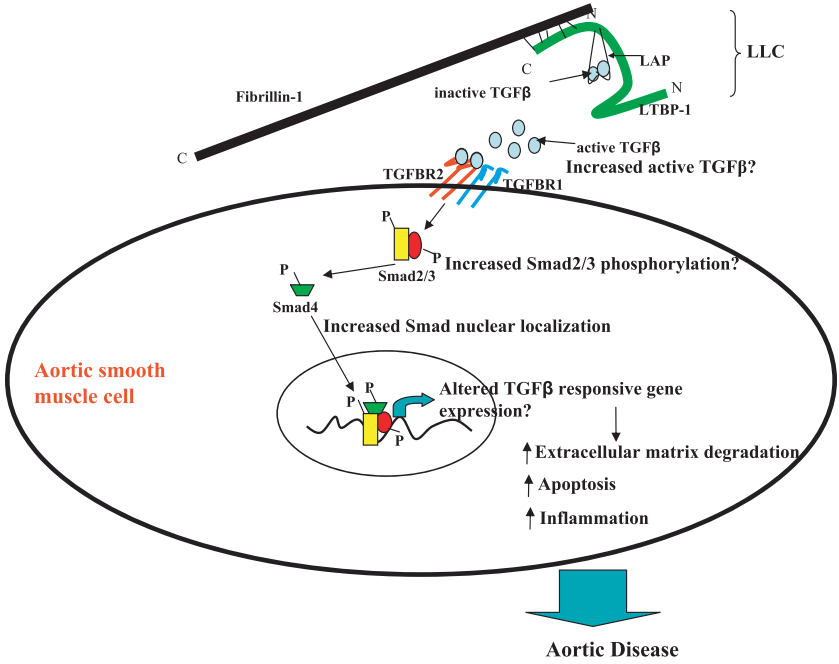

Figure 6.10 A potential molecular pathway of dysregulation of transforming growth factor (TGF)-β leading to aneurysms and dissections. TGF-β is secreted in a biologically inactive form and stored in the extracellular matrix in a complex termed as the large latent TGF-β complex, consisting of a TGF-β homodimer associated with the latency-associated peptide, and the latent TGF-β binding protein-1. Dysregulated TGF-β signaling results from mutations in *FBN1*, *TGFBR1*, or *TGFBR2*, leading to altered transcription of TGF-β responsive genes, and ultimately resulting in degenerative changes in the vessel wall leading to aneurysms and dissections. *Abbreviations*: LAP, latency-associated peptide; TGF, transforming growth factor; TGFBR, transforming growth β-receptor. *Source*: From Ref. 59.

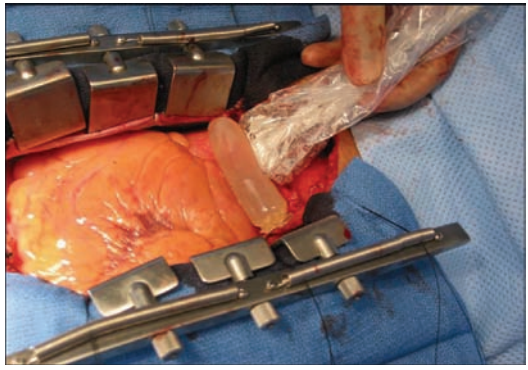

Figure 7.1 The technique of epi-aortic echocardiography. Note the fluid-filled interface between the probe and the aortic wall.

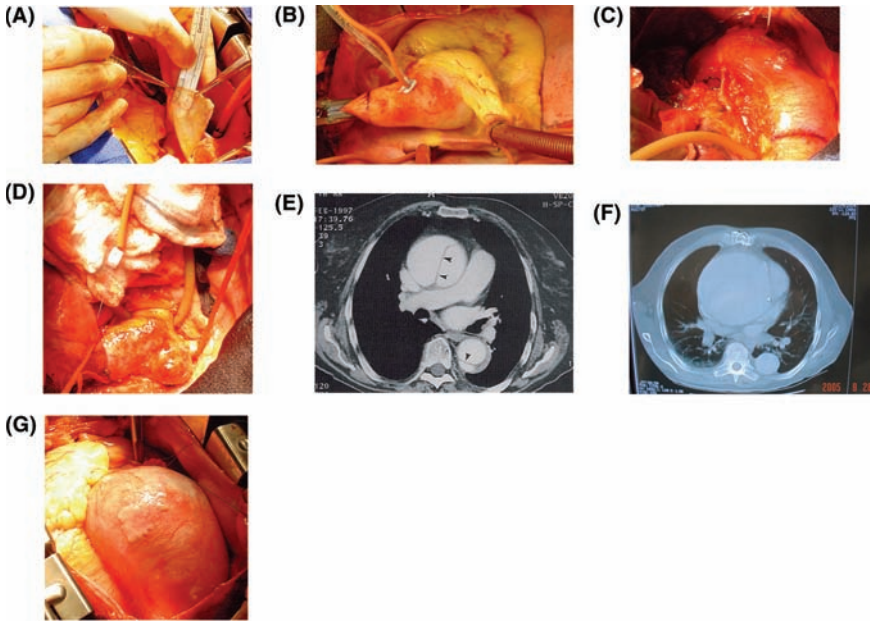

Figure 8.1 Dramatic clinical examples of aortic destruction, likely at least in part at the hands of excess lytic activity of matrix metalloproteinase. Clockwise, from upper left hand corner: (**A**) An ascending aorta rendered so thin that the markings on a ruler can be read right through the aortic wall. (**B**) Severe annulo-aortic ectasia. Note aneurysm partially hiding under right ventricular outflow tract. (**C**) Descending aortic aneurysm, with penetrating ulcer, appearing "ready to burst." (**D**) Massive descending aortic penetrating ulcer/saccular aneurysm-precarious in appearance. (**E**) Ascending aortic dissection, with descending aortic intramural hematoma. (**F**) Massive ascending aortic aneurysm on computed tomography scan. (**G**) Massive ascending aortic aneurysm at operation. (Head of patient is to right and below).

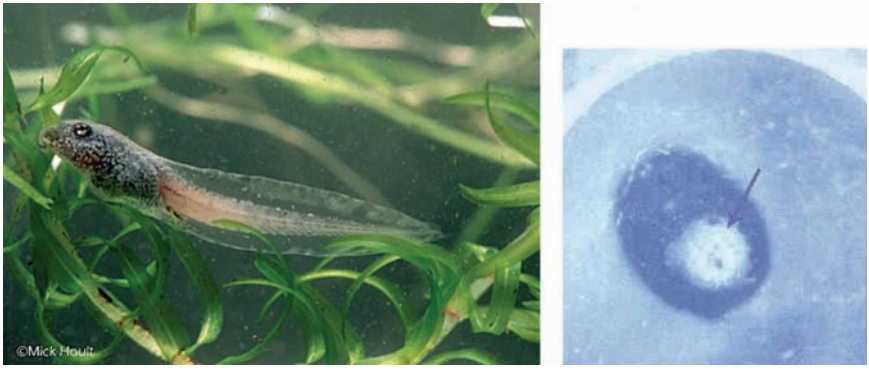

Figure 8.3 Matrix metalloproteinases were discovered when it was noticed that a piece of tadpole tail digested the collagen on a laboratory plate. *Source*: From Ref. 24.

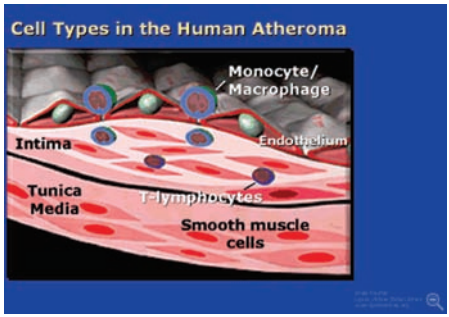

Figure 9.1 Histology of aortic wall, emphasizing the three layers of the aortic wall (intima, media, adventitia). Not the depiction of the vascular associated lymphoid tissue and vascular smooth muscle cells, which are so important in the inflammatory and lytic processes underlying the pathophysiology of aneurysm development. Note the lamellar architecture of the media (collagen and elastin) and the matrix.

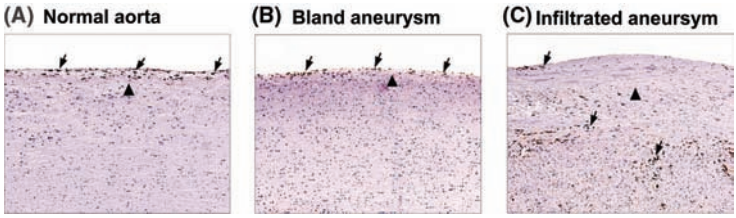

Figure 9.3 Stain for leukocytes in aortic wall (by immunohistochemistry using an antibody to the pan-leukocyte marker CD-45). Note relative paucity of leukocytes in normal aorta and "bland" ascending aortic aneurysm. Note marked leukocytic infiltration in "inflammatory" aneurysm. Arrows denote leukocytes. Arrowhead indicated border between media and adventitia.

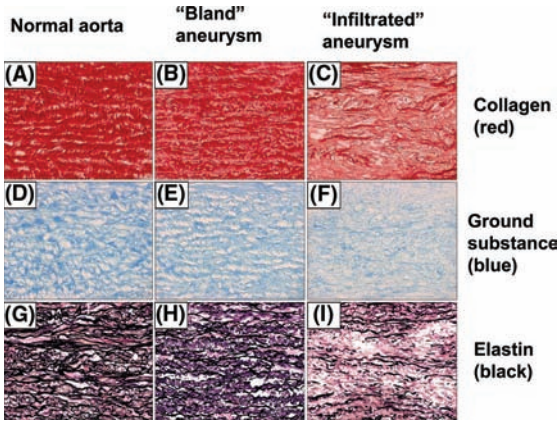

Figure 9.4 Demonstration of destruction of matrix proteins, progressively more severe in bland and then in inflammatory aneurysms. These figures depict the media of the aorta of the indicated categories. Sirius red is used to stain collagen. Alcian blue is used to label ground substance. EVG (black) is used to label elastin. Note marked degradation of collagen, ground substance, and elastin in inflammatory aneurysms. *Abbreviation*: EVG, Elasfica-van Gieson.

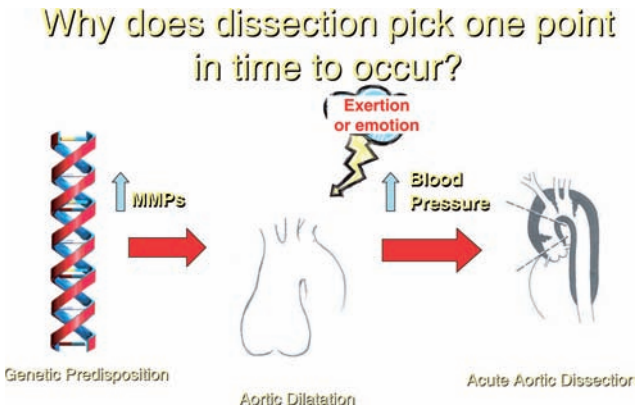

Figure 11.2 Proposed schema for the occurence of an acute aortic condition at one particular moment in time. *Abbreviation*: MMPs, matrix metalloproteinases.

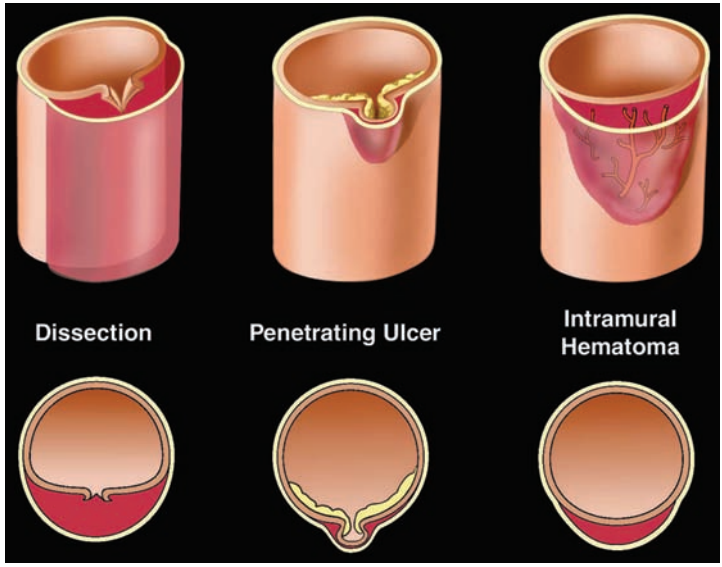

Figure 12.A Artist's schematic of variant forms of aortic dissection: typical dissection, penetrating ulcer, and intramural hematoma.

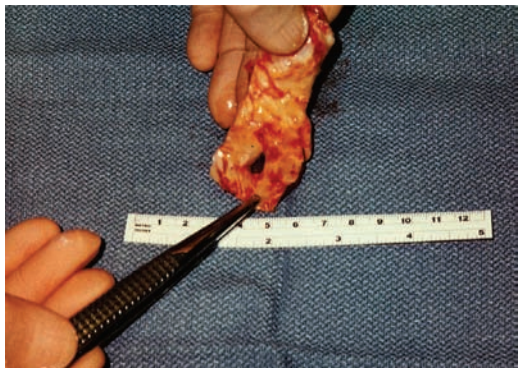

Figure 12.B Excised aortic specimen bearing penetrating ulcer of aorta. Note similarity in appearance to duodenal ulcer, for which this photo could easily be mistaken.

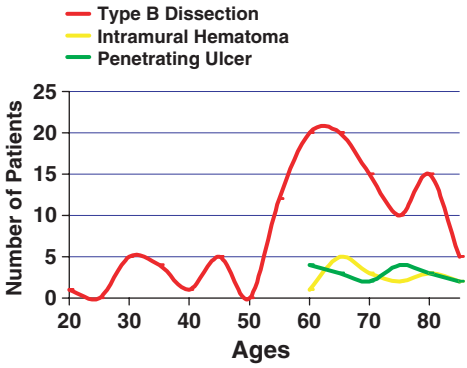

Figure 12.C Age distribution of variant forms of aortic dissection, compared to typical descending dissection. Note that intramural hematoma and penetrating ulcer are diseases of advanced age.

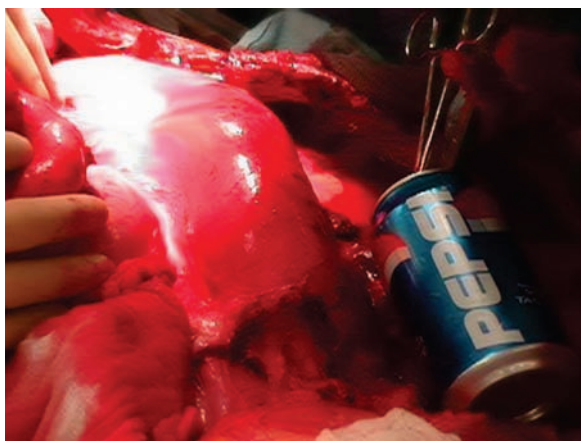

Figure 12.G A large thoracoabdominal aortic aneurysm. The head is to the top and the feet to the bottom of the picture. The chest and abdomen have been opened widely, revealing a large, extensive aneurysm of the thoracoabdominal aorta. A soda can is about 6 cm in diameter. If a patient's aorta is approaching this dimension, the aorta should be extirpated surgically to prevent rupture or dissection.

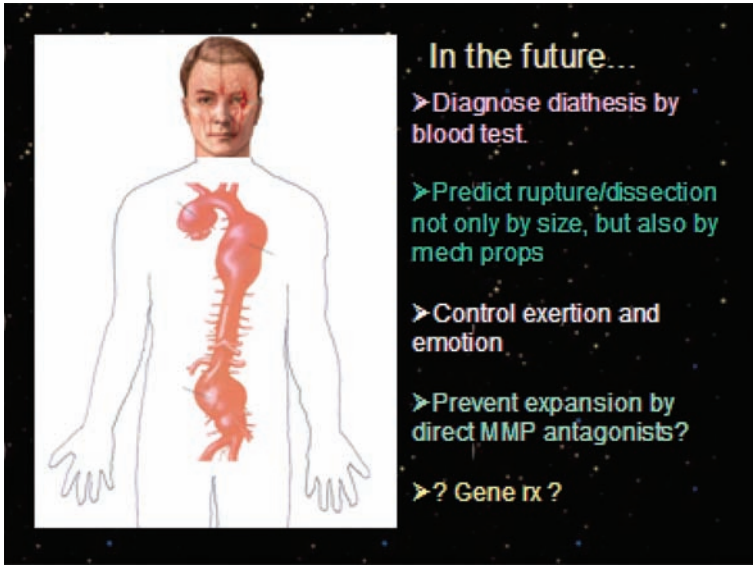

Figure 19.1 Future prospects in care of aneurysm disease.

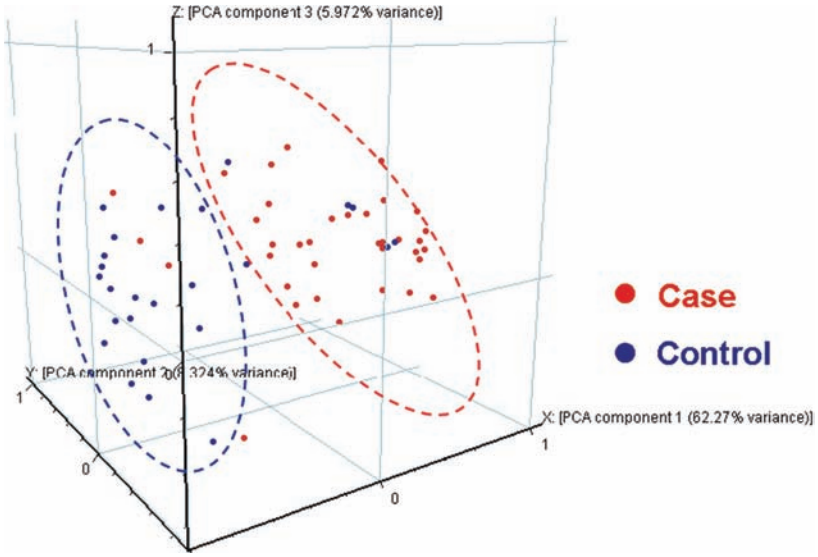

Figure 19.2 RNA "Signature" analysis allows effective discrimination (in three-dimensional space) of aneurysm patients ("cases") from controls, on the basis of examination of peripheral blood alone.

about the book . . .

Covering the pathophysiology, imaging, diagnosis, and treatment of a variety of aortic aneurysms and dissections, this source helps physicians effectively examine and evaluate affected individuals in clinical or emergency care settings. Offering a wide array of illustrations, x-rays, and operative photographs to emphasize key anatomic observations, this guide contains cutting-edge insight on the latest biologic, radiologic, clinical, and surgical developments that have taken place in the field. Presented in a reader-friendly format, this source provides end-of-chapter questions and a point–counterpoint format to analyze differing perspectives from renowned experts on these diseases. The Q & A and counterpoint involve the reader in an interactive interchange by opinion leaders.

Of vital importance for all emergency and cardiac units, this source prepares physicians and guides them in the identification and recognition of acute aortic conditions in day-to-day clinical care, the emergency room, or the coronary care unit…explains the genetics of aortic diseases…explores the influence of emotion and exercise on the incidence of aortic dissection… supplies cutting-edge insight on the imaging of aortic aneurysms and dissections, the mechanisms by which the aorta hurts patients, and modern treatment regimens for these conditions…devotes an entire chapter to lawsuits in relation to aortic diseases and supplies expert recommendations for their prevention…offers a reader-friendly format with bulleted lists, a Powerpoint™ format, and discussion commentaries at the end of each chapter…and summarizes the most important messages of each chapter in a bulleted list, compiled by the editor in the final chapter.

about the editor . . .

JOHN A. ELEFTERIADES is the William W.L. Glenn Professor of Cardiothoracic Surgery, and Chief, Section of Cardiothoracic Surgery, Yale University School of Medicine, New Haven, Connecticut, and Program Director, Thoracic Surgery Residency Program, Yale-New Haven Medical Center, Connecticut. Dr. Elefteriades received both his BA and MD degrees from Yale University. He served on the Board of Governors of the American College of Cardiology. He serves on the Editorial Boards of *The American Journal of Cardiology*, *Cardiology*, and the *Journal of Cardiac Surgery*. He was chosen among the Top 10 Doctors for men by *Men's Health* magazine. He has received the Walter Bleifeld and the John B. Chang awards for clinical research in aortic diseases. He was recently bestowed the prestigious Socrates Award for excellence in resident education and mentorship by the Thoracic Surgery Residents' Association and the Society of Thoracic Surgeons.

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