S. Serge Barold
Philippe Ritter *Editors*

Devices for Cardiac Resynchronization

Technologic and Clinical Aspects

Springer

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Edited by

S. Serge Barold, MD, FRACP, FACP
FACC, FESC, FHRS
Clinical Professor of Medicine
University of South Florida College of Medicine
and Division of Cardiology
Tampa General Hospital
Tampa, Florida, USA

Philippe Ritter, MD
Chairman, Cardiostim
InParys, St Cloud
Clinique Bizet, Paris
Clinique Chirurgicale Val d'Or
St Cloud, Paris, France

Springer

S. Serge Barold, MD, FRACP, FACP, FACC, FESC, FHRS
Clinical Professor of Medicine
University of South Florida College of Medicine and Division of Cardiology
Tampa General Hospital
Tampa, Florida, USA

Philippe Ritter, MD
Chairman Cardiostim
InParys, St. Cloud
Clinique Bizet, Paris
Clinique Chirurgicale Val d'Or
St. Cloud, Paris, France

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Preface

The last of an ongoing series of Cardiostim monographs all devoted to cardiac pacing, was published four years ago. Since then, cardiac resynchronization for the treatment of heart failure has undergone spectacular progress and has revolutionized device therapy. Many patients have benefited from ventricular resynchronization often combined with an implantable cardioverter-defibrillator. More implantations are likely in the future as the indications continue to evolve with more attention being paid to the primary prevention of heart failure in selected patients and the treatment of earlier stages of left ventricular dysfunction. Thus, we felt it was time for the current Cardiostim monograph to focus exclusively on cardiac resynchronization so as to review the remarkable technologic and clinical advances in the field. We are grateful to the contributors who worked so hard to complete their manuscripts on time and their diligence in presenting new concepts and technical details in an easily understandable fashion.

Working with the Springer publishers, especially Melissa Ramondetta, Executive Editor, Dianne Wuori, Editorial Assistant, and Candace Rosa, Production Editor, was a real pleasure. Their patience, courtesy and efficiency are very much appreciated.

S. Serge Barold
Philippe Ritter

List of Contributors

Christine Alonso, MD
InParys, St Cloud
Clinique Bizet, Paris
Clinique Chirurgicale Val d'Or
St Cloud, France

Juan M. Aranda, Jr., MD
Associate Professor of Medicine
Director Heart Transplant Program
University of Florida
Gainesville, Florida

Shane Bailey, MD, FACC
Department of Cardiovascular Medicine
Cleveland Clinic Foundation
Cleveland, Ohio

S. Serge Barold, MD, FRACP, FACP, FACC, FESC, FHRS
Clinical Professor of Medicine
University of South Florida College of Medicine
Cardiology Division
Tampa General Hospital
Tampa, Florida

Jeroen J. Bax, MD, PhD
Professor of Cardiology
Leiden University Medical Center
Leiden, The Netherlands

Jean-Jacques Blanc, MD
Professor of Cardiology
Head, Department of Cardiology
Hôpital de la Cavale Blanche
Brest University Hospital
Brest, France

Gabe B. Bleeker, MD
Cardiology Department

Leiden University Medical Center
Leiden, The Netherlands

Philippe Castellant, MD
Department of Cardiology
Hôpital de la Cavale Blanche
Brest University Hospital
Brest, France

Serge Cazeau, MD
InParys, St Cloud
Clinique Bizet, Paris
Clinique Chirurgicale Val d'Or
St Cloud, France

Olivier Césari, MD
Département de Cardiologie et Maladies Vasculaires,
Centre Cardio-Pneumologique
Hôpital Pontchaillou
Rennes, France

B. Judson Colley, MD, MPH
Division of Cardiology
Medical University of South Carolina
Charleston, South Carolina

Anne B. Curtis, MD, FACC, FHRS
Professor of Medicine
Chief, Division of Cardiology
University of South Florida College of Medicine
Tampa General Hospital
Tampa, Florida

J. Claude Daubert, MD, FACC, FESC
Professor of Cardiology
Département de Cardiologie et Maladies Vasculaires
Centre Cardio-Pneumologique
Hôpital Pontchaillou
Rennes, France

Yves Etienne, MD
Department of Cardiology
Hôpital de la Cavale Blanche
Brest University Hospital
Brest, France

Marjaneh Fatemi, MD
Department of Cardiology
Hôpital de la Cavale Blanche

Brest University Hospital
Brest, France

Jeffrey Wing-Hong Fung, MBChB (CUHK), FHKCP, FHKAM (Medicine), FRCP (London)
Division of Cardiology
Department of Medicine and Therapeutics, Prince of Wales Hospital
The Chinese University of Hong Kong
Hong Kong, China

Stéphane Garrigue, MD
Director, Cardiac Pacing and Electrophysiology Department
Clinique Saint Augustin
Bordeaux, France

Safwat A. Gassis, MD
Fellow in Cardiology
Emory University School of Medicine
Atlanta, Georgia

Michael Giudici, MD, FACC, FACP
Division of Cardiology
Genesis Heart Institute
Davenport, Iowa

Michael R. Gold, MD, PhD
Michael E Assey Professor of Medicine
Chief of Cardiology
Director of Heart & Vascular Center
Medical University of South Carolina
Charleston, South Carolina

Bengt Herweg, MD
Associate Professor of Medicine
Director, Electrophysiology and Arrhythmia Services
University of South Florida College of Medicine and Tampa General Hospital
Tampa, Florida

Arzu Ilercil, MD
Associate Professor of Medicine
Director, Non-Invasive Laboratory, University of South Florida College of Medicine
and Tampa General Hospital
Tampa, Florida

Carsten W. Israel, MD
Associate Professor of Internal Medicine
J. W. Goethe University
Department of Cardiology

Division of Clinical Electrophysiology
Frankfurt, Germany

Gaël Jauvert, MD
InParys, St Cloud
Clinique Bizet, Paris
Clinique Chirurgicale Val d'Or
St Cloud, France

Nadim G. Khan, MD
Assistant Professor of Medicine
Division of Cardiovascular Diseases
University of South Florida College of Medicine
and the James A. Haley VA Hospital
Tampa, Florida

Stéphane Laffitte, MD
Hôpital Cardiologique du Haut Lévêque,
Pessac-Bordeaux, France

Chu-Pak Lau, MD
William M.W. Mong Professor in Cardiology
Chief of Cardiology Division (Academic)
Professor of Medicine
University Department of Medicine
The University of Hong Kong
Hong Kong, China

Arnaud Lazarus, MD
InParys, St Cloud
Clinique Bizet, Paris
Clinique Chirurgicale Val d'Or
St Cloud, France

Christophe Leclercq, MD, PhD, FESC
Professor of Cardiology
Département de Cardiologie et Maladies Vasculaires
Centre Cardio-Pneumologique
Hôpital Pontchaillou
Rennes, France

Angel R. Leon, MD, FACC
The Linton and June Bishop Professor of Medicine
Emory University School of Medicine
Chief of Cardiology

Emory Crawford Long Hospital
Atlanta, Georgia

Philippe Mabo, MD
Professor of Cardiology and Head
Département de Cardiologie et Maladies Vasculaires
Centre Cardio-Pneumologique
Hôpital Pontchaillou
Rennes, France

Chris Madramootoo, BS
Cardiac Sonographer
University of South Florida College of Medicine
and Tampa General Hospital
Tampa, Florida

Sunil T. Mathew, MD
Fellow, Cardiovascular Diseases
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma

Arthur J. Moss, MD
Professor of Medicine (Cardiology)
Heart Research Follow-up Program
University of Rochester Medical Center
Rochester, New York

Christina M. Murray, MD
Fellow, Cardiovascular Diseases
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma

I. Eli Ovsyshcher, MD, PhD, FESC, FACC, FAHA
Professor of Medicine/Cardiology
Faculty of Health Sciences
Ben Gurion University of the Negev
Beer-Sheva, Israel

Luigi Padeletti, MD
Professor of Cardiology
Director of the Postgraduate School of Cardiology
University of Florence
Florence, Italy

Dwight W. Reynolds, MD, FACC, FHRS
President, Heart Rhythm Society
Professor and Chief, Cardiovascular Section
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma

Philippe Ritter, MD
Chairman Cardiostim
InParys, St Cloud
Clinique Bizet, Paris
Clinique Chirurgicale Val d'Or
St Cloud, France

Martin J. Schalij, MD, PhD
Professor of Cardiology
Leiden University Medical Center
Leiden, The Netherlands

Alfons F. Sinnaeve Ing
Emeritus Professor of Electrical Engineering
KHBO University
Ostende, Belgium

Roland X. Stroobandt, MD, PhD
Associate Professor of Medicine
Department of Cardiology
University of Ghent
Ghent, Belgium

Michael O. Sweeney, MD
Cardiac Arrhythmia Service
Brigham and Women's Hospital
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Hung-Fat Tse, MD
Professor of Medicine
Cardiology Division, Department of Medicine
The University of Hong Kong
Hong Kong, China

Lieselot van Erven, MD, PhD
Department of Cardiology
Leiden University Medical Center
Leiden, The Netherlands

Nico van der Veire, MD
Department of Cardiology
Leiden University Medical Center
Leiden, The Netherlands

Bruce L. Wilkoff, MD, FACC, FHRS
Professor of Medicine
Cleveland Clinic Lerner College of Medicine of Case
Western Reserve University

Director of Cardiac Pacing and Tachyarrhythmia Devices
Department of Cardiovascular Medicine
Cleveland Clinic Foundation
Cleveland, Ohio

Claudia Ypenburg, MD
Department of Cardiology
Leiden University Medical Center
Leiden, The Netherlands

Cheuk-Man Yu, MB ChB(CUHK), MRCP(UK), MD(CUHK), FHKCP, FHKAM(Medicine), FRACP, FRCP(Edin/London)
Professor and Head of the Division of Cardiology
Department of Medicine and Therapeutics, Prince of Wales Hospital
Director of the Institute of Vascular Medicine (Clinical)
The Chinese University of Hong Kong
Hong Kong, China

Section I

Indications and Implantation for Cardiac Resynchronization Therapy

1

Do the Official Guidelines for Cardiac Resynchronization Therapy Need to Be Changed?

Nadim G. Khan, Anne B. Curtis, Bengt Herweg, and S. Serge Barold

Heart failure (HF) an ongoing epidemic that shows no signs of abating, despite many advances in medicine. Approximately 5 million Americans and a similar number of Europeans are currently diagnosed with heart failure. More than 500,000 new cases are diagnosed each year in the United States [1, 2]. As our treatment of coronary artery disease, sudden cardiac arrest, and hypertension improves, more patients survive to develop HF. The obesity epidemic, with the accompanying metabolic syndrome, diabetes and hypertension, also contributes to the increasing number of patients with HF. In addition, the advancing age of the population has led to an even further increase in the incidence and prevalence of HF. The incidence of HF approaches 10 per 1,000 population after age 65. HF is the most common Medicare diagnosis-related group, and more dollars are spent in the United States for the diagnosis and treatment of HF than for any other diagnosis.

Over the past 15–20 years, the development of new pharmacologic therapy has lowered mortality by 30–40% in patients with advanced HF. However, despite the use of optimal pharmacologic therapy with beta-blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and diuretics, many patients still have significant symptoms that affect functional capacity and quality of life. More recently, cardiac resynchronization therapy (CRT) has been added to the armamentarium of HF therapies on the basis of strong evidence from well-designed clinical trials. Patients with evidence of ventricular dyssynchrony by virtue of prolonged QRS durations, typically with left bundle branch block, who have New York Heart Association (NYHA) class III–IV symptoms despite optimal medical therapy have been treated with atrial-synchronous, biventricular pacing using right ventricular leads as well as coronary sinus leads for left ventricular pacing [3]. Clinical trials have shown improvement in exercise capacity, NYHA class, and quality of life with CRT compared with continued medical therapy [4,5,6,7,8,9]. Landmark clinical trials such as COMPANION [10] and CARE-HF [11] have also shown a survival benefit with CRT. This therapy has opened up a whole new modality in the treatment of HF, focusing on electromechanical assistance to the failing heart.

Clinical Practice Guidelines

Clinical practice guidelines are the result of a rigorous methodologic approach that mandates the review and consideration of the available medical literature in a given field. These guidelines provide an evidence-based standard for effective patient care, weighing results from clinical trials and other studies in order to develop a consensus as to the appropriate indications for different therapeutic modalities and the patients most likely to benefit, with the intention of improving clinical outcomes. They guide clinical practice in the community and have effectively served to unify the practice of medicine.

The process of developing practice guidelines starts with the scientific and clinical documents committees of the major medical societies. Once a decision is made that a guidelines document either needs to be created or revised, a task force is appointed to do so. The document is written and goes through multiple revisions, and then there is a process of several levels of approval, usually including the board of trustees of the society, before the document is published. Often, other societies are asked to review the document and endorse it as well. This process is a time-consuming endeavor, such that it may take 1 to 2 years from the time a decision is made to develop a guidelines document until the actual publication and dissemination occur. The guidelines are then subjected to periodic review based on advances in the area of interest.

Current Guidelines for CRT

The most recent American College of Cardiology (ACC)/American Heart Association and (AHA)/ North American Society of Pacing and Electrophysiology (NASPE) guidelines for pacemakers and antiarrhythmia devices were published in 2002 [3]. These guidelines listed CRT as a class IIA indication with the highest level of evidence, A (data derived from multiple randomized clinical trials or meta-analyses). The indications for CRT in the 2002 guidelines are shown in Table 1.1. In addition, CRT was considered a class III indication (not useful/effective and in some cases harmful) for asymptomatic dilated cardiomyopathy and symptomatic cardiomyopathy that could be treated with drug therapy or revascularization.

The current indications for CRT were classified as class IIA (weight of evidence/opinion is in favor of usefulness/efficacy) and based on a number of randomized clinical trials [4, 5, 6, 7, 8]. Since then, there have been several landmark trials that have served to establish CRT even more firmly as an effective therapy, with robust data on more than 4,000 patients in randomized prospective clinical trials [9, 10, 11, 12]. In a meta-analysis of CRT trials,

Table 1.1 Indications for cardiac resynchronization therapy in the 2002 ACC/AHA/NASPE guidelines.

Symptomatic heart failure
New York Heart Association class III–IV
QRS duration $\geq$130 ms
Idiopathic dilated or ischemic cardiomyopathy with ejection fraction $\leq$35% and left ventricular end diastolic diameter $\geq$55 mm
Refractory symptoms despite optimal medical therapy

Source: Ref. 3.

HF hospitalizations were reduced by 29% and death from progressive heart failure was reduced by 51% with a positive trend toward reduction of all-cause mortality [13]. This meta-analysis included four randomized trials with 1,634 total patients up to 2002. Subsequently, COMPANION showed hospitalizations were reduced by 32% and all-cause mortality was reduced by 25% [10]. The mortality reduction in COMPANION was found in the group treated with CRT in conjunction with an Implantable cardioverter-defibrillator (ICD). CARE-HF [11] established a significant mortality reduction of 36% and reduction in HF hospitalizations by 52% by the addition of CRT pacemaker therapy without an ICD to optimal medical therapy.

The ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult revised the recommendations for CRT [14]. Patients with left ventricular ejection fraction (EF) $\leq$35%, sinus rhythm, and NYHA functional class III or ambulatory class IV symptoms despite optimal medical therapy who have left ventricular dyssynchrony defined by a QRS duration of greater than 120 ms should receive CRT unless contraindicated (class I recommendation with level of evidence A). These guidelines change the indication from class IIA to class I (evidence and/or general agreement that a given procedure is beneficial, useful, and effective), based on recent clinical trial data.

Current Directions in CRT Research

Having thus firmly established the benefit of CRT in the treatment of HF, research is currently focused on further maturation and refinement of this therapy. Recommended indications for CRT should optimize the proportion of patients who derive significant symptomatic benefit from this therapy on the one hand and should avoid this invasive treatment in patients with a low probability of clinical success of CRT on the other hand. Additional research has also focused on expansion of indications for CRT into the realm of prevention of advanced heart failure by retarding the progression of cardiac remodeling in patients with lesser degrees of HF. Current research is progressing chiefly in the areas outlined in Table 1.2. We will explore

Table 1.2 Areas of current research in cardiac resynchronization therapy.

1. Improvement of preprocedure accuracy in the prediction of response to CRT.
2. Improvement of response rates after implantation.
3. Echo-based techniques for the definition of mechanical dyssynchrony and their correlation with the current standard of prolonged QRS as a surrogate indicator of electrical dyssynchrony.
4. Further mechanistic elucidation of the pathophysiology of cardiac reverse remodeling.
5. Expansion of the current indications to include patient populations with atrial fibrillation, NYHA class I–II, patients with intraventricular conduction defects and right bundle branch block, and patients with significant conduction system disease and structural heart disease without overt heart failure.
6. Improvement in device function, lead performance, and delivery systems.
7. Development of continuous hemodynamic monitoring of heart failure.
8. Telemedicine for device interrogation and management.

possible changes to CRT guidelines in the future based on current data and the implications of ongoing research.

Definition of Response to CRT and Indices of Disease Progression

Several surrogate markers of clinical outcomes of CRT have been evaluated. These include NYHA functional class and quality of life, as well as objective measures of exercise capacity such as the 6-min walk test, exercise duration and VO_2 max. The clinical nonresponder rate is about 30%. Clinical response measures have the most relevance to the patient and the heart-failure physician. However, there is a significant placebo effect with device therapy; the MIRACLE study showed a response in 39% of controls [7]. The ultimate hard clinical end points are a reduction in HF hospitalization rate and mortality.

Several echocardiographic measures of left ventricular systolic function and dimension have been studied. These measures are objective and are independent of the placebo effect. The most frequently used parameter is a reduction of left ventricular end systolic volume by at least 15% by the process of reverse remodeling. The response rate measured by echocardiography is more prominent in nonischemic cardiomyopathy than in those patients with ischemic heart disease. It should be noted that the failure to meet an arbitrary target may not represent failure of therapy in this progressive disease. The prevention of further worsening of left ventricular systolic function could represent benefit from CRT that is difficult to measure. Indeed, without CRT, some of the nonresponders may have continued to remodel their left ventricles and worsen.

More patients are classified as responders by clinical measures than with echo-based techniques. Clinical and echocardiographic response to CRT may not always appear simultaneously in a given patient, who could respond to CRT clinically but not by an echo-based definition, and vice versa. Echo-based techniques that document reverse remodeling may be more important as an indicator to response to CRT in patients who are less symptomatic and clinical response indicators more important in more advanced HF. Clinical and echocardiographic parameters are probably complementary to each other, along the continuum of HF, in the evaluation of response to CRT. The long-term survival of patients with HF is better predicted by echocardiographic response rather than clinical response [15]. This observation underscores the importance of reverse remodeling as an important indicator of prevention of disease progression in heart failure.

Future clinical studies are likely to combine clinical response measures with echocardiographic indices that may be indicators of the arrest in HF progression and reverse remodeling. Such an approach will define the standard for response to CRT among various patient populations as well as help compare various selection criteria for CRT.

ECG Versus Echocardiography for Patient Selection

The QRS complex is a representation of the vectorial sum of electrical forces generated by both the left and right ventricles. The ECG displays poorly the conduction delay in the distal myocardium. Further, in cardiomyopathy there is significant fibrosis, changes in the extracellular matrix, and architectural disarray of the hypertrophied myocardium that have a bearing on

conduction and electrical dyssynchrony. The prevalence of bundle branch block is increased with worsening of left ventricular systolic function, with no threshold effect on mortality at 120 ms. Left ventricular dyssynchrony may be absent in up to 28% of patients with a QRS duration more than 150 ms [16]. This lack of dyssynchrony in some patients may partially explain the rate of nonresponders in large clinical studies. Studies using electro-anatomical mapping of left ventricular activation have indicated that there may be functional levels of block in patients with and without LBBB, and placement of the left ventricular lead lateral to the site of block may predict success of CRT [17].

Several echocardiographic parameters of dyssynchrony have been evaluated, as shown in Table 1.3. These parameters vary in methodology and complexity and have been compared with various end points to determine response to CRT.

Atrioventricular dyssynchrony is a result of a prolonged PR interval, delayed ventricular relaxation, and delayed interatrial conduction in the myopathic atrium. This in turn results in truncation of the a-wave, incomplete emptying of the left atrium, and premature closure of the mitral valve. Interventricular dyssynchrony is a result of delayed emptying of the left ventricle (LV) com pared with the right ventricle (RV). Data regarding the benefit of evaluation of interventricular delay have not been shown to be consistently useful [18].

Table 1.3 Echocardiographic measures of dyssynchrony.

1. Atrioventricular dyssynchrony
   - Two-dimensional mitral valve inflow pattern
2. Interventricular dyssynchrony
   - LV pre−ejection period−RV pre−ejection period >40 ms by pulse wave Doppler
3. Intraventricular dyssynchrony
   - M-mode septal to inferolateral wall delay >130 ms
   - Two-dimensional echo four-chamber view with automatic border detection; septal-lateral phase angle difference
   - Tissue Doppler imaging of two- and four-chamber apical views, septal to lateral wall and/or anteroseptal to inferolateral wall delay of >65 ms
   - Delayed longitudinal contraction or postsystolic shortening of basal and midlateral LV segments (more useful in nonischemic cardiomyopathy)
   - LV pre-ejection period >140 ms
   - Tissue synchronization imaging: quantitative and qualitative measures with automated color coding of time to peak contraction
   - Twelve-segment maximum delay difference between any two segments >105 ms
   - Twelve LV segment standard deviation >33 ms The standard deviation of the time to peak myocardial contraction in 12 myocardial segments (Ts-SD 12 or dyssynchrony index)
   - Three-dimensional echocardiography; real-time imaging with regional volume and EF

Intraventricular dyssynchrony of the LV (septal to inferolateral wall motion delay using tissue Doppler imaging) appears to be most useful in patient selection [19]. These parameters have also been compared with each other to determine the best predictor for response [18]. M-mode measurement is simple and universally available, has been shown to predict reverse remodeling, and has been studied in CARE-HF. Delayed longitudinal contraction predicts response in nonischemic cardiomyopathy. Tissue Doppler imaging–based techniques analyzing multiple segments appear to be more sensitive than those that measure the delay between two segments. The standard deviation of the time to peak myocardial contraction in 12 myocardial segments (Ts-SD-12 or the dyssynchrony index) may have the best predictive value [18]. Studies comparing the various echocardiographic parameters of dyssynchrony are small and usually single center. The identification of a simple, reproducible echocardiographic index for the prediction of response to CRT compared with both clinical and remodeling-based measures would be ideal. The PROSPECT trial may give further direction in this area. It is a prospective study evaluating echocardiographic parameters of systolic dyssynchrony in approximately 700 patients with standard indications for CRT to compare the utility of these different parameters in predicting response to CRT. The primary end points include a clinical composite criterion and a 15% decrease in left ventricular end systolic volume index (LVESVI). Quality of life, NYHA class, 6-min walk test, and EF are secondary end points [20]. The DESIRE trial will enroll 150 patients with NYHA III-IV HF, QRS <150 ms, Left Ventricular Ejection Fraction (LVEF) <40%, in sinus rhythm and left ventricular end diastolic dimension (LVEDD) >2.7 cm/m^2 on optimal medical therapy. This prospective randomized multicenter study will evaluate by echocardiography LV asynchrony and resynchronization and will follow patients for 12 months.

The quest for the best predictor of response to CRT continues. Tissue Doppler–based techniques evaluating intraventricular dyssynchrony show the most promise. In future guidelines, alternative selection criteria, most likely echo-based, are likely to be recommended.

Echocardiography in Patient Follow-up

It has been demonstrated that the response rate to CRT can be improved after implantation of the device by altering the Atrioventricular (A-V) and Interventricular (V-V) timing. The best setting for an individual patient may be determined by using the velocity time integral of the LV outflow tract with various RV–LV timing intervals [21]. The mitral inflow pattern has also been shown to be helpful in optimizing A-V synchrony in patients in sinus rhythm. Upon demonstration of the long-term benefit of postimplant optimization of A-V and V-V timing, these techniques could be added in the guidelines for optimal device management in patients with HF.

Possible Future Expansion of Indications

HF Prevention in NYHA Class II Patients

In the CONTAK CD trial, 33% of patients were in NYHA class II. These patients showed improvement in LVEF and echocardiographic indicators of

reverse remodeling. MIRACLE-ICD II was a double-blind, parallel controlled trial that randomized 186 patients with NYHA class II symptoms to CRT and defibrillator versus defibrillator with CRT turned off. This study showed no significant change in the 6-min walk test or quality of life score, but the patient's cardiac structure and function improved [22]. This study raises hope for prevention of HF worsening by halting and reversing the maladaptive cardiac remodeling. A recent study compared the benefit of CRT in patients with NYHA class II HF with patients in NYHA class III and IV HF. The class II patients had EF $\leq$35%, QRS >120 ms, and baseline LV dyssynchrony measured by tissue Doppler imaging that was comparable with that found in the patients with NYHA class III and IV symptoms [23]. The magnitude of clinical improvement in NYHA class II patients was significantly less; however, only a minority of patients progressed to class III HF. The mild HF patients had a statistically significant improvement in LVEF and echocardiographic indicators of LV reverse remodeling. As has been discussed earlier, the demonstration of cardiac remodeling better predicts improvement in survival compared with clinical indicators. CRT in NYHA class II HF may be clinically significant in reducing mortality and preventing progression of heart failure.

The REVERSE trial is a prospective, randomized, double-blind parallel study of about 500 patients with NYHA class I–II symptoms, QRS duration $\geq$120 ms, LVEF $\leq$40%, and LV end diastolic diameter $\geq$55 mm. This ongoing study will compare optimal medical therapy alone or with CRT ± ICD in the prevention of progression of HF using both clinical factors and LVESVI as end points at 1 year. The MADIT CRT study is also currently enrolling about 1,800 patients in NYHA class I–II, EF <30%, QRS >130 ms, in sinus rhythm. The primary end point would be a composite of all-cause mortality and HF events by 25%, and a measure of reverse remodeling would be a secondary end point. The results of these studies may expand the indications for CRT into the realm of prevention of HF.

AV Block and Mild HF

Most patients with bradycardia without HF tolerate RV apical pacing. However, in HF, the nonphysiologic effects of RV pacing cause asynchronous electrical activation of the LV, resulting in impaired LV systolic and diastolic function, cardiac remodeling, and HF progression. The MOST trial demonstrated that the risk of HF hospitalization and atrial fibrillation (AF) are directly related to the percentage of cumulative RV pacing [24]. The DAVID trial showed worsening of HF and death in patients with DDDR mode compared with the backup VVI mode [25]. The analysis of MADIT II data also reveals a similar adverse effect of RV pacing on HF. In the era of implantable defibrillators and aggressive beta-blockade, especially in the elderly, it is not uncommon to encounter the coexistence of HF and bradycardia. CRT may mitigate the adverse effects of RV pacing and prevent development or worsening of HF.

A recent study randomized 30 patients with standard indications for permanent ventricular pacing who had LV dysfunction as indicated by LV end diastolic dimension $\geq$60 mm and LV EF $\leq$40% in a prospective crossover design. A 3-month period of RV-only pacing was compared with 3 months

of CRT. CRT conferred significant improvement in LV function, quality of life indicators, exercise capacity, and neurohormonal markers [26]. The BLOCK HF trial is currently enrolling patients with AV block (advanced first degree through third degree, provided that pacing is anticipated to be necessary the great majority of the time), NYHA class I–III symptoms, and LV ejection fraction $\leq$50%. This prospective, multicenter, randomized, double-blind, parallel controlled clinical study compares RV pacing to biventricular pacing. The hypothesis is that CRT may prevent progression to HF compared with conventional RV pacing. The end points include time to first event for all-cause mortality, HF-related urgent care, or a significant change in the LVESVI. The ongoing BIOPACE study is designed to study the benefit of CRT over standard RV pacing, in patients with high degree AV block, regardless of EF and QRS duration. These results may further expand CRT indications into HF prevention.

Atrial Fibrillation

The incidence of AF is directly proportional to heart failure [27]. AF impacts the clinical course of up to 50% of patients with advanced HF who are eligible for CRT with a defibrillator (CRT-D). The likelihood of AF increases with severity of HF, with an annual incidence of approximately 5%. The development of AF doubles the risk of death in patients with HF. Many of the large clinical CRT trials have excluded patients with AF. Small single-center studies have collectively studied a little more than 100 patients and have shown clinical benefit and improvement in reverse remodeling parameters in patients with chronic AF.

The MUSTIC-AF trial studied 59 patients with LVEF <35%, advanced HF, permanent AF (at least 3 months duration), and wide QRS in a prospective randomized controlled trial [28]. Patients adequately treated with CRT showed improvement in 6-min walking distance, quality of life score, NYHA functional class, and HF hospitalizations. This study included patients with a slow ventricular rate that was either spontaneous or induced by AV node ablation. Another study in patients with AV nodal ablation for AF and advanced HF showed improvement in NYHA functional class, LVEF, LV dimensions, and HF hospitalizations [29].

It appears that the response rate to CRT may be lower in patients with chronic AF than in patients in sinus rhythm. However, the response rate is higher in patients with chronic AF who have undergone AV nodal ablation compared with those patients who have not. The PAVE study prospectively randomized patients with chronic AF who received AV nodal ablation to standard RV pacing versus CRT [30]. At 6 months after ablation, the patients in the CRT group showed significant improvement in exercise capacity with preservation of LVEF. This benefit was more prominent in patients with either impaired LV systolic function or symptomatic heart failure. In patients with HF who undergo AV nodal ablation for AF, CRT may become the method of choice for pacing.

A recent study followed approximately 600 HF patients prospectively in two European centers for up to 4 years. More than half of the 114 patients with AF in this study were not able to achieve an arbitrary device-derived cutoff of >85% CRT at 2 months, despite the usual pharmacologic and

device programming interventions [31]. These patients were subjected to AV nodal ablation in a nonrandomized format to ensure complete biventricular capture. This study demonstrated long-term improvements in LVEF, reverse remodeling, and functional capacity in both patients in sinus rhythm and AF. However, within the AF group, the patients who received AV nodal ablation and CRT showed statistically significant improvements in LVEF, LV dimensions, and clinical markers compared with patients without AV nodal ablation who had >85% biventricular pacing with standard rate control measures. Among patients with AF, the percentage of responders was threefold higher in the AV nodal ablation group compared with the nonablated group receiving standard pharmacologic rate control. The benefit of AV nodal ablation observed in this study could represent an overestimation of device-based percentage of CRT in the nonablated group due to fusion and pseudofusion, better rate control (and better diastolic function) in the ablated group, and inadvertent effects of rate control medications. The contribution of AV nodal ablation in patients with permanent AF to enhance the benefit of CRT in HF merits further attention in a randomized, adequately powered study.

The ongoing APAF trial is evaluating patients with permanent AF and refractory heart failure. These patients undergo AV nodal ablation and implantation of a biventricular pacemaker. They are then randomized to a strategy of RV pacing based on clinical indications with a strategy of early CRT based on echocardiographic optimization. About 500 patients will be followed for 2 years, with a short-term study involving clinical and echocardiographic indicators of response and a long-term study with a composite end point of HF events and cardiovascular mortality.

CRT in Patients with Narrow QRS

QRS duration >150 ms, especially in association with left bundle branch block, correlates well with LV mechanical dyssynchrony and consequently response to CRT. This relationship does not hold true in HF patients with narrow or mildly prolonged QRS duration. It has been appreciated that LV mechanical dyssynchrony can exist in up to 51% of patients with HF and QRS $\leq$120 ms [32]. Other studies have demonstrated the presence of left ventricular mechanical dyssynchrony in patients with QRS $\leq$120 ms, ranging from 27% to 43% depending on the methodology. Sogaard et al. have demonstrated that intraventricular mechanical dyssynchrony is a much better predictor of LV remodeling than QRS duration [33]. Achilli et al. showed response to CRT in patients with narrow QRS, having selected patients based on LV mechanical dyssynchrony [34]. The current CRT guidelines do not appreciate this indication. Future revisions should take into account this patient population, and emphasis on echo-based selection of patients will extend the benefit of CRT to this subpopulation of patients.

Functional (Secondary) Mitral Regurgitation

Up to 30% of patients with severe LV systolic dysfunction also have severe mitral regurgitation (MR). Typically, the valve structure itself is unaffected;

however, a multitude of factors, including change in LV and papillary muscle geometry, mitral annular dilation, regional wall motion abnormalities both due to ischemic heart disease and dyssynchrony, prolonged AV conduction, and LV volume overload, contribute to MR. MR in these patients demonstrates relentless progression and confers an annual survival rate of only 30–40% [35]. Though surgical correction is an option, the operative mortality tends to be high and often these patients are not referred for surgery. CRT has been shown to acutely (30–40% reduction) and chronically (10–20%) reduce the severity of MR [36]. This effect was directly proportional to the closing force on the mitral valve, which is improved by LV synchrony, including papillary muscle activation and reduction of the tethering forces on the mitral valve. With the accumulation of further long-term data, severe functional MR, in patients who are not surgical candidates, could be considered as an indication for CRT

Right Bundle Branch Block and Intraventricular Conduction Delay

The sparse retrospective data from subgroup analysis does not support the use of CRT in Right Bundle Branch Block (RBBB) and Intraventricular Conduction Delay (IVCD). Data from a pooled subset of 61 patients with RBBB from the MIRACLE and CONTAK CD trials did not demonstrate any significant benefit from CRT [37]. On the other hand, coexisting left anterior or left posterior hemiblock may indicate a favorable response to CRT [38]. ECG evidence of anterior wall myocardial infarction and RV dilation may predict lack of response to CRT [39]. Echocardiographic demonstration of significant intraventricular dyssynchrony in patients with RBBB and IVCD may help identify patients who could potentially benefit from CRT.

Upgrade of an RV Pacing System to CRT

RV apical pacing and the attendant LV dyssynchrony may lead in some cases to worsening or appearance of HF symptoms. Long-term RV pacing has been shown to be detrimental to LV function. Upgrading RV pacing systems to biventricular CRT modalities is a theoretically promising option, and small clinical studies seem to indicate such benefit [40]. It is not clear if dyssynchrony induced by RV pacing has the same pathophysiologic effect as left bundle branch block. The clinical benefit in this sometimes complicated procedure is yet to be determined in this situation. Echocardiographic elucidation of mechanical dyssynchrony may be beneficial in determining which patients will benefit from an upgrade to a CRT system. More data is required if this indication is to be included in future guidelines.

Conclusion

The indications for CRT continue to evolve and will expand as further studies identify those most likely to benefit. It is expected that some image-based measure of dyssynchrony will be recommended in addition to or instead of QRS duration in the selection of patients for CRT when the current ACC/AHA/NASPE guidelines are revised. Several new categories of patients

Table 1.4 New patient populations likely to receive at least class II recommendations in revised practice guidelines, pending results of clinical trials.

Heart failure prevention in class II patients
AV block
Atrial fibrillation
Narrow QRS width with echocardiographic indicators of mechanical dyssynchrony

should get at least a class II indication for CRT (Table 1.4). Ongoing trials will provide the level of evidence for these recommendations. The American College of Cardiology in association with the Heart Rhythm Society and the American Heart Association has already initiated the process of revision of guidelines for device-based therapy for heart rhythm abnormalities.

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2

Alternative Techniques for Left Ventricular Lead Placement

Shane Bailey and Bruce L. Wilkoff

The standard approach for insertion of left ventricular leads is performed transvenously with fluoroscopic guidance into the cardiac veins that branch from the coronary sinus. The procedure is performed percutaneously and precludes the need for thoracotomy and intubation with general anesthesia, which can lead to prolonged hospitalizations [1, 2]. However, in multiple studies, 8–14% of transvenous attempts to place a lead in a cardiac vein failed [3, 4]. There are multiple reasons for the inability to transvenously insert a left ventricular lead, including inability to cannulate the coronary sinus, small cardiac veins unsuitable to lead placement, stenosis within the coronary sinus or cardiac veins, and coronary sinus perforation. Additionally, long-term complications of left ventricular cardiac vein leads can include increases in pacing thresholds, lead dislodgment, and diaphragmatic stimulation. Within the MIRACLE trial, 6% of patients required repositioning or replacement of the coronary sinus lead within 6 months of the implant [4]. Similarly, in a study comparing epicardial versus coronary sinus leads, 11% of patients with a coronary sinus lead experienced long-term complications at 4 years [3]. Indeed, a learning curve exists for implanting coronary sinus leads, and success with implantation increases with experience and improvement in delivery systems and leads [5].

Surgical Epicardial Approach

Surgical placement of a left ventricular lead is a well-accepted alternative for resynchronization therapy when the transvenous approach fails. Left ventricular stimulation was, in fact, first achieved by the surgical epicardial approach performed by lateral thoracotomy. Recent advances in surgical techniques for left ventricular (LV) lead placement include the minimal thoracotomy approach, video-assisted thoracoscopy, and robotically assisted implantation. These newer techniques reduce wound size and result in shorter hospitalization but require general anesthesia with its inherent risks. Several advantages with surgical placement of left ventricular leads can be appreciated, including less fluoroscopy time, avoidance of intravenous contrast, shorter implant time, and possibly reduced lead-related complications. In a

recent study comparing surgically placed left ventricular leads and coronary sinus leads, pacing threshold increases and dislodgment were significantly reduced in the surgically treated patients [3]. Additionally, surgical placement by thoracotomy or endoscopic approach offers the advantage of direct visualization of the left ventricle for optimal lead position.

With the *minimal thoracotomy* approach, a 3- to 5-cm incision is made over the 4th or 5th intercostal space anterior to the midaxillary line [6] (Fig. 2.1). Single-lung ventilation is performed, and the pericardium is opened avoiding the phrenic nerve. Using an epicardial lead implant tool, two screw-in pacing leads are placed on the left ventricular wall. The leads are tested through the analyzer and subsequently tunneled to the pacemaker pocket where the lead with the lowest threshold is connected to the pulse generator. A chest tube is required postoperatively and is typically discontinued within 48 h. This technique is preferred for patients with severely enlarged left ventricles and prior open heart surgery. For these patients, thorascopic techniques are difficult secondary to limited space.

Video-assisted thoracoscopy (VATS) has become a routine endoscopic procedure in thoracic surgery. This approach requires the creation of the two or three ports within the 4th or 5th intercostal space along the anterior and midaxillary line [6, 7]. Similar to the limited thoracotomy approach, single-lung ventilation with a double-lumen tube is used. A camera is inserted through one port with instruments manipulated through the remaining. After the pericardium is opened and the phrenic nerve and marginal arteries are identified, the epicardial lead is screwed in through the instrumentation port (Fig. 2.2). The lead is then tunneled to the device pocket and attached to the generator. Gabor et al. reported on 15 patients who had LV epicardial lead

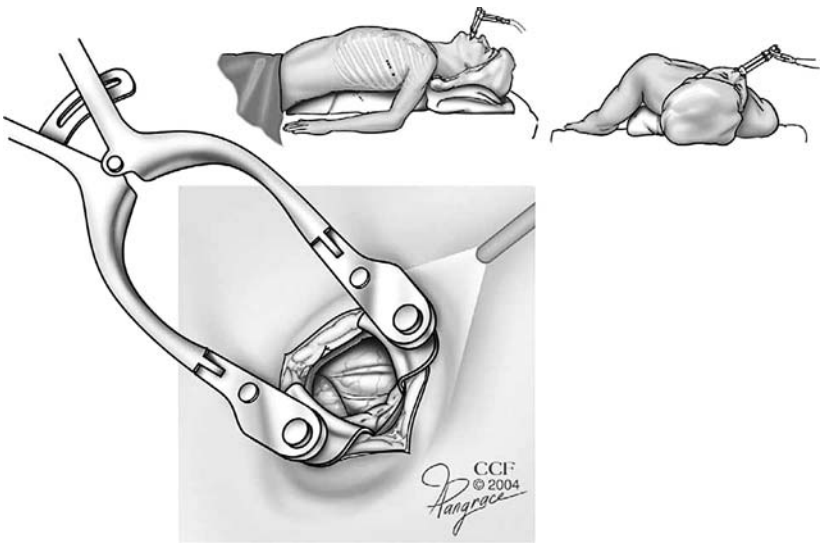

Fig. 2.1 Minithoracotomy approach for insertion of LV epicardial lead, illustrating incision site (upper left), patient position (upper right), and exposure with retractor.

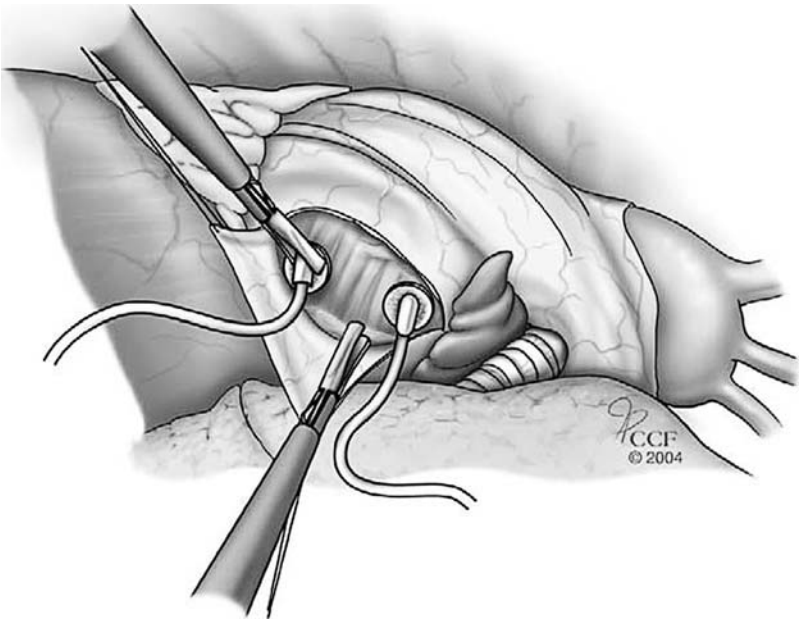

Fig. 2.2 Implantation of two left ventricular epicardial leads using video-assisted thoracoscopy.

placement by VATS after failure with a transvenous attempt. Mean operating time was 55 min with satisfactory pacing thresholds and no lead dislodgments at 7 months [7].

Robotically assisted left ventricular epicardial lead implantation is an emerging technique performed endoscopically. Anesthesia preparation is also performed with single-lung ventilation. Three ports are inserted into the chest cavity along the posterior axillary line through which an endoscope is placed through the center port (Fig. 2.3). Through the outer ports, specialized instruments are used that are capable of 7 degrees of freedom, similar to the human wrist. A fourth port is placed posterior to the camera port for introduction of the epicardial lead. The instruments are controlled by a surgeon located at a console away from the operating table. The robotic arms are then used to fix the lead into a posterobasal location on the left ventricle.

DeRose et al. describe their experience with 13 patients who had LV lead placement using the da Vinci Robotic Surgical System (Intuitive Surgical Inc., Sunnyvale, Calif., USA) [8]. All patients had successful implantation with significant improvements in exercise tolerance and ejection fraction, and no dislodgment or pacing threshold increases were seen. In a similar report, Jansens et al. describe 15 patients who had LV lead placement using the da Vinci robotic system after failure to implant in the cardiac veins [9]. Thirteen patients had successful implant with two requiring a small thoracotomy (one for lung adhesions from prior radiation and the other from epicardial bleeding after fixation of the lead).

Robotic technology provides for visualization of the entire posterolateral left ventricular wall and enables accurate surgical precision in implanting a lead. Other advantages include elimination of tremor and a magnified,

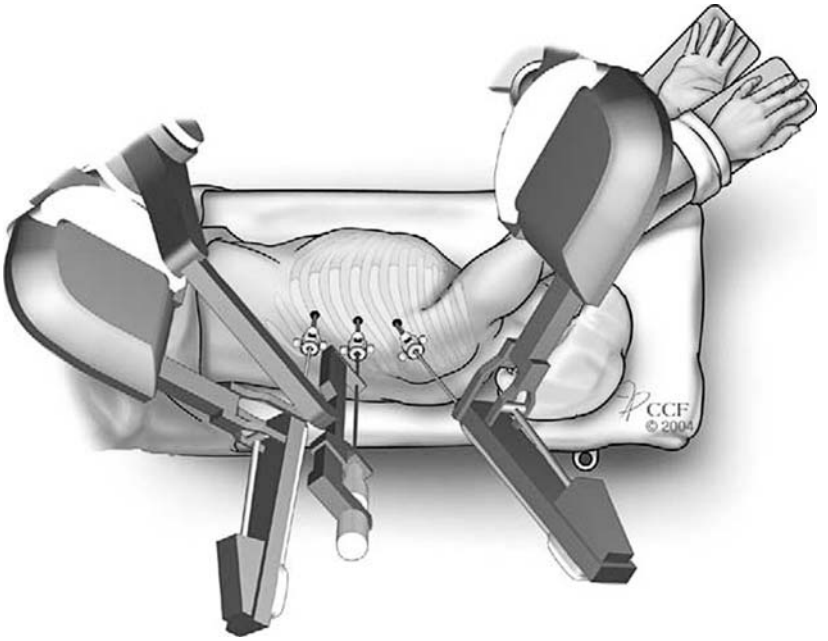

Fig. 2.3 Robotically assisted left ventricular epicardial lead implantation using the da Vinci system.

three-dimensional image that can be viewed through the surgical console. Similar to VATS, minimal incisions are made, and postoperative pain is minimized. Robotics can be helpful in patients with a small cardiothoracic ratio, for which VATS can be very challenging. Additionally, although not contraindicated, reoperations with robotics can be difficult [6].

Transseptal Approach

Left ventricular endocardial pacing has been described using the transseptal approach. This technique has been of interest in patients in whom coronary sinus anatomy is not amenable to placement of a left ventricular lead. As opposed to surgically placed epicardial leads, which require general anesthesia, the transseptal approach can be performed in the same setting as coronary sinus cannulation. Additionally, it has been suggested that endocardial pacing may have benefits in left ventricular contractility and improved synchrony over epicardial pacing, either by cardiac veins or surgically placed epicardial leads [10]. These benefits are contrasted with the risk of thromboembolic events and the transseptal procedure.

Jais et al. described this alternative pacing technique after multiple unsuccessful attempts to enter the coronary sinus in a 73-year-old man with end-stage congestive heart failure [11]. In their technique, transseptal puncture was performed from the right femoral vein through a snare positioned in the right atrium over the fossa ovalis (Fig. 2.4). The snare was introduced from the right internal jugular vein and functioned as a circular retrieval device capable of grasping objects advanced through its body. Once a guide wire

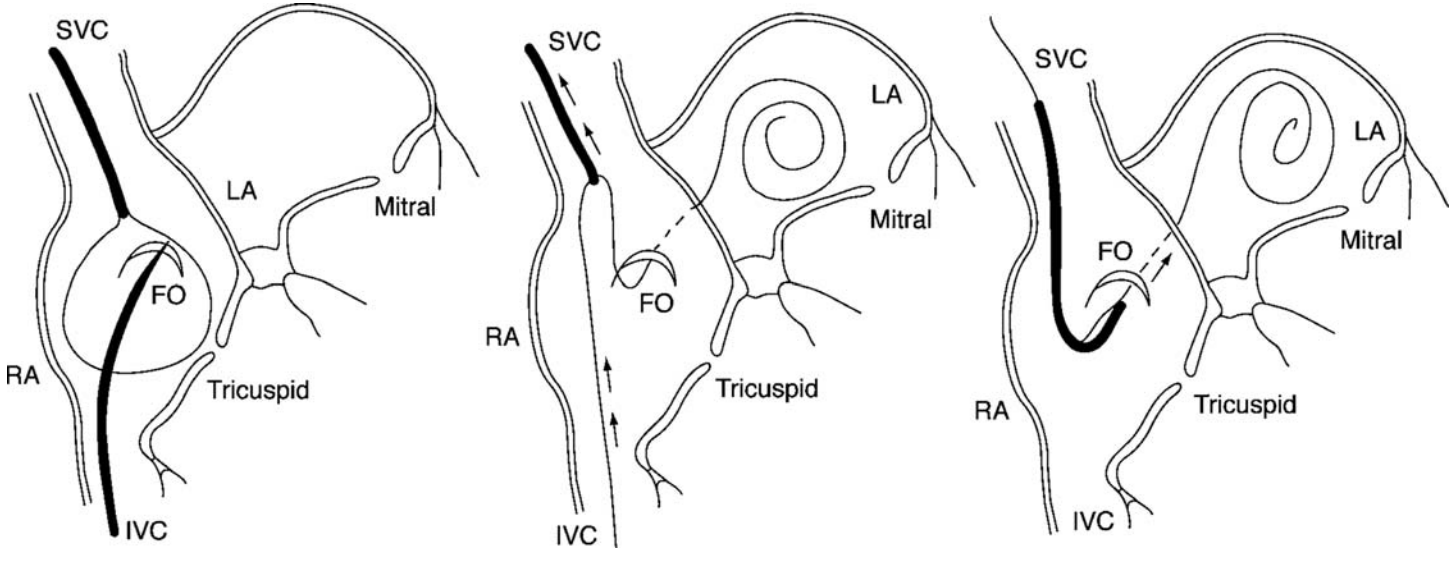

Fig. 2.4 Transseptal puncture is achieved via femoral venous access through which a wire is introduced into the left atrium. The wire is snared via right internal jugular venous access and pulled out the neck access through which the peel-away sheath is advanced across the intraatrial septum for placement of the LV endocardial lead.

was positioned in the left atrium, the sheath was withdrawn back across the septum, and the snare was used to retrieve and exteriorize the proximal portion of the guide wire through the right internal jugular vein. A transseptal sheath was then advanced into the left atrium from the right neck and a lead was able to be advanced into the left ventricle. Leclercq et al. described a modified transseptal catheterization technique in three similar patients [12]. In this approach, the septum was punctured directly from the right internal jugular vein utilizing fluoroscopy and transesophageal echocardiography. After being placed in the left ventricle, the lead was subsequently tunneled from the right neck to the pacemaker pocket. Of interest, in two of the three patients, dislodgment of the left ventricular lead occurred early requiring a second procedure.

In a series of 11 patients who had endocardial left ventricular lead placement via transseptal approach, Jais et al. report on a mean follow-up of 15 months [13]. In this group, seven patients had transseptal puncture with a combined femoral and internal jugular approach, as described above, and the remaining four had transseptal puncture directly from the right internal jugular vein. The procedure was successful in all patients with 10 of the 11 describing functional improvement. All patients were anticoagulated with warfarin. At follow-up, one transient ischemic attack occurred in a patient who interrupted anticoagulation.

The transseptal puncture has also been described from the left axillary vein. A 63-year-old man with severe heart failure requiring upgrade to a cardiac resynchronization therapy defibrillator (CRT-D) device had coronary sinus angiography, which demonstrated poor targets for a left ventricular lead. Surgical placement of an epicardial lead was not possible secondary to a history of tracheal stenosis precluding general anesthesia. Ji et al. describe using a standard transseptal needle shaped to match the contour of the innominate vein and superior vena cava (SVC) [14]. This approach has the advantage of avoiding the need for tunneling the lead as with the transjugular approach.

Epicardial and endocardial pacing has been suggested to result in differences in left ventricular contractility and synchrony. Garrigue et al. studied 15 patients that had epicardial lead placement through the coronary sinus and compared them with 8 patients with endocardial leads placed by transseptal puncture secondary to unsuitable coronary sinus anatomy [10]. Echocardiographic and Doppler characteristics were compared and included amplitude of left ventricular contractility and regional left ventricular electromechanical delay. They reported a significant improvement in the echocardiographic and Doppler variables in the patients that had endocardial pacing, however, no clinical differences were noted.

Pacing endocardially by the transseptal approach offers some advantages over surgical epicardial lead placement, such as obviating the need for general anesthesia and the possible hemodynamic benefits of endocardial pacing. However, this technique should not be routinely attempted in patients. There has not been long-term follow-up on this group of patients who are low in number. The risk of thromboembolic events is not known; however, in a review of patients who inadvertently had left-sided lead placement, the risk of cerebral embolism was more than 20% [15]. Although anticoagulation may reduce the risk of cerebral embolism, it is not negligible [16,17]. Additionally,

the transseptal puncture technique may not be routine for many physicians that implant devices and may result in significant complications rates, especially when attempted from the internal jugular approach.

Other Alternative Approaches

A different approach to left ventricular endocardial pacing not requiring a transseptal puncture was described by Grosfeld et al. [18]. *Left interventricular septal pacing* was described in an animal study using a pacemaker lead with a long insulated screw with only the distal two windings electrically active. Using a guiding sheath, the lead is screwed through the right ventricular septum until the endocardium of the left ventricle is paced, as confirmed by injury current and pacing thresholds. Additionally, contrast fluid was given through the guiding sheath to confirm lead position by fluoroscopy and echocardiography. In all animals, the positioning of the electrode was successful as confirmed by necropsy. Pacing thresholds and sensing characteristics were satisfactory, and no perforations were observed.

Percutaneous epicardial left heart pacing lead implantation has been described using a *subxiphoid videopericardioscopic device*. This method was tested in swine using a videopericardioscopic device composed of two parallel lumens, the superior port housing the endoscope and the inferior lumen used to accommodate the lead. The device is inserted through an incision made in the subxiphoid space until the pericardium is visualized (Fig. 2.5). With an endoscopic tool, the pericardium is incised and the device advanced into the pericardial space. The distal portion of the device is placed in angulated

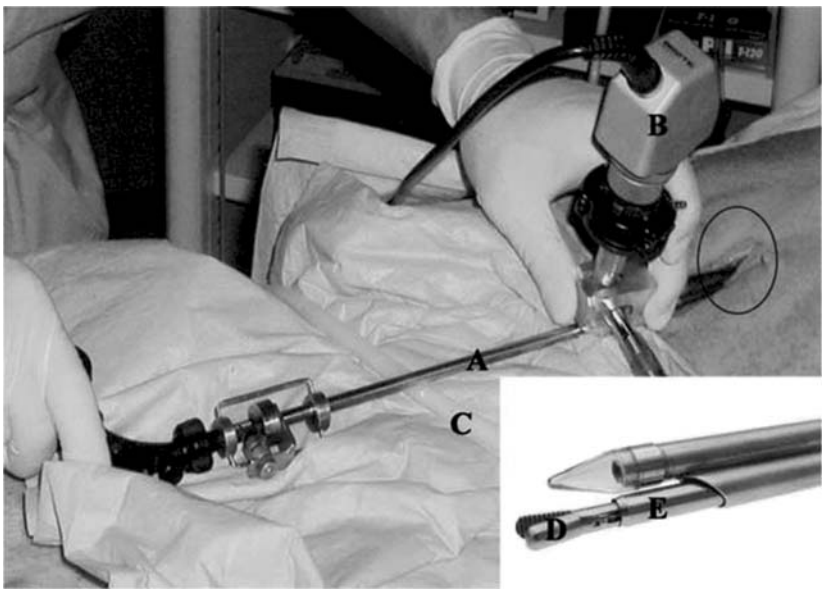

Fig. 2.5 Videopericardioscopic device advanced percutaneously through a subxiphoid incision (circled). A surgical instrument is advanced through the lower port (*A*&*C*) and the endoscope is seen above (*B*). The inset displays an instrument in the lower port for grasping (*D*) and cutting (*E*).

contact with the myocardium, and the lead is actively fixated. Limitations with this approach include difficultly in positioning the device for lead delivery over the posterolateral left ventricle, inability to maneuver the device through diseased or postoperative pericardium, and finally, the possibility of pericardial inflammation from the epicardial lead.

Conclusion

Various techniques are described to facilitate pacing of the left ventricle to allow for resynchronization in heart failure. The first-line approach remains the transvenous method by way of the coronary sinus. The success rate for this approach remains more than 85% in large series and continues to improve with experienced operators and better delivery systems. Surgical placement of epicardial leads is an acceptable alternative to LV lead placement when the transvenous route fails or is not possible. Several minimally invasive surgical approaches have been described and continue to evolve, allowing precise implantation of LV leads with smaller incisions, less pain, and reduced hospital stays. Transseptal placement of LV endocardial leads has not been thoroughly evaluated and may pose a thromboembolic risk, even with anticoagulation. Additionally, the transseptal puncture, whether from the femoral or jugular approach, may result in a higher rate of complications when not performed by operators routinely familiar with this technique. Other described techniques remain restricted to animal models and require further investigation and technology advancement.

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3

Importance of the Right Ventricular Pacing Site in Cardiac Resynchronization

Gaël Jauvert, Christine Alonso, Serge Cazeau, Arnaud Lazarus, and Philippe Ritter

Cardiac resynchronization therapy (CRT) has changed the clinical prognosis of patients with heart failure and mechanical ventricular dyssynchrony. Since its introduction in 1994, biventricular pacing has demonstrated a striking functional benefit and more recently a significant reduction of mortality by itself (i.e., with or without the addition of a defibrillator) [1, 2, 3, 4]. Yet, 20% to 30% of CRT recipients will not respond to the therapy [2]. This has fostered investigation to better understand the electromechanical disorders that are potentially reversible with multisite pacing. Echocardiography is by far the best noninvasive tool to evaluate the actual significance of intraventricular dyssynchrony (the result of electromechanical disturbances). Various echocardiographic parameters, simple or sophisticated, have been proposed to compensate for the lack of specificity/sensitivity of the QRS configuration and duration for screening of potentially good responders [5,6]. Nevertheless, a potentially good responder cannot receive the full expected hemodynamic benefit of CRT by "simply" pacing the two ventricles either simultaneously or sequentially without meticulous attention to the pacing sites. Therefore, an optimal clinical result requires the establishment of the optimal pacing site(s) and pacing configuration.

Seeking Optimal Pacing Site(s)

In CRT, the search for the best pacing site has focused exclusively on the left side. The midportion of the lateral or posterolateral wall seems to be the segment to target for the best hemodynamic or clinical result. Auricchio et al. showed better acute improvement of left ventricular dp/dt or pulse pressure when the left ventricular (LV) pacing site was located in the midlateral wall [7]. In a MUSTIC substudy, Alonso et al. found that left lateral wall pacing was correlated with a significant decrease of the QRS duration and a significant increase in functional status evaluated by the 6-min walk test [8]. In a retrospective study, Ansalone et al. suggested that improvement in LV end systolic volume (LVESD), LV ejection fraction (LVEF), and exercise

work load was greater when the LV pacing site and the most delayed LV segment (assessed by DTI measurements) were matched [9].

Basically, in everyday practice, the "optimal" LV pacing site is often a compromise. LV lead placement is highly dependent upon the coronary venous anatomy. The target vein must be accessible via the coronary sinus. Then, the LV lead has to remain in a stable position, with an acceptable threshold and without causing phrenic nerve stimulation. Despite these anatomical and electrical constraints, the success rate of LV lead implantation may reach 96% [3]. In reports discussing the optimal LV pacing site, it is highly likely that the right ventricular (RV) lead was in an apical position. So far, no consistent data supports the assumption that a lateral LV pacing site is really "optimal" when it is combined with an opposite nonapical RV pacing site.

Therefore, the goal of CRT is not necessarily the combination of the best LV pacing site and the best RV pacing site, but the optimal combination of both to achieve the best mechanical and clinical result.

As the selected LV pacing site is influenced by the stated constraints, determination of the optimal RV pacing site becomes mandatory. This implies that the LV lead is placed first, which is not routinely the case.

Detrimental Effects of RV Apical Pacing in Conventional Pacing

The RV apex is routinely targeted for conventional pacing indications of DDD or VVI pacemakers or ICDs. Using a passive unipolar or bipolar ventricular lead, implantation is easy and safe, providing good pacing and sensing thresholds.

However, it is now well established that in some patients, RV apical pacing may generate electromechanical disturbances responsible for long-term LV dyssynchrony, LV systolic dysfunction, and dilatation leading to hemodynamic impairment.

Dual-chamber pacing was supposed to bring a physiologic solution to the "pacemaker syndrome" by restoring the timing of left atrial and ventricular systoles in patients with sinus node dysfunction or third-degree AV block. However, in various large studies, no substantial benefit was observed with dual-chamber pacing with regard to total mortality, cardiovascular mortality, stroke, or quality of life [10, 11, 12]. In such studies, there was a striking absence of data about optimization of the AV delay. Yet, an appropriate AV delay is an important physiologic variable in dual-chamber pacing. So far, dual chamber pacing has certainly been associated with unnecessary RV apical pacing particularly in patients with underlying sinus node dysfunction. Sweeney et al. clearly demonstrated in this situation a correlation between long-term RV pacing and the development of heart failure and atrial fibrillation when the cumulative rate of ventricular pacing was >40% in the DDD mode and >80% in the VVI mode [14, 15]. Wilkoff et al. also observed the deleterious effects of unnecessary RV apical pacing in ICD recipients in terms of death or congestive heart failure hospitalization [16]. Recently, Thambo et al. reported the detrimental effects of long-term RV pacing in patients with congenital AV block when compared with a control group.

RV pacing was responsible for left intraventricular dyssynchrony assessed by echocardiography (tissue Doppler imaging measurement) [17]. These workers also observed significant delayed longitudinal contraction, septal-to-posterior wall-motion delay associated with asymmetrical hypertrophy, LV dilatation, and decreased cardiac output. Clinically, in this group of paced patients, the exercise capacity was also significantly reduced. Beneath this structural remodeling, severe histologic remodeling was also noted by others in the same type of population [18]. Spraag et al. demonstrated experimentally that contractile discoordination induced regional disparities in the expression of myocardial proteins in the region of late activation [19].

…and in CRT

A suboptimal result is expected in 20% to 30% of CRT candidates despite being considered potentially good responders at time of selection. Selection criteria should be reconsidered, but inadequate positioning of the leads at implantation may also be the reason for a poor outcome. Therefore, if the RV lead is positioned first and the LV lead afterward in a supposedly optimal site as described in literature, it means that the RV pacing site must necessarily be inappropriate or that the combination of the RV and LV pacing sites is inadequate. In this hypothesis, the optimal RV and LV pacing sites are *individually* unpredictable prior to implantation.

Cases of secondary clinical deterioration of CRT recipients (after an initial period of enhancement due to CRT) have been reported. In a series presented by Alonso et al., most RV leads were apical. The left pre-ejection interval was initially significantly reduced compared with the preimplantation value, but not dramatically. Some degree of interventricular delay (IVD) persisted. Compared with the initial findings, these two parameters then increased in duration, and the mechanical deterioration paralleled clinical deterioration [20].

Programmability of the V-V interval between RV and LV pacing was proposed as a solution to compensate for the possible persistent IVD after CRT [21]. However, the interventricular delay is the wrong parameter to be corrected as it is only the direct consequence of intraventricular dyssynchrony. It is the intraventricular conduction disturbance that is responsible for the delayed LV ejection creating interventricular delay. In the case of right bundle branch block, the delay in global RV activation may compensate for the IVD, equalizing the right and left pre-ejection delays despite actual LV dyssynchrony. As we reported, programming of the V-V interval probably fails to compensate completely for the persisting IVD and may have detrimental effects on LV activation [22]. Indeed, it was possible in all the patients to program a V-V delay equal to the persisting IVD. Most of the CRT candidates for CRT have normal AV conduction. Thus, if RV pacing is delayed, spontaneous right AV conduction may have sufficient time to occur before the right ventricular stimulus and cause loss of capture on the RV lead. Fusion of LV pacing with spontaneous activation of the right ventricle via the bundle branch may be hemodynamically beneficial in some patients. There are no long-term data to validate this concept. The correction of the persisting IVD in our study was due to a symmetrical impairment of right and left systoles as illustrated by a symmetrical lengthening in right and left pre-ejection delays and systole durations.

Avoiding RV Apical Pacing?

Various studies have evaluated alternative RV pacing sites in conventional dual-chamber pacing. Comparison of RV apical with RV outflow tract pacing in a meta-analysis indicated that RVOT pacing conferred a modest acute hemodynamic benefit [23]. Studies evaluating septal pacing are ongoing. Finally, targeting the para-Hisian area may be a smart approach to prevent LV dyssynchrony in patients with structurally normal hearts but not in those with dilated ventricles, infra-Hisian conduction disturbances, or intraventricular conduction delay involving the interventricular septum [24].

In conventional dual-chamber pacing, the evidence of the detrimental consequences of usual RV apical pacing and the "failure" to define a reliable alternative pacing site have engendered a new generation of atrial-based minimal ventricular pacing devices providing a physiologic AAI pacing mode with automatic and reversible backup in DDD pacing mode [25, 26]. These new pacing modes are obviously not applicable to CRT patients.

In CRT, the long-term consequences of RV apical pacing has changed pacemaker practice, pushing more and more implanters to use screw-in leads to target empirically the RVOT or the interventricular septum at the initial implantation.

Should CRT Be Used for All Patients with Conventional Indications in the Presence of Left Ventricular Dysfunction?

Patients with known LV dysfunction with or without LV dyssynchrony who require a pacemaker are currently not candidates for multisite pacing for their primary system if their New York Heart Association (NYHA) functional class is less than III. Predictably, some of these patients are likely to deteriorate clinically with permanent RV pacing, which tends to increase or unmask underlying LV dyssynchrony. Studies like HOBIPACE, which recently concluded that this population of patients benefits significantly in terms of hemodynamics from biventricular pacing, will certainly encourage prophylactic implantations [27]. Therefore, in these NYHA class I/II patients receiving CRT, those that do not end up as "responders" will most likely be worsened by biventricular pacing. Indeed, so-called responders may not be better symptomatically after CRT, but this does not mean that their long-term functional outcome is not improved. Therefore, for prophylactic CRT indications, finding the optimal combination of RV and LV pacing sites becomes vitally important.

Upgrading: Monochamber RV to Biventricular Pacing and Biventricular Pacing to Triple Ventricular Pacing

Upgrading PM/ICD recipients from monochamber RV pacing to biventricular pacing in selected patients is currently routine, and the numbers are growing. Hoijer et al. have confirmed in a controlled study that this option is valid [28]. The addition of a new LV lead several months or years after the

first implantation may present technical obstacles during the procedure. In such a case, the RV lead already in place, often apical, cannot be removed. Therefore, the outcome may not always be as desirable as expected. In case of a poor result, the addition of a second right ventricular lead creating a triple ventricular system is feasible. Such a complete "triangular" synchronous LV pacing arrangement has helped restore a homogenous LV activation sequence and reverse clinical deterioration [20]. What does it mean? Is triple ventricular pacing an "upgrading" solution to compensate the nonoptimal standard resynchronization? Are two leads, even ideally positioned, always enough to synchronize the entire LV? Finally, could triple ventricular pacing be a rather complex but realistic way to achieve better spatial synchrony at initial implantation? The Trip-HF study may bring part of the answer regarding the use of more than two ventricular leads. In this trial, the triple ventricular pacing configuration features one RV lead and two LV leads. A double left-sided lead implantation via the coronary sinus may be a technically difficult procedure.

Can the Optimal Pacing Sites Be Found at the Time of Implantation?

Seeking the "holy grail" to enhance the accuracy of CRT implantation is a desirable goal to obtain only responders and avoid rescue solutions like programming of the V-V interval or the addition of a third ventricular lead. There are several possible approaches:

1. Seeking the narrowest QRS width [5, 8].
2. Attaining the longest electromechanical delay before definitively screwing in the RV lead. Once the LV lead is positioned, it is possible to record endocavitary electrograms from the left free wall and from the interventricular septum. The longest recorded delay between the left and the tested right pacing sites is likely to be close to the maximum degree of LV dyssynchrony at baseline. Theoretically, pacing from these two points should optimize ventricular resynchronization.
3. Echocardiography using simple parameters such as the left pre-ejection delay, the diastolic regional contraction, even DTI parameters, which can all be measured during the implantation. Their maximum correction after implantation and during follow-up is likely to be correlated with the best resynchronization and clinical outcome.

Is it realistic to believe that the optimal combination of pacing sites can be found at time of implantation? Reverse remodeling can make a "rather poor" predischarge mechanical result much better after some weeks or months [28]. The degree of underlying histologic disturbances probably explains the less than spectacular acute mechanical result but does not necessarily predict a bad outcome. On the other hand, in some cases, apoptosis and fibrosis and induced dyssynchrony are so diffuse that even two "optimally" located pacing sites are not sufficient to achieve acceptable resynchronization. In these cases, more than two pacing points might be mandatory. Furthermore, anisotropy due to functional conduction blocks and inhomogeneous wavefront propagation from each pacing site may lead to worsened LV dyssynchrony. This sort of

"adverse remodeling" is certainly the underlying mechanical outcome of the "worsened" nonresponders. Thus, to validate a useful method, one must prove that the best pacing configuration determined at implantation (associated with the best initial mechanical result) is correlated with the best mechanical and clinical outcome after the remodeling period.

Is the RV Pacing Site Important?

Why would an RV septal site be less important than the LV free wall pacing site? Does biventricular pacing aim at resynchronizing all the LV segments and not both the LV and RV? The RV pacing site is crucial, because the LV pacing site is more often achieved "where we can" rather than "where we should," whereas it is much easier to place a screw-in lead on a site all over the right interventricular septum on the right side.

Seeking the optimal RV pacing site(s) in CRT is only the beginning of rethinking multisite pacing. Conceptual trials are needed to enhance the hemodynamic response of CRT if the indications are to increase for a wider patient population. New nonsurgical approaches to optimize the LV pacing site is one consideration to determine the possible role of more than two pacing sites.

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4

Alternative Means of Achieving Cardiac Resynchronization

Michael O. Sweeney

Importance of Achieving an Optimal Stimulation Site for Cardiac Resynchronization Therapy

The optimal site for left ventricular (LV) pacing is an unsettled and complex consideration. It is probably true that the optimal site varies between patients and is likely to be modified by venous anatomy, regional and global LV mechanical function, myocardial substrate, characterization of electrical delay, and other factors. In patients with abnormal ventricular conduction due to left bundle branch block and systolic heart failure, the stimulation site influences the response to LV pacing. The success of resynchronization is dependent on pacing from a site that causes a change in the sequence of ventricular activation that translates to an improvement in cardiac performance. Such systolic improvement and mechanical resynchronization does not require electrical synchrony [1] and explains the lack of correlation between change in QRS duration and clinical response to cardiac resynchronization therapy (CRT) [2]. Ideally, the pacing site or sites that produce the greatest hemodynamic effect would be selected.

However, current clinical evidence permits some generalizations regarding LV pacing site selection for optimal acute hemodynamic response. Multiple independent investigations comparing the acute and chronic effects of different pacing sites in similar dilated cardiomyopathy populations have reported concordant evidence that stimulation site is a primary determinant of CRT hemodynamic benefit.

Auricchio et al. [3,4] showed a positive correlation between the magnitude of pulse pressure and LV +dP/dt increases and left ventricular pacing site. The percent increases in pulse pressure and LV +dP/dt averaged over all atrioventricular (AV) delays were significantly larger at midlateral free wall LV epicardial pacing sites compared with any other sample left ventricular region. Furthermore, increases at the midanterior sites were smaller than all other sites.

These observations were extended in an analysis of 30 patients enrolled in the PATH-CHF II trial [5]. Left ventricular stimulation was delivered at the lateral free wall or midanterior wall. Free wall sites yielded significantly larger improvements in LV +dP/dt and pulse pressure than anterior

sites. Furthermore, in one third of patients, stimulation at anterior sites worsened acute LV hemodynamic performance, whereas free wall stimulation improved it, and the opposite pattern was never observed. This difference in acute hemodynamic response correlated with intrinsic conduction delays. This may be interpreted as evidence that stimulating a later-activated LV region produces a larger response because it more effectively restores regional activation synchrony. Thus, the negative effect of anterior wall stimulation at all AV delays in some patients may be due to preexcitation of an already relatively early-activated site thereby exaggerating intraventricular dyssynchrony [6].

Stimulation at the latest electrically activated (most delayed) region of the LV is associated with greatest hemodynamic response. This is usually on the posterior or posterolateral-basal wall as demonstrated by endocardial voltage mapping [7, 8, 9] and Doppler myocardial imaging [10, 11]. CRT with stimulation at a LV free wall site consistently improves short-term systolic function more than stimulation at an anterior site does. Lateral or posterolateral LV vein lead positions are associated with acute improvements in +dP/dt and pulse pressure [3, 5, 12], significant chronic improvements in functional capacity and ventricular function [13, 14], and possibly mortality compared with anterior vein sites in some [14] but not other studies [13]. However, within a specific coronary vein, the hemodynamic response to LV stimulation at different sites from apex to base is heterogenous, suggesting that optimization of specific pacing sites within a target vein might be necessary for optimal CRT response [12].

It is likely, then, that inadequate LV lead positions contribute significantly to CRT nonresponse. In the MIRACLE study, a lateral or posterolateral vein site was obtained in only 77% of patients, whereas the anterior interventricular vein or middle cardiac vein were used in 19.5% and 4.5% of patients, respectively. A similar situation was reported in the VENTAK CHF/CONTAK CD study where a lateral or posterolateral vein site was obtained in 67% of patients and an anterior interventricular vein site in the remaining 33% [15]. Furthermore, even among patients in whom the transvenous approach failed, necessitating surgical placement of LV leads, a lateral or posterolateral site was obtained in only 34%, whereas the remaining 66% were placed in the anterior or apical LV positions [15]. Thus, even in randomized clinical trials (RCTs) of CRT, as many as 23–33% of patients receive LV stimulation from a suboptimal site. It is conceivable that some of these patients were actually made worse by CRT due to LV pacing in the anterior vein, particularly those with relatively narrow QRSd (less than 150 ms) [5]. These differences in LV stimulation sites may partly account for the varied results and large individual difference observed among clinical studies.

Methods for identifying the best site during implantation are not yet of proven clinical benefit. Furthermore, even if optimal LV pacing sites could be identified a priori, access to such sites is potentially constrained by variations in coronary venous anatomy. The coronary venous circulation demonstrates considerably more variability than the parallel arterial circulation. Careful surveys of retrograde coronary venography have revealed that the anterior interventricular vein is present in 99% of patients and the middle cardiac vein is present in 100% [16, 17]. These veins are generally undesirable for resynchronization therapy because they do not reach the late-activated portion of the LV free wall. Unfortunately, approximately 50% of patients have only

a single vein serving the LV free wall [18]. Anatomically, this is a lateral marginal vein in slightly more than 75% and a true posterior vein that ascends the free wall in approximately 50% of patients [17].

Conventional Approach to CRT

Early attempts at LV pacing via the coronary veins were done with conventional endocardial pacing leads and unassisted coronary sinus (CS) cannulation [19]. This was only possible with stylet-driven leads and required considerable technical prowess. Conventional endocardial pacing leads were poorly suited to LV pacing via the coronary veins. The technique mandated selective bending of stylets to achieve a favorable shape of the tip of the lead to permit CS cannulation. Additional stylet shapes were necessary to permit engagement of the ostium of first- and second-order coronary venous branches. The electrodes, particularly the anodal ring of bipolar leads, prevented cornering of tortuous target vein take-offs. Even if the tip of such leads could be manipulated into the ostium of first-order target veins, the cross-sectional diameter of the lead body often exceeded the luminal diameter of the vein and prevented advancement. Ironically, the only relative merit of conventional pacing leads was the larger cross-sectional diameter that assisted with passive fixation within a target vein.

The contemporary conventional approach to CRT uses specially designed delivery sheaths and tools for cannulating the coronary sinus in order to permit delivery of pacing leads into the epicardial coronary venous circulation. Experienced implanters using currently available tools and using techniques and leads specifically designed for coronary veins can achieve optimal LV stimulation in >90% of cases. The techniques for transvenous delivery of CRT have been previously described [20].

Obstacles to Achieving Conventional Transvenous LV Lead Placement

Complex and unpredictable anatomic and technical considerations may preclude successful delivery of the LV lead to an optimal pacing site. These include inability to cannulate the CS and first- or second-order target veins, unacceptably high epicardial pacing thresholds, and a high incidence of lead dislodgment.

Ideally, a suboptimal LV lead position should be identified and rejected at the time of implantation. The most common mistake of the uninformed or uncommitted implanter is to place the LV lead in the anterior vein and "see how the patient does." If a patient is not responding to CRT and the LV lead is in the anterior vein, an attempt to reposition the LV lead (or a different lead) in a lateral vein should be made. If this is not possible due to limitations in coronary venous anatomy or other insuperable technical obstacles (see below), the patient should be referred for surgical placement of the LV lead in an optimal location.

Inability to Localize or Cannulate the CS Ostium

It is difficult to estimate the true percentage of cases in which the coronary sinus cannot be cannulated because this is clearly influenced by operator

experience. It is probably in the range of 1–5%. Besides operator inexperience, several anatomic situations may render localization of the CS ostium problematic. These include an unusually high or low position of the CS ostium or, very rarely, absence of the CS orifice. Some implanters advocate bolus contrast injections to visualize the CS ostium. The presence of myocardial staining with visible trabeculations indicates that the CS sheath (and guide catheter) is in the right ventricle (RV), whereas the absence of trabecular staining indicates an atrial position. It is often difficult, however, to achieve adequate opacification of the right atrium (RA) with small volume (10–20 cm^3) hand injections due to swirling of blood within the enlarged RA and torrential competitive flow out of the CS. In this situation, equipment for performing a power injection may be particularly useful.

Cannulation of the CS ostium can be facilitated by a working knowledge of the right heart anatomy. The CS ostium is bounded inferiorly by the Thebesian valve and on the atrial side by the Eustachian ridge. The Thebesian valve is usually thin and crescent-shaped in about one third of hearts but multiple variations have been described, including fibrous bands, strands, filigree network, and large redundant "fishnets" continuous with a Chiari network [21]. In one autopsy study, large membrane-like Thebesian valves almost completely occluded the CS ostium in 25% of specimens [22].

These structures tend to impede forward progress of the CS sheath and coronary guide catheter (or deflectable catheter) when approached from the atrial side. On the other hand, these structures (in particular, the Eustachian ridge) tend to direct the CS sheath and guide catheters into the ostium when approached from the ventricular side. Therefore, in difficult cases, it is useful to advance the tip of the CS sheath and guide catheters into the RV then rotate counterclockwise during gradual withdrawal so as to encounter the CS ostium. If this approach fails, an adaptation of the inferior approach described for complex electrophysiology procedures is often successful in localizing the CS ostium. Alternately, intracardiac ultrasound can be used to assist localization of the CS ostium.

Having localized the CS ostium, it is sometimes very difficult to advance the guide catheter or sheath due to kinking at the neck of the CS. This is most commonly encountered with a "goose neck" proximal CS, which is often associated with massive cardiomegaly. This can result in sheath kinking that prevents LV lead passage. This problem has been virtually eliminated by braided sheath designs (see above discussion of sheaths). Rarely, a combined inferior and superior approach is needed to overcome sheath kinking in the proximal CS. A deflectable electrophysiology catheter is placed in the CS ostium from the inferior approach and downward pressure is applied to "straighten" the "goose neck" segment. This may permit advancement of the CS sheath and guide catheters from the superior approach.

Coronary Venous Anatomy: Absent or Seemingly Inaccessible Target Veins

Despite rapid evolution of implantation techniques including guiding sheaths and catheters and over-the-wire (OTW) delivery systems, a suitable pacing site on the LV free wall cannot be achieved in 20–30% of patients. In many patients, this is simply because of absence of coronary veins reaching the LV free wall. In some instances, target veins are present but too small for

cannulation with existing lead systems or paradoxically too large to achieve mechanical fixation with reduced-diameter LV leads that rely primarily on "wedging" the lead tip into a distal site within the target vein for fixation such that the outer diameter of the lead closely approximates the inner luminal diameter of the vein.

Preventing and Overcoming High LV Stimulation Thresholds and Phrenic Nerve Stimulation

The principal limitation of the transvenous approach is that the selection of sites for pacing is entirely dictated by navigable coronary venous anatomy. A commonly encountered problem is that an apparently suitable target vein delivers the lead to a site where ventricular capture can be achieved at only very high output voltages or not at all, rendering potentially optimal target veins unsuitable for use. This presumably relates to the presence of scar on the epicardial surface of the heart underlying the target vein or inadequate contact with the epicardial surface and cannot be anticipated by fluoroscopic examination a priori. Occasionally, mapping of the proximal segment of such veins will yield sites with suitable capture thresholds. Upsizing of the LV lead, or use of a lead with a self-retaining S-shape or cant, may be required to achieve mechanical stability depending on the characteristics of the original lead selected. Similarly, before abandoning such veins, a subselective venogram should be performed because potentially useful tertiary branches are often not visualized during main body CS injection due to low flow and systolic compression. Such tertiary branches may serve a region of myocardium with an acceptable pacing threshold. Depending upon the size of the tertiary branch, downsizing of the LV lead to a purely OTW design may be necessary if not originally used. If this is not successful, surgical placement of LV leads permits more detailed mapping of viable sites in the anatomic region of interest.

A second common problem is that the target vein delivers the lead to a site that results in phrenic nerve stimulation and diaphragmatic pacing. Careful examination of cadaver hearts demonstrates that the phrenic nerve passes over the lateral coronary veins in ~80% of specimens and over the anterior interventricular vein in the remaining ~20% [23]. This presents a high probability of anatomic conflict between the optimal site for LV stimulation and unacceptable phrenic nerve stimulation. Phrenic stimulation can be difficult to demonstrate during implantation when the patient is supine and sedated but may be immediately evident when the patient is later active and changes body positions, even in the absence of lead dislodgment. It is important to recognize that once phrenic nerve stimulation is observed acutely (during implantation), it is almost invariably encountered during follow-up despite manipulation of output voltages, and therefore alternative site LV pacing is sought. As with high LV capture thresholds, phrenic nerve stimulation can often be overcome by repositioning the LV lead more proximally within the target vein. Occasionally, if there is a significant differential in the capture thresholds for phrenic nerve stimulation versus LV capture, this can be overcome by manipulation of LV voltage output in CRT-pacing (CRTP) or CRT-defibrillation (CRTD) devices that permit separate RV and LV outputs. More recently, some LV leads have two electrodes that permit selection of specific LV sites for dual cathodal biventricular stimulation, biventricular stimulation with true bipolar

LV stimulation, or true bipolar LV only univentricular stimulation. It has not been convincingly demonstrated that true bipolar LV stimulation reliably overcomes phrenic stimulation compared with dual cathodal or unipolar LV pacing. On the other hand, selecting alternate LV electrodes for dual cathodal biventricular stimulation may occasionally overcome phrenic stimulation by altering the LV–RV pacing vector. This can be achieved noninvasively using some pulse generators and is referred to as *electronic repositioning*. In either case, the problem of phrenic nerve stimulation is more reliably addressed by LV lead repositioning at implant. If phrenic stimulation during attempted transvenous LV pacing cannot be overcome by any means, surgical placement of LV leads should be considered. Phrenic stimulation can occur with surgically placed epicardial leads if careful visualization of the course of the nerve sheath is not performed prior to fixation. Chronic development of phrenic nerve stimulation results in permanent loss of CRT in about 1–2% of patients [24].

Loss of CRT Due to Differential LV Capture Threshold Rise

There is relatively limited data on long-term pacing thresholds with transvenous or thoracotomy leads for LV pacing. Loss of ventricular capture occurred in 10% of patients in the VENTAK CHF/CONTAK CD study and was the second most common cause of interrupted CRT [24]. Three quarters of these cases were due to gross dislodgment of the LV lead, whereas 23% were due to chronic pacing threshold elevation that was overcome by increasing voltage output in the majority of cases. The reasons for chronic increase in transvenous LV pacing thresholds are not well characterized. Possible explanations include "microdislodgment" not evident by radiographic examination or exit block that occurs as a consequence of inadequate mechanical stability. Hansky et al. [25] have pointed out that an important technique-related factor to postoperative increase in pacing thresholds is an unstable, but not grossly dislodged, lead position. This is based on speculation that repetitive chronic endothelial injuries due to "rocking" of the lead tip may result in progressive fibrotic reorganization of the adjacent vessel wall. It is also possible that late rises in previously acceptable transvenous LV thresholds relate to implantation technique. Aggressive lead manipulations, repeated lead exchanges, or guide-wire maneuvers may traumatize the endothelium of the target vein resulting in a fibrotic reaction, thrombosis, or dissection, all of which may degrade the pacing threshold.

Loss of CRT Due to Lead Dislodgment

Acute dislodgment of right atrial and right ventricular electrodes is uncommon, particularly with active fixation leads, although this is not a specific issue of CRT implantation. The incidence of LV lead dislodgment is considerably higher and has a reported incidence of 5–10% in larger studies [26, 27, 28]. This relates to implanter experience and other technical factors such as the lack of fixation mechanisms and stresses placed on the proximal portion of the lead at the junction of the right atrium and CS ostium. Lead dislodgments are readily identified by change in QRS duration and morphology on 12-lead electrocardiogram (ECG) as well as by chest radiography but usually suspected on the basis of device interrogation that discloses

a significant decline in local signal amplitude and/or change in pacing capture threshold. Typically, RA leads dislodge onto the floor of the RA, and RV leads dislodge toward the inflow of the RV. LV leads typically dislodge into the main body of the CS and less commonly into the RA.

Several techniques reduce the chance of LV lead dislodgment. Probably of most importance is an optimal match between the diameter of the LV lead and the luminal diameter of the target vein. Support at multiple (>2–3) positions increases mechanical stability. Larger leads with preformed shapes should be advanced sufficiently within the target vein to completely unfold. In the case of the smallest diameter purely OTW leads, it is useful to position the tip in a tertiary branch to achieve support at more than one position and increase mechanical stability.

Nonconventional and Alternative Approaches to CRT

In all of these situations where the conventional coronary venous approach fails due to seemingly insuperable anatomic constraints, nonconventional approaches may be useful to achieve successful LV pacing. A brief survey of these approaches includes (1) left vein pacing using telescoping sheaths, (2) coronary venoplasty and stents to facilitate lead placement and enhance mechanical stability, (3) active fixation leads to achieve mechanical stability, (4) transvenous LV endocardial pacing via transseptal puncture, (5) surgical placement of epicardial LV pacing leads, and (6) transcutaneous or transvenous approaches to the pericardial space for LV pacing. Multisite ("bifocal") RV pacing has been touted as an alternative to LV pacing for CRT; however, this will be discussed separately in view of dubious physiologic rationale and limited clinical exposure.

Left Vein Pacing Using Telescoping Sheaths

Another commonly encountered difficulty in transvenous LV lead placement is tortuosity of the target vessel take-off or main segment. These anatomic constraints can be extremely difficult to overcome and often require the use of multiple LV lead designs and delivery systems not specifically designed for this application. Large-diameter stylet-driven leads are likely to fail in this situation, and most implanters reflexively select the smallest diameter OTW lead upon inspection of the coronary venogram.

One approach uses coronary, renal, or other angiography catheters to selectively cannulate the small and tortuous target vein. Advancement of a percutaneous coronary intervention (PCI) guide wire will often straighten the tortuous segment of the vein permitting navigation with an OTW LV lead. Occasionally, the OTW lead cannot be advanced through the proximal segment despite a straight path of the guide wire. The likely explanation in this situation is that the guide wire has not truly straightened the tortuous segment of the target vein. This is more likely when the target vein has a relatively large diameter. In these conditions, the very-small-diameter guide wire may pursue a straight course through the vessel lumen without exerting any effective straightening pressure on the wall of the vein. Occasionally, this can be overcome by using a stiffer guide wire. However, more often, significant resistance to lead advancement persists despite a stiffer guide wire

and a "buddy wire technique" is required. This refers to one or more guide wires placed alongside the first, which may sufficiently straighten the vein to permit lead advancement. After successful placement of the LV lead but before sheath removal, the "buddy wires" are removed.

Despite these techniques, proximal segment tortuosity may persist and prevent advancement of even the smallest diameter OTW leads. An alternative technique that many experienced implanters have adopted as the first-line approach to this situation is the use of telescoping sheaths. Subselection of the target vein with an inner guiding sheath permits straightening of the tortuous proximal segment and direct delivery of the LV lead. This approach often eliminates the use of a guide wire altogether and permits delivery of large-diameter stylet-driven leads if desired, which would otherwise likely fail in this situation.

Telescoping sheaths may require the use of a larger diameter (i.e., 9 F) CS sheath. The target vein is typically cannulated with a stiff PCI guide wire as described above. A smaller diameter straight CS sheath is then advanced over the guide wire into the proximal segment of the target vein. Often, the PCI guide wire does not provide enough support for advancement of the inner straight sheath into the target vein. This can be overcome either by using multiple PCI guide wires or, preferably, a floppy-tipped 0.035-gauge guide wire. Occasionally, the inner straight sheath cannot be advanced into the target vein using any guide-wire technique. In this situation, an angiography catheter can be placed within the inner sheath (triple catheter/sheath approach) (Fig. 4.1). An angiography catheter that closely approximates the shape of the tortuous proximal segment of the target vein should be chosen. A "shepherd's hook" renal angiography catheter is particularly well suited to this requirement. The tip of the angiography catheter is manipulated into the target vein using puffs of contrast if needed. A floppy-tipped 0.035-gauge

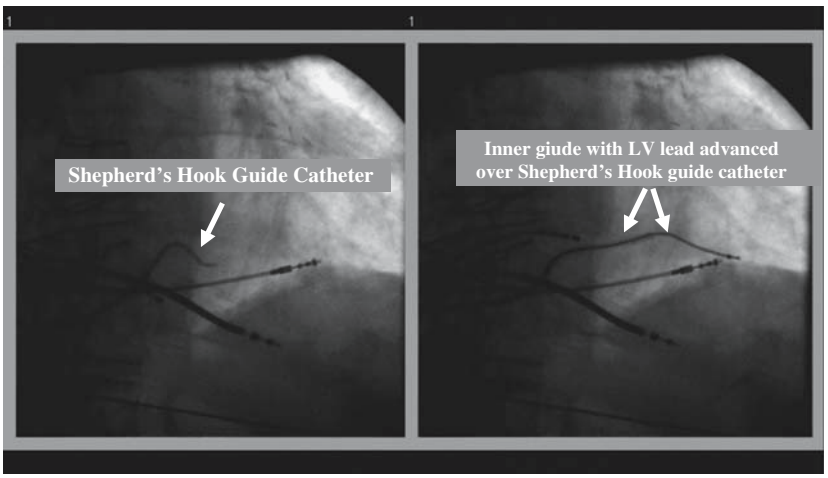

Fig. 4.1 "Triple catheter/sheath" for straightening tortuous proximal coronary veins. *Left:* 5-F shepherd's hook renal angiography catheter has engaged the ostium of a posterolateral vein. *Right:* Inner straight sheath is advanced over the angiography catheter, which was supported distally by an 0.035-gauge floppy-tip guide wire (not shown). Guide wire and angiography catheter are removed, and LV lead is delivered directly through the inner straight sheath.

guide wire is then placed for distal support. The inner straight sheath can then be advanced over the stiff angiography catheter, definitively straightening the tortuous proximal segment. The floppy-tipped guide wire and angiography catheter are then removed, and the LV lead of choice is delivered directly through the inner straight sheath. The inner straight sheath is then cut away using techniques previously described.

Some comments are necessary to reduce complications and increase success of the telescoping sheath technique. First, the patient should be prepped for urgent pericardiocentesis and thoracotomy (which is generally recommended for CRT implantation). Second, excessive force should not be applied to any guide wire or sheath within the coronary veins. Pressure on the vessel wall may causes tension and reduce the normal distensibility of the vein, increasing the probability of perforation. Resistance to advancement of the inner sheath (within or without an inner guide catheter for support) should sponsor a contrast injection to assess the mechanical situation. Third, the inner sheath should have a relatively soft tip segment. Lastly, the telescoping sheath technique should not be applied to small-diameter veins (i.e., <3–3.5 mm).

The telescoping sheath technique may not be ideally suited to lateral coronary veins that arise beyond the proximal one-third of the main body CS. Inability to apply forward axial pressure typically results in failure of this approach, despite the extra support of an 0.035-gauge guide wire or an angiography guide catheter. Additionally, straight LV sheaths are typically not long enough to reach the proximal segments of lateral veins that arise beyond the proximal one-third of the CS.

Therefore, the telescoping sheath technique is most useful for posterolateral veins that arise within 1–3 cm of the CS ostium. This approach is particularly helpful in the situation where the middle cardiac vein and posterolateral vein share a common ostium within the proximal neck of the CS. This anatomic arrangement poses a unique problem for LV lead placement using a single sheath. In order to permit cannulation of the target vein ostium with the LV lead or guide wire, the sheath must be withdrawn to within 1 cm or less of the CS ostium. This commonly results in abrupt dislodgment of the sheath to the floor of the right atrium, pulling the LV lead and guide wire along with it. Occasionally, using a stylet-driven lead and intentionally withdrawing the LV sheath from the CS in a controlled manner can defeat this. The lead is advanced to the midportion of the CS, and the sheath and lead are simultaneously withdrawn while rotating the lead tip into the ostium of the target vein. Attention must be paid to the point when the sheath exits the CS ostium so as to avoid the creation of a redundancy in the LV lead body that could result in prolapse onto the right atrial floor.

Alternatively, a variation of the telescoping sheath approach is often successful in the “common ostium” situation (Figs. 4.2–4.4). An inner guide catheter with a 45- to 60-degree tip angle (i.e., Bern or Berenstein) is advanced through the inner straight sheath (triple catheter/sheath approach) to the mid-CS. The outer LV sheath is withdrawn over the inner straight sheath until it has exited the CS ostium. The inner straight sheath and inner guide catheter are then simultaneously withdrawn while rotating the guide catheter tip until the ostium of the target vein is engaged. A floppy-tipped 0.035-gauge guide wire is advanced into the target vein, followed by the inner guide catheter and the inner straight sheath. The outer LV sheath is essentially irrelevant

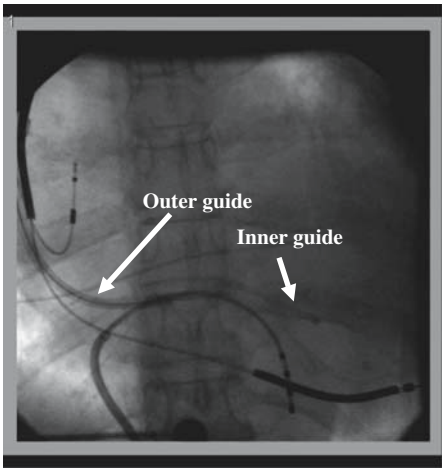

Fig. 4.2 Same technique as Fig. 4.1 Outer guide provides support within the right atrium. Inner telescoping sheath is delivered to posterolateral coronary vein.

at this point and can be withdrawn to the mid right atrium. The inner guide catheter and guide wire are removed, and the LV lead is delivered directly into the target vein through the inner straight sheath. The inner straight sheath and outer sheath are removed in the usual manner. Though these posterolateral veins present unique challenges to LV lead placement, they often yield mechanically stable positions because of the relatively straight course pursued from the low right atrium through the proximal coronary sinus to the lateral LV wall.

Inner guide catheters specifically packaged for coronary venous application are available. Some of these guide catheters have a deflectable tip to enhance subselection of target veins. These inner guide catheters serve a similar role as the coronary and renal angiographic catheters adapted for this role as described previously. Their primary purpose is to assist with delivery of

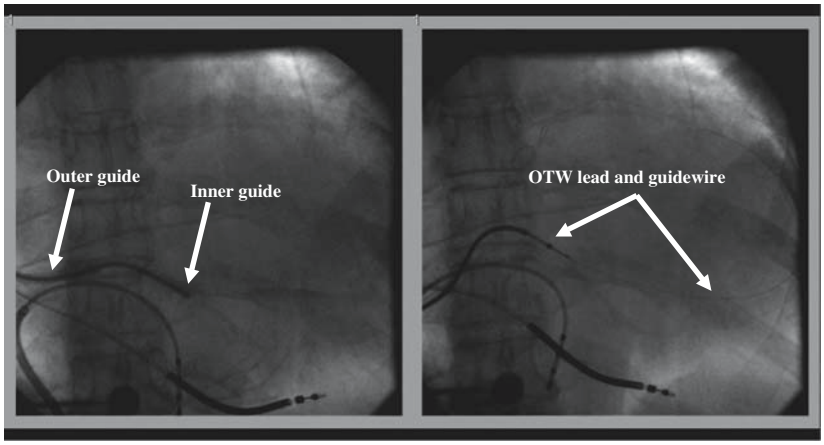

Fig. 4.3 Continuation of technique in Fig. 4.2 *Left:* Inner telescoping sheath in target vein. *Right:* Lead tip and guide wire in target vein.

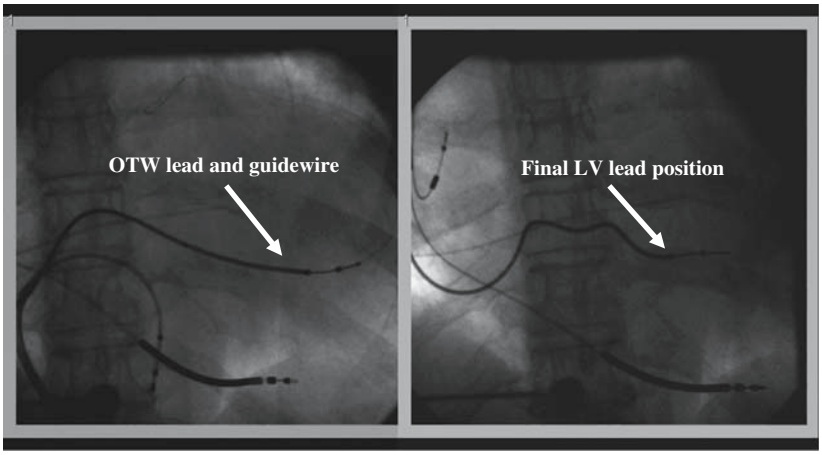

Fig. 4.4 Continuation of technique in Figs. 4.2and 4.3 *Left:* Lead advanced over guide wire. *Right:* Final LV lead placement in posterolateral vein via an inner straight sheath.

a guide wire to the target vein. More recently, inner sheaths of sufficient diameter to deliver LV leads directly have been developed. These have several different distal segment shapes (hockey stick, multipurpose, hook) intended to match patterns of coronary venous take-off anatomy (Figs. 4.5 and 4.6). Such inner sheaths are particularly useful for low-lying posterior and posterolateral veins but typically do not provide sufficient for use with mid and high lateral veins.

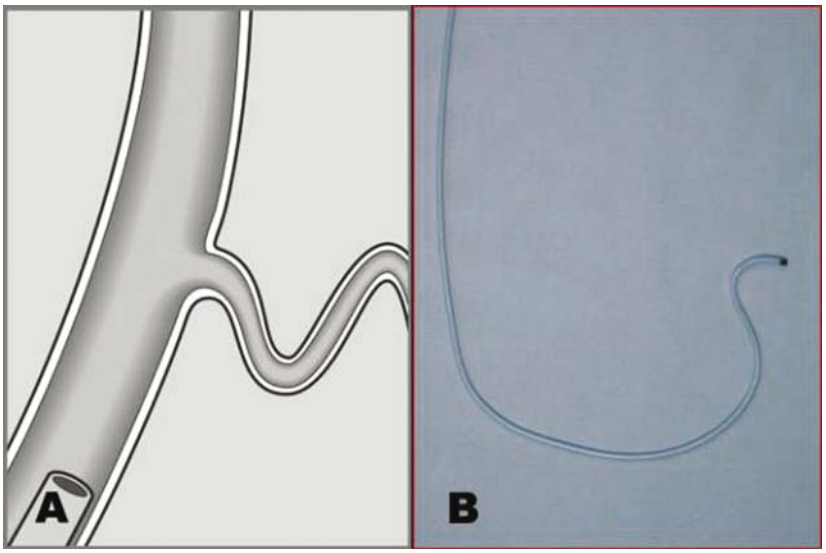

Fig. 4.5 Hockey stick preformed inner sheath for subselecting and straightening tortuous proximal target veins. *Left:* Tortuous proximal segment of target vein. *Right:* Hockey stick inner sheath.

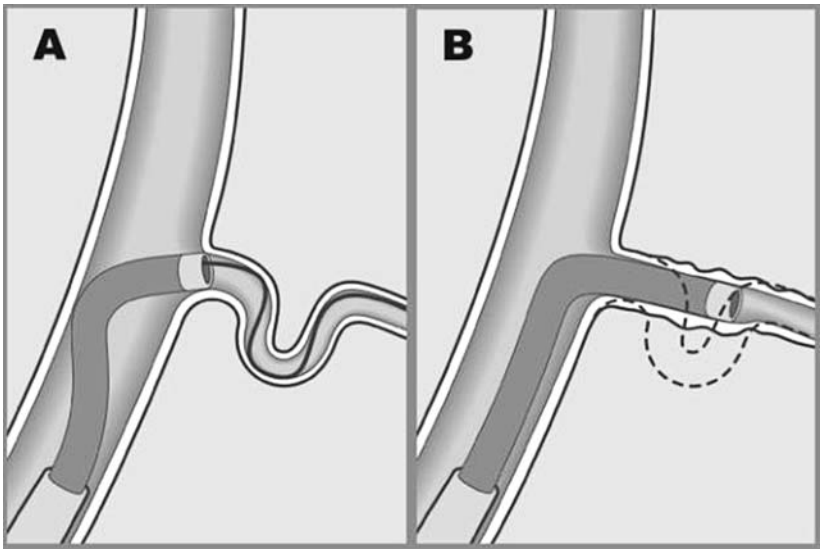

Fig. 4.6 Use of guide wire to direct preformed inner sheath through the tortuous proximal segment of the target vein (*left*), permitting direct deliver of the LV lead (*right*).

Coronary Venoplasty and Stents

A fairly common observation is that potentially ideal target veins serving the posterobasal LV wall are of insufficient caliber to accommodate any available LV lead. In this situation, coronary venoplasty can achieve sufficient cross-sectional diameter to permit successful LV lead placement [29]. This approach is also useful when the target vein cannot be navigated from the antegrade approach due to ostial kinking, proximal segment tortuosity, and so forth (Fig. 4.7). Careful inspection of the coronary venogram may often reveal collateralization of the distal target vein from another coronary vein. However, the collateral anastomosis may be quite small, and coronary venoplasty can be exploited to gain retrograde access to the target vein for successful LV lead placement (Fig. 4.8).

Prior cardiac surgery may impose further limitations on coronary venous anatomy. Rarely, mitral valve surgery may result in impassable strictures in the main body CS, presumably related to encroachment of the sewing ring. Similarly, adhesive bands that form after pericardiotomy may create coronary venous strictures. Both of these situations can be overcome with venoplasty [29]. However, great technical skill is required. Finally, secondary and tertiary coronary venous branches are often surgically ligated or clipped during arterial anastomosis, preventing advancement of LV pacing leads. This can be immediately recognized by coronary venography and cannot be overcome by any technique.

Coronary stents can also be used to overcome otherwise impassable strictures, stenoses, or tortuosity [30]. The use of stents in this application is not fundamentally different than balloon venoplasty (Figs. 4.9–4.12). In extreme situations, bare metal stents have been deployed in the coronary vein adjacent to the LV lead to achieve mechanical stability at a desired site [31] (Fig. 4.13).

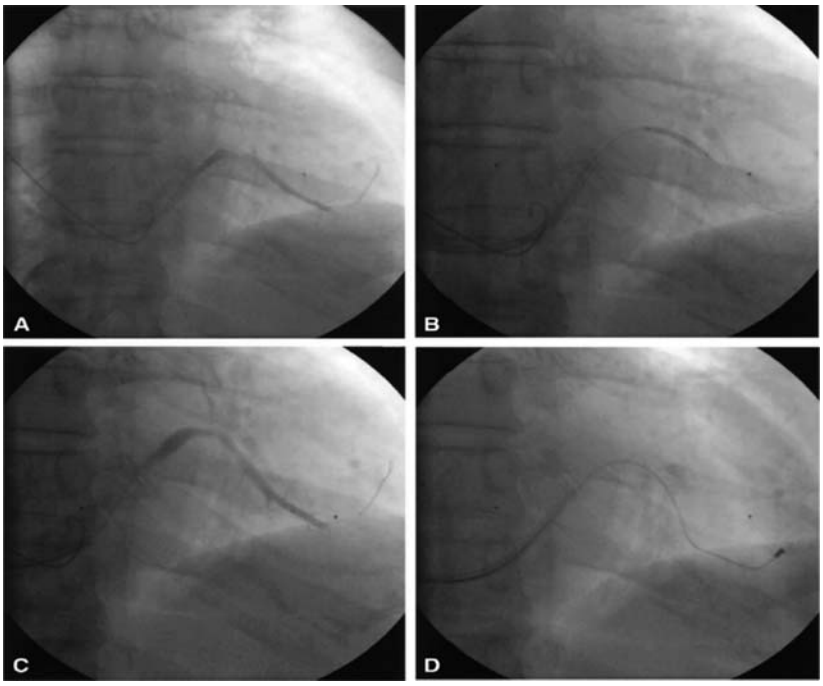

Fig. 4.7 Coronary venoplasty of primary target vessel for LV lead placement [29]. (**A**) Stenosis in target vein. (**B**) Balloon venoplasty. (**C**) Post-venoplasty contrast flow in target vein. (**D**) Lead advanced past stenosis into distal target vein.

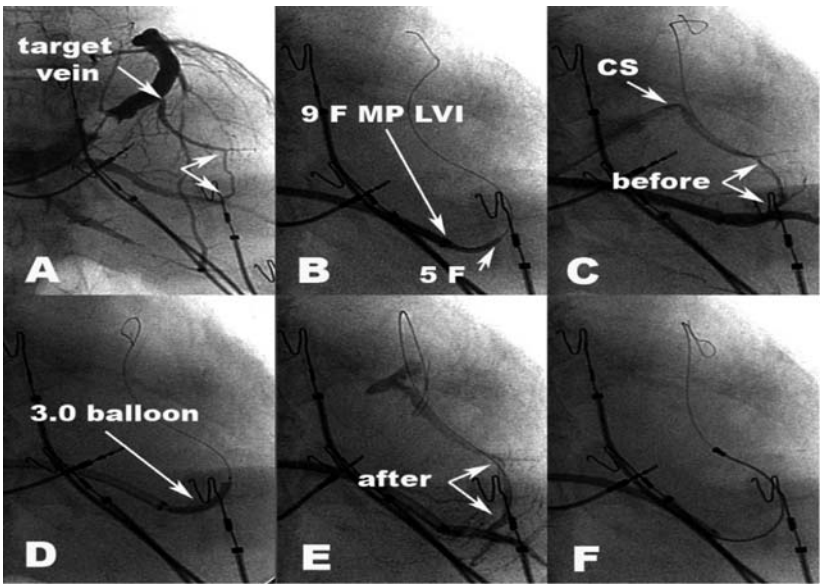

Fig. 4.8 Coronary venoplasty of collateral to primary target vessel for LV lead placement (S. Worley, personal communication). (**A**) Arrows indicate collateral from adjacent vein to target vein. (**B**) Guide catheter in adjacent vein. (**C**) Guide wire in collateral to target vein. (**D**, **E**) Balloon venoplasty of collateral vein. (**D**) Successful placement of LV lead in target vein via collateral from adjacent vein.

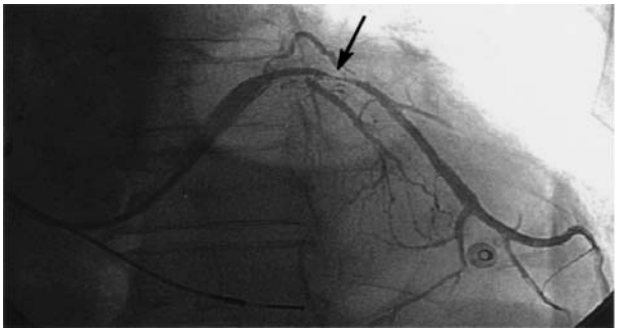

Fig. 4.9 Coronary stenting to obtain access to primary target vessel for LV lead placement [30]. Stenotic segment in proximal target vein (*arrow*).

This approach should be considered with great cautious as stent struts may damage lead insulation and probably render nonsurgical extraction of chronic coronary venous leads impossible due to the danger of vessel rupture.

Active Fixation Leads in the Coronary Venous System

More recently, enhancements to lead design have been directed at combining the maneuverability of smaller-diameter leads with the mechanical stability of large leads. This is achieved by incorporating reversible, self-retaining S- or pigtail-shaped curves at the lead tip, which increase the "effective" diameter of smaller leads for mechanical stability without degrading maneuverability.

The use of true active fixation pacing leads to achieve mechanical stability in the coronary venous system when all other approaches fail has recently been described. In one technique, a 4-F lumenless, catheter-delivered, fixed helix activation fixation pacing lead designed for endocardial use has been successfully and safely used in the coronary venous system. (B. Hansky, personal communication). The lead is delivered through a Judkins right coronary guide catheter within a conventional CS sheath (Figs. 4.14–4.16). The tip of the coronary guide catheter is used to deliver the lead only to the epicardial circumference of the vein in large-caliber veins and proximal segments. A key matter appears to be the choice of active fixation lead. Stiffer leads with preformed bends may be less desirable because they may adapt the distal vein

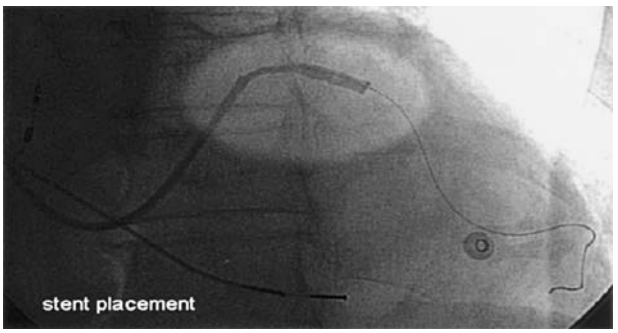

Fig. 4.10 Coronary stenting to obtain access to primary target vessel for LV lead placement [30]. Successful deployment of stent across stenotic segment in target vein.

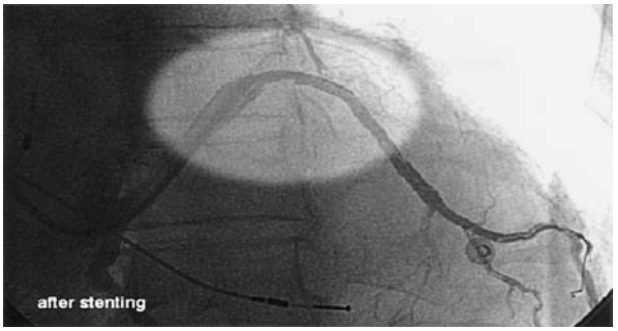

Fig. 4.11 Coronary stenting to obtain access to primary target vessel for LV lead placement [30]. Post-stenting contrast flow in target vein.

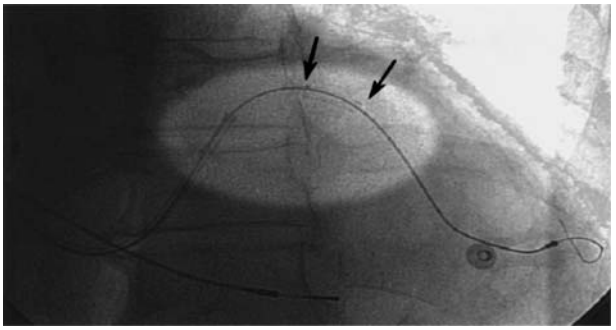

Fig. 4.12 Coronary stenting to obtain access to primary target vessel for LV lead placement [30]. Successful placement of LV lead across stent (*arrows*) in target vein.

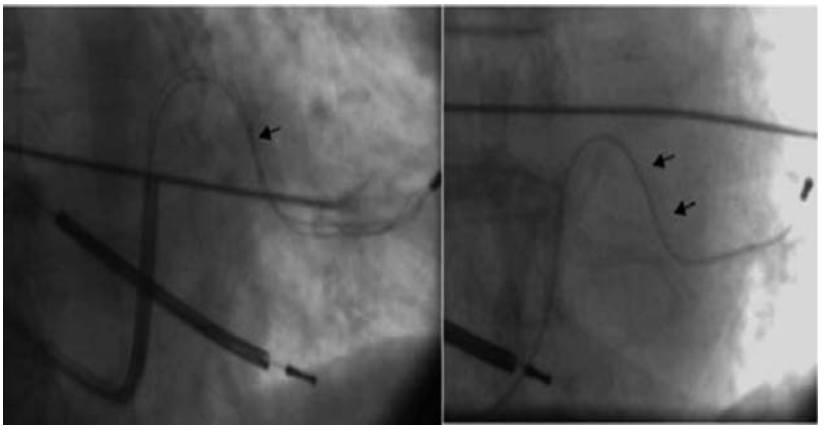

Fig. 4.13 Coronary stenting (*arrows*) to achieve mechanical stability in the coronary venous system [31].

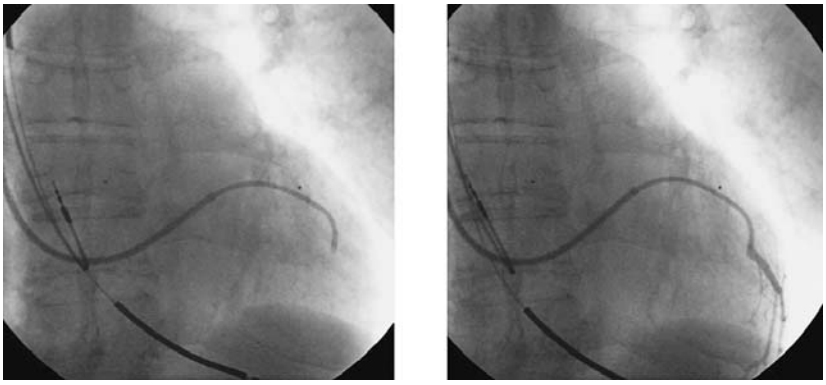

Fig. 4.14 Active fixation leads in the CS (B. Hansky, personal communication). *Left:* Right coronary guide catheter in target vein. *Right:* Venogram of target vein via right coronary guide.

to the lead, resulting in pericardial stimulation without ventricular capture or poor ventricular pacing thresholds. Many obvious questions regarding safety, long-term performance, and approach to removal will arise. Only the most experienced implanters should attempt such exotic approaches to coronary venous pacing.

Transvenous Endocardial LV Pacing

Transvenous left ventricular endocardial pacing via transseptal puncture has been described in the rare circumstance where neither the transvenous epicardial nor surgical options are viable. This was originally described using a right superior approach via the internal jugular vein. A conventional active fixation lead was placed across the mitral valve and on the LV endocardium, and the lead body was tunneled over the clavicle to the pectoral pocket [32, 33, 34]. More recently, a technique for a left superior approach entirely within the subclavicular venous system has been described Similar to the right

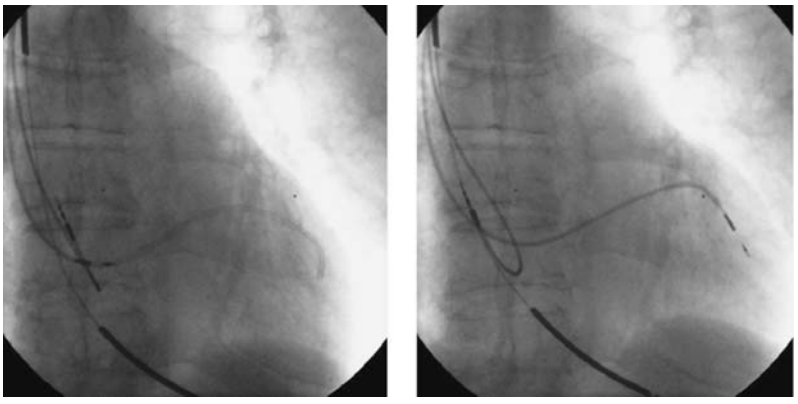

Fig. 4.15 Active fixation leads in the CS (B. Hansky, personal communication). *Left:* Right coronary guide catheter in target vein. *Right:* Delivery of active fix lead through coronary guide catheter.

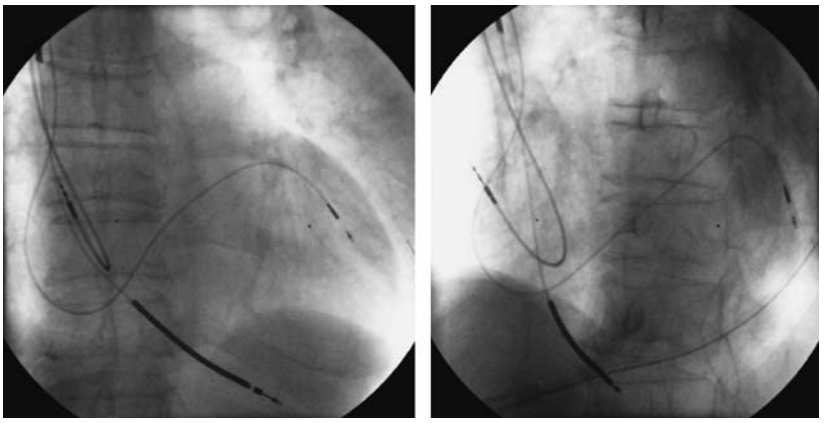

Fig. 4.16 Active fixation leads in the CS (B. Hansky, personal communication). Anterior-posterior (*left*) and left oblique (*right*) view of active fix lead in coronary vein.

superior approach, a standard transseptal puncture via the right femoral vein is performed first [35]. This serves to mark the site for a second transseptal puncture using a peel-away sheath via the left axillary vein. This approach requires manual reshaping of the transseptal needle (with the stylet inside the needle) to allow passage through the innominate vein, superior vena cava–right atrial junction, and then engage the fossa ovalis (Fig. 4.17).

Obviously, both approaches are suitable only in the hands of the most skilled implanters. Although there is some suggestion that LV endocardial pacing may have some physiologic advantages relative to epicardial pacing during CRT [32], there is insufficient experience to comment on the relative risks and benefits of this approach. Major concerns with this approach include thromboembolism and mitral valve disruptions related to the permanent presence of a pacing lead in the LV.

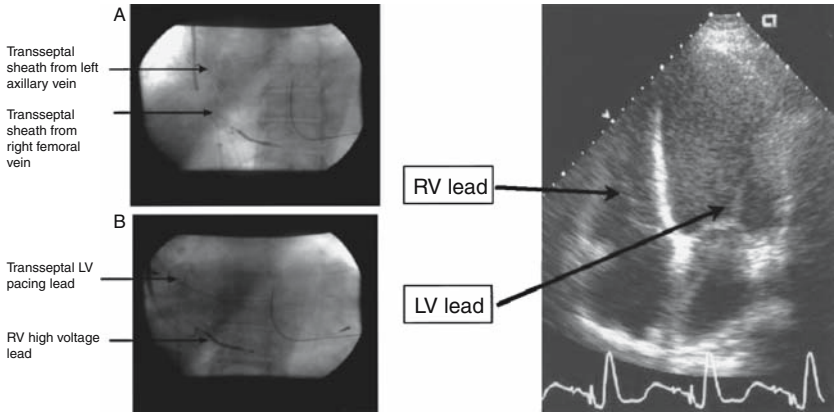

Fig. 4.17 LV endocardial pacing via transseptal puncture [35]. *Left:* Anterior-posterior view. *Right:* Apical four-chamber view of LV endocardial lead via transseptal puncture.

Cardiac Surgical Approach for LV Lead Placement

Left ventricular pacing lead placement can also be achieved under direct visualization using a cardiac surgical approach. The first clinical trial of CRT used a hybrid epicardial LV, endocardial RV pacing lead configuration for multisite ventricular stimulation simply because the technique for transvenous epicardial LV pacing had not been developed [36]. Currently, the cardiac surgical approach is almost exclusively confined to the situation where all other available approaches fail.

Because LV lead placement by the cardiac surgical approach is not limited by the coronary venous anatomy, the ability to achieve an optimal LV pacing site is often touted as a technical advantage. However, even using minimally invasive approaches, the surgical trauma is quite significant and far greater than that associated with the transvenous epicardial LV pacing. The physical stress of this approach on the patient with advanced systolic heart failure should not be underestimated. One critical difference in patient preparation for surgical versus transvenous LV lead placement is that it is better to have the patient a little "dry" (well diuresed) in the former and a little "wet" (diuretics withheld) in the latter. In the case of the transvenous approach, adequate hydration may minimize the risk of contrast-induced renal failure (see above). In contrast, during the surgical approach, volume overload may increase lung volume. This increases the hemodynamic consequences of single-lung ventilation, particularly on right heart function, and may limit LV visualization if complete left lung deflation cannot be achieved. Acute right heart failure complicated by ventricular arrhythmias and requiring cardiopulmonary resuscitation can occur during single-lung ventilation in the decompensated patient.

The approach to surgical implantation of epicardial LV leads depends on whether the reason is planned cardiothoracic surgery (i.e., coronary revascularization, valve repair/replacement) or because of failed transvenous approach for any reason. Epicardial lead placement during surgical procedures that use a standard sternotomy may be compromised by an inability to guarantee sufficient surgical exposure to the posterobasal LV wall. Epicardial lead placement during mitral valve repair from a right para-sternotomy approach may be impossible. In either situation, the surgeon must be willing to lift and rotate the heart to expose the posterobasal LV. The relative relationship of the phrenic nerve and LV pacing sites may be difficult to evaluate visually, and careful stimulation testing with the lungs inflated and heart filled while still on cardiopulmonary bypass is necessary to exclude extracardiac stimulation.

The surgical approach to de novo epicardial LV lead placement is quite different. Many surgeons still use a full left lateral thoracotomy, which permits full visualization of the posterobasal LV wall but results in significant postoperative pain and an extended recovery period. Using a limited left lateral thoracotomy can reduce these consequences. In this approach, the patient is prepped lying on his or her right side with left arm suspended over their head. A 4- to 5-cm incision is made in the left axillary space for access to the posterobasal LV wall (Figs. 4.18 and 4.19). Two epicardial LV leads are typically placed using the obtuse marginal branches of the circumflex coronary artery as regional landmarks, approximately 1 cm apical to the mitral annulus. After the leads are placed, the capped terminal pins are tunneled to a provisional pocket on the chest wall. The patient is then reprepped and draped on his or

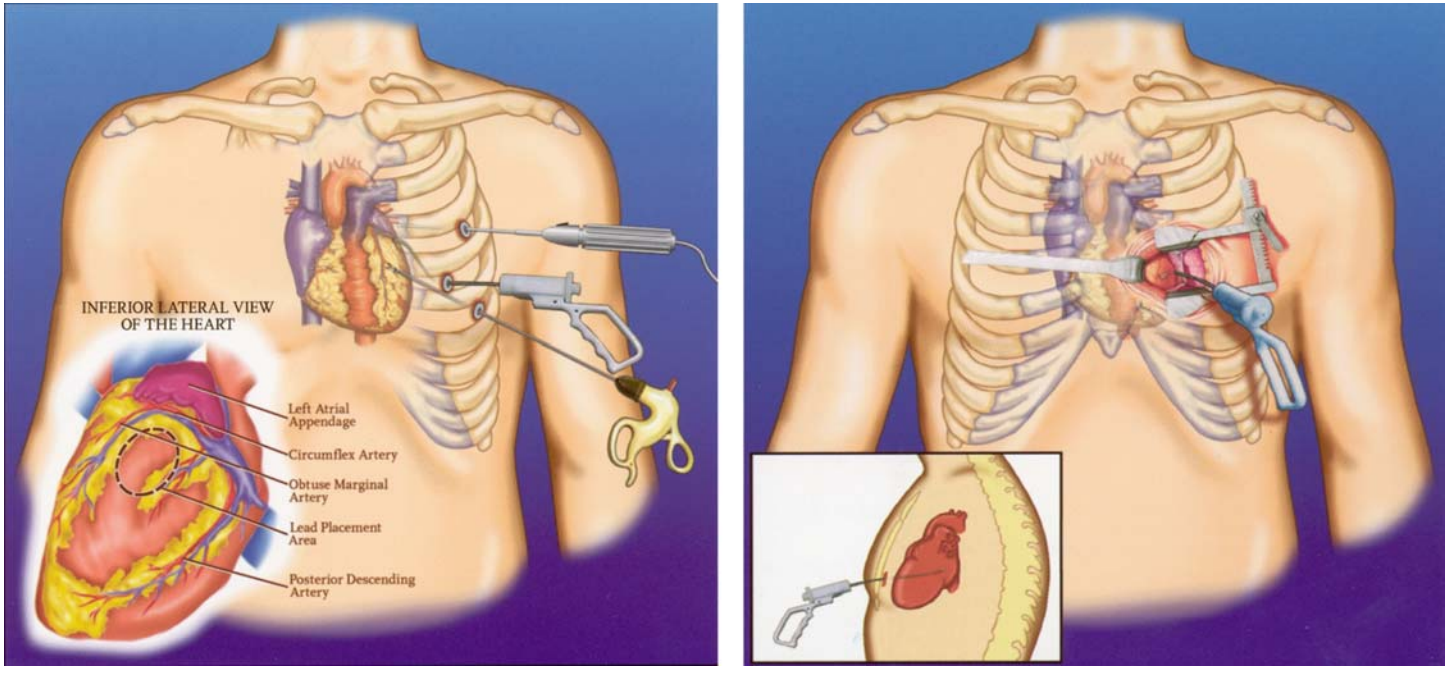

Fig. 4.18 Cardiac surgical approach to LV lead placement. *Left:* "Porthole" approach. *Right:* Limited left lateral thoracotomy approach.

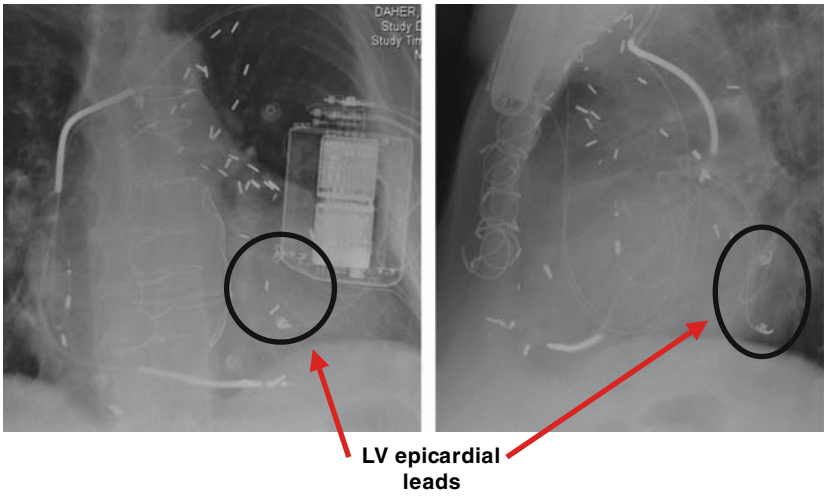

Fig. 4.19 Chest radiograph of LV epicardial leads.

her back; the provisional pocket is opened, and terminal pins are tunneled to the pectoral pocket.

In either of these approaches, muscle relaxants should be temporarily reversed to perform testing for phrenic stimulation. Some cardiac surgeons have touted even more minimally invasive approaches using two or three "porthole" incisions and fiberoptic visualization or robotic assistance. The potential disadvantage to this approach is limited visualization and access to the posterobasal LV that might compromise optimal lead placement.

A particularly difficult problem with chronic epicardial leads is exit block, which in some instances results in voltage thresholds that exceed pulse generator output and results in permanent loss of CRT. Though this is infrequent, it is a devastating problem for the patient, because the epicardial approach is usually taken only when the transvenous approach fails. Several factors contribute to this problem relating to lead design and surgical technique. The most commonly used epicardial pacing lead yielding typically poor long-term performance is a fixed helix mechanism without steroid, and chronic doubling of the implant threshold is common. Furthermore, this situation is made worse by multiple applications of the helix and incautious use of suturing, which increase local tissue trauma and the subsequent inflammatory response.

Therefore, regardless of the cardiac surgical approach, it is imperative that excessive local tissue trauma due to myocardial suturing techniques be avoided. Otherwise, this may result in acute edema and chronic fibrosis causing rapid, significant, and sustained threshold rises or even exit block exceeding the output capacity of the pulse generator. This undesirable outcome would appear to be more likely attending the use of epimyocardial "steroid dot" electrodes, which must be sutured in multiple locations to achieve mechanical stability. An undesirable local inflammatory response due to poor suturing technique could eliminate the otherwise anticipated chronic threshold advantages of local steroid delivery. Screw-in electrodes are more commonly used, particularly in the patient who has had prior surgery where the chronic

pericardial inflammatory response limits identification and exposure of viable epimyocardium.

A comparison of thoracotomy and transvenous lead system performance in 87 patients who received CRTD systems between 1998 and 2001 reported no significant differences in chronic thresholds with either approach, which on average were between 1.5 and 2.0 V up to 30 months after implant [37]. Similarly, there were no chronic threshold differences between transvenous lead designs (over-the-wire versus preformed shape). An interim progress report of the InSync Registry Post-Approval Study [38] in 903 patients showed similar range and stability of LV thresholds (mean, 1.88 ± 1.44 V) with two different preformed transvenous lead designs at 6 months that was retained at 36 months. In this same report, epicardial voltage thresholds were similarly stable but slightly higher (2.42 ± 0.74 V) at 12 months, though data were available on a much smaller number of patients.

Finally, it is critically important that the electrophysiologist attend cardiac surgical placement of LV epicardial leads. The cardiac surgeon is often uninformed about the requirements for adequate sensing and pacing thresholds, the need for minimally traumatizing suture techniques, and critical importance of LV lead positioning for optimal CRT response. In one report, a high incidence of anterior LV sites by cardiac surgical implantation was associated with a trend toward increased mortality due to progressive heart failure compared with posterobasal locations by the transvenous approach [14].

Transcutaneous or Transvenous Access to the Pericardial Space for LV Pacing

An alternative approach for delivering pacing leads to the epicardial surface of the LV could incorporate direct pericardial access without thoracotomy. This has been demonstrated to be feasible and safe during catheter ablation for ventricular tachycardia in the electrophysiology laboratory [39,40]. In one approach, percutaneous needle access to the pericardial space is obtained, and ablation sheaths are inserted into the pericardial space over a guide wire. This approach is more likely to be successful among patients who have not had prior cardiac surgical procedures. In the latter case, fibrous adhesions often prevent direct needle access of the pericardial space and limit sheath maneuverability. A limited subxiphoid incision and pericardiotomy is useful in this situation and similarly permits sheath and ablation electrode manipulation within the pericardial space (Fig. 4.20) [41]. Either of these approaches could easily be adapted for delivery of pacing leads to the epimyocardium. An alternate nonsurgical approach to the pericardial space for delivery of pacing leads has been demonstrated in animals. Direct puncture of the right atrium or superior vena cava is performed with a conventional transseptal needle and catheter [42]. The guide wire is advanced into the pericardial space, and a delivery sheath is advanced over the guide wire (Figs. 4.21–4.23). This approach has far less appeal in humans due to obvious safety concerns. Regardless of the technique for obtaining nonsurgical access to the pericardial space, current LV leads are not suitable for permanent pacing due to lack of fixation. Most likely, a new lead design with a deployable fixation mechanism would be required to prevent movement of the lead tip [42].

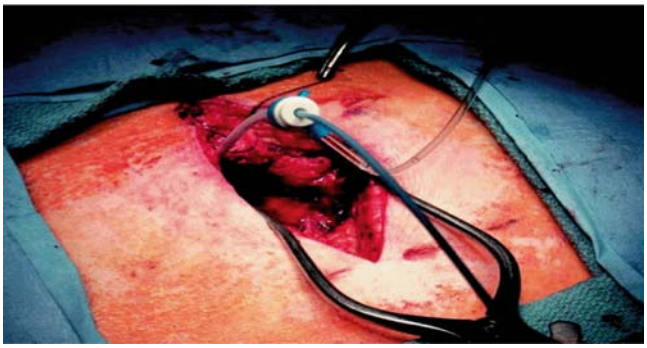

Fig. 4.20 Subxiphoid access to the pericardial space [41]. Diaphragmatic surface of pericardium is exposed by direct surgical visualization via subxiphoid approach. Pericardium is opened with scalpel. Electrophysiology catheter is delivered into pericardial space via 9-F sheath.

Dual Site RV Pacing as an Alternative to CRT

There is a small anecdotal literature that proposes dual-site ("bifocal") RV pacing as an alternative to conventional CRT when LV pacing cannot be achieved. Of course, LV pacing can almost always be achieved using various nonconventional approaches discussed above, and it is more accurate to state that the questionable justification for this approach is an unwillingness of the physician to sponsor the patient for cardiac surgery. Many of these reports are unaccompanied by any meaningful physiologic measures and are presented as "testimonials" of patient improvement without a comparison group [43,44,45,46,47,48].

More problematic is a fundamental misunderstanding or neglect of the physiologic basis of ventricular conduction, with particular attention to selective site pacing. For example, Vlay has repeatedly stated, "Restoring

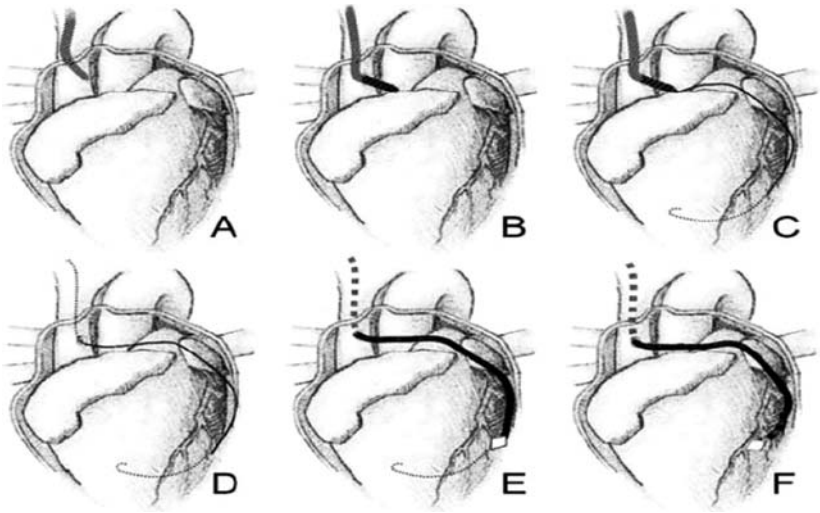

Fig. 4.21 Transvenous access to the pericardial space [42]. Schematic of LV pacing lead entering pericardial space via puncture of superior vena cava.

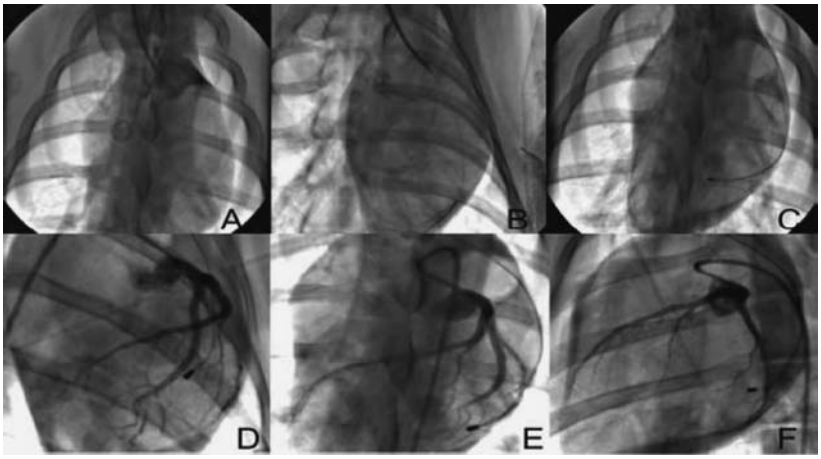

Fig. 4.22 Transvenous access to the pericardial space [42]. Fluoroscopic images of LV pacing lead in pericardial space via puncture of superior vena cava (**A–C**) and concomitant coronary angiography (**D–F**).

the origin of depolarization to the high ventricular septum, restores a more favorable contraction pattern. In addition, since the highest part of the septum is the thinnest, the impulse travels through the septum to depolarize the LV. This route may be an alternative way to achieve earlier LV depolarization" [44,45]. This physiologically incorrect thinking has appeared in other related publications (see Fig. 2 in Mateos et al. [43]).

Normal activation of ventricular muscle occurs from apex to base, not from base to apex, an error that is repeatedly committed in the "bifocal" RV literature [43,44,45]. Myerburg [49] demonstrated more than three decades ago that impulse propagation from the normal myocardium can only enter the Purkinje system at the apical sites where impulses exit the specialized conduction system during normal conduction (reviewed in Ref. 50). This corresponds with the lower one-quarter of the RV septum and the lower

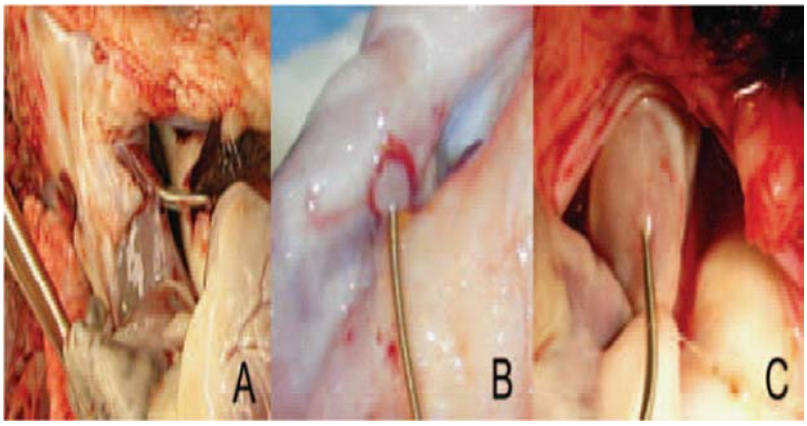

Fig. 4.23 Transvenous access to the pericardial space [42]. Appearance of healed puncture site in superior vena cava (**A**, acute; **B**, 17 days; **C**, 46 days).

one-third of the LV septum. The specialized conduction system (right and left bundle branches and their ramifications) is electrically insulated from the adjacent myocardium. Therefore, the electrical wavefront initiated by a pacing stimulus anywhere in the upper right ventricular septum or outflow tract must propagate through ventricular muscle and then enter the specialized conduction system in retrograde fashion. These basic relationships of normal ventricular conduction form the rationale for differential site RV pacing to distinguish retrograde atrial activation via a fast pathway versus a concealed accessory pathway, for example. "Early" activation of the LV is not physiologically possible from any alternate pacing site in the RV. Thus, the notion that "cardiac resynchronization" can be achieved by multisite RV pacing is physiologically flawed.

It is possible that alternate site RV pacing might be physiologically superior to RV apical pacing, though randomized clinical trial data is lacking. The (high) RV septum appears to be the most promising site within the RV. Acute hemodynamic studies generally, although not consistently, show an advantage of high septal over RV pacing (reviewed in Ref. 51). However, small enrollment and inconsistent experimental methods hinder the interpretation of these studies. Location of alternative pacing sites was not clearly specified, was largely topographic, and lacked consistent anatomic designation. There is conflicting evidence as to whether QRS duration can be used to find the pacing position resulting in the best LV pump function [52, 53]**.** Therefore, it is at least conceivable that among patients with systolic heart failure and left bundle branch block (LBBB) in whom LV pacing cannot be achieved but ventricular pacing support is clinically necessary, alternate RV sites might be superior to the RV apex. In this situation, the issue is not achieving resynchronization but rather reducing the total dose of cardiac desynchronization imposed by any form of RV pacing, which is composed of the paced QRS duration and the total ventricular pacing burden [54].

Interestingly, in the PATH-CHF study, a very small number of patients with heart failure and LBBB achieved optimal hemodynamic improvement with RV versus LV or biventricular pacing [36]. Electroanatomic mapping has demonstrated that the RV apex is frequently delayed in LBBB, and in select patients, left ventricular preexcitation can be achieved by RV apical pacing due to early breakthrough into the left ventricle at this site (A. Auricchio, personal communication).

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5

CRT-Pacing Only Versus CRT-Defibrillator

Arthur J. Moss

Background

In patients with ischemic and nonischemic heart disease and reduced left ventricular function, heart failure and ventricular arrhythmias are common, and affected individuals are at increased risk for sudden and nonsudden cardiac death. There are now several randomized clinical trials that have demonstrated improved survival with the implanted cardioverter defibrillator (ICD) in cardiac patients with ejection fraction ≤ 0.35 [1,2,3,4,5,6,7]. Recent secondary findings from the MADIT-II trial indicate that life-prolonging ICD therapy transforms a sudden death risk to a later heart failure risk [8]. Furthermore, it appears that the development of heart failure after enrollment in MADIT-II is a major risk factor for subsequent ventricular tachyarrhythmias and appropriate firing of the ICD for termination of these arrhythmias [9].

After the introduction of biventricular pacing (BIV) in the mid-1990s for resynchronization treatment of patients with advanced systolic heart failure, cardiac resynchronization therapy with pacing alone (CRT-P) has been demonstrated to improve ventricular function, reduce heart failure symptoms, improve the functional state of the affected patient, and reduce mortality [5, 10, 11, 12, 13, 14].

Only one randomized clinical trial to date has compared morbidity and mortality outcomes in patients with chronic heart failure treated with CRT-P versus CRT with defibrillator (CRT-D), and in that study patients treated with CRT-D had a somewhat better survival than those treated with CRT-P [5].

Because of the paucity of randomized trials directly comparing CRT-P versus CRT-D, it is unclear which therapy should be rendered in an individual patient with compromised left ventricular dysfunction and signs and symptoms of heart failure. Are the two therapies equivalent in comparable patients, and how does the severity of the underlying heart disease influence the efficacy of each of the therapies? A brief review will address these therapeutic questions.

COMPANION and CARE-HF Studies

The two large-scale, randomized trials that relate to the therapeutic question of CRT-D versus CRT-P are the three-arm COMPANION study published in 2004

(CRT-D, CRT-P, and pharmacologic therapy) [5] and the two-arm CARE-HF study published in 2005 (CRT-P, pharmacologic therapy) [15]. A comparison of the baseline clinical characteristics and the outcome of the patients enrolled in these two studies is presented in Table 5.1. Although the baseline characteristics of patients in the two studies are similar, a direct comparison of the two study populations reveals that the patients in the COMPANION study had more severe heart disease with a greater percentage having NYHA class IV heart failure and a lower ejection fraction than those in the CARE study. Furthermore, patients randomized to pharmacologic therapy in the COMPANION study had a higher 2-year mortality and 2-year mortality or hospitalization rate than pharmacologically treated patients in the CARE-HF study.

The fact that heart disease was more severe in the COMPANION than in the CARE-HF study makes a direct comparison of the efficacy of CRT-D versus CRT-P between the two studies difficult. Within the three-arm COMPANION study, the comparative effectiveness for mortality reduction was somewhat better in the CRT-D arm (hazard ratio 0.64, $p < 0.01$) than in the CRT-P arm (hazard ratio 0.76, $p = 0.06$) when compared with the pharmacologically treated patients.

Table 5.1 Clinical characteristics of patients enrolled in COMPANION and CARE-HF.

Characteristic	**COMPANION CRT-D arm* (N = 595)**	**CARE-HF CRT-P arm† (N = 409)**
Baseline		
Age	66	67
Male sex (%)	67	74
NYHA class IV (%)	14	6
Ischemic cardiomyopathy	55	40
Left ventricular ejection fraction	0.22	0.25
QRS duration (ms)	160	160
Heart rate (beats/min)	72	69
Blood pressure (mmHg)		
Systolic	112	110
Diastolic	68	70
Pharmacologic therapy (%)		
ACE inhibitor or angiotensin-receptor blocker	90	95
Beta-blocker	68	70
Outcome		
Two-year mortality (%)		
Medical therapy group	38	25
Device therapy	26	20
Hazard ratio for death (device:medical Rx)	0.64	0.64
Two-year mortality or hospitalization (%)		
Medical therapy group	80	50
Device therapy group	75	35
Hazard ratio for death or hospitalization (device:medical Rx)	0.80	0.63

*Source: Ref. 5.

†Source: Ref. 15.

Severity of Heart Disease

A recent observational study by Desai et al. provides useful information about the predictors of appropriate defibrillator therapy among patients receiving a CRT-D device [16]. The population of 501 patients was remarkably similar to those in the COMPANION study with mean age 66 years, 83% males, 67% NYHA class III–IV, QRS width 158 ms, and ejection fraction 0.21. NYHA class IV and a history of sustained ventricular arrhythmias are independent predictors of appropriate ICD therapy in the CRT-D population. Heart failure etiology and drug therapy had no significant impact on the rate of appropriate defibrillator therapy. These findings are in good alignment with the recent experience from MADIT-II in which time-dependent interim development of heart failure requiring hospitalization after enrollment was the only factor significantly associated with appropriate ICD firing for ventricular tachycardia and ventricular fibrillation.

Cardiac patients with low ejection are at increased risk for the development of atrial fibrillation, and this arrhythmia frequently exacerbates the development of heart failure and is also a marker for more severe heart disease. Almost all of the CRT-P trials to date have excluded patients with atrial fibrillation. In the recent publication by Gasparini et al. involving more than 600 patients treated with CRT-P, there were 114 patients with atrial fibrillation [17]. Most patients with atrial fibrillation did not receive adequate biventricular capture due to the rapid ventricular response rate from atrial fibrillation. Many of these patients underwent atrioventricular junctional ablation, and this combined therapy was associated with evidence of reverse remodeling and functional improvement. Clinical trials to evaluate CRT-D versus CRT-P in heart failure patients with atrial fibrillation with and without combined atrioventricular nodal ablation are likely to be initiated in the near future.

Clinical Recommendations

In cardiac patients with advanced left ventricular function, there is a high likelihood that cardiac dysfunction will progress over time despite optimal medical management. We cannot accurately predict who will develop life-threatening or fatal ventricular tachyarrhythmias, but we do know that the development of heart failure is a major factor contributing to arrhythmic instability. Furthermore, the available evidence indicates that appropriate ICD therapy for ventricular tachyarrhythmias in high-risk patients identifies subjects at increased risk for subsequent heart failure. At the present time, risk stratification studies have not been able to identify which cardiac patients will die from heart failure and which from sudden cardiac death. This being the case, then current logic favors the use of the CRT-D device in patients with advanced left ventricular dysfunction, especially in those with NYHA class III and IV heart failure and evidence of dyssynchrony. Although the CARE-HF study has shown impressive reduction in mortality and heart failure with CRT-P only in this high-risk group, this is not to say that we cannot achieve better results with CRT-D. The available evidence would favor the latter approach. At the present time, ICD-only is indicted for NYHA class I,

II, or III patients with Ejection fraction (EF) $\leq$0.35 and QRS <120 ms, and CRT-D seems the preferred therapy for patients with EF $\leq$0.35, NYHA class III or IV, and QRS $\geq$120 ms. The question whether CRT-D will inhibit the development of heart failure in addition to saving lives in NYHA class I or II patients with low ejection fraction and QRS $\geq$120 ms is currently under investigation in the MADIT-CRT trial [18].

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6

Upgrading Conventional Pacemakers to CRT: Indications and Technical Considerations

Safwat A. Gassis and Angel R. León

Indications and Clinical Implications of Upgrade to CRT

Introduction: CRT Utility and Current Guidelines

Cardiac resynchronization therapy (CRT) has been shown in numerous trials to improve symptoms, ventricular function, and survival in patients with left ventricular (LV) systolic dysfunction and left conduction delay or block [1,2,3,4,5,6,7,8,9]. The detrimental effects of a wide native QRS have been adequately documented [10, 11]. A large number of patients with previously implanted devices, however, develop or continue to have progression of heart failure. In a study of patients followed at a routine pacemaker clinic, one third of patients receiving dual or ventricular pacing were identified to have reduced ejection fraction (EF) <40%, 88% of whom were symptomatic at the time of clinic follow-up [12]. The upgrade to CRT devices emerges as an effective strategy to overcome native and iatrogenic dyssynchrony in patients with heart failure and chronic pacing.

Current guidelines for CRT include sinus rhythm with reduced EF <35%, marked heart failure symptoms, New York Heart Association (NYHA) class III and ambulatory class IV, and dyssynchrony demonstrated by a QRS >120 ms [13]. The current guidelines do not specifically address pacing-induced dyssynchrony as a criterion for CRT implantation or upgrade. However, a strong body of evidence is accumulating that supports upgrade to CRT in patients who do not fulfill criteria set for the implantation of CRT devices. The benefit of CRT in clinical trials has been demonstrated predominately in patients without antibradycardia indications for atrial and/or ventricular pacing. Patients with indications for antibradycardia pacing due to sinus node dysfunction, atrioventricular conduction abnormalities, or bradycardia in the setting of atrial arrhythmias require particular attention for choice of pacing device, pacing mode, and programmable parameters. This chapter addresses the indications and technical aspects for upgrading conventional pacing devices to CRT or CRT–implantable cardioverter defibrillator (CRT-ICD).

Detrimental Effects of Right Ventricular Pacing

The primary question raised is whether right ventricular (RV) pacing–induced left bundle branch block (LBBB) morphology is equivalent to intrinsic or native LBBB? If so, is congestive heart failure (CHF) associated with RV pacing–induced LBBB ameliorated with CRT in the same way as it is with intrinsic LBBB? Answers to these questions help us understand the utility of upgrading pacing devices to CRT systems.

RV pacing creates an activation pattern similar to LBBB and is characterized by worsened systolic and diastolic function [14, 15, 16]. Abnormal contractility patterns have been noted by magnetic resonance imaging during RV pacing in dog studies [17]. Studies of chronic RV pacing in humans with congenital atrioventricular (AV) block have shown histopathologic alteration and remodeling of atrial and ventricular myocardium [18]. These pathologic changes have mirrored clinical and echocardiographic deterioration of atrial and LV dimensions and function [19]. The deleterious effects of chronic right ventricular pacing on hemodynamics and cardiac function have clearly been documented in clinical trials [19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33].

Not all studies support the notion that a paced QRS is equivalent to native LBBB. In a report by Xiao et al., RV pacing–induced widening of the QRS was shown to exhibit different characteristics from native LBBB with respect to electromechanical delay, contraction and relaxation times, and extent of uncoordinated regional ventricular wall motion [34]. Cazeau et al. studied echocardiographic parameters as a guide to selection of patients for CRT. Almost half of the CRT recipients were upgrades from chronic RV pacing. Although the majority noted a clinical response, the mechanism of improved dyssynchrony after CRT was different between the upgrade patients and those receiving de novo CRT devices [35]. In a small study by Garrigue et al. evaluating the acute effects of RV pacing in the presence or absence of LBBB, 10 patients with heart failure and sinus node dysfunction (SND) underwent radionuclide ventriculography comparing single-chamber atrial pacing (AAI) and dual-chamber pacing (DDD) modes [36]. In patients with normal QRS, ventriculography demonstrated better global and regional contractility and less electromechanical dyssynchrony with AAI pacing. Conversely, the patients with LBBB demonstrated better global and regional contractility with DDD pacing than with AAI pacing [36]. The small study did not compare CRT with RV pacing in relation to presence or absence of underlying LBBB. It however demonstrated a difference between RV pacing–induced QRS prolongation and native LBBB that should be taken into consideration as a confounding factor in trials measuring the response to CRT upgrade. Despite these differences, iatrogenic LBBB morphology is similarly associated with progression of LV dysfunction.

One of the first randomized trials comparing rate modulated single-chamber atrial pacing (AAIR) with rate modulated dual-chamber pacing (DDDR) modes by Nielsen et al. showed that DDD modes resulted in a higher atrial fibrillation occurrence rate and increased left atrial diameter. With AV delay shortened to "physiologic" duration, there was a significant increase in percentage ventricular paced beats (90%) associated with a reduction in LV fractional shortening [33]. Data from the MOST trial, which compared dual-chamber versus single-chamber ventricular pacing in patients with SND and normal QRS duration, DDDR mode resulted in a median of 90% cumulative

ventricular pacing and rate modulated single chamber ventricular pacing (VVIR) mode in a median of 58% cumulative ventricular paced beats [25]. In the DDDR group, cumulative ventricular pacing up to 40% was associated with an increased risk for heart failure hospitalization (Hazard ratio (HR) = 1.54, p = 0.046). For every 10% increase in RV pacing, there was a 54% increase in heart failure hospitalization until RV pacing reached 40%. Despite maintenance of AV synchrony, the MOST trial showed only a modest benefit to dual-chamber pacing. The incremental benefit also included reduced incidence of atrial fibrillation with dual-chamber pacing. A moderate benefit in heart failure symptoms, also seen in other similar trials of RV pacing [37, 38, 39], may have been mitigated by the increased risk of ventricular dysfunction from chronic RV pacing.

A recent analysis from the MADIT II study population showed a remarkable difference in rate of new or worsened heart failure that was dependent on the frequency of RV pacing [31]. In contrast with the MOST trial and other studies of RV pacing, this analysis focused on patients with already reduced LV function, predominately symptomatic, and is therefore more representative of the patients who would be considered for CRT therapy with native LBBB. There was a bimodal distribution of percentage RV pacing at either extreme. Patients with >50% pacing (median percentage pacing = 95.6%) had a 30% incidence of new or worsened heart failure versus 17% in the group with <50% pacing (median percentage pacing = 0.2%). The association was also significant for increased rates of death and ventricular tachyarrhythmia requiring ICD therapy. This association remained significant even after controlling for presence of LBBB and prolonged QRS in the native rhythm.

Does the Duration of the Paced QRS Matter?

There has been conflicting evidence whether the extent of paced QRS prolongation closely tracks the degree of dyssynchrony produced. An echocardiographic study measuring indices of dyssynchrony in RV-paced patients with heart failure versus a control set of RV pacing but no heart failure showed that QRS duration alone with RV pacing does not predict dyssynchrony [40]. Rather, the authors suggest that interventricular or intraventricular electromechanical delays of >50 ms are superior to paced QRS duration for predicting dyssynchrony to guide the decision to upgrade to CRT. Whether echocardiographic parameters are reliable at identifying dyssynchrony in RV pacing ameliorated with CRT remains to be demonstrated in clinical trials.

The duration of the paced QRS complex has been correlated to increased heart failure hospitalization in an analysis of the MOST trial population [41]. This was subsequently illustrated in a study that showed a paced QRS duration >190 ms at implantation, or prolongation of the paced QRS over time, is a strong predictor of subsequent heart failure [30]. From a recent analysis of the MOST study population, Sweeney et al. described the risk of heart failure hospitalization with percentage ventricular pacing while considering potential confounding factors [28]. The analysis showed that prolonged QRS was a predictor of increased CHF hospitalization regardless of the etiology of QRS widening (intrinsic or RV pacing induced) at cumulative ventricular pacing >40% in DDDR mode or >80% in VVIR mode (i.e., relative increased risk remained the same). However, they noted that native QRS prolongation was

consistently associated with a twofold higher absolute risk of heart failure hospitalization over RV pacing–induced QRS prolongation. The incremental risk incurred by RV pacing was most pronounced in patients with structural heart disease (low EF, prior infarction and conduction abnormalities). Although the relative risk doubles with RV pacing, the absolute risk of CHF hospitalization in patients with no other structural disease increases from approximately 2% to 4%, whereas in patients with structural disease the risk increases from approximately 20% to 40%. Interestingly, the risk of heart failure increased incrementally with increasing QRS duration—both in the paced and nonpaced groups. Furthermore, patients with reduced EF showed an exaggerated increase in heart failure as the QRS duration increased. This latter effect was seen up until a QRS duration of 200 ms, at which interval both low EF and normal EF patients demonstrated equivalent rates of heart failure hospitalization [28]. This data suggest that a very wide QRS duration with RV pacing may serve as a stronger impetus to upgrade to CRT in select patients.

A change in QRS duration after biventricular pacing in patients with native left ventricular conduction delay or block is now not considered to be a sensitive marker for successful resynchronization. Multiple studies of CRT upgrade have noted a reduction in QRS duration from RV pacing, however, the prognostic value of the extent to which it is altered is yet unclear [40, 42, 43, 44, 45, 46, 47, 48].

Strategies to Consider Prior to Deciding to Upgrade to CRT

Patients with indications for antibradycardia pacing and narrow baseline QRS duration present a unique challenge. Chronic RV pacing as discussed above has been shown to be harmful particularly in patients with symptomatic CHF, therefore, every effort should be made to minimize ventricular pacing. Strategies to prevent frequent RV pacing include atrial-based pacing (AAI modes), atrial nontracking (DDI mode), programming a long AV interval delay, ventricular rate support set at low rates (VVI) [24], automated intrinsic AV adjustments [49], and managed ventricular pacing (MVP) mode [50]. These strategies are an appealing alternative to upgrading to CRT in select patients with symptomatic heart failure and with pacing indications.

To illustrate the effect of pacing mode choices, 225 patients with SND randomized to atrial-based pacing versus single-chamber VVIR ventricular-based pacing were followed [51]. After a mean follow-up of 5.5 years, mortality, atrial fibrillation, severity of CHF, and thromboembolic events were lower in the group randomized to atrial pacing. Atrial pacing conferred more favorable outcomes with a relative risk for survival of 0.66 ($p = 0.45$), cardiovascular mortality of 0.47 ($p = 0.0065$), atrial fibrillation of 0.54 ($p = 0.012$), freedom from thromboembolic events of 0.47 ($p = 0.023$), and lower NYHA class ($p = 0.01$). The higher frequency of atrial fibrillation and, therefore, higher thromboembolic risk, in the ventricular group probably stems from anatomical and electrical remodeling of the atria due to the AV dyssynchronous activation. The study demonstrated a low risk of heart block (0.6%) and, therefore, supports the idea that single-chamber atrial pacing is a viable treatment option for patients with SND and normal AV conduction. The presence of right bundle branch block (RBBB), however, was associated with increased risk for CHB that was consistent with prior studies [52]. In a more recent study, Nielsen et al. in a study comparing AAI versus DDD pacing

reported 3 of 51 patients programmed to AAI developed high-grade AV block (1.9% per year) requiring reprogramming to DDD modes [33].

Patients with CHF frequently have concomitant atrioventricular and intraventricular conduction abnormalities that may prolong the PR interval to a degree greater than would native AV conduction with dual-chamber devices. Furthermore, beta-blocker use in these patients may produce chronotropic and dromotropic incompetence such that frequent ventricular pacing becomes inevitable. In patients considered for upgrade to CRT on such basis, a careful evaluation of the patient's native AV conduction should be performed. Examination of the patient's underlying rhythm may reveal a prolonged AV interval only during rapid atrial rates in which case reprogramming to alternate modes (AAI or VVI at low backup rates) may present a viable option. Increasing atrial pacing rate alone may result in AV nodal Wenckebach at relatively low atrial rates. However, exercise invokes sympathetic enhancement of AV nodal conduction such that AV nodal Wenckebach may be reached at higher atrial rates than would be demonstrated with atrial pacing alone. Therefore, the evaluation should include the effect of activity on the overall heart rate and PR interval. The atrial rate at which ventricular pacing would become inevitable requires individualized assessment. For example, patients who are not active due to other comorbid conditions and thus do not elevate their sinus rates substantially may never reach their AV nodal Wenckebach rate and thus may not require continuous RV pacing. It should be determined, however, whether their reduced activity is due to lack of heart rate support or other limiting comorbid conditions. Studies involving extension of the programmed delay have been inconsistent in showing a significant reduction of ventricular pacing [33, 53]. Studies of dual-chamber pacing for Sick sinus syndrome (SSS) showed that a significant percentage of ventricular beats were paced despite programming a fixed long AV interval [53]. This observation was also demonstrated in a subsequent study involving long and short AV intervals in DDDR modes, which revealed an incidence of 17% of ventricular-paced beats using a programmed AV delay of 300 ms [33]. Furthermore, programming a long fixed AV delay interval limits the programmable upper heart rate and is associated with a high incidence of pacemaker syndrome and pacemaker-mediated tachycardia [53]. Newer algorithms for ventricular pacing management have shown superior efficacy in reducing ventricular pacing in dual-chamber devices in patients without AV block [49, 50].

The data demonstrating the detrimental effects of right ventricular apical pacing is abundant, but recent interest in alternative pacing sites in the RV may permit chronic pacing RV without the associated deterioration of LV function [54]. Right ventricular outflow tract (RVOT) or para-Hisian pacing allows stimulation of the septum and utilization of the native conduction system and, therefore, better mimics the natural activation of the ventricles. Whether dyssynchrony is reduced to the point of making future upgrade to CRT procedures unnecessary, or a viable alternative to CRT, has yet to be determined.

Detrimental Effects in Patients with Atrial Fibrillation Who Require Chronic Pacing

The issue of chronic ventricular pacing is encountered most frequently in patients with chronic atrial fibrillation who require ventricular pacing due to medication or junctional ablation. Although excluded from most of the

major CRT trials, patients with atrial fibrillation and antibradycardia pacing requirement constitute a substantial proportion of patients with heart failure. Some studies have shown no adverse effect of the "ablate and pace" strategy [55] and perhaps an improvement owing to better rate control [56]. The majority of studies with RV pacing in atrial fibrillation, however, have shown adverse LV remodeling effects and progression of CHF. The current guidelines do not support the use of CRT in patients with atrial fibrillation due to the limited number of such patients included in the clinical trials, although those included did show benefit. As such, a number of studies have investigated the role of CRT in this patient population [5, 13, 33, 42, 44, 47, 48, 57, 58].

Studies Comparing Right Ventricular Pacing and CRT: Does CRT Ameliorate the Abnormalities Caused by Right Ventricular Pacing?

Regardless of the modalities by which we define dyssynchrony, the most important question that remains is whether upgrading from conventional pacemakers results in hemodynamic, structural, and clinical improvement? Several recent studies have tested this question. Although acute hemodynamic studies have identified improvement of CRT over RV pacing in patients with atrial fibrillation and heart block [59], other studies suggested that heart rate irregularity at elevated rates was the primary determinant of acute hemodynamic deterioration [60]. Perhaps in this population, heart rate control and regularization of the R-R intervals may be the critical intervention rather than the choice of pacing modality. This is supported by the marked improvement in symptoms observed after AV junctional ablation and RV pacing.

In the PAVE trial comparing biventricular versus RV pacing in patients undergoing AV nodal ablation for atrial fibrillation with rapid ventricular rates, 184 patients were randomized to RV only or CRT [58]. Pacing mode was set to VVIR at a rate of 80 bpm for 4 weeks after the ablation. Patients were evaluated for functional improvement after 6 weeks, 3 months, and 6 months. Patients in both groups showed an improvement in functional status. However, it was at 6 months that a statistically significant difference in improvement in the 6-min walked distance with CRT was observed (31% above baseline in the CRT vs. 24% above baseline in the RV group, $p = 0.04$). This difference was largely due to a subsequent decline in the distance walked by patients in the RV-pacing group. In this study, however, there was no difference in the quality of life score. Although both groups had similar ejection fractions at baseline, the RV-pacing group showed a small decline in EF as early as 6 weeks after ablation that persisted to the 6-month mark (mean EF at 6 months 46% for CRT vs. 41% for RV pacing, $p = 0.03$). Interestingly, when stratified by the baseline EF (EF <45% vs. >45%), the CRT patients with EF <45% showed a markedly greater improvement in 6-min walked distance over the RV-paced group (73% greater), whereas in patients with EF >45%, there was no significant difference in improvement of 6-min walked distance between RV pacing and CRT. Similarly, patients with NYHA II and III demonstrated a 53% greater improvement in 6-min walked distance with CRT over RV pacing, in contrast with patients with NYHA I who showed no incremental benefit from either pacing modality. The study showed that although there was a functional improvement with either pacing mode (owing to the relief from tachycardia with atrial fibrillation), patients showed a greater improvement with CRT than RV pacing that was largely driven by the patients with more

symptomatic CHF and lower EF. Although a similar prior study showed no effect from the preablation QRS duration [61], the PAVE trial did not stratify patients according to baseline QRS duration, and therefore, it is unclear if in this study baseline QRS duration may have contributed to or mitigated the magnitude of the findings. Although the complication rate was observed to be higher in the CRT group, it was mainly due to the incremental risk of coronary sinus (CS) cannulation, LV lead implantation, and maintenance of CRT.

A retrospective study of 107 patients comparing the effects of CRT implanted using the standard indications versus dual-chamber pacing for patients with antibradycardia indications further exemplified the superiority of CRT over RV pacing [42]. Patients in the RV-paced group had narrow QRS duration at baseline but >180 ms when paced as inclusion criteria, whereas the CRT group had a mean QRS duration of 162 ms. Increased heart failure hospitalization and worsening of EF (43% to 38%) and NYHA class (2.1 to 2.9) at 6 months was seen in the RV-paced group. Despite that the patients in the CRT group had worse EF and NYHA at baseline, heart failure hospitalizations were less (12% with RV pacing vs. 6 % with CRT, $p < 0.05$), and there was an improvement in EF (23% to 31%) and NYHA class (3.1 to 2) at 6 months.

Kindermann et al. enrolled 30 patients with LV dysfunction (mean EF 26%) and antibradycardia pacing indication in a single-blind, crossover design with RV versus biventricular pacing evaluating clinical, echocardiographic, and biochemical markers [62]. They reported a significant improvement in echocardiographic dimensions, ejection fraction, NYHA class, symptom score, peak oxygen consumption, and natriuretic peptide levels. Multiple echocardiographic markers for both intra- and interventricular dyssynchrony were improved with CRT. The benefit was evident even when adjusting for potential confounders such as septal versus apical RV pacing positions, presence of atrial fibrillation, and presence of underlying LBBB. Although RV-pacing group derived some benefit, this was likely due to improvement in bradycardia, cardioversion in some patients, and optimization of medical therapy after study enrollment. The CRT effect was clearly demonstrable beyond these other interventions. Although the overall effect demonstrated superiority of CRT, there was a wide variation in the patient responses suggesting that the decision to upgrade to CRT in patients requiring chronic pacing requires individualized decision with better clinical, echocardiographic, and perhaps electrocardiographic predictors of response in this population. The ongoing COMBAT trial is also set to compare DDD with CRT using a crossover design in patients with heart failure and antibradycardia indications [63].

Studies of CRT Upgrade in Patients with Prior Right Ventricular Pacing (Table 6.1)

The feasibility, safety, and efficacy of the upgrade procedure from conventional pacemakers to CRT devices were assessed in 60 consecutive patients presenting for device upgrade [43]. Patients with NYHA class III and IV had the upgrade by an endovascular LV lead technique into the coronary sinus, which was successful in 54 (90%) patients. The complication rate was relatively low (8.3%) and included one lead dislodgment, one pocket

Table 6.1 Selected studies of upgrade from chronic RV pacing to CRT demonstrating feasibility and response to the upgrade procedure.

Study	Design/patient characteristics	No. patients	Follow-up	End points	Main findings
Witte et al. 2006 [64]	Comparison in CRT recipients: upgrade vs. de novo CRT implant	32 upgrade from RVP,39 de novo CRT	3 months	Echocardiographic, NYHA, symptoms score	De novo and upgraded patients showed equivalent benefit to CRT; upgrade and de novo group had similar baseline dyssynchrony
Hoijer et al. 2006 [65]	CRT vs. RVP in single-blind double-crossover design	10 patients (4 VVIR and 6 DDDR)	2-month crossover periods	6-min walked distance, NYHA, symptom score, proBNP	Symptom score and 6-min walked distance higher during CRT period; proBNP lower during CRT; 6 patients demanded early crossover to CRT; 9 of 10 patients preferred CRT pacing mode (1 undecided)
Leon et al. 2002 [44]	Chronic AF, prior AV ablation, NYHA III/IV, mean RVP period 26 months.	20 patients, all with atrial fibrillation	3–6 months	Echo, NYHA class, 6-min walked distance, no. hospitalizations	Improvement in all end points: NYHA 29% ($p < 0.001$), EF 44% ($p < 0.001$), LV dimensions, no. hospitalizations by 81% ($p < 0.001$), MLHF by 33% ($p < 0.01$)
Horwich et al. 2004 [45]	NYHA III/IV, low EF	15 upgrade to CRT (13 sinus, 2 atrial fibrillation)	Acute study	Echocardiographic indices, QRS duration	CRT reduced paced QRS duration, electromechanical delay, ejection time, and LV dimensions. EF and myocardial performance index improved.
Gronda et al. 2005 [46]	Patients from Insync/Insync ICD registries	243 upgraded to CRT and 989 de novo CRT implants	16 ±14 months	Clinical and echocardiographic indices	Clinical, mitral regurgitation and EF improvement in both groups. 71% in upgrade vs. 67% in de novo CRT groups were responders.

Eldadah et al. 2006 [66]	NYHA III, low EF	12 (9 sinus, 3 atrial fibrillation)	4–6 weeks	Echocardiographic, QRS duration, NYHA class	CRT reduced NYHA class, QRS duration, LV dimensions, peak systolic strain, and coefficient of variation from strain imaging. EF increased (30.7% to 35.8%)
Baker et al. 2002 [43]	Feasibility of upgrade from PPM to CRT	60	3 months	Success and complication rate, NYHA class, echo	Improved symptom score, NYHA (3.4 to 2.4, $p < 0.0001$), EF 23% to 29% ($p < 0.0003$). Low complication rate 8.3%.
Cazeau et al. 2003 [35]	NYHA III/IV with echocardiographic indices of dyssynchrony	35 de novo CRT and 31 upgrades	Acute echo study	Multiple echo indices, NYHA	Improved intraventricular electromechanical delay (EMD) in both groups mirroring clinical improvement; upgrade group showed more interventricular EMD improvement
Valls-Bertault et al. 2004 [47]	Chronic atrial fibrillation with prior junctional ablation	16 consecutive patients for CRT upgrade	6 months	NYHA class, echocardiographic data	Improved NYHA, LV dimensions, pulmonary pressure, mitral regurgitation, and fractional shortening. EF showed trend for improvement ($p = 0.11$). No change in 6-min walked distance.

MLHF, Minnesota Living with Heart Failure score

hematoma, and three pocket infections. The upgrade procedure was found to be feasible and safe and with favorable clinical effects despite that the study was performed at a time when the current commercial CRT devices, leads, and lead delivery tools were not available. CRT upgrade was achieved using Y-adapters to connect the RV and LV leads. In patients with persistent atrial fibrillation, a conventional pacemaker was used and the LV lead was plugged into the atrial port and AV delay was programmed to a minimum (10 ms). At 18 months after upgrade, there was a significant improvement in functional capacity (NYHA 3.4 ± 0.5 to 2.4 ± 0.7, p = 0.0003) and EF (23 ± 8% to 29 ± 11%, p = 0.0003). By 18 months, 10 (16.7%) patients had died, two of whom had failed the initial upgrade attempt. The paced QRS duration in this study showed a 17% decrease from RV pacing to biventricular pacing (206 ± 36 to 170 ± 34 ms).

An earlier study of upgrade of conventional pacemakers to CRT in heart failure patients chronically paced due to atrial fibrillation and prior AV junctional ablation was described in 20 patients [44]. The presence of atrial fibrillation in all patients in this study allowed evaluation of the site of pacing without the confounding influence of atrial transport function. All patients had advanced heart failure symptoms (NYHA class III or IV), reduced EF, and wide paced QRS duration (mean 213 ms). RV pacing had been present for 26 ± 12 months prior to upgrade. In this study, EF increased by 40%, from a mean of 21.5% to 30.9%, and the response was associated with improvement in functional status, LV dimensions, reduction in paced QRS duration, and reduction in heart failure hospitalizations. Other studies performed in similar patient populations showed similar improvement [47].

Witte et al. recently described the effects of CRT upgrade in patients with chronic RV pacing to patients with intrinsic LBBB receiving their first CRT device [64]. Patients with prior pacemakers were enrolled if >50% of the ventricular beats were paced. The authors reported that both groups of patients, who had similar functional limitations and echocardiographic indices, were equally as likely to respond to CRT. Although patients in the upgrade group had wider QRS complexes during RV pacing and higher proportion of patients with atrial fibrillation than in the intrinsic LBBB group, both groups had similar echocardiographic measures of dyssynchrony. The EF, along with other echocardiographic measures, improved in both groups (20% to 30% in the upgrade group and 20% to 27% in the native LBBB group, difference between groups p = 0.1). Clinical status also improved to the same extent in both groups (54% in the upgrade group and 57% in the native LBBB group showed >1 NYHA class improvement, difference p = 0.73). The study demonstrated that a widened QRS duration due to RV pacing was equally as likely to lead to dyssynchrony correctable with CRT as that produced by intrinsic LBBB. This was in contrast with other studies that showed that CRT upgrade, while leading to an improved contractility pattern acutely, induces different echocardiographic changes in patients upgraded to CRT from those receiving a de novo CRT system [35].

In a double-blind crossover design study of 10 patients with symptomatic CHF (NYHA class III and IV) who had no underlying LBBB but required chronic right ventricular pacing, upgrade to CRT was performed [65]. Although the percentage RV pacing was not reported, the patients had diagnosis of high-grade AV conduction disease or bradycardia (SND or atrial

fibrillation with a slow ventricular response) such that their rhythm was predominately ventricular paced. The median time from the initial pacemaker implantation to CRT upgrade was 5.7 years. After a 1-month run-in period after the upgrade, patients were randomized to receive biventricular or RV pacing in a 2-month crossover design. Upgrade to CRT was associated with a significant improvement in functional status and symptom score. The mean 6-min walked distance, which was 315 m at baseline, became 240 m (p = NS from baseline) with RV pacing and 400 m (p = 0.03 from baseline) with biventricular pacing. During the RV-pacing period, 6 of 10 patients requested an early crossover to biventricular pacing, whereas none in the CRT group requested crossover to RV pacing. Nine of the 10 patients blinded to the pacing modality preferred biventricular pacing and none preferred RV pacing (one patient was undecided). The study also showed a statistically significant decrease in proBNP after the biventricular pacing period compared with the patient's baseline and after the RV-pacing period. There were no measurable differences in echocardiographic parameters in this study.

In an echocardiographic study by Horwich et al., 15 patients with NYHA class III and IV systolic dysfunction and prolonged QRS who were chronically RV paced underwent upgrade to CRT [45]. Upgrade to CRT was associated with a reduction in QRS duration as well as improvement in echocardiographic measurements of dyssynchrony including intraventricular electromechanical delay, EF (decrease in diastolic and systolic dimensions), myocardial performance index, and ejection time. Only a trend to improved interventricular synchrony (p = NS) was observed. The average increase in EF was 7% and the degree of improvement correlated directly with the magnitude of QRS prolongation during RV pacing.

Eldadah et al. described upgrade to CRT in 12 patients with CHF who received a previous RV-pacing device (>90% ventricular paced) [66]. After 4–6 weeks of biventricular pacing, the mean EF improved from 30.8% to 35.8%, and 75% of the patients improved at least one NYHA class. The investigators also compared tissue Doppler and strain rate imaging to measure time to peak systolic strain and the coefficient of variation, both of which showed a significant improvement after the upgrade. The strain rate was unchanged with CRT, which was in contrast with prior studies of CRT for native LBBB [67], suggesting a possible difference in substrate between pacing-induced and native dyssynchrony. The study demonstrated amelioration of CHF symptoms at a magnitude similar to the de novo CRT trials, demonstrating that irrespective of the etiology of dyssynchrony (pacing-induced or intrinsic LBBB), CRT offers a superior therapeutic alternative to RV pacing.

There has been recent interest in use of CRT for the prevention of deterioration of heart failure in mildly symptomatic patients [68, 69]. In a review of patients from the Insync/Insync ICD registries, CRT upgrade recipients were compared with de novo CRT recipients [46]. Both groups demonstrated significant improvement in clinical and echocardiographic outcomes (71% and 67% were responders in the upgrade and de novo groups, respectively). Additionally, there was also a demonstrated benefit in patients with lower NYHA class symptoms, thus suggesting a possible prophylactic role for upgrading to CRT in chronically paced asymptomatic or mildly symptomatic patients for purposes of preventing progression of heart failure.

This concept, however, requires randomized prospective clinical study before being advocated further.

Technical Aspects of the Upgrade Procedure

Evaluation for Venous Stenosis

Endovascular upgrade to CRT obviously requires central venous access for the delivery of the LV lead. Venous stenosis presents perhaps the greatest obstacle to the upgrade procedure. It is frequently characterized by development of a collateral circulation draining the ipsilateral side via the internal jugular vein or chest wall vessels. Incidence of symptomatic venous obstruction after pacemaker implantation is estimated at 1–2% [70]. However, asymptomatic venous obstruction, which may still pose an obstacle for CRT upgrade, is estimated to occur at a much higher rate [71]. The overall incidence of venous obstruction after pacemaker lead implantation (symptomatic and asymptomatic) has been estimated at 23–45% [71, 72, 73, 74, 75]. These reported incidences, however, include obstructions that are not severe enough to prevent use of the affected vein for CRT upgrade but may make the procedure more challenging. The incidence of more severe yet asymptomatic obstruction (>75%) in ICD recipients is also not infrequent (7–14%) [76, 77].

In a study evaluating the incidence of venous obstruction before and after pacemaker lead implantation, 131 patients had digital subtraction angiography (DSA) where >60% narrowing was defined as obstruction [78]. In the patients without prior obstruction, follow-up DSA showed 32.9% of patients had developed venous obstruction at a mean of 44 months after implantation (a third of which were complete occlusions). There was no significant association with age, gender, left atrial size, ejection fraction, underlying heart disease, or number and size of leads implanted, which was corroborated in other studies [76, 79, 80]. An increased incidence of stenosis, however, is observed in patients with dual-coil ICD leads [77]. The presence of venous collateral flow does not separate complete from partial obstruction as a substantial number of patients with partial obstruction show development of a collateral circulation [71, 74, 78]. Most often, venous obstruction occurs at the level of the left innominate vein [74, 75, 78]. As such, it is important to visualize adequate flow of contrast not only through the subclavian vein but also proximally to opacify the innominate and superior vena cava before proceeding with the upgrade procedure.

Modalities for detection of asymptomatic venous obstruction primarily employ fluoroscopy. Other modalities include ultrasonography and computed tomography (CT) angiography. Magnetic resonance imaging (MRI) is not currently recommended as a screening modality because of the contraindication in patients with implanted pacemakers or ICDs. Ultrasonography, although it effectively identifies subclavian vein occlusion, is still of limited value as it fails to examine the more proximal venous segments at the level of the innominate vein and superior vena cava [75, 81].

Although studies have failed to document an association between number of chronically implanted leads and venous obstruction [74, 75, 78, 82], the implantation of a CRT device requires insertion of at least one additional lead, and frequently a high-voltage lead with dual coils that theoretically could

further crowd a partially obstructed vein. Furthermore, the LV lead delivery system uses a large-caliber catheter that requires significant maneuvering, which can be hindered by a partially obstructed vein. Because the majority of partial obstructions are associated with an already developed collateral circulation, even though CRT upgrade can lead to occlusion of a partially obstructed vein, it is unlikely that this will produce symptoms and edema.

Strategies When Venous Stenosis Is Encountered

Obstruction of the venous system as a result of a previous device and lead implantation presents a challenge that can be overcome in most cases. Careful venography of the ipsilateral veins prior to the procedure permits formulation of a strategy to allow successful upgrade of the system. At our institution, patients presenting for upgrade undergo venography under high-resolution fluoroscopy prior to sedation or draping to allow discussion with the patient about alternative upgrade options should there be a limiting obstruction. The venography film can also be used as a guide for venipuncture when traditional landmarks are obscured by the prior implant, although the older leads also serve as a guide for access to the subclavian vein. Frequently, obstruction occurs at the junction of the subclavian and innominate veins. A venogram obtained by injection of contrast solution from a peripheral intravenous site on the ipsilateral arm not only screens for central venous obstruction but also identifies patency of the cephalic vein, which can be used as a conduit for lead delivery (Figs. 6.1–6.6). When the veins are patent, upgrade can proceed without difficulty. Strictures and partial stenosis may limit manipulation of the catheters and lead delivery systems to cannulate the CS orifice. Use of a larger sheath that traverses a stenosis may enable catheter manipulation to the CS. If severe stenosis is present, extraction of one or more of the older leads may be necessary so as to bore a tract through which the upgrade leads can be delivered [83]. It is important in these situations to maintain access to the venous system as the extraction procedure may disrupt fibrotic tissue and completely obstruct the vein. If the region of luminal narrowing permits, a guide wire should be advanced past the stenosis and used to regain venous access after other leads are extracted. Alternatively, the sheath used to extract the older lead can be used as a conduit to advance a guide wire and maintain venous access before removal of the sheath from the vein. This may not always be feasible because in many situations both the extraction sheath and lead are removed from the body simultaneously.

When the ipsilateral vein is completely obstructed and flow is present only through small-caliber and tortuous vessels of a collateral circulation, the decision becomes whether to remove the old device and implant an entirely new system on the contralateral side, extract one or more of the older leads, or subcutaneously tunnel the required leads. Implanting an entirely new system is preferable when multiple leads for the upgrade are to be inserted. Tunneling the lead can be advantageous when the upgrade involves only one lead. A small incision is made overlying the contralateral delto-pectoral groove to implant the LV lead using standard techniques. The LV lead can then be either directly tunneled across the chest through the presternal tissue to the existing device pocket or connected to an extender, which is then tunneled across. The advantage of using a lead extender for the tunneled portion is

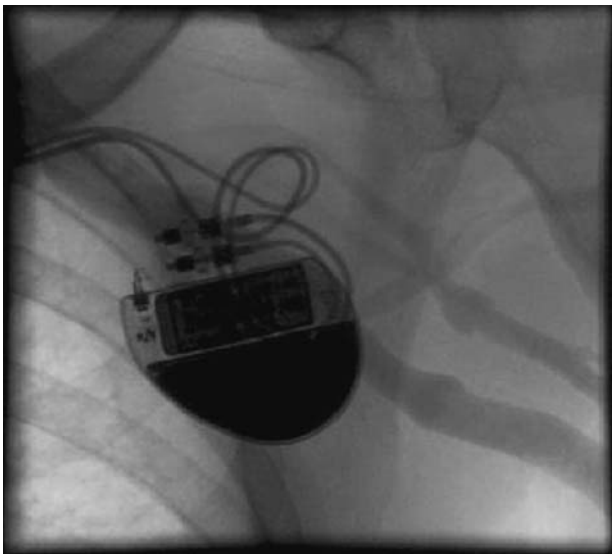

Fig. 6.1 Patent subclavian vein by contrast venography from an ipsilateral peripheral vein. Assessment of central venous patency guides formulation of an alternate upgrade strategy should significant obstruction be identified. This venogram also identifies a large patent cephalic vein, which can also be used for delivery of one or more leads.

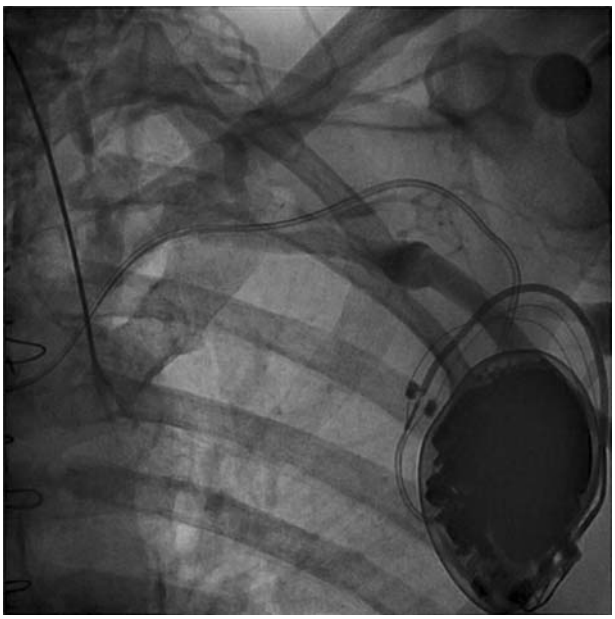

Fig. 6.2 Contrast venography identifies severe obstruction of the ipsilateral vein with well-developed collateral circulation. Identification of such obstruction prior to initiating the upgrade procedure prompts decision to use the contralateral vein or extraction of the old leads. In this situation, the patient elected to have implantation of a complete system via the right pectoral region.

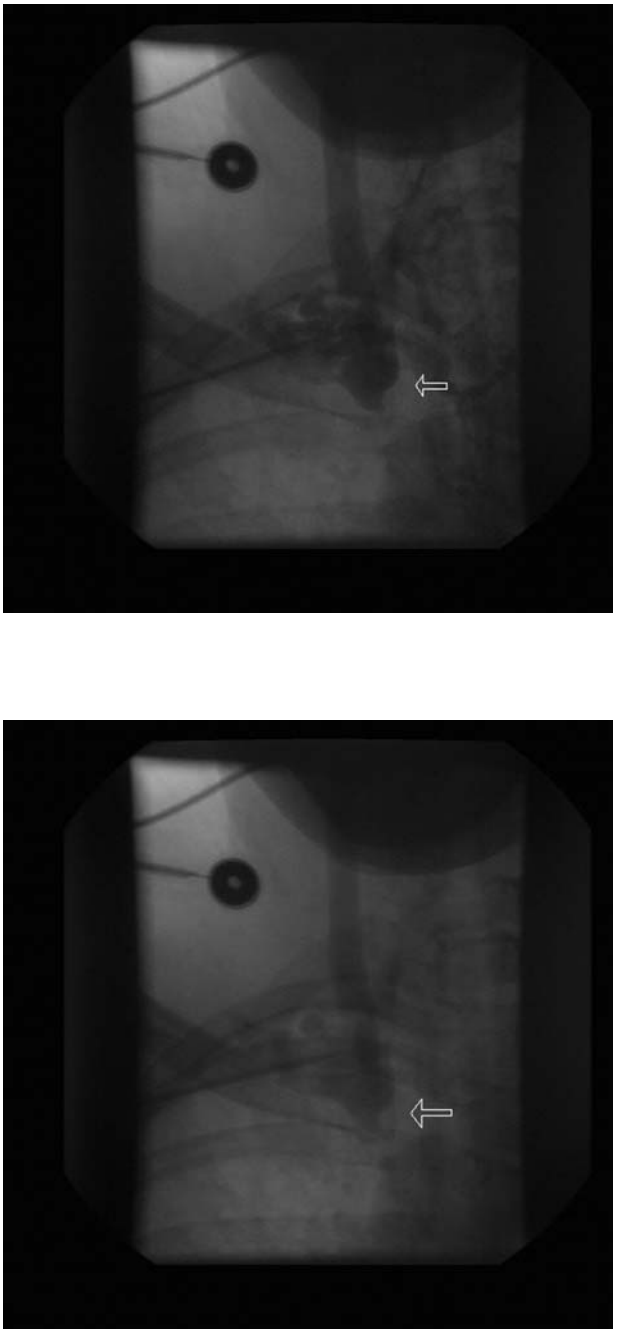

Fig. 6.3 Contrast venogram via sheath in the right subclavian vein showing sequential flow of contrast (**A** to **B** to **C**). Occlusion of the right brachiocephalic vein (*open arrow*) due to prior transvenous leads. Removal of the leads in this situation failed to restore flow through the brachiocephalic vein. Instead, blood flow was retrograde in the right jugular veins leading to collaterals (**B**) that ultimately drained into an enlarged azygous system (**C**) (*filled arrow*.)

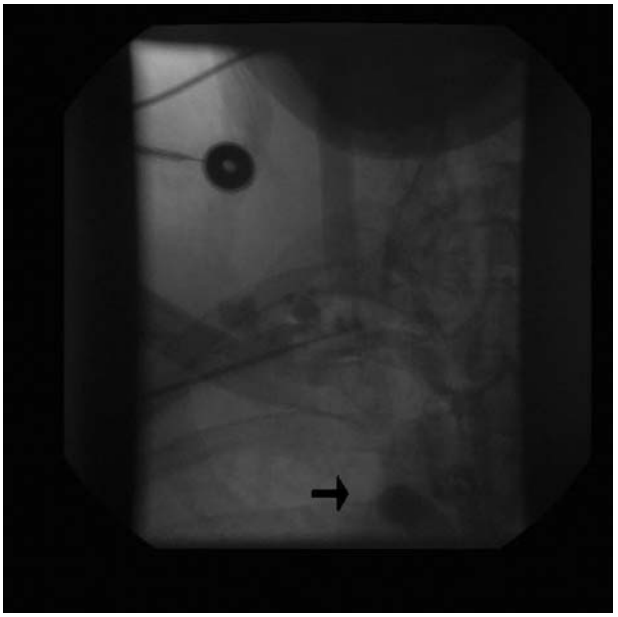

Fig. 6.3 *(Continued)*

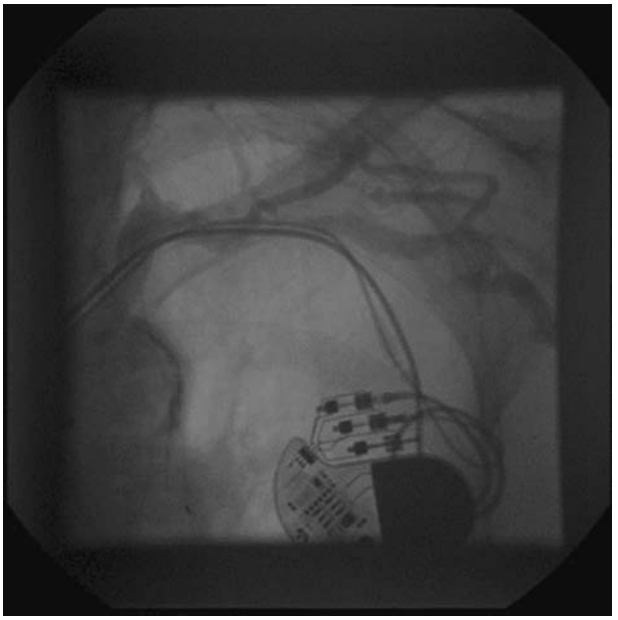

Fig. 6.4 A focal area of stenosis at the proximal left subclavian vein is identified by presence of extensive collaterals in this patient presenting for upgrade to a biventricular defibrillator. The area of stenosis was poorly visualized initially due to an inadequate volume of contrast, but the extent of collateralization is a useful marker to alert for presence of stenosis.

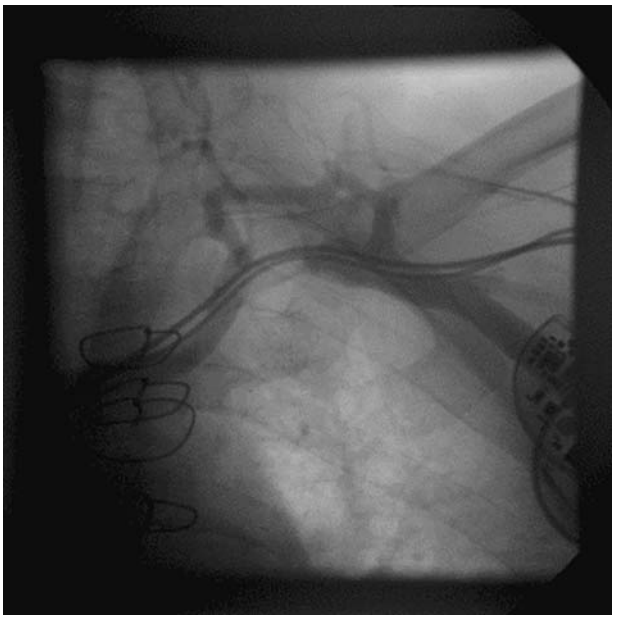

Fig. 6.5 An area of stenosis in the proximal subclavian vein was identified. The reconstituted (from collateral flow) proximal portion, however, was accessible by medial venipuncture that traversed the occluded region. Use of a larger diameter sheath allowed manipulation of the guiding catheter to the CS without significant friction. More medial venipunctures must be performed with caution. In this particular case, atherosclerotic calcification identified the location of the arterial structures—note the proximity of a calcified brachiocephalic artery coursing medial to the reconstituted vein (*arrow*).

that it permits opening of only one surgical site (the site of insertion into the vein) in cases where future repositioning of the lead becomes necessary due to dislodgment.

Venoplasty has been suggested as an option for opening a chronically occluded vein. The technical limitation here is that venoplasty may not preserve patency of the vein for long enough to allow use of the affected vein, probably due to the presence of a collateral circulation and reduced flow in the vein. Furthermore, venoplasty with stenting of the vein, although theoretically feasible, risks damage to the leads and may make future extraction of the jailed leads, should an infection develop, almost impossible. For patients with abdominal devices presenting for upgrade, it is rather cumbersome to attempt tunneling of multiple leads to the distant existing device pocket. These patients should almost always undergo explantation of the old system and implantation of an entirely new system.

When the combination of venous obstruction and poor candidacy for extraction, tunneling, or reimplanting a new system on the contralateral side are present, surgical implantation of an epicardial lead is another alterative. This is also a reasonable option in situations where placement of a stable LV lead position via the coronary sinus while obtaining adequate capture thresholds without extra cardiac stimulation is not possible. Thorascopic and minimally invasive techniques are continually developing to enhance this option for upgrade to CRT.

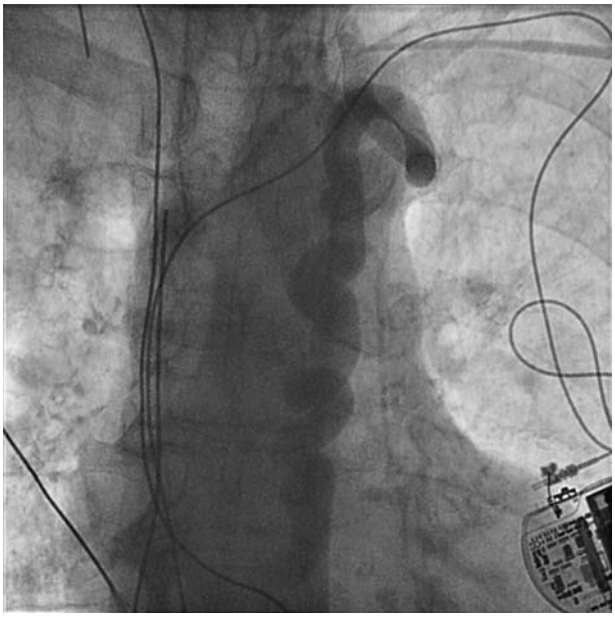

Fig. 6.6 The patient presented for upgrade to CRT. The patient had abandoned right-sided leads and the vein there was occluded. Venography from the left side also showed an occluded innominate vein and the region was drained by a very large thoracic vein. Because of the patient's wishes, extraction was not performed and upgrade to CRT was offered via a thorascopic epicardial approach.

Incorporating or Abandoning Components from the Older System

The upgrade procedure should be attempted ideally on the same side as the existing device. This is performed for multiple reasons. First, and most importantly, incorporation of the older leads with the upgraded system allows the minimal number of new leads to be implanted, thus minimizing the risk associated with implantation of new leads and procedure time. Patients with dual-chamber pacemakers can have addition of the left ventricular lead, and if the upgrade involves addition of an ICD, a new RV lead is inserted. Ideally, the older RV lead should be capped and not extracted unless necessary. The older lead should be tested for sensing and capture threshold and the parameters documented in the procedure report. This can become particularly useful in the event that at a future date the newly implanted RV lead malfunctions. If venous stenosis should develop after the upgrade prohibiting repositioning or implanting a new RV pacing/sensing lead, the older lead can therefore serve as a backup to be connected to the device. The atrial lead in dual-chamber systems should be incorporated into the new system as well if its pacing and sensing parameters are acceptable.

When a second RV lead is to be inserted, it is advisable to implant the new lead at a site distant from the old RV site. For example, one lead could remain at the apex and the other at the upper septal surface. This allows a choice in pacing location should a particular site develop unacceptable pacing or sensing parameters at a future time. The spatial separation of the leads also protects against possible mechanical interaction between the leads that may otherwise result in inappropriate sensing of noise signals.

Unipolar leads may be incorporated into the CRT system only if the upgrade is to a CRT pacemaker. Upgrade to a CRT-ICD requires abandoning or replacing RV or RA unipolar leads as these interfere with proper tachyarrhythmia detection. With upgrade to a CRT pacemaker, one can also take advantage of additional polarity configurations that would not otherwise be feasible with an ICD system. For, example, true unipolar configurations in addition to shared ring configurations for the LV lead can be tested if they enable better capture thresholds.

The device to be upgraded should be removed in all cases. In situations where entirely new CRT systems are implanted on the contralateral side, removal of the older device is still advised to prevent interaction with the new CRT system. Although theoretically it can be programmed to a very low backup rate, the device can cause unpredictable and undesirable effects at its end-of-life activity, especially if it switches to asynchronous unipolar pacing modes and becomes unprogrammable.

Conclusion

Although the role of CRT has been clearly defined for patients with symptomatic heart failure with left conduction disease, the current guidelines do not clearly define the utility of CRT in patients requiring antibradycardia ventricular rate support and are, therefore, lagging behind current clinical practice. The decision to upgrade to CRT from conventional pacing devices requires individualized evaluation of clinical, echocardiographic, and electrocardiographic parameters as well as the patient's requirement for frequent right ventricular pacing. The successful addition of cardiac resynchronization for these patients involves additional considerations that require specific technical skills and knowledge of device and lead management that are unique to the upgrade procedure. Issues related to venous access and stenosis present the greatest challenge.

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Section II

Cardiac Resynchronization for Heart Failure

7

Update of Cardiac Resynchronization Trials

S. Serge Barold and Bengt Herweg

Although cardiac resynchronization therapy (CRT) in heart failure (HF) started more than 12 years ago, major advances came mostly from large multicenter trials dating from 2001 (Fig. 7.1). The primary end points of many CRT trials focused on functionally based symptomatic improvement, quality of life, exercise tolerance (6-min walking test), and peak VO_2 with mortality as one of the secondary end points [1, 2, 3]. In the more recent Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) and CArdiac REsynchronization in Heart Failure (CARE-HF) trials, all-cause mortality was part of a combined primary end point [4,5]. This chapter focuses mostly on the CARE-HF trial [5], which is the most recent and the most informative CRT study regarding mortality.

The CARE-HF Trial

Unlike previous CRT trials of HF patients, CARE-HF assessed the mortality impact of CRT alone, with no defibrillator. The CARE-HF study enrolled a total of 813 patients at 82 centers in 12 European countries [5,6]. At baseline, all patients were receiving standard HF drug therapy and had New York Heart Association (NYHA) class III/IV HF, left ventricular (LV) dysfunction and dilatation (ejection fraction $\leq$35%), and QRS duration $\geq$150 ms alone or 120–150 ms with confirmed LV dyssynchrony. The CARE-HF trial was the first randomized CRT trial that incorporated echocardiographic evidence of LV dyssynchrony as the inclusion criteria. Eighty-eight percent of patients had a QRS $\geq$150 ms. However, only about 11% of the study consisted of patients with QRS $<$150 ms so that no conclusions can be drawn from this trial about the selection of patients on the basis of mechanical LV dyssynchrony. More than 90% of the patients enrolled in the study were in class III HF and about one-third had ischemic heart disease far less than the percentage of patients undergoing CRT in the United States.

Patients were randomized to one of two groups: a CRT therapy group that received InSync or InSync III Medtronic CRT devices (n = 409) along with standard drug therapy, or a control group that received optimal medical therapy alone (n = 404). The patients were followed for an average of 29.4

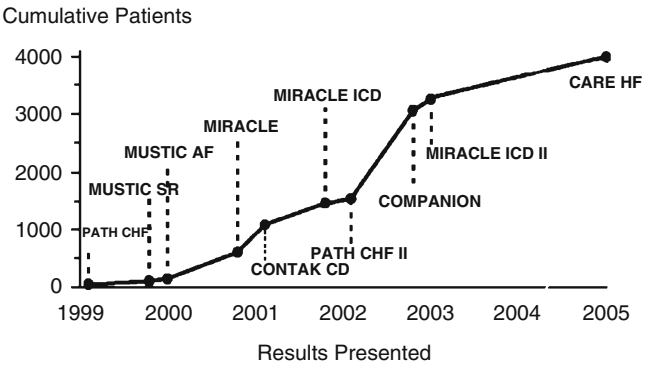


Fig. 7.1 Cumulative enrollment in randomized controlled trials of cardiac resynchronization therapy. (Reproduced with permission from Abraham WT. Cardiac resynchronization therapy. Prog Cardiovasc Dis 2006;48(4): 232–8).

months (by far the longest follow-up to date in trials involving CRT patients) and evaluated for mortality, morbidity, quality of life, and clinical changes in cardiac function. The primary end point was all-cause mortality or unplanned hospitalization for a cardiovascular event, and the principal secondary end point was all-cause mortality alone. The primary end point was reached by 159 patients in the CRT group compared with 224 patients in the medical-therapy group [39% vs. 55%; hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.51–0.77; $p < 0.001$].

Previous trials were relatively short-term (3–6 months) except the COMPANION trial (12 months) and the MUSTIC trial where the surviving patients remained stable with sustained improvement 1 and 2 years after the initial crossover phases [4, 7] (Fig. 7.2)

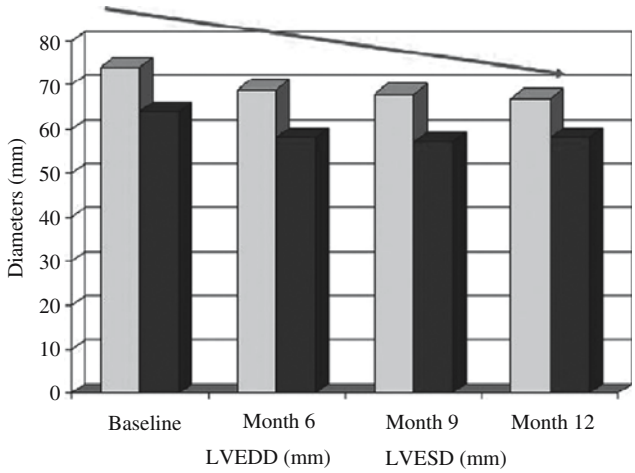


Fig. 7.2 Graphical representation of the progressive decrease in LV dimensions from baseline to the 12th month of follow-up after CRT device implantation in the MUSTIC trial. No control group is displayed as MUSTIC was a crossover study. LVEDD = left ventricular end-diastolic diameter, LVESD = left ventricular end-systolic diameter. (Reproduced with permission from Donal E, Leclercq C, Linde C, Daubert JC. Effects of cardiac resynchronization therapy on disease progression in chronic heart failure. Eur Heart J 2006:1018–25).

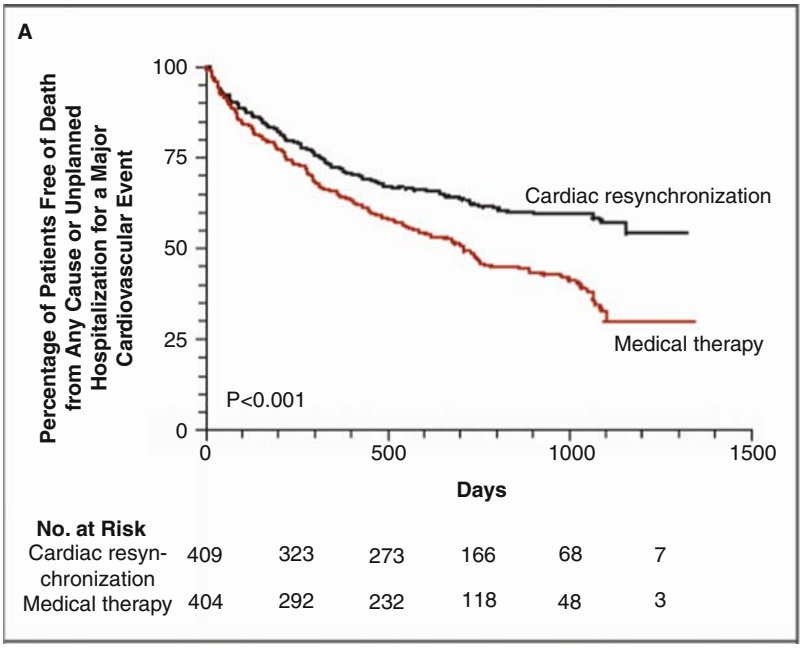
Table 7.1 CARE-HF: Primary and main secondary end points.

	Control (n = 404)	CRT (n = 409)	HR	95% CI	P
Primary end point:					
All-cause mortality or unplanned hospitalization for a CV event (%)	224 (55%)	159 (39%)	0.63	0.51–0.77	< 0.001
Secondary end points:					
All-cause mortality	120 (30%)	82 (20%)	0.64	0.48–0.85	< 0.002
All-cause mortality or unplanned hospitalization for worsening HF (%)	191 (47%)	118 (29%)	0.54	0.43–0.68	< 0.001

CI, confidence interval; CRT, cardiac resynchronization therapy; CV, cardiovascular; HF, heart failure; HR, hazard ratio.

At the end of the CARE-HF study, patients in the CRT group demonstrated the unequivocal benefit of CRT and confirmed its safety (Table 7.1). The results of the study remained consistent across various subgroups, including patients with and without ischemic heart disease. (1) Primary end point: A 37% relative risk reduction in the combined all-cause mortality or unplanned cardiovascular hospitalization in the CRT group (HR, 0.63; $p < 0.001$) (Fig. 7.3A). (2) Secondary end point: 36% relative risk reduction in all-cause mortality (HR, 0.64; $p = 0.002$) (Fig. 7.3B). The mortality was 20% in the CRT group ($n = 82$) versus 30% in the control group ($n = 120$). CARE-HF did not compare CRT-P (pacemaker only) with CRT-D (with defibrillator) directly. Nonetheless, it provided strong evidence in support of the potential for CRT-P alone to reduce mortality of HF patients significantly. CARE-HF was the first study to demonstrate a survival benefit attributable to CRT alone. The results were similar to the reduction of all-cause mortality found in COMPANION in the CRT-D arm. (3) Other secondary end points: The CARE-HF trial also found in that CRT significantly reduced end points of all-cause mortality combined with HF hospitalization by 46% and HF hospitalization alone by 52%. The effect on mortality was mainly attributable to a marked reduction in HF-related deaths. It is, however, noteworthy that the absolute number of sudden cardiac deaths was lower in the CRT group ($n = 29$) than in the control group ($n = 38$). (4) Reverse remodeling: Echocardiographic evidence of remodeling was seen at 18 months with improved left ventricular ejection fraction (LVEF), mitral regurgitation, and LV end-systolic volumes (Figs. 7.4 to 7.7). Furthermore, changes in LVEF were more pronounced in CRT patients with nonischemic versus ischemic disease (Fig. 7.8). Similar findings were also noted in the CRT group with respect to changes in LV end-systolic volume. These results confirm the reverse remodeling findings in the MIRACLE trial [8, 9]. The study also showed that CRT improves myocardial performance progressively over time. (5) Biochemical profile: CARE-HF was the first study to show that biochemical neurohormonal measures (e.g., N-terminal pro-brain natriuretic peptide) improve dramatically with CRT.

Cardiac resynchronization therapy in the CARE-HF trial thus showed significant improvement in survival, reduction in morbidity, and improvement



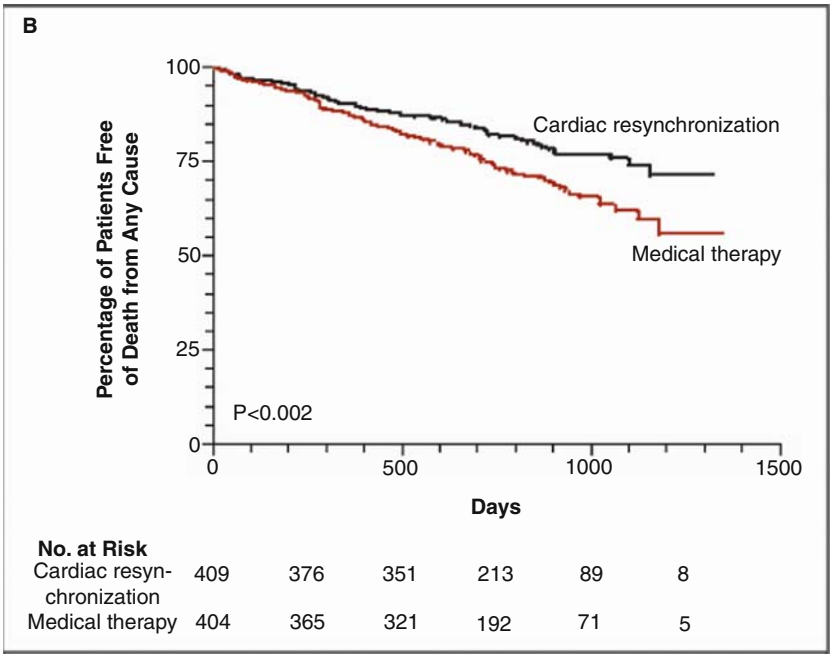


Fig. 7.3 (A) CARE-HF trial. Kaplan–Meier estimates of the time to the primary end point of death from any cause or an unplanned hospitalization for a major cardiovascular event. (B) CARE-HF trial. Kaplan–Meier estimates of the time to the principal secondary end point of death from any cause. (Reproduced with permission from Cleland JG, Daubert JC, Erdmann E, et al.; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539–49).

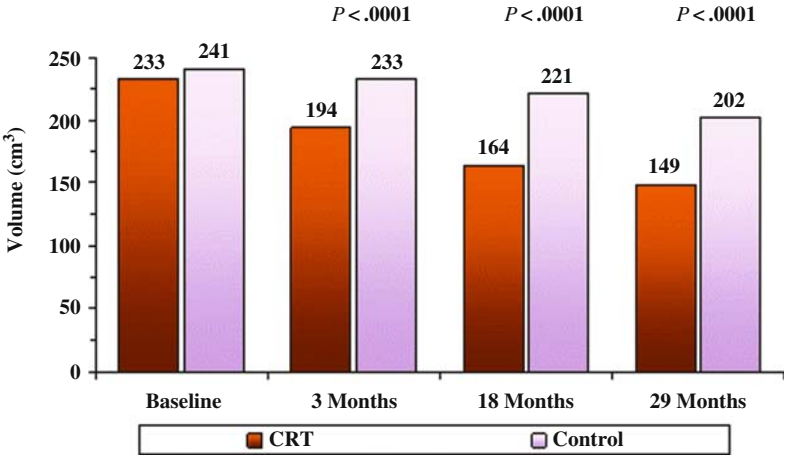


Fig. 7.4 CARE-HF trial. LV end-systolic volume index.

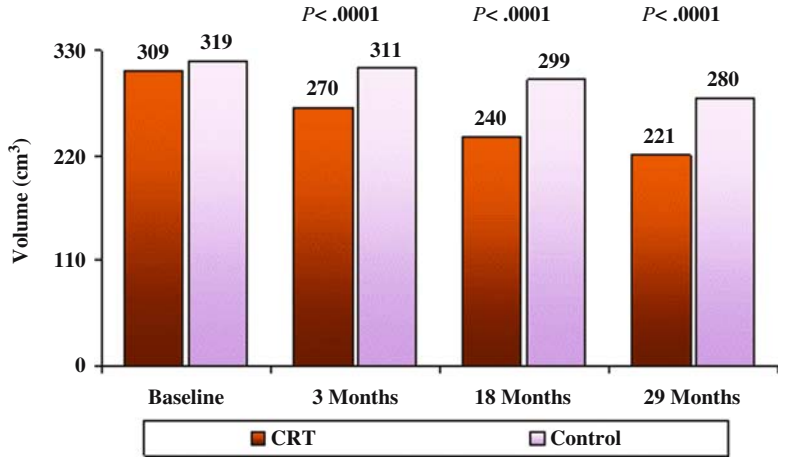


Fig. 7.5 CARE-HF trial. LV end-diastolic volume index.

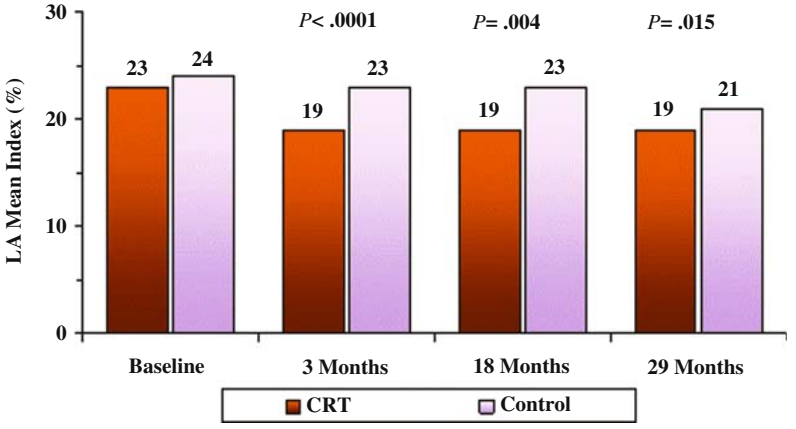


Fig. 7.6 CARE-HF trial. Mitral regurgitation index. LA = left atrial.

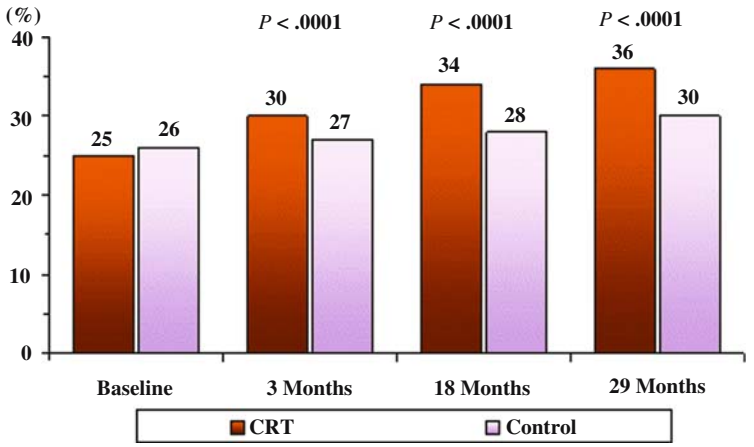


Fig. 7.7 CARE-HF trial. LV ejection fraction.

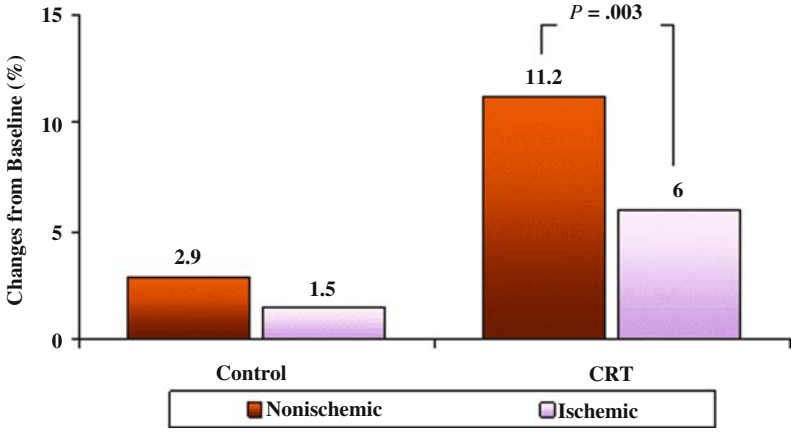


Fig. 7.8 CARE-HF trial. Change in LV ejection fraction from baseline: ischemic versus nonischemic etiology.

in cardiac function and heart failure symptoms in patients with moderate to severe heart failure. The trial demonstrated convincingly that CRT saves lives, slows the progression of heart failure, and improves symptoms and morbidity. A defibrillator might have reduced the risk of sudden death, as 7% of patients in the CRT group died suddenly in the CARE-HF trial.

Extension Phase of CARE-HF

The mean follow-up by the end of the CARE-HFP extension phase had increased from 29.4 months (range, 18.0–44.7) to 37.4 months [median, 37.6; interquartile range (IQR), 31.5–42.5; range, 26.1–52.6 months] [10]. There were 120 deaths in the main study and a further 34 in the extension phase leading to a total of 154 deaths (38.1, or 12.2% per annum) in 404 patients assigned to medical therapy. There were 82 deaths in the main study and

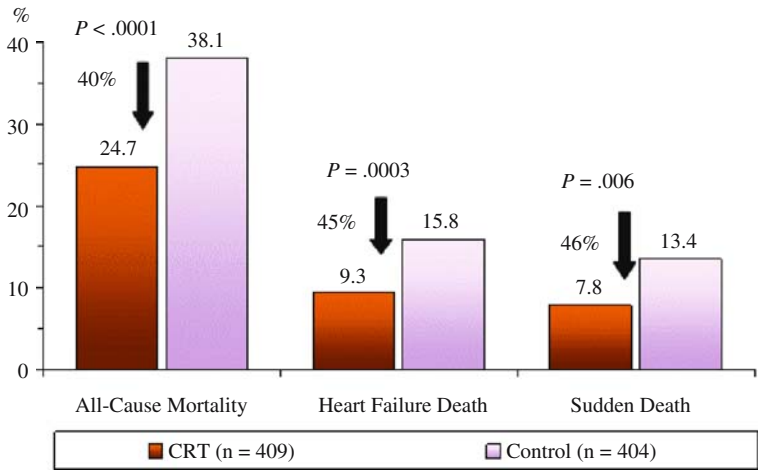


Fig. 7.9 Mortality results in the extension phase of the CARE-HF trial.

a further 19 in the extension phase leading to a total of 101 deaths (24.7, or 7.9% per annum) in 409 patients assigned to CRT (HR, 0.60; 95% CI, 0.47–0.77; $p < 0.0001$). Reductions in the risk of death due to HF (64 vs. 38 deaths, or 5.1% vs. 3.0% per annum; HR, 0.55; 95% CI, 0.37–0.82, $p = 0.003$) and sudden death were observed (54 vs. 32, or 4.3% vs. 2.5% per annum; HR, 0.54; 95% CI, 0.35–0.84, $p = 0.005$) (Fig. 7.9). Of 19 sudden deaths in the extension phase, 16 occurred in the control group.

The use of CRT compared to the control group was associated with a 40% reduction in the risk of all-cause mortality, a 45% reduction in the risk of heart failure mortality, and a 46% reduction in sudden death (Fig. 7.9). Thus, the CARE-HF extended trial provides overwhelming evidence that CRT reduces all-cause mortality and that CRT reduces sudden death and death due to worsening HF. CRT-P therapy may reduce the incidence of sudden cardiac death by slowing the progression of HF, improving the autonomic milieu, and causing anatomic remodeling.

Comparison of Mortality in the CARE-HF Versus COMPANION Trials

Although the predominant mode of death after CRT is progressive pump dysfunction, sudden death still accounts for a third of all deaths [5, 11, 12]. Furthermore, for those who benefit most from CRT, sudden death risk after CRT may actually increase proportionately compared with the risk of a pump death. The relative mortality reduction with CRT alone in the CARE-HF study was approximately the same as with CRT-D in the COMPANION trial [13] (Table 7.2). Figure 7.10 shows the percentage of deaths that were sudden in these two studies. In the COMPANION trial, 36% of the deaths in the CRT-P arm were sudden, very similar to the 35% in the CARE-HF study [13]. As one-third of the deaths in the CARE-HF study were sudden, a back-up defibrillator (i.e., CRT-D), might have prevented many of these sudden deaths. As seen in Figure 7.10, the CRT-D arm of the COMPANION trial reduced the sudden cardiac death incidence to 16%, a 55% relative risk

Table 7.2 Mortality and mode of death analysis:—CRT/CRT-D

Study	Mean follow-up (months)	Total mortality (%) / pump death (%)* / sudden death (%)*		
		OPT	CRT	CRT-D
COMPANION	16	25/44/23	21/40/37	17/50/16
CARE-HF	30	30/47/32	20/40/35	—
CARE-HF extension	37	38/42/36	25/38/32	—

OPT, optimal medical therapy; CRT, cardiac resynchronization therapy without a defibrillator; CRT-D, CRT with a defibrillator.
* Percent of deaths within each treatment group.

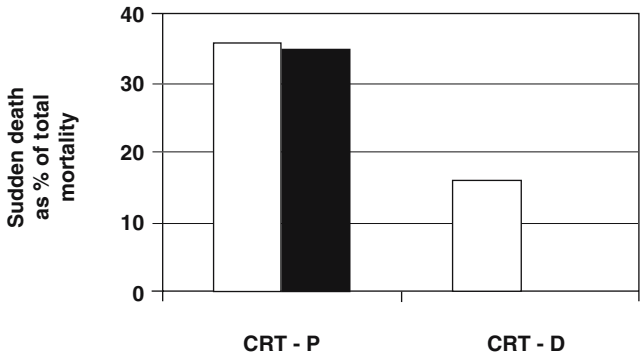


Fig. 7.10 Comparison of percentage of mortality attributable to sudden cardiac death in COMPANION trial and the CARE-HF study. ***Open bars***, the COMPANION trial; ***solid bars***, the CARE-HF study. *CRT-D*, cardiac resynchronization therapy pacemaker plus back-up defibrillation (implantable cardiac defibrillator); *CRT-P*, cardiac resynchronization therapy pacemaker. (Reproduced with permission from Saxon LA. More is better with cardiac resynchronization therapy—but is it enough? Eur Heart J 2006;27: 1891–2).

reduction for sudden cardiac death [13]. In terms of absolute mortality, 7% of patients in the CRT arm of the CARE-HF study died suddenly compared with only 2.9% in the CRT-D arm of the COMPANION trial.

Impact of CRT on Mortality Based on a Meta-analysis of Trials

A recent meta-analysis of CRT trials analyzed randomized trials performed in patients with advanced symptoms of HF due to LV systolic dysfunction where data on the effects of CRT alone versus optimal pharmacological therapy (control) were available [14]. Studies were excluded if they evaluated the effects of CRT-D and did not separately report data on CRT alone. Because the focus was on the chronic effects of CRT, studies with a follow-up of less than 3 months were excluded.

The study included a total of 2,371 patients: 1,028 controls and 1,343 CRT-treated patients. Five studies were identified and analyzed. When pooling data from all five studies together, using a fixed-effect model, CRT alone significantly showed a reduction of all-cause mortality by 29% [16.9% vs. 20.7%; odds ratio (OR), 0.71; 95% CI, 0.57–0.88] with respect to controls on optimal medical therapy. When considering mortality due to progressive HF, pooling the data of all trials, a significant 38% relative reduction in this end point was observed among patients treated with CRT alone (6.7% vs. 9.7%; OR, 0.62; 95% CI, 0.45–0.84). A neutral effect of CRT on sudden cardiac death (SCD) was observed (CRT group 6.4% vs. controls 5.9%; OR, 1.04; 95% CI, 0.73–1.46). After the extended phase, the CARE-HF study showed a significant reduction in SCD in patients treated with CRT. However, in the meta-analysis even after performing a sensitivity analysis including these results, no effect of CRT on SCD was observed (OR, 0.86; 95% CI, 0.63–1.19). Of the total amount of deaths in the control group (213 deaths), 47% were due to progressive HF and 28% were considered to be sudden, whereas in the CRT-treated patients (227 deaths), these represented 39% and 38%, respectively.

CRT-P or CRT-D?

The potential antiarrhythmic effect of CRT through inducing reverse remodeling needs further investigation. Results from the COMPANION trial [4] suggest that CRT-D may be more effective than CRT alone in reducing mortality. It is still not clear whether all patients meeting the criteria for CRT should also receive an implantable cardioverter-defibrillator (ICD) [11,15,16].

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8

Cardiac Resynchronization for Heart Failure: Do We Need More Trials?

Sunil T. Mathew, Christina M. Murray, and Dwight W. Reynolds

Cardiac Resynchronization Therapy: Past and Present Evidence

Background

Since Hochleitner and colleagues first proposed pacing therapy as treatment for drug-refractory heart failure [1], numerous studies and clinical trials have followed leading to the clinical indications for cardiac resynchronization therapy (CRT) as outlined in the consensus statement by the American College of Cardiology/American Heart Association Practice Guidelines on Implantable Devices in 2002 (class IIa) [2] and on Heart Failure in 2005 (class I) [3] (Table 8.1). Even though current scientific evidence appears compelling and advocates CRT, the complexity involved in appropriate patient selection using primarily electrical conduction defects as the surrogate for dyssynchrony and the challenging technical aspects of identifying optimal programming and pacing site selection among this substantially ill population is not straightforward. Thus, despite data from several prospective randomized controlled trials currently endorsing its safety and clinical efficacy, initiation of CRT into routine clinical practice requires some caution. Ongoing and future trial data may elucidate these complexities and allow for improved patient selection and therapy benefit as well as, possibly, expansion of indications. This chapter evaluates both the utility of our current data as well as additional information found in ongoing and future clinical trials that may further clarify our management options in this patient population despite the current level of evidence and practice recommendations.

Established Evidence from Clinical Studies

The major randomized clinical trials include the following: CARE-HF (the CArdiac REsynchronization-Heart Failure) [4], PATH-CHF (Pacing Therapy in Congestive Heart Failure) [5], MIRACLE (Multicenter InSync Randomized Clinical Evaluation) [6], MIRACLE-ICD [7], MUSTIC (Multisite Stimulation in Cardiomyopathies) [8], CONTAK-CD (CONTAK–cardiac resynchronization therapy defibrillator) [9], and COMPANION (Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure) [10], and these

Table 8.1 Current (class I) indications for cardiac resynchronization therapy.

Refractory heart failure after optimal medical therapy
Sinus rhythm
NYHA class III or IV ambulatory heart failure
QRS duration >120 ms
Left ventricular ejection fraction ≤35%
Ischemic, dilated, or idiopathic cardiomyopathies

have provided support for the efficacy of cardiac resynchronization therapy using biventricular pacing. COMPANION and CARE-HF were designed to assess hospitalization and all-cause mortality. MIRACLE and CONTAK-CD focused on the assessment of functional status and quality of life (QoL). Additionally, CARE-HF was one of the few trials that confirmed the presence of cardiac dyssynchrony prior to implant using parameters of aortic pre-ejection delay >140 ms, interventricular mechanical delay >40 ms, or delayed activation of the posterolateral left ventricular wall. CARE-HF required echocardiographic evidence of dyssynchrony in patients with QRS durations between 120 and 149 ms but not if ≥150 ms. The patients accumulated over time with these trials are plotted in Figure 8.1. Prior to these large trials, several authors reported on the potential benefit from the use of CRT. For example, Foster [11] and Cazeau [12] reported significant improvement in systemic vascular resistance and cardiac index with biventricular pacing after coronary artery bypass grafting. Leclercq showed a significant improvement in cardiac index by 35% and a decrease in pulmonary capillary wedge pressure by nearly 20% toward the baseline in New York Heart Association (NYHA) class III/IV patients with a wide QRS complex [13]. Hamdan demonstrated not

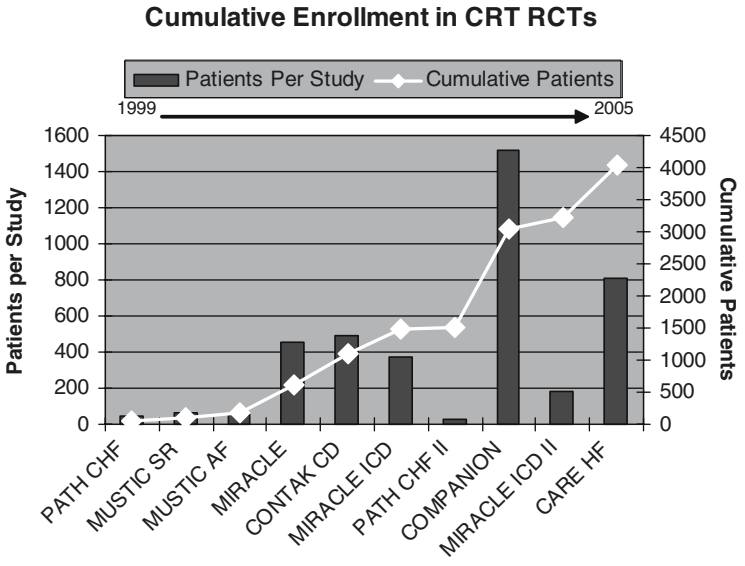

Fig. 8.1 A graphic representation of enrollment, both by study and cumulatively, of patients enrolled in published CRT randomized trials over the past several years.

only improvement in hemodynamic parameters but also a decrease in sympathetic nervous system activity [14]. Kass demonstrated that left ventricular pacing improved dP/dt in heart failure patients with left bundle branch block (LBBB) [15]. Other studies such as those by Innes [16] and Linde [17] failed to reveal significant improvement. Consequently, Brecker and Gibson [18] attempted to reconcile these inconsistencies by utilizing the following parameters to better predict potential benefit to CRT: functional mitral insufficiency duration of at least 450 ms, ventricular filling time less than 200 ms, and presence of a prolonged QRS complex.

Observational Studies

The principal observational studies include the French Pilot [19], InSync–Europe [20] and InSync–ICD [21] studies. These primarily focused on the efficacy of CRT. Most of these initial, often smaller trials used a crossover design in which patients served as their own controls. All of these studies demonstrated improvement in NYHA class with CRT. The QoL was shown to improve in all but the French Pilot study in which this factor was not assessed. However, the French Pilot study was the only study of the group that demonstrated improvement in peak oxygen consumption (VO_2) after CRT. Likewise, both InSync studies demonstrated improvement in 6-min walking capacity with CRT.

Clinical Trials

Trial Designs

The majority of the randomized trials used a parallel design where CRT devices were implanted in both control and treatment groups and with the comparison made between patients with the implanted CRT device turned on and those with the CRT function turned off. The results of these trials as well as two recent meta-analyses suggest that CRT yields benefit, in addition to optimal drug therapy, among patients with severe systolic heart failure who remain symptomatic.

Benefits Obtained from CRT

Trials have demonstrated improvements in functional and hemodynamic capacity [3, 5, 6, 7, 19, 20, 21]; reversal of ventricular remodeling [3, 5, 6, 7]; reduction in heart failure hospitalizations [4, 10]; and reduction in all-cause mortality [4, 10]. The survival benefits resemble those reported for angiotensin-converting enzyme inhibitors, beta-blockers, and aldosterone antagonists in recent trials [22, 23, 24, 25]. Cardiac resynchronization therapy also conferred statistically and clinically significant improvements in quality of life, functional status, and a variety of physiologic measurements including improvement on the Minnesota Living with Heart Failure Questionnaire [6]. The benefits derived, as gauged by this questionnaire, appear greater than those derived from the nominal difference established in placebo-controlled heart failure trials [26, 27, 28] and also greater than those reported in heart failure trials testing various pharmacologic therapies [29, 30].

The MUSTIC trial was one of the initial randomized CRT clinical trials. This study recruited 67 NYHA class III patients exhibiting a QRS complex duration exceeding 150 ms [8]. The patients were randomized in a single-blind

crossover fashion during two time periods: a 3-month period of predominately inhibited pacing (ventricular inhibited pacing at a basic rate of 40) and a 3-month period of atrial biventricular pacing. The primary end point was distance walked in 6 min. Secondary end points included quality of life, peak oxygen consumption, hospitalizations related to heart failure, mortality rate, and the patient's treatment preference. MUSTIC reported significant improvement in exercise tolerance, quality of life, and interventricular conduction delay.

MIRACLE evaluated the effects of CRT in a double-blind fashion, using CRT and control groups (n = 453). CRT patients had significant improvements in the primary end points of distance walked in 6 min, functional class, time on the treadmill during exercise testing, and ejection fraction. Combined secondary end point of death and hospitalization was also significant, with a 40% relative risk reduction in CRT patients.

The COMPANION trial used open-label treatment (sponsor, end-points committee, and steering committee were blinded), randomizing 1,520 patients with NYHA class III and IV heart failure to optimal medical therapy alone or in combination with a pacemaker or a pacemaker and defibrillator. The trial demonstrated a significant reduction in the primary end point, death or hospitalization, in both groups receiving CRT. CRT with defibrillation also significantly reduced the secondary end point of death alone ($p = 0.004$), and CRT alone nearly reached significance ($p = 0.06$).

CARE-HF recruited more than 800 patients worldwide [4]. The study analyzed the effect on mortality of adding CRT to already optimal pharmacologic therapy. The primary composite end point was all-cause mortality or unplanned hospitalization for major cardiovascular events. Secondary end points were unplanned hospitalizations for heart failure, quality of life score, patient symptoms as well as mechanistic variables associated with CRT delivery, cardiac function, and neuroendocrine status. A 96% success in CRT implantation with <5% crossover before primary end point was reported in CARE-HF [4]. In this trial, all-cause mortality or unplanned hospitalization for major cardiovascular events, the primary end point, was reduced by 16% ($p < 0.001$) and cardiovascular mortality was reduced by 7% (absolute risk reduction, over mean 29.4mm follow up). CARE-HF is notable in that these reductions in mortality occurred in the absence of defibrillation support. CARE-HF demonstrated that CRT should be considered as part of routine management for patients with moderate to severe heart failure after demonstrating significant reduction in morbidity and survival benefit that is in addition to pharmacological therapy (Fig. 8.2). Furthermore these benefits appear greater than those of the results of drug therapies used in recent heart failure trials [29, 30].

Specific morbidity and mortality rates comparing CARE-HF, MIRACLE, COMPANION, and meta-analyses [31, 32] are illustrated in Table 8.2.

Long-term Efficacy

Published CRT efficacy studies have been limited to an average follow-up of only 3 to 12 months [32]. The long-term efficacy of CRT is not known. This is compounded by design limitations of some early CRT trials. Specifically, several trials were limited to patients who successfully completed a specified follow-up period. Prior to CARE-HF, only one trial randomly assigned patients after successful device implantation. A recent study by Davis

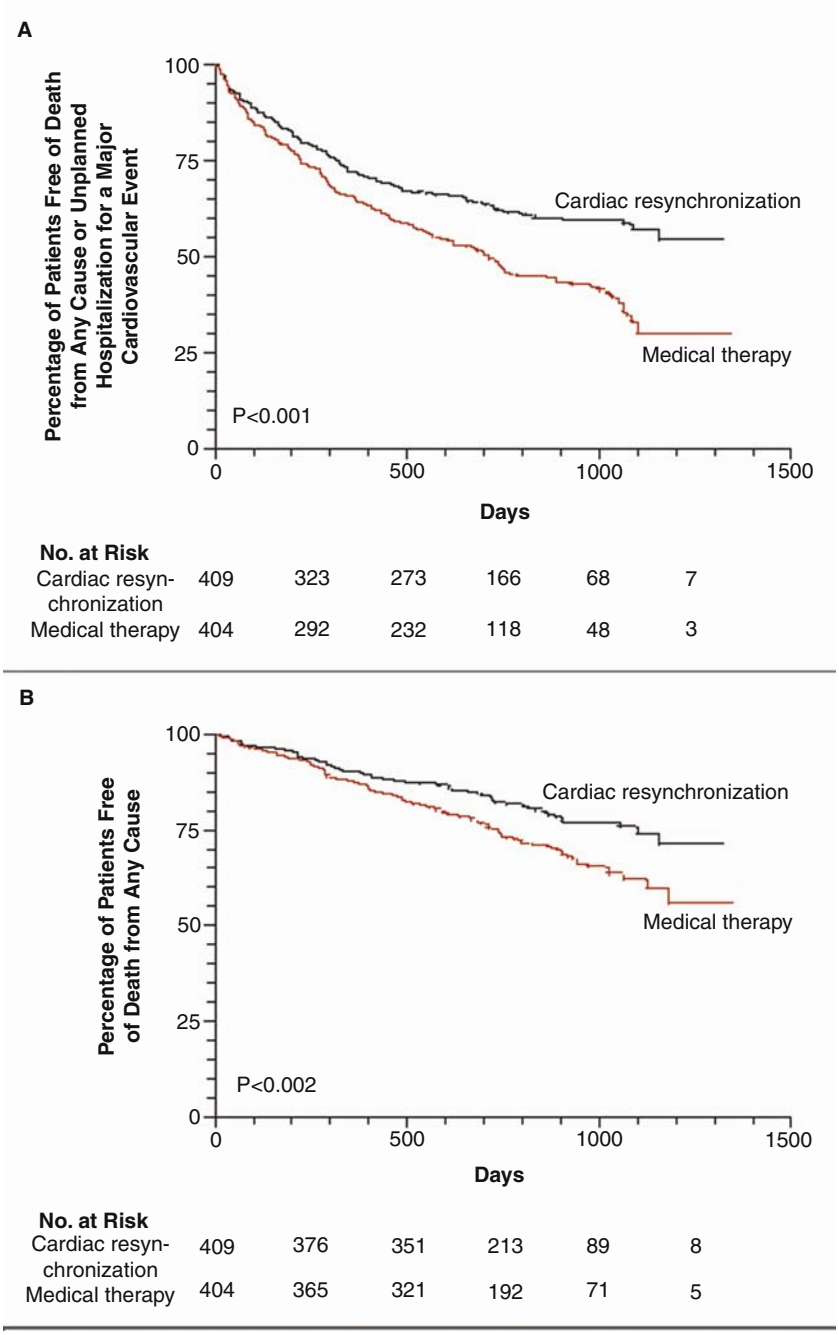

Fig. 8.2 Kaplan–Meier estimates of time to primary end point (**A**) and secondary end point (**B**) from CARE-HF. (From Cleland JG, Daubert JC, Erdmann E, et al. Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352[15]:1539–49, permission and copyright 2005 Massachusetts Medical Society, all rights reserved).

Table 8.2 Morbidity and mortality comparison.

Study(n randomized)	Follow-up	Treatment	Relative risk reduction with CRT or CRT + ICD				
			Mortality and hospitalization	Mortality and HF hospitalization	Mortality	HF mortality	HF hospitalization
COMPANION [10] (n = 1,520)	12 to 16 months (median)	CRT + ICD	20%*	40%*	36%*		
		CRT	20%*	34%*	24%		
MIRACLE [6] (n = 453)	6 months (protocol)	CRT		40%*	27%		50%*
CARE-HF [4]	29.4 months (mean >18 months per protocol)	CRT			36%*	40%	52%*
Bradley et al. [31] (meta-analysis) (n = 1,634)	3–6 months (protocol)	CRT			23%	51%*	29%*
McAllister et al. [32] (meta-analysis) (n = 3,216)	6 months (protocol)	Pooled: CRT and CRT + ICD			21%*	40%	32%

HF, heart failure.
*$p < 0.05$.

et al. [33], with cohort characteristics similar to CRT trials already reported, attempted to provide information about the long-term efficacy of CRT. This study followed patients for at least 24 months and had a mean follow-up of 36 months. These authors reported that among the cohort receiving CRT, no sudden death occurred and that survival and freedom from death or transplantation at 3 years were 63% and 58%, respectively.

Nonresponders Versus Responders

Despite the high rates (70% to 80%) of clinical improvement after CRT frequently cited, not all patients receive a sustained clinical benefit after the implantation of a CRT device [34]. Defining CRT success as a reduction of at least one NYHA functional class over 6 months, MIRACLE found that a net rate of positive CRT response was 30% after 6 months (68% of patients assigned to active therapy and 38% of control subjects responded to CRT). Other studies [35,36,37,38] defining CRT response based on objective improvement (i.e., left ventricular volumes or ejection fraction) reported that approximately 50% of patients with NYHA class III or IV symptoms, an ejection fraction of 0.35 or less, and a QRS duration of 130 ms or longer respond to CRT.

CRT nonresponse may be explained by a lack of baseline mechanical dyssynchrony, suboptimal placement of the left ventricular lead, or other less tangible factors [34, 36, 39, 40]. The major limitation is that lead placement options with transvenous implants are governed largely by the patient's venous anatomy, which shows considerable interindividual variability [41]. In addition, left phrenic nerve stimulation and high stimulation thresholds may occur. In up to 15% of cases, it may not be possible to achieve what is considered to be satisfactory left ventricular pacing position. These factors underscore the intricacies of the underlying complexities of heart failure, its coexisting illnesses, and the potential morbidity of the invasive procedure required for biventricular pacing.

Implantable Cardioverter Defibrillators Versus Cardiac Resynchronization Therapy

Most randomized trials have evaluated CRT pacemaker devices. However, the relative incremental benefit of resynchronization therapy with defibrillator backup in patients who are CRT candidates is the subject of ongoing studies such as Resynchronization/defibrillation for Advanced Heart Failure Trial (RAFT). Despite this, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) [42] has provided evidence that implantation of a defibrillator in addition to optimal medical therapy is an effective long-term (5-year) treatment compared with conventional optimal therapy alone or with the addition of amiodarone to prolong life in heart failure patients. COMPANION, unique in combining CRT with and without implantable cardioverter defibrillator (ICD) therapy, as well as comparing to optimal medical therapy, demonstrated marked reduction in combined measures of morbidity and mortality with both CRT alone and with CRT plus defibrillator backup with a similar 1-year event-free survival rate. However, when comparing the benefit of CRT alone, the relative risk reduction in all-cause mortality of 24% only trended toward significance ($p = 0.060$). CRT with defibrillator backup provided 36% relative risk reduction in all-cause mortality compared with optimal

drug therapy (p = 0.003). CARE-HF remains the single CRT pacing (without defibrillation) trial showing statistically significant reduction in mortality with CRT.

Number Needed to Treat

Meta-analyses by Bradley et al. [31] in 1,634 patients and McAllister et al. [32] in 3,216 patients demonstrated that CRT could potentially offer 23% and 20% relative reduction in all-cause mortality, respectively (largely driven by 51% and 40% reduction in deaths from progressive heart failure, respectively). The fairly wide confidence intervals reported in these meta-analyses suggest that the benefit from CRT may be offset by an increase in non–heart failure mortality. The number needed to treat for benefit (NNT) to prevent one death was estimated to be 24. Meta-analyses of time-to-death assessment suggest benefits of cardiac resynchronization therapy become apparent by about 3 months after implantation [32].

Complications

The average implant success rate for CRT devices is estimated to be $\geq$ 90%, and serious complications are uncommon. However, implantation of a biventricular pacemaker and, particularly, left ventricular lead implantation remain technically challenging and are not without risk. Systematic review estimates a 0.4% death rate during implantation [32]. This peri-implantation mortality is similar to the 0.7% reported in the Mode Selection in Sinus Node Dysfunction Trial in which conventional dual-chamber pacemakers were implanted in more than 2,000 patients [43]. Based on a systematic CRT review with a median 6-month follow-up [32], 9% of left ventricular leads became dislodged, and device malfunction occurred in 7% of CRT recipients [32]. Another review found rates of serious bleeding ranging from 1% to 6%, and pneumothorax in less than 1% of patients [44] and suggests that CRT patients might require more frequent monitoring. The electrophysiologic effects and the subsequent hemodynamic alterations of biventricular pacing in the setting of heart failure are complex; therefore careful programming may be important to accommodate each patient's physiology.

Cardiac Resynchronization Therapy: Areas for Future Investigation

Entry Criteria for Previous Randomized Clinical Trials

Knowledge of clinical trial inclusion and exclusion criteria remains critical in applying the evidence reported to clinical practice but also helps identify the limitations and uncertainties of therapy. Trials thus far reported show underrepresentation of NYHA class I, II and IV heart failure and atrial fibrillation as well as the absence of less severe left ventricular systolic dysfunction [i.e., left ventricular ejection fraction (LVEF) >35%)] and more narrow complex QRS (<120 ms). Consequently, CRT efficacy in these subpopulations is inconclusive. The vast majority of patients studied have been in sinus rhythm, with severe left ventricular systolic dysfunction (LVEF $\leq$35%), with symptomatic

(predominately class III) heart failure with evidence of dyssynchrony as evidenced by prolonged QRS duration of 120 ms or longer in three trials [10, 45, 46]; 130 ms or longer in two trials [6, 7]; longer than 140 ms in one trial [47]; longer than 150 ms in one trial [9]; longer than 180 ms in one trial [48]; and longer than 200 ms in one trial [49]. Although, recent data indicate that CRT may be efficacious in patients with mechanical dyssynchrony regardless of QRS duration [50], additional data are required before CRT can be recommended for these groups of patients excluded from previous trials.

Atrial Fibrillation and CRT

CRT has not been well studied in patients with atrial fibrillation (AF) despite the relatively large number of patients with concurrent heart failure (with other CRT indications) and AF. Most major clinical CRT trials, to date, have had inclusion or exclusion criteria that prohibited the enrollment of patients with AF. Small trials have attempted to assess the effect of CRT in AF. In MUSTIC-AF, a single-blind crossover study design was used to evaluate the efficacy of CRT versus conventional VVIR pacing in patients with a wide paced rhythm (the majority having received an AV nodal ablation). CRT was found to improve exercise tolerance and was preferred by patients [49]. In another trial, patients with a history of AV junction ablation for permanent AF who had received RV pacing for at least 6 months were upgraded to biventricular pacing. This resulted in improved NHYA functional class, decreased number of hospitalizations, increased mean left ventricular EF, and improved echocardiographically measured LV dimensions [51]. Finally, the PAVE study randomized AF patients, after AV nodal ablation, to receive CRT or a right ventricular pacing system [52]. CRT produced significant improvement in functional status and ejection fraction. While the benefit was greater in those patients with impaired systolic function ($\leq$45%), this was thought to be due to loss of function and lowered ejection fraction in the RV pacing group, suggesting not only that CRT can be successfully applied in patients with AF, but also that CRT may be superior regardless of QRS duration in patients in whom ventricular pacing is necessary.

Indirect assessment of CRT in atrial fibrillation can be taken from patients who were enrolled in the CARE-HF trial. Those who received CRT were no more likely to develop AF; but those who did develop AF still benefited from CRT with regard to all-cause mortality and other predefined end points [53]. These small studies are suggestive of benefit for patients in atrial fibrillation.

Future trials will evaluate AF and CRT. One such trial, MASCOT, will evaluate use of atrial tachyarrhythmia suppression algorithms in single-blind fashion, with the CRT-only group compared with the CRT with AF suppression group [54].

QRS Duration and Morphology in CRT

Right Bundle Branch Block

Most patients enrolled in major trials have had left bundle branch block. Little randomized trial data exist to evaluate the effect of CRT in patients with right bundle branch block (RBBB). Published data are conflicting in conclusions. For this subgroup of patients, the number included in trials has typically

been ≤10% of the total. An initial analysis of MIRACLE data suggested that patients with RBBB or IVCD did benefit from CRT [55]. In COMPANION, patients classified as "BBB other than left" appear to have less benefit from CRT than those with LBBB. A pooled analysis of data from MIRACLE and CONTAK CD did not support the use of CRT in RBBB, likening the therapy to placebo in those patients [56]. Patients with such QRS morphology are currently eligible for CRT according to current criteria.

QRS Duration

Most trials have used QRS duration criteria for enrollment. For example, the COMPANION trial required a QRS of ≥120 ms. Most have excluded patients with QRS duration <120 to <130 ms. When COMPANION data was stratified by QRS duration, there were apparent differences in response to CRT using combined end points and death, which seem to favor a more significant response in those patients with a longer QRS (Fig. 8.3). CARE-HF showed a similar trend (Fig. 8.4). The CARE-HF trial inclusion criteria required not only the same QRS criteria (>120 ms) but also echocardiographically documented dyssynchrony if the QRS fell below 150 ms. Standard measures of dyssynchrony were used (aortic pre-ejection delay >140 ms, interventricular mechanical delay >40 ms, and posterolateral delay). This may account for some of the strength of the CARE-HF data.

Limited studies have demonstrated benefit of CRT to patients with narrow QRS. In the presence of documented interventricular and intraventricular dyssynchrony, the benefit is similar to that obtained in patients selected by standard criteria in a small study with 52 patients [57]. In patients with heart failure, intraventricular dyssynchrony can be documented in >40% of patients with QRS <120 ms and in three-quarters of patients with QRS >120 ms [58]. This leaves a rather large population of patients with normal to mildly prolonged QRS who might potentially benefit from CRT but in whom data are wanting.

Echocardiography in CRT

Echocardiography holds promise in determining, prior to implant, which patients may benefit the most from CRT. Novel modalities including tissue Doppler imaging (TDI), tissue tracking, strain rate analysis, and time to peak systolic velocity have been used to quantitate dyssynchrony, along with the previously mentioned M-mode parameters.

Studies have shown the promise of the use of echocardiographic techniques to prescribe CRT, possibly even favoring it over QRS duration. Using TDI, delayed longitudinal contraction (contraction during diastole indicating mechanical left ventricular dyssynchrony), but not QRS, has been shown to be predictive of response to CRT and improvement in standard outcome measures, both clinically and echocardiographically [39]. A tissue Doppler index of multiple measures accurately predicts response to CRT-induced left ventricular reverse remodeling, whereas baseline QRS did not (Fig. 8.5) [59]. These techniques may provide the ability to accurately delineate who might benefit from CRT prospectively.

Future trials will attempt prospective use of these parameters. The PROSPECT trial, which is currently in progress, is one such trial. It is

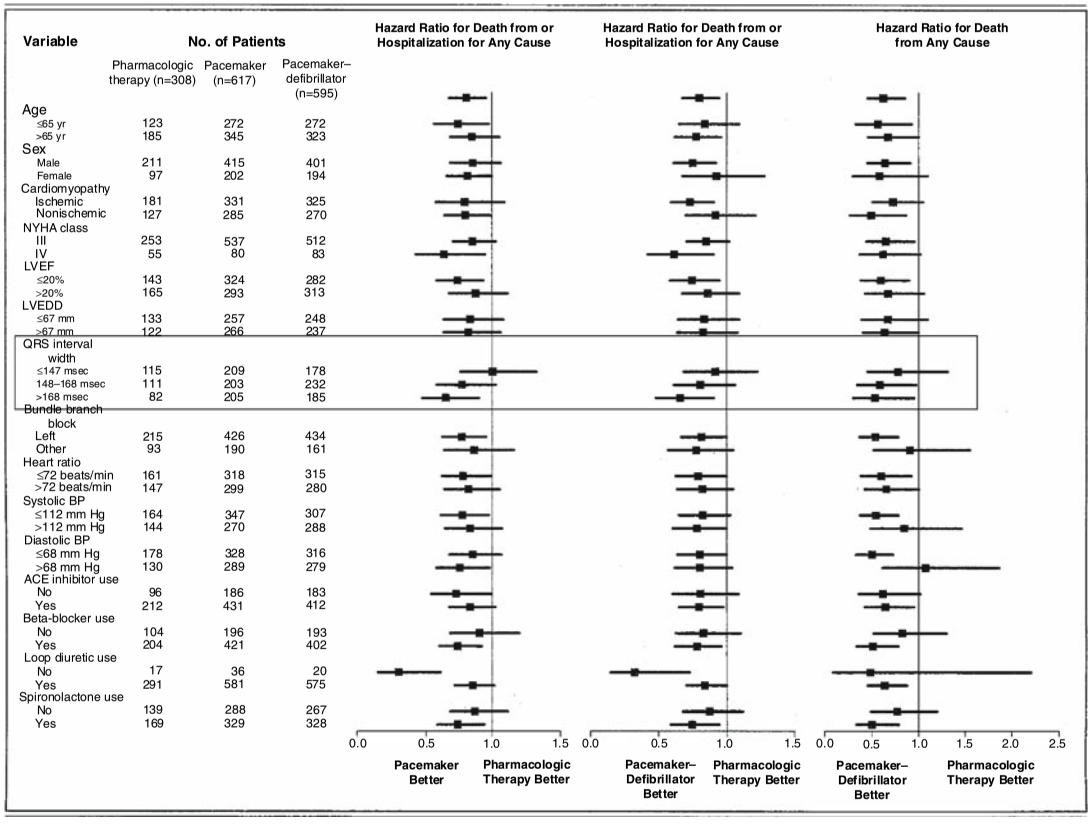

Fig. 8.3 Hazard ratios and 95% confidence intervals for the primary end point (death from or hospitalization for any cause) in COMPANION. The inserted box highlights the differences in response in patients with different QRS durations. (From Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–50, permission and copyright 2004 Massachusetts Medical Society, all rights reserved).

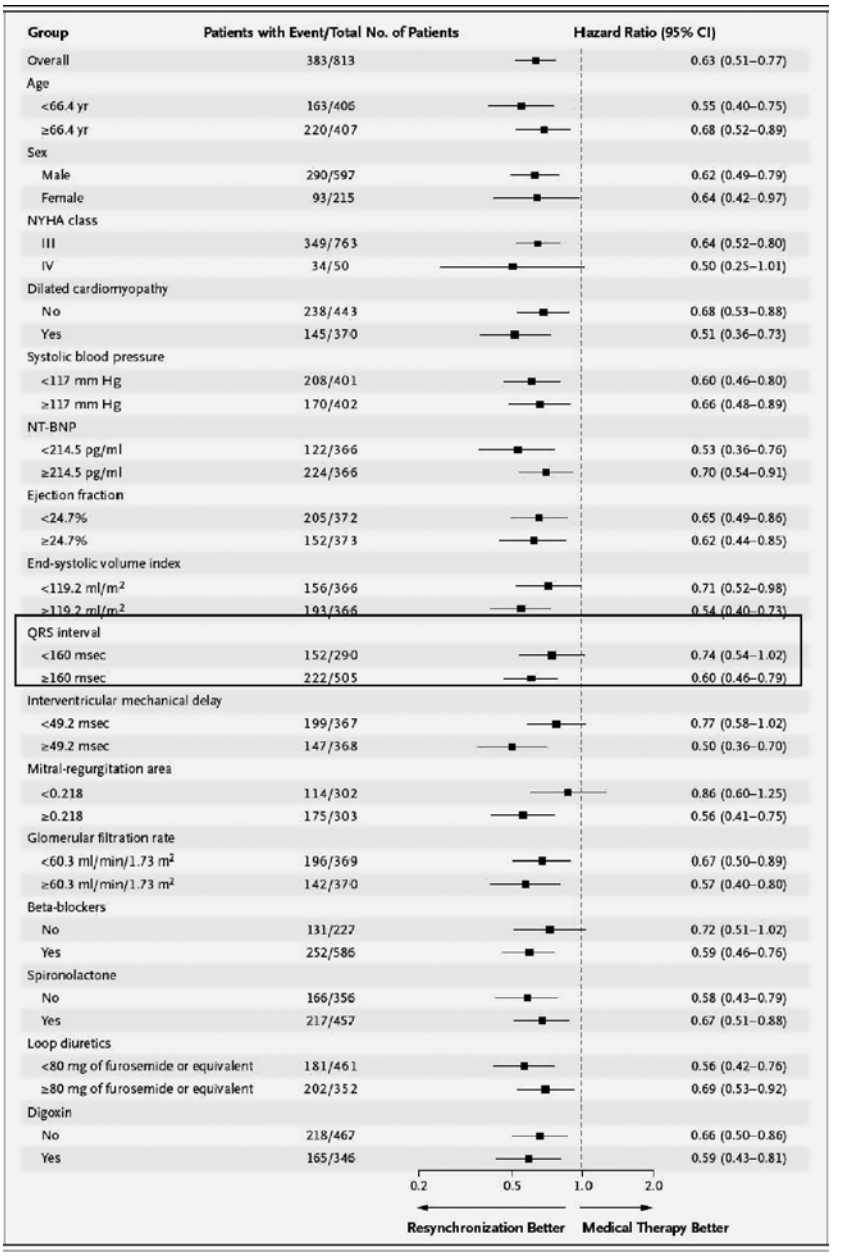

Fig. 8.4 Hazard ratios and 95% confidence intervals for the primary end point (death from any cause or hospitalization for major cardiovascular events) from CARE-HF. The inserted box highlights the differences in response in patients with different QRS durations, remembering that all patients with QRS duration ≤149 ms had to have echocardiographic dyssynchrony to be included in the study. (From Cleland JG, Daubert JC, Erdmann E, et al. Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352[15]:1539–49, permission and copyright 2005 Massachusetts Medical Society, all rights reserved).

a multicenter, nonrandomized prospective global trial to identify reliable echocardiographic predictors of positive response to CRT [60].

Echocardiographic use in postimplant optimization of CRT is an area that needs further clarification. Atrioventricular (A-V) optimization is performed with varying degrees of regularity, often dependent on center experience and in patients who are deemed to be "nonresponders" due to lack of clinical improvement. A recent retrospective analysis [61] showed that in patients who were assessed for the need for A-V optimization in the days after implant, 40% had significant changes made to their A-V interval in order to optimize diastolic filling but did not demonstrate differences in ejection fraction, NYHA class, or mortality. This report concluded that the importance of A-V optimization remains controversial and that inherent abnormalities of cardiac function (mitral regurgitation) may limit the application of A-V optimization, but that there was at least no harm demonstrated with changed settings.

Left Ventricular Pacing Site

The placement of the left ventricular lead in the CRT device is thought to have significant bearing on patient response to therapy. Early studies demonstrated poor hemodynamic response to pacing of the anterior wall (via the great cardiac vein) in comparison with pacing the LV free wall (lateral or posterior vein) [62]. A prospective study has concluded that reverse remodeling can be achieved by pacing at the site of maximum mechanical delay, more so than adjacent or remote areas [63].

Further questions remain regarding placement of the left ventricular lead including whether there are inherent differences in optimal pacing sites comparing patients with ischemic versus nonischemic cardiomyopathy.

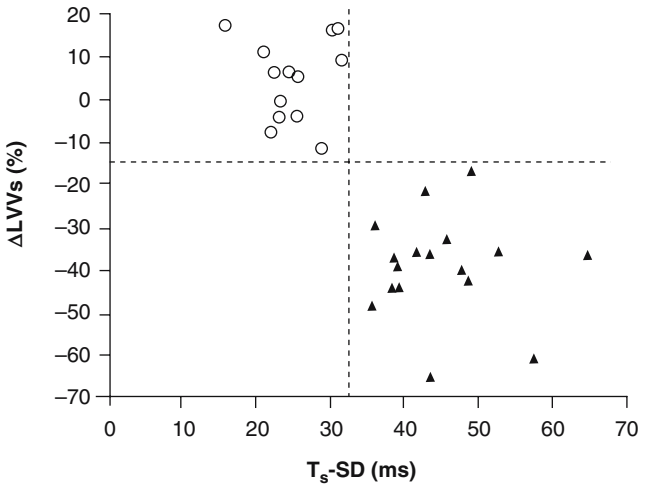

Fig. 8.5 An echocardiographic index of dyssynchrony can accurately delineate CRT responders from nonresponders (figure shows change in LV end systolic volume vs. severity of systolic dyssynchrony). (From Yu C, Fung W, Lin H, et al. Predictors of left ventricular reverse remodeling after cardiac resynchronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. Am J Cardiol 2002;91:684–8).

Advanced echo techniques or magnetic resonance imaging (MRI) may allow for targeted placement of pacing leads, although with MRI there is currently limited opportunity for follow-up studies. It is unknown what degree of benefit such targeted pacing might provide.

New York Heart Association Classes

Although current guidelines include class IV heart failure as an indication for CRT, few patients with such advanced disease have actually been enrolled in trials. In CARE-HF 6% of patients (N = 813) and in COMPANION 14.5% of patients (N = 1,520) were NYHA class IV. It is unclear what benefit is derived from CRT in this population, including what economic impact this therapy may have in patients who have 1-year mortality rate that likely exceeds 50%.

It is unknown what effect earlier treatment may have on progression of heart failure, specifically in patients with class I and class II heart failure who are minimally or mildly symptomatic. Only two large CRT trials, PATH-CHF II and CONTAK CD, included such patients. Potential benefits such as prevention of remodeling need to be further characterized. REVERSE will enroll NYHA class I and II patients, with QRS $\geq$120, LVEF $\leq$40%, LVEDD (left ventricular end diastolic dimension) $\geq$55 mm, with no pacing indications, with or without defibrillators, with a clinical composite primary end point (quality of life, NYHA class, CHF hospitalization and mortality) and echocardiographic secondary end point data [64]. RAFT is a Canadian multicenter trial that will evaluate COMPANION end points and will include class II patients. MADIT CRT/MADIT III will compare CRT-D versus ICD in patients with NYHA class I–II CHF, prior myocardial infarction, and QRS >120 ms.

Left Ventricular Ejection Fraction Parameters

Trials published in recent years have indicated the deleterious effects of right ventricular pacing. MADIT II noted a higher rate of new or worsened hospitalization in the defibrillator group, although this finding did not reach statistical significance [65]. The DAVID trial compared dual-chamber pacing and low rate ventricular backup pacing in patients with an ICD indication. The trial demonstrated that not only was there no advantage to dual-chamber pacing at a higher rate, but also it actually appeared to be deleterious, with a higher incidence of the combined end points of death and heart failure hospitalization [66]. Future trials will enroll patients with AV block, without traditional CRT indications, in order to evaluate the effects of CRT compared with RV pacing on the development of heart failure symptoms and also on combined end point including mortality (BLOCK-HF).

Conclusion

The value of CRT in specific populations is well established. Refinement in subpopulations already studied may allow us to better prospectively determine who will be responders and nonresponders to CRT. Furthermore, it is likely that future studies will provide information that will expand indications for CRT into other specific patient populations.

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9

Should Cardiac Resynchronization Be Considered for the Prevention of Heart Failure?

I. Eli Ovsyshcher and S. Serge Barold

The bulk of clinical evidence strongly endorses the use of cardiac resynchronization therapy (CRT) in symptomatic patients with either ischemic or nonischemic cardiomyopathy, heart failure, and New York Heart Association (NYHA) functional class III or IV despite optimal medical therapy, a left ventricular ejection fraction (LVEF) ≤ 0.35, and a QRS complex duration >120 ms [1,2] There are several unresolved issues involving the possible use of CRT in patients with a less advanced stage of heart failure [3,4]. This chapter treats the role of CRT in the prevention of heart failure progression and deterioration of left ventricular (LV) function specifically in patients with mild heart failure, NYHA functional class II, or with less depression of LVEF (>35%). Other aspects of evolving CRT indications are described elsewhere in this book.

CRT in Patients with an Intraventricular Conduction Delay and Less Advanced Heart Disease

Although CRT generally produces substantial clinical improvement in NYHA functional class, exercise performance and quality of life in NYHA class III and IV patients [5], such symptomatic improvement cannot be expected in patients with mild heart failure in functional class II NYHA. However, because class II patients also exhibit a reduced LVEF and LV dilatation in combination with a widened QRS complex, it can be postulated that patients with mild heart failure may also benefit from CRT, primarily by preventing progression of LV remodeling and resultant heart failure progression.

Several trials have assessed the benefit of CRT in patients with less advanced heart disease who were not CRT candidates according to the standard guidelines.

MIRACLE ICD Trial: NYHA Class II Patients

The MIRACLE ICD II Trial [6,7,8] was a randomized, double-blind, parallel, controlled trial of CRT in NYHA class II patients on optimal medical

management with LVEF ≤35%, QRS ≤130 ms, and a class I indication for an implantable cardioverter defibrillator (ICD). The study randomized 186 patients who received a combined CRT-D (i.e., CRT and ICD) device to CRT-on (n = 85) or CRT-off (ICD only [n = 101] serving as the control group). A total of 98 control and 82 CRT patients completed the study through a 6-month follow-up. After 6 months, patients who received CRT demonstrated improvements over the control group in exercise time, 6-min walk distance, and peak VO_2 (the study's primary end point), although none of these parameters reached statistical significance. However, significant reverse LV remodeling was observed: The CRT group did show statistically significant differences compared with the control group in ventilatory response to exercise (VE/VCO_2; p = 0.01), NYHA class (p = 0.05), percentage of patients with improved overall clinical status (p = 0.01), and several echocardiographic functional parameters, including LV end diastolic volume (LVEDV) (p = 0.04), LV end systolic volume (LVESV) (p = 0.01), and LVEF (p = 0.02) (Fig. 9.1). According to the MIRACLE ICD II trial investigators, the fact that CRT did not significantly improve exercise capacity was not particularly surprising, because exercise capacity at baseline in class II patients is typically only mildly impaired. However, the workers noted that the patients in the study, despite having mild heart failure symptoms, already showed signs of extensive cardiac remodeling at baseline, comparable with that seen in class III/IV patients. The significant improvement of LVEDV, LVESV, and LVEF indicated that CRT promotes reverse remodeling even at an earlier stage in heart failure patients. The investigators also concluded that the improvement in the CRT group and the composite clinical response suggest that CRT acts to limit disease progression in patients with mild heart failure symptoms.

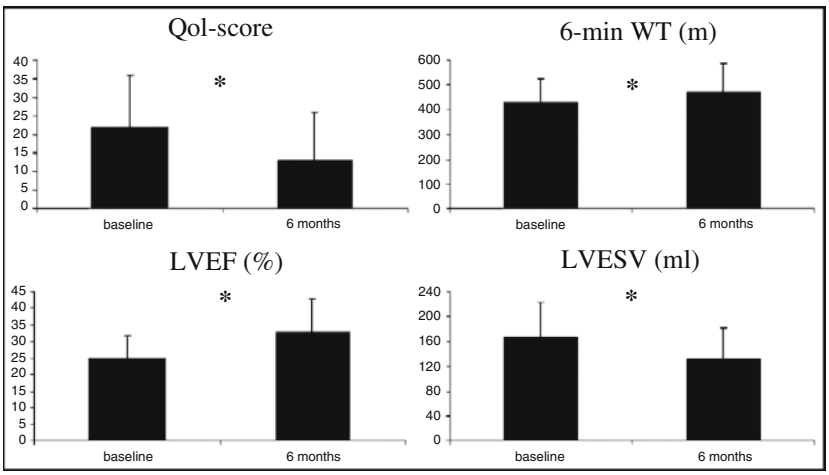

Fig. 9.1 Change in LV volumes and LVEF after 6 months of CRT or no pacing in NYHA class II patients. See text for details. (Reproduced with permission from Abraham WT, Young JB, Leon AR, et al. Multicenter InSync ICD II Study Group. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. Circulation 2004;110:2864–2868).

CONTAK CD Trial: NYHA Class II Patients

The CONTAK CD trial [9] was another randomized, double-blind, parallel, controlled trial of CRT that included NYHA class II–IV heart failure patients; the trial's inclusion criteria were otherwise similar to those of the MIRACLE trials [6,7,8]. When the results were broken down by NYHA class III/IV and class II, the findings were very consistent with those seen in the aforementioned MIRACLE data. In addition to significant reductions in LV internal diameter in diastole and LV internal diameter in systole observed in class III/IV patients treated with CRT, significant reductions in both parameters were also noted with CRT (vs. control) in class II patients ($p = 0.024$ and $p = 0.014$, respectively).

Leiden Trial: NYHA Class II Patients

Fifty consecutive patients in NYHA class II heart failure and 50 consecutive patients in NYHA classes III to IV (control group) were prospectively evaluated for the impact of CRT [10]. All patients had LV ejection fraction $\leq$35% and QRS duration >120 ms. The effects of CRT in NYHA class II patients were compared with the results obtained in both groups. The severity of baseline LV dyssynchrony (assessed with color-coded tissue Doppler imaging) was comparable between patients in NYHA class II versus those in NYHA classes III to IV (83 ± 49 vs. 96 ± 51 ms, p = NS). Surprisingly, a modest but significant improvement in mean NYHA class was observed in the class II group from 2 ± 0 to 1.7 ± 0.6 ($p < 0.01$). The quality-of-life score improved from 22 ± 14 to 13 ± 13 ($p < 0.001$), and a small but significant improvement was observed in the 6-min walking distance (from 430 ± 94 to 469 ± 118 m, $p < 0.01$) (Figs. 9.2 and 9.3). In contrast with the minor improvements in clinical symptoms in class II patients, the improvements in LV function after 6 months of CRT were substantial, as evidenced by considerable LV reverse remodeling and markedly improved LVEF. NYHA class II patients showed a significant improvement in LVEF (from 25 ± 7% to 33 ± 10%, $p < 0.001$) and reduction in LVESV (from 168 ± 55 ml to 132 ± 51 ml, $p < 0.001$) after CRT, similar to patients in NYHA class III/IV. Only 8% of NYHA class II patients exhibited progression of heart failure symptoms. In line with previous studies, only the patients with substantial LV dyssynchrony demonstrated improved LV function and showed reduction in LV dyssynchrony. CRT had comparable effects in patients in NYHA class II and in NYHA classes III to IV heart failure in terms of LV resynchronization, improvement in LVEF, and LV reverse remodeling. The lack of a control group of NYHA class II patients without CRT represents a limitation of this study. However, the MIRACLE ICD study [7] had previously demonstrated less progression of heart failure in NYHA class II patients who underwent CRT than in a control group of NYHA class II patients treated medically.

HOBIPACE Trial: Moderate Impairment of Left Ventricular Function

The Homburg Biventricular Pacing Evaluation (HOBIPACE) was a randomized controlled study that compared the biventricular pacing approach with conventional right ventricular (RV) pacing in patients with LV

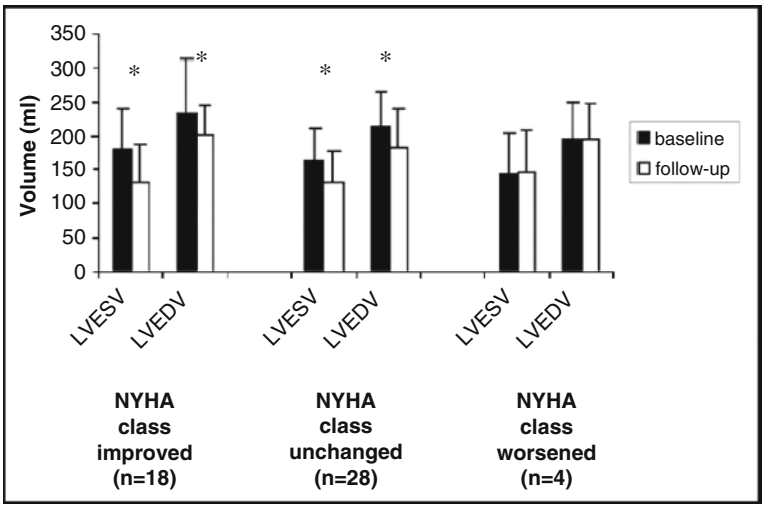

Fig. 9.2 Improvements in clinical and echocardiographic parameters at 6 months of CRT follow-up in patients in NYHA class II. *p < 0.05. 6-min WT, 6-min walking test; LVESV, left ventricular end-systolic volume; Qol, quality-of-life. See text for details. (Reproduced with permission from Bleeker GB, Schalij MJ, Holman ER, et al. Cardiac resynchronization therapy in patients with systolic left ventricular dysfunction and symptoms of mild heart failure secondary to ischemic or nonischemic cardiomyopathy. Am J Cardiol 2006;98:230–235).

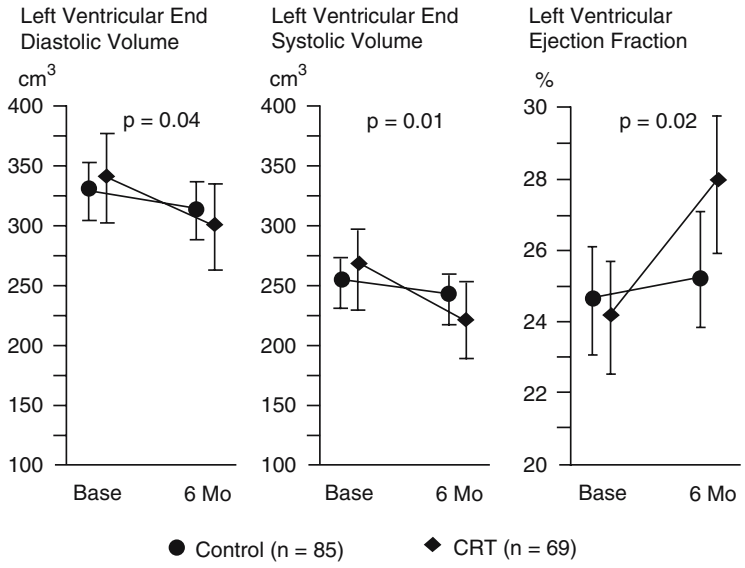

Fig. 9.3 Magnitude of LV reverse remodeling at 6 months of follow-up in CRT patients in NYHA class II with improvement in NYHA class (n = 18) versus those with unchanged NYHA class (n = 28) or with deterioration in NYHA class (n = 4). Black bars, baseline; white bars, follow-up. *p <0.05. LVEDV, left ventricular end-diastolic volume; other abbreviation as in Fig. 9.2. (Reproduced with permission from Bleeker GB, Schalij MJ, Holman ER, et al. Cardiac resynchronization therapy in patients with systolic left ventricular dysfunction and symptoms of mild heart failure secondary to ischemic or nonischemic cardiomyopathy. Am J Cardiol 2006;98:230–235).

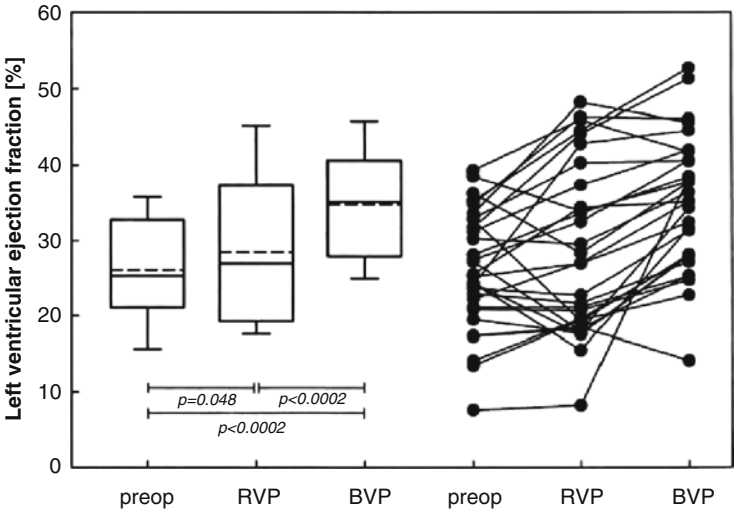

Fig. 9.4 Summarized (*box plots*) and individual values (*black circles*) of left ventricular ejection fraction before implantation of the study CRT device (*preop*) and after 3 months of right (*RVP*) and biventricular (*BVP*) pacing. In the box plot graph, the boundaries of the box indicate the 25th and 75th percentiles, the whiskers indicate the 10th and 90th percentiles, and the solid and dashed horizontal lines mark the median and mean value, respectively. (Reproduced with permission from Kindermann M, Hennen B, Jung J, et al. Biventricular versus conventional right ventricular stimulation for patients with standard pacing indication and left ventricular dysfunction: The Homburg Biventricular Pacing Evaluation (HOBIPACE). J Am Coll Cardiol 2006;47:1927–1937).

dysfunction and a standard indication for ventricular antibradycardia pacing [11]. Thirty patients with standard indication for permanent ventricular pacing and LV dysfunction defined by an LV end-diastolic diameter $\geq$60 mm, LVEF $\leq$40% and NYHA functional class II–IV were included. Using a prospective, randomized crossover design, 3 months of RV pacing were compared with 3 months of biventricular pacing with regard to LV function, N-terminal pro-B-type natriuretic peptide (NT-proBNP) serum concentration, exercise capacity, and quality of life. When compared with RV pacing, biventricular stimulation reduced LV end-diastolic (–9.0%, $p = 0.022$) and end-systolic volumes (–16.9%, $p < 0.001$), NT-proBNP level (–31.0%, $p < 0.002$), and the Minnesota Living with Heart Failure score (–18.9%, $p = 0.01$). LVEF (+22.1%), peak oxygen consumption (+12.0%), and oxygen uptake at the ventilatory threshold (+12.5%), were higher ($p < 0.0002$) with BV pacing (Fig. 9.4). The benefit of biventricular over RV pacing was similar for patients with ($n = 9$) and without ($n = 21$) atrial fibrillation. RV function was not affected by biventricular pacing.

NYHA Class III Patients with Moderate Depression of Left Ventricular Ejection Fraction

Fung et al. [12] conducted a prospective CRT study in 15 optimally treated patients (age: 66.1 ± 12.8 years; male = 13) with NYHA class III, LV ejection fraction >35% and <45% and QRS duration >120 ms. The magnitude of

echocardiographic measurements was compared with 30 age, sex, NYHA class, and heart failure etiology matched patients with conventional CRT indication. After 3 months, there were significant reductions in LV end-systolic (86.2 ± 24.1 ml to 69.7 ± 22.2 ml, $p < 0.01$)/end-diastolic (135.5 ± 36.8 ml to 120.5 ± 34.6 ml, $p < 0.01$) volumes, improvement in LVEF (39.1 ± 2.2% to 44.2 ± 5.5%, $p = 0.01$), and NYHA class (3.0 ± 0.0 to 2.07 ± 0.46, $p < 0.001$). There was no difference in changes in LV volumes, LVEF, NYHA class, and exercise capacity before and after CRT between the study and conventional groups except for greater improvement in the quality of life score in the conventional group.

Overall Benefit of CRT in Patients with Less Advanced Heart Disease

It cannot be expected that patients with milder form of heart disease would show marked improvement compared with those with more severe forms of disease. However, in all the aforementioned studies, markers of deleterious ventricular remodeling were attenuated. LV function improved considerably with CRT (LV ejection fraction and reverse remodeling), and this improvement was comparable with that observed in those with more severe forms of a disease (NYHA class III/IV). Thus, it appears that CRT can provide significant benefit in terms of retardation or delay in heart failure progression for class II patients with LV ejection fraction $\leq$35% or class III patients with LV ejection fraction between 35% and 45% functional improvement as well as reverse LV remodeling.

Ongoing Trials in Patients with Less Advanced Heart Disease

Two large studies are under way to confirm these findings, which may result in future guidelines being expanded to include class II patients.

The REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study is a prospective, multicenter, randomized, double-blind, parallel, controlled clinical trial designed to establish whether CRT combined with optimal medical treatment can attenuate heart failure disease progression compared with optimal medical treatment alone in patients with either asymptomatic LV dysfunction (NYHA class I American College of Cardiology/American Heart Association stage C) or mild (NYHA functional class II) heart failure, QRS duration >120 ms, LVEF <40%, and LV end-diastolic diameter >55 mm [13]. The primary end point is the heart failure morbidity by clinical composite response, and reverse LV remodeling by LV end-systolic volume index is the first-order secondary end point. Approximately 600 patients from 100 centers in the United States, Canada, and Europe will be double-blinded randomized 2:1 to CRT versus no CRT. The follow-up is 5 years in total with the primary and first secondary end points reported at 12 months. Enrollment began in September 2004 and is expected to be completed in 2006.

The MADIT-CRT trial [14] aims at investigating whether prophylactic CRT inhibits or slows asymptomatic or mildly symptomatic heart failure. Patients with previous myocardial infarction and NYHA functional class I–II or patients with nonischemic cardiomyopathy in NYHA class II will be included if they have LVEF <30%, sinus rhythm, and QRS >130 ms. The primary end point is the time to first all-cause mortality or heart failure

event analyzed from randomization. This study will include 1,820 subjects with an estimated follow-up time of 24 months.

CRT for Primary Implantation in Patients with a Conventional Indication for Antibradycardia Pacing

The widespread acceptance that long-term RV apical pacing can impair LV function and precipitate heart failure raises the question whether biventricular pacing should be considered for the "primary prevention" of LV remodeling and development of heart failure [15]. It would be useful to identify a subset of patients who are susceptible to the adverse effects of RV apex pacing before pacemaker implantation. Currently, only patients with preexisting LV dysfunction seem more likely to develop LV dyssynchrony after RV pacing. It can be hypothesized that patients requiring pacing for a conventional indication, NYHA class III/IV and LVEF $\leq$35% (regardless of the underlying configuration of the spontaneous QRS complex) might benefit from CRT at the time of the initial pacemaker implantation. The impressive 36% reduction in all-cause mortality ($p = 0.002$) produced by CRT (according to accepted indications) in the CARE-HF trial lends some validity to the idea of primary prevention [16]. The results of CRT in patients with less advanced heart disease (discussed above) could be logically extrapolated to selected patients requiring conventional RV antibradycardia pacing [17].

We believe that a CRT approach for initial pacemaker implantation might be worthwhile in selected patients with bradycardia. On the basis of little data [17, 18], a number of workers now believe that it is reasonable to consider biventricular pacing if frequent or continuous RV pacing (i.e., when a large cumulative percentage of RV pacing as in complete atrioventricular (AV) block) is expected in the setting of LVEF $\leq$35% (even without clinical heart failure) especially with associated mitral regurgitation. The cutoff point for LVEF is likely to change in the future with the emergence of more supportive data about the benefit of CRT in patients with less advanced forms of heart disease. At this juncture, all patients with sinus node dysfunction and especially with LVEF $\leq$35% should receive a conventional RV pacemaker with appropriate algorithms to minimize RV pacing if the clinical situation suggests that RV pacing is likely to be infrequent. The suggestion to consider biventricular pacing in selected patients requiring antibradycardia pacing is based on the concept derived from the Mode Selection Trial (MOST) that it is the cumulative percentage of RV pacing time that ultimately determines the incidence of hospitalizations for CHF, and the frequency of AF [19, 20].

Right Ventricular Pacing After AV Nodal Ablation for Atrial Fibrillation

PAVE Trial

The PAVE trial was the first randomized trial designed to evaluate prospectively the long-term effects of pacing in patients with chronic atrial fibrillation

(AF) [18]. The patients underwent AV node ablation and pacemaker implantation comparing chronic biventricular pacing with RV pacing Patients were in NYHA class I–III on stable cardiovascular medications and had to be able to walk <450 m on a 6-min walk test. Those with NYHA class IV were excluded. One hundred eighty-four patients requiring AV node ablation were randomized to receive a biventricular pacing system (n = 103) or an RV pacing system (n = 81). The study end points were change in the 6-min hallway walk test, quality of life, and LVEF. Patient characteristics were similar (64% male; age 69 ± 10 years; LVEF 0.46 ± 0.16; 83% NYHA class II or III). At 6 months after ablation, patients treated with cardiac resynchronization had a significant improvement in 6-min walk distance (31%) above baseline (82.9 ± 94.7 m) compared with patients receiving RV pacing (24%) above baseline (61.2 ± 90.0 m) (p = 0.04). There were no significant differences in the quality-of-life parameters. At 6 months after ablation, the LVEF in the biventricular group (0.46 ± 0.13) was significantly greater in comparison with patients receiving RV pacing (0.41 ± 0.13, p = 0.03). Patients with an LVEF ≤45% or with NYHA class II/III symptoms receiving a biventricular pacemaker appear to have a greater improvement in 6-min walk distance compared with patients with normal systolic function or class I symptoms. Thus, the beneficial effects of cardiac resynchronization appeared to be greater in patients with impaired systolic function or with symptomatic heart failure.

Leiden Atrial Fibrillation Trial

The long-term consequences of RV pacing were studied in 55 patients with drug-refractory AF and AV node ablation [21]. After long-term RV pacing (after a mean of 3.8 ± 1.7 years), 27 patients (49%) developed LV dyssynchrony (by M-mode echocardiography and tissue Doppler imaging). Concomitantly, these patients worsened in heart failure symptoms (NYHA functional class increased from 1.8 ± 0.6 to 2.2 ± 0.7, $p < 0.05$), with a decrease in LVEF (from 48 ± 7% to 43 ± 7%, $p < 0.05$) and an increase in LV end-diastolic volume (from 116 ± 39 ml to 130 ± 52 ml, $p < 0.05$) (Fig. 9.5). Conversely, patients without LV dyssynchrony did not deteriorate in heart failure symptoms, LV function, or LV volumes. Thus, long-term RV pacing induced LV dyssynchrony in almost 50% of patients treated with AV node ablation for chronic AF. The development of LV dyssynchrony was associated with deterioration in heart failure symptoms, systolic LV function, and LV dilatation. Unfortunately, the patient's baseline clinical characteristics in this study did not predict the development of ventricular dyssynchrony after RV pacing.

The data from these two studies [18,21] involving patients with AF (thereby excluding the effect of AV synchrony) requiring continual RV pacing extends the findings from previous studies and shows that LV dyssynchrony induced by RV pacing results in progressive LV remodeling and deterioration of LV function. The use of echocardiographic techniques, such as M-mode and tissue Doppler imaging, to detect LV dyssynchrony after RV pacing could also identify those patients who are at risk of developing long-term LV dysfunction. The findings also suggest that there may be a place for primary prevention of LV remodeling or its progression (secondary prevention) with biventricular pacing at least in patients with an LVEF ≤45%.

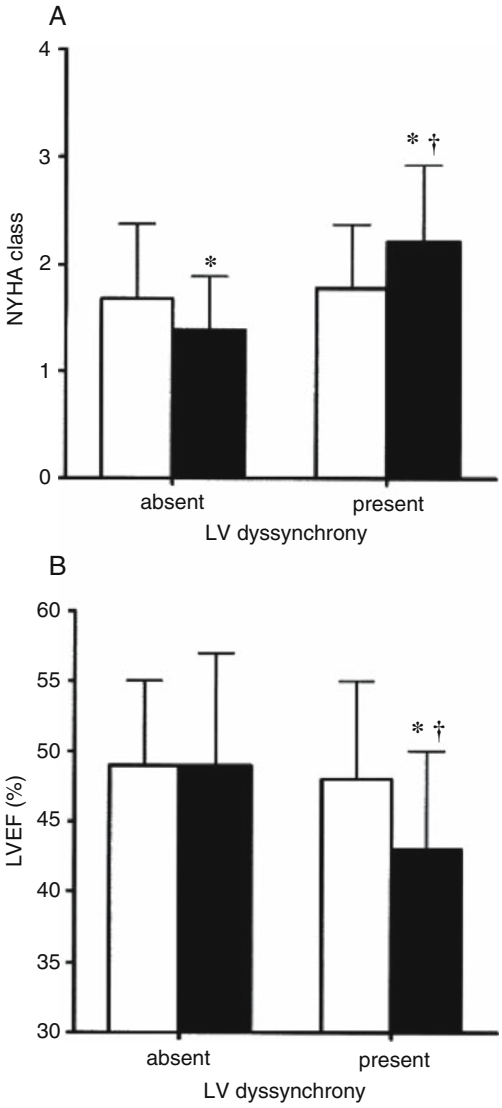

Fig. 9.5 Effects of long-term right ventricular (RV) pacing on clinical status and left ventricular ejection fraction (LVEF). (**A**) In patients with LV dyssynchrony, New York Heart Association (NYHA) functional class deteriorated significantly, whereas NYHA functional class improved significantly in patients without LV dyssynchrony. (**B**) LV ejection fraction decreased significantly in patients with LV dyssynchrony after long-term RV pacing. *$p < 0.05$ baseline versus follow-up; †$p < 0.05$ with dyssynchrony versus without dyssynchrony. White columns, baseline; black columns, follow-up. (Reproduced with permission from Tops LF, Schalij MJ, Holman ER, et al. Right ventricular pacing can induce ventricular dyssynchrony in patients with atrial fibrillation after atrioventricular node ablation. J Am Coll Cardiol 2006;48: 1642–1648).

Upgrading of Conventional Pacing Systems

Upgrading from RV to biventricular (BV) pacing now constitutes an important and rapidly growing segment of pacemaker practice involving NYHA class III–IV patients with heart failure and LVEF ≤35% despite an optimal AV delay 11, 22–35]. About 20% of resynchronization devices are now implanted to upgrade a conventional RV pacemaker for the treatment of heart failure. The growing number of upgrading procedures from RV to biventricular pacing in regular pacemaker patients with heart failure should be interpreted as a wake-up call to seriously consider and investigate the role of primary prevention of heart failure in selected patients at the time of initial pacemaker implantation. In this setting, the potential advantages of CRT should be weighed against procedural difficulties and complications. The decision process would be facilitated with the future studies and development of faster and easier methods to achieve LV pacing.

In patients with systolic heart failure and an implanted RV pacemaker, upgrading to a biventricular system produces an immediate improvement in LV function and reduction of functional mitral regurgitation on the basis of a more coordinated LV contraction [22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35]. On a long-term basis, there is evidence that pacemaker patients with an upgraded system exhibit further improvement of LV function on the basis of reverse remodeling [22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35]. The acute and long-term responses to upgrading an RV pacing system appear similar to those seen in patients (without a pacemaker) undergoing cardiac resynchronization for standard indications (poor systolic LV function and LV dyssynchrony) [22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35]. The question of primary prevention of heart failure is becoming important in patients with conventional RV pacemakers. We believe that upgrading to a biventricular system should be considered earlier than waiting for the development of heart failure with an LVEF ≤35%. Hence the importance of careful follow-up to detect progressive deterioration of LV function.

Monitoring Left Ventricular Function in Pacemaker Patients

The impact of CRT therapy has increased the importance of monitoring LV function in patients attending a routine pacemaker follow-up service. In this respect, a study involving 307 pacemaker patients in a routine pacemaker follow-up service revealed an LVEF <40% in 31% of the patients [36]. These findings suggest that if "prevention is better than a cure," one should adopt a proactive approach and periodically evaluate the LVEF of pacemaker patients to determine whether upgrading to BV pacing might be beneficial before marked deterioration of LV function and the onset of heart failure, which carries a dismal prognosis in the elderly.

Deterioration of LV function over time was highlighted by the recent study [37] that evaluated the change of the nuclear determined LVEF (baseline 25–40%) over a period of approximately 18 months in 207 patients with a variety of conditions including some patients with RV pacemakers. The analysis was limited to patients with an increase of ≥10% (148 patients) and those with a decrease of ≥7% (59 patients) of the LVEF. Among pacemaker patients (mostly dual chamber rate responsive (DDDR)), 27% showed an increase in LVEF and 50% showed a decrease. The strongest independent predictor of LVEF decrease was the presence of a permanent RV pacemaker (odds ratio

6.6, p = 0.002). Although the presence of a pacemaker probably identified a sicker group of patients at the beginning of the study, the results do highlight the importance of carefully following LV function in pacemaker patients.

Thus, follow-up of LV function is an effective way to determine potential candidates for upgrading patients undergoing RV pacing. However, the main flaw of this approach, as well as usage of current indications for CRT, is absence of indices to prediction a positive response to upgrading.

The recently published report from the Ablate and Pace in Atrial Fibrillation (APAF) group [38] attempted to resolve this problem. This study evaluated how pacing from the RV apex affected LV electromechanical activation and assessed whether the extent of LV dyssynchrony during RV pacing can be predicted by clinical, ECG, or echocardiographic findings obtained during sinus rhythm. The authors evaluated 56 patients (all in sinus rhythm except for three in atrial fibrillation) with a normal QRS complex and preserved AV conduction who received permanent backup RV pacemakers. Intra-LV electromechanical activation was assessed during sinus rhythm and during RV pacing. An abnormal electromechanical LV delay was found in 27% of patients all during sinus rhythm and *only* in 50% of patients during RV pacing ($p < 0.001$). This data is in full agreement with the results of the Leiden AF trial [21]. An abnormal baseline electromechanical LV delay (in sinus rhythm) and QRS >85 ms were independent predictors of an abnormal electromechanical LV delay during RV pacing. Thus, RV apical pacing induces mechanical LV dyssynchrony in a substantial percentage of pacemaker patients but not all. In some patients with complete AV block, RV pacing may even improve LV function [11, 37]. Although normal baseline electromechanical LV activation cannot exclude the development of significant dyssynchrony during RV pacing, the presence of preimplantation LV dyssynchrony predicts worsening of this detrimental problem. These observations should encourage the search of additional indices that predict a positive response to CRT in patients with conventional pacemakers (as well as in patients with accepted indications for CRT). These data can also begin to explain why not all the patients with RV pacing develop LV dysfunction and heart failure.

Enhanced Follow-up of Patients with Conventional Pacemakers and Preimplant Prediction of Deleterious Effect of RV Pacing

QRS Duration

Preimplantation and postimplantation paced QRS duration was recently shown to be a strong predictor of heart failure hospitalization (HFH) and death in pacemaker patients [20, 38, 39, 40, 41]. According to Sweeney et al. [39], the risk of HFH increased incrementally with increasing QRS duration, independent of whether the prolonged QRS duration occurred spontaneously or was caused by RV apical pacing (Fig. 9.6). Importantly, the absolute risk of HFH was always twofold higher for a prolonged QRS duration that occurred spontaneously versus that due to RV apical pacing for any given value of QRS duration. This study also provided strong evidence that the increased relative risk of HFH associated with a more prolonged QRS duration is equivalent for prolongation that either occurs spontaneously or is due to RVA pacing. The increased risk of HFH associated with increasing QRS duration was slightly

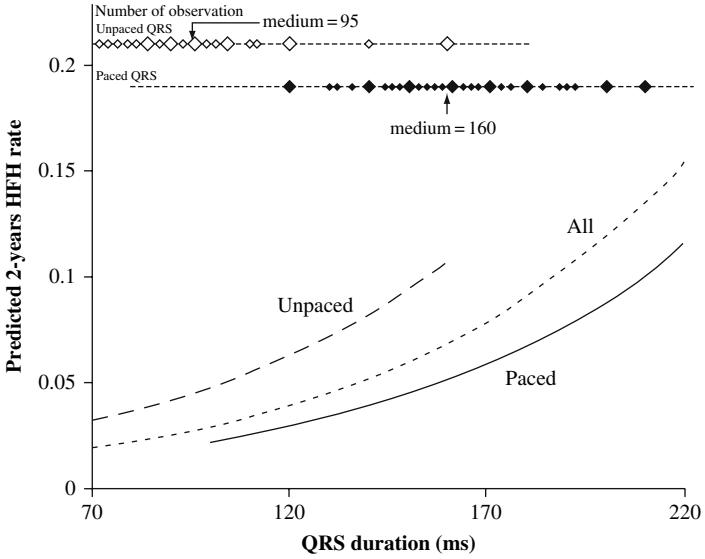

Fig. 9.6 Relationship between duration of the spontaneous and paced QRS complex and heart failure hospitalization. (Reproduced with permission from Sweeney MO, Hellkamp AS. Heart failure during cardiac pacing. Circulation 2006;113:2082–2088).

greater in patients with a normal versus a low LVEF. As was mentioned above, an abnormal baseline electromechanical LV delay and QRS >85 ms are independent predictors of an abnormal electromechanical LV delay during RV pacing and possible development of heart failure [38].

Serial Measurement of LVEF and LV Dyssynchrony

The recent report of Tops et al. [21] suggests that it may be possible to predict the development of LV dysfunction induced by RV pacing by measuring the degree of LV dyssynchrony by tissue Doppler imaging.

Conclusion

It is reasonable to hypothesize at this juncture that an improved activation sequence provided by biventricular pacing as opposed to monochamber RV stimulation will reduce chronic changes in myocardial cellular structure that contribute to LV remodeling with impaired hemodynamic performance, mitral regurgitation, and increased left atrial size [20,42,43]. Presumably, avoidance of these adverse structural effects of RV pacing could reduce the risk of heart failure, atrial fibrillation, and possibly death, the latter suggested by the results of the CARE-HF trial [16]. As patients who develop LV dysfunction and/or heart failure with RV pacing cannot be predicted according to our current knowledge, selection of alternative pacing sites or modes should be considered when the preservation and improvement of LV function are important. The question of primary prevention of LV dysfunction and heart failure with various pacing techniques and sites needs to be addressed in large randomized trials. Current data favors biventricular pacing rather than alternative site RV pacing for primary heart failure prevention in patients with impaired LV

function likely to need pacing most of the time. In this setting, the potential advantages of biventricular pacing should be weighed against procedural time and difficulties, shorter battery life, higher cost, and complications. The routine use of LV-based pacing for bradycardia in the majority of patients is currently impractical, but the process would be facilitated with the future development of faster and easier methods to achieve LV pacing, endocardial via coronary sinus, as well as epicardial.

The long-term benefit of alternative RV pacing sites (outflow tract, septum and dual RV site) remains inconclusive [44] and needs to be proved in patients with normal LVEF for primary prevention of heart failure and LV dysfunction compared with biventricular and monochamber LV pacing.

The growing realization that long-term RV apical pacing may be detrimental may eventually radically transform pacemaker practice. It is possible that univentricular RV apical pacing may be relegated to a far lesser role and partially replaced by other preferred sites.

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10

Left Bundle Branch Block–Induced Cardiomyopathy: A New Concept of Mechanically Induced Cardiomyopathy

Jean Jacques Blanc, Marjaneh Fatemi, Philippe Castellant, and Yves Etienne

Dilated nonischemic cardiomyopathy (DCM) has recently been defined in an American Heart Association statement as "a common and largely irreversible form of heart muscle disease with an estimated prevalence of 1:2500" [1]. Its causes were listed in the same document and included infectious agents, toxins (chemotherapeutic agents, metal), and autoimmune, systemic, neuromuscular, mitochondrial, endocrine, and nutritional disorders. In fact in many cases, the etiology of DCM remains unknown and it is therefore qualified as "idiopathic." The "irreversible" character of this disease included in its definition outlines the poor prognosis associated with DCM. In fact, it has been reported that in some rare cases, long-standing DCM could reverse to normal or near normal heart; this is encountered in few patients who agree to stop alcohol intoxication or in patients with incessant tachycardia who can be effectively treated by ablation, for example. There is no precise data in the literature to quantify the percentage of patients with a DCM that could be completely reversed, but it is certainly less than 5%.

Aim of the Current Study

Our goal is to try to show that the list of the causes of DCM could be incremented by one line not already included in the actual mechanisms of the disease and that this cause is curable in a significant proportion of patients by currently available treatment.

It is classically considered that intraventricular conduction disturbances and particularly left bundle branch block (LBBB) in patients with DCM is the consequence of the dilation of the cavity and this assumption has been recently recalled in the above-mentioned statement [1]. Our hypothesis was that the reverse proposal is also true and that, at least in some patients, LBBB could be responsible for the induction of DCM [2].

How to Detect a New Cause of DCM

There are schematically two strategies to detect a new cause of DCM: [1] select a group of patients with the suspected cause and a normal heart and follow this group to observe if some over time develop DCM or [2] select a group of patients with DCM, withdraw the incriminated cause, and follow this group to observe if some patients recover a normal heart. The first strategy needs to include a large cohort of patients and to follow them probably for a long period of time with the limitation of been criticized on the reality of the "normal" heart at baseline. The second strategy is the most commonly used and has been considered adequate to extract from the group of "idiopathic DCM" the alcohol- and tachycardia-related cardiomyopathies. This strategy will then be followed in our study.

Study Design

As we have selected the "second" strategy, the problem was to exclude the LBBB. This is no longer an impossible task as we have learned by resynchronization therapy that it is possible to transform a native LBBB in a right bundle branch block pattern by pacing the left epicardial or endocardial part of the left ventricle.

Patient Selection and Methods

Patients selected for the current study were consecutively admitted in our department and were included if they fulfilled the following criteria: long-standing history of heart failure (NYHA class III or IV at the time of implantation) in spite of optimal medical treatment due to idiopathic (patients with suspected curable cause of their DCM; for example, those with excessive alcohol consumption were excluded) nonischemic (all the patients had coronary angiography that excluded significant stenosis) DCM (left ventricular ejection fraction $\leq$35% and left ventricular end diastolic diameter $\geq$60 mm) wide QRS complexes consecutive to the presence of a LBBB, sinus rhythm, and successful implantation of a left ventricular–based pacing system (left ventricular lead positioned in a lateral tributary of the coronary sinus). These patients were prospectively followed at 1, 6, and 12 months after implantation and every year after the first year. At every visit, clinical, electrocardiographic, pacing, radionuclide, and echocardiographic parameters were evaluated and compared with baseline values. Patients were considered to recover a normal left ventricular ejection fraction (LVEF) when the radionuclide value was $\leq$50%. This cutoff point was accepted because the normal value of LVEF in our laboratory was measured at 55 ± 3%.

Results

Population

Twenty-nine patients (19 males; mean age 70 ± 7.7 years) who fulfilled inclusion criteria [2] were successfully implanted with a permanent LV-based pacing device (LV only, 24 patients; biventricular, 5 patients). Five patients

(17%; group 1), whose baseline characteristics are reported in Table 10.1, showed a normalization of their LVEF (from 19 ± 6% to 55 ± 3% p = 0.001) at the 12-month follow-up visit. These individuals had also exhibited a parallel improvement in their clinical status, exercise tolerance, and echocardiographic data (Table 10.2). On the other hand, despite a significant functional improvement (NYHA class from 3.5 ± 0.5 to 2.8 ± 0.9; $p < 0.001$), 24 patients (group 2) did not demonstrate any significant LV dysfunction reversal (LVEF from 21 ± 8% to 23 ± 11%; NS) at the 12-month visit or at the last intermediate follow-up visit for the seven patients, all from group 2, who died during the first year (six patients from intractable CHF and one patient from noncardiac cause).

The five group 1 patients received a conventional medical treatment before implantation: diuretics and angiotensin converting inhibitors or angiotensin receptor antagonist in all, digitalis in one patient, and beta-blockers in three patients. In one patient, beta-blockers were contraindicated due to chronic obstructive pulmonary disease. In another patient, beta-blockers were discontinued due to initial worsening of CHF; however, this drug was successfully prescribed 6 months after implantation of the LV-based pacing because LV function had already dramatically improved. This was the only significant change in medical treatment in this group during the 12-month follow-up period.

Long-term Follow-up of Patients with LVEF >50%

Among the group 1 patients, three were subsequently followed between 1 and 2 years without deterioration in their clinical and LVEF status. The two remaining patients were followed for longer periods and had a complete evaluation 3 and 7 years after implantation; both remained asymptomatic and had normal LVEF and end diastolic diameters.

Predictive Factors of LV Dysfunction Reversal

Analysis of baseline parameters did not provide a precise means of identifying which LBBB DCM patients would exhibit an improved EF with LV-based pacing (Table 10.2). Baseline parameters were identical in the two groups. Of note, however, despite identical baseline QRS duration and similar ventricular pacing configuration (uni-LV or biventricular), the paced QRS duration just after implantation was shorter in group 1 than was the case for group 2 (146 ± 21 vs. 176 ± 18 ms; p = 0.003). Further, location of the LV leads in group 1 patients did not differ from that in group 2 patients.

Discussion

This study suggests that in a certain proportion of patients with DCM, LBBB per se may contribute to the development of DCM, giving rise to a new concept of LBBB-induced cardiomyopathy.

Did the Study Population Exhibit an Idiopathic Cardiomyopathy?

Our patient population had severe nonischemic DCM as demonstrated by baseline clinical characteristics with a mean LVEF and end diastolic diameter

Table 10.1 Baseline characteristics of the five patients who completely normalized their left ventricular ejection fraction.

Patient no.	Age	Gender	NYHA class	Heart failure duration (months)	Left bundle branch block duration (months)	QRS duration (ms)	Left ventricular ejection fraction (%)	Peak oxygen consumption (ml min^{-1} kg^{-1})
1	59	F	4	120	120	230	11	5.8
2	70	M	3	36	36	140	18	14.5
3	74	F	3	16	16	180	16	14.0
4	69	F	4	36	36	175	26	9
5	76	M	3	42	42	180	26	16.2
Mean	69.6 ± 7			50 ± 40	50 ± 40	181 ± 32	19 ± 6	11.9 ± 4

Table 10.2 Comparison of data between baseline and the 12 month follow-up visit in patients with normalization of LV function during pacing (group 1: n = 5) and between baseline and the last follow-up visit in patients without normalization of LV function (group 2: n = 24), and comparison of mean data between the two groups.

	Group 1 (n = 5)			Group 2 (n = 24)		
	Baseline	**Follow-up**	**p**	**Baseline**	**Follow-up**	**p**
NYHA class (mean)	3.4 ± 0.5	1.8 ± 0.4	0.016	3.5 ± .5	2.8 ± .9	0.001
6-min test distance (m)	300 ± 136	444 ± 75	0.12	342 ± 117	392 ± 123	0.96
Peak oxygen consumption (ml min^{-1} kg^{-1})	11.9 ± 4.3	15.8 ± 2	0.03	111 ± 1.7	12 ± 2.6	0.35
QRS duration (ms)	181 ± 32	146 ± 21	0.09	176 ± 20	176 ± 18*	0.09
Left ventricular ejection fraction (%)	19 ± 6	55 ± 3	0.001	21 ± 8	22.8 ± 11	0.23
Left ventricular diastolic diameter (mm)	78.0 ± 6.1	57.2 ± 5.2	0.002	76 ± 9	75 ± 8	0.22
Left ventricular fractional shortening (%)	13.6 ± 2.7	31.0 ± 2.7	0.0001	11.9 ± 4	13.5 ± 5	0.06
Mitral regurgitation area (cm^2)	9.1 ± 4.4	1.2 ± 1.8	0.001	8.3 ± 5.4	7.1 ± 1.4	0.39

*$p < 0.01$.

of 21% and 78 mm, respectively, and normal coronary angiography. Further, we carefully excluded those with a suspected known reversible causes of cardiomyopathy

Even if some cases of clear improvement of idiopathic DCM have been reported, "complete" recovery is rare, and when it did occur, the patients were usually young and had had a short duration of symptoms; neither of these characteristics apply to our study population. In our cases, the long-lasting (over several years) evolution of CHF symptoms essentially excludes the possibility of either "spontaneous" recovery or of the DCM being of acute myocarditis origin. Consequently, it could be reasonably assumed that our patients indeed had exhibited a severe idiopathic DCM upon entry into this study.

Was the Reversal of LV Dysfunction Real?

Our findings indicate that the reversal of LV dysfunction encompassed not only LVEF but also end diastolic diameter and mitral regurgitation. A remaining important question to consider is whether this reversal is complete or not. It seems complete, comparing baseline values of radionuclide angiography and echocardiography with those at the 12-month follow-up, supporting the view that the cardiac status of the group 1 patients could be considered "normal."

Mechanism of LV Dysfunction

It has long been known that LBBB induces an abnormal LV contraction pattern resulting in LV dysfunction with a decrease in EF. Whether this abnormal contraction pattern could provoke over time a DCM remains unknown, but the possibility is supported by Framingham data in which LBBB was reported to precede appearance of CHF in a subset of individuals.

Exclusion of LBBB induced by LV-based cardiac pacing may substantially diminish the mechanically deleterious effects of the intraventricular dyssynchrony. The outcome is progressive improvement in LV function. Further, the observation that after cessation of pacing the QRS duration tended to decrease in group 1 patients supports the notion that LBBB-induced dyssynchrony leads to a form of LV dysfunction that aggravates intraventricular conduction disturbances. Presumably, LV-based pacing interrupts this vicious circle and thereby tends to improve intraventricular contractions synchrony over time.

Predictive Factors of LV Dysfunction Reversal

The small number of patients who normalized their LV function limits identification of predictors of reverse remodeling. It should be stressed that many potential discriminating factors have not been analyzed either because they were not included in the database or because they are still undetermined.

How Many Patients with DCM Could Be Cured?

In series evaluating patients with DCM, a wide QRS complex was found in approximately 25% to 30% of the population. Considering the 17% reversal rate observed in our study, it seems that 5% of all the patients with DCM could have a complete reversal to normal of their left ventricular function.

Unresolved Issues

There remain many unresolved issues with respect to the LBBB-induced DCM issue. Why some patients with long-term evolution of well-defined DCM and LBBB had, after LV pacing, normalization of their LV function whereas others did not is unclear. Had the left ventricular lead pacing site some influence? Are some environmental or genetically transmitted factors responsible for different outcomes?

Conclusion

Among patients with DCM and LBBB, there is a significant subset of patients (17%) that can be cured by left ventricular–based pacing. This observation gives rise to the new concept of LBBB-induced DCM or more extensively to the concept of dyssynchrony or mechanical-induced DCM.

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11

Role of Echocardiography Before CRT Implantation: Can We Predict Nonresponders?

Gabe B. Bleeker, Nico van der Veire, Martin J. Schalij, and Jeroen J. Bax

Introduction

Currently, cardiac resynchronization therapy (CRT) is considered an important step forward in the treatment of selected patients with drug-refractory heart failure. Recent large, randomized trials, such as the MIRACLE and the COMPANION trials, have clearly demonstrated the beneficial effects of CRT on left ventricular (LV) hemodynamics, heart failure symptoms, and LV volumes [1, 2, 3]. In addition, the recent CARE-HF trial demonstrated an improved survival in heart failure patients undergoing CRT compared with patients who received optimal medical therapy alone [4].

However, parallel to the impressive results of CRT in these large trials, a consistent number of patients did not improve (referred to as nonresponders) when the established CRT selection criteria were applied. Based on the American College of Cardiology (ACC) / American Heart Association (AHA) / European Society of Cardiology (ESC) guidelines, the selection criteria include moderate-to-severe heart failure (New York Heart Association [NYHA] class III to IV), LV ejection fraction $\leq$35%, and a widened QRS complex >120 ms [1,5,6,7,8,9].

When response to CRT is defined according to clinical parameters (e.g., improvement in NYHA class or quality-of-life score), the prevalence of nonresponders is around 30%, but when echocardiographic parameters (LV reverse remodeling or improvement in LV ejection fraction) are used to define response, the number of nonresponders is usually around 40% [7,8,9].

In order to avoid unnecessary health care costs and procedure risks, the relatively high percentage of nonresponders to CRT should be reduced. To achieve this goal, the current CRT selection criteria need adjustment. In addition, refinement of the selection criteria may also include other groups of heart failure patients who may benefit from CRT but are not covered by the current indications. Recent data have suggested that (novel) echocardiographic techniques aiming at assessing the extent of preimplantation LV dyssynchrony are able the increase the likelihood of response to CRT [8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31].

This chapter will provide information on the potential mechanisms of (non-) response to CRT, followed by an overview of the most important echocardiographic techniques that can be used to improve patient selection for CRT.

Mechanism of Benefit from CRT

For many years it has been recognized that in failing hearts, LV function is affected not only by a depressed contractile status of the myocardium but frequently also by a dyssynchronous activation of the heart, resulting in an inefficient cardiac pumping function and poor hemodynamics [32, 33, 34, 35, 36]. The aim of CRT is to correct the dyssynchronous activation of the heart through biventricular pacemaker stimulation, thereby improving LV hemodynamics and cardiac efficiency.

Dyssynchronous activation of the heart is a relatively common problem in heart failure patients and can be divided into three types: atrioventricular dyssynchrony, interventricular dyssynchrony (dyssynchrony between the left and the right ventricle), and (intra-) LV dyssynchrony (dyssynchrony within the left ventricle).

Atrioventricular Dyssynchrony

Atrioventricular (AV) dyssynchrony results from a prolonged AV conduction time. As a consequence, the diastolic filling period, in particular the early passive diastolic filling time, is reduced leading to suboptimal ventricular filling. This negatively affects ventricular performance, particularly in patients with already impaired LV function. In addition, a late diastolic mitral regurgitation may occur.

By definition, CRT reduces the AV conduction interval (in patients with intact atrioventricular conduction), because the ventricles have to be preexcited in order to achieve biventricular stimulation. The reduction of the AV interval by CRT improves diastolic filling time, which has proved to be beneficial in patients undergoing CRT [37].

Interventricular Dyssynchrony

In normal hearts, left-and-right ventricular contractions occur almost simultaneously. However, heart failure patients frequently exhibit interventricular dyssynchrony, which is usually the result of the delayed activation of the left ventricle. Early activation of the right ventricle may push the interventricular septum into the left ventricle resulting in a dyssynchrony within the left ventricle (LV dyssynchrony). It has been shown that CRT is able to reduce interventricular dyssynchrony, and early studies have used the level of interventricular dyssynchrony to predict response to CRT [7, 21, 38]. More recent studies, however, have demonstrated that the extent of interventricular dyssynchrony was not that different between responders and nonresponders to CRT and may therefore not optimally predict response to CRT [8, 20].

Left Ventricular Dyssynchrony

A substantial number of heart failure patients demonstrates dyssynchronous activation within the left ventricle, referred to as LV dyssynchrony [39]. Studies have indicated that LV dyssynchrony can heavily affect LV function and pumping efficiency, and it has recently been shown to be an important predictor of poor outcome [34, 35, 36, 40]. The abnormal activation of the left ventricle in LV dyssynchrony results in a stretch of the late-activated LV segments (usually the [postero-] lateral LV wall) during activation of the early activated segments (usually the interventricular septum) and vice versa, resulting in substantial blood volume shifts between early and late activated LV segments, rather than the ejection of blood into the aorta [34,35,36]. Several studies have demonstrated that CRT reduces LV dyssynchrony resulting in an improvement in LV hemodynamics. For example Bax et al. evaluated 25 patients undergoing CRT and reported an acute improvement in LV ejection fraction, associated with an immediate reduction in LV dyssynchrony (from 97 $\pm$ 35 ms to 28 $\pm$ 21 ms, $p < 0.05$) [14]. Subsequent studies demonstrated that patients with extensive baseline LV dyssynchrony had a high likelihood of response to CRT, whereas patients without LV dyssynchrony did not respond [8, 9, 15, 16]. Moreover, all other parameters, including interventricular dyssynchrony, were unable to predict response to CRT [8,15,20]. Consequently, the presence of LV dyssynchrony and its subsequent reduction after CRT is believed to be the key mechanism of benefit.

Detection of LV Dyssynchrony to Predict Response to CRT

Traditionally, a widened QRS complex on the surface electrocardiogram (ECG) has been used as a marker of LV dyssynchrony [1, 2, 3, 4, 5, 6]. However, the QRS duration proved to be a poor predictor of response to CRT [39, 41, 42, 43]. For example, Molhoek et al. observed in 61 patients that QRS duration was not different between responders (179 $\pm$ 30 ms) and nonresponders (171 $\pm$ 32 ms) to CRT [44]. This was explained recently by the observation that the QRS duration is an accurate reflection of interventricular dyssynchrony, but it does not reliably represent LV dyssynchrony [39,43]. In particular, 30–40% of the heart failure patients with a wide QRS complex do not have LV dyssynchrony [39] (Fig. 11.1). In addition, 20–50% of patients with a narrow QRS complex (who are currently not eligible for CRT) appeared to have substantial LV dyssynchrony, suggesting that CRT may also be beneficial in a subset of heart failure patients with a narrow QRS complex [39,41].

Since the observation that QRS duration is a poor marker of LV dyssynchrony, several cardiac imaging techniques have been tested for their ability to detect and quantify LV dyssynchrony to identify those patients that have a high likelihood of response to CRT. Among these different techniques, echocardiography proved particularly well suited for detection of LV dyssynchrony in the clinical setting.

The most important echocardiographic techniques to detect LV dyssynchrony in CRT patients will be discussed below, ranging from simple M-mode echocardiography to more sophisticated echocardiographic techniques, such as tissue Doppler imaging (TDI), strain rate imaging, and three-dimensional (3D) echocardiography.

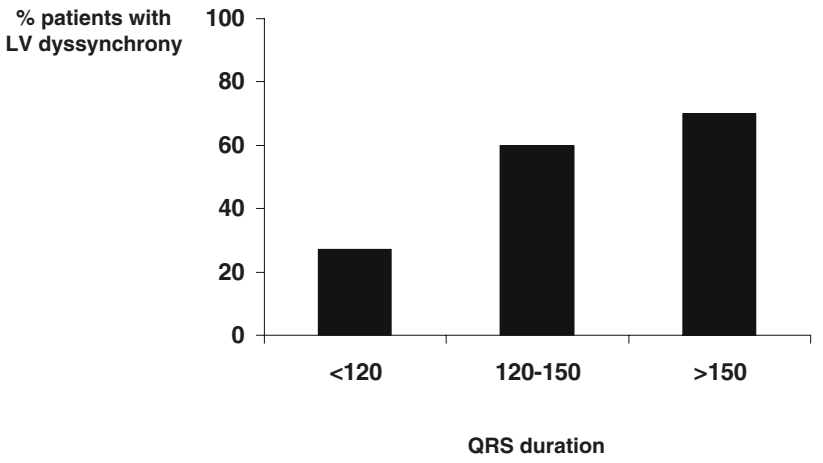


Fig. 11.1 Prevalence of substantial LV dyssynchrony in heart failure patients (left ventricular ejection fraction <35%, NYHA class III–IV) in relation to the QRS duration. (Adapted from Bleeker GB, Schalij MJ, Molhoek SG, et al. Relationship between QRS duration and left ventricular dyssynchrony in patients with end-stage heart failure. J Cardiovasc Electrophysiol 2004:15:544–549).

M-mode Echocardiography

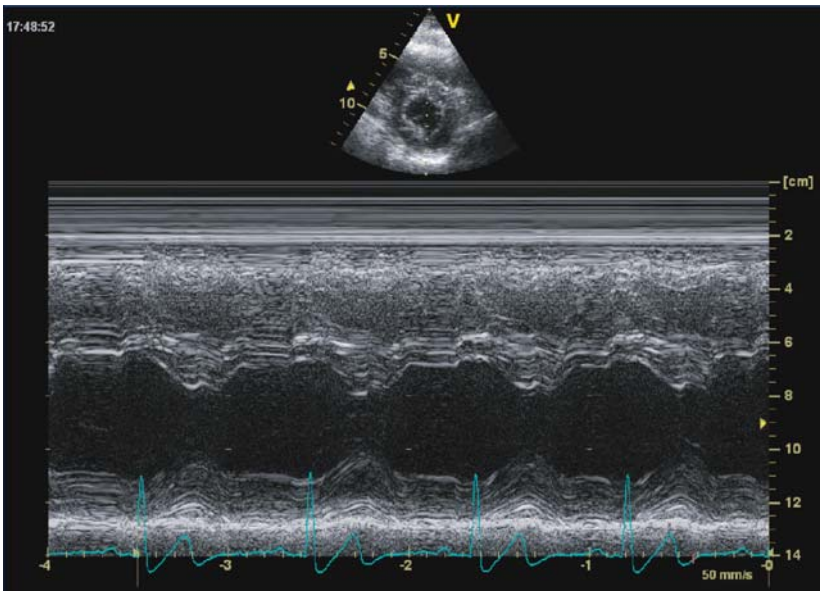
A relatively simple and elegant echocardiographic technique for the detection of LV dyssynchrony has been developed by Pitzalis et al., who used M-mode echocardiography to measure the delay between the systolic excursion of the (antero-) septum and the posterior wall on the parasternal short-axis view, the so-called septal to posterior wall motion delay (SPWMD) [10, 11] (Fig. 11.2A). In an initial study, including 20 patients, responders to CRT had a significantly larger SPWMD compared with nonresponders. Using a cutoff value of 130 ms, SPWMD yielded an accuracy of 85% (sensitivity 100%, specificity 63%) to predict response to CRT [10]. In a subsequent study, the same authors evaluated another 60 patients and demonstrated that the cutoff value of 130 ms was a strong predictor of long-term outcome after CRT [11].

Recent data from Marcus et al., however, revealed less favorable results. The SPWMD measurement was applied retrospectively in a large cohort (n = 79 patients, 72% ischemic cardiomyopathy) of heart failure patients who were included in the CONTAK-CD trial [12]. The authors reported difficulties in interpretation of M-mode recordings in more than 50% of patients, mainly due to the absence of a clear definition of the systolic deflection of the septal and/or posterior walls (Fig. 11.2B). Similar results were reported by de Sutter et al., who evaluated 138 patients with heart failure, showing failure to assess the SPWMD in 56% of patients [45]. In addition, the predictive value (sensitivity 24%, specificity 66%) for response to CRT was poor [12].

Tissue Doppler Imaging

One of the most widely used techniques for the assessment of LV dyssynchrony in the selection of CRT patients is tissue Doppler imaging (TDI) [13, 14, 15, 16, 17, 18, 19, 20, 21].

(A)



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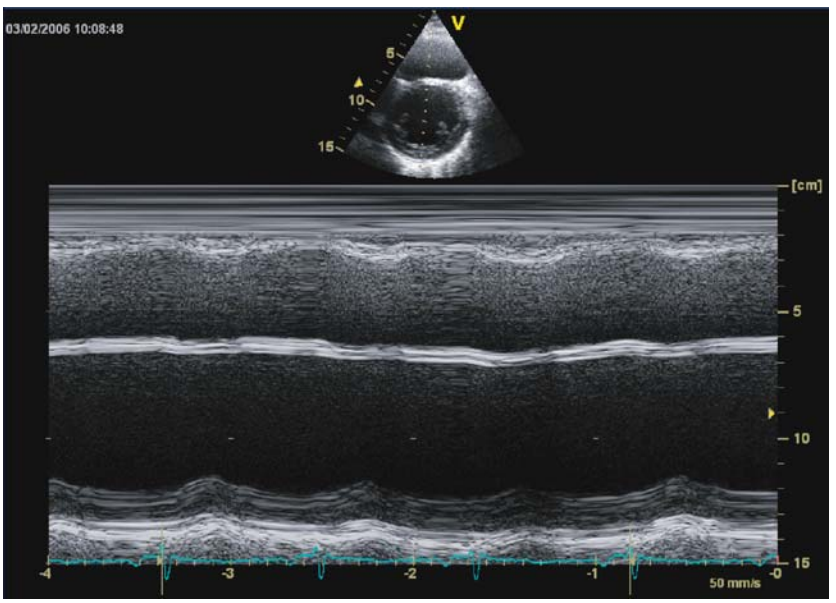


Fig. 11.2 (**A**) Example of the measurement of the septal to posterior wall motion delay using M-mode echocardiography in a normal individual without LV dyssynchrony. A parasternal short-axis view was selected at the level of the papillary muscles. In this view, the M-mode recording was obtained through the septum and posterior LV wall. LV dyssynchrony is calculated by measuring the shortest interval between the maximal posterior displacement of the septum and the maximum displacement of the LV posterior wall. Arrows indicate maximal systolic displacement. (**B**) Example of a patient in whom assessment of left ventricular dyssynchrony using M-mode echocardiography was not possible due to akinesia of the anteroseptal wall.

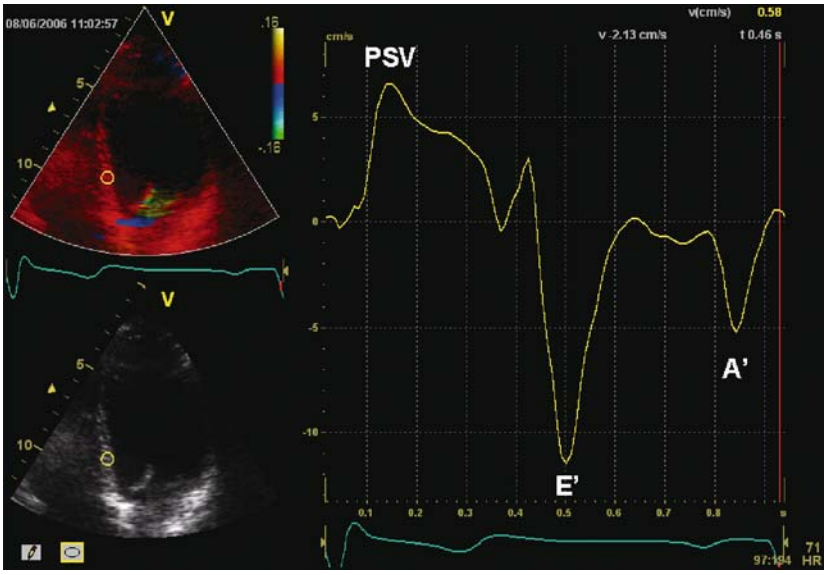


Fig. 11.3 Pulsed-wave tissue Doppler imaging in the apical four-chamber view in a normal individual. The pulsed-wave sample is placed on-line in the region of interest (basal part of the interventricular septum) and the myocardial velocity curve is derived. (*PSV*, peak systolic velocity; *E'* and *A'* represent diastolic parameters).

TDI is a relatively recent application of the Doppler principle and can be used to measure both the velocity and the direction of the velocity of different myocardial segments throughout the cardiac cycle from so-called myocardial velocity curves.

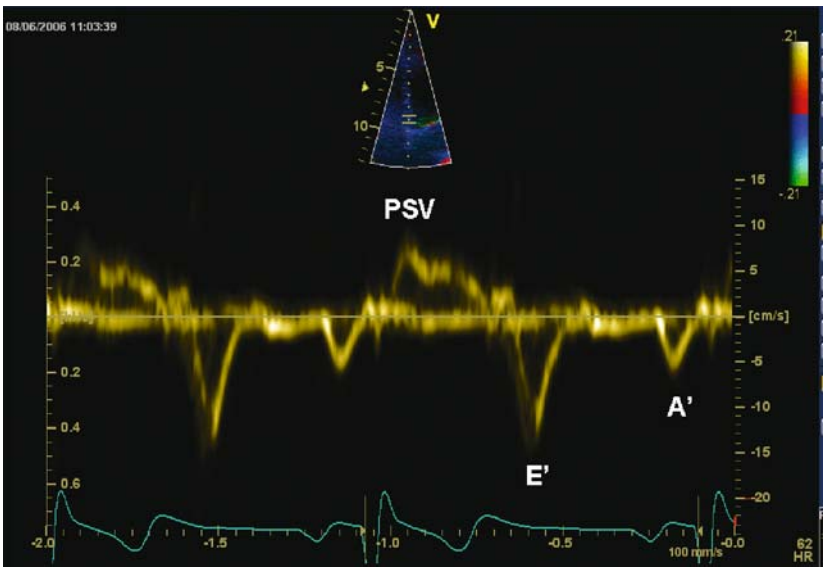


Fig. 11.4 Color-coded tissue Doppler imaging in the apical four-chamber view of a normal individual. The sample volume can be placed off-line in the previously recorded color-coded TDI image. The myocardial velocity curve is derived from a sample placed in the basal part of the interventricular septum. (*PSV*, peak systolic velocity; *E'* and *A'* represent diastolic parameters).

The myocardial velocity curves can be recorded either on-line from pulsed-wave TDI or reconstructed off-line from two-dimensional (2D) color-coded TDI images (Figs. 11.3 and 11.4).

TDI can be used to detect and quantify LV dyssynchrony by comparing the difference in timing of systolic velocities among two or more different LV segments. The most evaluated approach is to measure the difference in time (from the beginning of the QRS complex) to the peak systolic velocity of a particular myocardial segment; comparison of two or more different segments indicates the extent of LV dyssynchrony.

Color-Coded TDI

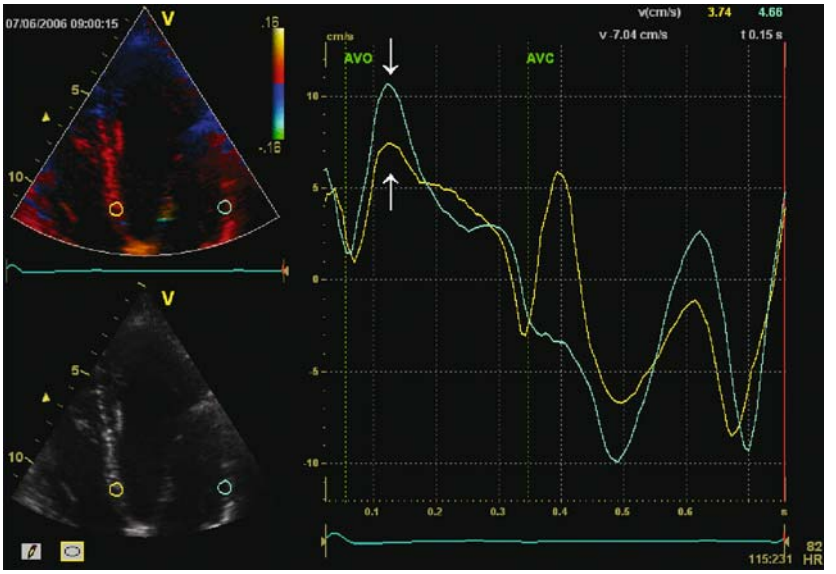
Color-coded TDI allows the off-line analysis of myocardial velocity curves. This offers a distinct advantage over pulsed-wave TDI, as different regions of interest can be selected off-line from the 2D color-coded TDI images. In addition, color-coded TDI offers the possibility of comparing different myocardial segments in one view (i.e., during one heartbeat), whereas with pulsed-wave TDI the region of interest has to be selected on-line and simultaneous comparison of multiple LV segments is not possible making the analysis sensitive to changes in cardiac frequency and more time consuming.

Most studies using color-coded TDI have compared the time from beginning of the QRS complex to the *peak systolic velocity* between different LV segments. To ensure highly interpretable and reproducible TDI curves with minimal artefacts, two issues are of key importance. The frame rate of the TDI recording should be as high as possible to minimize artifacts. The highest frame rate can be achieved by recording the smallest possible TDI views of the left ventricle (i.e., exclusion of the right ventricle and atria). In addition, only peak systolic velocities within the ejection period should be measured. This can be achieved by measuring the timing of the opening and closure of the aortic valve. The aortic valve opening and closure times can be measured from the routine pulsed-wave Doppler signals in the LV outflow tract and be superimposed on the myocardial velocity curves in order to define the ejection period.

The most frequently described model for the quantification of LV dyssynchrony using color-coded TDI is the two-segment approach, which measures the time delay in peak systolic velocity between the basal septum and lateral wall in the four-chamber TDI view [8, 13, 14] (Fig. 11.5). Using this technique, Bax et al. demonstrated that CRT resulted in an acute reduction in LV dyssynchrony [8, 13, 14]. In addition, this technique was highly predictive for response to CRT. In 85 patients undergoing CRT, preimplant LV dyssynchrony was the only baseline parameter that was different between responders and nonresponders to CRT (87 ± 49 ms vs. 35 ± 20 ms, $p < 0.01$). Using a cutoff value of 65 ms for LV dyssynchrony, a sensitivity and specificity of 80% to predict clinical response and 92% to predict LV reverse remodeling at 6 months follow-up were obtained. In addition, patients with LV dyssynchrony $\geq$65 ms had a superior long-term survival at 1-year follow-up (6% event rate) compared with a 50% event rate in patients with dyssynchrony <65 ms [8].

Notobartolo et al. used a six LV-segment model to quantify LV dyssynchrony in a group of 49 patients undergoing CRT [9]. Using the apical four-chamber, two-chamber and long-axis views, the time to peak systolic

(A)



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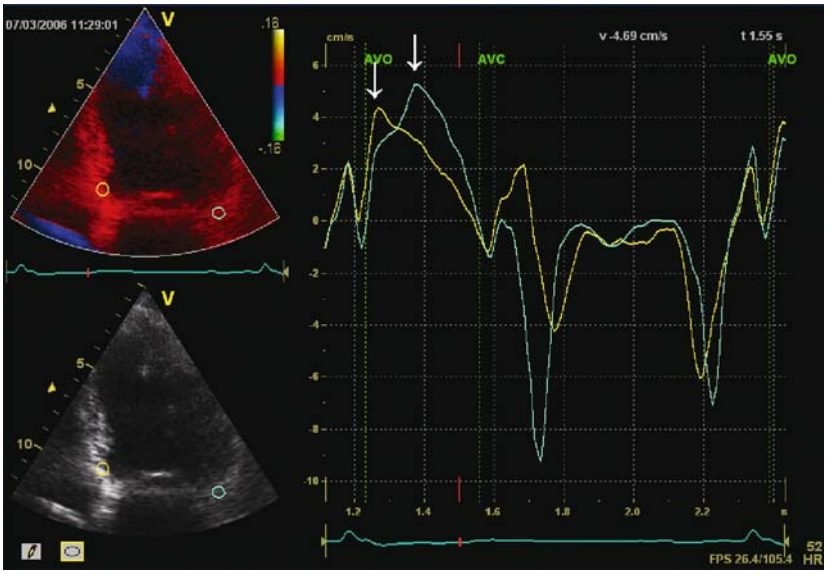

Fig. 11.5 (**A**) Color-coded tissue Doppler image of a normal individual without LV dyssynchrony. The sample volumes are placed in the basal part of the septum and lateral wall, and tracings are derived (*yellow curve*, septum; *green curve*, lateral wall; *arrows* indicate peak systolic velocities). (**B**) Color-coded tissue Doppler image of a patient with severe heart failure and substantial LV dyssynchrony (*yellow curve*, septum; *green curve*, lateral wall; *arrows* indicate peak systolic velocity).

velocities were measured in the six basal LV segments (septal, lateral, inferior, anterior, anteroseptal, and posterior). Calculating the difference between the longest and shortest time to peak systolic velocity across the six regions yielded the peak systolic difference. Again, the TDI-derived parameter of LV dyssynchrony was the only baseline parameter that predicted (echocardiographic) response to CRT. A predefined cutoff value of 110 ms in peak systolic difference had a sensitivity of 97% with a specificity of 55% to predict LV reverse remodeling at 3 months follow-up [9].

Yu et al. have published extensively on the use of color-coded TDI to predict response to CRT. The authors developed a 12-segment model of LV dyssynchrony by measuring the peak systolic velocities from six basal and six mid-LV segments on the three apical views. The dyssynchrony index was calculated as the standard deviation of the time to peak systolic velocity from all 12 segments [7,15,16,17]. Preliminary data showed that the dyssynchrony index improved significantly in 25 patients undergoing CRT (from 37.7 $\pm$ 10.9 to 29.3 $\pm$ 8.3, $p < 0.05$), and it was concluded that improvement of LV dyssynchrony seemed to be the predominant mechanism of response to CRT [7]. In subsequent studies, the dyssynchrony index proved highly predictive of response [15]. Sophisticated analysis revealed that the optimal cutoff value of 31.4 ms yielded a sensitivity of 96% with a specificity of 78% to predict LV reverse remodeling at 3 months follow-up [16].

Pulsed-Wave TDI

Pulsed-wave TDI can be used for the on-line recording of myocardial velocity curves by placing the pulsed-wave Doppler sample in the region of interest. This approach does not allow simultaneous calculations of multiple segments in one view, and changes in cardiac frequency should be avoided in different recordings in order to obtain an accurate comparison of the timing of systolic events among different LV segments.

Studies using pulsed-wave TDI usually calculate the time from beginning of the QRS complex to the *onset of systolic velocity*, because the peak systolic velocity is often less clearly defined compared with color-coded TDI (Figs. 11.3 and 11.4).

Ansalone et al. used a six-segment model in 21 nonischemic heart failure patients and demonstrated that CRT significantly reduced desynchronized contractions in at least one third of the LV basal segments [19].

Bordachar et al. studied 41 patients by measuring both the largest delay in peak and the onset of systolic velocity and the standard deviation of peak to systolic velocity in six basal and six mid-LV segments from the apical views. The authors concluded that the improvement in cardiac output and the reduction in mitral regurgitation were significantly correlated with the degree of preimplantation LV dyssynchrony. In addition, the authors conclude that the degree in interventricular dyssynchrony was not related to hemodynamic improvements following CRT [20]. The work by Penicka et al. defined LV dyssynchrony as the maximal electromechanical delay among the three basal LV segments (septal, lateral, and posterior wall) and interventricular dyssynchrony as the maximal delay between the basal right ventricular segment and the three LV sites [22]. The authors suggested that summation of the LV and interventricular dyssynchrony had a high predictive

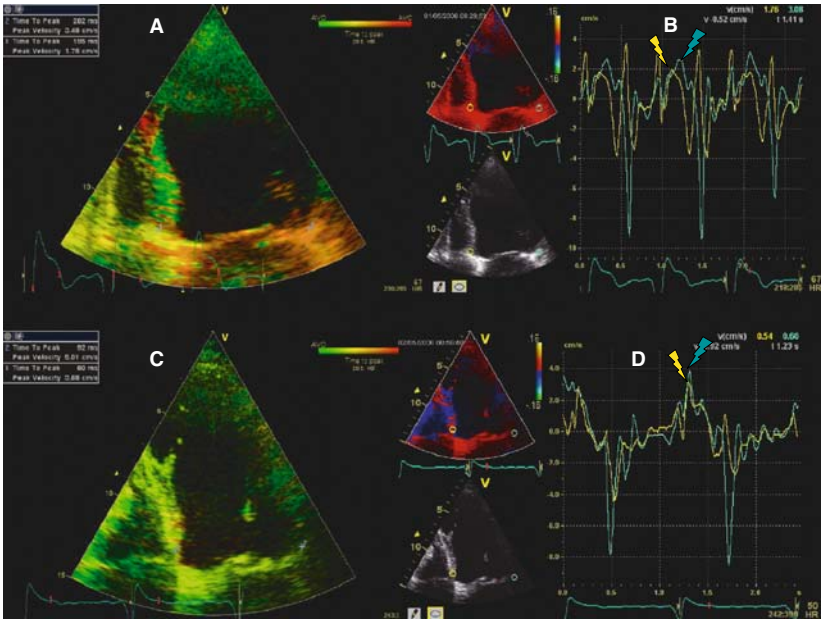

Fig. 11.6 Tissue synchronization imaging (TSI) of a patient with ischemic cardiomyopathy in the apical four-chamber view. The colors represent time to peak systolic velocity. Green corresponds with early mechanical activation; yellow/orange indicates a delayed peak systolic velocity. Panel *A* shows delayed activation of the lateral wall before implantation of CRT. Sample volumes were placed in the basal parts of the septum and lateral wall. TSI automatically calculates the time to peak systolic velocity of both regions: 195 and 282 ms, respectively, yielding an intraventricular dyssynchrony of 87 ms. Panel *B* illustrates the manual calculation of the septal to lateral delay (90 ms) by analyzing the myocardial velocity curves of the basal septal and lateral walls. Panel *C* shows the TSI analysis after CRT implantation. The green color indicates absence of significant intraventricular asynchrony. Panel *D* shows the myocardial velocity curves after implantation, confirming the TSI findings.

value for CRT response, which was defined as a relative increase in LV ejection fraction by 25%. Using a cutoff value of 102 ms, an accuracy of 88% to predict response was reported [21].

Tissue Synchronization Imaging

Tissue synchronization imaging (TSI) is a further development of TDI, which is able to automatically calculate the to time peak systolic velocities and portrays regional dyssynchrony as a color-map on the 2D TSI images [22, 23, 24] (Fig. 11.6). This allows the immediate qualitative assessment of the early activated segments (displayed in green) and identification of the latest activated segments (displayed in red), without the need for analysis of the TDI curves. In addition, quantitative assessment of regional delay is still possible (through construction of myocardial velocity curves, similar to color-coded TDI).

Yu et al. studied this qualitative approach in 56 heart failure patients and reported a sensitivity of 82% with a specificity of 87% to predict response to CRT [23].

Strain (Rate) Imaging

One potentially interesting derivation from color-coded TDI is strain (and strain rate) imaging. This technique is able to calculate the cumulative amount of myocardial deformation (strain) throughout the cardiac cycle, whereas TDI only examines the velocity of the myocardium. Accordingly, a potential advantage of strain (rate) imaging over TDI is to differentiate between active and passive myocardial motion, which is not possible with TDI. Using strain (rate) imaging, the extent of LV dyssynchrony can be quantified by measuring the time delays in time to peak systolic strain among different LV segments, comparable with TDI (Fig. 11.7) [25,26,27,28,29]. Breithardt et al. used strain rate imaging to study the regional deformation patterns in patients undergoing CRT and measured the delay in peak strain between the septum and lateral wall on the apical four-chamber view (assessing longitudinal strain) [26]. The authors showed that CRT acutely reversed the septal-lateral difference in midsegmental peak strain from -46 ± 94 ms to 17 ± 92 ms ($p < 0.05$). The frequently observed phenomenon of early systolic wall lengthening was virtually eliminated by CRT, indicating more energy-efficient contraction, less energy wasting, and more homogeneous wall stress distribution [25].
The first study to evaluate the predictive value of strain rate imaging for response to CRT was published by Yu et al., who performed a head-to-head comparison between TDI and strain rate imaging for the predictive value of response to CRT. The results revealed the superiority of TDI over strain rate imaging for the prediction of LV reverse remodeling [16]. The main shortcomings of strain rate imaging were the limited reproducibility and the relatively high angle dependency.

(A)

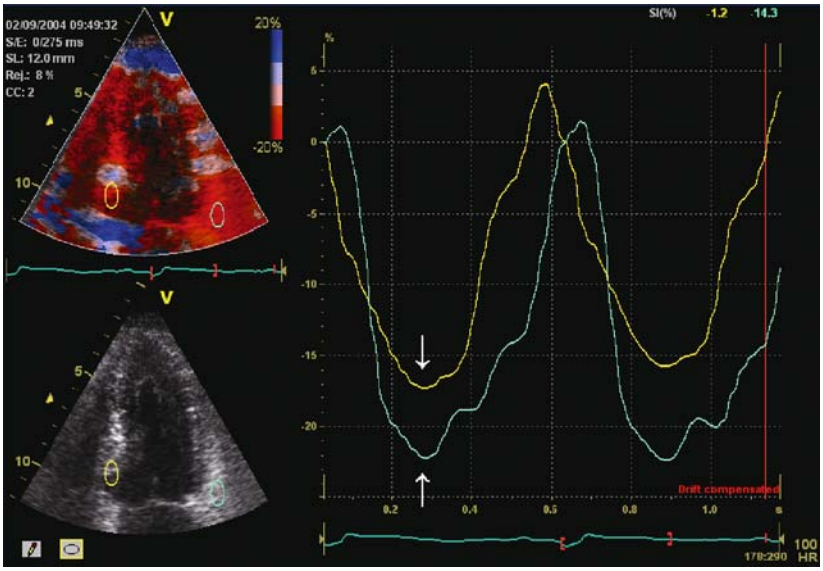

Fig. 11.7 (Continued)

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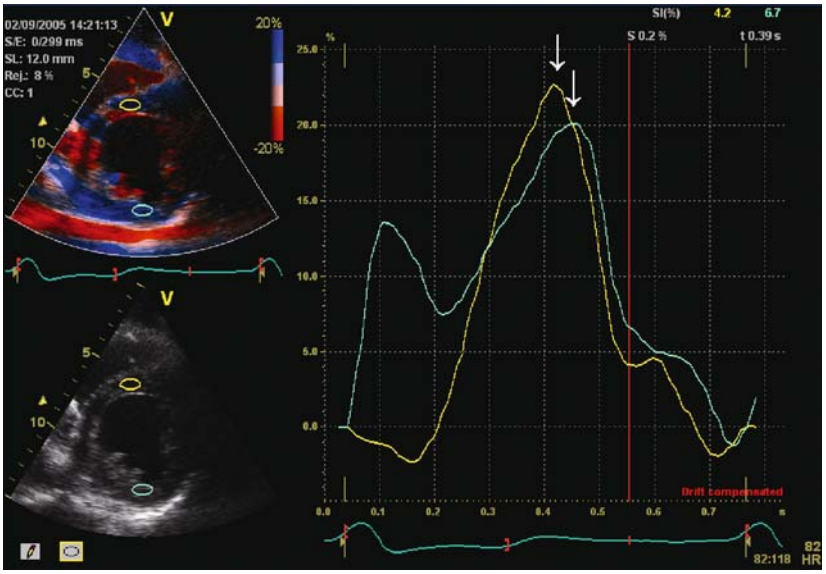


Fig. 11.7 (**A**) Tissue Doppler–derived longitudinal strain imaging in the apical four-chamber view. *Arrows* indicate peak strain of the interventricular septum (*yellow curve*) and the lateral wall (*green curve*). (**B**) Tissue Doppler–derived radial strain imaging at mid–left ventricular short-axis level. Arrows indicate peak strain of the anteroseptum (*yellow curve*) and the posterior wall (*green curve*).

More recently, Dohi et al. published more promising results using strain imaging [26]. In contrast with the measurement of strain in the longitudinal direction (as performed in the earlier studies), the authors measured strain in the radial direction and demonstrated that a ≥130 ms difference in septal versus posterior wall peak strain was strongly predictive for immediate improv ement in stroke volume after CRT (sensitivity 95%, specificity 88%) [26].

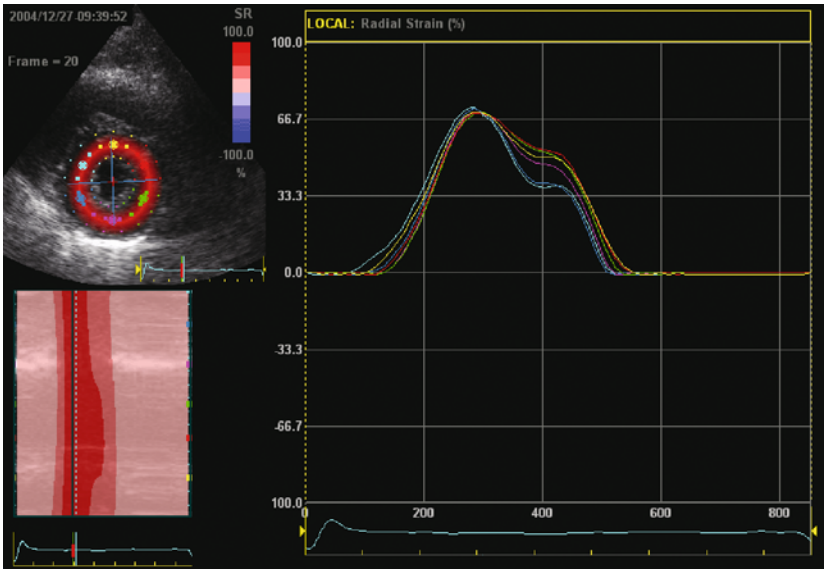
A promising new echocardiographic method was introduced recently that allows calculation of strain from regular 2D echocardiography. This novel approach (called speckle tracking) has the advantage over strain (rate) imaging of being angle-independent (Fig. 11.8). Suffoletto et al. applied this approach to 64 heart failure patients and showed that dyssynchrony in the radial direction of ≥130 ms predicted an immediate increase in stroke volume with a sensitivity of 91% and a specificity of 75% [29].

Three-Dimensional Echocardiography

The advantage of real-time 3D (RT3DE) echocardiography for the assessment of LV dyssynchrony over 2D echo techniques is that it can easily provide information about the activation of all LV segments in one single heartbeat, whereas analysis of a high number of segments from 2D techniques is often time-consuming and requires the recording of views [30, 31].

Recently, Kapetanakis et al. tested the ability of RT3DE to quantify LV dyssynchrony (16-segment model) in 174 unselected patients referred for

(A)



(B)

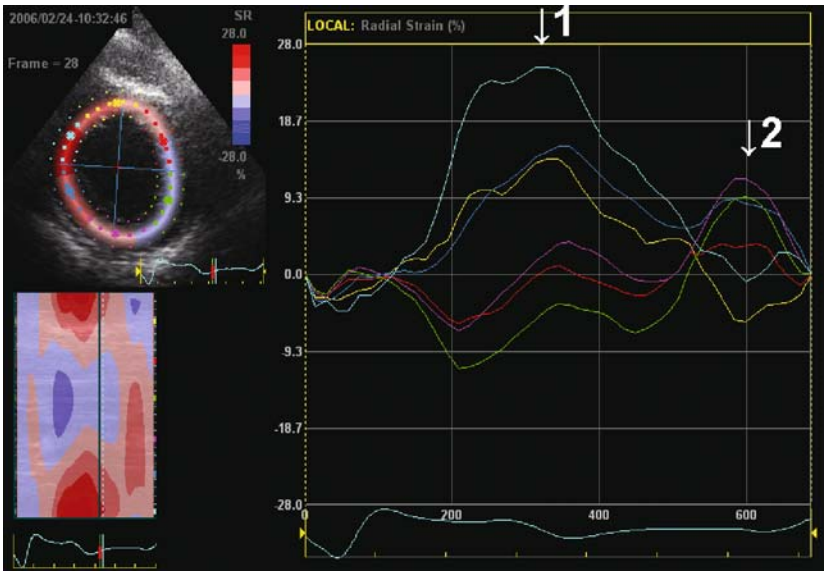


Fig. 11.8 (**A**) Example of radial time-strain curves from speckle tracking in a normal individual. Radial strain is calculated from multiple circumferential points over the cardiac cycle. The curves are color-coded in accordance with the segments on the short-axis view. The time to peak strain occurs simultaneously in all six segments (arrow). (**B**) Example of radial time-strain curves from speckle tracking in a heart failure patient with LV dyssynchrony. The septal (*light blue*) and anteroseptal (*yellow*) curves reach peak strain early in systole (*arrow 1*), whereas the lateral (*purple*) and posterior (*green*) curves reach peak strain late in systole (*arrow 2*).

routine echocardiography LV dyssynchrony was calculated as the standard deviation of times to minimal regional volume for each of the 16 segments, referred to as the systolic dyssynchrony index. The authors concluded that RT3DE is highly reproducible and able to quantify global LV dyssynchrony. In addition, preliminary results in 26 patients undergoing CRT showed that the baseline systolic dyssynchrony index was significantly different between responders and nonresponders [31]. To date, no study has provided an optimal cutoff value for the systolic dyssynchrony index assessed by RT3DE to predict response to CRT.

Besides its use for the detection and quantification of LV dyssynchrony, RT3DE can potentially play an important role in identifying the most suitable location for the LV pacing lead. Recent studies have indicated that the LV pacing lead should ideally be positioned in the area of latest LV activation [22, 29]. Because of its ability to quantify regional LV dyssynchrony in a large number of LV segments, in a 3D fashion, RT3DE may prove to be an ideal tool to guide LV lead placement.

Another method to obtain 3D information on LV dyssynchrony is now available in the form of triplane TSI (Fig. 11.9). This technique allows simultaneous recording and analysis of peak systolic velocity in the four-, two-, and three-chamber views in one single heartbeat. Off-line analysis

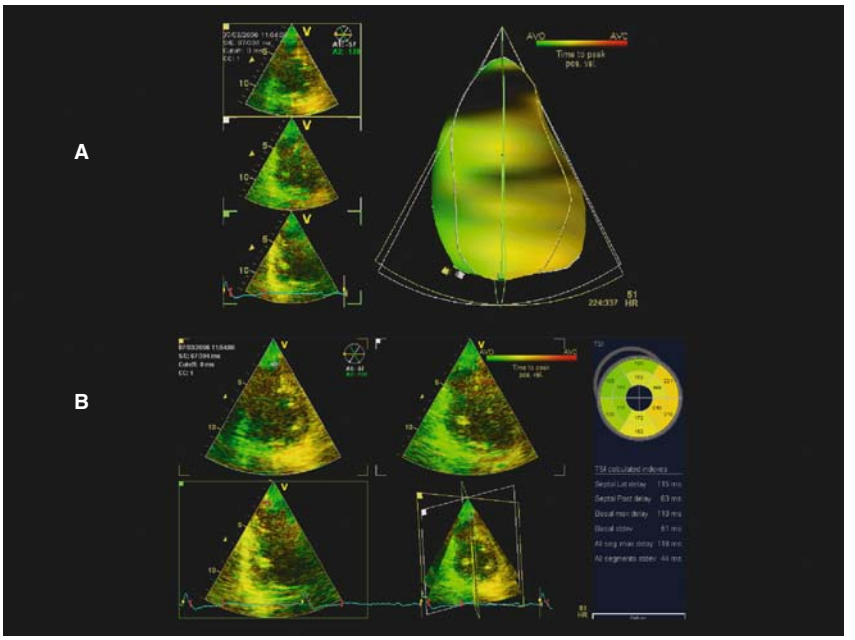


Fig. 11.9 Triplane tissue synchronization imaging (TSI) allows automatic analysis of time to peak systolic velocities in various LV segments during the same heartbeat. Panel *A* illustrates TSI combined with surface mapping. The 3D reconstructed image of the left ventricle shows a delayed activation of the anterolateral wall represented by the yellow color. Panel *B* shows that by placing markers in 12 left ventricular segments, TSI automatically generates the time to peak systolic velocity of these segments. The results are presented in a polar plot confirming delayed activation of the anterolateral segments. Septal to lateral delay and standard deviation of the six basal or all 12 left ventricular segments are calculated automatically.

with a dedicated software program (Echopac, General Electric-Vingmed, Milwaukee, Wis., USA) allows parametric imaging with a 3D color-coded volume based on the triplane data set allowing a visual representation of the area of latest mechanical activation. The software program also automatically calculates the time to peak systolic velocity in 12 segments of the left ventricle and summarizes these quantitative data in a polar plot. Various indices of dyssynchrony such as septal to lateral delay and standard deviations are calculated automatically. Future studies are needed to show the value of this technique for assessment of the area of latest LV activation.

Other Factors Related to Response

Although a large number of studies has demonstrated the value of substantial LV dyssynchrony to predict response to CRT [8,9,15,16], other factors may also influence the response to CRT. In particular, the location of the LV pacing lead and the presence of (posterolateral) scar tissue (in patients with ischemic cardiomyopathy) may be important factors influencing response to CRT.

Currently, the LV pacing lead is preferably positioned in the lateral or the posterolateral LV region. Several studies have indeed indicated that positioning the LV lead in this region resulted in the largest improvement in hemodynamics. For example, Rossillo et al. retrospectively evaluated 233 patients showing who underwent successful CRT implantation and noted that patients with an anterior or anterolateral lead position ($n = 66$) did not improve in LV ejection fraction, whereas patients with a lateral or posterolateral lead position showed a significant increase in LV ejection fraction (from 19% to 27%, $p < 0.01$) [46].

More recent studies emphasized the importance of positioning the LV lead in the area of latest LV activation, which is usually the posterior/lateral region. Murphy et al. [22] used TSI to study the effects of LV lead positioning in relation to the area of latest LV activation. The authors demonstrated a larger reduction in end-systolic volume (indicating reverse LV remodeling) in patients with the LV lead positioned in the area of latest activation (23% reduction in LV end-systolic volume) compared with patients with the lead positioned in an adjacent (15% reduction) or a remote (9% increase) region. Similar results were reported by Suffoletto et al. showing that LV pacing in the area of latest activation increased LV ejection fraction by $10 \pm 5\%$ compared with $6 \pm 5\%$ ($p < 0.05$) when a remote area was paced [29].

LV lead placement in the area of latest LV activation will require a patient-tailored approach, and 3D TSI or RT3DE may be the preferred techniques to provide this information.

A second factor that influences the response to CRT and may have potential implications for patient selection is the presence and localization of myocardial scar tissue; this is an issue only in patients with ischemic cardiomyopathy and previous infarction. Bleeker et al. recently addressed this issue in an elegant study using contrast-enhanced magnetic resonance imaging (MRI) to assess scar tissue [47]. Contrast-enhanced MRI is an excellent technique for this purpose, because the high spatial resolution permits precise delineation of scar tissue and even permits distinction between subendocardial

and transmural scar tissue. The authors first noted that patients with transmural scar tissue in the posterolateral LV segments had a low response rate compared with patients without posterolateral scar tissue (14% vs. 81%, $p < 0.05$). Also, TDI analysis showed that CRT was not able to reduce LV dyssynchrony in the presence of posterolateral scar tissue (84 ± 46 ms versus 78 ± 41 ms, p = NS). Patients without posterolateral scar tissue and severe baseline dyssynchrony ($\geq$65 ms) showed an excellent response rate of 95% compared with patients with a posterolateral scar and/or absent preimplant LV dyssynchrony [47]. Besides the location of scar tissue, the total extent of scar tissue is also important. Hummel et al. recently demonstrated that the extent of viability (the counterpart of scar tissue) was predictive for both acute and long-term response to CRT [48]. It is thus anticipated that integrated assessment of LV dyssynchrony, the site of latest activation, the extent of viability, and the location of scar tissue will further optimize selection of patients who may respond favorably to CRT.

Conclusion

Despite the impressive results of CRT in large, randomized trials, 30–40% of patients fail to improve after CRT when the established selection criteria are applied. In the search for better selection criteria, it was consistently shown that LV dyssynchrony (and subsequent resynchronization after CRT) is mandatory for response to CRT.

Various echocardiographic approaches have been introduced for the detection of LV dyssynchrony. At present, most experience has been obtained with color-coded TDI; various groups have independently reported high predictive accuracy for response to CRT. The precise cutoff criteria for the extent of LV dyssynchrony are not yet established, and the exact number of segments to be included in the analysis is also not clear. Some of these issues will be addressed in the PROSPECT trial, and results are expected in 2007 [49].

Besides TDI, strain rate imaging, speckle tracking, and 3D imaging are currently being explored for assessment of LV dyssynchrony; these techniques have different advantages over TDI, and initial results are promising.

Although the relative merits of all these different techniques for prediction of response to CRT remain to be defined, it has become clear that assessment of LV dyssynchrony is of paramount importance in the prediction of response to CRT. It may thus be necessary to extend the current selection criteria for CRT and include the assessment of LV dyssynchrony in the ACC/AHA/ESC guidelines.

Finally, recent data highlighted the importance of other issues for response to CRT. In particular, the assessment of site of latest activation appears mandatory for response to CRT. Various echocardiographic techniques are available (including 3D TSI and RT3DE), but more evidence is needed before recommendations can be made. In addition, assessment of scar tissue in the LV pacing area is important; large areas of scar tissue in the left ventricle appear to reduce benefit of CRT, in particular when transmural scar tissue is located in the posterolateral region. It may thus be considered to include preimplantation assessment of scar tissue by contrast-enhanced MRI.

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12

Role of Echocardiography After Implantation of a Cardiac Resynchronization System

Serge Cazeau, Stéphane Garrigue, Stéphane Laffitte, Philippe Ritter, and S. Serge Barold

Introduction

The role of echocardiography in cardiac resynchronization therapy (CRT) is not limited to the selection of candidates for device implantation or assistance in lead placement during the CRT procedure. After the latter, echocardiography plays a short-term key role in the verification of CRT effectiveness and in the programming of several variables such as the atrioventricular (AV) or the interventricular (V-V) delay. On a long-term basis, echocardiography provides monitoring of evolving cardiac function and, in some cases, the detection of delayed undesirable changes in the synchronization settings possibly requiring a repeat procedure.

Short-term Considerations

Effectiveness of Therapy

Confirming the effectiveness of therapy depends on observing the correction of abnormalities that preceded CRT implantation at the AV, V-V, and intraventricular levels [1].

AV dyssynchrony, which is easier to identify during sinus rhythm, is due to the abnormal timing of the terminal left ventricular (LV) filling phase and the beginning of ventricular systole, a situation often enhanced by prolonged AV conduction during sinus rhythm (Fig. 12.1).

AV dyssynchrony is characterized by an abbreviated diastolic filling period and occasionally accompanied by the summation of the early passive (E-wave) and late active (A-wave) phases of atrial emptying. This abnormality can be normalized in a conventional dual-chamber pacing system by optimizing the AV delay using Doppler echocardiographic imaging in the presence of sinus rhythm [2].

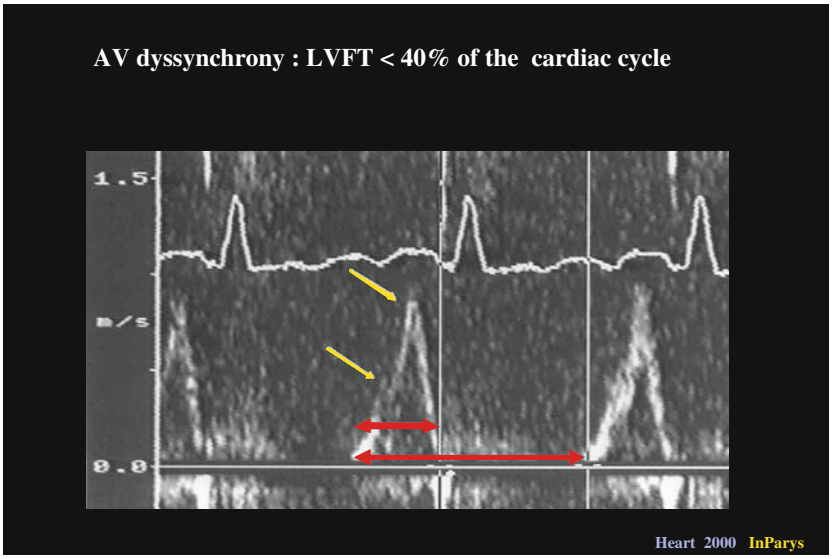

Fig. 12.1 Summation of early passive E-waves and late active A-waves by a double mechanism of prolongation of the PR interval and intraventricular conduction delay. Duration of left ventricular filling <40% of the cardiac cycle at rest (as shown by the shorter *red double-arrow*) always needs to be corrected.

Interventricular dyssynchrony is also evaluated using Doppler imaging. The duration and temporal shifts of right and LV systoles are measured by comparing the duration of the left and right pre-ejection delays between the onset of the QRS and the onset of the pulmonary and aortic ejection flows, respectively. A duration >40 ms is considered abnormal (Fig. 12.2).

A shortening of left and right pre-ejection intervals is generally associated with an overall shortening of systole and a reduction of the interventricular interval.

Intraventricular Dyssynchrony

Intraventricular conduction may be so heterogeneous as to result in the coexistence of systole and diastole in different regions of the same ventricle. The standard electrocardiogram is of no diagnostic value for the detection of this type of mechanical *dyssynchrony*. Intraventricular dyssynchrony can be assessed by various echocardiographic tools. Its presence and its correction is often predictive of CRT efficacy [3,4], though the various indices of dyssynchrony have not yet been compared. As a rule, a difference in the timing of the contraction of different LV segments is associated with significant intraventricular dyssynchrony. In this respect, investigators have proposed cutoff values that are not uniformly standardized, and at this juncture these measurements depend on the techniques used [3, 5]. Dyssynchrony is qualified as "spatial" between the different segments (Fig. 12.3).

Nevertheless, intraventricular dyssynchrony can be viewed in terms of persistent contraction after the end of systole, during the diastole, defining a so-called diastolic contraction. The duration of this diastolic contraction of important LV segments (for instance, the septum and the lateral wall) can be measured (preferably by tissue Doppler imaging that discriminates between active from passive movement) after closure of the aortic valve. It can even be prolonged beyond the opening of the mitral valve in the next cardiac

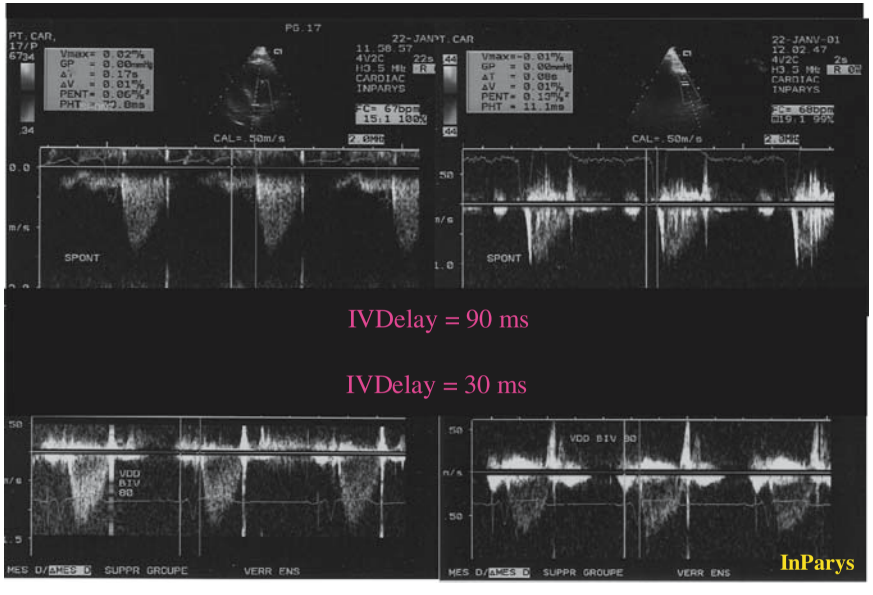

Fig. 12.2 Preoperative interventricular delay of 90 ms corrected after CRT implantation to 30 ms. See text for details.

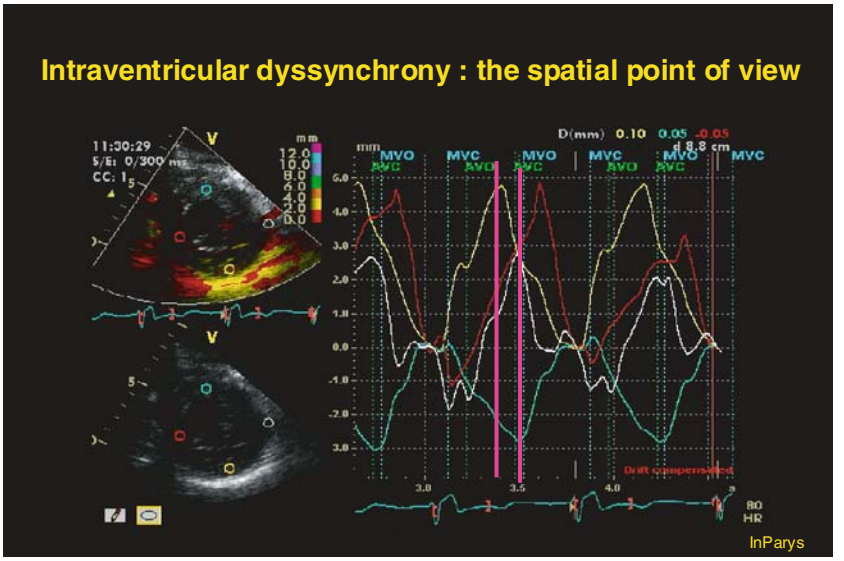

Fig. 12.3 Short-axis view (Doppler tissue imaging): the *pink bars* show the difference of contraction timings of the anterior and the posterior walls providing evidence of spatial intraventricular dyssynchrony.

cycle. If so, it defines positive overlapping with ventricular filling. If not, the measurement of the overlap has a negative sign, meaning that the diastolic contraction respects an isovolumic relaxation at the level of this segment. The dyssynchrony is qualified as "temporal" [6] and is shown in Fig. 12.4.

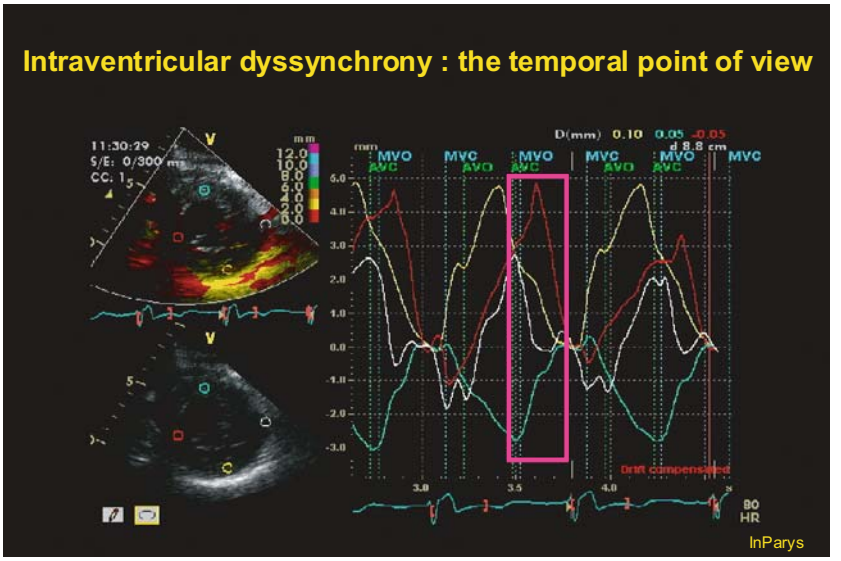

Fig. 12.4 Same view as in Fig. 12.3 with Doppler tissue imaging. The attention is now focused on the persisting diastolic contraction after closure of the aortic valve (*green bar*, AVC) and opening of the mitral valve (*blue bar*, MVO) of all LV segments except the anterior segment.

A homogeneous temporal dyssynchrony identical in all the segments of the LV will not be diagnosed when using only the concept of spatial dyssynchrony (Fig. 12.5).

A heterogeneous temporal dyssynchrony will be associated with some differences between two or more LV segments timings and will create a spatial dyssynchrony.

Programming the Device

Before starting echocardiography, one should check the electrical function of the various leads (thresholds, impedance) and their percentage of stimulation via the Holter memory of the device to verify that it stimulates and is not frequently inhibited by sensed spontaneous beats. A cardiac resynchronization device is not only a pacemaker but also a system that modifies spontaneous ventricular activation.

Atrioventricular Resynchronization and Atrioventricular Delay

The objective of optimal AV delay programming is to lengthen the period of LV filling, measured between the onset of E-waves and end of A-waves and expressed as a percentage of the cardiac cycle.

The aim is to optimize the beginning of the ventricular filling phase. In the presence of abnormal intraventricular conduction, (1) the duration of systole is lengthened, mostly by the prolongation of the left pre-ejection interval, (2) the time devoted to diastole and ventricular filling is shortened, and (3) the E-wave tends to merge with the A-wave in end diastole. Ventricular preexcitation with biventricular stimulation attempts to advance the onset of ejection by shortening the pre-ejection interval and, if possible, the overall duration of systole. This advances the following E-wave and lengthens the duration of ventricular filling.

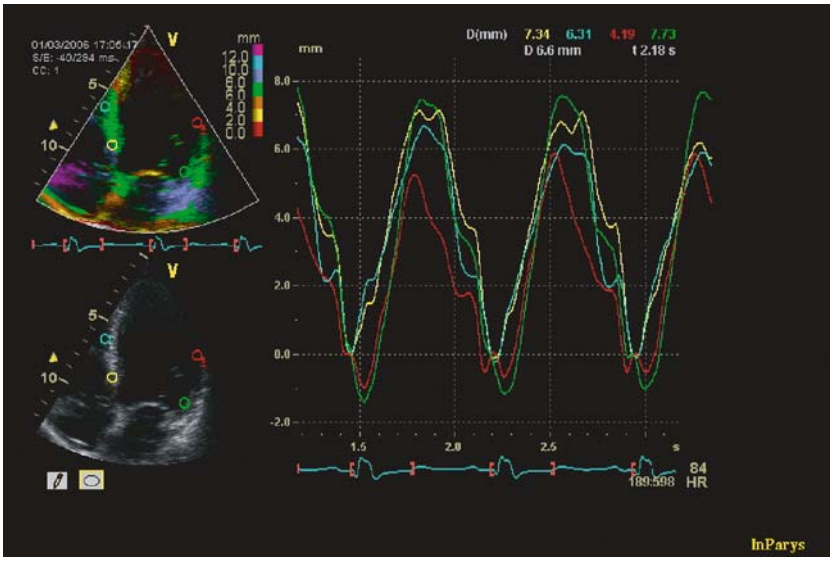

Fig. 12.5 Doppler tissue imaging. Homogeneous temporal intraventricular dyssynchrony with absence of spatial dyssynchrony.

The role of the echocardiography, then, consists in optimizing the end of the filling phase by adapting the AV delay according to Ritter's formula or any other method, with a view to program the shortest delay that allows the longest filling without encroaching on the A-wave by premature closure of the mitral valve. This maneuver is performed during VDD (on sensed waves) pacing, with P wave sensing, and during atrial (DDD (on paced atria)) pacing, in order to correct for electromechanical delays during atrial stimulation.

Ritter's formula uses transmitral inflow Doppler measurements made with two different AV delays. Both AV delays must be applied under the same condition of either atrial sensing or atrial pacing. It is recommended to begin with sensed P-waves, that is, atrial contraction must be spontaneous (not paced), and ventricular contraction must be stimulated. The same measurements are repeated during atrial pacing. The paced AV delay must be longer than the sensed AV delay.

Instructions:

1. Program a long AVD (e.g., 150 ms) and record the transmitral inflow Doppler from the apical view and measure the QA interval from ventricular pacing spike to end of the A-wave of the transmitral Doppler signal (Fig. 12.6).
2. Program a short AV delay (e.g., 50 ms) and record the transmitral inflow Doppler from the apical view and measure the QA interval from ventricular pacing spike to end of the A-wave of the transmitral Doppler signal (Fig. 12.7).
3. Calculate the optimal AV delay.

The difference between the long and short AV delays, minus the difference between the short and long QA, is the excess shortening of the AV delay. This value should be added to the short AV delay to obtain the optimal AV delay for

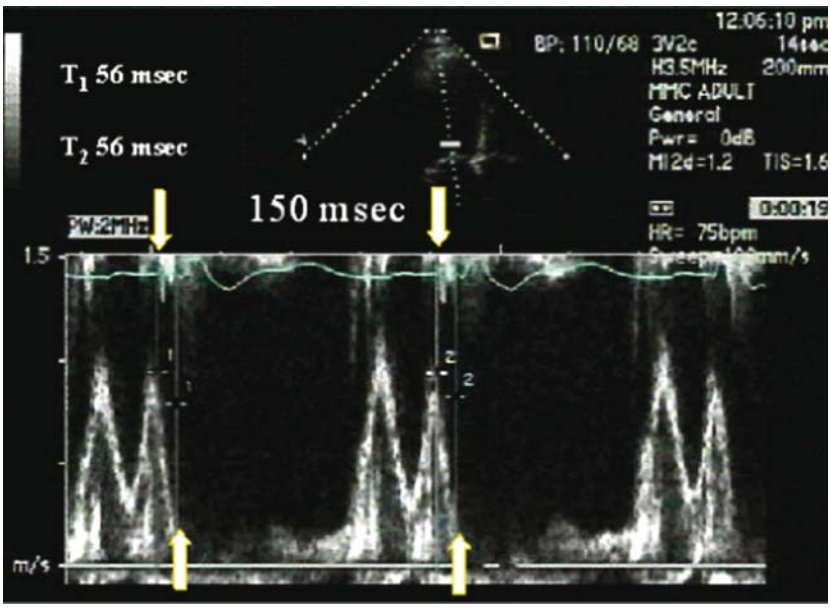

Fig. 12.6 Measurement of the QA interval. In this example, a long AV delay of 150 ms results in a QA interval of 56 ms.

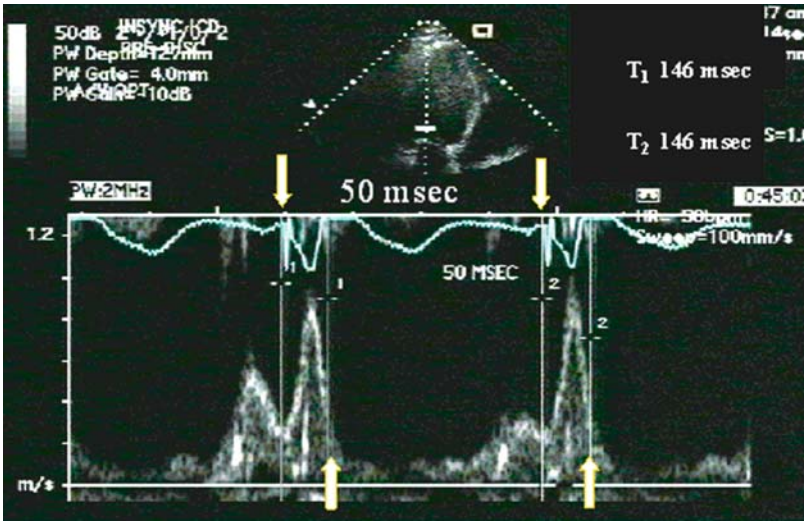

Fig. 12.7 Measurement of the QA interval for the short AV Delay. In this example, a short AV delay of 50 ms results in a QA interval of 146 ms.

ventricular filling. It represents the shortest AV delay that allows the longest filling period without interrupting the end of the A-wave by premature mitral valve closure. In this particular example, the value is [(150 ms – 50 ms) – (146 ms – 56 ms)] = 10 ms. This is the value that is added to the short AV delay (i.e., 50 ms). According to Ritter's formula, the optimal AV delay is 60 ms.

However, when AV conduction is partially preserved, this standard approach might not be the best, because a prolongation of the AV delay might, paradoxically, lengthen the period of ventricular filling. Indeed, lengthening of the AV delay can result in fusion between activation originating from the stimulating leads and activation via the Purkinje system. This causes shortening of systole by the earlier activation of a greater number of sites and, therefore, a considerable increase in the time occupied by diastole and ventricular filling. This action affects the beginning of the filling phase only and is possible for a short range of values of the AV delay. To maintain the same fusion between spontaneous activation and stimulated activation, the AV delay value should closely follow the variations in spontaneous PR interval, modulated by the autonomic nervous system. This, however, is not systematically the case, and a flawless optimization at rest is often accompanied by loss of capture during activity.

Interventricular Resynchronization and Interventricular Delay

At the interventricular level, the preoperative mechanical interventricular delay, considered abnormal beyond 40 ms, must be shortened. This is the duty of biventricular stimulation, which hinges more on a proper lead placement than on postoperative reprogramming of the device. There are, nevertheless, two means of shortening of the interventricular interval: (1) by shortening the abnormally long left pre-ejection interval or (2) by shortening the right pre-ejection interval, which is often within normal limits. The improvement of interventricular synchrony between the left ventricle and right ventricle (RV) by CRT is far less important clinically than the reduction or elimination of intraventricular LV dyssynchrony.

It remains to be determined whether the interventricular interval is a marker or a cause of dyssynchrony, though it is clear that its shortening after implantation of the CRT system has an impact on the optimal AV delay. The persistence of a long interval implies that an AV delay that is optimal for the filling of the left cardiac chambers is not optimal for RV filling. Indeed, in the presence of a persistently long interventricular delay, the AV delay associated with the longest filling period in the left cardiac chambers will certainly be too short for the RV and is likely to encroach on the end of the right-sided A-wave. The equalization of the left and right pre-ejection intervals allows the programming of the same optimal AV delay for the left and right cardiac chambers (Fig. 12.8).

The V-V interval can be used to shorten the interventricular delay by "advancing" the delayed ventricle [7]. Although it shortens the interventricular delay by shortening the pre-ejection interval of that ventricle, this programming step is also likely to have an opposite effect on the pre-ejection interval of the other ventricle. While the interventricular delay has been shortened, the overall duration of systole is sometimes ultimately lengthened. The clinical value of V-V programming and its precise indications have not been fully established at the present time.

Intraventricular Resynchronization

The assessment of intraventricular resynchronization is a critical step in the echocardiographic evaluation after CRT implantation. Intraventricular dyssynchronization can be detected (a) in the spatial dimension, by comparing the contraction delays among the various myocardial segments, or (b) in the time dimension, by the detection of one or several segments that end their contraction after the aortic valve closure or even during the next cardiac filling cycle.

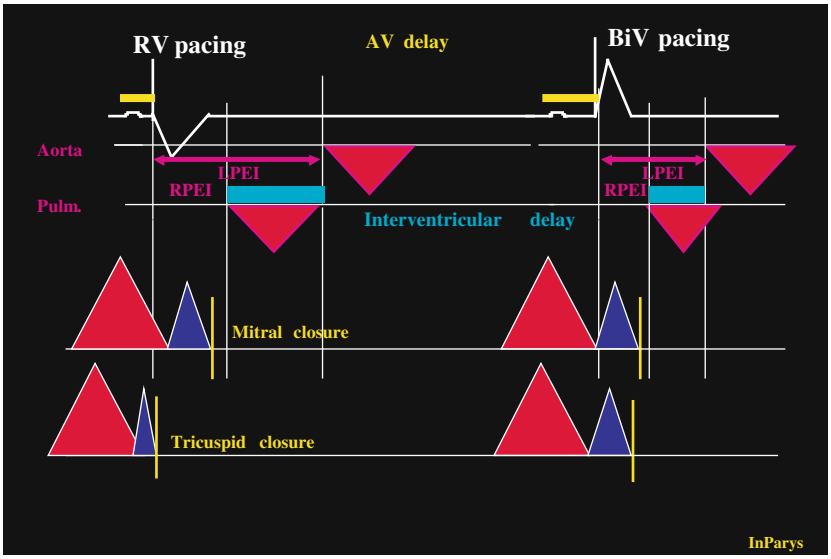

Fig. 12.8 During RV pacing with a significant interventricular delay, the optimal AV delay for LV filling is too short for optimal RV filling. During biventricular pacing, equalization of left and right pre-ejection intervals enhances the programming of an AV delay "optimal" for both the right and left ventricles. *LPEI* and *RPEI* are the respective left and right pre-ejection intervals.

Spatial intraventricular dyssynchrony can be corrected by either delaying the contraction of the earliest segments or by advancing the most delayed ones. Whereas the latter choice seems intuitively the most judicious, its merit has never been confirmed. Spatial dyssynchronization is, in fact, a heterogeneous temporal dyssynchronization among the various myocardial segments. Reducing temporal dyssynchronization invariably reduces spatial dyssynchronization. Reducing temporal dyssynchronization also shortens the duration of systole, hence it lengthens diastole.

Echocardiography performed immediately after CRT implantation is complex with conflicting issues as attempts are being made to optimize resynchronization. Its value, however, has been abundantly demonstrated in CRT patients undergoing a first implantation, as well as in patients whose standard DDD pacing systems have been upgraded.

The acute effect of CRT occurs within one heartbeat and is manifested by an increase in the aortic systolic pressure, stroke volume, and the maximum rate of rise of LV pressure (dP/dt) as well as a reduction in functional mitral regurgitation.

At the end of the echocardiographic procedure, one should not forget to program basic rate, upper rate limit, refractory periods, safety algorithms, and Holter function of the device. One should be cognizant of the fact that AV delay is a somewhat "tricky" parameter not only linked to AV synchronization but also to atrial refractory periods, 2 to 1 upper rate point, and a timing cycle with the potential of interfering with safety algorithms such as mode switching or anti-pacemaker-mediated tachycardia functions. The automatic shortening of the AV delay on exercise may be programmed if it can be demonstrated that this function is beneficial on exercise.

Long-term Considerations

Postimplantation echocardiography is indispensable for the long-term follow-up of the underlying heart disease, for the standard measurements of chamber diameters and volumes, ventricular ejection fractions, pressures, for the estimation of AV valve regurgitation, and for the regulation of medical therapy with a view to decreasing the dose of diuretics and increasing the administration of beta-adrenergic blockade and angiotensin-converting enzyme inhibitors. There is no consensus on whether LV reverse remodeling or clinical status should be employed as end points for assessing response to CRT.

Several studies have shown the beneficial time-dependent effects of CRT on ventricular geometry (less spherical LV shape) and function consistent with reverse LV remodeling of the heart, judged by a decrease in end-systolic LV volume, end-diastolic LV volume (8–15%), and increase in LV ejection fraction (4–7%) [8,9,10,11,12,13,14,15,16,17]. There is also further reduction of mitral regurgitation related to distortion of mitral apparatus by LV dyssynchrony (compared with the immediate reduction at the start of CRT) as a result of improved myocardial contractility, reduction of ventricular size, and improved coordinated timing of mechanical activation of papillary muscle insertion sites, left atrial size, and attenuation of the interventricular electromechanical delay [8] (Table 12.1). Reverse remodeling (greater in patients with nonischemic cardiomyopathy) is correlated with the presence of

Table 12.1 Effects of CRT on LV function and dimensions in patients with moderate to severe heart failure (NYHA class III–IV).

Study	Baseline	CRT FU	Control FU	p
MUSTIC [18, 19] (n = 34)		9 months		
LVED (mm)	73 ± 8	64 ± 7		<0.001
LVESD (mm)	62 ± 8	53 ± 8		<0.001
Aortic ITV (cm)	14.9 ± 5.6	17.9 ± 6.6		<0.001
PATH-CHF [20] (n = 25)		6 months		
LVESD (mm)	63 ± 11	58 ± 11		0.007
FS (%)	12 ± 6	15 ± 7		NS
CONTAK-CD [21] (n = 227)		6 months	6 months	
LVEDD (mm)	71.5 ± 10.5	–4.9 ± 1	–0.2 ± 1.1	0.001
LVESD	59.5 ± 11	–5.4 ± 1.1	–0.6 ± 1.1	0.002
LVEF (%)	21 ± 6	6 ± 1.1	2.3 ± 1.2	0.029
MIRACLE [22] (n = 172)		6 months	6 months	
LVED volume (ml)	295.6 ± 102.6	–27.2	+4.7	<0.05
LVES volume (ml)	227.7 ± 93.7	–25.6	+0.3	<0.05
LVEF (%)	24.5 ± 6.8	+3.6	–0.4	<0.05
CARE-HF [8] (n = 409)		18 months	18 months	
LVESVI (ml/m^2)	121 (92–151)	–84.4	–26.4	<0.0001
LVEF (%)	25 (21–29)	+6.9	+2.1	<0.0001

LVESD, left ventricular end-systolic diameter; LVED volume, left ventricular end-diastolic volume; LVES volume, left ventricular end-systolic volume; LVESVI, left ventricular end-systolic volume index; FS, fractional shortening ; FS, TVI, total isovolumic time; LVEDD, Left ventriculae end-diastolic diameter; FU, followup. In parentheses are figured the changes observed in the control group of each randomized study in opposition to changes observed in the CRT group. MUSTIC and PATH-CHF were crossover studies without any control group.

Source: Reproduced with permission from Donal E, Leclercq C, Linde C, Daubert JC. Effects of cardiac resynchronization therapy on disease progression in chronic heart failure. Eur Heart J 2006;27:1018–25.

mechanical LV dyssynchrony before device implantation and appears as early as 1 month after implantation and can be documented at 3 months after which it is mostly sustained on a long-term basis with data available as long as 2–3 years after the onset of CRT. Improvement may take as long as 6 months. A reduction in LV end-systolic volume of 10% signifies clinically relevant reverse remodeling, which is a strong predictor of lower long-term mortality and heart failure events [15]. Reverse remodeling provides a stimulus for regression of LV mass and improved contractile function. Regression of LV mass occurs more slowly than the reduction of LV volumes. Patients who do not improve clinically generally show little or no evidence of reverse remodeling and no change in LV ejection fraction.

In a study where pacing was transiently discontinued after 3 months of CRT, the LV volumes did not change despite an acute reversal of dP/dt max, a response consistent with a true remodeling effect. When pacing was kept off for the next month, further reversal of the systolic benefit was observed together with reappearance of LV dilatation [4].

Refractory Heart Failure After Initial Improvement with CRT

Postoperative echocardiography is also useful on a long-term basis for the detection of the late development of recurrent dyssynchronization despite satisfactory initial resynchronization and considerable early hemodynamic improvement. In patients who present with recurrent, refractory congestive heart failure (CHF), the addition of a third ventricular lead may be helpful in the presence of LV dyssynchrony. We investigated the addition of a third lead in the RV in such patients (two RV leads and one LV lead) [23]. These three-ventricular lead systems were evaluated clinically and echocardiographically before versus during biventricular stimulation, and before versus after the addition of the third ventricular lead, in five men and two women (mean age = 74 ± 9 years) with idiopathic (n = 5) or ischemic (n = 2) cardiomyopathy. All patients initially had undergone implantation of a CRT system for the management of New York Heart Association (NYHA) functional class III (n = 3) or IV (n = 4) for CHF despite optimal drug therapy. Chronic atrial fibrillation was present in three patients at the time of implantation. A significant improvement was observed in six patients after implantation of the biventricular stimulation system. However, after a mean of 40 ± 26 months (range, 2 to 75), refractory CHF reappeared. The LV lead had originally been placed in a lateral vein in five and in a posterolateral vein in two patients. The original RV lead was apical in six and septal in one patient. The additional third ventricular lead was affixed to the right interventricular septum in six and to the RV outflow tract in one patient. Late, recurrent inter- and intraventricular dyssynchrony was corrected by the third ventricular lead, and an increase in mean LV ejection fraction and decrease in mean NYHA functional class were observed. These pilot observations warrant pursuit in controlled trials.

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Section III

Advances in Technology

13

Recent Advances in the Technology of Cardiac Resynchronization Therapy

Carsten W. Israel and S. Serge Barold

The most striking recent advances in the hardware of cardiac resynchronization therapy (CRT) primarily involve facilitation of device implantation with the development of better introducers and a large variety of left ventricular leads designed for easier manipulation and placement within the coronary venous system [1]. Additionally, new devices offer several advanced features to improve overall CRT function and facilitate follow-up. Some of these advances (e.g., automatic optimization of the AV and VV interval) are presented elsewhere in this book. This chapter summarizes other recent advances in CRT device technology and algorithms.

Device Hardware Technology

Physical Characteristics

Implantable cardioverter-defibrillators (ICD) have recently decreased significantly in size, weight, and thickness (Table 13.1). Though seemingly trivial, these improvements represent important progress because they facilitate implantation and particularly pulse generator replacement. Today, implantation of most devices is feasible in a subcutaneous subclavian site (despite the common development of cardiac cachexia in patients with a CRT indication). In tandem with decreasing device size, all manufacturers have been able to develop systems with a high-energy output for shock delivery (up to 41 J) so that effective shocks with a sufficient safety margin can be guaranteed to almost all heart failure patients with typically markedly enlarged hearts. Yet, the projected battery longevity has been maintained.

Battery

Conventional lithium/silver–vanadium oxide batteries are called cathode-limited because the capacity of the cathode must not exceed the capacity of the anode (lithium). Such batteries exhibit a first voltage plateau at 3.2 V and a second characteristic voltage plateau at around 2.6 V with elective replacement indication occurring as the voltage declines below 2.55 V. A new type of battery is anode-limited and has the advantage of maintaining a higher

Table 13.1 Sizes of current CRT devices.

System	Year	Size	Weight	Thickness
Biotronik Stratos LV-T	2004	14.0 cm^3	27.5 g	6 mm
Biotronik Lumax 300 HF-T	2006	37.1 cm^3	83 g	12 mm
Ela Medical Talent 3 MSP	2003	13.8 cm^3	32 g	8 mm
Ela Medical Ovatio CRT	2006	30.0 cm^3	87 g	11 mm
Guidant Contak TR2	2003	14 cm^3	26 g	8.5 mm
Guidant Renewal 4	2004	37 cm^3	89 g	12 mm
Medtronic InSync III 8042	2001	16.0 cm^3	26 g	7.0 mm
Medtronic Concerto C174	2006	38 cm^3	68 g	15 mm
Sorin NewLiving CHF	2005	15.0 cm^3	35 g	7 mm
St. Jude Medical Frontier II	2004	11 cm^3	25 g	6 mm
St. Jude Medical Epic II HF	2006	36 cm^3	73 g	12.7 mm

voltage throughout the life of the battery. The constituents of the battery are rebalanced with a lesser amount of lithium. The altered composition of the battery eliminates the second voltage plateau of cathode-limited batteries. The battery discharge is substantially completed as the open circuit battery voltage drops to about 2.6 V. With the new battery, the depletion curve is quite linear after the first plateau (no dual-plateau depletion curve as in cathode-limited batteries) with elective replacement indicator at about 2.62 V. ICDs with cathode-limited batteries eventually require automatic monthly reforming of the capacitors to keep the charge time acceptably low. Reforming the capacitor uses roughly 2 weeks of battery capacity, so the battery will not last as long. ICDs with the new battery are nominally set to reform capacitors every 6 months and not to increase the frequency of reformation as the ICD ages. Anode-limited batteries provide an additional improvement over cathode-limited batteries in terms of shorter capacitor charge time as the battery ages.

Lead Connectors: Hardware and Software

Although CRT devices have been reduced significantly in size, CRT lead connector blocks require more space than single- or dual-chamber systems to accommodate right atrial, right ventricular, left ventricular, distal, and possibly proximal coil electrodes for defibrillation. Separate connection and programmability for right and left ventricular leads are certainly highly welcome; together with additional random access memory (RAM) in contemporary CRT devices, this permits more versatile programmability, such as separate right- and left-channel programmability of ventricular output, sensitivity, and blanking periods. However, the additional space required for the connector block may cause a problem after subcutaneous device implantation. Additionally, the loops of redundant leads (particularly with 88-cm left ventricular leads) should be secured behind the can and may multiply the thickness of the implanted system. Therefore, the new DF-4 connector (Fig. 13.1) is likely to improve CRT implantation by reducing the size of the connector block (only one connection for the sense/pace/defibrillation lead) and eliminating the separate connections of the right ventricular lead. The reduction of the number of leads may also reduce lead complications

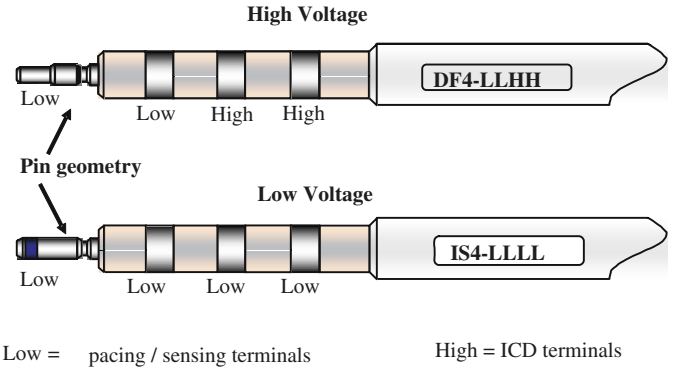

Fig. 13.1 The new DF4 and IS4 connectors. For high-energy leads, the DF4 connector turns three connections (right ventricular sense/pace electrode, right ventricular shock coil, superior vena cava shock coil) into one. For left ventricular leads, the IS4 connector allows connection of four electrodes (tip or ring) to provide the selection of the best pair of electrodes in terms of myocardial pacing performance and avoidance of phrenic nerve stimulation.

(e.g., insulation failure at sites of lead crossings), the "Achilles' heel" of CRT. In parallel, an IS-4 connector is being developed that allows the connection of four electrodes (one tip, three rings) of a single lead (Figs. 13.1 and 13.2). This may improve the transvenous implantation success of left ventricular (LV) leads as it allows the selection of the optimal combination of electrodes to ensure ventricular capture and avoid phrenic nerve stimulation.

Together with hardware solutions related to LV lead placement and capture, special programmable options allow programming of lead function in terms of anodal or cathodal bipolar LV pacing as well as pseudo-unipolar pacing using the right ventricular ring as an anode and the LV tip or ring as the cathode. (Fig. 13.3). This enables more flexibility in LV lead placements

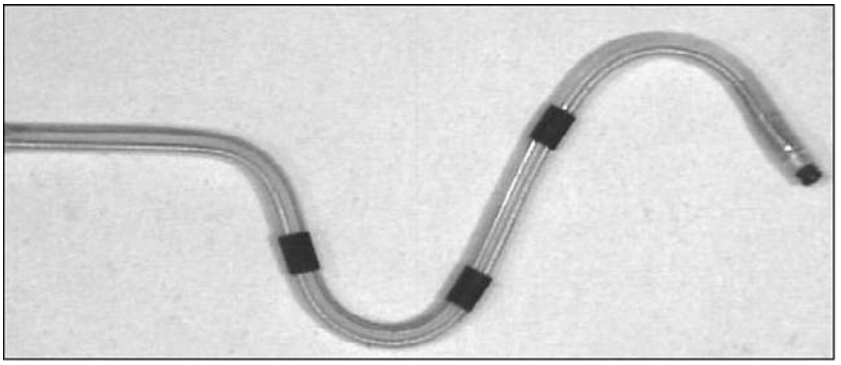

Fig. 13.2 Quadripolar left ventricular lead. Using one tip and three ring electrodes with an IS4 connector, the left ventricular lead can be implanted more easily with the choice of the electrode configuration for optimal myocardial stimulation values and avoidance of phrenic nerve stimulation.

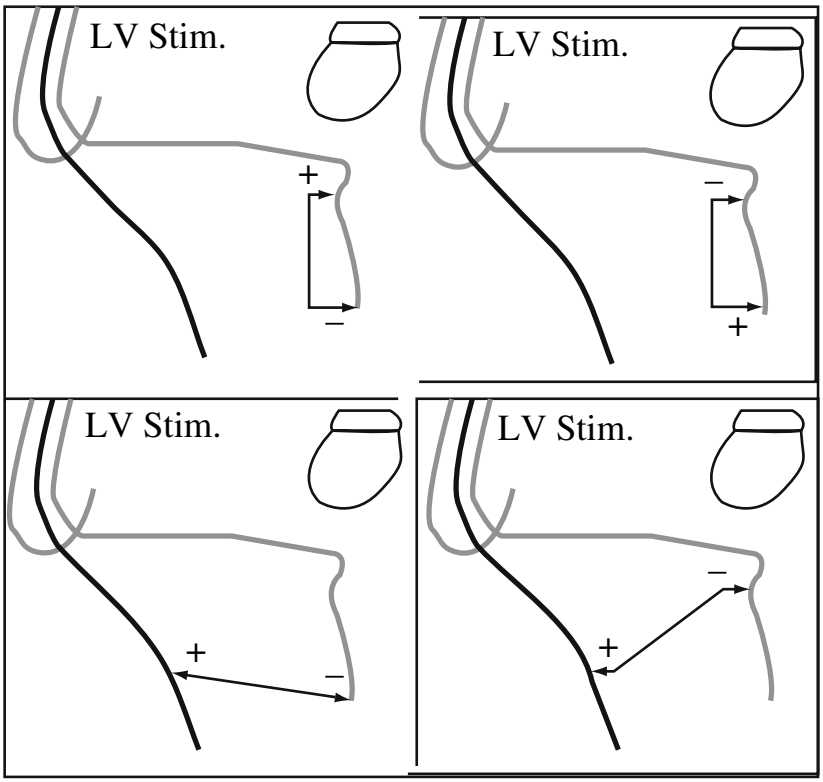

Fig. 13.3 Programmability of Left ventricular pacing. Refined CRT features allow programmability of electrode polarity ("reverse pacing polarity") in the bipolar and pseudo-unipolar (left ventricular tip or ring vs. right ventricular ring) mode.

and helps to overcome problems with high LV pacing thresholds and phrenic nerve stimulation [2].

Device Memory Functions

In advanced pacemaker and ICD systems, multiple counters, histograms, and other memory functions are widely available (Table 13.2). The increased capacity for data memorization provides collection, storage, and retrieval of longer recordings of atrial and ventricular electrograms for more episodes of ventricular and supraventricular tachyarrhythmias as well as specific triggers such as endless loop tachycardia and "sensed" episodes of intrinsic AV conduction. Similarly, stored data can document the occurrence of inappropriate automatic mode switching. Finally, additional RAM made possible new functions specifically applicable to CRT, such as dedicated sensors for the evaluation of heart failure. The following memory functions are particularly important in CRT systems for recording disturbances that may require reprogramming. The memorized events discussed below should be sought by scrutinizing device memory data, and reprogramming should be performed accordingly [3]. Memorized data is useful in troubleshooting in situations where device behavior is difficult to interpret [4, 5].

Table 13.2 Memory functions in CRT systems (examples).

Counters
Percentage of pacing versus sensing in atrium and ventricle
Percentage of time in atrial fibrillation
No. of episodes of atrial fibrillation and ventricular runs/tachyarrhythmias
No. of pacemaker-mediated tachycardias
Histograms
Atrial and ventricular rate histograms
Duration and maximum sensed rate of atrial tachyarrhythmias
Duration and time of onset of atrial tachyarrhythmias
Ventricular rate during periods of atrial tachyarrhythmia
AV conduction
Sensor rate
VA interval
Other graphs
Atrial tachyarrhythmia burden in % per day/week
Ventricular rate during atrial tachyarrhythmia
Heart rate variability
Ventricular rate during day versus night
Physical activity detected by the sensor in hours per day
Minute ventilation sensor input
Thoracic impedance (intrathoracic fluid status)
Sensed atrial and ventricular amplitudes
Atrial/ventricular pacing impedance, atrial/ventricular pacing threshold (including automatic capture verification)
Battery impedance/voltage
Stored electrograms
Mode switching (beginning, end)
Atrial tachyarrhythmia detection (beginning, end)
Nonsustained and sustained ventricular tachyarrhythmia (onset, termination)
Pacemaker-mediated tachycardia
Episodes of intrinsic ventricular rhythm
Patient-triggered recordings

Loss of Ventricular Resynchronization

The percentage of biventricular pacing and ventricular sensing must be carefully checked in the stored memorized data retrieved from the device. The physician must ensure that biventricular pacing takes place >95% or ideally 100% of the time. Ventricular resynchronization devices that memorize episodes of ventricular sensing together with preceding events have facilitated the diagnosis of loss of ventricular resynchronization. Such long-term stored data in resynchronization devices are diagnostically far superior to detect sensing of the spontaneous QRS complex than conventional 24-h Holter recordings. Periods without ventricular resynchronization may be caused by atrial rates above the upper tracking limit, atrial tachyarrhythmias, junctional rhythms, ventricular premature beats, nonsustained ventricular tachycardia, and many other causes (Table 13.3). A counter providing the time at/above the upper tracking limit (with sensing of the spontaneous QRS complex) indicates that the programmed upper rate is too low, a situation requiring either reprogramming or adding rate-slowing medication. Some CRT devices are shipped with less useful values for the upper tracking limit (110–120 ppm). These are

Table 13.3 Loss of cardiac resynchronization during DDD(R) pacing.

Intrinsic causes
Atrial undersensing of low amplitude atrial signals
Ventricular oversensing (e.g., T-wave oversensing, diaphragmatic potentials)
Long PR interval
Circumstances that push the P-wave into the PVARP (e.g., junctional or idioventricular rhythms)
Atrial fibrillation with fast AV conduction
Nonsustained, often slow ventricular tachycardia (common and often asymptomatic)
Ventricular double counting and sensing of far-field atrial activity, particularly in first-generation devices with a common sensing channel
Extrinsic causes
Inappropriate programming of the AV delay or any function that prolongs the AV delay (rate smoothing, AV search hysteresis, etc.)
Low maximum tracking rate
Slowing of the atrial rate upon exit from upper rate behavior
Functional atrial undersensing below the programmed upper rate: (A) precipitated by an atrial premature beat or ventricular premature beat; (B) long PVARP including automatic PVARP extension after a premature ventricular complex and single beat PVARP extension related to algorithms for automatic termination of endless loop tachycardia
Inappropriately slow programmed lower rate permitting junctional escape (cycle length < lower rate interval) in patients with periodic sinus arrest
Intraatrial conduction delay where sensing of AS is delayed in the right atrial appendage. A short AS–VP interval may not be able to achieve biventricular pacing

AV, atrioventricular; RV, right ventricle; LV, left ventricle; VPC, ventricular premature complex; PVARP, postventricular atrial refractory period; AS, atrial sensed event; VP, ventricular paced event.

inappropriate for heart failure patients who frequently develop higher sinus rates despite beta-blocker therapy and would lose effective CRT whenever the sinus rhythm exceeds the upper tracking limit. In heart failure patients (without a bradycardia), the upper tracking limit should typically be programmed to 150–160 ppm to allow CRT under all circumstances including exercise. Also, frequent premature ventricular beats such as sustained ventricular bigeminy may significantly reduce the cumulative CRT "dose."

Atrial Fibrillation, Junctional Rhythms, Inappropriate Mode Switching, Endless Loop Tachycardia

Periods without AV sequence or with a ventriculo-artrial (VA) sequence may decrease cardiac output. This may be caused by atrial tachyarrhythmias, particularly atrial fibrillation, which is frequent in patients with heart failure and one of the most important causes of CRT interruption [6]. However, junctional rhythms (faster than a slower programmed lower rate) are also not uncommon in heart failure patients and can cause a critical decrease in cardiac output when they become the prevailing rhythm [7]. Similarly, inappropriate mode switching (causing functional VVI pacing with possible retrograde VA conduction) and endless loop tachycardia may turn the AV into a VA sequence with occasional dramatic deterioration of cardiac output [8]. Automatic mode switching may cause loss of CRT if the destination pacing rate (if equal to the programmed lower rate) during the DDIR mode is slower than the spontaneous rate. These arrhythmias and inappropriate device

reactions should be searched for device memory functions and reprogramming done accordingly (e.g., blanking out far-field signals in the atrium to avoid inappropriate mode switching, prolongation of atrial refractory periods to avoid endless loop tachycardia.

Ventricular Tachyarrhythmias

Nonsustained and sustained ventricular tachyarrhythmias are frequent in patients with heart failure and particularly important in patients with CRT pacemaker systems who should then be considered for an upgrade to a CRT defibrillator system.

Heart Failure and Physical Activity

In patients with advanced heart failure, monitoring the manifestations of cardiac decompensation is of special interest. The importance of this type of monitoring is reflected in the results from large trials (e.g., COMPANION [9]) that have shown that only about 20% of patients with New York Heart Association (NYHA) class III heart failure and left bundle branch block have an event-free survival after 2 years, despite optimal medical therapy. Also, most clinical events in CRT patients were due to decompensated heart failure. Therefore, monitoring of special heart failure manifestations may play an important role in patient management by detecting worsening of heart failure at an early stage. Several functions to monitor the clinical state of the patient are available. As part of "overall information," the cumulative time of physical activity can be derived from input of activity sensors such as accelerometers (Fig. 13.4). A reduction of physical activity can be detected and correlated with potential causes (intercurrent pulmonary infection, left ventricular lead dislodgment, atrial fibrillation, etc.). More specific devices with dual sensors (activity, minute ventilation) can correlate minute ventilation with physical activity. Worsening of heart failure can be detected if minute ventilation sensor input increases in relation to activity sensor input or if baseline ventilation increases without signs of physical activity (Fig. 13.5). Finally, direct measurement of the thoracic impedance correlates with the intrathoracic fluid volume [10]. Modern CRT devices can thus continuously monitor the amount of intrathoracic fluid and send an alarm whenever a predefined limit is exceeded (Fig. 13.6). This may be a powerful tool to prevent heart failure hospitalization [11] given the fact that this was the most frequent significant event in all studies on CRT.

Sleep Apnea Monitoring

Sleep apnea syndrome is a common problem in patients with heart failure. Devices with minute ventilation sensors offer the opportunity to continuously monitor breathing function in patients with heart failure and to detect and quantify apnea or hypopnea [12] (Fig. 13.7).

Data Display

Integrated memory functions displaying numerous parameters in parallel on a single graph are helpful to understand significant trends of rhythm state, device function, and the patient's clinical state at a glance (Fig. 13.8).

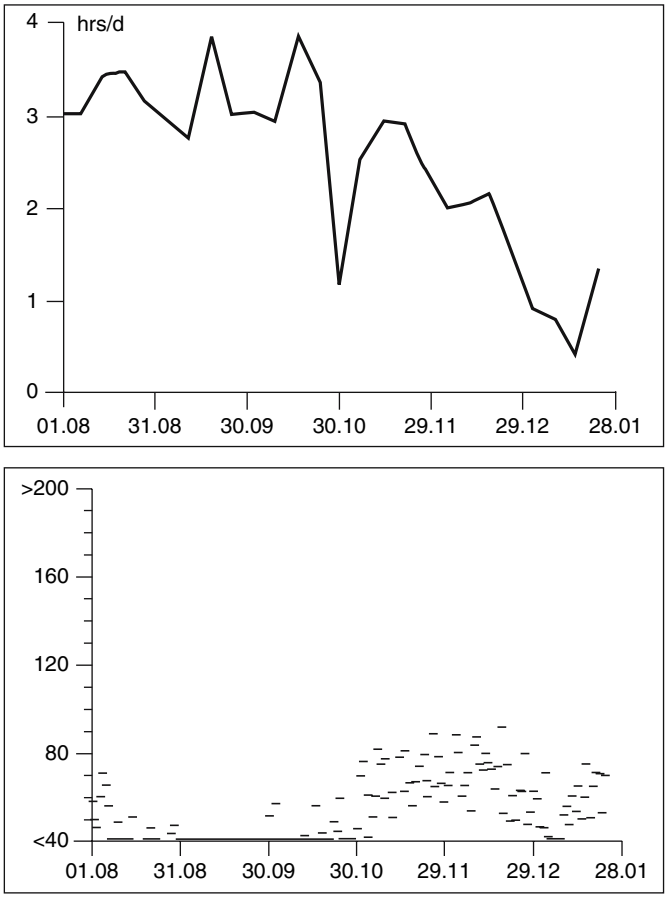

Fig. 13.4 Cumulative daily activity (in hours per day) and variability of the ventricular rate (in ms). This patient with dilated cardiomyopathy and heart failure (functional class NYHA III) reported worsening of exercise tolerance since October. The monitor for physical activity (ordinate: hours per day with physical activity detected by the accelerometer) shows a sharp decrease at the end of September. When questioned about it, the patient reported a "flu-like illness" at that time. After that, he recovered but subsequently showed a steady decrease of activity from 3 to less than 1 h per day. In parallel, the heart rate shows a sudden increase exactly at the same time as the decrease of daily activity (lower panel, ordinate: standard variation of the median heart rate during 5 min). Taken together, these recordings show that the patient developed atrial fibrillation during/after his bronchitis, which caused severe cardiac decompensation.

Algorithms Related to CRT

Like drugs for the treatment of heart failure, CRT requires continuous follow-up and adjustment of its effect. For this, understanding the sometimes complex surface electrocardiogram (ECG) [13] and device memory functions is essential, as outlined above. Atrial tachyarrhythmias [6], left ventricular exit block, and atrial undersensing (true or functional) can interrupt CRT. In addition, in some patients an optimal effect is only achieved with individual AV and VV intervals. To accomodate these needs, several specific algorithms have been developed.

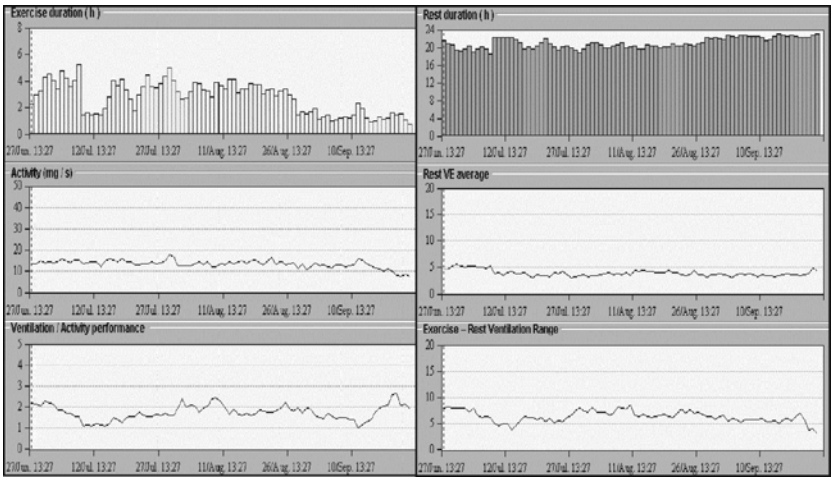

Fig. 13.5 Integration of dual sensor input (activity and ventilation sensor). This device monitor displays the exercise and rest duration in hours per day (*upper row*), input from the activity sensor and minute ventilation at rest (*middle row*), a "ventilation/activity ratio," which displays the minute ventilation sensor input per activity sensor input, and a display of ventilation variation during rest and exercise (*lower row*). In this example, daily activity declined before this interrogation (*red circle in middle row*) while ventilation remained the same or even increased slightly. As a result, the "ventilation per activity" ratio increased (*circle in lower row*) indicating worsening of heart failure.

Atrial Refractory Sensing

Atrial sensing during the postventricular atrial refractory period (PVARP) represents a cause of CRT interruption that may also occur unrelated to upper rate behavior [14]. This form of electrical desynchronization is characterized by sequences consisting of an atrial event sensed in the atrial refractory period (AR) followed by a conducted and sensed ventricular event (VS) (AR–VS sequences) creating a rate below the programmed upper rate. The AR–VS interval is longer than the programmed AV delay initiated by atrial sensing. The development of ventricular desynchronization (at atrial rates slower than the programmed upper rate) is favored by a relatively fast sinus rate (but below the programmed upper rate), first-degree AV block, and a relatively long PVARP. The initiating mechanism often involves ventricular premature beats. In some CRT devices, the programmed initial PVARP may vary as a function of the atrial rate or sensor rate ("automatic," "sensor-varied," "rate-adaptive," etc., PVARP) so that the PVARP shortens with activity or at a faster atrial rate. The relatively long PVARP at rest at lower rates can result in persistent loss of AV synchrony in CRT patients. These features are best left turned off in CRT patients. Electrical ventricular desynchronization can be precipitated by a variety of mechanisms (Table 13.3). Based on these considerations, one should aim to program a short PVARP. The PVARP extension after a ventricular premature complex should be turned off as well as the pacemaker-mediated tachycardia termination algorithm based on PVARP prolongation for one cycle [15]. "Locking" of the P-wave can often be prevented (barring reprogramming the device to eliminate a specific initiating mechanism such as T-wave oversensing) with a shorter PVARP and slowing the sinus rate with drugs.

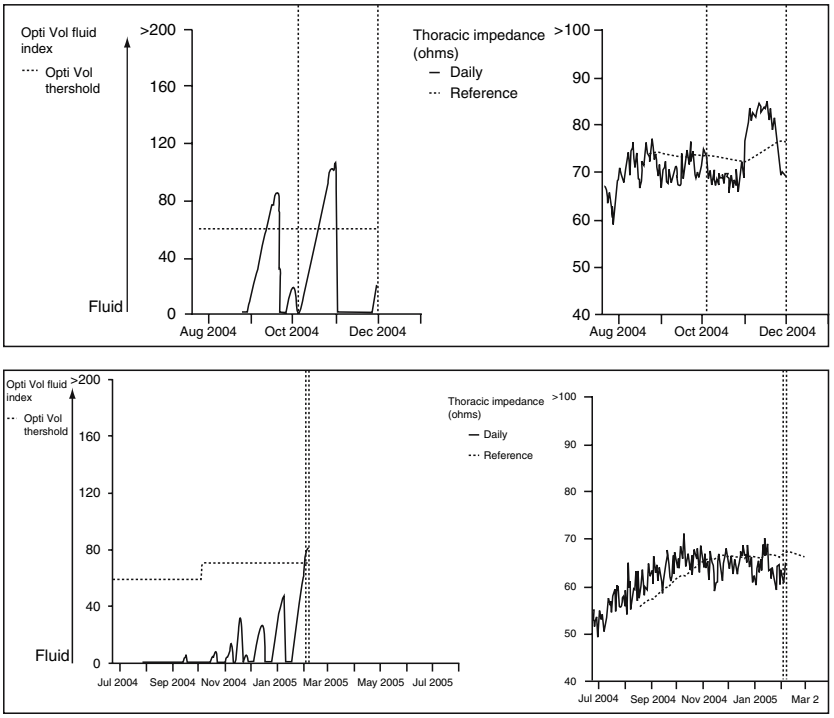

Fig. 13.6 Examples of a CRT device monitor for continuous measurement of intrathoracic fluid. the patient in the upper panel experienced two periods of severe deterioration of heart failure, the first in October 2004 associated with pneumonia, and the second in November 2004 without an obvious cause. In both situations, the sensor measured a fluid index above the threshold (60, *dotted line*) triggering an audible device alert. The daily thoracic impedance measurements (*bold line* in right graph) showed a strong increase. The patient in the lower panel had her CRT device implanted in August. In November, no cardiac decompensation had occurred; the fluid index threshold was checked and reprogrammed from 60 to 70 (*dotted line*). During the following months, there were several periods where the thoracic fluid increased but eventually went back to normal. Finally, in March 2005, the patient returned for an unscheduled visit after she heard an audible alert. By that time, she had a slight decrease in exercise performance and had gained 3 kg body weight. She received a higher dose of frusemide and a hospitalization was prevented. (Courtesy of B. Lamp, Heart Center Bad Oeynhausen, Germany).

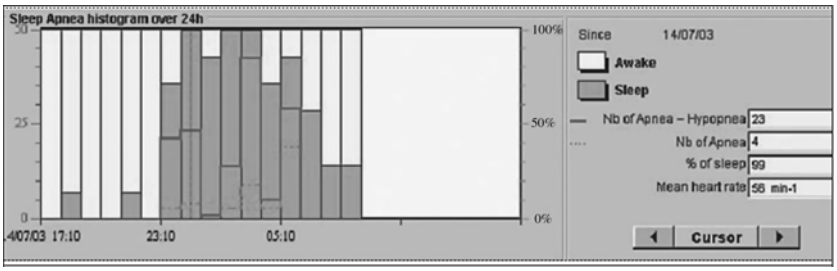

Fig. 13.7 Sleep apnea monitor. Using the input from the minute ventilation and activity sensors, the device can quantify the time that the patient sleeps (no activity input), and frequently during this time, he shows spells of apnea or hypopnea. For both, the definition (i.e., the breathing pause) can be programmed.

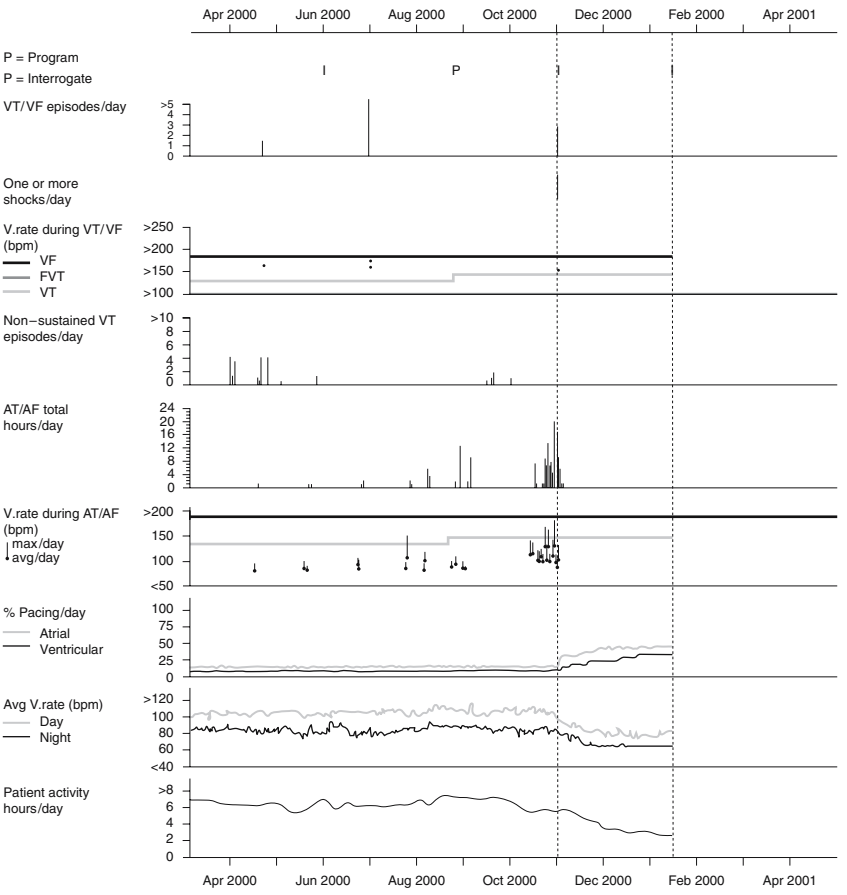

Fig. 13.8 Cardiac Compass as an example of integrated memory functions. On this single page, a number of parameters and events that occurred between April 2000 and January 2001 are displayed: device interrogation (*I*) and programming (*P*), number of shocks, rate of ventricular tachyarrhythmia (*VT*) episodes and *VT/VF* zone programming, nonsustained VTs, atrial tachyarrhythmia/fibrillation (*AT/AF*) in hours per day, ventricular rate during episodes of AT/AF, percentage of atrial and ventricular pacing, average ventricular rate during day and night, and patient activity. In this example of a dual-chamber device, it seems as if the patient's activity decreased in October 2000 (worsening of heart failure?), then atrial fibrillation occurred in November, which terminated shortly after a shock that was applied for a VT/VF episode, which interestingly occurred during AT/AF. The heart rate gradually decreased over the next months after this shock and the pacing percentage increased, and there was no recurrence of AT/AF (antiarrhythmic drugs such as amiodarone?). However, patient activity continued to decrease as a sign of heart failure progression, probably caused by an increase of right ventricular pacing.

Special algorithms can be programmed to restore 1:1 atrial tracking at rates slower than the programmed upper rate. They are particularly useful in patients with sinus tachycardia and first-degree AV block in whom prolonged locking of P-waves inside the PVARP is an important problem. The algorithms automatically identify an AR–VS pattern of cardiac activity followed by PVARP shortening and the restoration of atrial tracking (Fig. 13.9). These algorithms do not function when the atrial rate is faster than the programmed upper rate or during automatic mode switching. Algorithms such as the *atrial tracking recovery* algorithm promote 1:1 atrial tracking whenever the effective

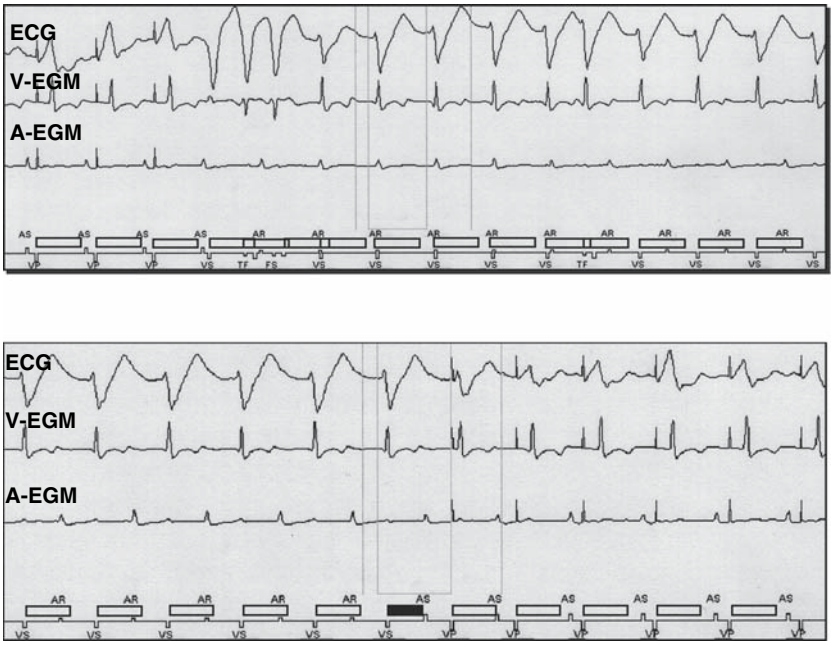

Fig. 13.9 Function of the atrial tracking recovery algorithm. After three ventricular premature beats (*upper tracing*), sinus beats coincide with the postventricular atrial refractory period (PVARP, *transparent boxes*) and are thus not tracked. Because of intrinsic AV conduction with a long PR interval, sinus activity continues to appear during the PVARP and is no longer tracked. After several such cycles, the atrial tracking recovery algorithm shortens a single PVARP (*black box*) to allow sensing and tracking of the atrial signal beyond the PVARP. This shifts the following PVARP intervals so that all consecutive atrial signals are now outside the PVARP and now tracked. *AS*, atrial sensed signal; *AR*, atrial refractory signal; *VS*, ventricular sensed signal; *VP*, ventricular paced event; *FS*, signal in the VF zone; *TF*, signal in the fast VT zone. Surface ECG, right ventricular electrogram, atrial electrogram, marker annotations, paper speed 25 mm/s.

or prevailing total atrial refractory period [(AR – VS) + PVARP] prevents atrial tracking at rates below the programmed upper rate. The algorithm is triggered by AR–VS sequences suggestive of ventricular desynchronization whereupon temporary PVARP abbreviation permits the device to sense a sinus P-wave beyond the PVARP and restore atrial tracking and ventricular resynchronization (Fig. 13.9). In other words, the algorithm shortens the total atrial refractory period. A P-wave falling in the postventricular atrial blanking period cannot activate the special algorithm. Subsequent AS–VP (AS = atrial sensed event) intervals are shortened even more as the intervention proceeds in an attempt to terminate the AR–VS pattern. The shortening of the sensed AV interval (initiated by atrial sensing) however, is a function of the pacemaker upper rate behavior [14].

Attempts at Restoring Ventricular Resynchronization in Special Situations

Atrial Fibrillation

Some devices have programmable algorithms that increase the percentage of biventricular pacing during atrial fibrillation so as to promote some degree

of rate regularization (without an overall increase in the ventricular rate) by dynamic matching with the patient's own ventricular responses (up to the programmed maximum tracking rate). Activation of this algorithm does not result in control of the ventricular rate and should not be a substitute for ablation of the AV junction in patients with drug-refractory rapid ventricular rates.

Ventricular Triggered Mode

The ventricular triggered mode in some resynchronization devices automatically attempts to provide resynchronization in the presence of ventricular sensing. A ventricular sensed event initiates an immediate (<10 ms) emission of a ventricular or usually a biventricular output (according to the programmed settings) in conformity with the programmed upper rate interval. For example, Medtronic devices offer this function in the VVIR mode, but in dual-chamber devices triggering occurs upon sensing only within the programmed AV delay. The ventricular output will be ineffectual in the chamber where sensing was initiated because the myocardium is physiologically refractory. The stimulus to the other ventricle thus attempts to provide a measure of resynchronization. Ventricular triggering may be helpful in some patients, but its true benefit is difficult to assess as the ventricles may be activated in an order that may not be hemodynamically favorable.

Automatic Optimization of the AV and VV Delay

Optimization of the AV and VV delay can significantly improve CRT performance [16]. However, echocardiographic optimization of AV and VV settings is time-consuming and may have to be repeated regularly as ventricular dimensions and conduction velocity change. Therefore, new algorithms for automatic AV and VV delay optimization may be highly useful. Two such algorithms have been developed. One uses electrograms to automatically measure AV and VV conduction. AV/VV optimization based on these measurements correlates well with echocardiographic and invasive measurements. This algorithm is explained in detail elsewhere in this book. Another algorithm uses the peak endocardial acceleration (PEA) measured by a piezocrystal sensor in the lead tip (Fig. 13.10). The PEA signal is closely correlated with myocardial contractility; AV/VV optimization based on automatic PEA measurements showed a correlation of 0.93 with echocardiographic AV optimization using the Ritter method [17].

Left Ventricular Automatic Capture Verification

Loss of left ventricular capture and phrenic nerve stimulation (requiring a lower left ventricular output for elimination) are two important causes of CRT interruption [6]. To maintain effective left ventricular capture with a minimal output, automatic algorithms for capture verification may be helpful. As an example, the *left ventricular capture management* (LVCM) algorithm of Medtronic measures the time from an atrial stimulus to the right ventricular sensed event in one test cycle as the intrinsic AV interval (e.g., 200 ms). Thereafter, it measures the interval from left ventricular pacing to the right ventricular sensed event in another test cycle. Only if this VV interval is significantly (at least 80 ms) shorter than the intrinsic AV interval, the algorithm assumes capture. Using this algorithm, left ventricular output can

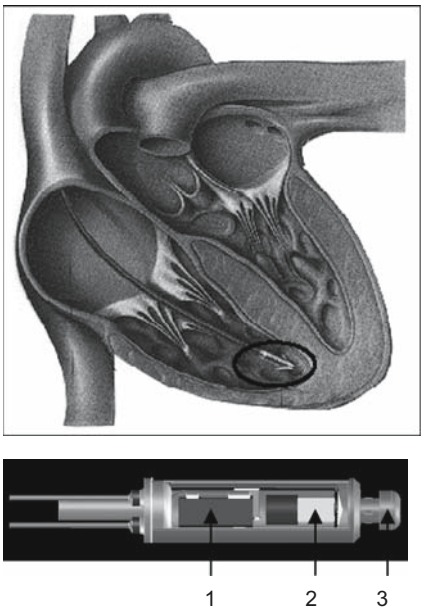

Fig. 13.10 Measurement of the peak endocardial acceleration (PEA) for automatic optimization of the AV and VV delay. Located in the lead tip, a piezoelectric crystal measures myocardial contractility. Automatic AV optimization based on this measurement correlates with echocardiographic optimization to an extent of 93%. *1*, electronic converter; *2*, piezo crystal; *3*, electrode tip.

be programmed just above the threshold value, reducing battery current drain, improving resynchronization success, and decreasing phrenic nerve stimulation.

Atrial Tachyarrhythmia Therapies

Atrial tachyarrhythmias, particularly atrial fibrillation, are a frequent problem in CRT patients. They may cause CRT interruption, loss of atrial systole, and high ventricular rates that frequently cause clinical deterioration (see Fig. 13.4). New CRT devices provide a wide range of therapies for the prevention and termination of atrial tachyarrhythmias (Table 13.4):

1. *Atrial preventive pacing*. These algorithms are designed to permanently overdrive intrinsic atrial rhythms (suppression of ectopic activity), prevent post-extrasystolic pauses (reduction of dispersion of atrial refractoriness), and provide temporary high-rate overdrive pacing after arrhythmia termination (prevention of immediate reinitiation of atrial tachyarrhythmia).
2. *Atrial antitachycardia pacing (ATP)*. Several burst, ramp, scan, and high-rate burst (e.g., 50 Hz) therapies are programmable; these may start immediately after tachyarrhythmia detection, after a delay of 1 or several minutes (to verify persistence of atrial tachyarrhythmia), or later when the device automatically detects transition of the arrhythmia to a higher degree of organization ("reactive ATP") rendering pace-termination more likely. Typically, these therapies should not be applied if the arrhythmia persists for more than 48 h to prevent embolic complications in patients without anticoagulation.

Table 13.4 CRT devices with atrial therapies.

	APP	Post-APB	Post-MS	Burst/Ramp/Scan	20–50 Hz	Automatic shocks	Patient-triggered shocks
Biotronik Tupos LV/ATx	–	–	–	+	+	+	–
Ela Talent MSP AF	+	+	–	–	–	–	–
Guidant Renewal 4	+	+	+	+	+	+	+
Medtronic Concerto	+	+	+	+	+	+	+
St. Jude Medical Frontier II	+	–	–	–	–	–	–
St. Jude Medical Atlas II HF/Epic II HF	+	–	–	–	–	–	–

APP, atrial preventive pacing (continuous sinus rhythm overdrive pacing); post-APB, pacing after atrial premature beats; post-MS, pacing after mode switching back to tracking mode.

3. *Atrial shocks*. Modern CRT devices offer R-wave–synchronized atrial shocks with an output programmable from 0.1 J to 41 J. These can be applied via conventional defibrillation electrodes (best via dual-coil shock electrodes) in mono- or biphasic shape and with reverse polarity. Of note, shocks can be applied immediately after detection of atrial fibrillation or with a delay programmable to a maximum of several hours. This delay can refer to an automatic or patient-activated ICD discharge. In the latter mode, the patient applies a special activator triggering device-confirmation of atrial tachyarrhythmia. Upon this, the device can apply an R-wave–synchronized shock immediately or after a delay of 20 s to 6 h (e.g., if the patient prefers to take a sedative before ICD discharge). As a safety feature, the maximum number of atrial shocks in a programmable time interval (e.g., 24 h) can be limited to 1–5.

Results on pacing for prevention of atrial tachyarrhythmias have been less promising than expected, therefore it is not considered as a "stand-alone" indication [18]. However, if patients receive a device for an indication other than atrial tachyarrhythmia, these algorithms may prove highly successful and beneficial in individual patients. This may particularly apply to patients with CRT devices because one of the shortcomings of atrial preventive pacing therapy was the increase in right ventricular pacing in dual-chamber devices [19], which may cancel all positive effects of atrial preventive pacing. Similarly, atrial antitachycardia pacing has been successful in some studies [20, 21] while unsuccessful in others [22, 23, 24] in reducing the cumulative arrhythmia burden, mainly due to methodological shortcomings in these studies (arrhythmia burden too low in the control groups). A significant effect of atrial antitachycardia pacing can only be expected if it exceeds a success rate of approximately 60%, leading to reverse electrical atrial remodeling [25]. Interestingly, antitachycardia pacing is much more successful than it could be expected in patients with atrial fibrillation because most patients with atrial fibrillation also have intermittent periods of highly organized atrial tachyarrhythmia, which may represent forms of atrial flutter (Figs. 13.11 and 13.12) [26]. Such arrhythmias precede the development of atrial fibrillation

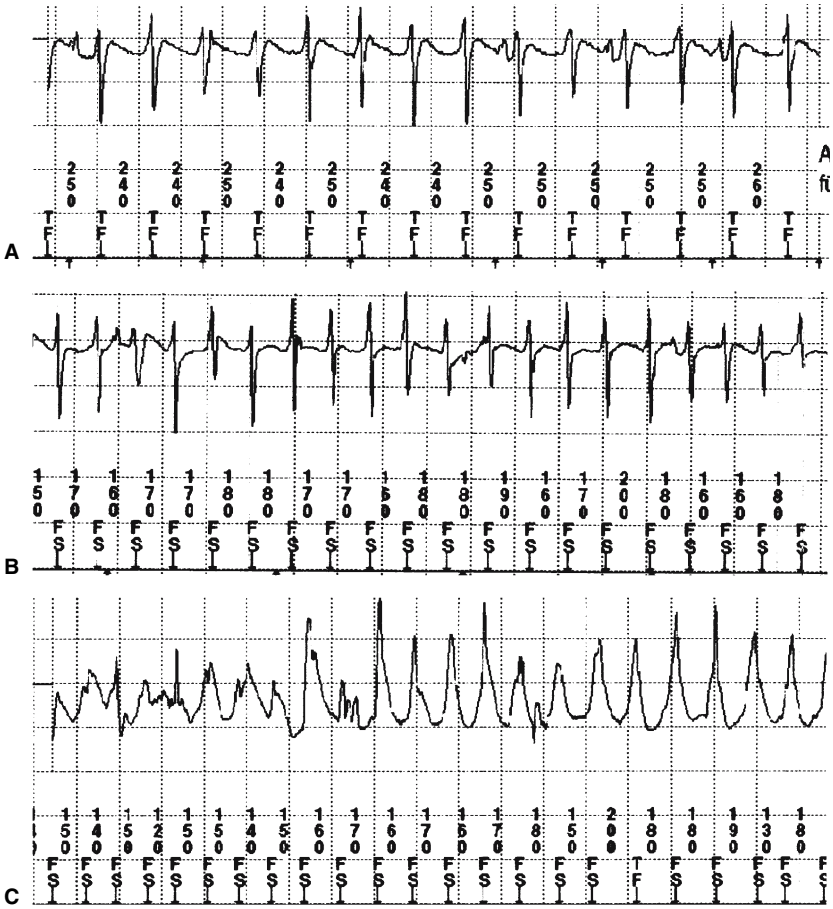

Fig. 13.11 Types of atrial tachyarrhythmia organization in bipolar atrial electrograms. (**A**) Type I: Monomorphic, narrow, regular potentials with minimum cycle length >200 ms and a visible isoelectric baseline. (**B**) Type II: Neither type I nor type III. In this case, the electrogram appears relatively regular with an isoelectrical baseline but minimal cycle length is clearly below 200 ms. (**C**) Type III: Polymorphic, broad, irregular potentials with minimum cycle length <200 ms, loss of a clear isoelectric baseline. Numbers signify milliseconds. *FS*, fibrillation sense; *TF*, tachycardia/fibrillation overlap zone.

and if rapidly treated by ATP, atrial fibrillation may be prevented. Finally, atrial shock therapy has shown some improvement in patients with dual-chamber ICDs and atrial tachyarrhythmias [20, 27]. Because the adverse side-effects of atrial fibrillation are particularly prominent in patients with heart failure, it may be expected that automatic atrial therapies are even more valuable in CRT than in patients with dual-chamber pacemaker or ICD systems.

Remote Control, Patient Alerts, and Telemonitoring

Current CRT devices are equipped with functions that allow new forms of telemetry turning these systems into permanent monitors and alert systems for a variety of biological parameters. By the use of an antenna attached to the connector, telemetry without a wand from a distance of several meters is

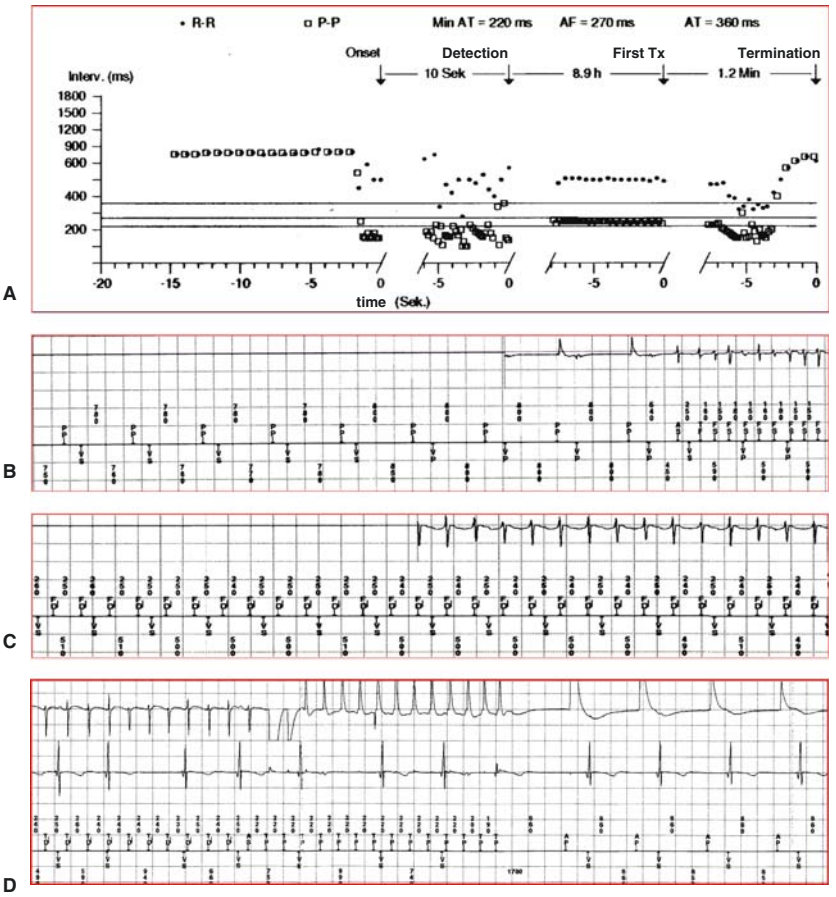

Fig. 13.12 Example of successful atrial antitachycardia pacing in a patient with atrial fibrillation. (**A**) Event summary. In this patient, an atrial tachyarrhythmia with a cycle length <200 ms and irregular atrial and ventricular cycles occurred, most likely atrial fibrillation. After almost 9 h, this tachyarrhythmia has organized to a very regular atrial cycle length of approximately 240 ms with a regular 2:1 AV conduction. The first antitachycardia pacing therapy terminates the arrhythmia. (**B**) Electrogram at arrhythmia onset. The atrial electrogram shows a fast, irregular atrial rhythm. (**C**) Electrogram 8.9 h later. The arrhythmia has organized to a very regular morphology and cycle length. (**D**) The arrhythmia is terminated by a simple burst+ train. Electrograms at paper speed 25 mm/s. *AS*, atrial sensed event; *FDI*, fibrillation detection interval; *FS*, fibrillation sense; *PP*, preventive pacing; *TDI*, tachycardia detection interval; *TF*, tachycardia/fibrillation overlap zone; *TP*, tachy-pacing; *TS*, tachy sense; *Tx*, therapy; *VP*, ventricular pacing; *VS*, ventricular sense. Numbers in the tracings represent milliseconds.

possible. This may facilitate interrogation during implantation and follow-up visits, and can provide a surface ECG without attaching electrodes to the patients' skin ("leadless ECG"), using the SVC coil and device housing as skin electrode substitutes (Fig. 13.13).

Most current devices offer an audible alert whenever automatic functions detect a potentially dangerous event, for example, an electrode problem (pacing impedance out of range), multiple arrhythmias, or signs of deterioration of heart failure [28, 29, 30].

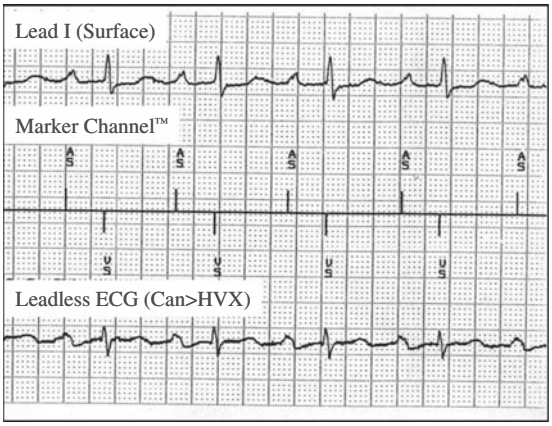

Fig. 13.13 "Leadless ECG." Without attaching electrodes to the skin and without a wand, the programmer can register an ECG between the device housing (*can*) and the vena cava shock coil (*HVX*, *lower tracing*), which resembles the surface ECG (lead I, *upper tracing*). *Middle tracing*: marker annotations *AS*, atrial sensing; *VS*, ventricular sensing.

The antenna allows automatic transmission of device data via a sender located within some meters from the patient as on the bedside table. Data can also be transmitted to a service center that forwards them to the physician in charge of the patient (marking transmissions with abnormal results) or to an Internet site where the patient can access his own data via a password [31,32]. Thus, automatic daily transmission of detected arrhythmias (even with electrograms) is possible, which allows a quicker response to such problems as asymptomatic ventricular tachyarrhythmias terminated by antitachycardia pacing or asymptomatic atrial fibrillation triggering action such as anticoagulation or changes of heart failure medication or drugs that slow AV conduction. At the same time, data on device function are transmitted permitting detection of lead problems (insulation failure, fracture, dislocation) before any event occurs. Data collection and transmission via the device/sender unit can include other parameters such as blood pressure and body weight if the patient uses instruments that via Bluetooth wireless technology can connect to the sender. This allows collecting integrated information (e.g., graphs displaying the mean daily heart rate, the atrial rhythm, body weight, and blood pressure). Given results showing that daily measurement of the body weight by the patient can reduce heart failure hospitalizations and trips to the emergency room [33], these device features may revolutionize heart failure treatment. In the near future, modern devices can use GSM or UMTS allowing location of the patient in any case of emergency, also on an automatic base.

Conclusion

Technological advances in CRT have primarily addressed lead and introducer technology to facilitate CRT system implantation. Other improvements involve the device itself with the design of separate right and left ventricular connections (including IS4 and DF4 connectors), extensive programmability, high-output/small-volume systems, and computer chips with more memory

capacity than before. More RAM means that more programmable functions are feasible, including left ventricular lead polarity, automatic AV and VV optimization, extensive storage of arrhythmia episodes, and availability of algorithms for restoration of atrial tracking when biventricular pacing is interrupted. The percentage of biventricular pacing and ventricular sensing must be carefully checked in the stored memorized data retrieved from the device. Devices must be programmed and followed carefully to prevent electrical desynchronization. Finally, heart failure management can be dramatically changed if CRT devices are also systematically used to collect and transmit biological signals other than arrhythmias, such as intrathoracic fluid. This may enable physicians to detect worsening of heart failure at an early stage (actually without even seeing the patient) and take adequate measures to prevent heart failure hospitalization.

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14

Advances in Left Ventricular Pacing Leads

Luigi Padeletti

Introduction

Cardiac resynchronization therapy (CRT) is now an accepted treatment for patients with drug-refractory congestive heart failure, severe left ventricular (LV) systolic dysfunction, and an interventricular conduction delay. Clinical trials of CRT have consistently demonstrated improvement in functional class, exercise capacity, and quality of life and a reduction of recurrent hospitalizations for exacerbation of heart failure [1, 2, 3]. CRT has been shown to decrease ventricular volumes and improve left ventricular ejection fraction [4].

Early attempts at pacing from the coronary veins used unipolar, standard endocardial leads that were modified for coronary venous placement by removing the tines and subsequently used leads specially designed for left ventricular pacing the coronary venous system [5,6]. Initially, these were leads dedicated to left atrial pacing, and subsequently these leads were specially designed for left ventricular pacing, which resulted in a higher success rate at implantation [7]. The development of the over-the-wire pacing lead technology increased the likelihood of a successful CRT implantation.

The coronary sinus ostium lies at the base of the triangle of Koch, whose dimensions have been reported to vary considerably, even in the absence of heart failure [8, 9, 10]. In patients undergoing CRT, cannulation of coronary sinus may occasionally be extremely difficult. The right atrial anatomy may be considerably distorted and the tricuspid valve as well the various fossae extremely dilated. Moreover, the failing heart is associated with right ventricular and left atrial enlargement, upward rotation of the long axis, posterior rotation of the short axis of the heart and mitral annulus dilatation. All these abnormalities change the relative position of the Coronary Sinus (CS) ostium within the right atrium and the orientation of the CS relative to normal fluoroscopic landmark. The CS takes a more vertical and posterior location requiring the guiding catheter to engage the ostium from a location more inferiorly in the right atrium.

Variations in coronary sinus shape, diameter, angulation, and branches anatomy increase the difficulty of the insertion of permanent pacing leads [11, 12, 13].

Table 14.1 Implant success rates and complications in seven major published trials (MIRACLE, MIRACLE-ICD, InSync III, InSync ICD, CONTAK CD, COMPANION, and CARE-HF).

Implant attempted	4,844
Implant success	4,386 (90.5%)
Procedural death	20 (0.4%)
30-day mortality	63*
LV lead complications	256 (5.3%)†
Coronary sinus trauma/complications	74 (1.5%)

* NA for CARE-HF.
† NA for COMPANION.

The analysis of the outcomes of transvenous CRT system implantation in 4,844 patients from MIRACLE, MIRACLE ICD, InSync III, CONTAK CD, COMPANION, and CARE-HF studies indicates that the implant attempt succeeded in 4,386 of 4,844 (90.5%) patients. A total of 20 deaths were procedure related. A total of 74 patients experienced coronary sinus complications (dissections, perforations). A total of 256 LV lead dislodgments was reported [14, 15] (Table 14.1).

Guiding Catheters

The guiding catheters are intended to cannulate the coronary sinus and facilitate the delivery of the LV lead into the selected coronary vein (Table 14.2).

The catheters offer carefully engineered stiffness, that guarantees precise handling and torque response to enhance maneuverability and at the same time minimize the risk of trauma to endocardial tissues and blood vessels (lesions, dissections, or perforations) (Table 14.3).

The design of the catheter permits simple and stable engagement of the coronary sinus and allows the introduction of the LV pacing lead together with its guiding tools, in order to reach an optimal pacing site.

Due to the wide differences existing in anatomical cardiac structures of patients with cardiomyopathies, frequently associated with history of cardiac surgery (Coronary artery bypass graft (CABG), valvular surgery),

Table 14.2 Endocardial approach for coronary sinus left ventricular lead placement.

Venous access
Insertion of the right atrial and ventricular leads
Connection of the right ventricular lead to an external demand pacemaker
Coronary sinus cannulation with the most appropriate catheter shape
Visualization of the CS venous tree
Identification of the target vein
Selective engagement of the target vein
Selection of the lead according to the size and tortuosity of the target vein
LV lead location and testing
Removal of the implanting tools

Table 14.3 LV lead delivery tools properties.

Pushability and torqueability
Kink resistance
Soft, flexible, atraumatic tip
Family of shapes for CS access
Inner catheters to subselect branch veins of many angulations
Lumen for guide-wire delivery and contrast injection
Visibility
Easy removal

manufacturers have proposed guiding catheters with several shapes and lengths to enhance the success rate in finding and accessing coronary sinus (Fig. 14.1).

Dedicated catheters have also been proposed to facilitate the access through the right subclavian vein, generally used in case of infected implants in left pectoral pockets or occlusions of left venous system, instead of the most common left approach. They are specifically designed to benefit by the support offered by the anatomical structures, such as the superior vena cava.

The length of the catheter usually ranges from 45 to 60 cm, and the most complete systems offer different lengths for each distal curve, in order to facilitate the procedure, regardless of the height of the subject and the volume of the heart. A more supportive mid-shaft section is designed for increased

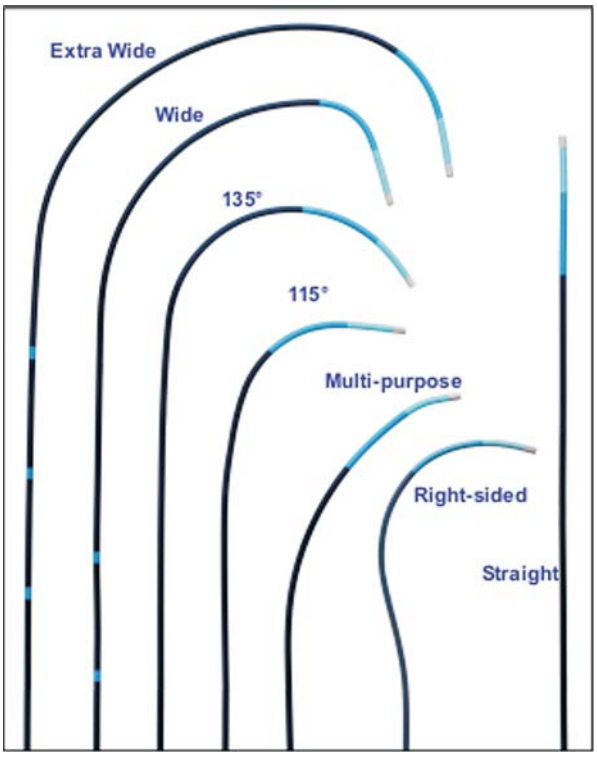

Fig. 14.1 Curve models of guide catheters.

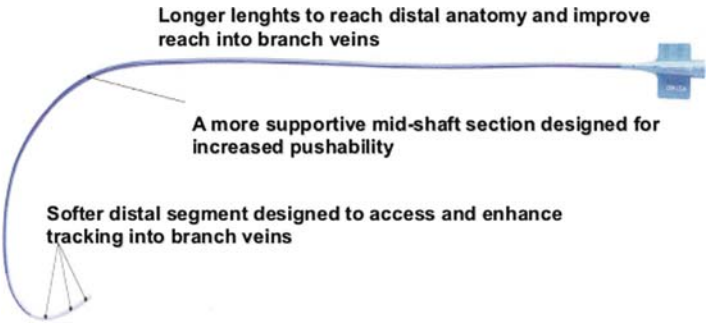

Fig. 14.2 Guide catheter features: reach, access, and support.

pushability and a softer distal segment is designed to access and enhance tracking into branch veins (Fig. 14.2).

The internal lumen of the catheter permits the insertion of electrophysiology diagnostic and Swan–Ganz catheters (typically ranging from 5 to 7 F).

Recently, in addition to the standard fixed-curve catheters, deflectable guiding catheters have been developed to address each patient's unique anatomy during CS cannulation (Fig. 14.3).

Once the pacing lead is positioned in the final site, depending on the size of the lead connector, the guiding catheter is peeled away, cut with a dedicated slitter or simply removed over the connector (Fig. 14.4).

A further approach uses double-catheter systems. An inner catheter, with internal lumen, telescopes inside a larger-diameter guiding catheter and enables the user to maneuver it with different degrees of freedom (Fig. 14.5). The straight or curved inner catheters help cannulation of the coronary sinus or facilitate vessel subselection. In particular, straight catheters with their soft distal ends are designed to cross partially blocked or narrowed veins,

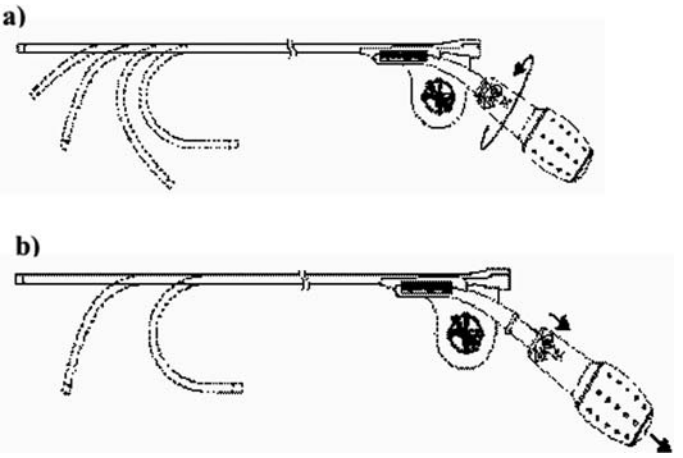

Fig. 14.3 Deflectable guide catheter. (**a**) Rotating handle: slowly deflects tip and holds curve in place when handle is released. (**b**) Pulling handle: curve quickly deflects then straightens when handle is released.

Fig. 14.4 Peel-away removal (left) and slitter removal (right).

while curved-tip catheters are used to access swiftly and smoothly veins with sharply angled side branches.

In addition to fixed-curve inner catheters, steerable inner catheters are also available (Fig. 14.6).

Potential advantages of this approach are improved maneuverability and reduction of coronary sinus cannulation times; deeper cannulation with the outer catheter (the one that can guide the pacing lead); performance of a selective venogram without a Swan–Ganz catheter; and deeper seating of guide wires into the target branch vein.

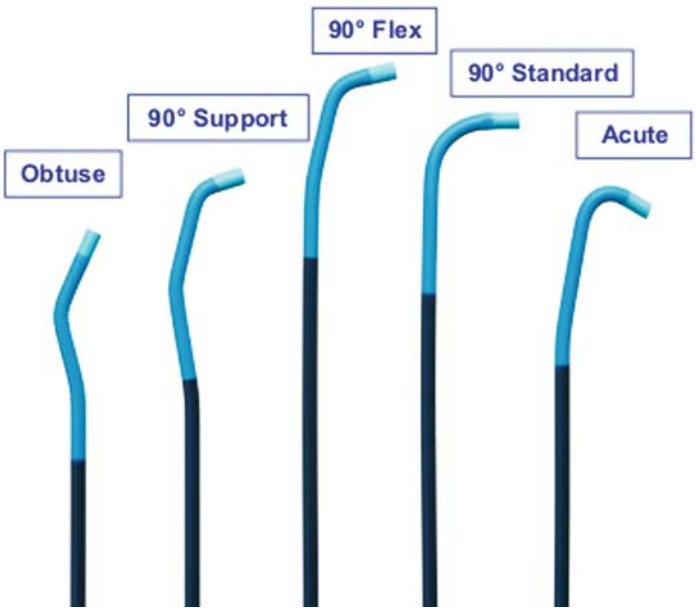

Fig. 14.5 Fixed-curve inner catheters.

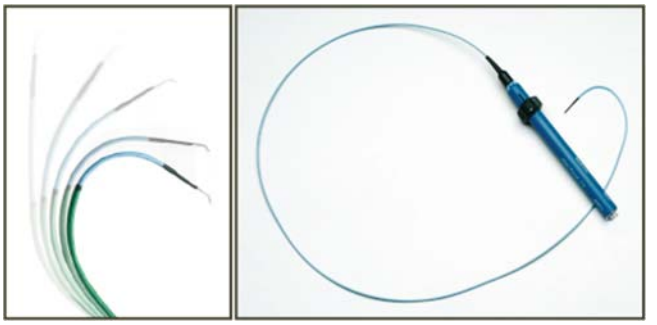

Fig. 14.6 Steerable inner catheter.

Left Ventricular Leads

The integrated system of steerable and fixed-shape catheters and over-the-wire leads have increased implantation success rate, lowered dislodgment rates, and improved electrical performance. The currently available over-the-wire leads have different diameters and lengths, straight and preshaped tip unipolar leads, straight and preshaped tip bipolar leads, allowing advancement and fixation of the lead into small and large branch veins, at the desired pacing site.

The straight lead must be wedged deep in the vein for stability, but in the bipolar configuration the ring may be floating in the vein, without electric contact. (Fig 14.7). Preshaped end leads allow navigation of acute angles and can be positioned at a stable site in a wide range of vein sizes and tortuousities. Different tip shapes have been introduced: angled, S-shaped,

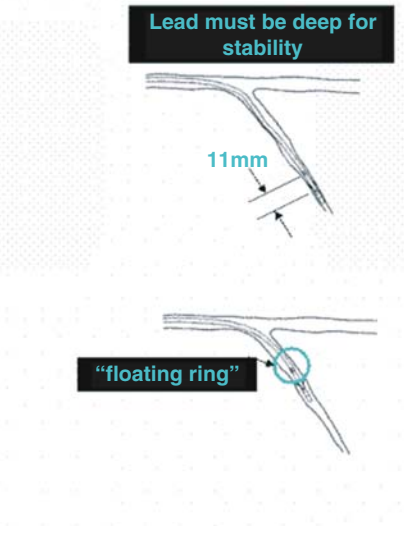

Fig. 14.7 Floating ring of a bipolar straight lead.

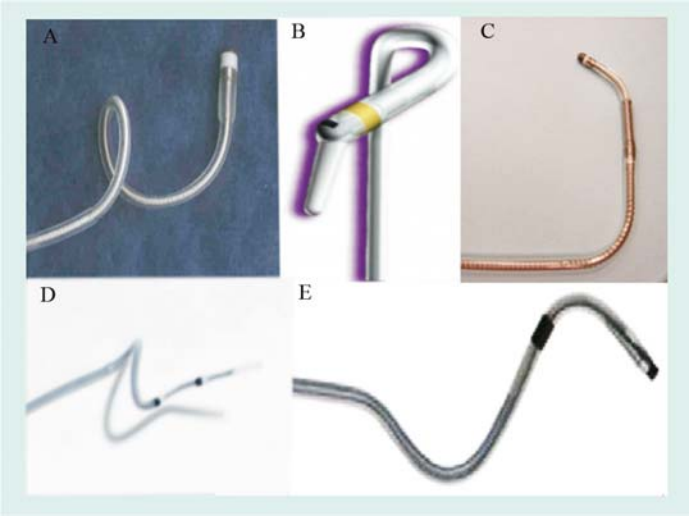

Fig. 14.8 Different tip shapes available: *A*, Helix tip; *B*, double leftward curve tip; *C*, angled tip; *D*, spiral tip; *E*, S-shaped tip.

helix, spiral, double-leftward curvature (Fig 14.8). Steroid elution ensures low acute and chronic thresholds. The proximal body may be coated by polyurethane for better pushing and handling, while the flexible distal body is coated by silicone for tracking. The leads may also be equipped with a stylet, whose stop is located near the tip, which allows full straightening of and maximal load transmission to the distal end of the lead. Some manufacturers provide an integrated distal tip seal, which prevents or reduces blood intrusion into the lead lumen during the implantation procedure and once implanted (Fig. 14.9). A fluoroscopic marker, when present, is a further assist in correct placement. Preshaped and bipolar leads allowing a more basal stimulation are the best way to avoid phrenic nerve stimulation and to obtain acceptable thresholds. Moreover, thresholds tend to become lower when anodal surface area is significantly larger than the cathodal surface area.

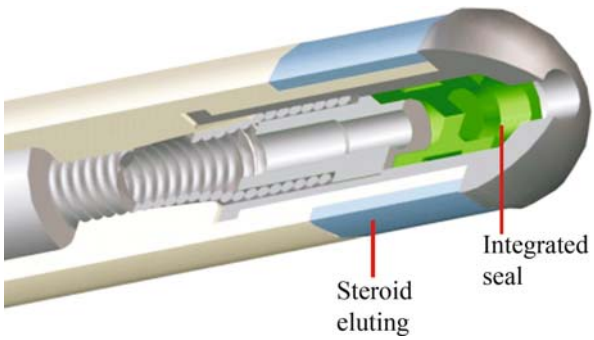

Fig. 14.9 Section of the tip of bipolar lead.

Fig. 14.10 A deployable lobes tip lead.

One of the main challenges in LV implantation is stability of the lead. Recently, a specifically designed lead to address this issue, by means of a unique active fixation system, has been introduced.

The lead body presents three sets of deployable lobes that improve fixation in medium to large veins and allow positioning in more proximal locations. The lobes are soft and conform to veins, and their maximum deployment is approximately 6.6–8.0 mm (approximately 22–24 F). A radiopaque indicator ring is placed between each set of lobes. The spacing between rings indicates the degree of deployment under fluoroscopy.

A push tubing is present all along the lead to facilitate lobe deployment and undeployment. It is made of polyurethane and has a hydrophilic coating on the inner diameter. Moreover, the lead presents an angled distal end to help subselect cardiac veins and maintain electrode tip wall contact, as well as over-the-wire and stylet delivery method options, as the most recent commercially available leads (Fig. 14.10).

For almost five decades, the predominant insulation use in implantable cardiac leads has been one of two choices: silicon rubber (a thermoset) or

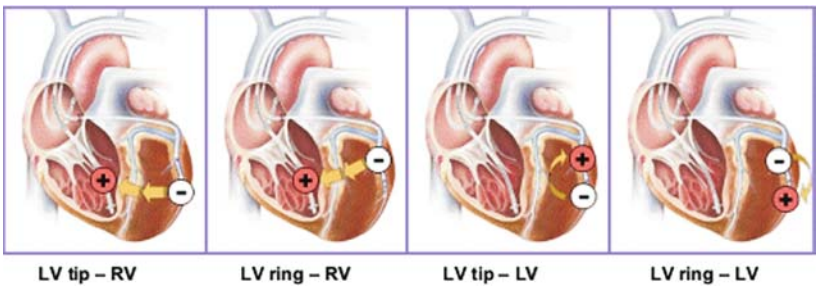

Fig. 14.11 Electronic repositioning.

polyether polyurethane (a thermoplastic). A new material, called Optim™, has recently been made available in both pacing and ICD leads.

It was developed to combine the desirable attributes of both silicon rubber and polyurethane, but none of the undesirable attributes. It is expected that leads made with the new Optim™ material will have significantly improved features, such as handling and else of implant and especially better reliability.

Newer CRT systems, that use a bipolar left ventricular lead, offer an option for noninvasively programming multiple pacing configurations (Fig. 14.11). Thus, the physician may choose the lowest threshold configuration and overcome phrenic nerve stimulation, thus preventing invasive lead repositioning [16]. There are several potential mechanisms underlying this "electronic repositioning" [17]: change of the amount of excitable myocardium, change of the relationship of the electrical vector to fiber orientation, change of the cathodal site [16, 18, 19], but the main reason why switching to a different pacing configuration improves the capture threshold remains unknown.

Conclusion

Tools for cardiac resynchronization continue to undergo rapid technological evolution: the new lead systems that successfully navigate and achieve effective, safe, and permanent pacing of the left ventricle increase the success rate in providing beneficial therapy to appropriate candidates.

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15

New Pacing Algorithms and Functions in CRT Devices

Roland X. Stroobandt, Alfons F. Sinnaeve, and S. Serge Barold

Cardiac resynchronization therapy (CRT) using biventricular (BiV) pacing reduces morbidity and mortality [1] in patients with mechanical left ventricular asynchrony and heart failure refractory to optimal medical treatment. By partially restoring the coordination between both ventricles, CRT improves systolic mechanical efficiency [2], reduces mitral regurgitation [3], and enhances ventricular relaxation [4].

To obtain maximal hemodynamic benefit by CRT, constant delivery of biventricular pacing is required, and atrioventricular (AV) delay [5, 6] and VV timing [7] should be optimized.

This chapter describes new algorithms that provide automaticity to some of the functions of CRT devices.

Automatic Left Ventricular Threshold Measurement

Experience with CRT therapy has shown that a number of factors can affect left ventricular (LV) pacing and interfere with the consistent delivery of optimal CRT. Leads in the coronary veins are more prone to dislodgment and may develop high or variable pacing thresholds. In contrast with right ventricular (RV) leads, there are no data about daily threshold fluctuations related to LV pacing. Moreover, the safety margin for LV pacing may have to be reduced to avoid phrenic nerve stimulation.

LV Capture Management (LVCM) is a new feature developed by Medtronic, Inc., Minneapolis, USA to address LV pacing.

CRT devices differ from conventional pacemakers and ICDs by using leads in the right ventricle and left ventricle. Consequently, capture in one ventricle could potentially be assessed by sensing the response in the opposite ventricle. For instance, an LV paced event will conduct to the RV where it can be sensed by the RV electrodes (Fig. 15.1).

LVCM automates LV threshold measurements by using an LV capture detection algorithm based on timing of the RV sensed event that follows a LV paced event. The algorithm operates in the tracking (DDD, DDDR) and nontracking modes (VVIR, DDIR).

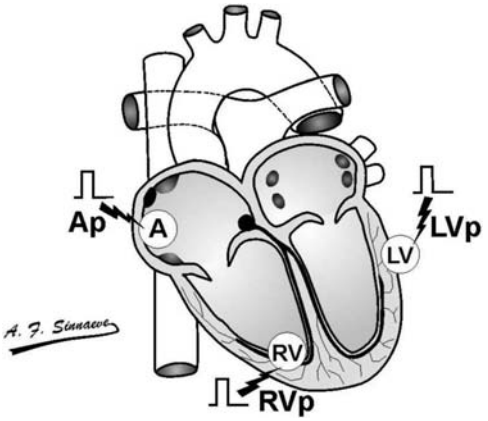

Fig. 15.1 Scheme of a biventricular device. Capture in one ventricle can be assessed by sensing the response in the opposite ventricle. *A*, atrium; *Ap*, atrial pacing pulse; *LV*, left ventricle; *LVp*, left ventricle pacing pulse; *RV*, right ventricle; *RVp*, right ventricle pacing.

LVCM in Tracking Modes

During *tracking modes* in patients with both intact AV conduction and interventricular conduction, an RV sensed (RVs) event after an LV paced (LVp) event may either be due to conduction over the AV node depolarizing the RV or interventricular conduction from the left ventricle to the right ventricle.

Therefore, the algorithm needs to differentiate between interventricular conduction intervals (LV to RV) related to capture by LVp and AV intervals caused by loss of LV capture (Fig. 15.2).

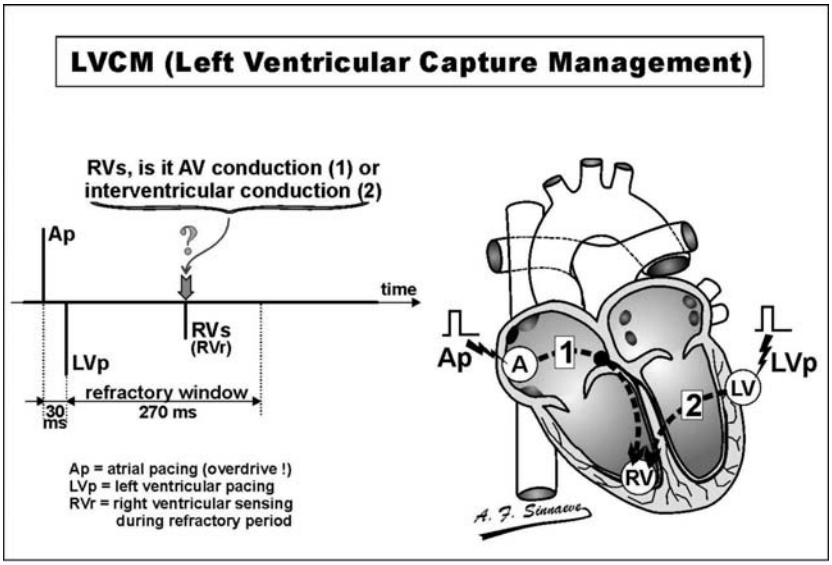

Fig. 15.2 Differentiation between atrioventricular and interventricular conduction during tracking modes. *RVs*, sensed right ventricle event; *A*, atrium; *LV*, left ventricle; *RV*, right ventricle.

Capture is determined when RVs event is secondary to interventricular conduction (i.e., from LV to RV). In order to measure the LVp–RVs time, RV blanking is shortened and the interventricular refractory period defined so that the first intrinsic ventricular event falling within it will be considered refractory (as RVr) and not affect pacemaker timing.

LV to RV Conduction Test

The algorithm first performs an *LV to RV conduction test* (Fig. 15.3). The device overdrives the heart, looks for an RVs event within a capture detection window, and measures the LVp to RVs conduction time in consecutive cycles. If unstable interventricular conduction is detected (four consecutive LV–RV intervals differing by >30 ms) the LV pacing threshold search (LVPTS) is aborted. If the device does not pass the LVp–RVs conduction test, the LVPTS is retried after 30 min.

AV Conduction Test

After performing the LVp–RVs conduction test, the device performs an *AV conduction test* (Fig. 15.4). The device continues overdrive pacing at a rate faster than the sinus rate to promote extension of AV conduction. The AV conduction time is then measured.

LV Capture

Capture is considered to have occurred whenever an RVs event is detected within the *capture detection window* (Fig. 15.5).

Absence of an RVs event within that window is consistent with spontaneous AV conduction and indicates loss of capture.

LV Threshold Measurement

An *LV threshold measurement* is performed once a day (with a first attempt at 1 AM). If conditions are unfavorable (e.g., rate too fast, atrial and ventricular

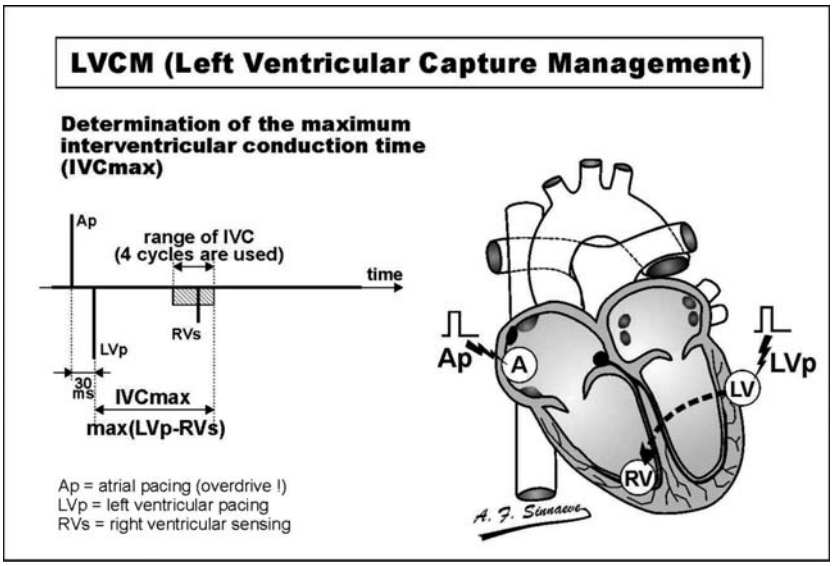

Fig. 15.3 LV to RV conduction test (see text for explanation). *IVC*, interventricular conduction.

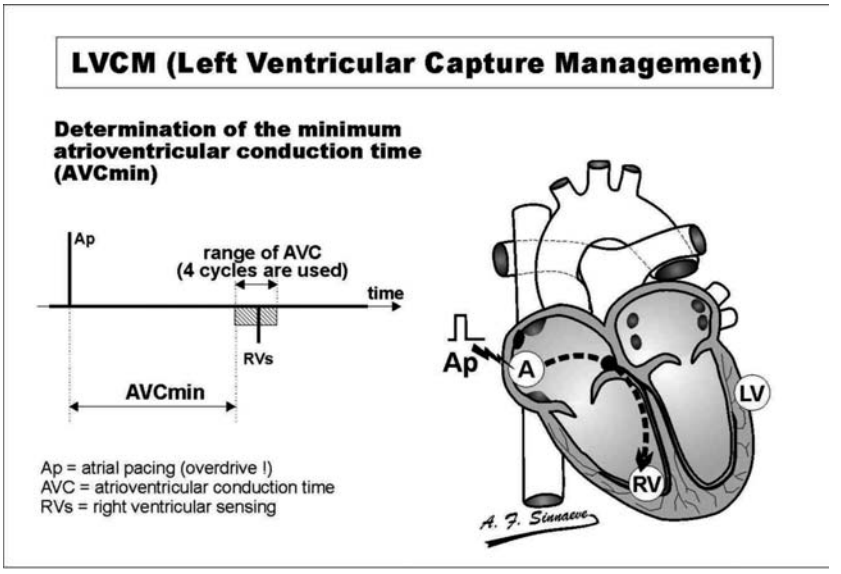

Fig. 15.4 Atrioventricular conduction test (see text for explanation). *AV min*, minimum AV interval

extrasystoles), the measurement is delayed by 30 min. The threshold search starts at a setting below the last measured threshold and decrements until a subthreshold setting is discovered (Fig. 15.6). The output is then incremented until a suprathreshold impulse is confirmed. The nominal voltage safety margin is 1.5 V greater than the LV threshold. The clinician can choose to limit the output to maximum-adapted amplitude to avoid phrenic

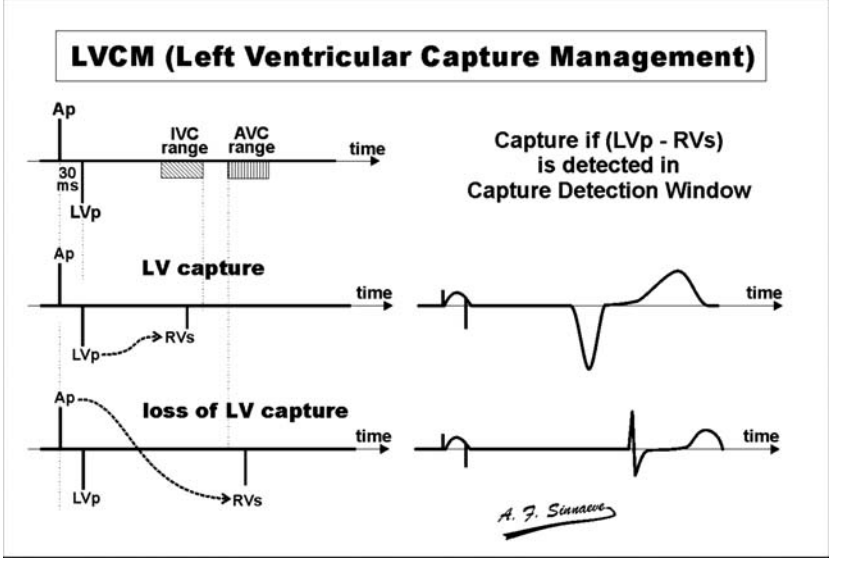

Fig. 15.5 LV capture (see text for explanation). *Ap*, atrial pacing; *LVp*, left ventricular pacing; *IVC*, interventricular conduction time; *AVC*, atrioventricular conduction time; *RVs*, sensed RV event.

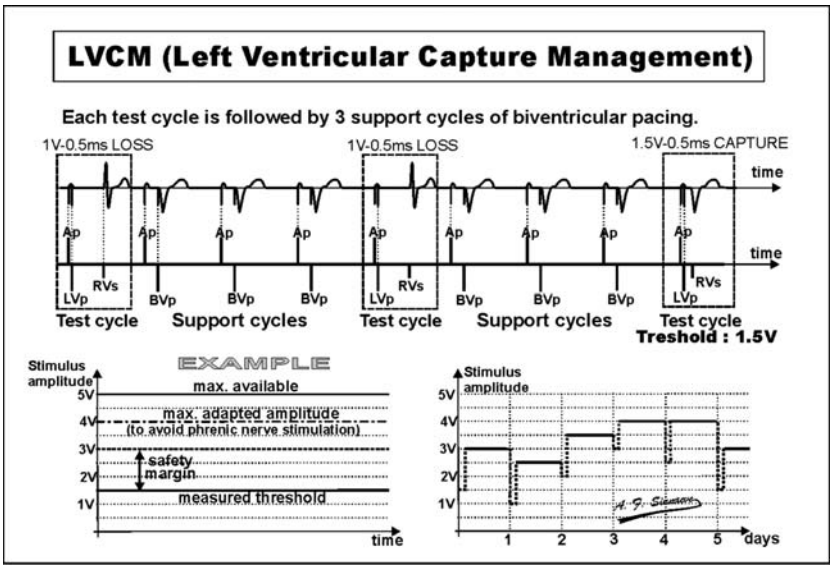

Fig. 15.6 LV threshold measurement *Upper panel*: During a test cycle, the threshold search starts at a setting below the last measured threshold and decrements the output until a subthreshold setting is discovered (loss of capture). Each test cycle is followed by a support cycle. The output is then incremented until a suprathreshold impulse is confirmed (capture). *Left lower panel*: After determining the LV threshold, the output will be set at a safety margin of 1.5 V above threshold. To avoid phrenic nerve stimulation, a maximum LV amplitude can be programmed. *Right lower panel*: Example of daily LV threshold measurements. *Ap*, atrial pacing; *LVp*, left ventricular pacing; *RVs*, sensed RV event; *BVp*, biventricular pacing; *V*, volt.

nerve stimulation. The LV amplitude value will not be increased above this setting, even if the voltage margin cannot be maintained. The maximum programmable output in the Concerto-D, Medtronic is up to 8 V.

LVCM in Non-Tracking Modes

LVCM also operates in nontracking modes (VVIR or DDIR). In this situation, the test paced event is delivered early enough to differentiate interventricular conduction (LV–RV) from the underlying rhythm. With a *subthreshold LVp*, the time measured to the RVs event reflects the underlying ventricular rhythm, while with a *suprathreshold LVp event,* the time measured to the RVs event constitutes the LV–RV interval.

Automatic Optimization of AV Delay and VV Timing

Maximum hemodynamic benefit requires optimization of atrioventricular (AV) and interventricular (VV) intervals [8]. These procedures not only need a lot of expertise but they are also time-consuming and costly.

AV Optimization

A number of *Doppler echocardiographic indices* has been investigated and correlated with invasive hemodynamic measurements to determine the optimal AV delay in CRT patients [5] (Fig. 15.7).

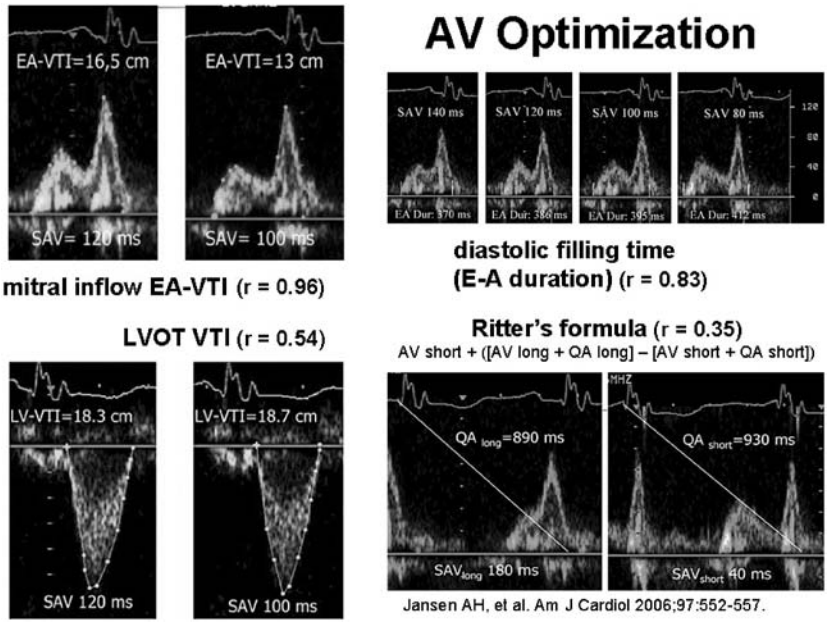

Fig. 15.7 AV optimization. Correlation of different Doppler echocardiographic indices used to determine the optimal AV delay (with permission of the authors). *SAV*, sensed AV interval; *VTI*, velocity time integral; *LVOT*, left ventricular outflow tract.

In a recent study comparing various echocardiographic indices with the invasively obtained (dP/dt)max, the best performing Doppler echocardiographic method was the velocity time integral (VTI) of the transmitral flow showing a correlation of 0.96, followed by diastolic filling time (or EA duration) showing a correlation of 0.83. The aortic VTI performed less well (r = 0.54), and Ritter's formula showed the worst correlation (0.35). Ritter's formula was developed for evaluating patients with DDD pacemakers for high-degree AV block [9]. In heart failure with elevated LV end-diastolic pressure, the mitral valve closure point will immediately follow the A-wave making it difficult with the Ritter method to judge whether the A-wave is abbreviated or not.

VV Optimization

Doppler echocardiographic and acute invasive hemodynamic studies have shown that programming of the V-V delay may further increase stroke volume after optimizing the AV delay [7, 10]. V-V programming may be especially important in patients with ischemic cardiomyopathy where slow conduction in the presence of scar tissue necessitates LV preexcitation.

Automatic AV Delay and VV Interval Timing in CRT Devices

A new algorithm called QuickOpt (available in all CRT-D devices) to optimize CRT therapy automatically was developed by St. Jude Medical, St. Paul, Minneapolis, USA.

Automatic AV Optimization

Optimal AV Delay During Atrial Sensing During atrial sensing, the algorithm first measures the P-wave duration. By means of a proprietary formula, the optimal AV delay during atrial sensing (PVopt) is then calculated (Fig. 15.8).

Optimal AV Delay During Atrial Pacing The optimal AV delay during atrial pacing (AVopt) is then calculated using the optimal AV delay obtained during atrial sensing (PVopt) using another formula (Fig. 15.9).

Automatic Optimization of VV Delay

The goal of the intracardiac electrogram-based VV system is to optimize VV timing so that the LV is fully depolarized as fast as possible depending upon the intrinsic and paced interventricular conduction patterns (Fig.. 15.10).

For optimization of the VV delay, the algorithm first measures the *intrinsic interventricular depolarization delay* delta (△) between the RV and LV during atrial pacing or sensing (Fig. 15.11). The device assumes that the ventricle that is detected last will have to be stimulated first. Internally, the device assigns a "sign" to the measured delta (positive if LV has to be paced first, negative in case of RV first).

After measurement of the intrinsic depolarization, the algorithm determines the *RV to LV and LV to RV conduction time* by pacing one ventricle and looking for the response in the opposite ventricle (Fig. 15.12). Epsilon (ε) represents the difference between the LV–RV and RV–LV conduction intervals and is a measure of the interventricular conduction delay. As epsilon is used as a correction factor depending on wave front velocity, the sign (plus-minus) is important. This means that if the conduction is slower from the left lead, "epsilon" will be positive.

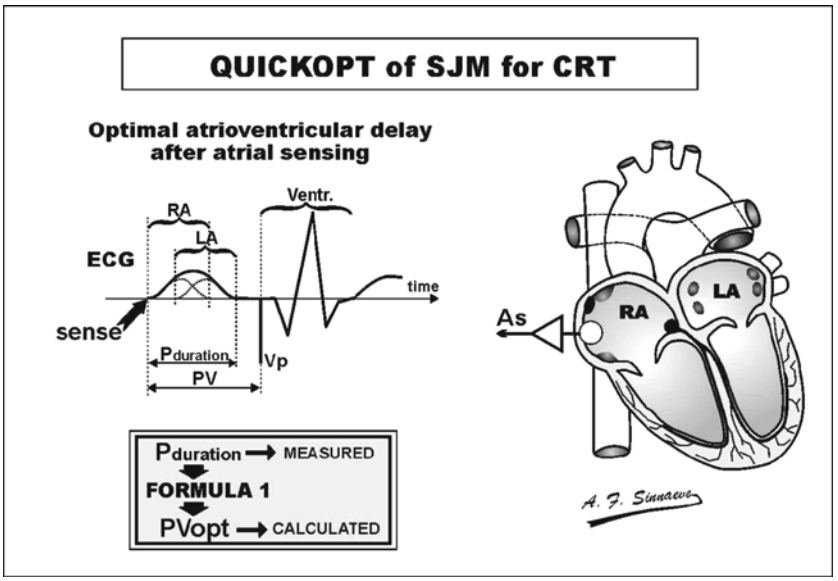

Fig. 15.8 Calculation of the optimal atrioventricular delay after atrial sensing. *RA*, right atrium; *LA*, left atrium; *As*, atrial sensing; *FF LA*, far-field atrial electrogram; *Ventr*., ventricular electrogram; *Vp*, ventricular pacing; *PE*, P-wave electrogram; *PV*, PV delay; *PVopt*, optimal AV delay during atrial sensing.

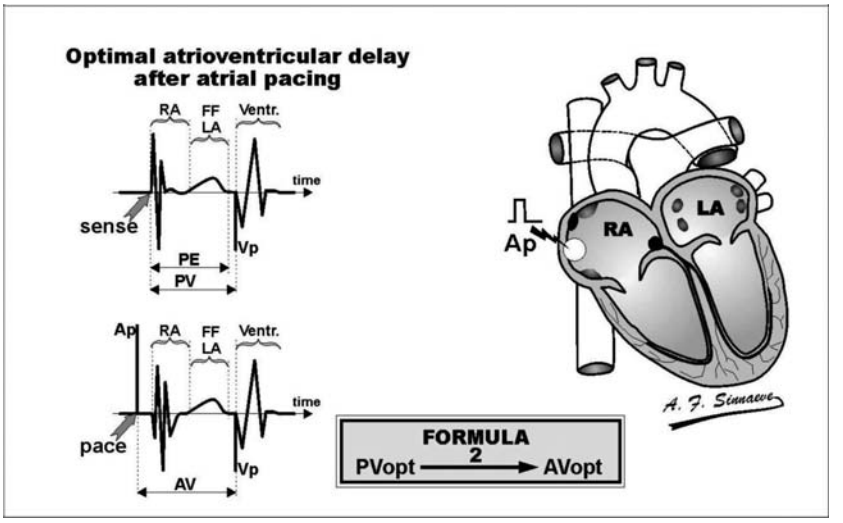

Fig. 15.9 Calculation of the optimal atrioventricular delay after atrial pacing. *RA*, right atrium; *LA*, left atrium; *Ap*, atrial pacing; *Ventr*., ventricular electrogram; *Vp*, ventricular pacing; *PV*, PV delay; *PVopt*, optimal AV delay during atrial sensing; *AV opt*, optimal AV delay during atrial pacing

Finally the *optimal V-V delay* (VVopt) is determined (Fig. 15.13) as half the sum of the intrinsic depolarization delay and the interventricular conduction delay [0.5 × (delta + epsilon)].

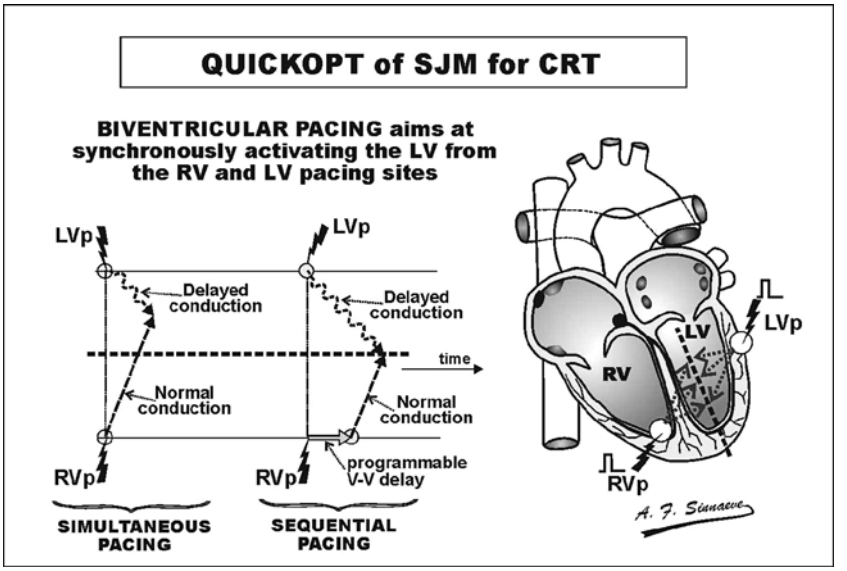

Fig. 15.10 Simultaneous versus sequential biventricular pacing. During simultaneous RV and LV pacing, the ventricle may contract asynchronously due to delayed conduction in the LV. Using sequential pacing by pacing the LV first (programming negative LV offset), the LV contracts synchronously. *RV*, right ventricle; *RVp*, RV pacing; *LV*, left ventricle; *LVp*, left ventricular pacing.

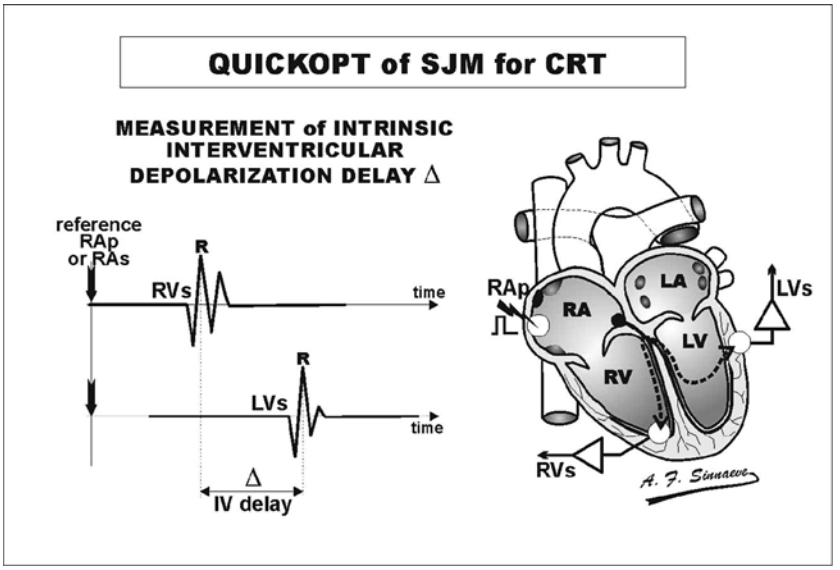

Fig. 15.11 Measurement of the intrinsic interventricular depolarization delay during atrial pacing or sensing. *RA*, right atrium; *RAp*, right atrial pacing; *RAs*, right atrial sensing; *LA*, left atrium; *R*, R-wave; *RV*, right ventricle; *RVs*, sensed RV electrogram; *LV*, left ventricle; *LVs*, sensed LV electrogram; *IV* , interventricular

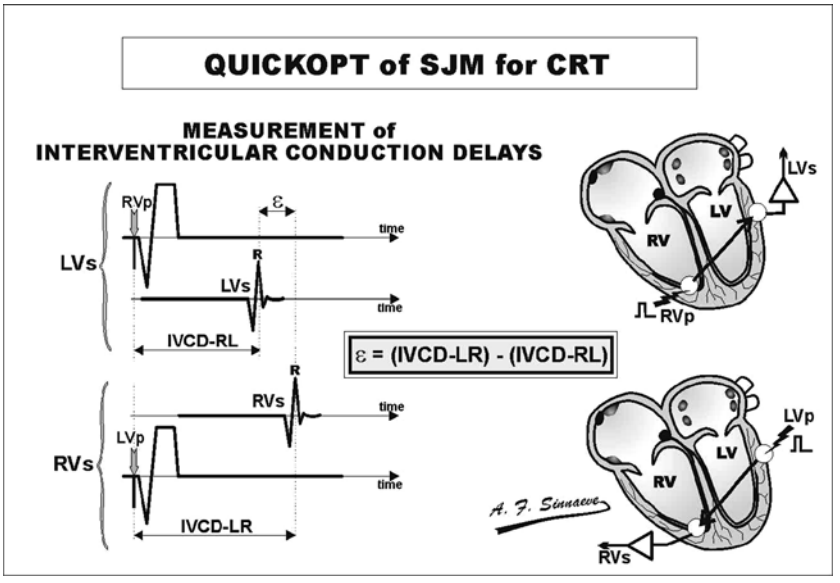

Fig. 15.12 Measurement of interventricular conduction delays. *LV*, left ventricle; *LVs*, sensed LV electrogram; *LVp*, left ventricular pacing; *R*, R-wave; *RV*, right ventricle; *RVp*, right ventricular pacing; *RVs*, sensed RV electrogram; *ε*, epsilon is a correction factor; *IV*, interventricular; *IVCD-LR*, interventricular conduction delay between left and right ventricle; *IVCD-RL*, interventricular conduction delay between right and left ventricle.

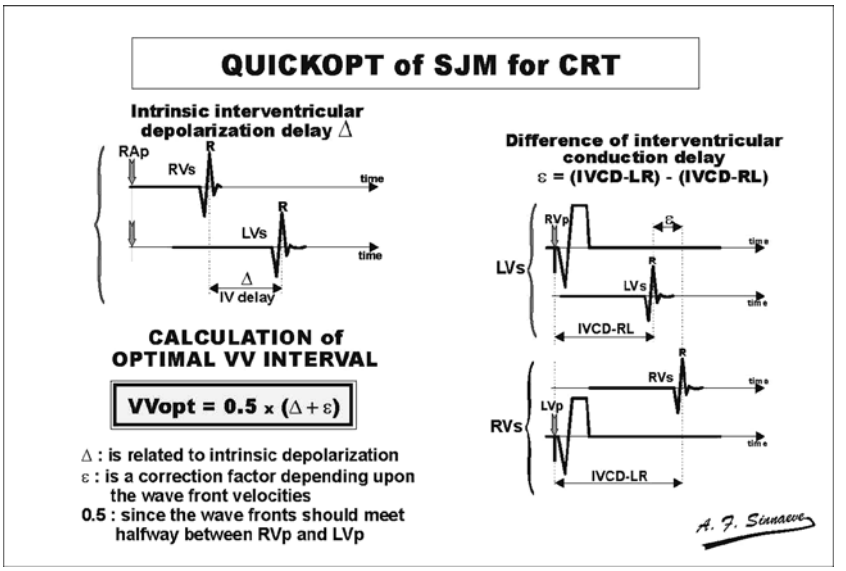

Fig. 15.13 Calculation of optimal VV interval. *VVopt*, optimal VV interval; *LV*, left ventricle; *LVs*, sensed LV electrogram; *LVp*, left ventricular pacing; *R*, R-wave; *RV*, right ventricle; *RVp*, right ventricular pacing; *RVs*, sensed RV electrogram; *ε*, epsilon is a correction factor; *IV*, interventricular; *IVCD-LR*, interventricular conduction delay between left and right ventricle; *IVCD-RL*, interventricular conduction delay between right and left ventricle

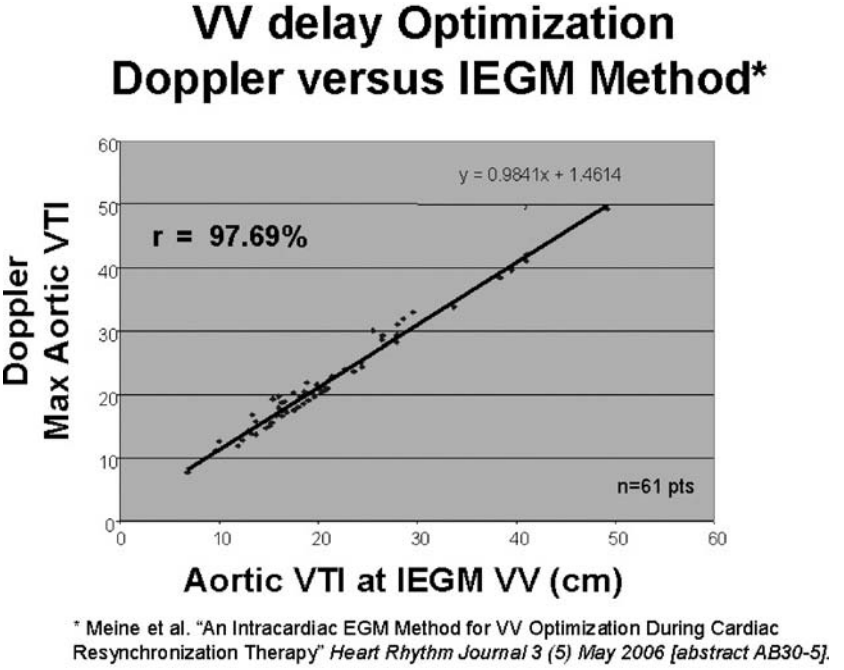

Fig. 15.14 VV delay optimization. Correlation between Doppler versus intracardiac electrogram method. *VTI*, velocity time integral; *IEGM*, intracardiac electrogram.

If delta is positive and epsilon positive, the sum is positive and LV is first. If delta is negative and epsilon negative, the sum is negative and RV is first. If delta is positive and epsilon negative (or vice versa), the sum can either be positive or negative depending on the relative values of delta and epsilon. But in any case, if the sum is positive, LV will be activated first. If the sum is negative, the RV will be activated first. The device performs programming of the VV delay automatically according to the obtained values.

The VV optimization was validated in a study comparing the optimal aortic VTI determined either by Doppler measurements or intracardiac electrogram method [11]. Both methods were concordant showing a correlation coefficient of 97.69% with 95% confidence (Fig. 15.14).

Conclusion

In CRT patients the consistent delivery of BiV pacing is essential. Automatic measurement and adaptation of the LV threshold may be helpful in managing patients with BiV devices. This is particularly important because there are no data about fluctuations of the LV threshold from day to day. Control of LV pacing output just above threshold could be important in patients with phrenic nerve stimulation. Furthermore, the current testing procedures for AV and VV optimization require a great deal of skill in echocardiographic and Doppler measurements, which is not always available. These new algorithms may bring us closer and closer to the fully automatic device for CRT.

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16

Significance of Latency During Left Ventricular Pacing for Cardiac Resynchronization Therapy

Bengt Herweg, Arzu Ilercil, Chris Madramootoo, Nadim G. Khan, and S. Serge Barold

Simultaneous biventricular pacing is unsuccessful in approximately 30% of patients [1, 2, 3, 4, 5, 6]. In some patients, lack of hemodynamic improvement with cardiac resynchronization therapy (CRT) may be due to regional variations in electrical excitability and impulse propagation such as electrical latency, slow impulse propagation in proximity of the lead, or more globally delayed intra- and interventricular conduction [7, 8, 9, 10]. All of these conditions may affect the balance between right ventricular (RV) and left ventricular (LV) activation during biventricular stimulation and affect LV contractility. This discussion reviews the significance of electrical latency during LV stimulation from the coronary venous system and describes the electrocardiographic and hemodynamic findings encountered in patients with LV latency complicating CRT.

Definition and Pathophysiology of Latency

The interval from the pacemaker stimulus to the onset of the earliest paced QRS complex on the 12-lead ECG is called *latency*, and during RV pacing this interval normally measures <40 ms. Pronounced latency is uncommon during RV pacing at physiologic rates [11]. A prolonged latency interval represents first-degree pacemaker exit block [12]. The latter may progress to type I second-degree Wenckebach exit block characterized by gradual prolongation of the spike to QRS interval eventually resulting in an ineffectual stimulus (Fig. 16.1) [7, 12, 13]. Further progression leads to 2:1 or more severe forms of exit block and eventually to complete loss of capture. Latency must be differentiated from so-called exit block, which is a physiologic phenomenon related to complete or occasional failure of ventricular depolarization at the pacing threshold in the absence of a prolonged stimulus–QRS interval.

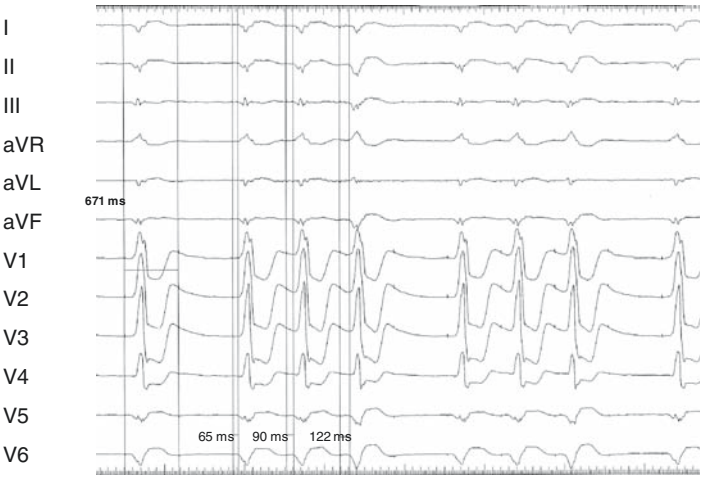

Fig. 16.1 Twelve-lead ECG during left ventricular pacing at 90 beats/min near the pacing threshold (2.5 V at 0.1 ms) showing type I second-degree (Wenckebach) pacemaker exit block characterized by progressive prolongation of the latency interval culminating in total exit block and lack of capture. There is a change in QRS morphology in the extremity leads associated with the longest latency interval during the sequence of Wenckebach exit block. This is probably related to a change in the myocardial conduction pathway in the setting of pronounced exit block from the paced site. (Reproduced with permission from Herweg B, Ilercil A, Madramootoo C, et al. Latency during left ventricular pacing from the lateral cardiac veins: A cause of ineffectual biventricular pacing. Pacing Clin Electrophysiol 2006;29: 574–81).

Latency may be related to non-homogeneous impulse propagation from the paced site, conduction block in proximity to the electrode, or prolonged refractoriness. The conventional surface electrocardiogram (ECG) cannot differentiate latent excitation from delayed propagation in the myocardium around the electrode.

Latency During RV Pacing

The causes of RV latency include RV infarction, anterior myocardial infarction, ischemia, severe myocardial disease, hyperkalemia, and antiarrhythmic drug toxicity (usually class I sodium channel blocking agents) [11,13,14,15]. These abnormalities usually occur in terminal states often as a combination of severe myocardial disease, ischemia, acidosis, hypoxia, antiarrhythmic drug effect, and hyperkalemia (the last two causes being potentially reversible). Consequently, a prolonged latency interval is often associated with a paced QRS complex wider than usual.

Effect of Pacing Rate and Output

Second-degree Wenckebach type pacemaker exit block typically occurs when the pacemaker stimulus is near the capture threshold and excites the surrounding myocardium more slowly than a suprathreshold stimulus [16,17].

Pacemaker exit block usually depends on the amplitude and rate of stimulation. An increase in the pacing rate may prolong the stimulus to QRS interval (and worsen type I exit block) while an increase in the stimulus amplitude may shorten the stimulus–QRS interval and convert type I second-degree to first-degree exit block [16, 17]. Prolonged latency intervals will improve in first-degree exit block by slowing the pacing rate and/or increasing the pacemaker output and worsen by increasing the pacing rate and/or decreasing the pacemaker output. These phenomena, previously documented during RV pacing, were recently observed to occur during LV pacing for CRT (Figs. 16.1 and 16.2) [7].

Latency During LV Pacing

Prolonged LV latency intervals during stimulation from within *epicardial* cardiac veins may be due to interposed venous tissue and epicardial fat preventing direct contact between electrode and LV myocardium. This may also account for the elevated thresholds encountered during LV pacing from cardiac veins. LV latency (normal or abnormal) has not yet been quantified and may be more frequent and more pronounced than latency during *endocardial* RV or LV stimulation. Prolonged LV latency intervals with delayed LV activation can result in a suboptimal hemodynamic CRT response that is potentially correctable by advancing LV stimulation (before RV stimulation) via a programmable interventricular (V-V) delay (Fig. 16.6 and 16.7) [7]. Although LV latency may be one of the explanations of improved hemodynamic response to sequential biventricular pacing, it was not discussed in recent reports about the important role of LV pre-excitation for hemodynamic optimization [18, 19, 20, 21, 22, 23, 24, 25, 26, 27].

Prevalence and Degree of LV Latency

The exact incidence of prolonged latency intervals during LV pacing is unknown. In a series of 150 patients, we have observed latency (>50 ms) during LV pacing on seven occasions. The duration of LV activation delay during simultaneous biventricular pacing that will result in a significant hemodynamic disturbance is unknown. We measured latency intervals on the 12-lead ECG acquired at a speed of 100 mm/s in six patients with CRT devices not suspected of having significantly prolonged latency. The latency interval during RV pacing was 13 ± 12 ms compared with 30 ± 10 ms during LV pacing ($p = 0.06$). LV latency intervals measured in eight patients at double the voltage threshold (24.4 ± 22.0 ms) were longer when compared with latency intervals when pacing at maximum pacemaker output (20.6 ± 19.1 ms, $p < 0.05$) independent of the site of pacing. The difference (delta latency) between right- and left-sided latency intervals during biventricular pacing rather than absolute values determines the hemodynamic consequence of this phenomenon.

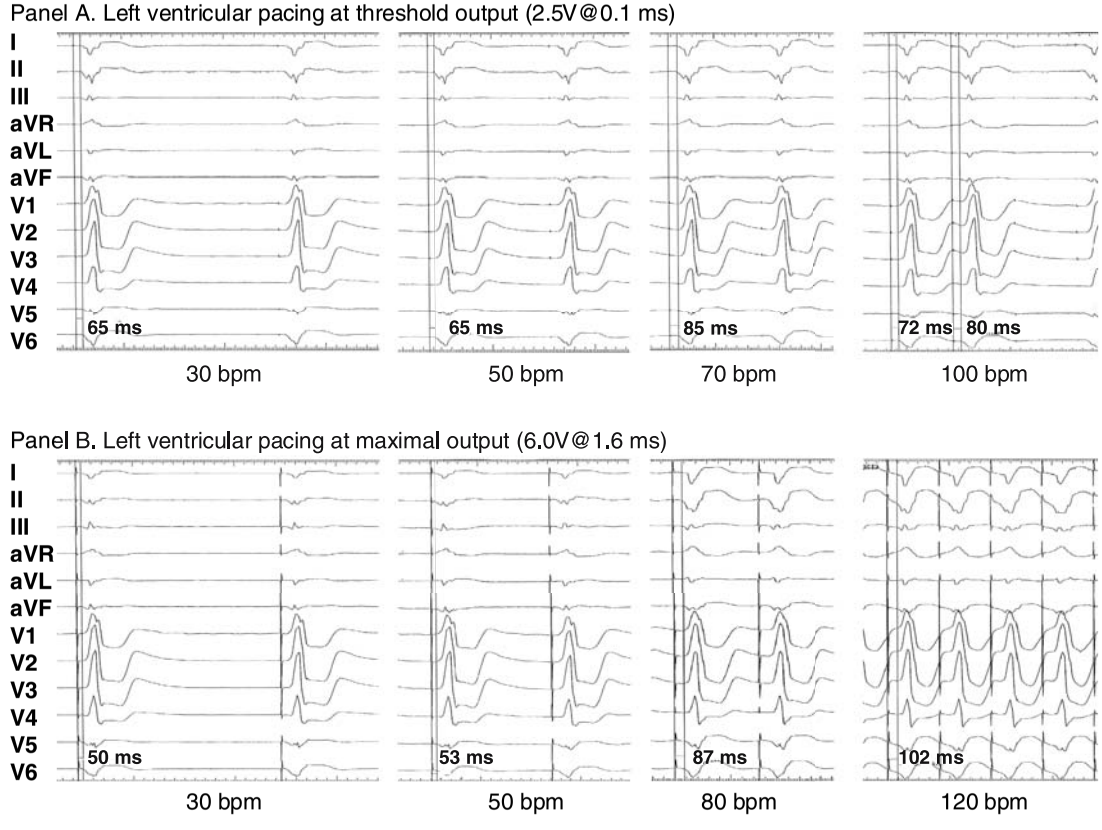

Fig. 16.2 Rate and stimulus-strength dependency of latency during left ventricular (LV) pacing. LV pacing at threshold output (*panel A*) and maximal output (*panel B*) at increasing rates. At both outputs there is rate-dependent prolongation of the latency interval less pronounced at maximal output. At threshold (*panel A*), LV pacing at 100 beats/min results in type I second-degree exit block (as in Fig. 16.1), which was not induced at maximal output at 120 beats/min (*panel B*). There are also rate- and output-dependent changes in QRS morphology indicating that the myocardial conduction pathway is influenced by the prevailing electrophysiologic substrate produced by changing pacing parameters. *bpm*, beats/min. (Reproduced with permission from Herweg B, Ilercil A, Madramootoo C, et al. Latency during left ventricular pacing from the lateral cardiac veins: A cause of ineffectual biventricular pacing. Pacing Clin Electrophysiol 2006;29:574–81).

Electrocardiographic Characteristics of LV Latency

During biventricular pacing with RV apical stimulation, the paced QRS complex is typically characterized by a dominant R-wave in lead V_1, which indicates significant contribution of LV pacing to the fused biventricular paced QRS complex [28,29]. A negative QRS complex in lead V_1 may occasionally occur and probably reflects a different balance between RV and LV activation that may be due to a heterogeneous myocardial substrate (ischemia, scar, His–Purkinje participation, etc.). Although a negative QRS complex in lead V_1 may not necessarily indicate a poor clinical response, several problematic situations should be ruled out. These include incorrect placement of lead V_1 (too high on the chest), lack of LV capture, suboptimal LV lead position or LV lead displacement, ventricular fusion with the conducted QRS complex, and LV latency. Delayed LV depolarization during simultaneous biventricular pacing produces an ECG pattern dominated by RV pacing (Fig. 16.3). In patients with LV latency, programming of incremental left to right ventricular (V-V) delays can unmask a dominant R-wave in lead V_1 during biventricular pacing (Fig. 16.4) [7]. The relationship between the presence and/or amplitude of the paced R-wave in lead V_1 has not yet been correlated with the best hemodynamic response during programming of the V-V interval.

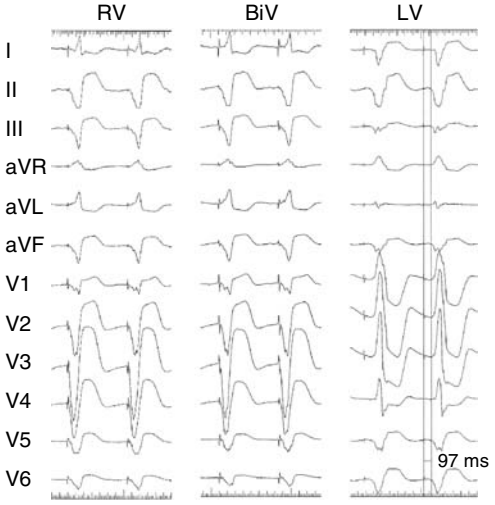

Fig. 16.3 Comparison of QRS morphology in 12-lead ECGs during right, biventricular, and left ventricular pacing in the VVI mode at 80 beats/min. The patient was in atrial fibrillation with complete AV block (excluding fusion with the spontaneous QRS complex). Right and left ventricular outputs were each at twice the threshold voltage. During biventricular pacing (VV delay = 0), the QRS morphology is identical to that of right ventricular pacing (no evidence of biventricular fusion). During left ventricular pacing, the stimulus to QRS latency interval measures 97 ms. *BiV*, biventricular; *LV*, left ventricular; *RV*, right ventricular. (Reproduced with permission from Herweg B, Ilercil A, Madramootoo C, et al. Latency during left ventricular pacing from the lateral cardiac veins: A cause of ineffectual biventricular pacing. Pacing Clin Electrophysiol 2006;29:574–81).

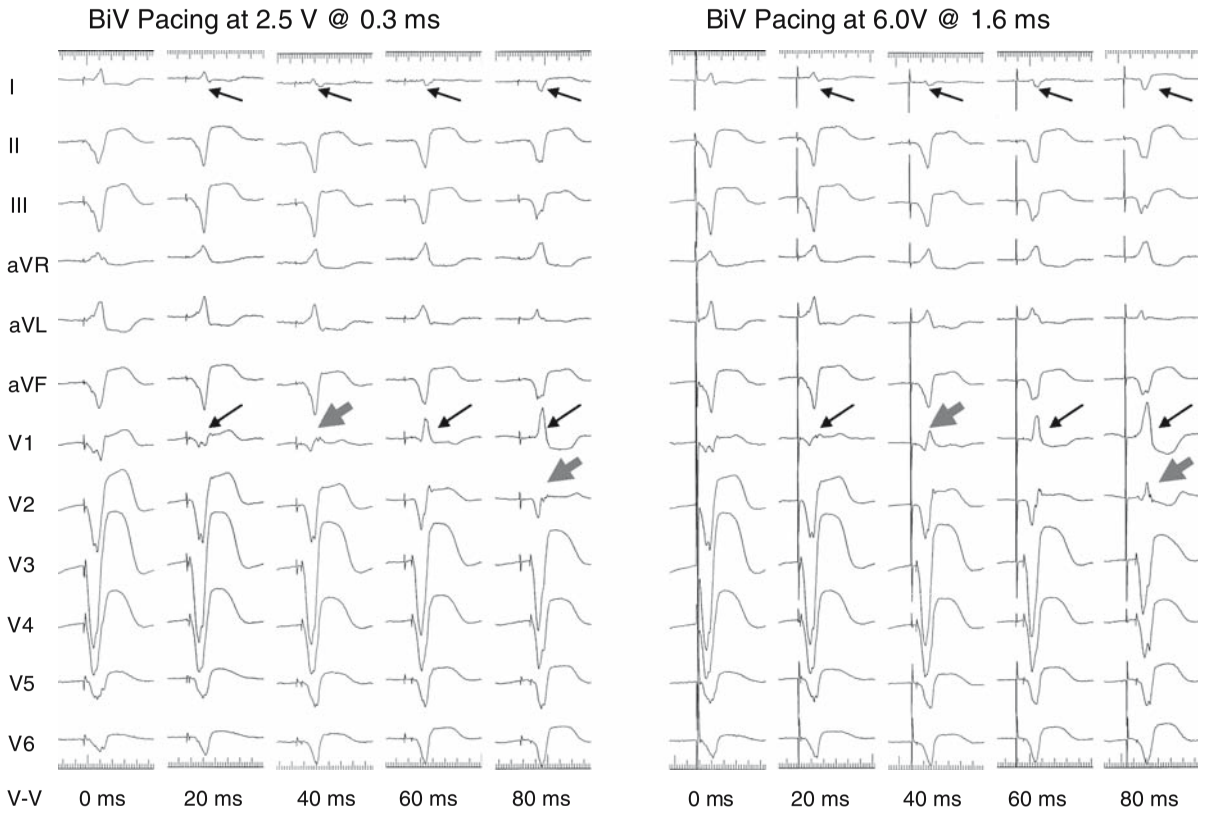

Fig. 16.4 Impact of left ventricular latency on QRS morphology during biventricular pacing (80 beats/min) at incremental left to right ventricular (V-V) delay at 2.5 V at 0.3 ms on the left and 6.0 V at 1.6 ms (maximal output) on the right. There is subtle evidence of biventricular fusion at a V-V delay of 20 ms (*small arrows*). At the same V-V delay during maximal output pacing (*right panel*), the ECG pattern suggests a greater LV contribution to the QRS complex (*large arrows*). *BiV*, biventricular pacing. (Reproduced with permission from Herweg B, Ilercil A, Madramootoo C, et al. Latency during left ventricular pacing from the lateral cardiac veins: A cause of ineffectual biventricular pacing. Pacing Clin Electrophysiol 2006;29: 574–81).

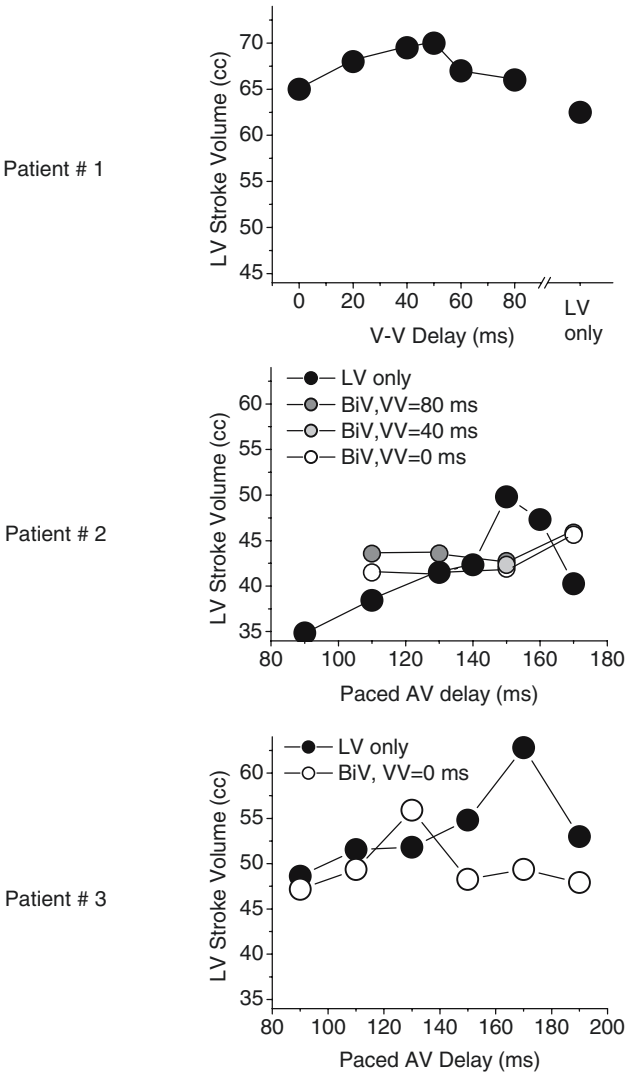

Fig. 16.5 Doppler-derived stroke volume (product of LV outflow tract area and LV outflow tract velocity time integral) during optimization of interventricular and atrioventricular timing measured at a rate of 80 beats/min. Patient 1 (*upper panel*; LV latency interval = 97 ms) was in permanent atrial fibrillation and complete AV block and hence only interventricular (V-V) timing in the VVI mode was assessed. Stroke volume was maximal (70 cm^3) when LV stimulation was advanced by 50 ms when compared with simultaneous biventricular pacing (65 cm^3). In patients 2 and 3 (LV latency intervals 97 and 40 ms, respectively), AV sequential left ventricular pacing was superior to AV sequential biventricular pacing. In patient 2 (*middle panel*), who had a device with programmable V-V timing, AV sequential left ventricular pacing was superior to biventricular pacing with advanced left ventricular activation. *AV*, atrioventricular; *BiV*, biventricular; *LV*, left ventricular. (Reproduced with permission from Herweg B, Ilercil A, Madramootoo C, et al. Latency during left ventricular pacing from the lateral cardiac veins: A cause of ineffectual biventricular pacing. Pacing Clin Electrophysiol 2006;29:574–81).

Echocardiographic Findings Associated with LV Latency

In patients with LV latency, echocardiographic guided V-V optimization may show higher Doppler-derived stroke volumes (product of LV outflow tract area and LV outflow tract velocity time integral) and ejection fraction during monochamber LV pacing or when LV stimulation is advanced when compared with simultaneous biventricular pacing (Fig. 16.5).

We have observed inferolateral akinesis or severe hypokinesis in some patients with prolonged LV latency intervals [7]. In these patients, independent of the etiology of the underlying cardiomyopathy, severe wall motion abnormalities involved the area of the LV lead implantation site. This is concordant with recent reports about low response rates to CRT in patients with LV dyssynchrony and posterolateral scar as demonstrated by echocardiography and contrast-enhanced magnetic resonance imaging (MRI) [30, 31]. In these studies, the role of latency was not mentioned, and no adjustments to pacing mode or V-V interval were made during the first 6 months of CRT. Discordant with these observations is one report where LV lead proximity to akinetic segments did not affect acute hemodynamic and clinical response to CRT [32].

Device Programming in Patients with LV Latency

Contemporary biventricular devices permit programming of the interventricular (V-V) interval to optimize LV hemodynamics. To advance LV stimulation in patients with a unipolar LV lead (and a shared anode on the RV lead), the LV output needs to be programmed below the threshold for RV anodal capture (in some patients, this may be impossible due to loss of LV capture above the anodal threshold) [33, 34, 35]. Our observations suggest that patients with pronounced LV latency and an older biventricular device without programmability of the V-V interval or one with an insufficiently long V-V interval may obtain a better hemodynamic response with monochamber LV pacing with the RV channel turned off (or to subthreshold output)[7].

We reported that LV latency intervals can be shortened by increasing the stimulus strength [7]. Other investigators have shown that increasing LV stimulus output decreases interventricular conduction time in patients with biventricular pacing systems [36, 37]. Increasing output strength in all likelihood depolarizes larger volumes of myocardium by creating a larger virtual electrode, and this may be of particular importance during pacing of diseased myocardium.

Conclusion

LV latency can be the cause of a suboptimal hemodynamic response to simultaneous biventricular pacing. Delayed LV depolarization related to latency during simultaneous biventricular pacing generates an electrocardiographic pattern dominated by RV stimulation. Advancing LV stimulation or programming the device to monochamber LV pacing can result in immediate hemodynamic and symptomatic improvement.

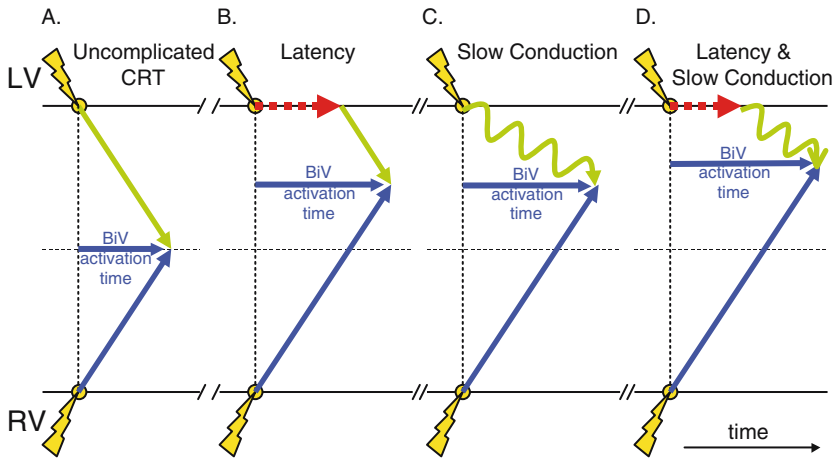

Fig. 16.6 Diagrammatic depiction of the significance of LV latency and slow conduction during simultaneous biventricular pacing. (**A**) During uncomplicated cardiac resynchronization therapy (CRT), there is undisturbed impulse propagation from both pacing sites leading to balanced fusion of right and left ventricular wavefronts. (**B**) In presence of prolonged LV latency (*red arrow*), LV activation occurs late and more myocardium is depolarized by the RV wavefront leading to a prolonged biventricular activation time. (**C**) Slow conduction in proximity to the LV pacing site (due to scar tissue or myocardial fibrosis) has similar implications. (**D**) Abnormal LV latency and slow conduction in proximity to the LV pacing site may coexist in some patients. Major portions of the LV are depolarized by the RV wavefront with minimal fusion and further prolongation of the biventricular activation time. *BiV*, biventricular; *LV*, left ventricular; *RV*, right ventricular.

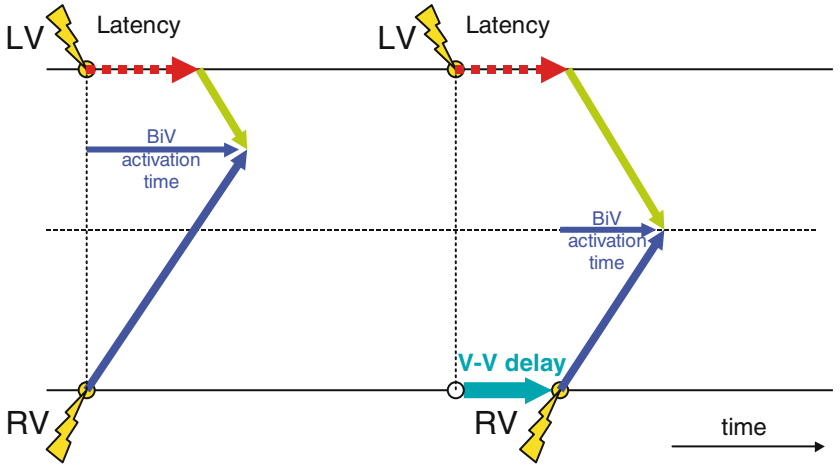

Fig. 16.7 Compensatory programming for LV latency. In presence of abnormal LV latency (*red arrow*), simultaneous stimulation of both ventricles (*left*) results in late LV activation, and more myocardium is depolarized by the RV wavefront. Programmability of the interventricular (V-V) interval permits preactivation of the left ventricle to compensate for LV latency. In this way, both ventricles are activated synchronously resulting in a shorter biventricular activation time. BiV, biventricular; LV, left ventricular; RV, right ventricular.

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17

Programmability of the Interventricular Interval During Cardiac Resynchronization Therapy

S. Serge Barold, Arzu Ilercil, and Bengt Herweg

Doppler echocardiographic methods for AV optimization in patients receiving cardiac resynchronization therapy (CRT) are almost universally used for programming the optimal interventricular (V-V) delay (Fig. 17.1). There is, however, growing interest in non-echocardiographic techniques such as plethysmography (Fig. 17.2) or radionuclide angiography and a variety of automatic techniques because echocardiography is time-consuming and requires trained sonographers [1,2,3,4]. Echocardiographic techniques include mitral, left ventricular (LV) outflow tract, and aortic blood flow velocity profiles using conventional pulsed and continuous wave and determination of LV dP/dt as derived from the continuous wave Doppler profile of mitral regurgitation [5,6,7,8,9]. The maximal or peak rate of increase of intraventricular pressure during isovolumetric contraction (dP/dt max) is one of the most sensitive indices of LV contractility [6, 10, 11, 12, 13, 14, 15]. Conventional M-mode echocardiography for the measurement of LV dyssynchrony using septal to posterior wall motion delay may be unreliable and poorly reproducible [16]. Determination of the extent of residual LV dyssynchrony after V-V programming requires more sophisticated echocardiographic techniques such as tissue Doppler techniques (peak velocity time difference, delayed longitudinal contraction score, etc.), three-dimensional echocardiography, and automatic endocardial border detection [5,7,17,18,19,20,21] (Fig. 17.3).

Programmability of the V-V Interval

Contemporary biventricular devices permit programming of the V-V interval usually in steps from +80 ms (LV first) to –80 ms (right ventricle first) to optimize LV hemodynamics. This design is based on mounting evidence that simultaneous activation of the two ventricles for CRT is illogical and that the best mechanical efficiency in CRT is not necessarily achieved by simultaneous pacing of the two ventricles [13] (Fig. 17.4).

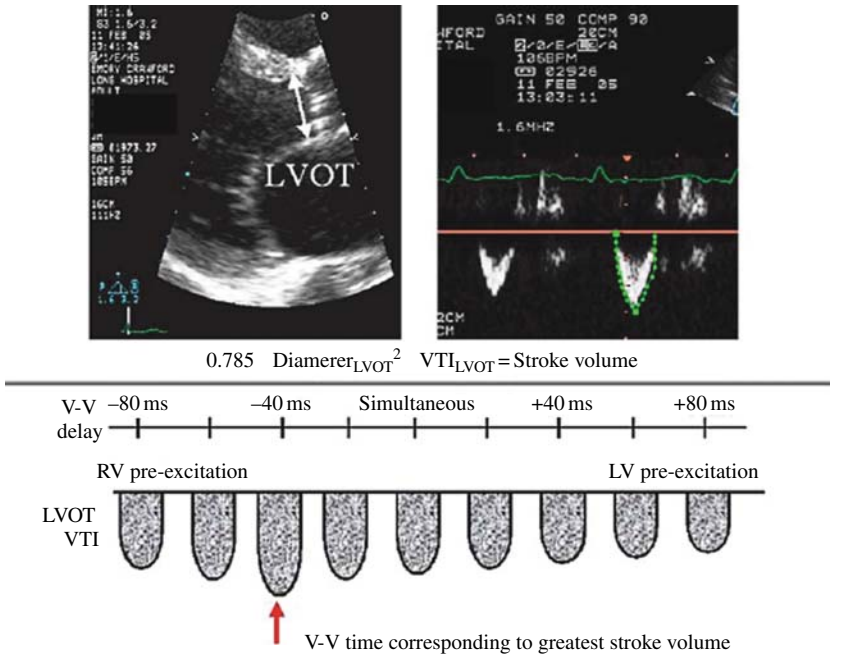


Fig. 17.1 Interventricular interval delay using left ventricular outflow tract (*LVOT*) measurements of blood flow velocities for estimation of stroke volume (*SV*). SV is exponentially related to the LVOT diameter and directly to the velocity time integral (*VTI*) of the LVOT. Variation of the interventricular interval (*V-V*) interval affects the SV as evidenced by varying VTI measurements that can serve as surrogate markers for resynchronization. The optimal V-V interval in this example is derived from pacing the right ventricle (*RV*) 40 ms before the left ventricle (*LV*). The optimal AV delay becomes equal to (optimal AS-LVP) minus the 40-ms V-V interval. *LVP*, monochamber LV pacing. AS = atrial sensed event. (Reproduced with permission from Gassis S, Leon AR. Cardiac resynchronization therapy: Strategies for device programming\troubleshooting and follow-up. J Interv Card Electrophysiol 2005;13:209–22).

Pathophysiologic Basis for Programming the Interventricular Interval

(1) In normal hearts, activation of the two ventricles does not occur simultaneously, that is, epicardial right ventricular (RV) depolarization starts a few milliseconds earlier than LV depolarization [22, 23]. (2) In CRT, epicardial LV pacing delays transmission of activation that is supposed to reach in the normal situation the subendocardial conduction system before it spreads to the remaining ventricle. (3) In advanced cardiomyopathy, RV to LV interactions can be different from those in normal hearts. (4) Myocardial disease is associated with different location and size of scars and heterogeneity of conduction abnormalities. The baseline ventricular conduction defect differs considerably from case to case especially in patients with a QRS duration >150 ms [24]. Slow conduction in the presence of scar tissue in ischemic cardiomyopathy may necessitate more LV preexcitation than the substrate in nonischemic cardiomyopathy. Conduction delay may not be caused by

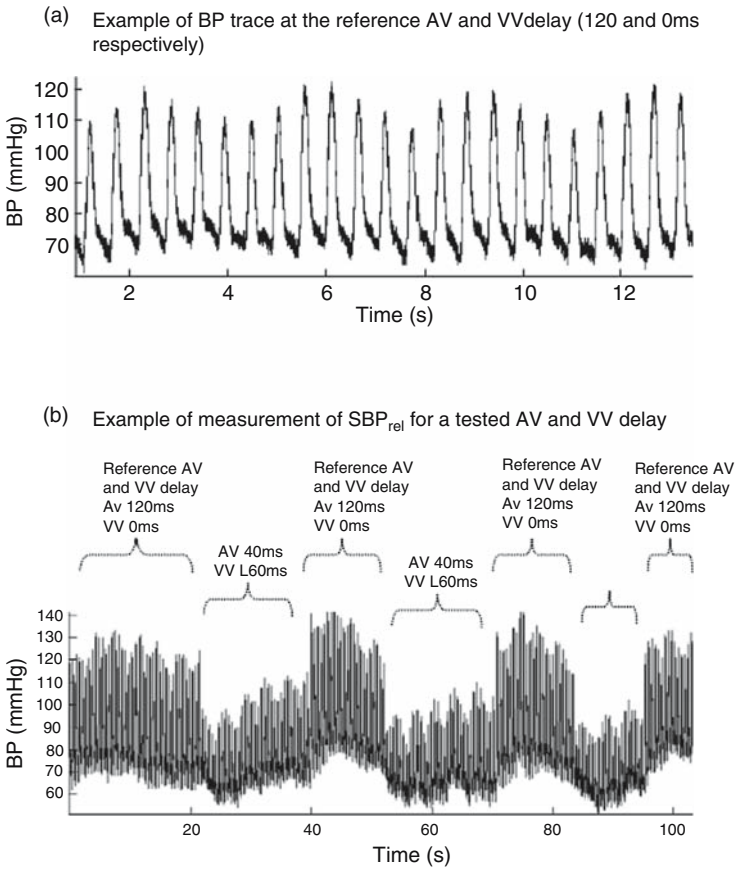
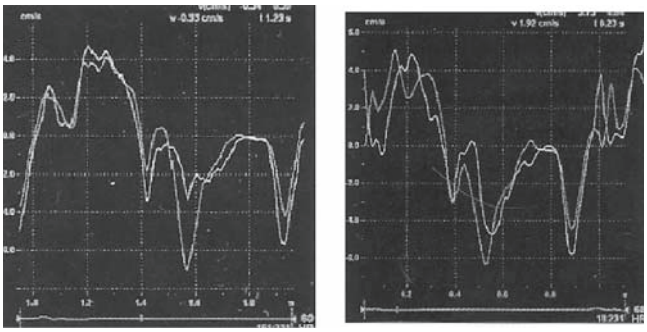


Fig. 17.2 Example of the data acquired by photoplethysmography for measuring relative change in systolic blood pressure for tested AV and V-V delays. Each tested AV and V-V delay was compared with the reference AV and V-V delays (AV 120 ms and V-V 40 ms on top). The recording was returned to this reference delay (top) between each tested delay. The relative change in systolic blood pressure (SBP_{rel}) was calculated as the mean of 10 beats prior to a change and the 10 beats immediately after a change. The mean was established for at least six replicate transitions. (Reproduced with permission from Whinnett ZI, Davies JE, Willson K, et al. Determination of optimal atrioventricular delay for cardiac resynchronization therapy using acute non-invasive blood pressure. Europace 2006;8:358–66).

isolated left bundle branch block but also by more global anisotropic disturbances of the conduction system and/or a variety of scarred areas, latency of LV stimulation, and delayed global depolarization [25, 26, 27, 28]. Despite virtually similar surface QRS morphology, heart failure (HF) patients with left bundle branch block and patients with LV dyssynchrony exhibit different locations and patterns of mechanical dyssynchrony [29]. (5) The ventricular leads (particularly LV leads) are placed in quite different anatomic positions, depending on the operator's choice and the limitations imposed by variable coronary sinus anatomy. Thus, paced ventricular activation patterns may differ from patient to patient. The presence and varying degree of fusion with the spontaneous QRS complex alters the configuration of the paced QRS complex.



- 60 ms + 60 ms

Fig. 17.3 Tissue Doppler imaging evaluation of V-V programming. In this patient, a V-V interval of –60 ms (left ventricle before right ventricle) resulted in the highest aortic velocity time integral (VTI) and perfect left ventricular synchronicity indicated by the superposition of the peak myocardial systolic velocities sampled from the septal and lateral segments. In contrast, the lowest aortic VTI and the highest degree of dyssynchrony was found at a V-V interval of 60 ms (right ventricle before left ventricle). (Reproduced with permission from Schalij MJ, van Erven L, Bleeker GB, Bax JJ. Device-specific features in cardiac resynchronization therapy. In: Yu CM,. Hayes DL, Auricchio A, eds. Cardiac Resynchronization Therapy. Malden, MA: Blackwell Futura; 2006:141–51).

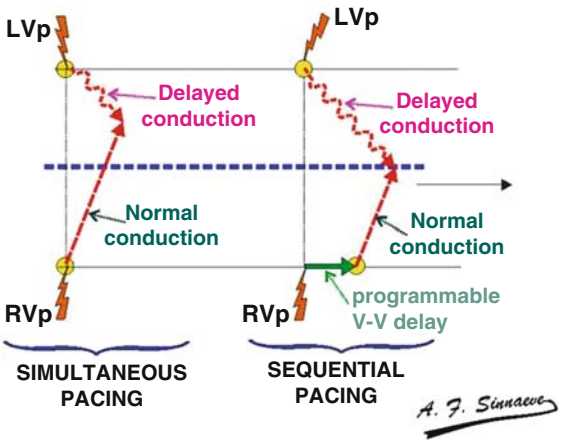


Fig. 17.4 Diagrammatic representation of left ventricular (*LV*) conduction delay interfering with synchronous activation of the two ventricles at the broken horizontal line. Programmability of the interventricular (*V-V*) interval permits preactivation of the LV to compensate for the LV conduction delay. In this way, both ventricles are activated synchronously at the broken horizontal line. *LVp*, left ventricular pacing event; *RVp*, right ventricular pacing event.

Clinical Considerations

On the basis of the above arguments, it is therefore not surprising that V-V programmability has shown a heterogeneous response with great variability of the optimal V-V delay from patient to patient. V-V programmability may partially compensate for less than optimal LV lead position by tailoring ventricular timing and may also correct for individual heterogeneous ventricular

activation patterns commonly found in patients with LV dysfunction and HF. The benefit of V-V programming is additive to AV delay optimization. The optimal V-V delay cannot be identified clinically in the majority of patients (Table 17.1) [3, 12, 13, 14, 15, 29, 30, 31, 32, 33, 34, 35, 36]. Consequently adjustment of the V-V delay like the AV delay must be individualized (Table 17.1; Fig. 17.1). In addition, assessment of the role of V-V programmability reported in the literature is difficult to evaluate because of the varied cutoff of the spontaneous QRS duration for inclusion in the various studies, the different testing procedures to determine the optimum V-V delay, and the timing and methodology of AV delay optimization performed in the setting of V-V programming.

Although V-V programmability produces a rather limited improvement in LV function or stroke volume, the response is important in patients with a less than desirable response to CRT (Fig. 17.5). It is currently unknown whether AV and/or V-V interval optimization can actually decrease the percentage of nonresponders to CRT. The optimal V-V delay should decrease LV dyssynchrony and provide a more homogeneous LV activation with faster LV emptying and improved and longer diastolic filling. V-V programmability may increase LV ejection fraction and other indices of LV function and may also reduce mitral regurgitation in some patients [37], but overall improvement is only moderate (Fig. 17.6).

The range of optimal V-V delays is relatively narrow and most commonly involves LV preexcitation by 20 ms. LV preexcitation is required in most patients.

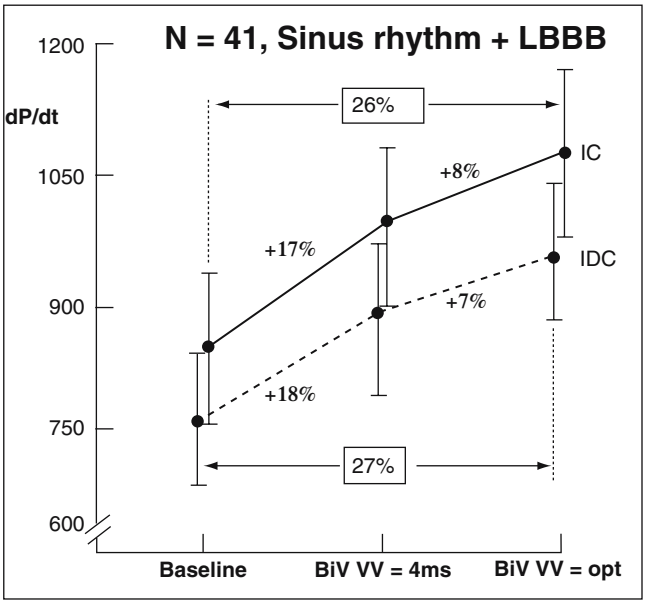


Fig. 17.5 Comparison of simultaneous biventricular pacing (*BiV V-V* = 4 ms), and optimized biventricular pacing (*BiV V-V opt*) on left ventricular dP/dt max in patients with sinus rhythm and ischemic cardiomyopathy (*IC*) and idiopathic dilated cardiomyopathy (*IDC*). *LBBB*, left bundle branch block. $p < 0.05$ for differences between baseline and simultaneous biventricular pacing and between simultaneous biventricular pacing and optimized pacing. (Reproduced with permission from van Gelder BM, Bracke FA, Meijer A, Lakerveld LJ, Pijls NH. Effect of optimizing the VV interval on left ventricular contractility in cardiac resynchronization therapy. Am J Cardiol 2004;93:1500–1503).

Table 17.1 Studies of sequential biventricular pacing.

Reference	Year	No. Patients	QRS(ms)	Parameter	Results*
Sogaard et al. [62]	2002	20	>130	TDI and 3D echocardiography	LV_1 9, RV_1 11 patients
Perego et al. [18]	2003	12	≥150	Invasive dP/dt max	LV_1 9, BiV_0 3 patients
Hay et al. [17]	2004	9 AF	152 ± 44 7 LBBB, 1 RBBB, 1 normal	Invasive dP/dt max	$BiV_0 > RV_1$, LV_1 minimal effect
Van Gelder et al. [20]	2004	53 41 SR 12 AF	>150	Invasive LV dP/dt max	LV_1 44 (84%), BiV_0 6, and RV_1 3 patients. Mean V-V interval was greater for ischemic than idiopathic cardiomyopathy.
Mortensen et al. [28]	2004	34	≥130 ≥180PM-dependent patients	Echo Doppler determination of stroke volume	LV_1 62%
Kurzidim et al. [19]	2005	22	>130	Invasive LV dP/dt max	Sequential pacing 41% patients with only 1 RV_1 patient. Others BiV_0 equivalent.
Burri et al. [10]	2005	27	>120	Radionuclide angiography (LVEF)	LV_1 45%, BiV_0 33%, RV_1 22%
Porciani et al. [25]	2005	21	>130	Echocardiography MPI	LV_1 48%, RV_1 48%, BiV_0 4%
Riedlbauchova et al. [26]	2005	19	≥150	Echo Doppler determination of cardiac output	LV_1 best in most patients, RV_1 best in 2 patients
Vanderheyden et al. [29]	2005	20	≥130	LVOT VTI	LV_1 12, RV_1 5, BiV_0 3 patients
Leon et al. [54]	2005	207 BiV_0 359 sequential	≥130	Echo Doppler determination of stroke volume	At 6 months: LV_1 58%, BiV_0 19%, RV_1 23%
Bordachar et al. [34]	2006	23	>120	Aortic VTI	LV_1 60%, BiV_0 22%, RV_1 18%
Boriani et al. [30]	2006	86	>150	Echo Doppler determination of stroke volume	LV_1 36%, RV_1 35%, BiV_0 29%

LV, left ventricle; RV, right ventricle; LV_1, LV preactivation; RV_1, right ventricular preactivation; BiV_0, simultaneous biventricular pacing; LBBB, left bundle branch block; RBBB, right bundle branch block; LVOT, left ventricular outflow tract; SR, sinus rhythm; AF, atrial fibrillation; PM, pacemaker; TDI, tissue Doppler imaging; VTI, velocity-time integral; LVEF, left ventricular ejection fraction; 3D, three-dimensional; MPI, myocardial performance index.
*The results indicate the distribution of the optimal V-V delay according to its corresponding pacing mode, LV_1 , RV_1, and BiV_0, in terms of the number of patients or percentage. All patients were in sinus rhythm unless indicated otherwise (AF).

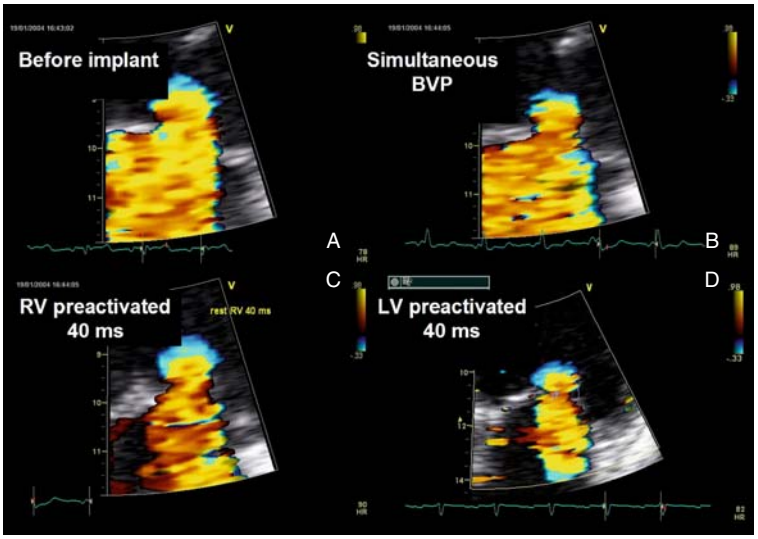


Fig. 17.6 Reduction of mitral regurgitation with optimized sequential cardiac resynchronization therapy (CRT). (**A**) Preimplant effective regurgitant orifice area (EROA): 31 mm^2. (**B**) Simultaneous CRT EROA: 22 mm^2. (**C**) Sequential CRT with right ventricular preactivation of 40 ms EROA: 21 mm^2. (**D**) Optimized sequential CRT with left ventricular preactivation of 40 ms EROA: 10 mm^2. (Adapted with permission from Bordachar P, Lafitte S, Reuter S, et al.. Echocardiographic parameters of ventricular dyssynchrony validation in patients with heart failure using sequential biventricular pacing. J Am Coll Cardiol 2004;44:2157–65).

RV preexcitation should be used cautiously because advancing RV activation may cause a decline of LV function. Consequently, RV preexcitation should be reserved for patients with dyssynchrony in the septal and inferior segments provided there is hemodynamic proof of benefit [29]. Patients with ischemic cardiomyopathy (with slower conducting scars) may require more preexcitation than those with idiopathic dilated cardiomyopathy [15]. V-V programming is of particular benefit in patients with a previous myocardial infarction [34].

Clinical Studies

Table 17.1 outlines data from studies of V-V programming involving a relatively small number of patients as well as the large and important InSync III study. The overall results of the smaller studies are basically similar to those of the larger InSync III study.

InSync III Study

The InSync III clinical study is a landmark large-scale investigation that firmly established the importance of V-V timing in CRT patients [34]. It used a multicenter, prospective, nonrandomized design to evaluate the clinical effectiveness of sequential biventricular CRT [34]. All patients (359 with sequential devices and 216 with simultaneous CRT devices) underwent reassessment of quality-of-life, follow-up 6-min hall-walk test, estimation of New York Heart Association (NYHA) functional class before hospital discharge and

at 1, 3, and 6 months after implant. At follow-up, optimization of the AV and V-V stimulation intervals was carried out. Echo Doppler interrogation first determined the optimal AV interval that maximized transmitral filling using the Ritter method. The right-atrium-to-LV interval was kept constant at the optimal setting while varying the LV–RV interval in random sequence -80 (RV first) to +80 ms (LV first) to identify the V-V offset producing the greatest LV stroke volume. Doppler-derived stroke volume at each V-V setting was determined by LV outflow tract velocity time integral (VTI) multiplied by the LV outflow tract cross-sectional area. The improvement in stroke volume was defined as the difference between the stroke volume at the optimal V-V setting and stroke volume at the nominal, or simultaneous, V-V setting (Fig. 17.7).

Figure 17.8 illustrates the distribution of the optimal LV–RV settings prior to hospital discharge and at 3 and 6 months follow-up. More than 75% of patients at each assessment had an optimal LV–RV setting between -40 ms to +40 ms. The majority of patients had an optimal V-V setting delivering LV stimulation first (55%, 54%, and 58% at hospital discharge and 3- and 6-month visits, respectively). The proportion of patients with a simultaneous optimal V-V setting remained fairly stable over time (23%, 20%, and 19% at hospital discharge and 3 and 6 months, respectively). The proportion of patients with an optimal V-V setting delivering RV stimulation first also remained consistent at the three follow-up visits (23%, 26%, and 23%, respectively) (Fig. 17.8). Individual patient changes during follow-up were not performed. Increased stroke volume was found in 81% of the V-V patients at 6 months. Stroke volume improved (optimal vs. simultaneous V-V setting) by 8.6% (median percentage) prior to hospital discharge, 8.4% at 3 months, and 7.3% at 6 months. Sixty-four patients (17%) prior to hospital discharge, 49 patients (14%) at 3 months, and 49 patients (14%) at 6 months experienced a $\geq$20% improvement in stroke volume during sequential pacing. Patients with a history of myocardial infarction were identified as experiencing statistically significant improvement in stroke volume ($p = 0.03$) during optimal V-V programming versus nominal V-V setting. The improvement in stroke volume at the optimal V-V interval continued throughout all follow-up intervals (prior to hospital discharge and 3 and 6 months). This suggests that the ability to vary V-V timing compensated for infarct-related conduction block. Increase in stroke volume in NYHA functional class IV patients with an optimized V-V setting was not statistically significant ($p = 0.1344$), yet it was consistent across all follow-up intervals (prior to hospital discharge and at 3 and 6 months).

There was no significant difference in the effect of optimized sequential and simultaneous CRT on NYHA functional class or quality-of-life score and functional capacity. However, the V-V group experienced a greater improvement in 6-min hall walk from baseline to 6 months compared with the simultaneous CRT group ($p = 0.0015$). There was no correlation between improvement in stroke volume and improved exercise capacity.

V-V Programming in Patients with Permanent Atrial Fibrillation

Most of the studies listed in Table 17.1 excluded patients with atrial fibrillation. The study of van Gelder et al. [15] suggests that V-V programming

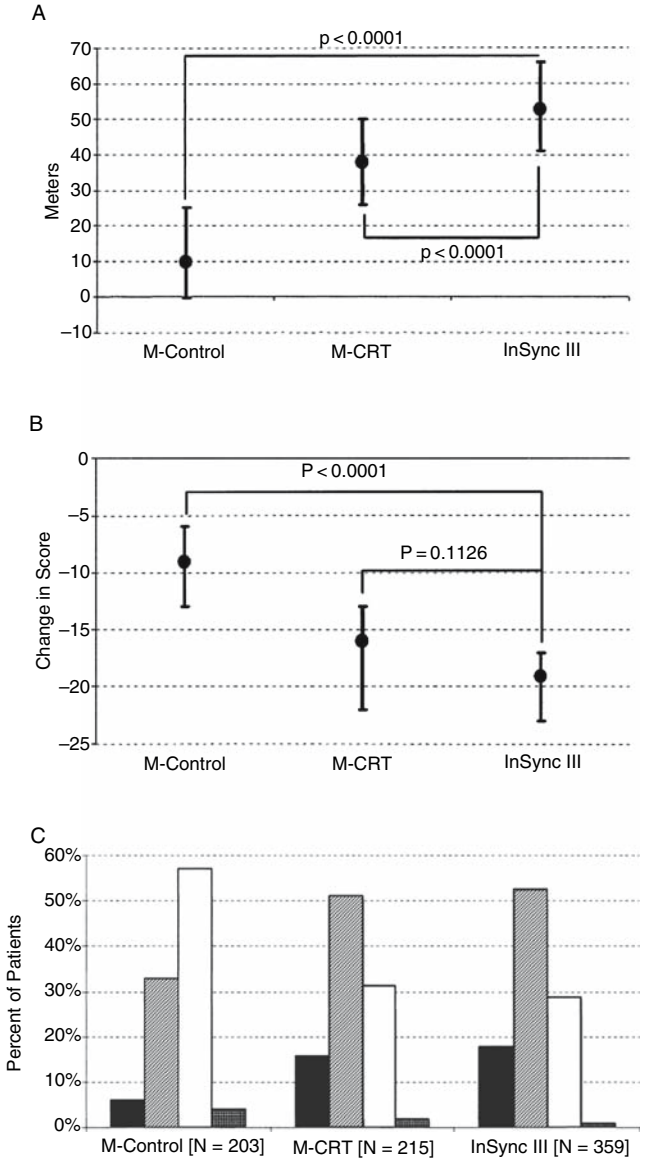


Fig. 17.7 InSync III study comparing simultaneous biventricular pacing with sequential biventricular pacing. Changes in 6-min hall walk (**A**), quality-of-life score (**B**), and changes in New York Heart Association functional class (**C**) after 6 months. *Black bars*, improved two or more; *diagonally lined bars*, improved; *white bars*, no change; *dotted bars*, worsened. *M*, Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial; *M-CRT*, MIRACLE Cardiac Resynchronization Therapy trial. (Reproduced with permission from Leon AR, Abraham WT, Brozena S, et al.; InSync III Clinical Study Investigators. Cardiac resynchronization with sequential biventricular pacing for the treatment of moderate-to-severe heart failure. J Am Coll Cardiol 2005;46:2298–304).

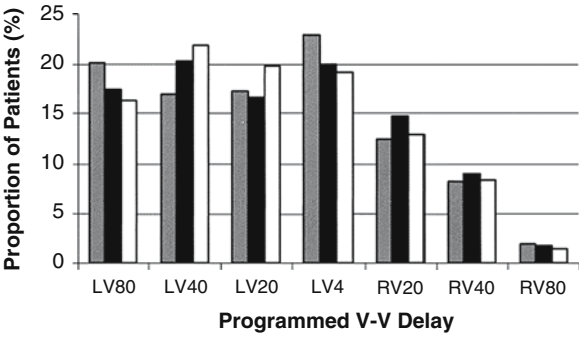


Fig. 17.8 Optimal interventricular timing settings in the InSync III trial (simultaneous vs. sequential biventricular pacing) at prehospital discharge and 3 and 6 months. Diagonally lined bars, prehospital discharge; black bars, 3 months; white bars, 6 months. (Reproduced with permission from Leon AR, Abraham WT, Brozena S, et al.; InSync III Clinical Study Investigators. Cardiac resynchronization with sequential biventricular pacing for the treatment of moderate-to-severe heart failure. J Am Coll Cardiol 2005;46:2298–304).

is also beneficial in CRT patients with atrial fibrillation and continual biventricular pacing, but further work is required to confirm these results [8].

Order of AV and V-V Programming

The optimal AV delay is determined from the time of sensing in the right atrium to the LV stimulus (AS–LV delay) during monochamber LV pacing. This AV delay remains optimized if the RV is not preexcited simply because the LV is activated at the end of the programmed AV delay (except for Guidant devices as discussed below). RV preexcitation should be used cautiously because it may impair the optimal AV delay by delaying the left-sided AV delay. With RV preexcitation, the optimal AV delay (except for Guidant devices) becomes equal to the optimal AS–LV delay minus the programmed V-V interval [38] (Fig. 17.1). The timing of the AV delay in Guidant devices is RV-based. Consequently, the programmed AV delay for LV preexcitation is equal to the optimal AV delay + (V-V interval).

Long-term Stability of the Optimal V-V Interval and Clinical Response

The optimal V-V delay may change with the passage of time, and individual changes cannot be accurately predicted. Detailed, regular reevaluations and reprogramming of optimal parameters seems appropriate.

Boriani et al. [36] reported disappointing results at the 6-month follow-up after V-V optimization. They selected patients at random and compared the results of CRT with simultaneous biventricular pacing (n = 23) versus V-V optimized devices (n = 72) after a follow-up of 6 months. There was no difference in symptoms, quality-of-life, and functional capacity between the two groups. These results are difficult to explain, but they may be related to the selection of sicker patients (QRS $\geq$150 ms), different methodology

for optimization the AV delay, a change in the optimal V-V interval after 6 months, or progression of disease. Furthermore, the optimal V-V interval was not determined after hospital discharge. In this respect, O'Donnell et al. [39] studied 40 recipients of CRT devices. Optimized V-V delays were determined according to echocardiographic criteria. There was a trend toward reduction in the LV predominance of the optimal V-V delay during follow-up. The mean optimal V-V delay at implantation was 22 ms (–12 to +32 ms) with the LV activated first versus 12 ms (–16 to +32 ms) at 9 months. These observations are partially supported by the data of Mortensen et al. [30], who found that the optimal V-V interval changed in 56% of CRT patients at the 3-month follow-up. Some of these results are difficult to compare with data from the InSync III trial where the changes during follow-up were not analyzed in individual patients.

V-V Interval Optimization on Exercise

A recent study assessed the impact of sequential biventricular pacing during exercise [37]. Simultaneous biventricular pacing was optimal during exercise in only about 25% of patients (Fig. 17.9). Most of the improvement was observed with short V-V delays, ranging from 12 to 20 ms. Optimized sequential biventricular pacing offered substantial additional benefit when considering the aortic VTI and mitral regurgitation. Differences between resting and exercise optimization were observed in greater than one-half of the patients. With future technologic advances, separate automatic programming between resting and exercise for V-V delay may become possible by means of sensors or other ways to control the hemodynamic at rest and with activity. Recent data from the same group suggests that the degree of LV dyssynchrony varies with exercise and may diminish in some patients.

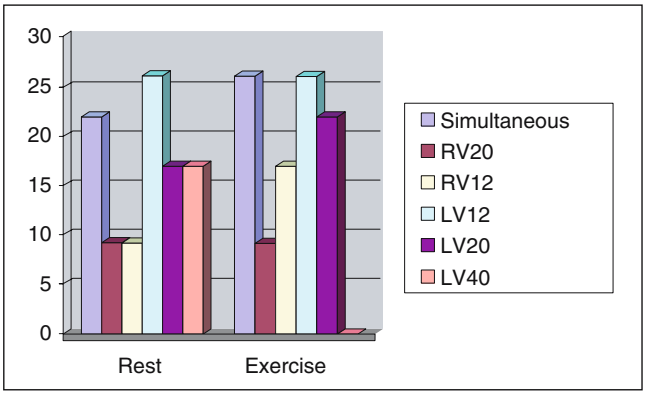


Fig. 17.9 Optimal V-V delay at rest and during exercise. LV12, LV lead preexcitation 12 ms; LV20, LV lead preexcitation 20 ms; LV40, LV lead preexcitation 40 ms; RV12, right ventricular lead preexcitation 12 ms; RV20, right ventricular lead preexcitation 20 ms. (Reproduced from Bordachar P, Lafitte S, Reuter S, et al. Echocardiographic assessment during exercise of heart failure patients with cardiac resynchronization therapy. Am J Cardiol 2006;97:1622–5 with permission).

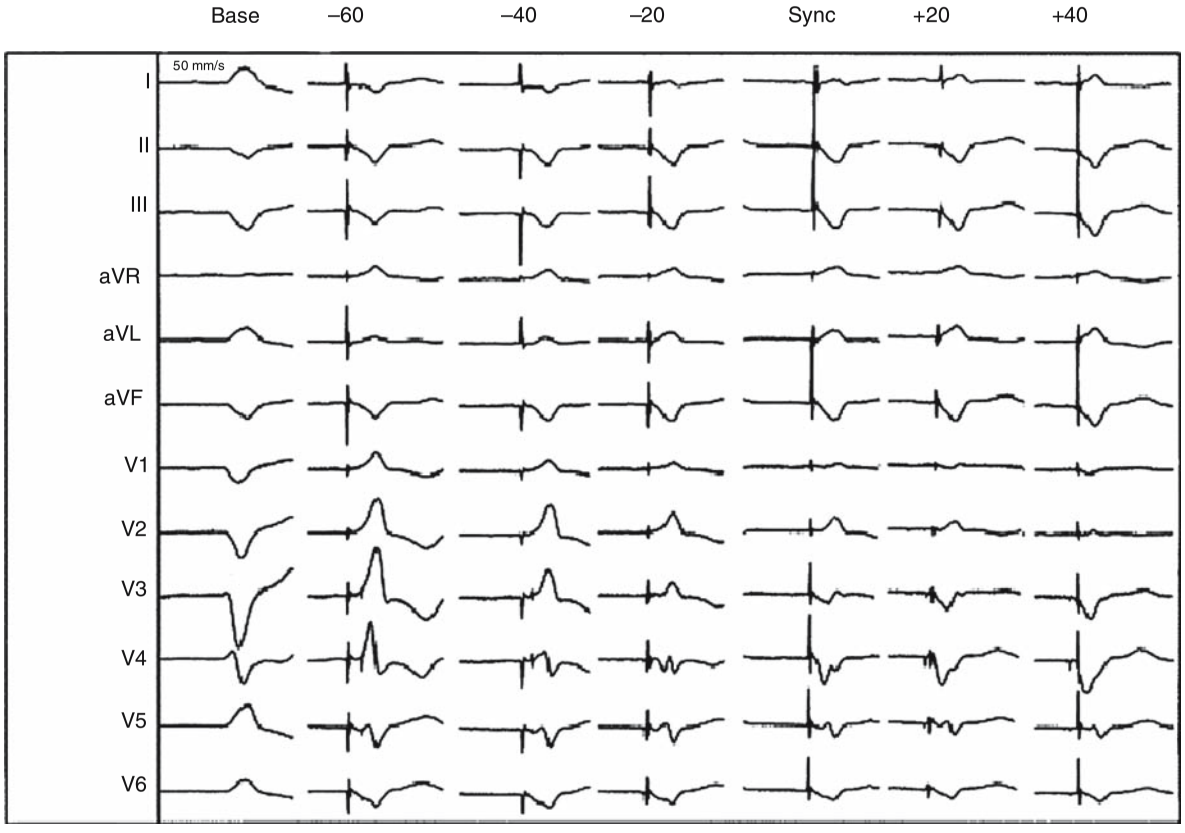


Fig. 17.10 Electrocardiograms showing gradual transition from a right bundle branch to a left bundle branch pattern from progressive change of the V-V interval. On the left, left ventricular pacing precedes right ventricular pacing, and on the right the right ventricle is paced before the left ventricle. (Reproduced with permission from Perego GB, Chianca R, Facchini M, et al. Simultaneous vs. sequential biventricular pacing in dilated cardiomyopathy: An acute hemodynamic study. Eur J Heart Fail 2003;5:305–13).

Effect of Anodal Stimulation on the V-V Interval

In the absence of anodal stimulation, increasing the V-V interval gradually to 80 ms (LV first) will progressively increase the duration of the paced QRS complex, altering its morphology with a larger R-wave in lead V_1 indicating more dominant LV depolarization (Fig. 17.10). There are no data at present to suggest that the varying QRS configuration in lead V_1 (dominant R-wave) with different V-V intervals can be correlated with the hemodynamic response.

RV anodal stimulation during biventricular pacing may interfere with a programmed V-V delay (often programmed with the LV preceding the RV). This interference occurs because RV anodal capture causes simultaneous RV and LV activation (the V-V interval becomes zero). In the presence of anodal stimulation, the ECG morphology and its duration will not change if the device is programmed with V-V intervals of 80, 60, and 40 ms (LV before RV). The delayed RV cathodal output (80, 60, 40 ms) then falls in the myocardial refractory period initiated by the preceding anodal stimulation. At V-V intervals $\leq$20 ms, the paced QRS may change because the short LV–RV interval prevents propagation of activation from the site of RV anodal capture in time to render the cathodal site refractory. Thus, the cathode also captures the RV and contributes to RV depolarization, which then takes place from two sites: RV anode and RV cathode [40, 41].

Automatic Device-Based Optimization of the V-V Delay

St. Jude Medical (Sylmar, CA, USA) recently introduced a method whereby the programmer can determine and then program the V-V delay automatically [4]. This feature is described in detail in the chapter on new algorithms.

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18

Hemodynamic Sensors in Heart Failure Devices

Chu-Pak Lau and Hung-Fat Tse

Introduction

Implantable sensors have been incorporated in pacemakers and implantable cardioverter-defibrillators (ICDs) for many years to optimize heart rate response during exercise [1]. In patients with chronotropic incompetence, applications of sensors in implantable devices have been shown to improve exercise capacity and quality of life compared with fixed-rate pacing. As sensors achieve rate adaptation through measuring changes in the physical or internal environment of the body, it is not surprising that they can also be used to monitor cardiovascular changes secondary to heart failure. With the introduction of cardiac resynchronization therapy (CRT) for treatment of heart failure, sensors are now commonly incorporated into CRT and other heart failure devices for hemodynamic monitoring.

The type of sensors that are useful for heart failure devices can be classified according to their technical instrumentation (Table 18.1). They include piezoelectric/accelerometers to detect body vibrations during exercise, paced QRS complexes, impedance to detect stroke volume and pulmonary fluid, and different varieties of special lead sensors that measure hemodynamic variables inside the cardiac chambers.

Role of Sensors in Heart Failure Devices

Similar to a bradycardia device, sensor-driven CRT may confer additional functional benefit in heart failure patients with concomitant chronotropic incompetence (Table 18.2). Furthermore, continuous and noninvasive hemodynamic assessment in patients with heart failure is attractive, both to titrate medical therapy and to prevent acute heart failure, which often requires hospitalization. Increase in complexity of CRT programming can be simplified with sensors that automatically achieve optimization of device intervals such as atrioventricular (AV) intervals and right (RV) and left (LV) ventricular intervals. Finally, in CRT with defibrillator (CRT-D), sensors can further assist in differentiating atrial tachyarrhythmias from ventricular arrhythmias and to introduce shock only during hemodynamically unstable ventricular tachycardia or ventricular fibrillation.

Table 18.1 Classifications of sensors for hemodynamic monitoring.

Technology	Examples
Accelerometer/piezoelectric crystal	Activity sensing, Positional sensing
Paced QRS	QT, evoked R wave
Impedance	Respiratory parameters, pulmonary fluid, contractility, and stroke volume
Special lead sensors	Oxygen saturation, right ventricular and pulmonary arterial pressures, peak endocardial acceleration

Table 18.2 Role of sensors in heart failure devices.

1. Rate adaptation in patients with heart failure with chronotropic incompetence
2. Heart failure monitoring Titrate medical/device therapy Acute exacerbation
3. Hemodynamic optimization AVI, VV timing
4. Arrhythmia discrimination

Sensor-Driven CRT

Exercise Hemodynamics

At rest, AV synchrony contributes 20–30% to cardiac output (CO). During exercise, an increase in heart rate is the primary determinant of increase in CO [2]. This is particularly important in patients with heart failure and elevated LV filling pressure, in which atrial contribution to augment stroke volume will become insignificant [3].

Rate Adaptation in CRT

A recent study [4] examined the changes in cardiac contractility at rest as measured by first derivative of the LV pressure (LV dP/dt) when pacing rates are changed acutely. During RV pacing in patients with heart failure and CRT indication, there was no increase in LV dP/dt max when pacing rate was increased from 80, 100, 120, to 140 bpm. An increase in LV dP/dt was observed at rest with LV only pacing over RV pacing. However, with biventricular (BV) pacing, a progressive increase in LV dP/dt occurred (913 ± 28 to 119 ± 50 mmHg/s, $p < 0.001$) which was not observed with either RV or LV pacing alone. This suggests rate adaptation may further increase cardiac contractility when applied in the CRT mode. This is at odds with earlier results that used atrial pacing to increase the heart rate in heart failure patients with uncertain LV synchronous status. These earlier studies reported that LV contractility and CO occurred at an optimal heart rate and tended to decrease when the pacing rate was artificially increased [5].

Several parameters are liable to change during exercise: rate (atrial pacing or sensing), AV interval, and other pathophysiologic changes such as inter-atrial conduction time and exercise-induced dyssynchrony. Adaptation of AV interval with rate during exercise is of interest, as this will not only affect filling but also determine if complete BV capture occurs or only a

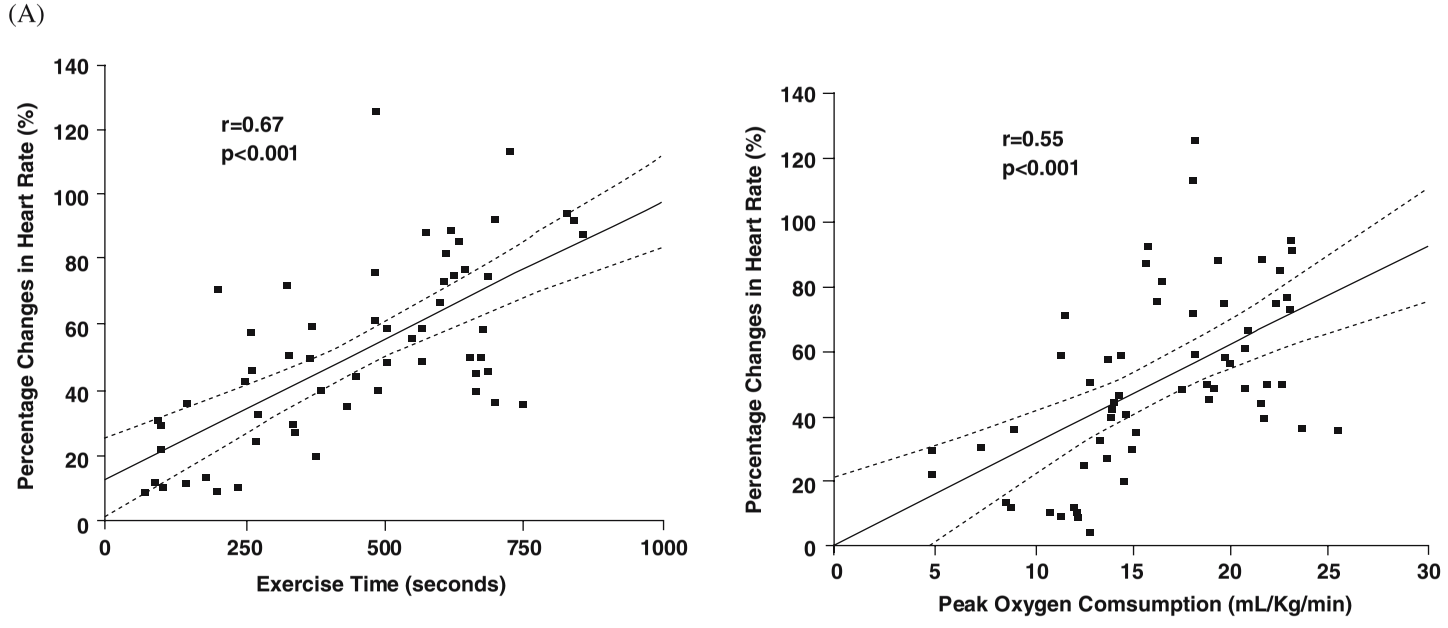

Fig. 18.1 The role of rate adaptation in CRT. (**A**) Relationship between heart rate changes during exercise and oxygen consumption. (**B**) The effect of reversal of chronotropic incompetence in heart failure by an implantable rate adaptive sensor. See text for details. *HR*, heart rate. (Reproduced with permission from Tse HF et al. JACC 2005;46:2292–7).

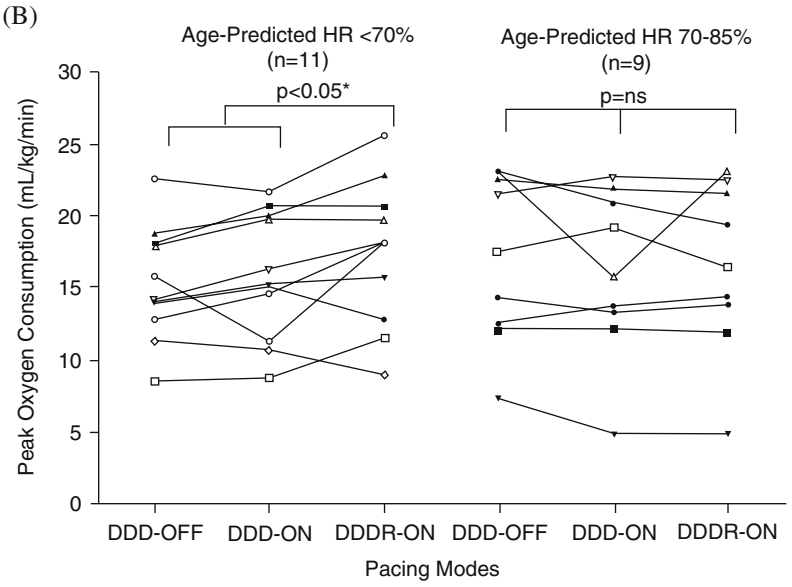

Fig. 18.1 *(Continued)*

variable fusion pacing. Tse et al. [6] examined this scenario in 20 patients with CRT, programmed randomly in DDD with AV interval adaptation off (DDD-OFF), DDD with AV interval adaptation on (DDD-ON), and DDDR with AV interval adaptation activated. All patients had chronotropic incompetence (maximum heart rate <85% predicted), and all underwent single-blinded maximum treadmill exercise cardiopulmonary testing. The AV interval was optimized individually at rest using transmitral echo Doppler flow. There was no significant differences between DDD-ON versus DDD-OFF in all exercise parameters, suggesting that further AV interval shortening during exercise is not important during exercise in patients with heart failure. However, there is a strong correlation between the extent of rate increase and exercise capacity, exercise time, and oxygen uptake (Fig. 18.1). When patients were separated into those with severe chronotropic incompetence (<70% maximum predicted heart rate), DDDR pacing mode further increase peak oxygen consumption (VO_2 max) during peak exercise. These findings suggest that rate-adaptive sensors might have an important role in enhancing exercise tolerance in patients with heart failure. Whereas the AV interval may not be important at peak exercise, the role of AV adaptation (and RV to LV timing) during submaximal exercise remains to be determined.

Monitoring in Heart Failure

Sensors can also be used to monitor cardiac hemodynamics on an ambulatory, noninvasive basis, with the aims to (1) titrate medical therapy both in outpatient and in acute care settings and (2) predict and therefore to treat early recurrence of heart failure.

Does Close Monitoring Prevent Heart Failure Hospitalization?

Heart failure with acute decompensation is associated with a high mortality and morbidity and significant costs [7]. In the United States, $29.6 billion was used for taking care of heart failure patients in 2005, with the majority being spent on hospitalization. Furthermore, in a study that examined 1,150 patients admitted with heart failure, 22% died within 9 months and 46% survivors were readmitted [8]. Thus, prevention of heart failure hospitalization is critical to reduce mortality, morbidity, and cost.

Close monitoring of heart failure patients through heart failure nurses and dedicated heart failure clinics has been shown to reduce hospitalization. This involves telephone supervision, frequent follow-up, and early outpatient administration of diuretics. In a meta-analysis of seven randomized studies [9], hospital readmission due to heart failure was significantly reduced, with a magnitude that ranged from 36% to 85% in these studies. Furthermore, the total cost was reduced even after adjusting for the cost of the heart failure clinic and nurses. However, this clinical practice is costly in its own, and may be impractical in less-specialized centers in which heart failure is not a subspecialty. Thus, the opportunity to use implantable sensors to detect early manifestations of heart failure will be a useful alternative option.

Prerequisite for Hemodynamic Sensors

The attributes of a hemodynamic sensor for hemodynamic monitoring are listed in Table 18.3. The sensor used should be of a size that is compatible with an implantable system. As the sensor is exposed to the internal body's environment, it should be tolerable and induce no adverse reactions in the patient. Conversely, the sensor should be robust enough to remain stable and intact inside the body. As monitoring is likely to be long-term, the amount of battery energy expenditure should be acceptable.

From the clinical point of view, the physiologic change should antedate the development of clinical heart failure so that prompt corrective measures can be taken to prevent heart failure. This also implies that the sensor information be made available to either the physician or the patient. The system as a whole should give high sensitivity and specificity and minimize the false alarm rate. Finally, hemodynamic monitoring is a burden to the patient and the physician. Therefore, clinical proof that it reduces morbidity (e.g., reduces hospitalization) and mortality will be essential for its wider application.

Table 18.3 Requirement of a sensor for hemodynamic monitoring.

Technical aspects
Compatible with an implantable system
Stability
Acceptable battery energy consumption
Clinical aspects
Changes in parameter should antedate the onset of clinical heart failure so that corrective measures can be taken
Sensor data should be readily available (patient, physician)
Acceptably low false-alarm rate
Clinical proof

Different Types of Hemodynamic Sensors

Activity

An activity sensor (piezoelectric or accelerometer) detects body movement and is an indication for patient daily activity. In one study [10], when the accelerometer signal collected by an external accelerometer at the cardiac apex was calibrated at a threshold of 50 mG, it corresponded with a walking speed of 2 mph (or 2.8 METS). Using this activity "log," it was reported that the percentage of activity predicted the 6-min walking distance, with a correlation of 0.7 (Fig. 18.2). However, the accuracy of using activity data to predict heart failure is dependent on the volition of the patient and, to some extent, the type of activities performed. The level of activity may not decease early enough before the onset of heart failure decompensation, especially in subjects with advanced heart failure who are mostly sedentary.

Heart Rate Variability

Heart rate variability (HRV) is a measure of autonomic tone; it reflects the severity of heart failure and is a marker of prognosis. In patients with CRT devices, either in the VDD mode or when the percentage of atrial pacing is minimal, it is possible to measure both the short-term and long-term HRV of the intrinsic sinus rhythm. In Insyn III (model 8043; Medtronic Inc., Minneapolis, MN, USA), the median sensed atrial–atrial (AA) intervals are continuously measured over 5 min. The standard deviation of all median AA intervals over 5 min and consecutively acquired in a 24-h period is considered to represent HRV over the 24-h period (SDAAM). In the presence of atrial high rate episodes or when atrial pacing exceeds 80% of the 24 h, the SDAAM for that day is excluded. The rolling average of SDAAM is used to represent an average HRV over a period of time, say, 4–6 weeks. In one study [11], the 4-week averaged SDAAM was used to predict the risk of death or hospitalization. In 397 patients with New York Heart Association (NYHA) class III/IV heart failure, patients with a 4-week averaged SDAAM <50 ms had a higher risk of death or hospitalization compared with those with SDAAM >100 ms (increased by 3.2 times ($p < 0.22$) (Fig. 18.3).

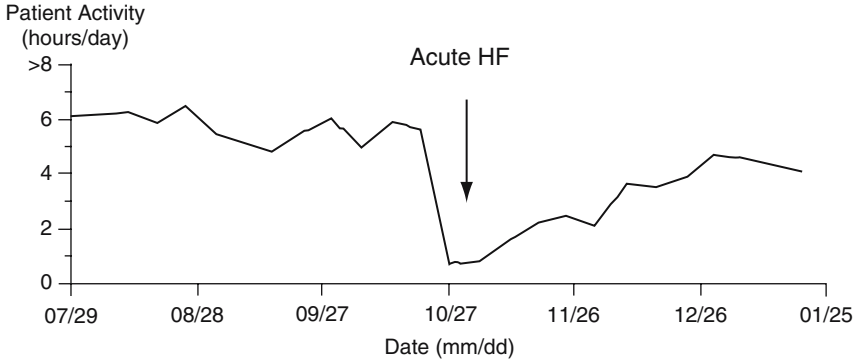

Fig. 18.2 Reduction in activity counts in a patient with a CRT during acute heart failure. Activity log collected on a daily basis is represented as number of hours active per day. *HF*, heart failure. (Courtesy Contact-CD ICD, Boston Scientific, Natick, MA, USA).

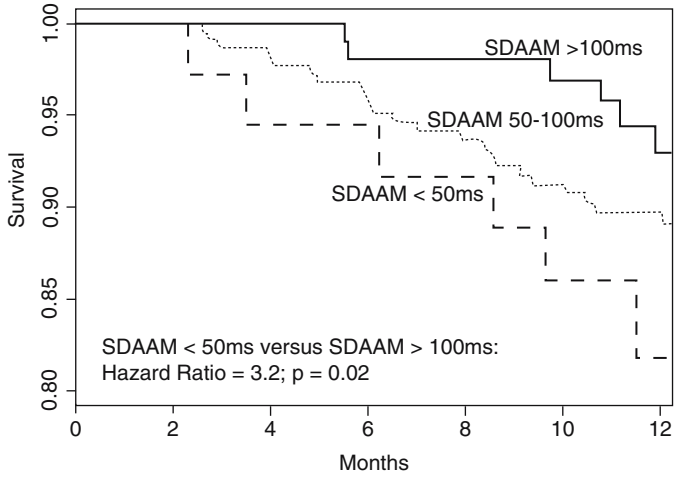

Fig. 18.3 The use of heart rate variability derived from the InSyn III SDAAM to predict death and hospitalization (see text for details). *SDAAM*, standard deviation of the median AA interval over 5 min in 24 h. (Reproduced with permission from Adamson PB et al. Circulation 2004;110:2394–9).

Over a period of 85.7 patient-years monitoring, SDAAM has 70% sensitivity in predicting hospitalization with 2.4 false-positive alarms/year (Fig. 18.4). Interestingly, the change in SDAAM occurs at 16 days before the index hospitalization event and may be a useful marker for early therapeutic intervention. Compared with activity sensing or the use of nighttime heart rate for monitoring, SDAAM is superior in sensitivity at the same level of false-positive detection (sensitivity to detect heart failure was 50% for activity and 33% for nighttime heart rate).

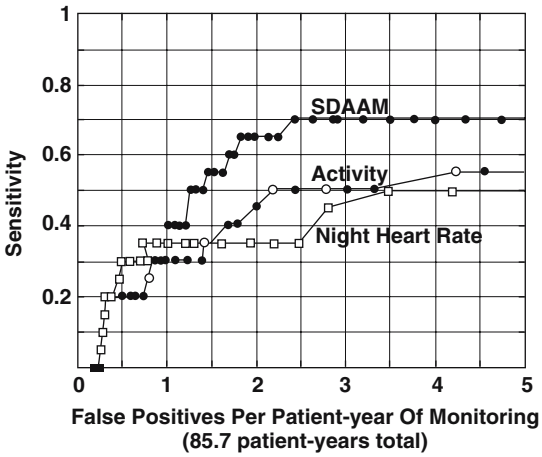

Fig. 18.4 Receiver operator curves for the use of SDAAM, activity level, and nighttime heart rate to predict hospitalization. SDAAM has superior positive predictive accuracy over activity and nighttime heart rate monitoring. (Reproduced with permission from Adamson PB et al. Circulation 2004;110:2394–9).

The advantages of HRV measurement are its simplicity (it does not require additional hardware) and minimal battery expenditure. However, it cannot be used in patients who require a significant percentage of atrial pacing. While the use of beta-blocker was controlled for in the above study [12], changes in medications that affect the sinus rate are likely to affect HRV independent of the status of heart failure. Patients with frequent atrial tachyarrhythmias will obviously invalidate HRV measurement.

A more sophisticated representation of HRV is used in the Boston Scientific Contact-ICD devices. Beat-to-beat AA interval change at each intrinsic heart rate is measured over 24 h and is profiled as a "footprint" (Fig. 18.5). In this footprint, the beat-to-beat variability is represented on the Y axis, and the intrinsic sinus rate is represented on the X axis. The frequency of beat variability at each heart rate is indicated by color, with red and orange representing more frequent, and blue and gray less frequent. Improving heart failure will be reflected by an increase in the footprint area and the standard deviation of atrial intervals [12]. This may be used as a reflection of heart failure control and response to CRT.

Central Venous Oxygen Saturation

This is one of the earliest sensors proposed to monitor cardiac hemodynamics as central venous oxygen saturation (CVO_2) reflects CO and peripheral oxygen consumption. When CO is reduced due to heart failure, CVO_2 falls at the same degree as body oxygen uptake and thus is a good reflection of heart failure. A CVO_2 sensor that is incorporated into a RV pacing lead has been developed to measure CVO_2 [13, 14].

In the implantable hemodynamic monitor system (1HM-I, model 10040; Medtronic Inc.), one lead (model 4327A; Medtronic Inc.) contains an oxygen sensor placed at 2.8 cm from a RV tip, and a second lead with a pressure sensor (model 4328) at 3 cm from a lead to be placed at the RV outflow region. This radiometric reflectance oxygen saturation sensor measures CVO_2 at 2-s intervals immediately after R-wave. Two wavelengths of light are emitted: one in the red color, and one in the infracted wave spectrum. This dual-wavelength

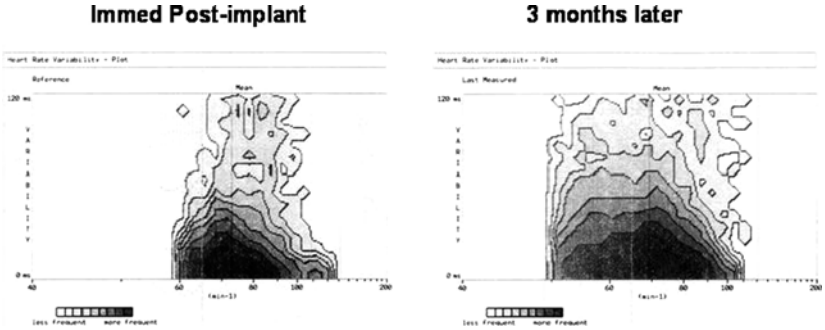

Fig. 18.5 HRV represented as a "footprint" in the Boston Scientific CRT devices. The base of the footprint measures the range of heart rate and the Y-axis profile the beat-to-beat variability at each heart rate. Thus, the overall size and variation will determine the overall HRV and is expressed in units. (**A**) Footprint of a patient soon after implantation. (**B**) Improving in size and variability of footprint after 3 months of CRT.

detection may compensate for any fibrin deposition on the CVO_2 sensor, which otherwise will cause a drift in the oxygen level detected. The long-term stability of this sensor has been reported [14]. In 21 patients implanted with this sensor, repeated invasive hemodynamic studies at 2, 6, and 12 months were made. CVO_2 derived from the sensor was well correlated with invasive measurement of CO using Swan–Ganz catheter, with $r^2 = 0.79$. The sensor underestimated the actual level by 1.6% and was consistently so across provocation and stable over 12 months, which should be relatively easy to compensate. On the other hand, sensor malfunction was observed in 12 of 21 devices, raising concern on the technical stability. CVO_2 is a highly physiologic sensor although technically difficult to achieve on the long-term basis.

RV Pressures

Pulmonary artery (PA) wedge pressure reflects left ventricle filling pressure and is thus an excellent method to measure the severity of heart failure. Although it is difficult to measure PA wedge pressure continuously, the PA diastolic pressure is a surrogate marker of the wedge pressure. With the use of piezoelectric sensor, digital PA or RV pressure can be derived [15].

The Chronicle Implantable Hemodynamic monitor (Medtronic Inc.) is a heart failure diagnostic device that incorporates such a sensor in the RV lead. The tined V lead is placed at the RV outflow tract, and the sensor is positioned at 3 cm from the tip. The device has a 128K random-access memory and continuously records digital pressures and electrograms (Fig. 18.6). The RV systolic and RV diastolic pressures were measured. The first derivative of the RV pressure (dP/dt) is determined, and the maximum positive of RV dP/dt is found to mark the onset of RV pressure increase [16]. Using an implantable

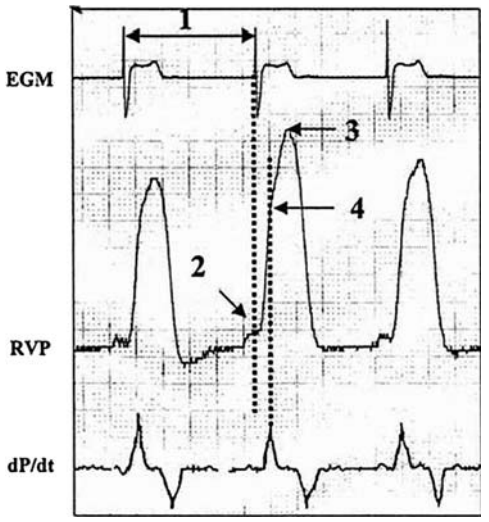

Fig. 18.6 Measurement of right ventricular (RV) pressures from an implantable pressure sensor, the Chronicle IHM (Medtronic Inc.). *EGM* (electrogram), *RVP* (right ventricular pressure), and dP/dt shown without calibration. *1*, RR interval; *2*, RV diastolic pressure (at peak of waveform); *4*, estimated PA diastolic pressure (at maximum positive dP/dt). (Reproduced with permission from Adamson PB et al. JACC 2003;41;565–71).

system in 32 patients with 36 volume overloaded events, it was found that a 25 ± 4% change in RV systolic pressure and heart rate increase of 11 ± 2% occurred at the onset of heart failure events. Sustained increase (>20%) in at least one pressure parameter occurred in 9 of 12 hospitalizations 4 ± 2 days before exacerbation, compared with 9 of 24 during minor heart failure. This study is a proof of concept study, and the relevant pressure data were not made available for clinicians to alter heart failure management. However, when these data were then made available to the clinicians, the hospitalization rate was reduced from 1.08 per patient-year to 0.7 per patient-year when the monitoring data were used to guide heart failure therapy.

The preliminary results of a multicenter trial in which Chronicle-derived heart failure data guided heart failure therapy have recently been reported. (presented as Late Breaking Trials in American College of Cardiology Conference in Orlando, 2005) [17]. In this Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure (COMPASS_HF) trial, 134 Chronicle-guided patients were compared with 140 patients in a conventional therapy arm, and the baseline characteristics were similar in the two groups. Heart failure nurses and heart failure clinics were used in both of them. All the sensors were functional throughout the study, although device-related complications occurred in almost 8% of patients. Chronicle-guided therapy resulted in an insignificant 22% reduction of heart failure events. In class III patients, the time to the first heart failure event was prolonged, and hospitalization rate was significantly reduced (–41%). This monitoring may be cost-effective in reducing hospitalization.

Pulmonary Fluid Content

With the onset of heart failure, pulmonary congestion and edema will set in and contribute to symptoms. Intrathoracic impedance measures resistivity in the chest, and the impedance will decrease in the presence of pulmonary fluid. This concept has been examined in an implanted device, the Medtronic Impedance Diagnostics in Heart Failure Patients Trial (MIDHeFT) [18]. A modified VVI pacemaker (Kappa; Medtronic Inc.) was used to inject impedance current through a standard defibrillator coil in the RV apex. Impedance was sourced between the coil and the pacemaker casing. A total of 2,048 consecutive impedance measurements were collected and averaged over 2 min to minimize the effects of cardiac and respiratory cycles. The average impedance over a 6-h period (12 noon to 6 PM) was sampled and was forced to reach a steady stage in about 2 weeks. In 22 patients with NYHA class III–IV heart failure implanted with this device, 11 of them were hospitalized for heart failure 25 times. The average reduction in impedance was 12.3 ± 5.3% at the onset of heart failure. In some patients with acute heart failure in whom a PA line was inserted, PA wedge pressure was significantly correlated with impedance volume ($r = –0.61$, $p < 0.0001$) (Fig. 18.7). With diuresis and improving heart function, impedance increased along with a fall in wedge pressure. An algorithm was derived to detect heart failure and is 76.9% sensitive at the expense of 1.5 false alarms per patient year (Fig. 18.8). Compared with symptoms that typically developed only 3 days before hospitalization, impedance change occurred in all patients at well over 10 days before hospitalization, thus giving the physician and the patient a window for corrective therapy.

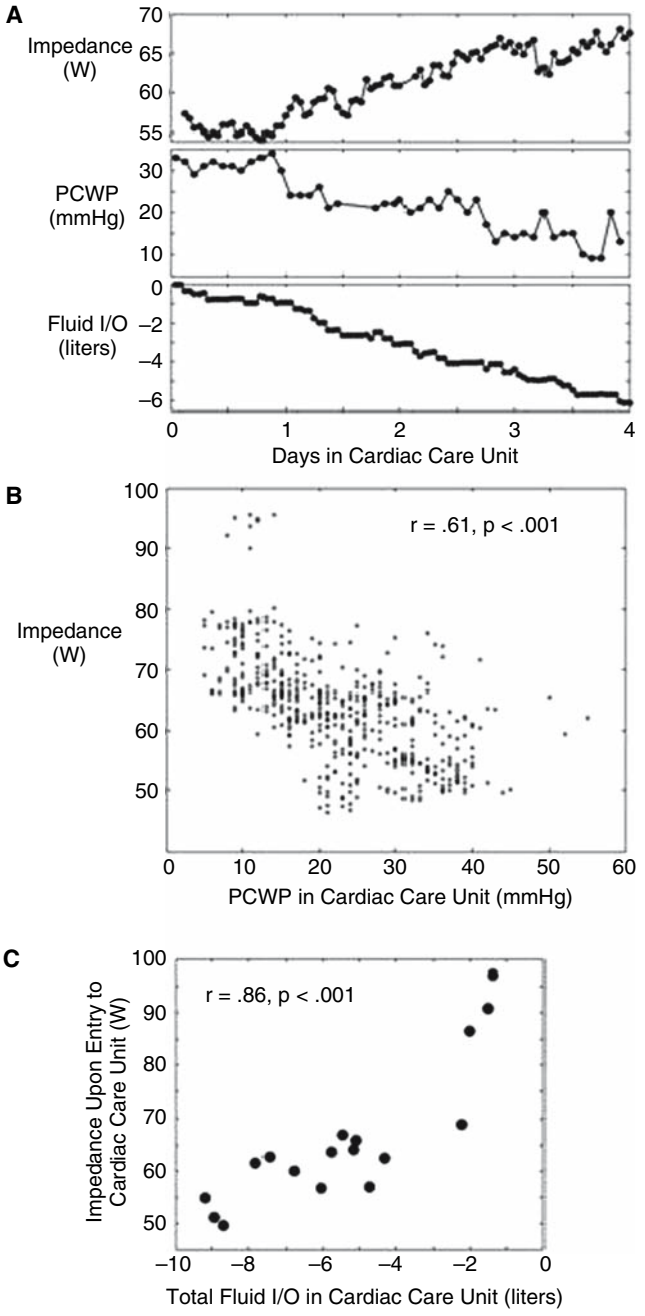

Fig. 18.7 (**A**) Example from a patient with an impedance monitoring device to measure pulmonary fluid. Relationship between intrathoracic impedance, pulmonary capillary wedge pressure (*PCWP*), and net fluid loss (*I/O*) during 4 days of intensive diuresis in CCU. (**B**) Pooled data from all patients. Relationship between intrathoracic impedance and pulmonary capillary wedge pressure during intensive diuresis in CCU pooled from 14 heart failure hospitalizations in 5 patients. (**C**) Relationship between intrathoracic impedance measurement at admission to CCU and overall amount of fluid loss that occurred during CCU stay from 17 heart failure hospitalizations in six patients. (Reproduced with permission from Yu CM et al. Circulation 2005;112:841–8).

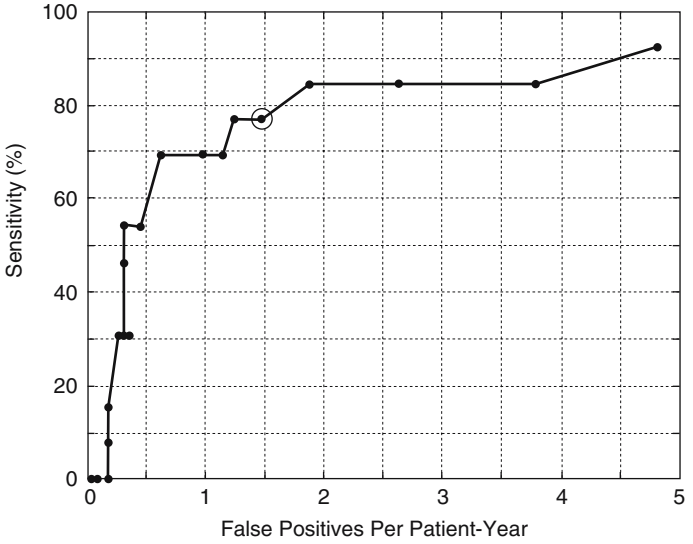

Fig. 18.8 The validation of an impedance algorithm to detect pulmonary fluid in the MIDHeFT study. Detector performance curve shows trade-off between sensitivity and false-positive rate as threshold for detection changes. For validation data set, nominal threshold of 60 Ω · day resulted in sensitivity of 76.9% and false-positive rate of 1.5 false-positives per patient-year of monitoring, as highlighted by the *circle*. (Reproduced with permission from Yu CM et al. Circulation 2005;112:841–8).

The system is now incorporated in Medtronic InSync Sentry (Medtronic Inc.). The Optivol fluid status monitoring system collects impedance signal between 12 PM and 6 PM, as this time period was shown earlier to best reflect fluid accumulation [19]. This impedance level is averaged once per day to create a reference range, known as the Optivol fluid index. If the daily impedance exceeds the reference (30–180 Ω· day default at 60 Ω · day), incipient heart failure is suggested (Fig. 18.9).

Intrathoracic impedance represents a major development in heart failure monitoring, as it can be instrumented in standard ICD systems. It is simple to use with low acceptable alarm rate. The disadvantages are that it cannot be used in the presence of significant lung disease, and other changes of heart failure such as pedal edema and ascites will not be detected. Long-term clinical benefit based on pulmonary fluid status monitoring will be the subject of several ongoing trials.

Myocardial Contractility

The close-loop stimulation sensor measures local impedance as a reflection of cardiac contractility and has been suggested to be a useful marker for monitoring heart failure [19]. The peak endocardial acceleration (PEA) sensor incorporates a piezoelectric system totally sealed in the distal pole of a RV lead. Low-frequency cardiac heart sounds reflects cardiac contractility [20]. The PEA sensor has been used for rate adaptation. In 13 patients with heart failure with a wide QRS complex [21], a DDD-PEA device had been implanted with an additional LV lead connected to the atrial port. Patients were programmed to RV pacing, LV pacing, and/or BV pacing. BV pacing resulted in an increase in PEA of 43% and 38% over RV and LV only pacing,

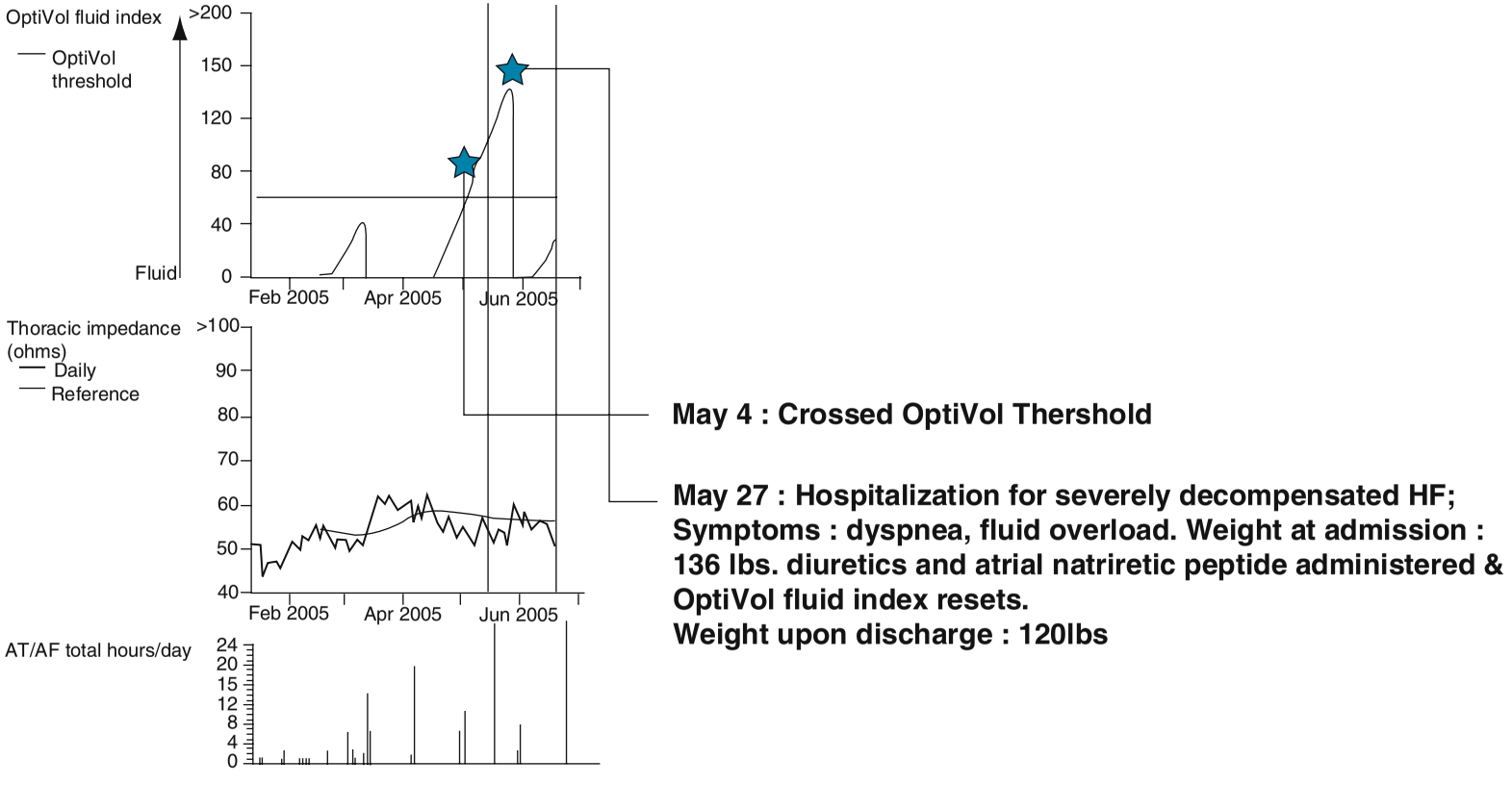

Fig. 18.9 Detection of incipient heart failure with the Optivol fluid monitor in a patient with InSyn Sentry. (Courtesy of Medtronic Inc., Minneapolis, MN, USA).

respectively, along with an increase in velocity integral by 21% and 37%, respectively. The ability to use this sensor to monitor and optimize AV and VV interval is under study.

Other Sensors

Other sensors have been proposed to monitor heart failure. Minute ventilation and respiratory rate have already been used as sensors for rate adaptation, and these parameters may be useful as an adjunct to monitor respiratory changes during heart failure. A dilated LV is associated with a decrease in evoked response and can be detected with a LV lead in a CRT device. It

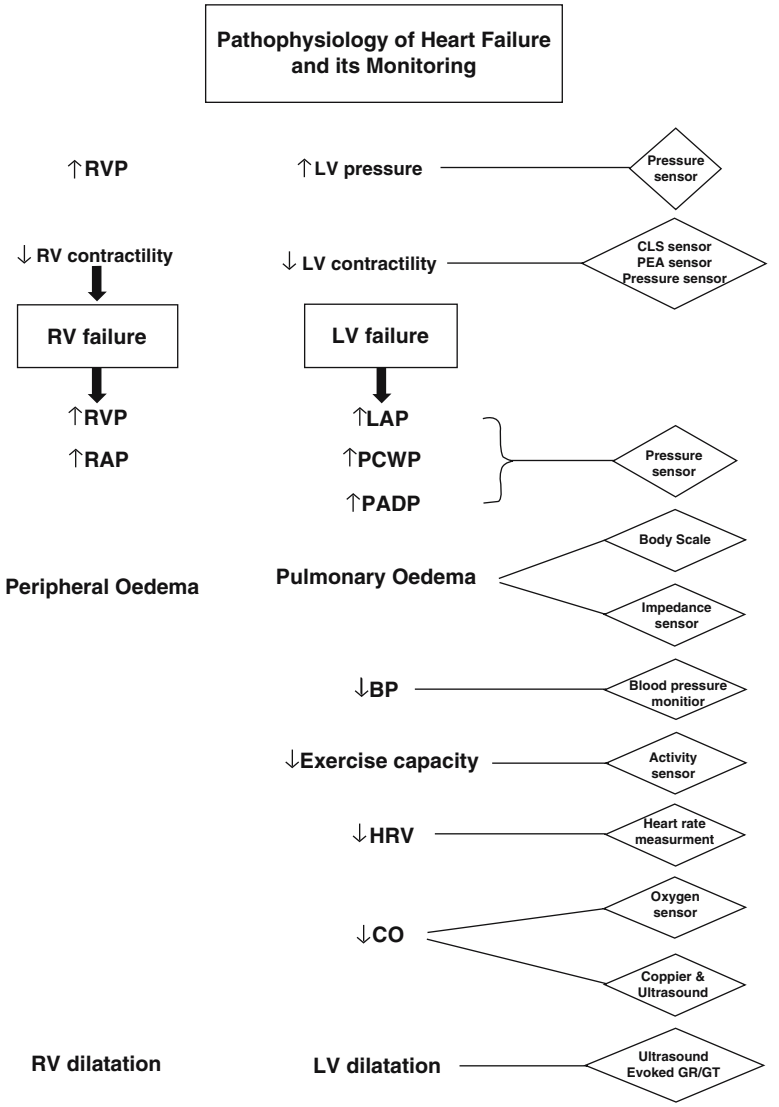

Fig. 18.10 Causes and consequences of right and left heart failure and the use of sensors for their detection. RVP = Right Ventricular Pressure, LV = Left Ventricle, RV = Right Ventricle, LAP- Left Atrial Pressure, RAP = Right Atrial Pressure, PCWP = Pulnomary Capillary Wedge Pressure, PADP = Pulmonary Arterial Diastolic Pressure, BP = Blood Pressure, HRV = Heart rate variability, CO = cardiac output.

Table 18.4 Current feasibility of implantable sensors for heart failure

Type	Activity	HRV	CVo2	RVP	PEA	Pulmonary impedance
Special lead	–	–	+	+	+	–
Energy consumption	Low	Low	Moderate	Moderate	Moderate	Moderate
Changes precedes HF	–	16 days	–	4–5 days	–	18 days
Web-based data availability	Yes	–	–	Yes	–	Pending
False-positive	N/A	2.4/year	N/A	N/A	N/A	1.5/year
Clinical proof in randomized trials	–	–	–	+	–	–

HRV, heart rate variability; CVO_2, central venous oxygen saturation; RVP, right ventricular pressures; PEA, peak endocardial acceleration.

may be able to track the extent of LV reverse remodeling over time after CRT. Likewise, QT interval may change with the onset of heart failure or ischemia and may be a useful detection method for heart failure. It is possible to combine data from an implanted system with clinical measures that can be taken by patients themselves such as their own body weight and blood pressure. All this information can be incorporated in a Web-based system for fine-tuning heart failure monitoring and treatment. Figure 18.10 shows the pathophysiologic consequences of right and left heart failure that can be monitored by sensors to guide heart failure therapy.

Conclusion

The current possibility of sensors to monitor heart failure is detailed in Table 18.4. Impedance and RV pressure sensing are now in clinical use. It is expected that advances will be made such that a sensor will be used in all heart failure devices for monitoring, rate adaptation, and to assist programming. It is expected that multiple sensors will be available to look at different pathophysiologic consequences of heart failure.

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19

Assessment of Single-Shock Defibrillation Testing of Biventricular ICDs

B. Judson Colley and Michael R Gold

Introduction

The implantable cardioverter-defibrillator (ICD) is now first-line therapy for several large cohorts of patients at increased risk of sudden cardiac death [1, 2, 3, 4]. A vast majority of implantations are performed today for primary prevention, with simple clinical criteria used to select patients. These include the presence of ischemic heart disease, a markedly reduced left ventricular ejection fraction, and congestive heart failure (CHF). Because most patients have no history or documentation of ventricular arrhythmias, programming of devices is often empiric.

Evaluation of ICD function at implantation or before hospital discharge has been routine since these devices were first developed more than 20 years ago and is generally accepted to be safe [5, 6]. However, the need for testing and the optimal method to evaluate defibrillation efficacy has been questioned recently for several reasons. First, modern devices are very reliable for defibrillation. With biphasic waveforms, active pectoral pulse generators and dual coil transvenous leads, it is rare to fail defibrillation. In addition, diagnostic features in devices can often identify problems noninvasively. Finally, ICD patients have progressively more comorbidities, which may increase the risk of such testing.

Concern is often raised about defibrillation testing in patients with advanced CHF and very low left ventricular ejection fractions (EFs). A subset of these patients will receive cardiac resynchronization therapy (CRT) devices [7, 8, 9]. The optimal testing protocol for such biventricular devices, with defibrillation backup (CRT-D), is unknown. On one hand, patients with New York Heart Association (NYHA) III–IV CHF may not tolerate extensive defibrillation testing as well as less ill patients. In addition, the multiple inductions of ventricular fibrillation may increase the risk of lead dislodgments or of heart failure exacerbation. On the other hand, these patients typically have the most dilated hearts, which may be a risk factor for defibrillation failure. Moreover, amiodarone therapy is more common in advance heart failure, and this may also reduce defibrillation efficacy [10, 11]. One compromise is to minimize

testing in this cohort. Such minimal testing strategies include inductionless evaluation of the upper limit of vulnerability or a single trial of defibrillation. The potential role of the latter strategy will be reviewed in this chapter.

Defibrillation Testing Algorithms

Despite the remarkable advances in ICD technology, the fundamental and distinguishing aspect of an implantable defibrillator is the ability to deliver high-energy shocks automatically to treat ventricular tachyarrhythmias. It is this shock therapy that is responsible for the mortality reductions observed with these devices. Accordingly, it is critical that a very high efficacy of defibrillation shocks be maintained.

A necessary aspect of all defibrillation efficacy protocols is the measurement of the defibrillation energy requirement (DER), often by defibrillation threshold testing (DFT). Whereas threshold implies an all-or-none phenomenon, defibrillation is in fact a highly probabilistic outcome and is best represented by a success curve that transitions from low to high probability of success over a range of several joules, rather than at one distinct energy. Although a single number is often use to describe the DFT of a patient, with a given lead system and waveform, studies have shown that even consecutive DFT measurements can vary dramatically [12]. Traditionally, the DFT is measured in energy (joules), either delivered or stored. However, the DFT can also be expressed as the peak voltage or current. In fact, early studies of transthoracic defibrillation indicate that current is the critical factor needed to achieve defibrillation [13].

A variety of DFT protocols are used to assess defibrillation efficacy. Historically, a step-down DFT protocol was the method of choice (Fig. 19.1). After ventricular fibrillation (VF) induction, the first shock is delivered at a relatively high energy with a high probability of terminating the arrhythmia. If successful, subsequent shocks are delivered at progressively lower energies until defibrillation fails. Theoretically, this identifies on average the energy that successfully defibrillates about 70% of the time (DFT_{70}). Another popular method to measure DFT is the binary search DFT protocol (Fig. 19.2). In this method, energy at about the predicted 50% success for defibrillation (DFT_{50}) is used for the first shock. Using higher first-shock energy after a failure and lower energy after a success, subsequent shocks are delivered midway between previously tested energies (or the range minimum or maximum) until the desired resolution of the DFT is achieved. This method offers the advantage of having a predetermined number of shocks in the protocol, whereas the step-down method requires more episodes/shocks for patients with lower DFTs. Though theoretical differences exist between the DFTs estimated using these two methods, no difference in measured DFTs was observed in clinical evaluation [14]. Finally, another DFT method used in some research studies is a step-up DFT. In this protocol, the first-shock energy is delivered using a very low energy that is likely to fail, with subsequent shocks delivered at progressively higher energies. Unlike the first two methods, shocks are delivered into the same episode of induced VF until defibrillation is successful. Like the step-down method, the number of shocks depends on the DFT. However, with this method, duration of VF also depends on the DFT, with the potential for long VF episodes associated with high DFTs being a significant drawback.

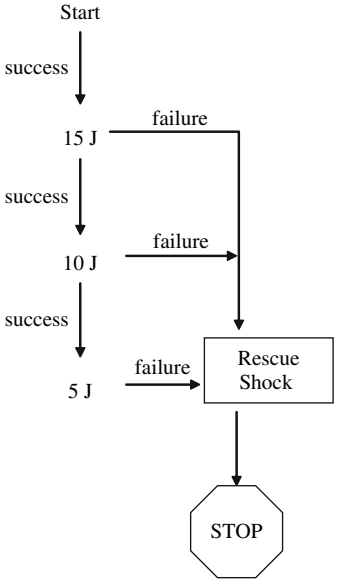

Fig. 19.1 A flow diagram of a step-down DFT protocol. Testing is initiated at 15 J delivered energy, which has a high probability of success. Energy is decreased on subsequent trials until first-shock failure. The DFT is defined as the lowest energy shock to terminate VF.

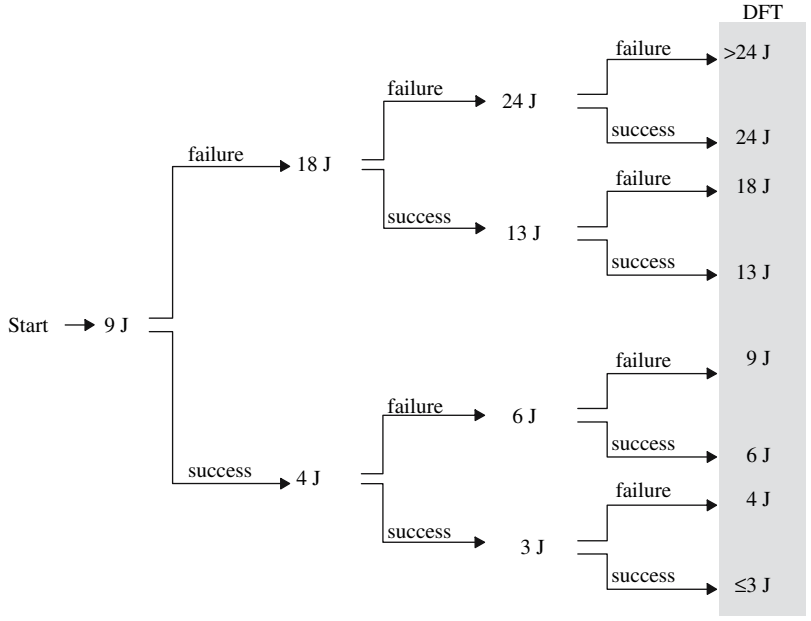

Fig. 19.2 A flow diagram of a binary search DFT algorithm. Testing is initiated at 9 J delivered energy, which is close to the estimated median DFT for the population. Energy is increased after failed first shocks and decreased after successful shocks. With three inductions of VF, the DFT is determined.

A step-up DFT is used more commonly for atrial defibrillation testing, where the duration of the arrhythmia is not of concern. Surprisingly, a comparison of step-up and binary search protocols has also shown no difference in DFT, with the average total time in VF actually less for the step-up method, even though longer single episodes of VF may occur [15].

Other methods of ensuring an adequate defibrillation safety margin have been developed. Swerdlow reported that inductionless implantations could be performed using a vulnerability safety margin based on a T-wave scan at 15 J. Instead of the traditional induction of VF at implant, the minimal shock energy required to induce VF (upper limit of vulnerability) plus a safety margin could be reliably used to define defibrillation threshold. They estimate that >80% of ICD implants could be implanted using this method, avoiding VF induction [16]. Critics of this method note this technique may require a greater number of shocks, as well as the failure to document adequate sensing of VF during testing.

Defibrillation Efficacy Testing

Though important for defibrillation research, a true DFT is measured in <10% of ICD implants at present. Rather, shocks are most often given at a single energy level to assess the defibrillation safety margin. This is based on empiric observations of patients with epicardial patch electrodes and monophasic waveform ICDs; the presence of at least a 10-J safety margin was predictive of a high success rates for terminating spontaneous ventricular arrhythmias [17]. Defibrillation testing of modern-day implants is still most often performed by observing success using two inductions with termination by shocks at 10 J below the maximum output of the ICD (i.e., 10-J safety margin). Although these strategies are supported by long-standing clinical practice, statistical models provide evidence that the sensitivity and specificity of implant test protocols are significantly less than perceived, bringing into question the value of basing implant decisions on such limited testing [20, 21].

It is common for patients with limited defibrillation success at implant and apparently high DFTs to exhibit adequate defibrillation efficacy during testing on another day. It is not clear if this was merely a probabilistic phenomenon (e.g., regression to the mean) or a transient period when the patient has higher defibrillation energy requirements. In either case, these observations imply that extensive lead revision or subcutaneous array placement should not be performed at initial ICD implant. Rather, retesting several days later or adding a class III antiarrhythmic drug, such as dofetilide or sotalol, may be a simpler strategy [20, 21].

As noted above, another important reason for defibrillation testing is to demonstrate adequate sensing capabilities at implantation. Without proper R-wave sensing, ventricular fibrillation may go undetected, so shocks are never delivered. R-waves of at least 5 mV in sinus rhythm usually ensure adequate sensing of VF [22], but the most reliable and direct assessment of sensing is to observe the ICD response to induced VF in a controlled environment during DFT evaluation. This also allows the evaluation of oversensing due to T-waves or diaphragmatic myopotentials.

The Low Energy Safety Study (LESS) was designed to test the hypothesis that a 5-J safety margin may be adequate if three successive terminations of

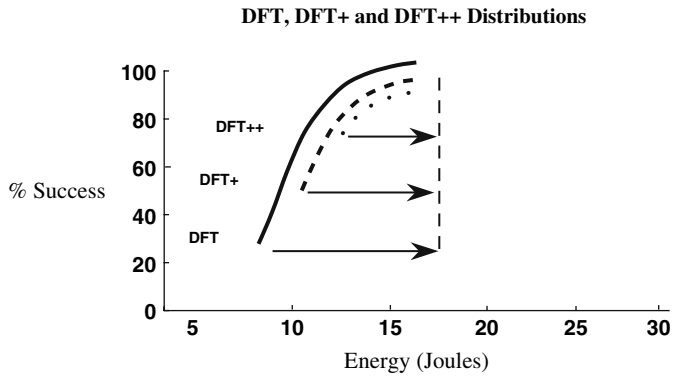

Fig. 19.3 The effect of enhanced DFT step-down testing on the probability of defibrillation success. Confirmation testing to establish two (DFT+) or three (DFT++) consecutive successful defibrillations at the DFT energy results in progressive reductions of the probability distribution of defibrillation success. This allows for programming with a smaller safety margin, as the DFT is ensured to be closer to the maximum or top of the defibrillation efficacy distribution.

VF are demonstrated [23]. This is because the more successive successful shocks for VF termination that are obtained, the more likely that this energy is at the higher part of the DFT probability curve. This is shown graphically in Figure 19.3. Although a step-down DFT may most commonly predict the DFT_{70} point on the defibrillation efficacy curve, there is a wide range of error in this point estimate. As the number of successive shocks at DFT increases (e.g., DFT+ and DFT++), the distribution on the defibrillation efficacy curve decreases with higher probabilities of being at the upper end and thus requiring lower safety margins.

In LESS, 720 patients were enrolled of whom 636 had full testing in the protocol. The first trial of DFT testing was at 14 J stored energy. If successful, the energy was decreased in small steps of about 2–3 J on successive trials. After a failed first shock to establish the DFT, subsequent inductions were performed at the next highest energy to establish the energy that was successful two consecutive times (DFT+) and three consecutive times (DFT++). The DFT was 7.9 ± 3.7 J for this cohort, whereas the DFT++ was 9.1 ± 3.8 J. The DFT++ energy is used for subsequent induced VF testing and for a randomized comparison of low energy safety margin versus full output shocks for spontaneous episodes of ventricular tachyarrhythmias [24]. In this study, programming the first two shocks at two steps (4–6 J) above the DFT++ resulted in comparable defibrillation efficacy as full output shocks, both for induced episodes of VF and spontaneous episodes of rapid ventricular tachyarrhythmias.

One-Shock DFT Testing

The long-term safety and efficacy of single-shock defibrillation testing has not been evaluated prospectively. LESS was not designed specifically to evaluate one-shock DFT testing. Rather, it was intended to evaluate more extensive testing to allow for downsized lower output pulse generators. With improvements in capacitor technology and ICD design, low-output devices are no

longer a goal for this technology. However, this remains the largest database of DFT testing with long-term follow-up, allowing for further analyses of testing strategies. One such retrospective analysis was the predictive value of a first-shock success at 14 J. We demonstrated that a single shock at 14 J, as criterion for implantation, resulted in similar success of 31-J shocks for the termination of spontaneous or induced VF episodes, compared with more extensive testing to establish the DFT++ [25]. The criterion of a single successful shock at 14 J is also comparable with a more traditional clinical approach of two successful shocks at 21 J for a 31-J maximal output device [26]. These data suggest that single-shock testing may be adequate, but a larger safety margin is required.

Several clinical trials have assessed the potential implications of implanting defibrillators without standard testing. Buob and colleagues reported their experience with defibrillation testing at implant [27]. Important problems requiring immediate attention were detected in 11% of ICD implants. Moreover, there were no complications resulting from DFT testing, suggesting that testing is a good strategy. A similar study by Higgins also found a significant number of patients with elevated defibrillation energy requirements [28]. Both of these trials used a step-down method for determination of DFTs. Overall, the incidence of complications resulting from defibrillation testing is quite small and therefore should not discourage testing, except in rare circumstances of clinically unstable patients.

Defibrillation Testing in Biventricular Pacing Devices

As with the traditional ICD system, DFT testing in CRT-D devices is the standard of care to ensure adequate defibrillation efficacy for spontaneous arrhythmias. The clinical trials used to judge the safety and efficacy of these devices relied either upon step-down defibrillation testing protocol or confirmation of a 10-J safety margin by a minimum of two VF inductions. The rational to perform such testing was based on concept that CRT-D devices carry the same probabilistic nature of defibrillation as the traditional single- and dual-chambered systems. These methods provide the best opportunity to define the DER, overcoming the risk of achieving a successful defibrillation by chance alone with an inadequate safety margin. However, given the longer procedure times and sicker patients receiving CRT devices, minimizing defibrillation testing is an intriguing goal. In this regard, performing single-shock defibrillation testing has been proposed as a method to achieve such a goal, and this may be even more important in the CRT population. This is because of the concern regarding prolonged testing among patients with advanced heart failure and the growing trend towards no testing in this group, despite the lack of data to support that strategy.

Although the results of LESS suggest that a single shock with a safety margin of 15–20 J may be sufficient to ensure high probability of long-term ICD shock success, this was not a study of CRT devices. In fact, only about 25% of subjects in LESS had NYHA III–IV CHF functional status, while another 45% had NYHA II symptoms.

Whereas it may be appropriate to extrapolate the results of LESS to CRT devices, there are reasons to be concerned that this is unjustified.

There are certainly characteristics of the CRT-D population that are different from the typical ICD patient population, including more advanced CHF symptoms. Procedure times are also longer due to the placement of an extra left ventricular pacing lead into a sometimes technically challenging position. Both of these characteristics have been identified as predictors of elevated defibrillation energy requirements. Other predictors of elevated DFTs identified that are more likely to be present in the CRT-D candidate are wide QRS and increased LV mass [29].

Despite the identification of these predictors of high DFTs in the CRT population, recently published studies indicate that there are similar DERs between traditional ICD and CRT-D devices. In a preliminary report, Gilliam et al. retrospectively evaluated 1,257 ICD and 743 CRT-D patients from previous clinical trials. There was no significant difference in the DER in the CRT-D group compared with the ICD group [30]. Likewise, Schuger et al. reported data obtained from the VENTAK CHF/CONTAK CD Study Investigators evaluating the defibrillation energy requirements in CRT-D devices compared with those undergoing implantation of conventional ICD devices [31]. Of the 501 patients enrolled, 89% had successful implant defibrillation testing. The remaining 11% either demonstrated <10-J safety margin or could not be adequately tested due to safety concerns. Other interesting findings of this study included identification of elevated DER in individuals with increased left ventricular internal diameter during diastole and those requiring long procedure times. No association between amiodarone use and defibrillation energy was found. They concluded that defibrillation testing can be safely conducted and useful in detecting a significant number of patients who will have an elevated DER.

To compare DERs and the safety of one-shock testing in the CHF population, we analyzed two CRT-D and four ICD clinical trials [32]. All trials were part of regulatory studies for new indications or devices, so rigorous protocols and follow-up were required. For the purposes of this analysis, patients were grouped according to their NYHA class of CHF (I/II vs. III/IV). Using an inclusion criterion of an initial successful shock (<l7 J) at implant, patients were then monitored for successful shock termination of spontaneous, appropriate episodes of ventricular tachyarrhythmias in the VF zone. There were 94 subjects in the advanced heart failure cohort (group 1) and 114 in the mild CHF cohort (group 2). A comparison of the patient populations is shown in Table 19.1. As expected, the mean EF was somewhat lower for patients with NYHA III/IV CHF. Interestingly, the programmed energies for both spontaneous and induced testing were higher for the advanced CHF cohort, indicative of both slightly higher DFTs, as well as a tendency for programming higher safety margins in these patients. However, there were no differences in first-shock success to terminate appropriate ventricular arrhythmias (Fig. 19.4). About 8–10% of patients will fail to convert a spontaneous episode of rapid ventricular tachycardia (VT) or VF with the first shock in both groups. At first glance, this seems like a high percentage of failed shocks, but it is similar to previous studies [24]. Reinitiation of ventricular tachyarrhythmias during the redetection period and arrhythmias terminated with the second shock are classified as failures, which likely contribute to the apparent low termination rate observed.

Table 19.1 Clinical characteristics of ICD patients with advanced (group 1) and mild (group 2) CHF.

Characteristic	Group 1	Group 2	p value
Gender [N (%)]			
Male	77 (81.9)	92 (80.7)	0.8235
Female	17 (18.1)	22 (19.3)	
Age (years; mean ± SD)	66.8 ± 11.2	65.4 ± 11.9	0.4139
LVEF (%; mean ± SD)	21.4 ± 6.5	29.6 ± 13.8	<0.0001
Primary tachyarrhythmia			
Monomorphic VT	58 (61.7)	73 (64.6)	0.1847
Nonsustained VT	16 (17.0)	10 (8.8)	
Polymorphic VT	4 (4.3)	4 (3.5)	
Ventricular fibrillation	13 (13.8)	25 (22.1)	
Other	3 (3.2)	1 (0.9)	
NYHA class [N (%)]			
I		32 (28.1)	N/A
II		82 (71.9)	
III	81 (86.2)		
IV	13 (13.8)		

An alternative to single-shock testing of ICDs was proposed recently. Specifically, this was delayed testing. It is argued that those undergoing CRT-D implantation are a high-risk cohort. Conscious sedation and defibrillation testing add to the morbidity of the device implant. Accordingly, delaying DFT testing until CHF stabilization has been achieved is proposed as an alternative approach. Gasparini et al. address this issue by delaying testing until 2 months after implant. This method appears safe in this series and allows for adequate CHF stabilization prior to defibrillation testing. However, patients are subjected to a 2-month risk of potential inadequate safety margin or undersensing of VF while still subsequently undergoing testing, which requires a second procedure [33].

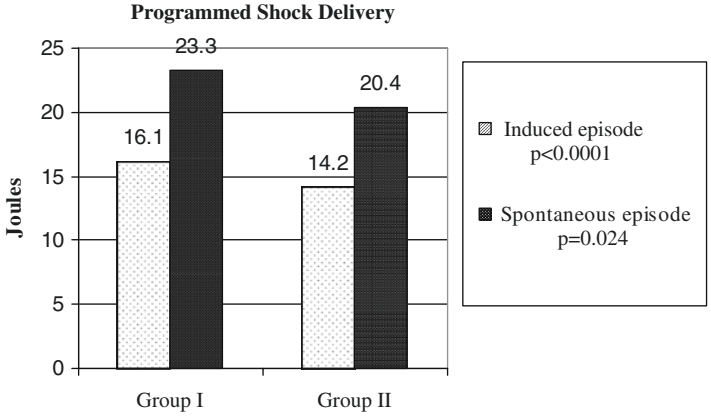

Fig. 19.4 First-shock energy programming for group 1 (class III–IV CHF) and group 2 (class I–II CHF). The shock energies for both induced and spontaneous episodes are shown, demonstrating that programmed energies are higher among patients with more advanced heart failure.

Conclusion

With the tremendous growth of CRT-D implants over the past 5 years, attention has been drawn to simplifying this procedure and reducing surgical morbidity. This has sparked renewed enthusiasm for modifying or eliminating traditional defibrillation efficacy testing. Proposed strategies include upper limit of vulnerability (ULV) measurements with no induction of VF, delayed testing, minimal testing, or no defibrillation testing at all. All of these approaches have the limitation of no large prospective data validating the strategy in the CRT population. ULV testing is well founded in scientific data but can be time consuming and requires multiple shocks even if VF is not induced. Delayed testing requires a second procedure with the uncertainty of defibrillation efficacy after implantation. No testing fails to identify the subgroup of patients with inadequate sensing or defibrillation function. Modeling and previous clinical trials suggest that this may represent 5–10% of the population. One-shock testing appears to be a reasonable compromise to minimize testing while still establishing the ability to sense and defibrillate. However, a safety margin of 15–20 J is needed to ensure a high probability of defibrillation success for spontaneous arrhythmias. Further prospective studies to validate this approach are warranted.

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Section IV

Follow-up

20

How to Program CRT Devices

Christophe Leclercq, Oliver Césari, Philippe Mabo, and J. Claude Daubert

Introduction

Cardiac resynchronization therapy (CRT) a validated treatment for patients with moderate to severe (drug-refractory) heart failure with left ventricular (LV) systolic dysfunction and evidence of ventricular dyssynchrony defined by a QRS duration equal to or greater than 120 ms [1, 2]. CRT improves symptoms, exercise tolerance, and quality of life [3, 4, 5, 6, 7]. More importantly, recent trials specifically designed to evaluate the effects of CRT on morbidity and mortality have shown a significant reduction in hospitalization rates, mainly for decompensated heart failure, and a significant reduction in overall mortality and sudden cardiac death even when CRT is not coupled with ventricular defibrillation capability [6, 8]. Moreover, different cost-effectiveness analyses have demonstrated that CRT is attractive in terms of health care use despite the initial price of the devices [8, 9]. The recent European and U.S. guidelines for the treatment of chronic heart failure have recommended CRT for improving symptoms and reducing hospitalization (class IA) and mortality (class IB) in advanced heart failure patients (New York Heart Association [NYHA] class III and IV) despite optimal drug treatment in the setting of poor systolic LV function, LV dilatation, and a wide QRS >120 ms on the surface electrocardiogram (ECG) [1, 2]. Thus, we can reasonably assume that the implantation of CRT devices will dramatically increase in the next few years.

The first step in the process of implantation of a CRT device, CRT pacemaker (CRT-P), or CRT defibrillator (CRT-D) is patient selection. So far, the U.S. and European guidelines have based the selection of CRT patients on the inclusion criteria of the major clinical trials. However, promising new imaging modalities, especially echocardiographic techniques, are rapidly growing in importance for the assessment of LV mechanical dyssynchrony. However, controlled studies specifically designed to validate these imaging techniques are currently lacking so that these modalities are not yet included in the guidelines of learned societies. The second step is the implantation of the CRT device, mostly using the transvenous approach inserting the LV lead into a tributary of the coronary sinus. Devices with a common ventricular channel for both pacing and sensing (as well as those using a Y-connector) are now obsolete so that the problems of ventricular double counting have been virtually eliminated in contemporary generators by restricting sensing to the right ventricular channel. The third step

(before hospital discharge) is optimization of the atrioventricular (AV) delay to ensure appropriate LV filling and in some cases the interventricular delay. These very important steps based on echocardiographic techniques are discussed elsewhere in this book. New features designed to automatically optimize AV and interventricular delays are currently being developed and are under clinical evaluation. The last step is long-term follow-up, requiring tailored programming of the device. Indeed, a patient with a CRT-P or a CRT-D has to be followed up very carefully, and this should not consist of only an "electric" or device follow-up. CRT patients often have severe heart failure with evidence of AV, inter- and intraventricular asynchrony. The complexity of CRT devices and the need for careful management of these very sick patients underscore the need for a multidisciplinary approach that includes a heart failure physician an echocardiographer and an electrophysiologist to evaluate the proper functioning of the device and the delivery of CRT. Careful medical management and monitoring of CRT patients before, during, and also after device implantation promotes the benefit of CRT and decreases the complications rates. In this chapter, we focus on device programming to optimize the delivery of CRT during the follow-up.

Initial Device Programming

After implantation of the CRT device, initial programming includes the choice of the pacing mode (VDD, DDD, DDDR, or VVIR in case of permanent atrial fibrillation), lower and upper rate limits, AV delay after atrial sensing, and pacing and rate limits to activate antitachycardia therapy in case of implantation of a CRT-D. Most of the published data in the literature involves patients with normal sinus rhythm with atrial-synchronous biventricular pacing (VDD mode). However, some patients with associated sinus node dysfunction or atrial chronotropic incompetence require sensor-driven pacing modes (DDDR mode). A recent study demonstrated that systematic atrial pacing might worsen LV function (DDD mode) compared with VDD mode with atrial sensing [10]. These results suggest that atrial pacing or sensor-driven pacing should not be activated routinely, and an evaluation of the heart rate during exercise should be performed. Usually, the AV delay is initially programmed empirically with a range of 80 to 120 ms during atrial sensing with an additional offset of 30 to 50 ms during atrial pacing.

During hospitalization, confirmation of biventricular capture has to be assessed regularly with the analysis of the surface ECG, which is compared with the ECG templates recorded at the time of implantation [11, 12, 13, 14]. Atrial and ventricular threshold data for pacing and sensing are measured and recorded before hospital discharge, providing a reference for further follow-up. Usually, the LV output is programmed at a value of at least 1.5–2 times the pacing threshold or much higher as desired during the acute phase. If available, optimal sensed and paced AV delay and optimal VV timing are programmed usually based on the results of echocardiographic evaluation.

How to Detect Loss of Biventricular Capture

Permanent or continual biventricular capture is the key to CRT success. The patient should be paced as often as possible or always in both ventricles. The loss of biventricular capture under a number of circumstances has to be avoided by appropriate and careful programming.

The diagnosis of loss of biventricular capture is easy if the situation is stable (not intermittent) and is documented with analysis of the QRS complexes on surface ECG. If the loss of biventricular capture is transient, the diagnosis is more difficult and may require different techniques, such as exercise testing or evaluation of the percentage of biventricular pacing obtained from memorized monitoring capabilities of the biventricular devices or a 24-h Holter recording.

Electrocardiographic Follow-up of Biventricular Pacemakers

Biventricular pacing has generated a new dimension to the electrocardiographic assessment of pacemaker function [16, 17, 18, 19, 20]. With monochamber right ventricular (RV) pacing, the role of 12-lead ECG was

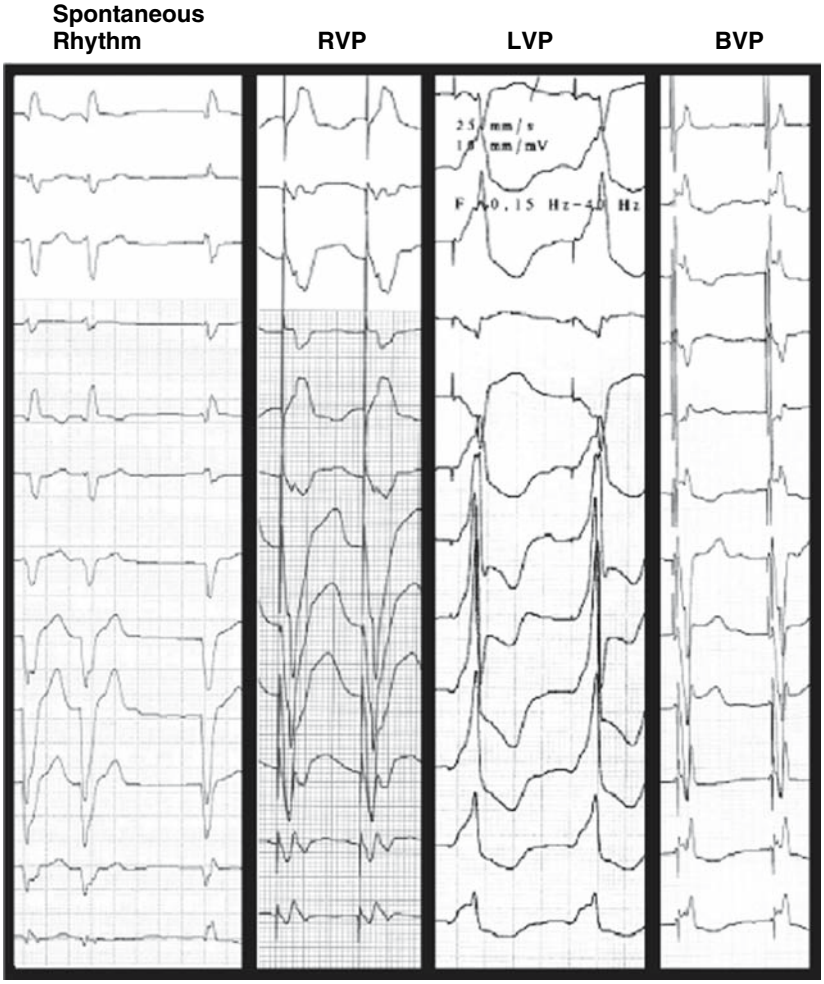

Fig. 20.1 Twelve-lead ECG illustrating the QRS pattern with spontaneous sinus rhythm, right ventricular (*RVP*), left ventricular (*LVP*), and biventricular (*BVP*) pacing in a patient with heart failure, permanent atrial fibrillation, and left bundle branch block. (Reproduced with permission from Garrigue S, Barold SS, Clémenty J. Electrocardiography of multisite ventricular pacing. In: Barold SS, Mugica J, eds. The Fifth Decade of Cardiac Pacing. Elmsford, NY: Blackwell-Futura; 2004:84–100).

minor. Biventricular pacing has created new interest in the 12-lead paced ECG, which is an indispensable tool for CRT assessment [16]. During the implantation procedure, a 12-lead ECG should be recorded to identify the ECG pattern of the intrinsic rhythm, RV pacing, LV pacing, and biventricular pacing (Fig. 20.1). This is of major importance to demonstrate the differences between the different pacing configurations and the information is to be used for further evaluation during follow-up.

In patients selected on the basis of the current guidelines, biventricular pacing is usually associated with a significant decrease in QRS duration on average 20 to 40 ms (in the main clinical trials) and typical changes in the frontal plane QRS axis, which usually points to the right superior quadrant if the RV lead is at the apex (Fig. 20.2) [3, 4, 5, 6, 7]. The MUSTIC trial has shown that the reduction of QRS width with effective biventricular pacing remains stable over time [15]. As illustrated in Figure 20.3, the loss of LV or RV pacing is generally easy to identify on the surface ECG. Generally, loss of biventricular capture is due to loss of LV pacing, which often has the higher pacing threshold. Loss of LV pacing yields the configuration of unichamber RV pacing on the surface ECG.

Loss of capture of one ventricular lead will convert the morphology of the paced 12-lead ECG to the pattern generated by the other stimulating lead. The analysis of the frontal plane axis may be helpful to establish loss of capture of one ventricle [16, 17]. With the first-generation devices with a common ventricular output, loss of capture of one ventricle (usually the LV capture first during threshold testing), the diagnosis required continuous recording of 12-lead surface ECG and telemetered markers and intracardiac electrograms (EGM) (Fig. 20.4). With capture of both ventricles, the evoked response (ventricular EGM) shows a monophasic complex different from the two ventricular deflections observed with spontaneous left bundle branch block or left intraventricular conduction delay [19, 20]. In the new generation

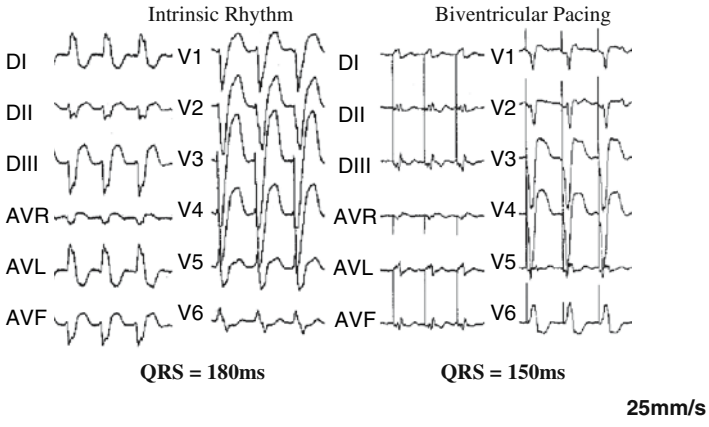

Fig. 20.2 Twelve-lead surface ECG showing a reduction in QRS duration from 180 ms with intrinsic rhythm (no biventricular pacing) on the left panel to 150 ms with biventricular pacing on the right ventricular panel associated with a significant change in the QRS axis in the frontal plane shifting from a left axis deviation to a normal axis.

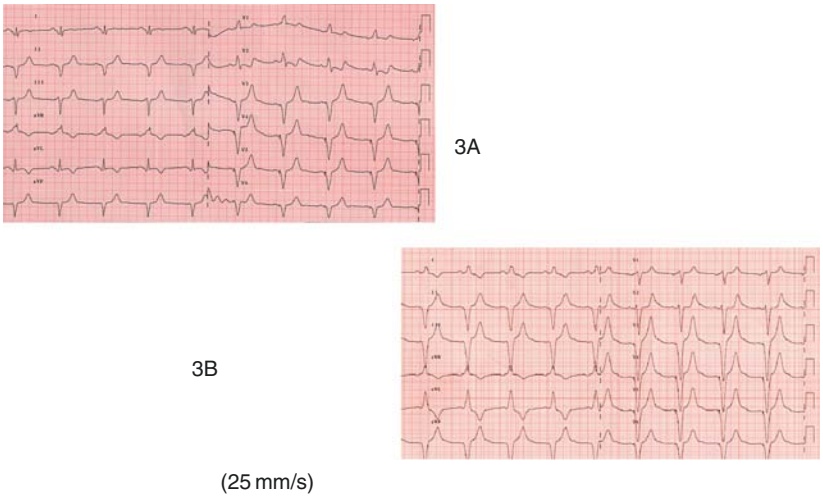

Fig. 20.3 (**A**) Twelve-lead ECG with biventricular capture. (**B**) Twelve-lead ECG in the same patient 1 month later, showing loss of LV capture associated with hemodynamic deterioration. Loss of LV capture was due to lead dislodgment requiring reoperation.

of CRT devices with independent ventricular ports, the evaluation of pacing threshold of the RV and LV leads is easier with the capability of independent measurement of the RV and LV pacing thresholds as illustrated in Figure 20.5.

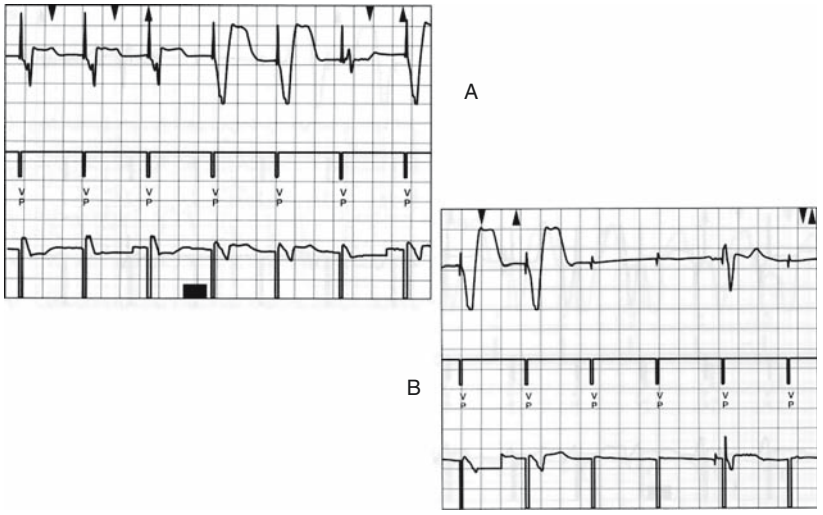

Fig. 20.4 (**A**) Determination of ventricular pacing threshold with progressive decrease of pacing output. The first three beats show biventricular capture. The following two QRS complexes show loss of LV capture and display monochamber RV pacing. The next complex is a fusion beat between RV pacing and intrinsic conduction. (**B**) Further decrease in the ventricular output results in loss of RV capture an the emergence of the intrinsic rhythm. (Reproduced with permission from Asirvatham S. Electrocardiogram interpretation with biventricular pacing devices. In: Hayes DL, Wang PJ, Sackner-Bernstein J, Asirvatham S, eds. Resynchronization and Defibrillation for Heart Failure: A Practical Approach. Elmsford, NY: Blackwell-Futura; 2004:73–99).

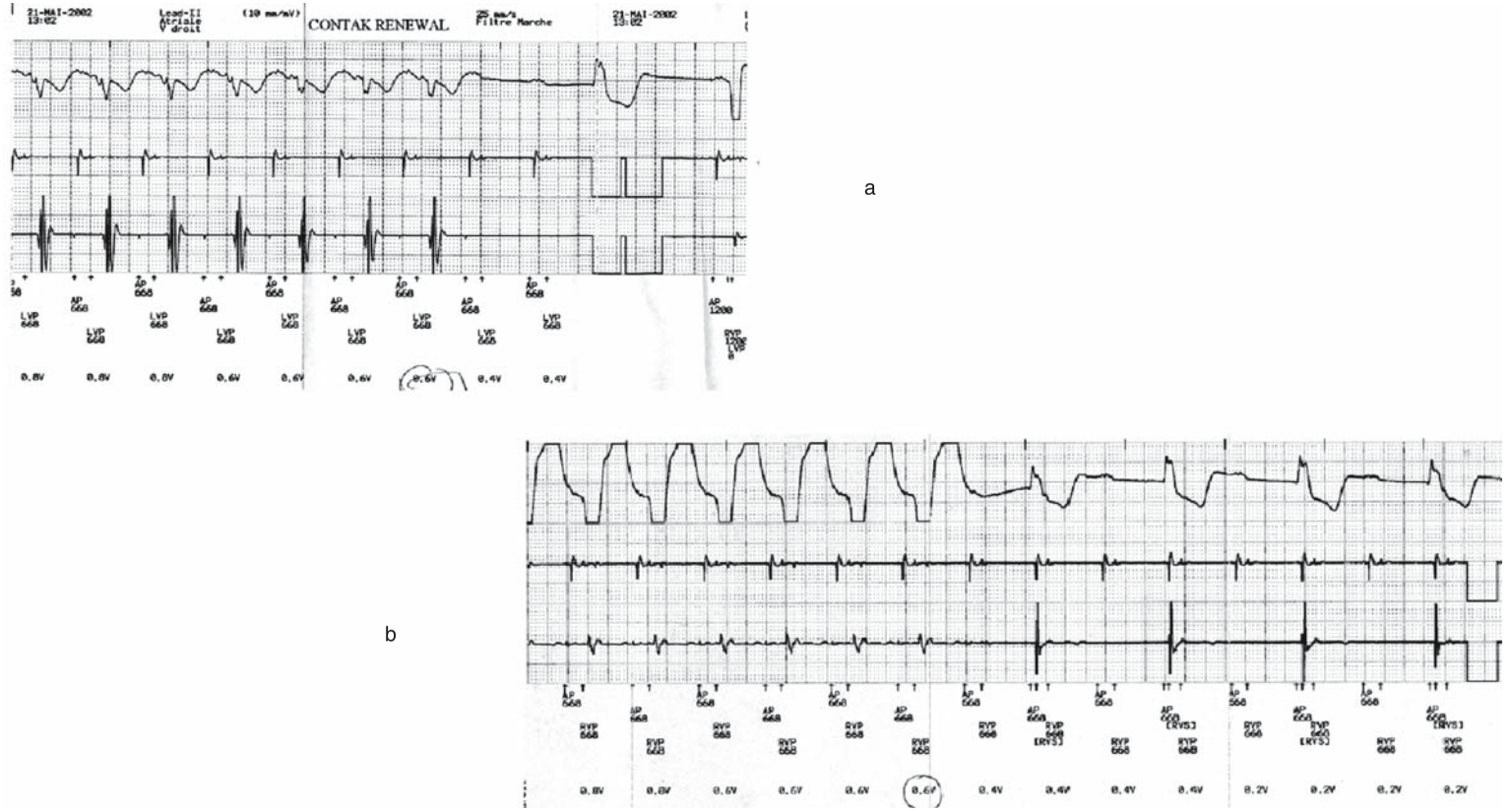

Fig. 20.5 (**A**) Measurement of LV pacing threshold in a CRT device with independent ventricular ports. The pacing threshold was 0.6 V with a pulse width at 0.5 ms. (**B**) Measurement of RV pacing threshold in the same patient. The RV pacing threshold was also measured at 0.6 V with a pulse width at 0.5 ms.

How to Assess Adequate Programming During Exercise

A patient with a CRT device will exercise, so that the assessment of biventricular capture should include exercise testing. There are many reasons why biventricular capture may fail during exercise: loss of atrial sensing, frequent premature ventricular complexes (PVCs), atrial tachyarrhythmias, and spontaneous AV conduction that is more rapid than the programmed AV delay. Generally, RV and LV pacing channels are programmed in the bipolar mode to avoid potential pectoral stimulation. To better identify atrial and ventricular spikes reprogramming, ventricular and atrial pacing into the unipolar mode may be useful as illustrated in Figure 20.6. The shape of atrial and ventricular complexes is similar with the two pacing modes (unipolar and bipolar). The analysis of ventricular complexes is of major importance to assess biventricular capture during exercise. Changes of the QRS complexes during exercise may suggest (as illustrated in Fig. 20.7) the loss of capture in one ventricle. The programmed AV delay at rest but also the adaptation of the AV delay during exercise needs to be assessed carefully. Figure 20.8 illustrates adequate programming of the AV delay at rest and during exercise. By contrast, in Figure 20.9, the rate-adaptive AV delay was not optimized during exercise resulting in the loss of LV capture. The loss of biventricular capture during exercise due to an excessively long programmed AV delay may be also assessed using the device telemarkers (Fig. 20.10). In patients with permanent atrial fibrillation and without AV node ablation, exercise testing has to be performed to verify the constancy of biventricular capture. In these patients, apparent adequate biventricular capture at rest may not be

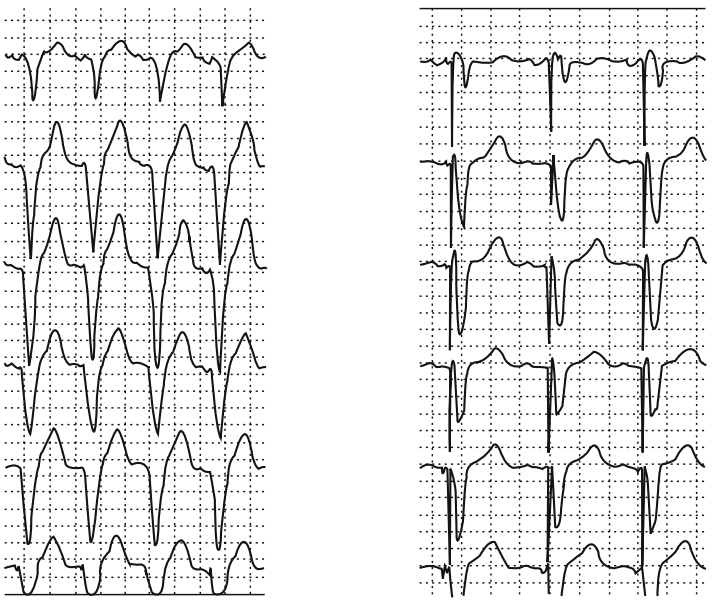

Fig. 20.6 Temporary switching from a bipolar configuration (*left panel*) to an unipolar configuration (*right panel*) before an exercise test to improve identification of the ventricular spikes.

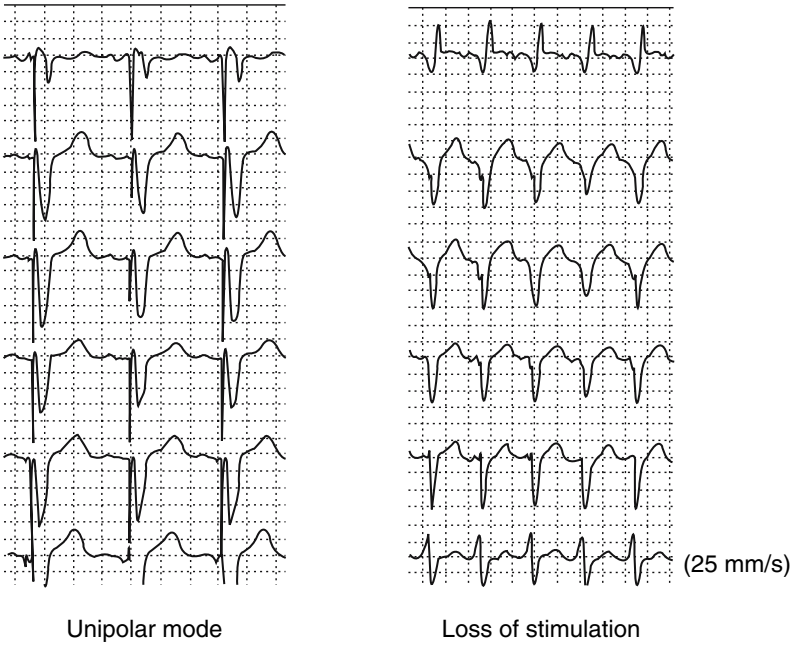

Fig. 20.7 Loss of biventricular pacing during exercise. *Left panel*: Biventricular paced QRS complexes with unipolar configuration at rest. *Right panel*: During the exercise test, there is loss of biventricular capture with the loss of ventricular spike and changes in QRS morphology.

a reliable marker of satisfactory biventricular capture because intrinsic AV conduction on exercise may inhibit biventricular capture when the spontaneous ventricular rate exceeds the sensor-driven pacemaker rate (Fig. 20.11).

Hemodynamic deterioration during exercise may sometimes be due to a loss of atrial sensing with preservation of biventricular capture, a situation requiring reprogramming of the atrial sensitivity (Fig. 20.12).

Finally, the evaluation of a patient with a rate-adaptive pacemaker has to consider the type of rate-adaptive sensor. For example, patients with an activity sensor may not exhibit an increase of heart rate during an exercise performed on a cyclo-ergometer. An exercise test performed on a treadmill in the same patient without changing the sensor settings may demonstrate better adaptation of the heart rate (Fig. 20.13).

Importance of Upper Rate Programming

Upper Rate Behavior in Biventricular Devices

A common reason of loss of biventricular capture is related to sensing an atrial rate close to the programmed maximal tracking rate [21, 22, 23]. Upper rate behavior of biventricular pacemakers may take the form of a traditional pacemaker Wenckebach response or the equivalent of fixed-ratio block as in conventional antibradycardia pacemakers defined by the programmed upper tracking rate and the total atrial refractory period (TARP). When the atrial rate exceeds the programmed upper rate but the P-P interval remains longer

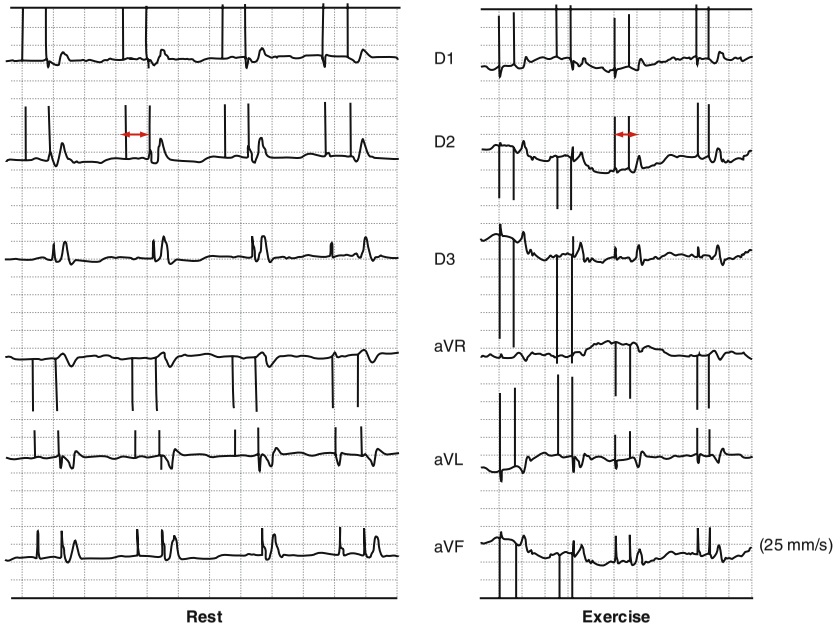

Fig. 20.8 *Left panel*: Apparently adequate programming of the AV delay. The surface ECG at rest shows unipolar atrial and ventricular spikes and an AV delay of 150 ms. *Right panel*: During exercise, the heart rate increases and the AV delay shortens ensuring continual biventricular capture.

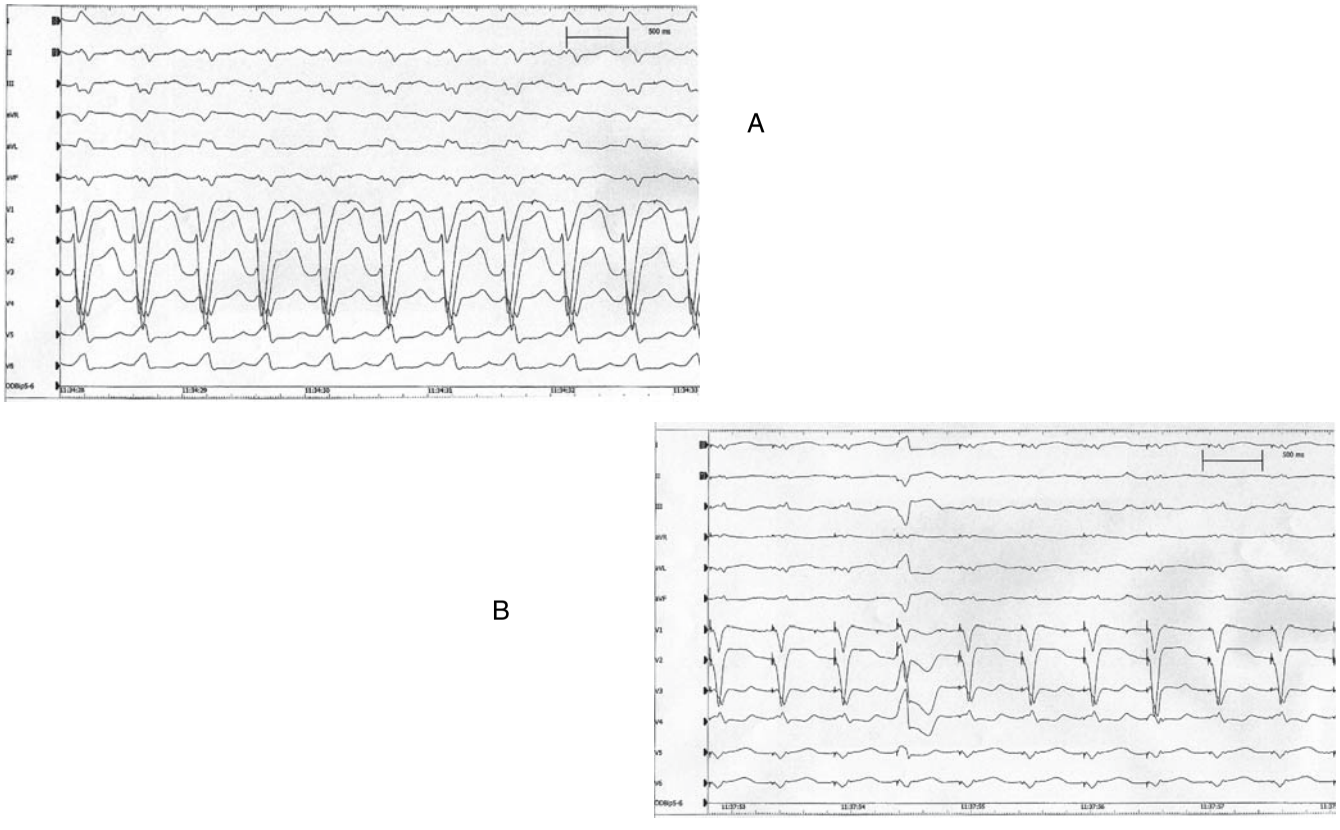

Fig. 20.9 (**A**) Inadequate programming of the AV delay shown in 12-lead ECGs during an exercise test in a patient with a CRT pacemaker. The patient had not improved with biventricular pacing because of the low percentage (60%) of biventricular capture caused by an excessively long programmed AV delay. Programming a shorter AV delay during exercise resulted in consistent biventricular capture during exercise and significant symptomatic improvement.

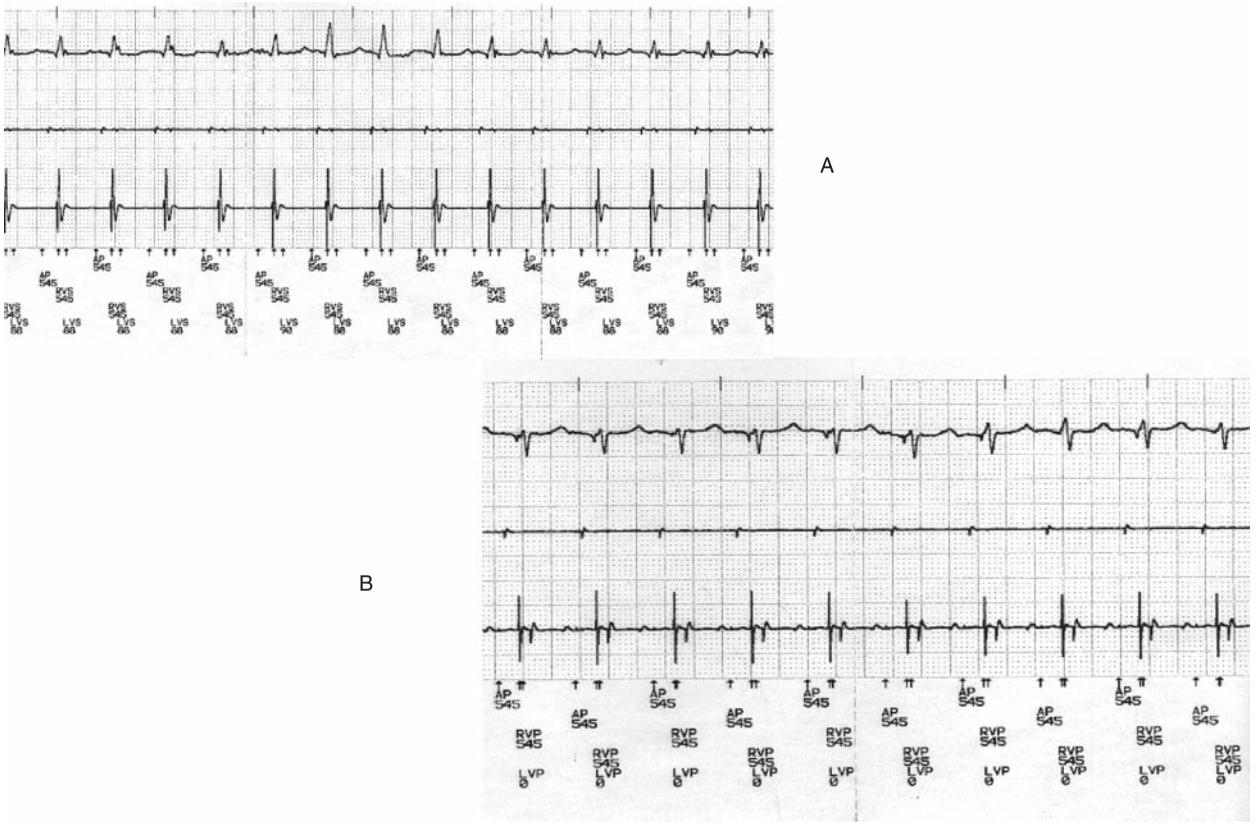

Fig. 20.10 Inadequate AV delay programming. (**A**) Six-minute walking test performed in a patient implanted with a biventricular pacemaker. Inadequate programming of the AV resulted in the lack of biventricular pacing as illustrated by the ECG channel and the markers channels (middle and lower recordings). *AP*, atrial paced event; *RVS*, right ventricular sensed event; *LVS*, left ventricular sensed event. Optimization of the AV delay provided continual biventricular capture.

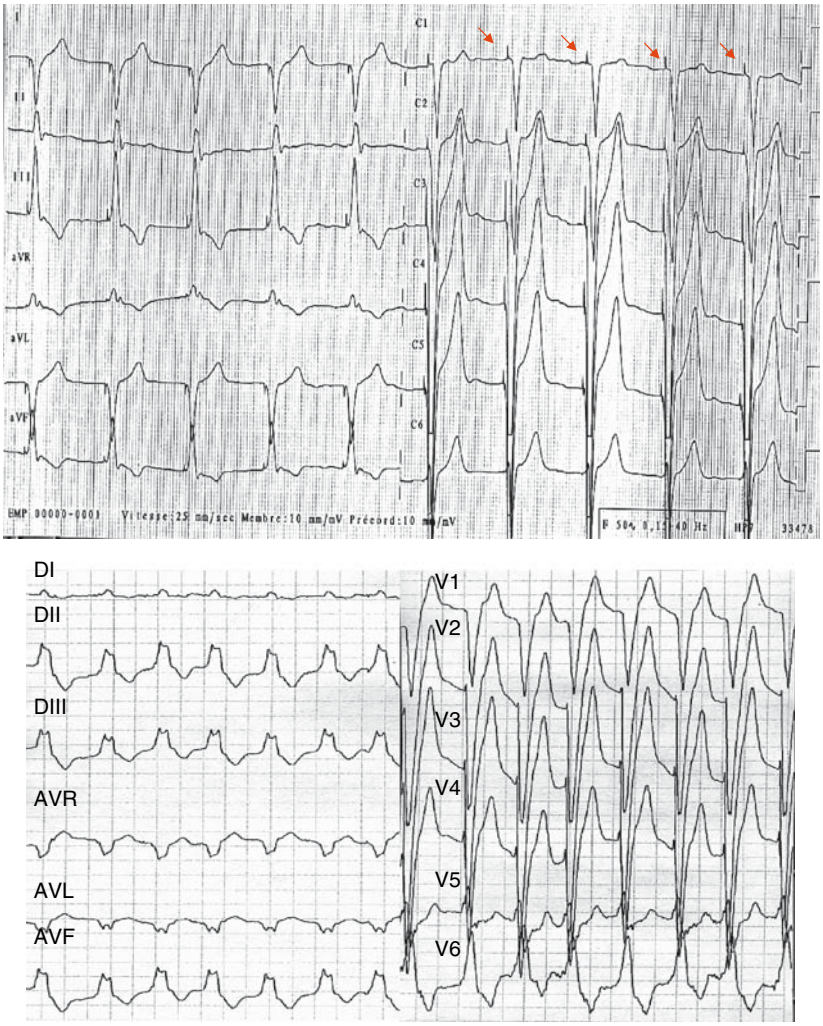

Fig. 20.11 Loss of biventricular capture during exercise in a CRT patient with permanent atrial fibrillation. (**A**) Twelve-lead ECG with a 130-ms QRS duration in a CRT patient with permanent atrial fibrillation. (**B**) Twelve-lead ECG in the same patient during an exercise test resulting in the loss of CRT and the development of spontaneous left bundle branch block. After AV nodal ablation, the patient was permanently paced in both ventricles with resultant functional improvement.

than the TARP, the pacemaker exhibits a Wenckebach response. If the P-P interval becomes shorter than the TARP (which is equal to the sum of the prevailing AV delay and the postventricular atrial refractory period, or PVARP), 2:1 block (in patients with AV block) occurs whenever every other atrial event falls in PVARP. CRT patients often have relatively normal AV conduction. Consequently fixed-ratio 2:1 block does not occur when the P-P interval becomes shorter than the prevailing TARP. Rather, every P-wave becomes locked inside the PVARP, a situation that permits spontaneous AV conduction. The device then senses the conducted spontaneous QRS complex thereby perpetuating loss of CRT.

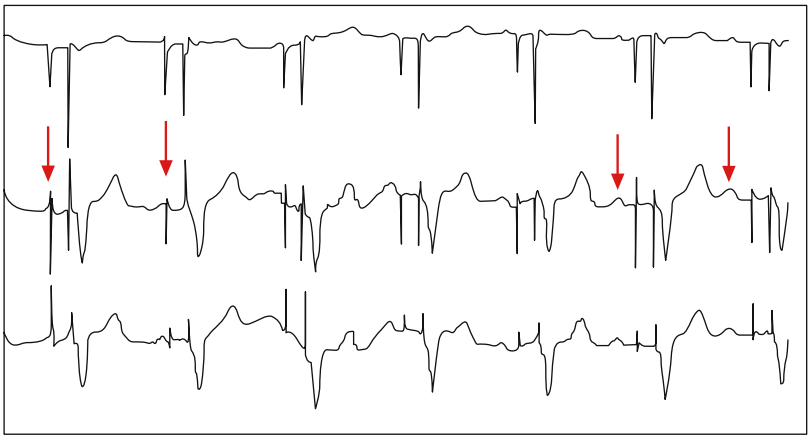

Fig. 20.12 Loss of atrial sensing during exercise (*arrows*) in a CRT patient. Increase in the atrial sensitivity yielded appropriate atrial detection during a subsequent exercise test.

The TARP is prolonged during intrinsic rhythm because the AV delay (interval from atrial event sensed in the PVARP to ventricular sensed event) is longer than the programmed AV delay (interval from atrial sensed event outside the PVARP to ventricular paced event). Thus, atrial tracking and ventricular pacing may not occur at atrial rates slower than the heart rates theoretically predicted by of the sum of the programmed AV delay and the PVARP. This phenomenon may become manifest especially after a premature ventricular complex (PVC) with or without an automatic PVARP extension. After a PVC, the next atrial event falls within the PVARP and permits spontaneous AV conduction, which inhibits biventricular pacing. The process then becomes self-perpetuating. Specific algorithms of new CRT devices by shortening the PVARP at rates lower than the programmed upper rate permit restoration of atrial tracking. (Figs. 20.14 and 20.15).

Preempted Wenckebach Upper Rate Response

In a conventional Wenckebach upper rate response, a dual-chamber pacemaker delivers a ventricular stimulus only at the completion of the upper rate interval driven by the atria. The AV delay initiated by a sensed P-wave increases progressively because the ventricular channel waits to deliver its output at the end of the upper rate interval. When a P-wave falls in the PVARP, a pause occurs and the ventricular paced sequence repeats itself. In CRT patients with normal or near normal sinus node function and AV conduction, the Wenckebach upper rate response takes the form of a repetitive preempted process that consists of an attempted Wenckebach upper response with each cycle, associated with continual partial or incomplete extension of the programmed AV interval. This produces a response with no evident paced complexes. (Fig. 20.16) [21, 22]. The process starts with a traditional Wenckebach upper rate response characterized by a gradual prolongation of the atrial sensed, ventricular paced interval and fusion of the ventricular paced beat and the intrinsic QRS with a progressive decrease in the contribution of the ventricular paced beat. In the so-called preempted Wenckebach upper rate response, the spontaneous QRS complex continually occurs before completion

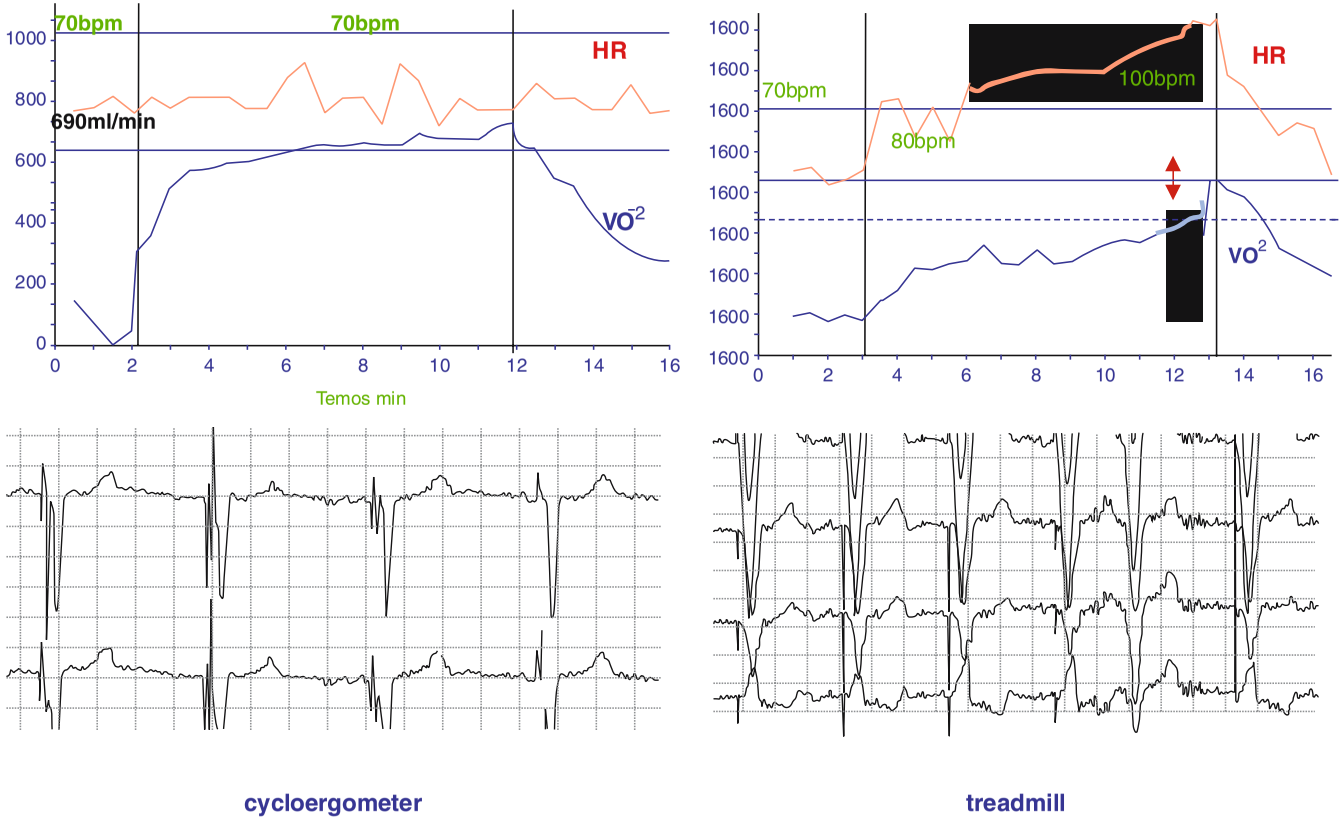

Fig. 20.13 Importance of the type of exercise test in patients with sensor-driven pacemakers. In the *left panel* with an exercise test performed on a cyclo-ergometer, the programmed sensor was not activated and the heart rate (*HR*) remained below 70 bpm. By contrast, in the *right panel*, when the exercise test was performed on a treadmill, the sensor with the same settings was activated with a significant increase in heart rate.

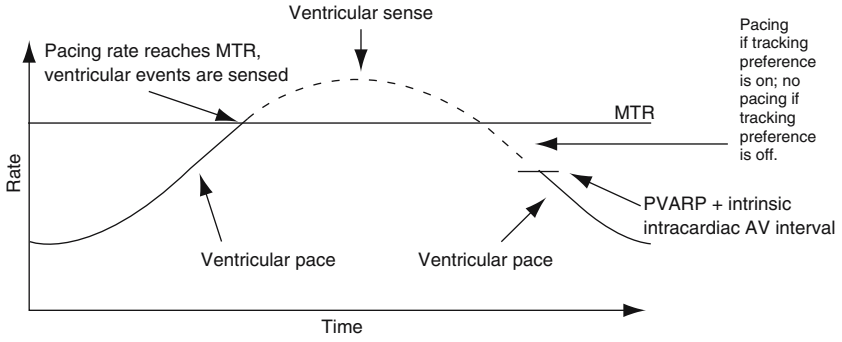

Fig. 20.14 Tracking preference is designed to maintain atrial-tracked ventricular pacing in DDD(R) and VDD modes by identifying atrial events that should be tracked but are hidden in the PVARP. Hidden atrial events can occur when a patient has a combination of long intrinsic intracardiac AV interval and a long PVARP. This algorithm allows the delivery of cardiac resynchronization therapy for atrial rates below but near the maximal tracking rate (Courtesy of Guidant Corporation, St Paul, MN, USA).

of the upper rate interval. It is therefore sensed by the device, and ventricular pacing is preempted. This form of upper rate response is more likely observed with relatively normal AV conduction, a short programmed AV delay, a relatively slow programmed upper rate (driven by the atria), and a sinus rate greater than the programmed upper rate. Moreover, this phenomenon may occur on exercise or in circumstances with a high adrenergic tone.

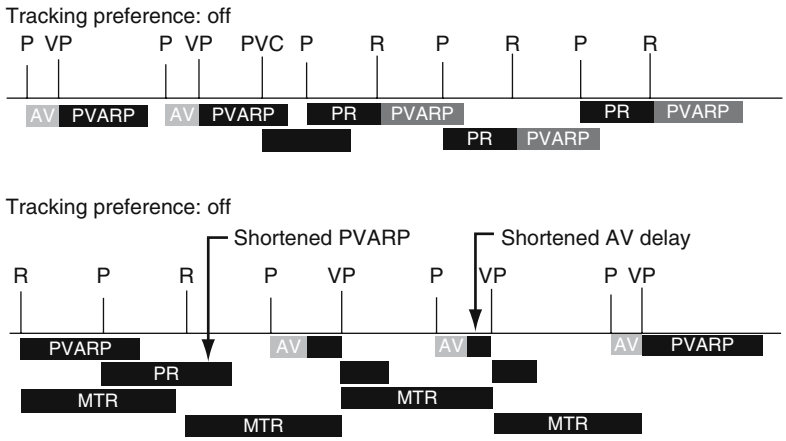

Fig. 20.15 Atrial tracking preference function of the Guidant Renewal ICD. If two successive cycles occur in which a sensed RV event is preceded by an atrial event that occurs in the PVARP, the PVARP shortens until normal atrial tracking is established. By programming "Tracking Preference On," continuous cardiac resynchronization therapy is delivered at rates below maximal tracking rate, rates that otherwise might be inhibited when the sum of PVARP and intrinsic intracardiac atrioventricular interval is longer than the prevailing maximal tracking rate interval. At rates above maximal rate tracking (MRT), atrial tracking preference is disabled. (Courtesy of Guidant Corporation, St Paul, MN, USA).

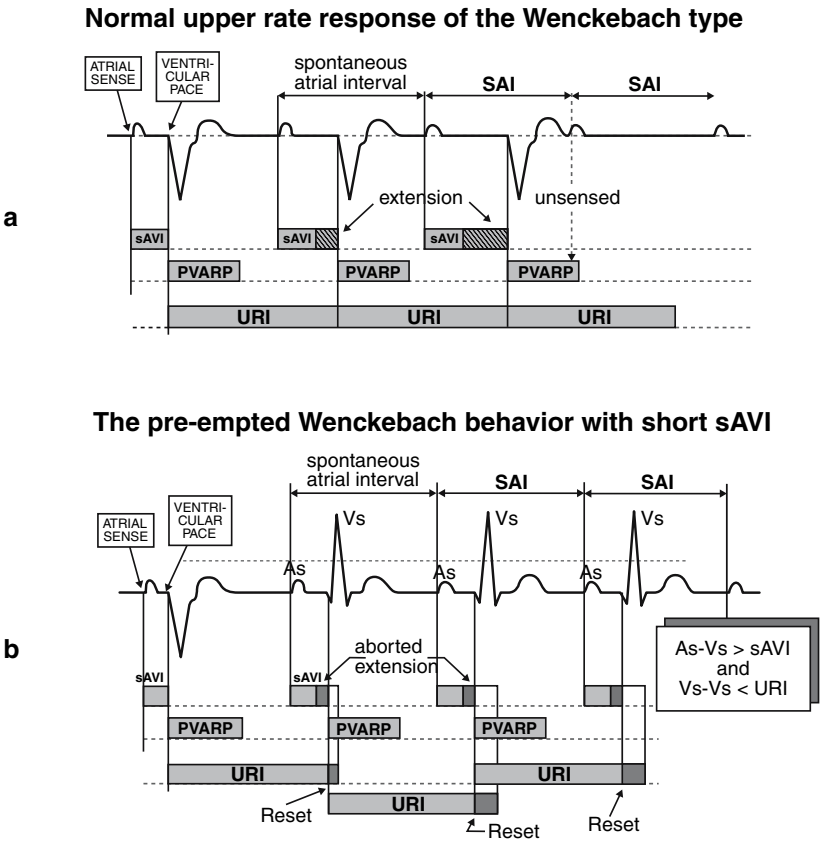

Fig. 20.16 Wenckebach upper rate response. (**A**) Wenckebach upper rate response in a conventional dual-chamber pacemaker response. (**B**) Repetitive preempted Wenckebach upper rate response during CRT. *AS*, atrial sense; *Vs*, ventricular sense; *sAVI*, AV delay after sensing; *URI*, upper rate interval; *SAI*, spontaneous atrial interval. See text for details. (Reproduced with permission from Barold SS, Garrigue S, Israel C.W, Gallardo I, Clémenty J. Arrhythmias of biventricular pacemakers and implantable cardioverter defibrillators. In: Barold SS, Mugica J, eds. The Fifth Decade of Cardiac Pacing. Elmsford, NY: Blackwell-Futura; 2004:100–117).

Programming and Paroxysmal Atrial Arrhythmias

In patients with severe heart failure, atrial arrhythmias and especially atrial fibrillation (AF) occur in up to 40% with a significant correlation with the severity of heart failure [24, 25, 26, 27, 28]. The occurrence of AF in CRT patients may produce major hemodynamic deterioration due to the loss of the atrial contribution to cardiac output. AF may also interfere with programming functions of the CRT device. Atrial arrhythmias may cause loss of biventricular pacing during rapid spontaneous ventricular rates or induce excessively rapid ventricular pacing during atrial tracking. Atrial arrhythmias may be the cause of poor resynchronization in up to 20% of CRT patients [29].

In case of paroxysmal AF, the mode-switching activation may avoid a rapid ventricular rate in patients with AV block. For example, in the Medtronic InSync Sentry device, the mode-switch function detects an atrial tachyarrhythmia if the A-A median (the median of the last 12 A-A intervals)

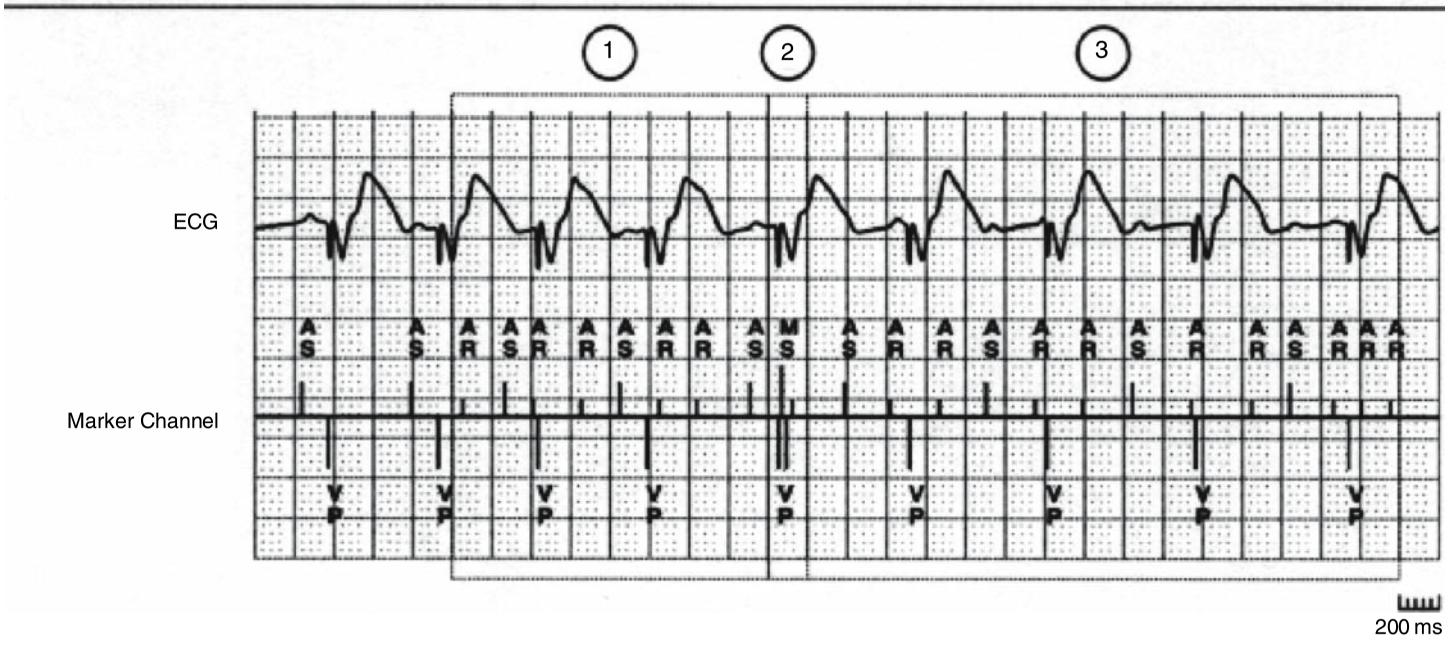

Fig. 20.17 Mode switch of the Medtronic InSync Sentry. *1*, An atrial tachyarrhythmia starts, causing rapid ventricular pacing. *2*, The onset of atrial tachyarrhythmia occurs, and "Mode Switch" changes the pacing mode to DDIR. *3*, The device gradually changes from the faster ventricular pacing rate to the slower sensor-indicated rate (Courtesy of Medtronic Inc., Minneapolis, MN, USA).

exceeds the programmable atrial detection rate and satisfies the atrial fibrillation/atrial tachycardia (AF/AT) evidence criterion. When an atrial tachyarrhythmia is detected, the device reduces the ventricular pacing rate smoothly from the atrial synchronous rate to the sensor-indicated rate. The smooth rate reduction prevents an abrupt drop in the ventricular rate (Fig. 20.17). The termination of atrial tachyarrhythmia is detected when the atrial rate is less than or equal to the upper tracking rate. After the atrial tachyarrhythmia ends, the device reverts to either the DDD or DDDR mode.

To optimize AV synchrony, some algorithms attempt to prevent atrial tachyarrhythmias. For example, the *noncompetitive atrial pacing* (NCAP) delays an atrial paced event scheduled to fall within the relative myocardial atrial refractory period to prevent the precipitation of atrial tachyarrhythmias. Using the NCAP interval parameter, it is possible to program how long to postpone an atrial paced event if an atrial event is sensed within the PVARP: If an atrial paced event is scheduled to occur during the NCAP interval, the atrial paced event is delayed until the NCAP interval terminates. If no atrial pace is scheduled to be delivered during the NCAP interval, pacemaker timing is not affected (Fig. 20.18).

However, preventing competitive atrial pacing may be obtained by reprogramming pacing parameters as illustrated in Figure 20.19. For example, with programming an upper sensor rate at 120 ppm with an AV delay of 180 ms and a PVARP of 310 ms, the minimal interval between the end of the

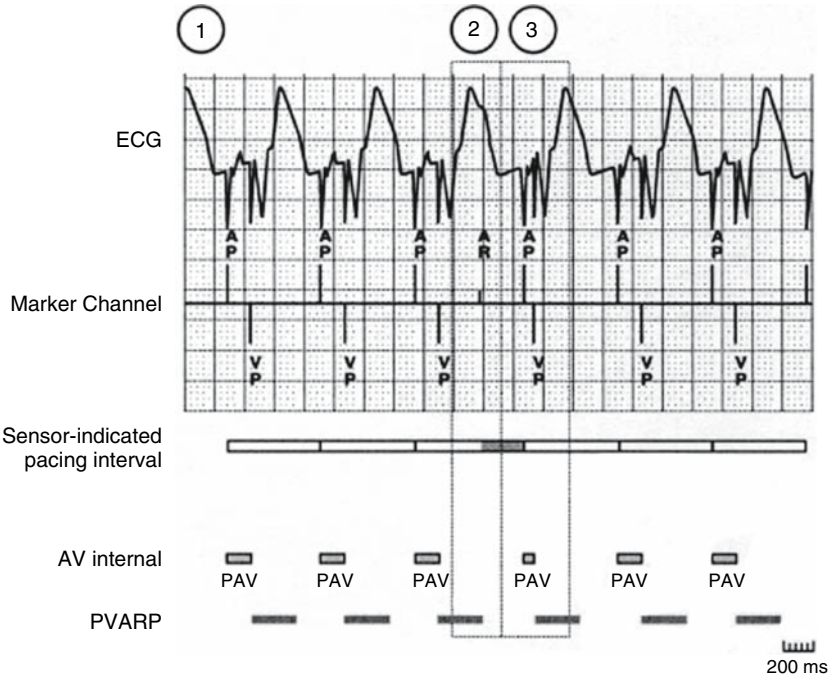

Fig. 20.18 Noncompetitive atrial pacing (NCAP). *1*, The device is pacing at the upper sensor rate of 120 bpm. *2*, An atrial refractory sensed event occurs, starting an NCAP interval (300 ms in this case). *3*, After the NCAP interval terminates, the device paces the atrium and then paces the ventricle after a shortened paced AV interval. (Courtesy of Medtronic Inc., Minneapolis, MN, USA).

PVARP and the next atrial pace becomes 10 ms. In this case, an atrial pacing stimulus is delivered immediately after an atrial refractory period, which may induce an atrial tachycardia. In the same patient, with programming the upper sensor rate at 100 ppm with an AV delay of 100 ms and a shorter PVARP at

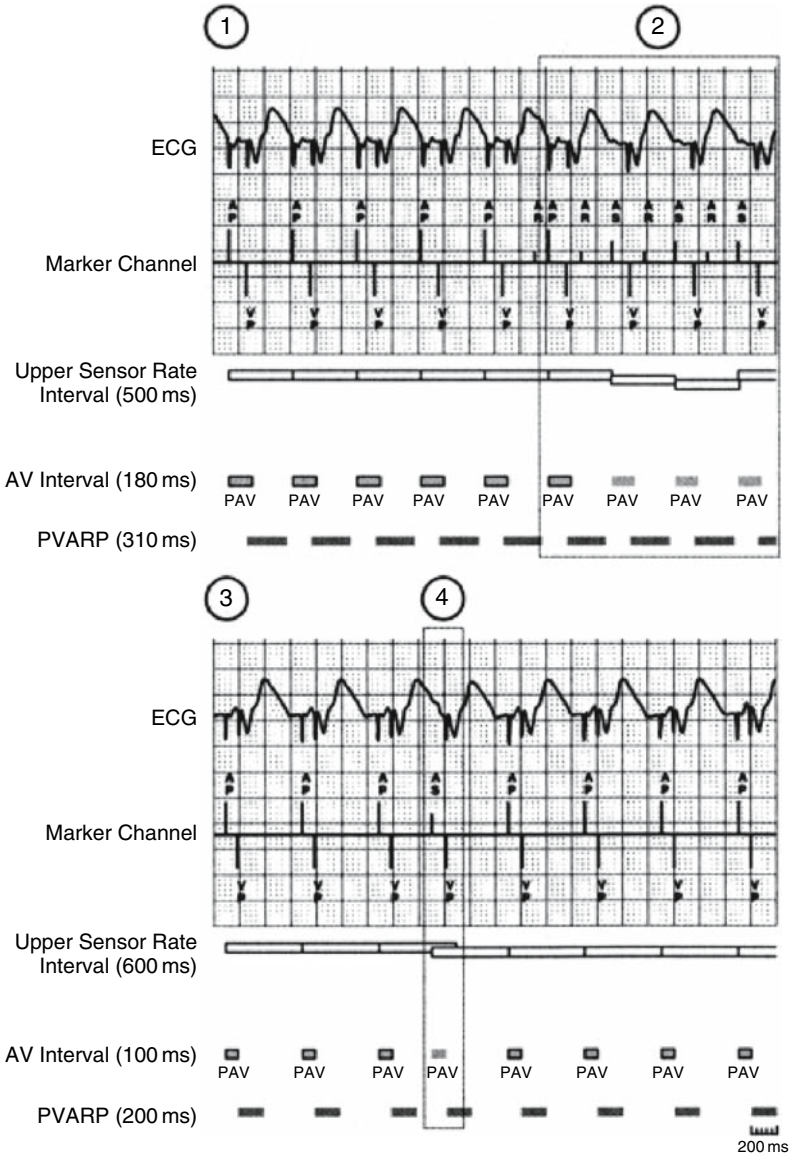

Fig. 20.19 Prevention of competitive atrial pacing by a special programmable function. *1*, With pacing occurring at the upper sensor rate of 120 min^{-1}, A-V interval = 180 ms, and PVARP = 310 ms, the minimum interval between the end of PVARP and the next atrial pace is 10 ms. *2*, An atrial paced event is delivered immediately after an atrial refractory sensed event, causing competitive atrial pacing, which triggers an atrial tachyarrhythmia. *3*, With pacing occurring at the upper sensor rate of 100 min^{-1}, A-V interval = 100 ms, and PVARP = 200 ms, the minimum interval between the end of PVARP and the next atrial paced event is 300 ms. *4*, An intrinsic atrial event occurs after the shorter PVARP interval and is sensed. (Courtesy of Medtronic Inc., Minneapolis, MN, USA).

200 ms, the minimum interval between the end of the PVARP and the next atrial paced event is 300 ms, so that an intrinsic atrial event occurs after the shorter PVARP interval and is sensed (Fig. 20.19).

New features are available in the most recent devices to optimize the percentage of ventricular pacing with little or no increase in the daily mean heart rate and so to promote delivery of cardiac resynchronization therapy during atrial fibrillation/atrial tachyarrhythmias episodes. The conducted atrial fibrillation response of a CRT device regularizes the ventricular rate by adjusting the pacing escape interval after each ventricular beat. The escape interval increases or decreases, depending on whether the preceding events were paced or sensed. The result is a higher percentage of ventricular pacing at an average rate that closely matches the patient's own ventricular response (Figs. 20.20 and 20.21). These types of algorithm operate only in nontracking modes. Therefore, when the DDD or DDDR mode is programmed, the conducted AF response operates only during mode switching.

Programming and Permanent Atrial Fibrillation

Almost all the clinical trials designed to assess CRT efficacy included patients with stable sinus rhythm, the presence of a permanent AF being an exclusion criterion. Thus, only sparse data are available regarding CRT efficacy in patients with permanent AF. Moreover, these data were obtained from uncontrolled and nonrandomized studies except the MUSTIC AF study and the OPSITE trial [30, 31]. The MUSTIC AF study included 49 patients in a prospective, randomized trial with two 3-month crossover periods. The patients were in permanent AF requiring ventricular pacemaker implantation because of a slow ventricular rate either spontaneous or induced by AV node radiofrequency ablation. The biventricular pacing mode was compared with monochamber RV pacing mode. The results of the MUSTIC AF trial highlighted the major importance of continual biventricular capture as a prerequisite of CRT efficacy. Because of a higher than expected dropout rate, only 37 patients completed the two crossover periods. The intention to treat analysis did not show any significant changes between the two pacing modes for the 6-min walk distance, the quality of life, or the peak oxygen uptake [30]. Analyzing 24-h Holter recordings and pacemaker files showed that some patients without AV ablation had a low percentage of paced ventricular cycles (less than 50%). By contrast, all the other patients (who had undergone AV ablation) had a permanent or almost permanent biventricular capture between 97% and 100% of the time. In the subgroup of patients with permanent biventricular pacing, CRT significantly improved the 6-min walking distance and the peak oxygen uptake but also significantly reduced the number of all-causes and heart failure hospitalizations [30]. In permanent AF, continual biventricular capture has to be assessed at rest and during exercise as previously emphasized. Usually in permanent AF, patients without spontaneous or radiofrequency-induced AV block, ventricular rate control is achieved with beta-blockers, calcium blockers, or digoxin, alone or in combination. At rest, the rate control with these drugs may be effective, but it may it be unsatisfactory as soon as the patient starts exercising. In these patients with a low percentage of paced ventricular cycles, radiofrequency AV node ablation is recommended to optimize CRT delivery. Some workers have suggested the

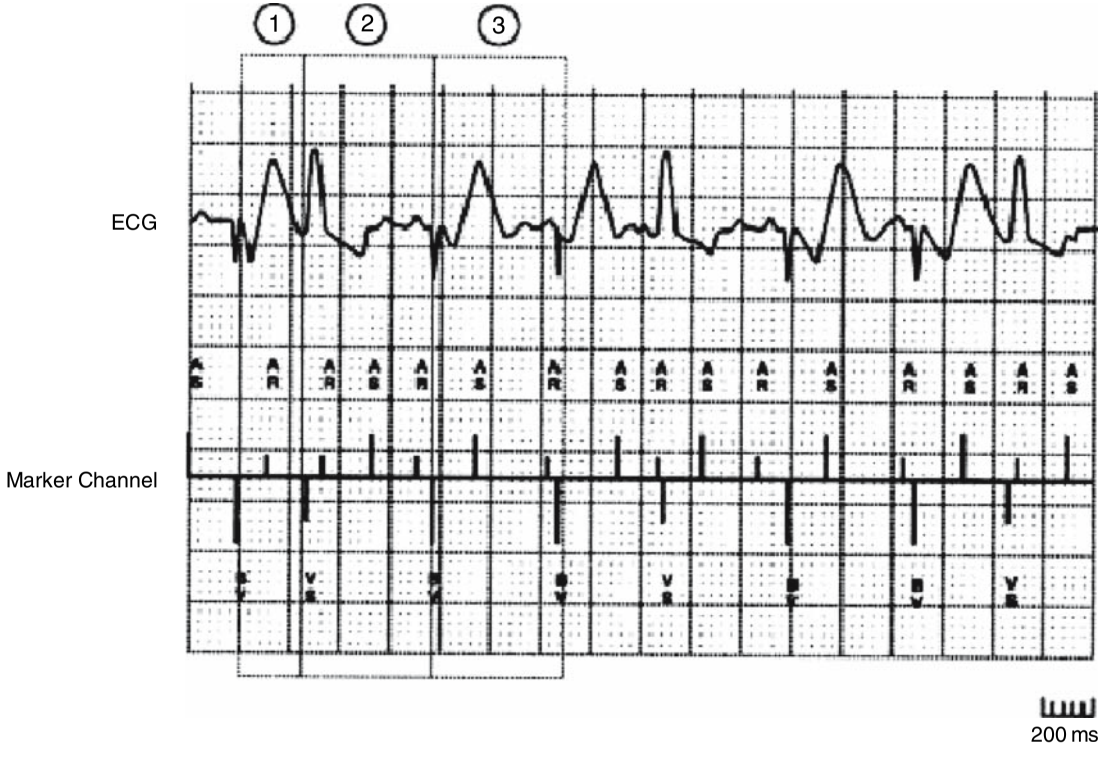

Fig. 20.20 Conducted atrial fibrillation response operation in the Medtronic InSync Sentry device. *BV*, biventricular pacing; *AR*, atrial refractory event; *VS*, ventricular sensed event. *1*, BV–AR–VS sequence causes the ventricular pacing rate to increase by 1 min^{-1} if response level is programmed to low or medium. *2*, VS–BV sequence causes ventricular pacing rate to be unchanged. *3*, BV–BV sequence causes pacing rate to decrease by 1 min^{-1}. (Courtesy of Medtronic Inc., Minneapolis, MN, USA).

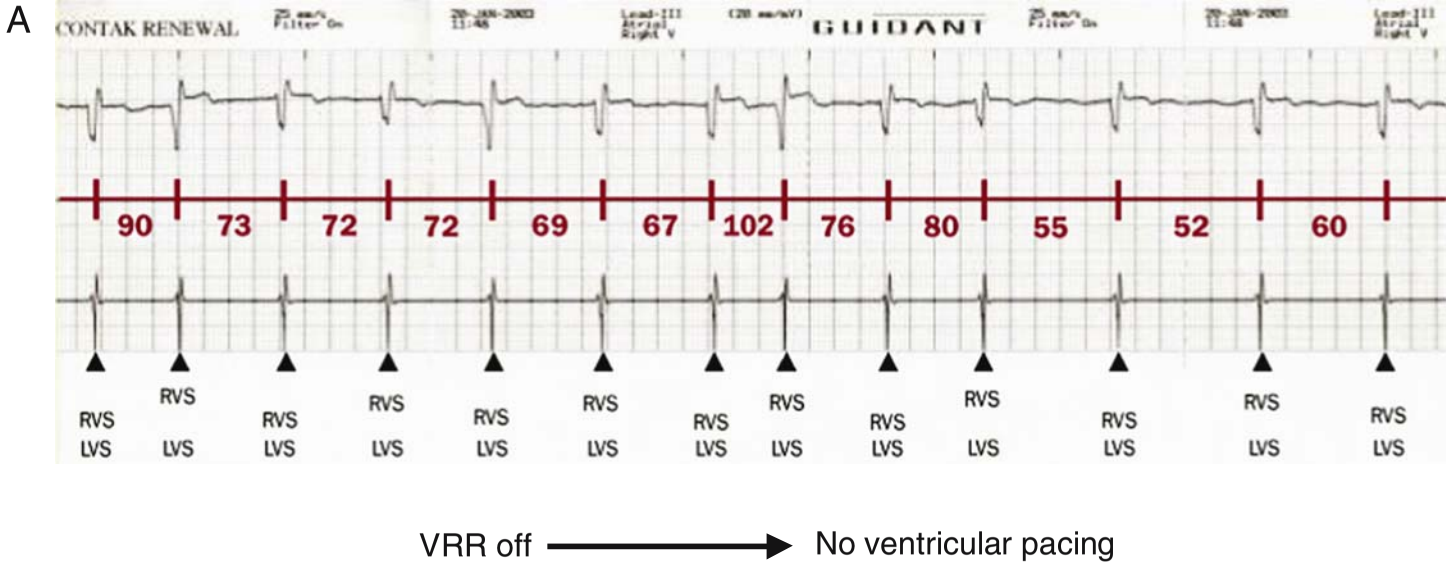

Fig. 20.21 Ventricular rate regularization. (**A**) Recording from a patient with a CRT device and permanent atrial fibrillation with a spontaneous ventricular rate ranging from 55 to 102 bpm. The ventricular rate regularization algorithm is not activated and the RV and LV are not paced. (**B**) In the same patient after switching on the ventricular rate regularization (VRR) feature, there is biventricular pacing in 84% of the cardiac cycles with a more regular heart rate. (Courtesy of Guidant Corporation, St Paul, MN, USA).

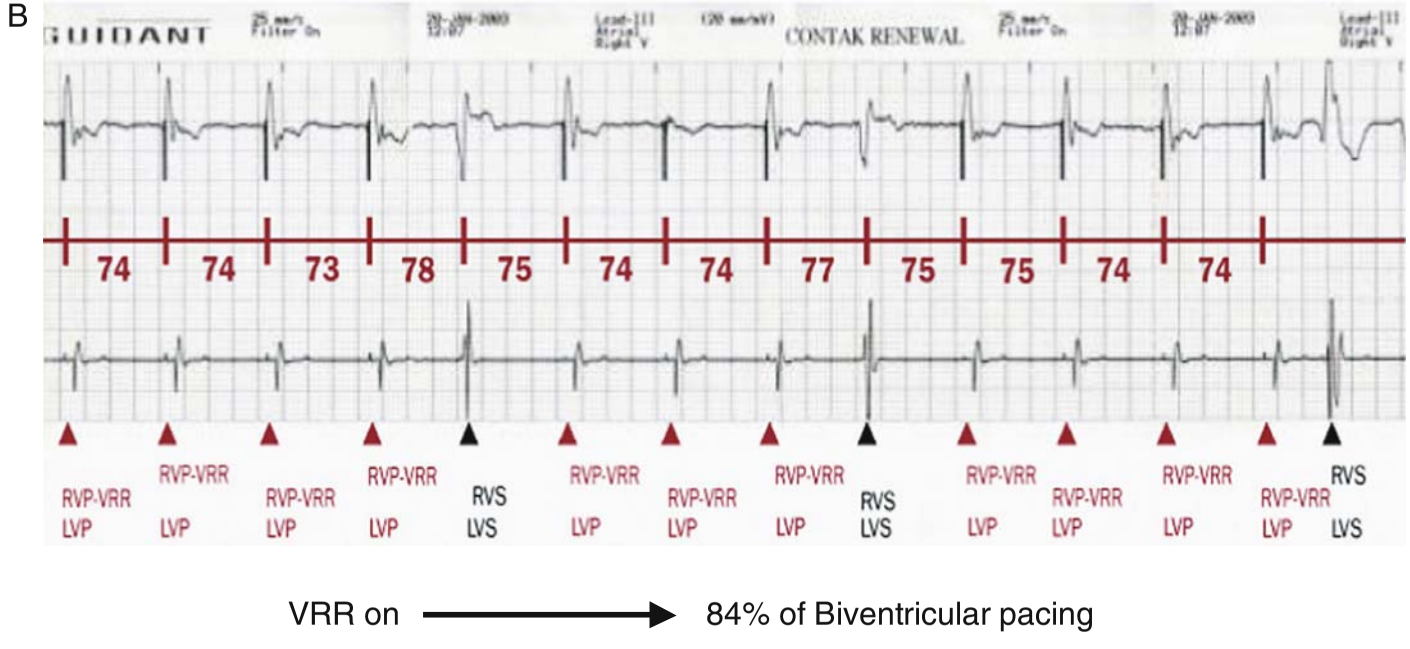

Fig. 20.21 *(continued)*

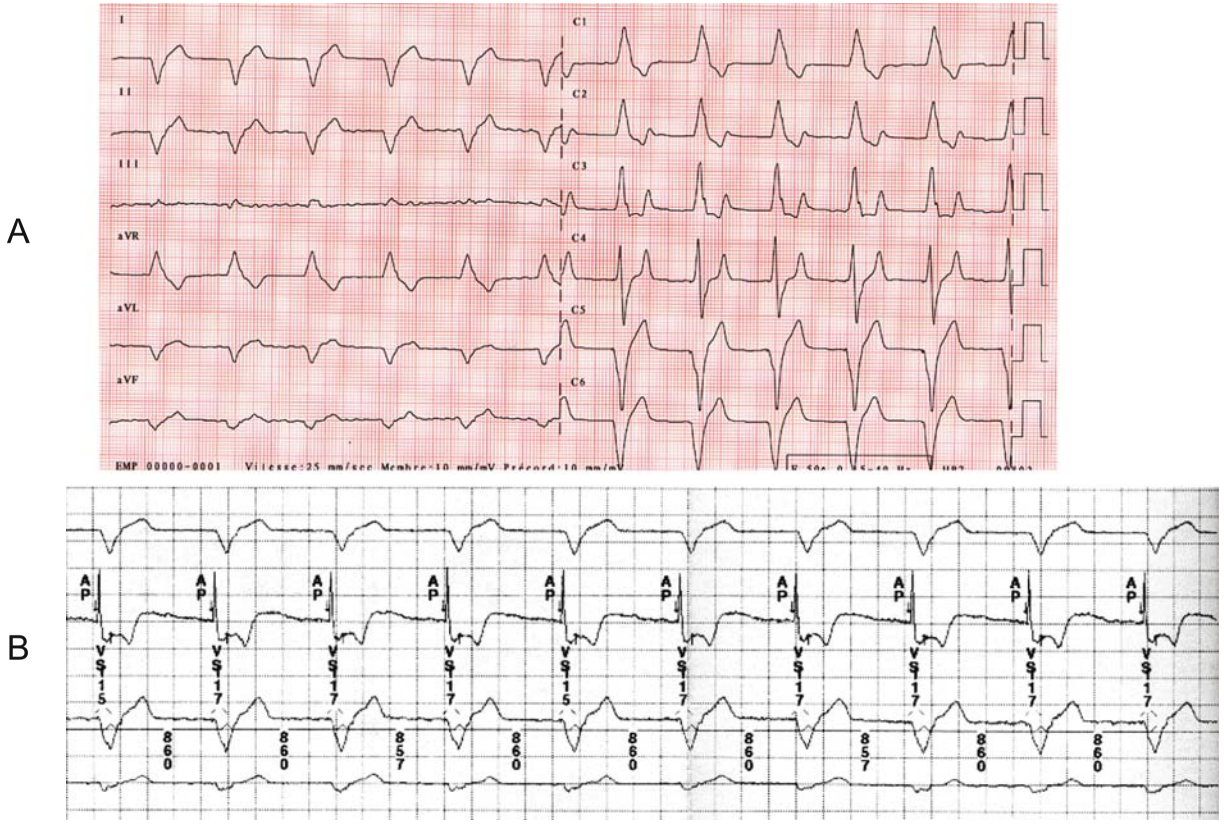

Fig. 20.22 Inadequate programming of a conventional DDD pacemaker (used for CTR) in patient with permanent atrial fibrillation (AF). (**A**) Twelve-lead ECG after an AV nodal ablation performed at the time of pacemaker implantation. The ECG shows a right bundle branch block due to monochamber LV pacing. (**B**) Markers from the pacemaker show that the LV is being paced (*AP*) and the LV lead is being connected to the atrial port and the RV lead to the ventricular port. The AV delay was set at 30 ms. The RV is sensed (*VS*). The AV delay hysteresis was not disabled resulting in a prolongation of the AV delay with loss of biventricular capture and no RV pacing.

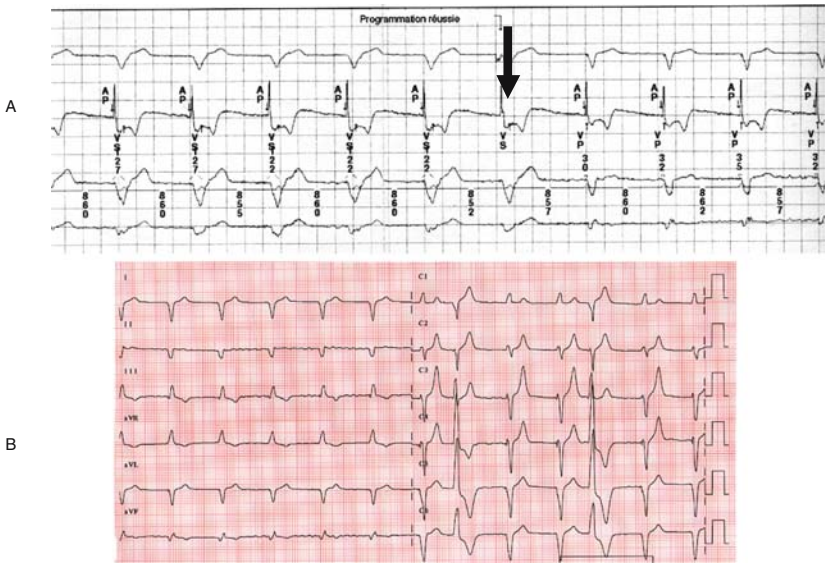

Fig. 20.23 Correction of the inappropriate programming shown in Figure 20.22. (**A**) By switching off the AV delay hysteresis (*arrow*), RV and LV were paced (AP and VP). (**B**) The 12-lead ECG displays biventricular paced complexes.

use of routine AV ablation at the time of CRT implantation or 1 month later after verification of proper device function. Gasparini et al. did show that the efficacy of CRT on exercise tolerance and disease progression in patients with AF and AV node ablation was similar than those observed in sinus rhythm patients. By contrast, AF patients without AV node ablation did not improve with CRT, underlying the importance of AV node ablation [32].

Classically, to provide CRT in patients with permanent AF, a conventional dual-chamber pacemaker can be implanted with the LV lead connected to the atrial port and the RV lead to the ventricular port. The pacemaker is programmed to the DDDR or best to the DVIR mode with the shortest available AV delay to achieve near-simultaneous biventricular pacing. Figures 20.22 and 20.23 illustrate loss of biventricular capture due to inadequate device programming. The pacemaker was programmed to the DDDR mode with an AV delay of 30 ms. However, AV hysteresis was programmed resulting in a prolongation of the AV delay of 52 ms, the RV was sensed, and the patient was paced only in the LV. This case illustrates the limitation of conventional dual-chamber pacemakers for CRT and suggests the superiority of a dedicated triple-chamber device (plugging the atrial port) for patients with permanent AF. Furthermore, triple-chamber devices allow V-V interval optimization if necessary.

Programming and Premature Ventricular Complexes

The presence of frequent premature ventricular complexes (PVCs) represents another potential cause of CRT loss or reduction of CRT "dosage."

A device generally defines a PVC as a sensed ventricular event following a ventricular event without an intervening detected atrial event. In a common

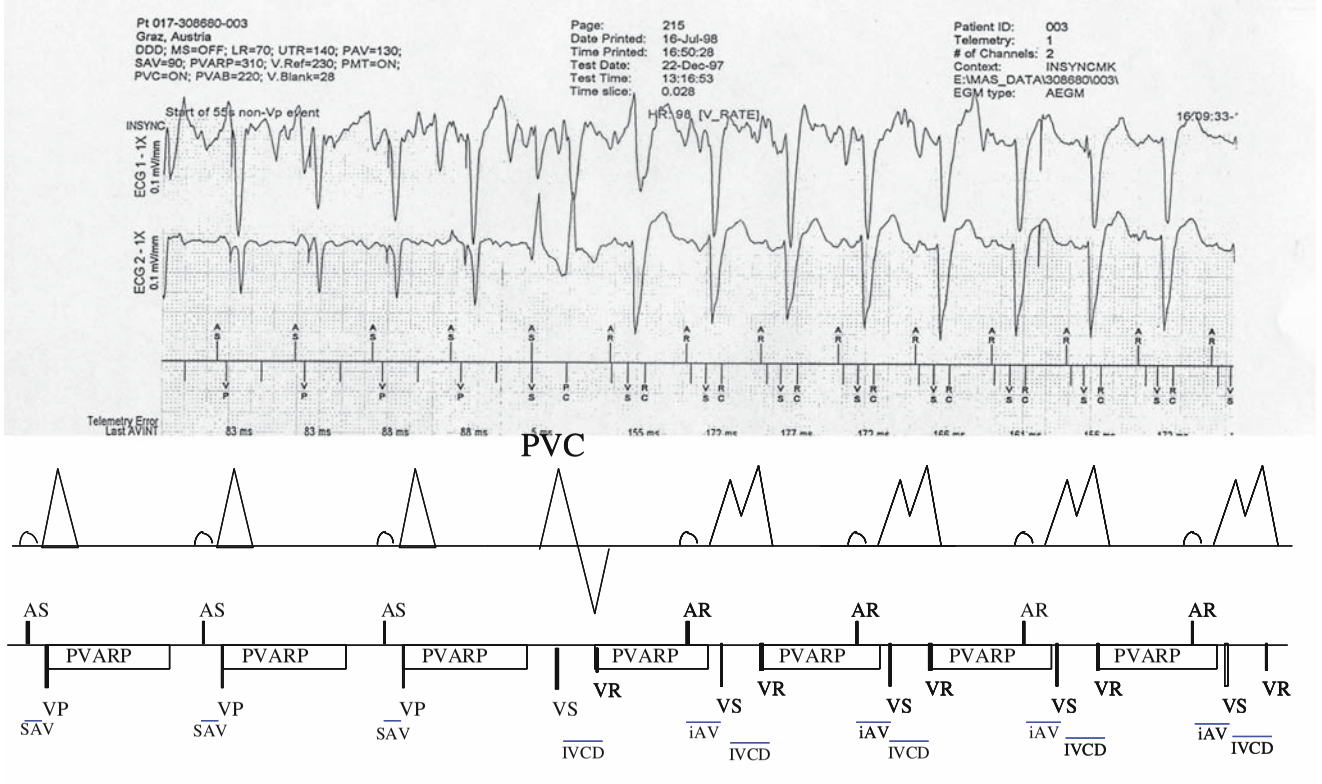

Fig. 20.24 Loss of biventricular capture in a CRT device with a common ventricular sensing channel. induced by a premature ventricular complex (*PVC*) associated with double counting of the ventricular electrogram. A new PVARP is initiated by the second sensed ventricular signal. This shifts the timing of the PVARP so that the following atrial event falls within the reset PVARP where it cannot be tracked. This results in inhibition of biventricular capture and emergence of the intrinsic rhythm. (Courtesy of Medtronic Inc., Minneapolis, MN, USA).

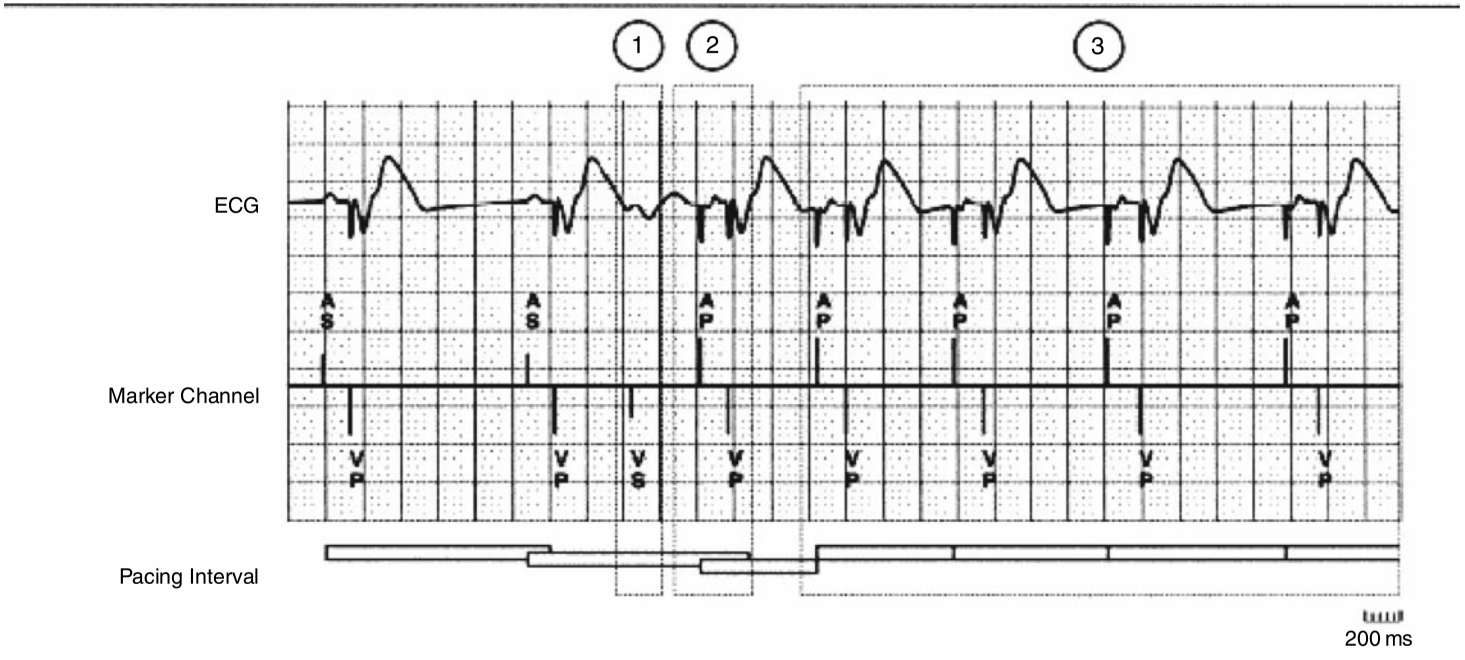

Fig. 20.25 Ventricular rate stabilization of the Medtronic InSync Sentry. *1*, A PVC occurs, causing a short V-V interval. *2*, VRS paces the ventricle at the previous V-V interval plus the programmed "Interval Increment" (and schedules the atrial pace early to maintain AV synchrony). *3*, With each successive VRS pace, the pacing interval increases by the programmed "Interval Increment." *PVC*, premature ventricular contraction; *VRS*, ventricular rate stabilization.

special pacemaker function, the detection of a PVC generates a PVARP extension (e.g., 400 ms) to prevent pacemaker-mediated tachycardia. This feature need not be programmed routinely. It should be used cautiously in CRT devices. With extension of the PVARP or a relatively long PVARP, a P-wave may occur during the atrial refractory period where it cannot trigger a ventricular stimulus. This situation favors the occurrence of a conducted spontaneous QRS complex as most CRT patients do not have AV block [21]. Intrinsic AV conduction then begets intrinsic AV conduction resulting in permanent loss of biventricular capture. In order to restore atrial tracking and CRT delivery, atrial events have to fall outside the intrinsic total atrial refractory period (equal to intrinsic PR interval plus PVARP). Some algorithms by temporally shortening the PVARP and so reducing the total atrial refractory period may restore atrial tracking and CRT delivery (Fig. 20.24). In some devices, a ventricular event detected during the AV interval may trigger an immediate ventricular pacing stimulus with a 2.5 ms V-V pace delay.

Premature ventricular contractions are generally followed by a long pause. These short–long interval sequences may generate in some cases spontaneous ventricular arrhythmias. To eliminate these short–long sequences, some algorithms have been developed to stabilize the ventricular rate (Fig. 20.25).

Programming and Slow Ventricular Tachycardia

In CRT patients, slow ventricular tachycardia (VT) may cause loss of biventricular capture. Moreover, there is an interaction between CRT and ICD tachycardia detection zones without the possibility of antitachycardia pacing to address slow VT. For CRT ICDs, the lowest programmable VT detection zone is 5 bpm above the maximal tracking rate. This may result in trade-offs between the rates of CRT delivery and the slowest detected VT rate. For example, a patient with a monomorphic VT at 130 bpm will require programming of the VT detection rate to 120 bpm. With this VT detection rate, CRT will be limited to tracking of atrial rates <115 bpm. With an increase in the maximal tracking rate, for example up to 140 bpm, the slow VT at 130 bpm will not be detected. Some devices now offer the capability to treat slow VT with antitachycardia pacing within a zone below the upper tracking limit. Thus, in patients with slow VT, alternative VT therapies such as antiarrhythmic drugs or radiofrequency ablation should be explored to ensure effective CRT at physiologic rates.

Interventricular Refractory Period

The interventricular refractory period prevents restarting the ventricular refractory period, postventricular atrial blanking and refractory periods, and upper rate timers when a second sensed depolarization is seen after a paced or sensed event (Fig. 20.26). This function is not required during monochamber sensing but may be useful with biventricular sensing (from RV tip to LV tip; the interventricular refractory period should be programmed to the patient's intraventricular conduction delay + 30 ms).

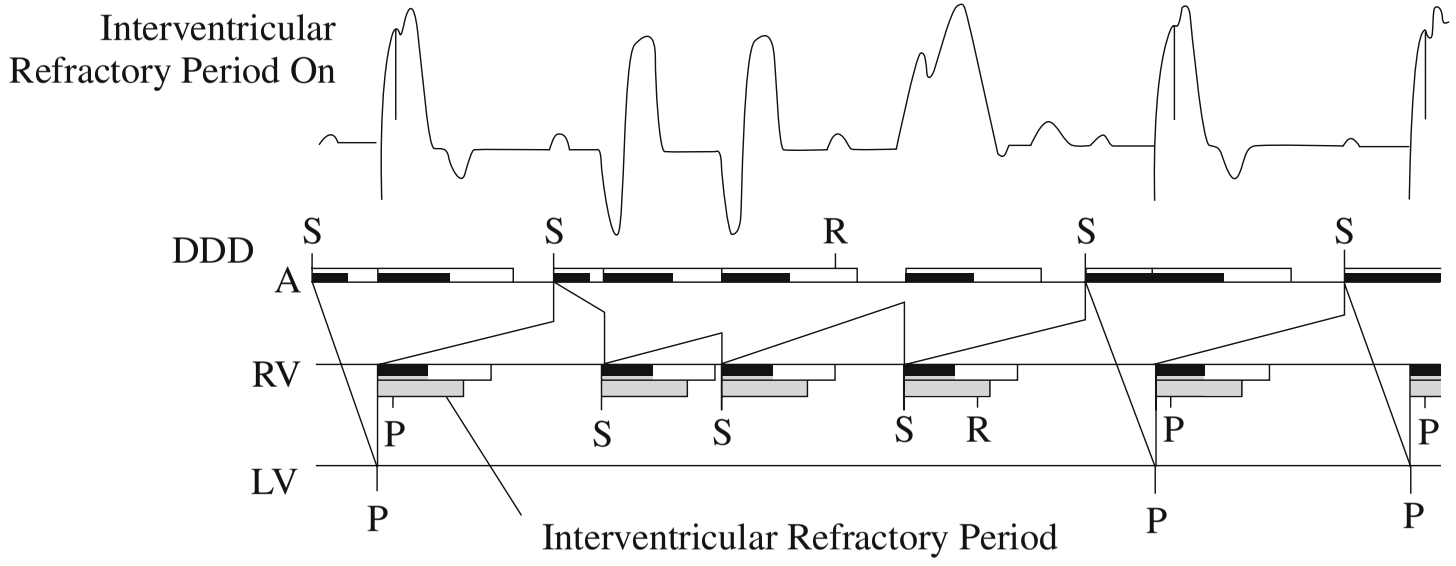

Fig. 20.26 Diagrammatic representation of the interventricular refractory period (IRP) in the Medtronic InSync III pacemaker. The IRP prevents sensing of a second ventricular depolarization when the RV and LV do not depolarize simultaneously. Thus, a sensed event in the IRP (either after a ventricular paced event or a nonrefractory sensed event) does not initiate new timing cycles. *A*, atrium; *RV*, right ventricle; *LV*, left ventricle; *S*, nonrefractory sensed event; *P*, paced event; *R*, refractory sensed event. Note the short P-P intervals representing the V-V delay or the timing difference between LV and RV stimulation. (Courtesy of Medtronic Inc., Minneapolis, MN, USA).

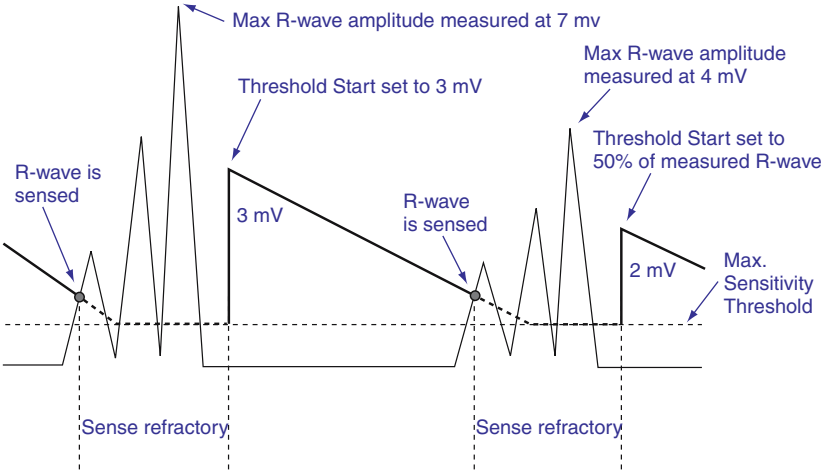

Fig. 20.27 "Automatic Sensitivity Control." This feature allows accurate sensing in both the atrium and the right ventricle over a wide range of signal amplitudes. "Threshold Start" begins at 50% of the measured R-wave (if the R-wave is between 2 and 6 mV) and decays linearly until the next sensed beat or until it reaches the "Maximum Sensitivity Threshold." If the maximum R-wave amplitude is greater than 6 mV or less than 2 mV, "Threshold Start" is set to 3 mV or 1 mV, respectively. Sensing in the atrium is identical, with the "Threshold Start" being 50% of the measured P-waveif the P-wave is between 0.6 and 3 mV. After a paced event, the "Threshold Start" is nominally set to 0.8 mV in the atrium and to adjust automatically based on the pacing rate in the right ventricle. (Courtesy of St. Jude Medical, Sylmar, CA).

Automatic Sensitivity Control

Automatic sensitivity controls allow accurate sensing in both the atrium and the ventricle over a wide range of signal amplitudes. As shown in Figure 20.27, threshold starts at 50% of the measured R-wave (if the R-wave is between 2 and 6 mV) and decays linearly until the next sensed beat or until it reaches the maximum sensitivity threshold. If the maximum R-wave amplitude is greater than 6 mV or less than 2 mV, "Threshold Start" is set to 3 mV or 1 mV, respectively. To prevent oversensing, a *decay delay* can be programmed: decay delay is the amount of time after the sensed or paced refractory period

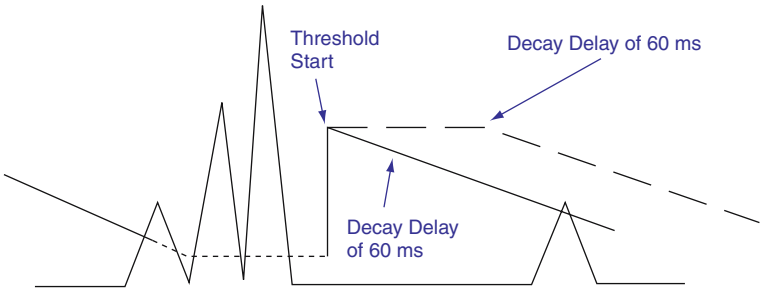

Fig. 20.28 St. Jude Medical algorithm to prevent oversensing from the decay delay in the St. Jude Atlas + HF. Decay delay is the amount of time after the sensed or paced refractory period that the threshold remains at the "Threshold Start" value before beginning its decay. If necessary, increasing the decay delay can prevent oversensing of P-waves in the atrium and T-waves in the ventricle. (Courtesy of St. Jude Medical, Sylmar, CA).

that the threshold remains at the "Threshold Start" value before beginning its decay (Fig. 20.28). If necessary, increasing the decay delay can prevent oversensing of P-waves in the atrium and T-waves in the ventricle.

Diaphragmatic Stimulation

Diaphragmatic stimulation is a complication related to LV lead implantation. In CRT patients, permanent or paroxysmal diaphragmatic stimulation may occur in up to 5% to 10% of patients, resulting in major discomfort [11, 12, 13, 14]. This complication is related to the anatomic vicinity of the left phrenic nerve to the LV pacing site, especially when the LV lead is implanted into a posterior or posterolateral vein of the coronary sinus. It may also be caused by LV lead dislodgment. With the recent development of thinner LV leads, and using the over-the-wire technology, this complication seems to occur more frequently, perhaps due to the more distal position of the LV lead in the coronary vein. During the LV lead implantation, phrenic nerve stimulation is assessed by using a high-voltage output at 10 V and deep breathing maneuvers. In case of phrenic nerve stimulation during LV lead implantation, it is recommended to consider another LV pacing site. However, despite various precautions, permanent or paroxysmal diaphragmatic stimulation (during upright posture or physical activity) may occur, requiring active therapy. An alternative strategy involves keeping the same pacing site only if the LV pacing threshold is low and the phrenic nerve stimulation threshold is high, but the absence of recurrent phrenic nerve stimulation with this approach cannot be guaranteed.

The occurrence of phrenic nerve stimulation early after LV lead implantation may signal LV lead migration, sometimes without significant changes

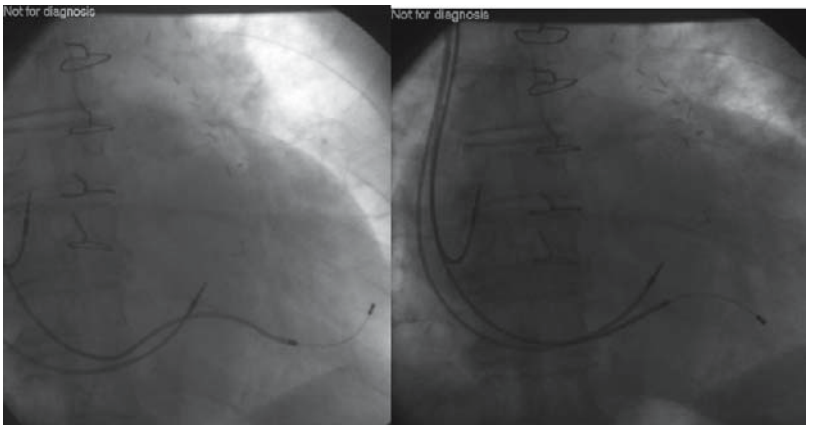

Fig. 20.29 Phrenic nerve stimulation. (**A**) Intraoperative chest x-ray film showing an atrial lead placed in the right appendage, an RV lead screwed in the mid interventricular septum, and an LV lead inserted into a posterolateral vein of the coronary sinus. Diaphragmatic stimulation occurred even with a low LV output (1 V). The LV pacing threshold was measured at 0.75 V with a pulse width of 0.5 ms. (**B**) With a more proximal position of the LV lead in the posterolateral vein, diaphragmatic stimulation disappeared even at a high output (10 V) in the setting of an acceptable LV pacing threshold at 1.25 V.

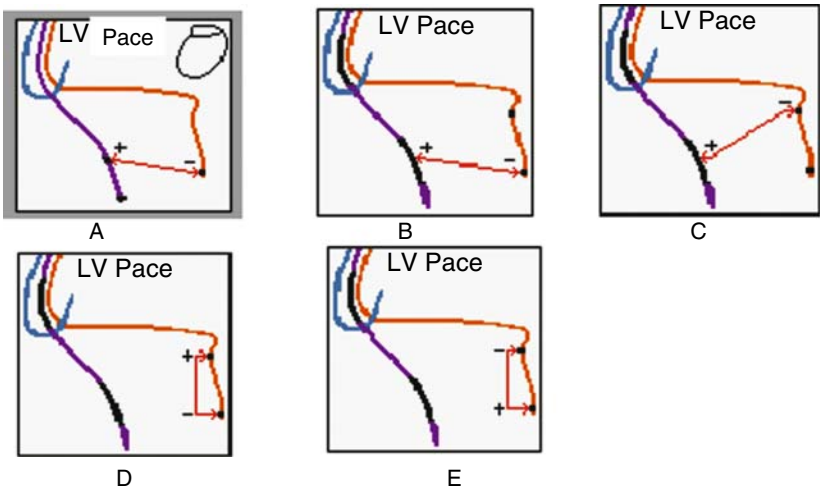

Fig. 20.30 Programmability of pacing configurations of the Guidant Renewal. (**A**) When the "Single" (extended bipolar) configuration is programmed, the pacing stimulus is applied between the LV coronary venous lead tip and the RV distal coil electrode (Tip≫Coil). (**B**) When "Tip≫Coil" (extended bipolar) is selected for dual configuration, the pacing stimulus is applied between the LV coronary venous lead tip and the RV distal coil electrode. (**C**) When "Ring≫Coil" (extended bipolar) is selected for "Dual" configuration, the pacing stimulus is applied between the left ventricular coronary venous (proximal) lead ring and the right ventricular distal coil electrode. (**D**) When "Tip≫Ring" (standard bipolar) is selected for "Dual" configuration, the pacing stimulus is applied between the LV coronary venous lead tip and the LV coronary venous (proximal) lead ring electrode. (**E**) When "Ring≫Tip" (standard bipolar) is selected for "Dual" configuration, the pacing stimulus is applied between the LV coronary venous (proximal) lead ring electrode and the LV coronary venous lead tip electrode. (Courtesy of Guidant Corporation, St Paul, MN, USA).

in the chest x-ray. The LV capture threshold and that of phrenic nerve stimulation thresholds should be assessed. If the LV capture threshold falls far from below the phrenic nerve stimulation threshold, a reduction of LV pacing amplitude below the phrenic nerve stimulation threshold may simply solve the problem. However, overlapping or minimally different thresholds that preclude a programmable solution mandate repositioning of the LV lead as illustrated in Figure 20.29. Programming the LV amplitude at or barely above the LV capture may result in the loss of CRT. One alternative solution in some cases is to decrease the LV ventricular output and to increase the pulse width. With this compromise, LV capture may be achieved without the discomfort of phrenic nerve stimulation. Recently, bipolar pacing LV leads and devices allowing reprogramming of the LV lead pacing configuration may be useful to decrease phrenic nerve stimulation without the need of invasive LV lead manipulation or replacement (Fig. 20.30).

Conclusion

The clinical follow-up of CRT patients requires a multidisciplinary approach. Programming of CRT devices has to be carefully evaluated to ensure continual biventricular capture at rest and during exercise. This requires aggressive therapy of atrial and/or ventricular tachyarrhythmias. With the technical

improvement of recent CRT devices and appropriate fine-tuning of devices with specific algorithms designed to improve CRT delivery, we can reasonably expect that the relatively high number of partial or complete nonresponders will decrease. However, programming of a CRT device remains complex and has to be tailored for the individual patient.

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21

Programming and Follow-up of CRT and CRTD Devices

Michael O. Sweeney

Introduction

Optimal programming of implanted electrical devices for cardiac resynchronization therapy (CRT) requires a sophisticated understanding of the pathophysiologic electrical and mechanical substrates that occur in some patients with symptomatic heart failure due to dilated cardiomyopathy (DCM). Furthermore, it cannot be overemphasized that optimal CRT programming is an active process that requires sustained vigilance for the remainder of the patient's life and must anticipate the potential for dynamic and related changes in patient condition or device system operation. This is a critically important distinction to conventional pacemakers, which reliably provide bradycardia support with minimal need for periodic programming intervention, particularly with recent enhancements to automaticity. Similarly, though conventional implantable cardioverter-defibrillators (ICDs) require a slightly higher level of surveillance than pacemakers due to the possibility of clinically silent but important ventricular detections and therapies and several other considerations, they reside primarily in a passive state for the duration of the patient's life. The hybridization of CRT with defibrillation systems (CRTD) therefore invokes all of the complex considerations of optimal CRT and ICD programming. This introduces particularly unique challenges because the device must simultaneously exist in two fundamentally opposed states of operation: continuous delivery of ventricular pacing and continuous surveillance for ventricular arrhythmia.

Abnormal Electrical Timing in Heart Failure Associated with Dilated Cardiomyopathy

Disordered electrical timing frequently accompanies heart failure associated with DCM. Abnormal electrical timing alters critical mechanical relationships that further impair left ventricular (LV) performance. It is now recognized that there are four levels of electromechanical abnormalities associated with heart failure associated with DCM [1,2]. These must be understood and applied to optimal CRT programming and troubleshooting.

Prolonged Atrioventricular Delay

Optimal left-sided atrioventricular (AV) coupling is necessary for maximum ventricular pumping performance. The normal AV interval results in atrial contraction just before the pre-ejection (isovolumic) period of ventricular contraction that maximizes ventricular filling (LV end diastolic pressure, or preload) and cardiac output by the Starling mechanisms. This optimal timing relationship also results in diastolic filling throughout the entire diastolic filling period, prevents diastolic mitral regurgitation (MR), and maintains mean left atrial pressure at low levels (Fig. 21.1).

Alterations in the AV coupling can be understood by analysis of Doppler mitral inflow patterns (Figs. 21.2 and 21.3). Prolonged AV conduction disrupts these relationships and may degrade ventricular performance. Significantly prolonged AV conduction results in displacement of atrial contraction earlier in diastole such that atrial contraction may occur immediately after or even within the preceding ventricular contraction. This may result in atrial contraction before venous return is completed and reduce the atrial contribution to preload that may diminish ventricular volume and contractile force. It may also initiate early mitral valve closure, limiting diastolic filling time. Diastolic MR may also occur with prolonged AV conduction because once closed, valve cusps may separate again before ventricular contraction as a result of the development of a left ventricular–left atrial gradient in diastole induced by atrial contraction with premature and incomplete mitral valve closure.

Prolonged Ventricular Conduction

Optimal inter- and intraventricular coupling is more important than AV coupling for maximum ventricular pumping function. Normal ventricular electrical activation is rapid and homogeneous with minimal temporal dispersion throughout the wall. This elicits a synchronous mechanical activation and ventricular contraction. Exploration of the link between the sequence of cardiac electrical activation and mechanical function is one of the most exciting contemporary areas of research in heart failure, but recognition of the importance of normal ventricular activation patterns for optimal pumping function dates back 75 years. Wiggers observed that asynchronous delayed activation of the ventricular musculature induced by electrical stimulation had adverse hemodynamic consequences in mammals and proposed that the more muscle activated before excitation of the Purkinje system, the greater the asynchrony and the weaker the resulting contraction [3].

Chronic DCM is often accompanied by delayed ventricular electrical activation manifest as prolonged QRS duration (QRSd), most commonly in the form of left bundle branch block (LBBB). The prevalence of prolonged QRSd in heart failure associated with DCM varies between studies but appears to be in the range of 25–50%. Prolonged QRSd is a potent predictor of mortality in heart failure associated with DCM. The association between LBBB in DCM and increased risk of sudden death and total mortality in DCM has subsequently been demonstrated in large population studies [4].

Interventricular Delay

Interventricular coupling refers to coordinated contraction of the right ventricle and left ventricle. *Interventricular delay* refers to a relative delay

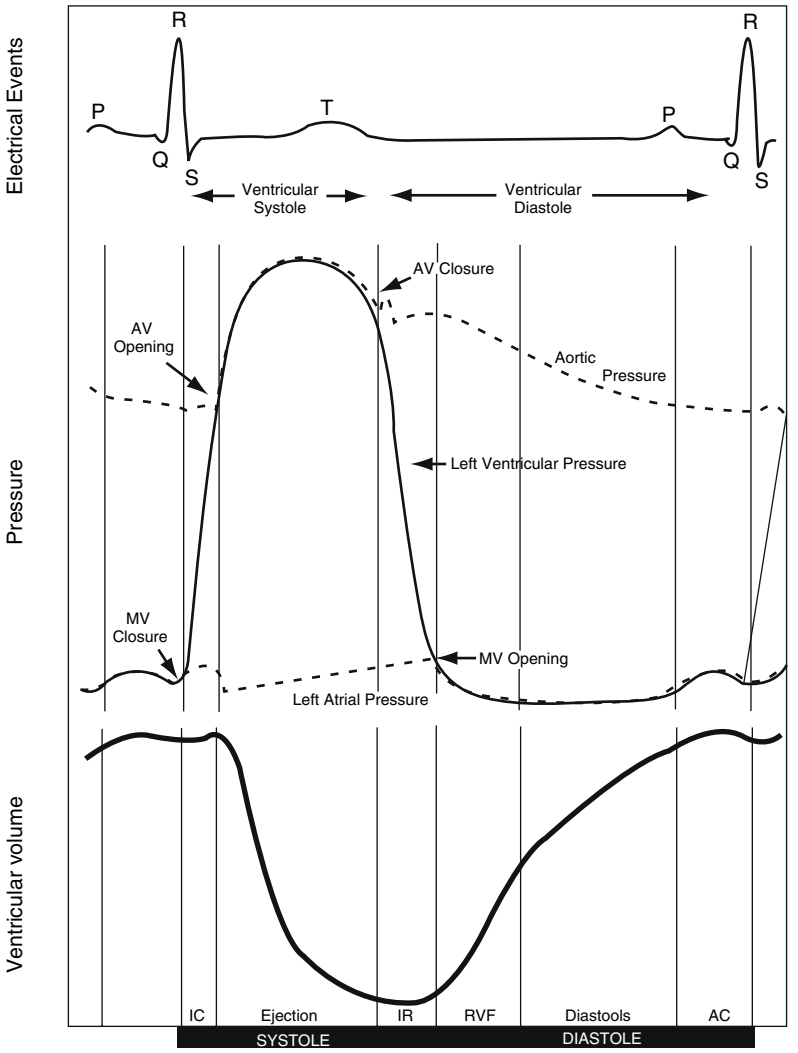


Fig. 21.1 Events of the cardiac electrical cycle. Atrial contraction followed by relaxation produces a negative pressure gradient, causing a surge of blood in the left ventricle at end diastole. Reversal of the AV pressure gradient initiates mitral valve (MV) closure because of a rapid decrease in pressure between the MV cusps pulling them into apposition. A brief period of isovolumetric contraction exists after MV closure and before AV opening during which the maximum rate of pressure change (peak +dP/dt) occurs. Rapid ejection occurs during ventricular systole and is terminated when ventricular pressure falls below aortic pressure, closing the AV. A brief period of isovolumic relaxation follows during which the maximum rate of pressure decline (peak –dP/dt) occurs. As the LV pressure continues to decline and fall below atrial pressure, the MV opens and diastolic ventricular filling begins. Normal diastolic filling is characterized by an initial rapid increase in ventricular filling during early diastole followed by a slow phase of filling during mid-diastole. A second rapid increase in ventricular filling occurs in late diastole as a result of atrial contraction.

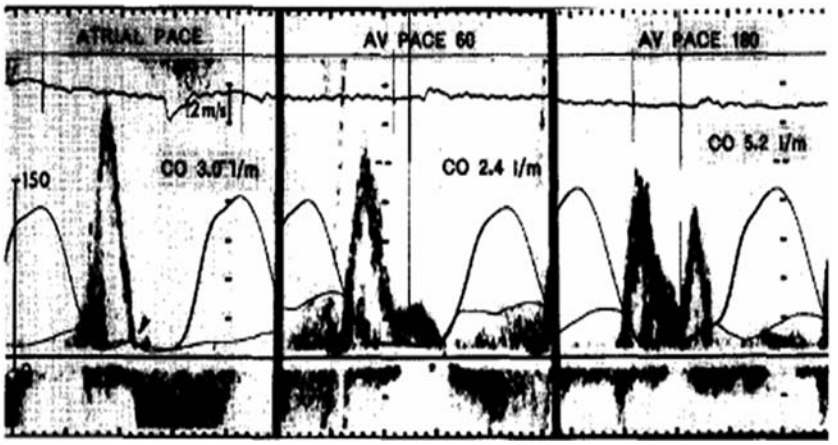


Fig. 21.2 Doppler mitral inflow patterns at various AV delays. *Left:* Atrial pacing with long PR interval. Arrow indicates increase in left ventricular end-diastolic pressure above left atrial pressure during atrial relaxation in mid-diastole, resulting in shortening of diastolic filling time and diastolic mitral regurgitation. *Middle:* AV pacing at short AV delay. Diastolic filling occurs throughout diastole but cardiac output declines due to ineffectual atrial contraction, which occurs synchronously with ventricular contraction. Note significantly elevated atrial pressure throughout. *Right:* AV pacing at optimal AV delay. Diastolic filling occurs throughout diastole and the relation of atrial to ventricular contraction is now optimal, just before ventricular contraction. Mean left atrial pressure is low and cardiac output is higher. (From Nishimura RA, Hayes DL, Holmes DR, Tajik AJ. Mechanism of hemodynamic improvement by dual-chamber pacing for severe left ventricular dysfunction: An acute Doppler and catheterization study. J Am Coll Cardiol 1995;25:281–288.)

in mechanical activation of each ventricle, most commonly LBBB where the right ventricle begins its contraction before the left ventricle. The delay in onset of left ventricular activation results in reversal of the normal sequence between right and left ventricular mechanical events that persists throughout the cardiac cycle [5]. Asynchronous ventricular contraction and relaxation results in dynamic changes in ventricular pressures and volumes throughout the cardiac cycle. This results in abnormal septal deflections that alter the regional contribution to global ejection fraction. Earliest ventricular depolarization is recorded over the anterior surface of the right ventricle and latest at the basal-lateral left ventricle [6]. In canine models with induced LBBB, increasing the delay between right ventricular (RV) and LV contraction increases the delay between the upslope of LV and RV systolic pressure. The increase in interventricular delay was associated with decreased LV +dP/dt and decreased stroke work, presumptively the result of ventricular interdependence and impairment of the septal contribution to LV ejection due to displacement after onset of RV ejection [7].

Intraventricular Delay

The third level of synchrony exists within each ventricle, most importantly the left ventricle. Rapid spread of contraction from the LV septum endocardially to the base of the heart creates coordinated, efficient contraction. Synchrony of contraction is important because it results in a more effective and energetically efficient ejection [8]. Asynchronous electrical activation reduces LV

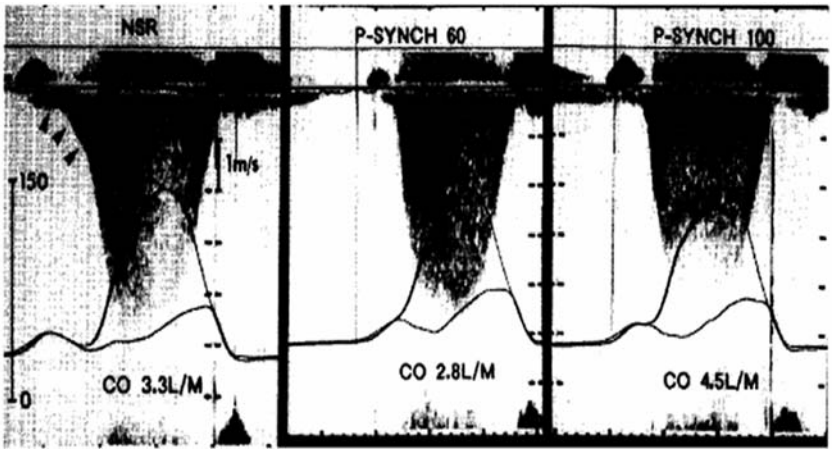


Fig. 21.3 Effect of various AV delays on mitral regurgitation, left atrial pressure, and cardiac output. *Left:* Sinus rhythm with long PR interval. Diastolic mitral regurgitation is due to an increase in left ventricular end-diastolic pressure above left atrial pressure before ventricular contraction. *Middle:* During atrial synchronous pacing at AV delay 60 ms, diastolic mitral regurgitation is eliminated, but there is a decrease in cardiac output due to atrial contraction that is ineffective because it occurs coincident with ventricular contraction. *Right:* Atrial synchronous ventricular pacing at optimal AV delay 100 ms; diastolic mitral regurgitation is no longer present. Left ventricular end-diastolic pressure increases appropriate at onset of ventricular contraction. (From Nishimura RA, Hayes DL, Holmes DR, Tajik AJ. Mechanism of hemodynamic improvement by dual-chamber pacing for severe left ventricular dysfunction: An acute Doppler and catheterization study. J Am Coll Cardiol 1995;25:281–288.)

pump function [9]. The mechanical effect of asynchronous electrical activation is quite dramatic, because the various regions not only differ in the time of onset of contraction but also in the pattern of contraction. Early contraction of regions close to the pacing site cause stretching of not yet activated remote regions. This stretching further delays shortening of these late-activation regions and increases their force of local contraction by virtue of the (local) Frank–Starling mechanism. Due to their vigorous contraction, the late-activated regions imposed loading on the earlier-activated territories, which now undergo systolic paradoxical stretch. This reciprocated stretching of regions within the LV wall causes a less effective and energetically efficient contraction [8].

The hemodynamic consequences of the discoordinate LV contraction are reduction in contractility and relaxation. The poorer contractility is reflected by decreases in stroke work and rate of rise of LV pressure, and a rightward shift of the LV end-systolic pressure–volume relationship [9]. The latter indicates that the left ventricle operates at a consistently larger volume [10,11]. The combination of these effects leads to a decrease in LV ejection time and ejection fraction (EF).

Premature relaxation in early-activated regions and delayed contraction in others also causes abnormal relaxation [9]. This is expressed as decrease in –dP/dt (maximal rate of fall of LV pressure), increase in the relaxation time constant tau, and decrease of E-wave velocity amplitude on Doppler echocardiograms. Moreover, the longer contraction and relaxation times lead to a reduction in diastolic filling time, leading to reduced preload.

Pacing models can be used to induce asynchronous ventricular activation, with early activation occurring at the pacing site [12, 13]. Regions of late activation are subject to greater wall stress and develop local myocyte hypertrophy accompanied by reductions in sarcoplasmic reticulum calcium-ATPase and phospholamban [14]. Chronic asynchronous ventricular activation redistributes the mechanical load within the ventricular wall and leads to reduction of blood flow and myocardial wall thickness over the site of early activation [13, 15]. This ventricular remodeling may contribute to progression of heart failure. In addition to these effects, delayed, sequential activation of papillary muscles may aggravate mitral regurgitation [16].

Intramural Delay

Studies of activation maps have shown different activation timing and sequence between endocardial and transmural activation. This suggests the possibility of intramural activation delay between the endocardial and myocardial layer [17]. The negative effects, if any, of intramural delay on ventricular pumping function are uncertain.

Mechanisms of CRT

Recognition of the contribution of disordered electrical timing to reduced ventricular performance suggested the possibility that pacing techniques could favorably modulate contractile dyssynchrony and delayed AV timing. The fundamental premise of this therapeutic strategy is that LV pacing may correct inter- and intraventricular conduction delays and permit optimization of left-sided AV delay, thereby improving ventricular pumping function.

The first report of the potential hemodynamic benefit of left univentricular pacing used epicardial leads placed on the high right atrium and lateral LV free wall during surgery for aortic valve replacement in patients with LBBB [18]. de Teresa et al. [18] noted that LV ejection fraction was maximal when septal motion was simultaneous with free wall contraction and diminished when septal and free wall motion were dyssynchronous, such as during spontaneous activation with LBBB or during RV apical pacing. The term *cardiac resynchronization* was first used 10 years later when Cazeau et al. [19] used epicardial leads on all four cardiac chambers to modify the ventricular activation sequence and improve hemodynamic performance in heart failure due to dilated cardiomyopathy accompanied by LBBB.

Improved Pumping Function: AV Optimization and Ventricular Resynchronization

Correction of physiologically disadvantageous prolonged AV conduction (*AV optimization*) can be achieved with LV pacing. Optimization of the AV interval during CRT can be conceptualized by examining mitral flow velocity curves using two-dimensional (2D) echocardiography.

When left ventricular preexcitation is inadequate, the result is similar to a prolonged AV interval as shown in Figure 21.4. Note atrial contraction occurs too early and does not contribute to increased left ventricular end diastolic pressure (LVEDP), indicated by absence of A-wave on mitral inflow velocity. Atrial contraction occurs before venous return is completed causing reduced ventricular volume and contractile force. It may also initiate early mitral valve

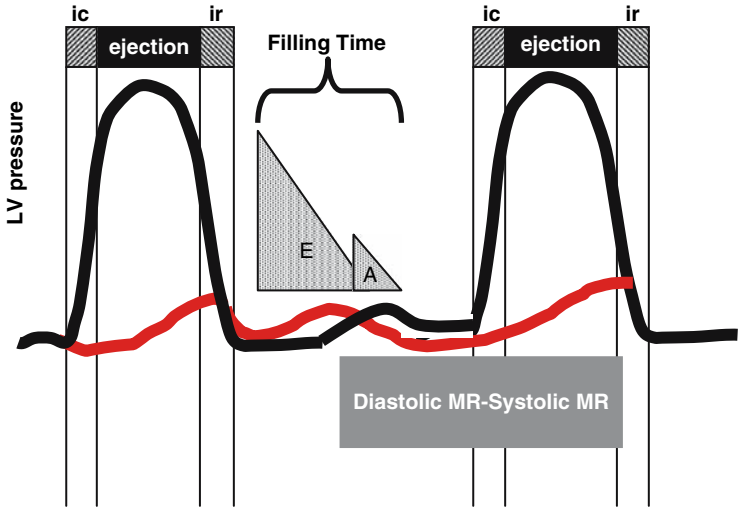


Fig. 21.4 Schematic representation of hemodynamic effects of long AV interval on left ventricular performance. When the AV delay is too long, mitral valve closure may not be complete, as atrial contraction is not followed by a properly timed ventricular systole. LV pressure increases above the LA pressure at the end of the diastolic filling period and results in diastolic, or "presystolic" MR.

closure, thereby limiting diastolic filling time. Diastolic MR may also occur because once closed, the mitral valve may drift open again before ventricular contraction.

When the programmed AV interval is too short, LV contraction occurs too early relative to atrial systole (Fig. 21.5). Note that diastolic filling occurs throughout all of diastole. Atrial contraction now occurs simultaneously with LV contraction resulting in increased left atrial pressure and loss of atrial contribution to ventricular systole, reducing cardiac output. A shorter AV

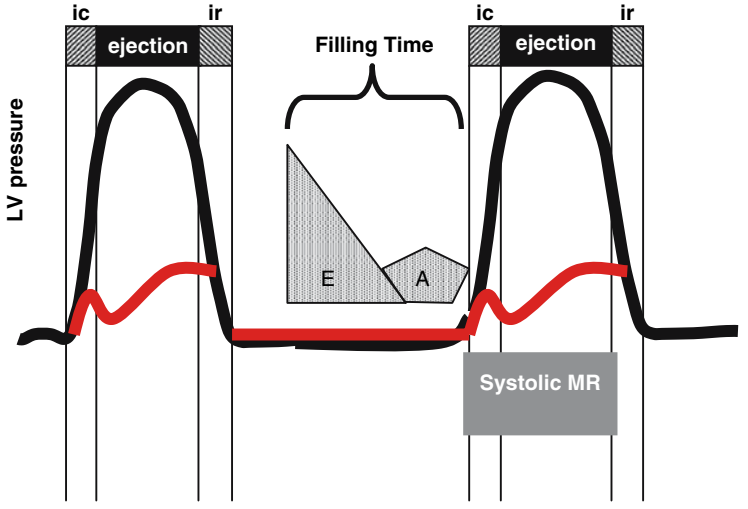


Fig. 21.5 Schematic representation of hemodynamic effects of short AV interval on left ventricular performance . Note truncation of diastolic filling period due to premature closure of mitral valve (atrial and ventricular contraction occur simultaneously).

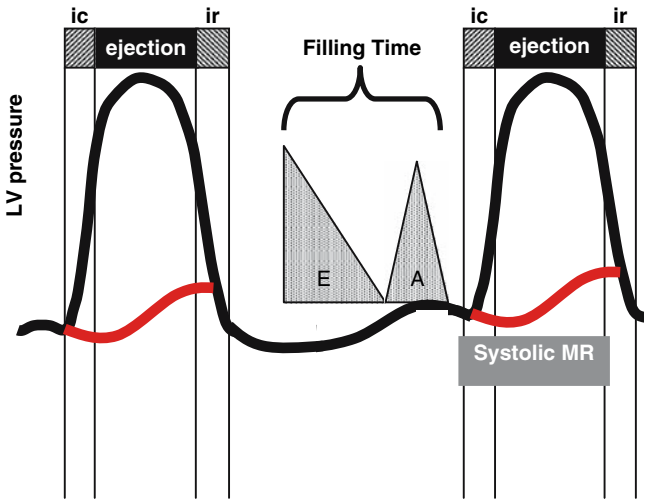


Fig. 21.6 Schematic representation of hemodynamic effects of optimal AV interval on left ventricular performance. The relation of atrial contraction to the onset of ventricular contraction is now optimal, resulting in diastolic filling throughout the entire diastolic filling period. An appropriate relation now exists between mechanical left atrial and left ventricular contraction so that mean left atrial pressure is maintained at a low level with left atrial contraction occurring just before left ventricular contraction. AV optimization is noted by return of the normal E-wave (ventricular filling)–A-wave (atrial contraction) separation. Transmitral flood and LV diastolic filling time are increased, which improves to increased CO. If a large amount of diastolic MR can be abolished, a beneficial effect is obtained because of lower left atrial and higher left ventricular preload at the onset of ventricular contraction.

interval lengthens the diastolic filling period by abolishing premature mitral valve closure due to the LV–left atrial pressure gradient seen with long AV delays. This also eliminates diastolic MR. However, the diastolic filling period should not be used as the only guideline to optimize the AV interval. Despite optimization of the diastolic filling period, hemodynamic deterioration will occur at too short an AV interval if atrial contraction occurs against a

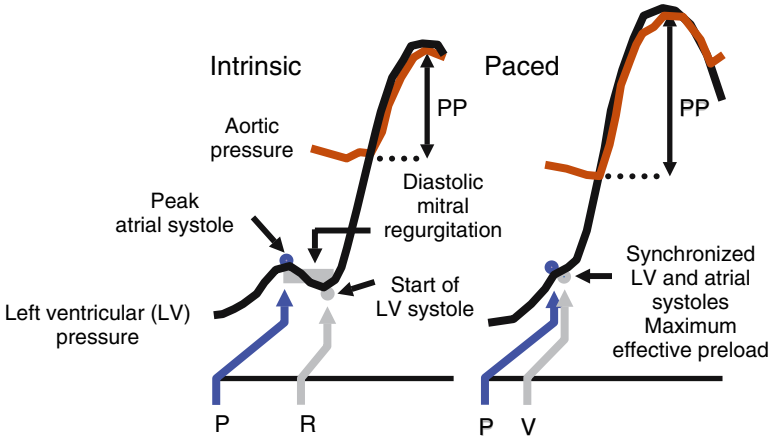


Fig. 21.7 Mechanisms of CRT: AV optimization.

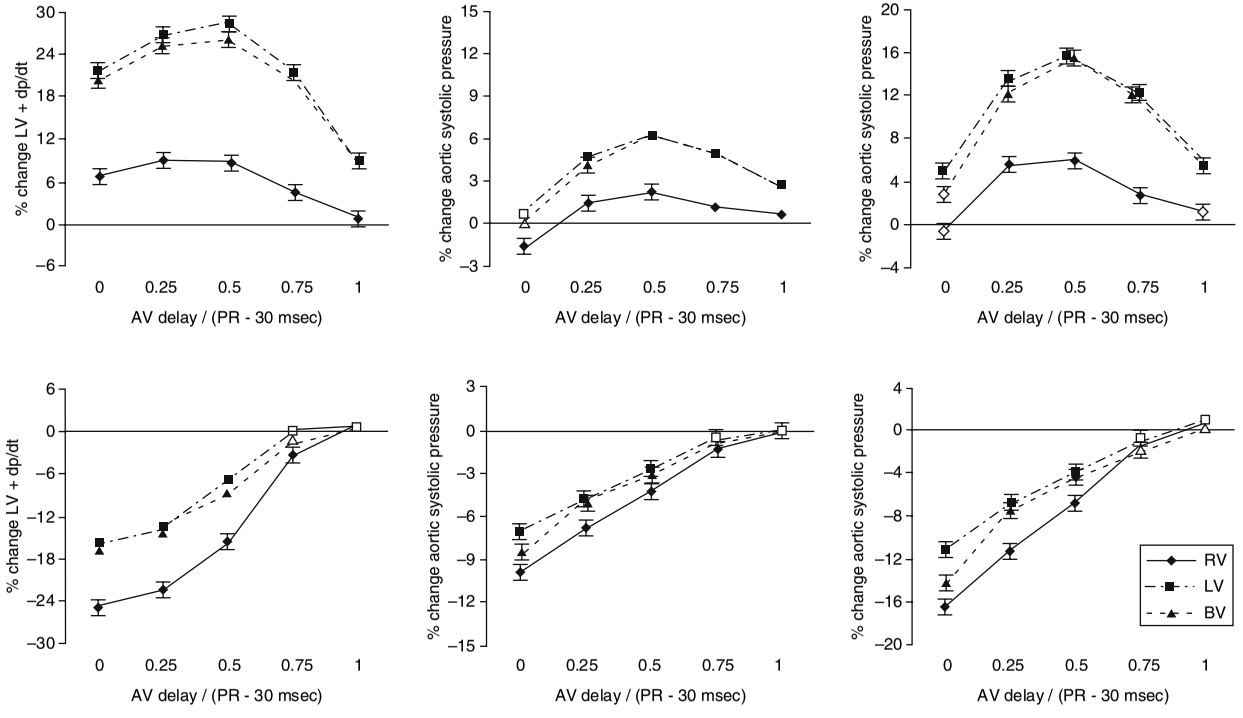


Fig. 21.8 Dose–response curves for acute hemodynamic response to CRT at various AV delays in responders versus nonresponders (see text). (From Auricchio A, Stellbrink C, Block M, et al. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The Pacing Therapies for Congestive Heart Failure Study Group. The Guidant Congestive Heart Failure Research Group. Circulation 1999;99[23]:2993–3001.)

closed mitral valve. This could result in a decrease in cardiac output and increase in mean left atrial pressure despite optimization of the diastolic filling period.

LV contraction at the optimal AV interval if shown in Figure 21.6. The relation of atrial contraction to the onset of ventricular contraction is now optimal, resulting in diastolic filling throughout the entire diastolic filling period. An appropriate relation now exists between mechanical left atrial and LV contraction so that mean left atrial pressure is maintained at a low level with left atrial contraction occurring just before left ventricular contraction. This causes an increase in LVEDP (preload) and cardiac output (Fig. 21.7). Note diastolic MR is eliminated and systolic MR is reduced.

Acute hemodynamic studies have shown that AV delay is a significant determinant of changes in all LV systolic parameters (+dP/dt, aortic systolic pressure, aortic pulse pressure) [20, 21] (Fig. 21.7). For CRT "responders" (see below), LV +dP/dt and aortic pulse pressure AV delay functions are positive and unimodal, with a peak effect at approximately 50% of the native PR interval (Fig. 21.8). The optimal AV delays for the same pacing chamber and parameter varied widely among patients and often differed for pulse pressure and LV +dP/dt within an individual [20]. The acute increase in LV +dP/dt with optimal AV delay may be in the range 15–45% [20,22]. For CRT "nonresponders," the LV +dP/dt and aortic pulse pressure AV delay functions are negative and the greatest response is achieve closest to the native AV delay (Fig. 21.8).

The hemodynamic benefit of LV preexcitation is primarily due to *ventricular resynchronization* rather than AV optimization, however. The

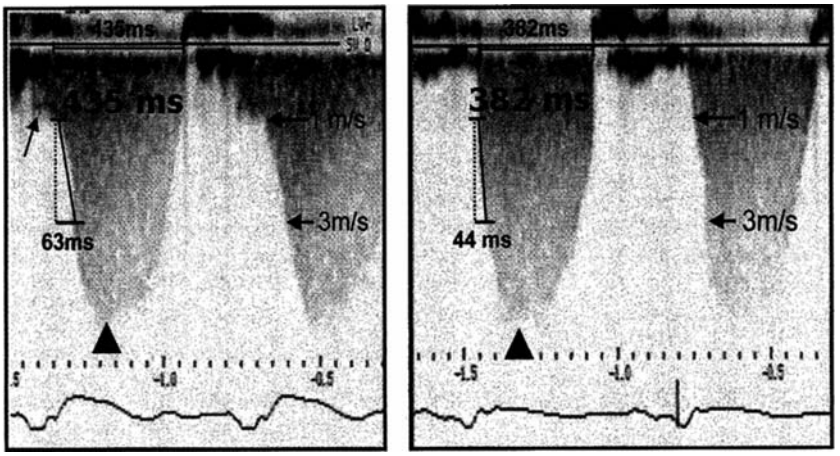


Fig. 21.9 Reduced functional mitral regurgitation during CRT. Maximal rate of LV systolic pressure rise (LV +dP/dt_{max}) is estimated by measuring the time interval between 1 m/s and 3 m/s on the downslope of the Doppler mitral regurgitant jet. In this patient, the estimated LV +dP/dt_{max} rises from approximately 510 mm Hg/s (approximately 63 ms) to approximately 720 mm Hg/s (approximately 44 ms). Transmitral pressure gradient peak occurs earlier in systole (*arrows*). Duration of functional mitral regurgitation (excluding the presystolic component) decreased from 435 ms (CRT OFF) to 382 ms (CRT ON). (From Breithardt OA, Sinha AM, Schwammenthal E , et al. Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. J Am Coll Cardiol 2003;203:765–770.)

decreased LV +dP/dt and decreased stroke work associated with intraventricular delay can be eliminated by CRT [7, 23] and improvements in RV to LV delay correlate with improvements in EF [24]. Furthermore, CRT improves pumping function while decreasing myocardial energy consumption [25].

Reverse LV Remodeling

In addition to improvement in acute hemodynamic performance and clinical symptoms, it has now been clearly demonstrated that CRT improves chronic LV pumping function. This improvement is accompanied by Doppler echocardiographic (conventional 2D and tissue imaging) evidence of reverse LV remodeling [26, 27, 28, 29, 30, 31, 32]. These remodeling effects include increased ejection fraction, reduction in LV volume, redistribution of cardiac mass, reduced mitral orifice size, and reduced mitral regurgitation.

Other Effects of CRT: Reduction in Functional Mitral Regurgitation

Functional MR frequently accompanies DCM and results from an imbalance between the closing and tethering forces that act on the mitral leaflets and

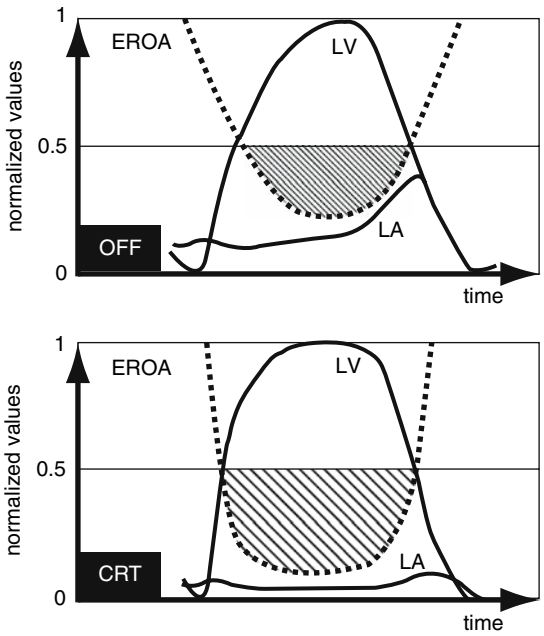


Fig. 21.10 CRT acutely reduces the severity of functional mitral regurgitation by decreasing the effective regurgitant orifice area. This effect is directly related to an improvement in left ventricular systolic function (LV +dP/dt) causing an accelerated rise in transmitral pressure, which counteracts the increased tethering forces that impair mitral valve competence. The acute effect is independent from geometric changes (reverse remodeling) and may exert further beneficial effects on functional mitral regurgitation severity. (From Breithardt OA, Sinha AM, Schwammenthal E , et al. Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. J Am Coll Cardiol 2003;203:765–770.)

has been elegantly described by Breithardt et al. [16]. This is strongly dependent on alterations in ventricular shape as the tethering forces that act on the mitral leaflets are higher in dilated, more spherical ventricles. These geometric changes alter the balance between tethering and closing forces and impede effective mitral closure. Ventricular dilatation and increased chamber sphericity increase the distance between the papillary muscles to the enlarged mitral annulus as well as to each other, restricting leaflet motion and increasing the force needed for effective mitral valve closure. This mitral valve closing force is determined by the systolic left ventricular pressure–left atrial pressure difference, which is called the transmitral pressure gradient. Under these conditions, the mitral regurgitant orifice area will be largely determined by the phasic changes in transmitral pressure. Increasing the transmitral pressure can reduce the effective regurgitant orifice area. CRT acutely reduces the severity of functional MR, and this reduction is quantitatively related to an increase in LV $+dP/dt_{max}$ and transmitral pressure [16] (Figs. 21.9 and 21.10). This is distinct from the reduction in MR due to reduced LV dimensions from remodeling associated with chronic CRT.

Delayed sequential activation of the papillary muscles due to intraventricular delay also contributes to functional mitral regurgitation. Kanzaki et al. used longitudinal strain to produce mechanical activation maps of the left ventricle immediately before and after CRT. Patients with intraventricular

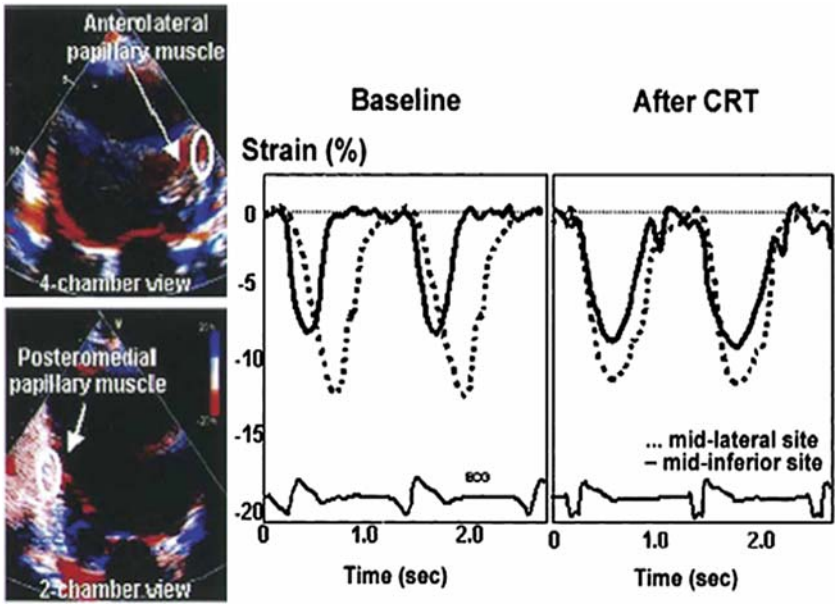


Fig. 21.11 Reduced interpapillary muscle delay during CRT. Echocardiographic strain images from the four-chamber view and two-chamber view, with corresponding time–strain plots from sites adjacent to papillary muscles before and after CRT. Baseline plots demonstrate delayed peak strain occurring in the anterolateral papillary muscle site compared with the posteromedial papillary muscle site. CRT results in time alignment of peak strain at papillary muscles. (From Kanzaki H, Bazaz R, Schwartzman D, Dohi K, Sade LE, Gorscan J 3rd. A mechanism for immediate reduction in mitral regurgitation after cardiac resynchronization therapy: Insights from mechanical activation strain mapping. J Am Coll Cardiol 2004;44(8):1619–1625.)

conduction delay had significantly increased times to peak strain between papillary muscle insertion sites compared with normal controls (Figs. 21.11 and 21.12). This interpapillary muscle delay shortened from 106 ± 74 ms to 39 ± 43 ms immediately after institution of CRT and was correlated with significant reduction in mitral regurgitant fraction [33]. This suggests that the acute reduction in MR associated with CRT is likely due to a complexity of factors, including increased +dP/dt as well as more coordinate papillary muscle activation.

Alterations in regional distribution of mechanical strain probably account for the development of severe MR reported in some patients after institution of RV apical pacing that mimics the activation sequence of LBBB and causes

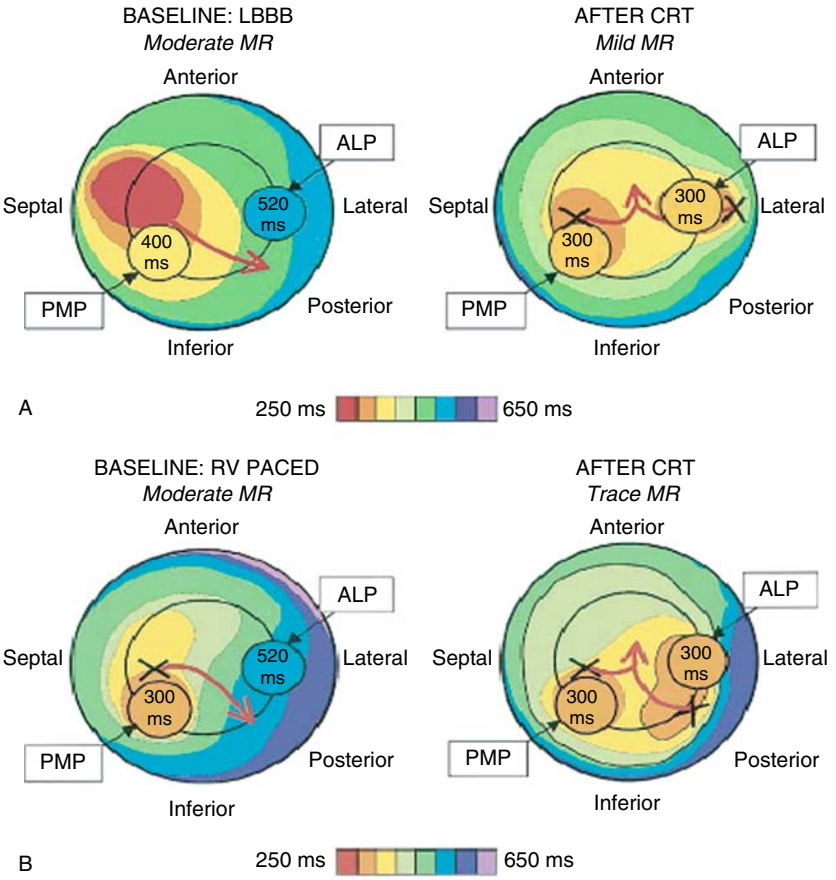


Fig. 21.12 Effect of CRT on interpapillary muscle time delay during LBBB (**A**) and RV apical pacing (**B**). Time to peak systolic strain is color-coded with lines representing isochromes of mechanical activation times at 50-ms intervals. The X indicates sites of lead placement, and the arrow indicates the direction of the propagating mechanical activation. Time to peak strain of sites adjacent to anterolateral (ALP) and posteromedial (PMP) papillary muscles are shown. A decrease in interpapillary muscle time delay was associated with decreased mitral regurgitation (MR). (From Kanzaki H, Bazaz R, Schwartzman D, Dohi K, Sade LE, Gorscan J 3rd. A mechanism for immediate reduction in mitral regurgitation after cardiac resynchronization therapy: Insights from mechanical activation strain mapping. J Am Coll Cardiol 2004;44(8):1619–1625.)

ventricular desynchronization [34, 35, 36, 37, 38, 39, 40]. This can be ameliorated in some cases by CRT [40, 41].

CRT Hardware Systems

Leads and Electrodes

Nonindependently Programmable Ventricular Polarity Configurations

Transvenous and epicardial LV pacing leads may be either unipolar or bipolar, though the former dominates current applications. Multiple ventricular pacing polarity configurations are therefore possible. Because programmed polarity settings are common to both ventricular leads and because the type (bipolar or unipolar) of these leads may not be the same, the following considerations apply.

In a dual bipolar polarity configuration, both lead tips are the active electrodes (cathodes), and the ring(s) are the common (nonstimulating) anode. However, the type of ventricular leads implanted defines the pacing/sensing vector (Figs. 21.13 and 21.14). With two unipolar leads, the bipolar setting results in no pacing or sensing. If both leads are bipolar, both rings act as the common electrode. If one lead is bipolar (RV) and the other lead is unipolar (typically LV), the ring on the bipolar lead acts as the common electrode (nonstimulating anode). This configuration results in *shared-ring* bipolar pacing and sensing. This hybrid bipolar/unipolar stimulation configuration (*dual cathodal*) is employed in most contemporary CRT pacing systems.

In a dual unipolar polarity configuration, the lead tips are the active electrodes; the noninsulated device case is the common electrode. This configuration is uncommonly used in CRT pacing systems and is not feasible in CRTD systems due to the concerns regarding ventricular oversensing associated with the unipolar pacing stimulus.

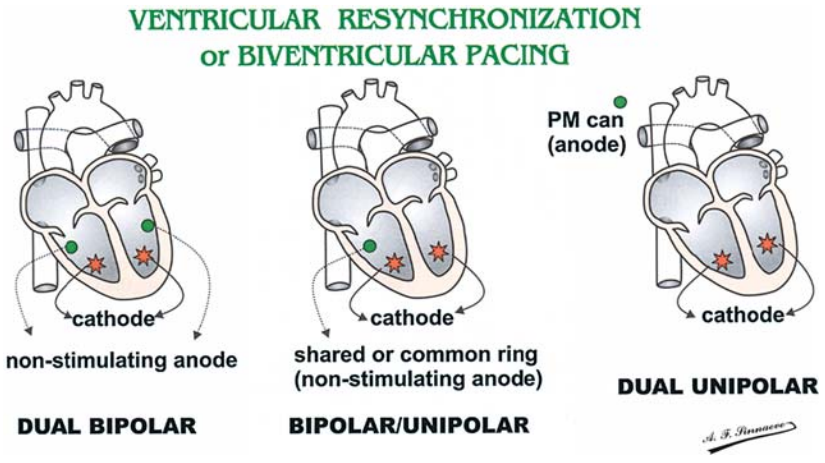


Fig. 21.13 Biventricular pacing configurations. (From Barold SS, Stroobandt RX, Sinnaeve AF. Cardiac Pacemakers Step by Step: An Illustrated Guide. Malden, MA: Blackwell; 2004.)

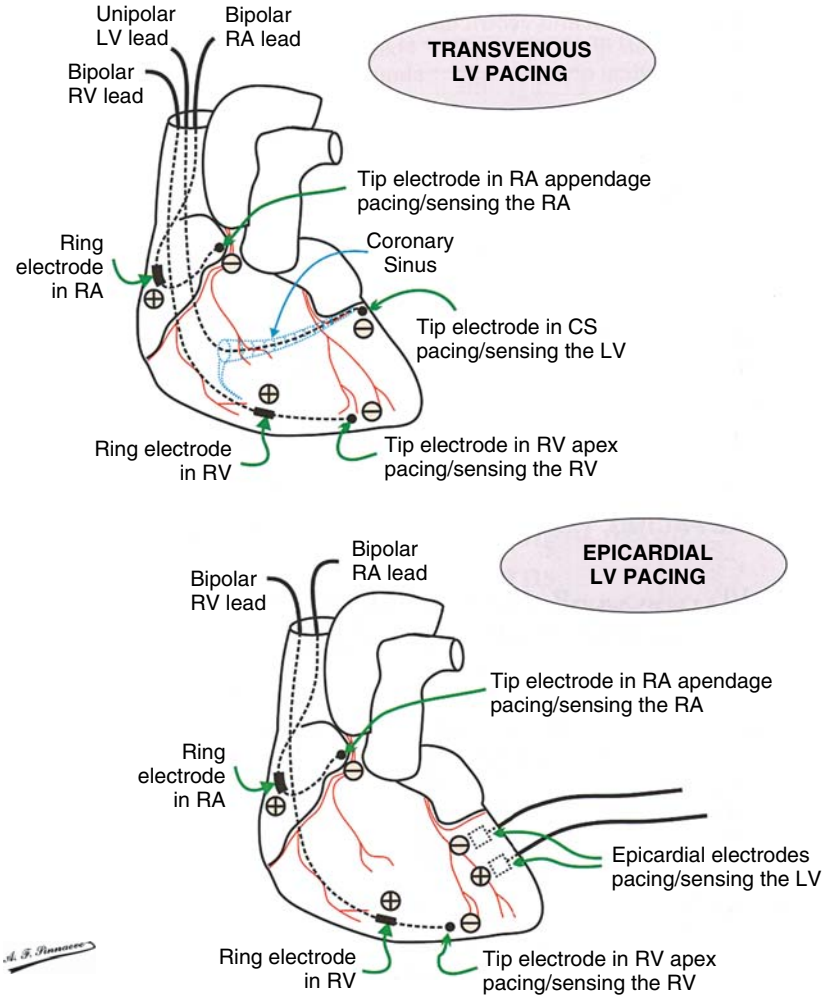


Fig. 21.14 Leads and electrodes for biventricular pacing. (From Barold SS, Stroobandt RX, Sinnaeve AF. Cardiac Pacemakers Step by Step: An Illustrated Guide. Malden, MA: Blackwell; 2004.)

Pulse Generators (Fig. 21.15)

Conventional dual-chamber pulse generators or specially designed multisite pacing pulse generators may be used for CRT applications. A conventional dual-chamber pulse generator is well suited for CRT in patients with permanent atrial fibrillation (AF). In this situation, the ventricular port is used for the RV lead and the atrial port is used for the LV lead. This permits programming of independent outputs and ventricular–ventricular timing by manipulation of the AV delay. The programming mode can be either DDD/R or DVI/R (see below). A conventional dual-chamber pulse generator can also be used for atrial-synchronous biventricular pacing. The single ventricular output must be divided to provide simultaneous stimulation of the right ventricle and left ventricle (dual cathodal system with parallel outputs). This is achieved with a Y-adaptor and results in simultaneous RV and LV sensing, which may result in ventricular double-counting and loss of CRT (see later)

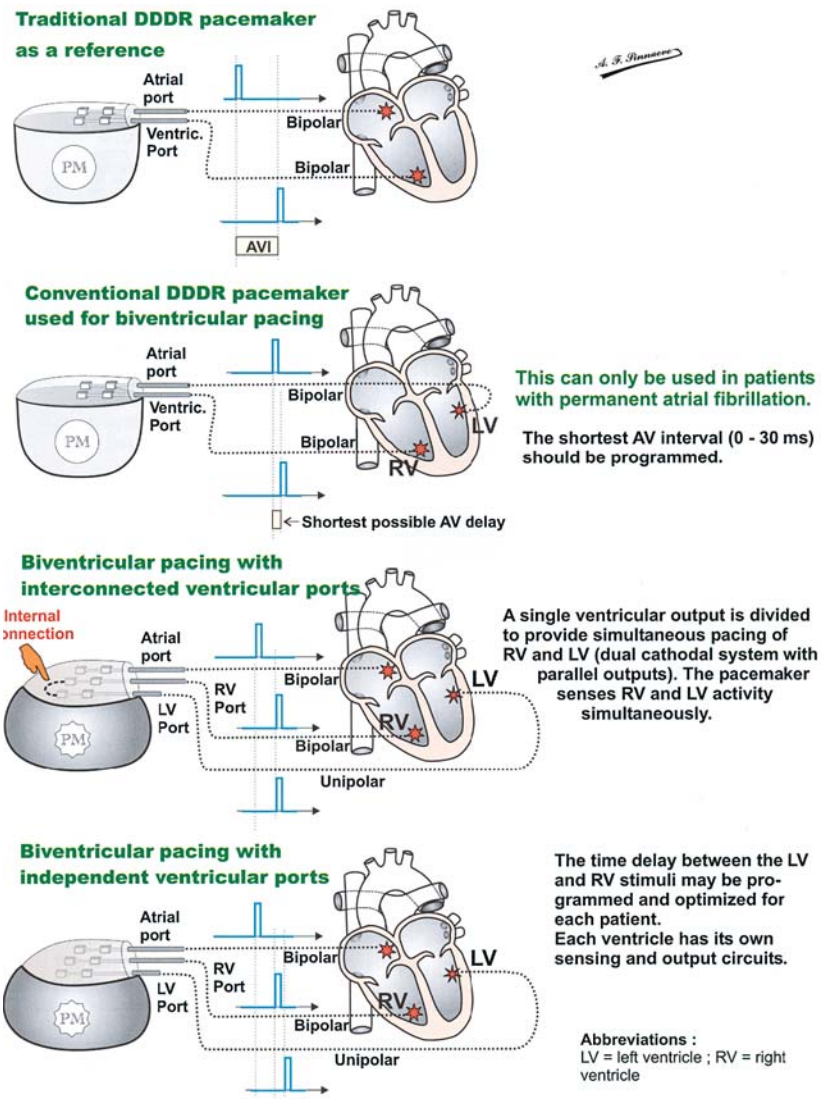


Fig. 21.15 Pulse generators for biventricular pacing. (From Barold SS, Stroobandt RX, Sinnaeve AF. Cardiac Pacemakers Step by Step: An Illustrated Guide. Malden, MA: Blackwell; 2004.)

or pacemaker inhibition in the case of LV lead dislodgment into the coronary sinus with sensing of atrial activity [42].

First-generation multisite pacing pulse generators similarly provide a single ventricular output for simultaneous RV and LV stimulation, however, two separate ventricular channels internally connect in parallel. This connection is made for both the lead tip and ring connections and eliminates the need for a Y-adaptor. However, this configuration still provides simultaneous RV and LV sensing with associated limitations.

Second-generation multisite pacing pulse generators have independent ventricular ports. Each ventricular lead therefore has separate sensing and output circuits. This arrangement permits optimal programming of outputs

and time delay between RV and LV stimulation for each patient. It also eliminates the potential complications of biventricular sensing.

Programming Considerations for CRT

Pacing Modes

It is axiomatic that for maximal delivery of CRT, ventricular pacing must be continuous. DDD mode (atrial and ventricular pacing/sensing) guarantees AV synchrony by synchronizing ventricular pacing to all atrial events except during episodes of atrial tachycardia or atrial fibrillation. However, DDD mode increases the probability of atrial pacing (depending upon programmed lower rate limit) that may alter the left-sided AV timing relationship due to interatrial conduction time and atrial pacing latency.

VDD mode (atrial sensing only, ventricular pacing and sensing) guarantees the absence of atrial pacing and synchronizes all atrial events to ventricular pacing at the programmed AV delay. However, if the sinus rate is below the lower programmed rate limit, AV synchrony is lost because the VDD mode is operationally VVI (ventricular-only sensing and pacing).

Although conventional dual-chamber pacing systems are not designed for biventricular pacing and generally do not allow programming of an AV delay of zero, or near zero, they are being increasingly used with their shortest AV delay (0–30 ms) for CRT in patients with permanent AF. The advantages include programming flexibility, elimination of the Y-adaptor (required for conventional VVIR devices), protection against far-field sensing of atrial activity (an inherent risk of dual cathodal devices with simultaneous sensing from both ventricles), and cost. When a conventional dual-chamber pacemaker is used for CRT, the LV lead is usually connected to the atrial port and the RV lead to the ventricular port. This provides for (1) LV stimulation before RV activation (LV preexcitation); (2) protection against ventricular asystole related to oversensing of far-field atrial activity when the LV lead is dislodged toward the AV groove. The DVIR mode is ideally suited for this application. The DVIR mode (committed atrial pacing, ventricular pacing and sensing) behaves like the VVIR mode except that there are always two closely coupled independent ventricular stimuli thereby facilitating comprehensive evaluation of RV and LV pacing and sensing performance. The DVIR mode also provides absolute protection against far-field sensing of atrial activity in case of LV lead dislodgment, as no sensing occurs on the "atrial" (LV) lead in the DVIR mode.

Determining LV and RV Capture: Importance of Electrocardiography

The 12-lead ECG is essential to ascertain RV and LV capture during follow-up of CRT systems without separately programmable ventricular outputs. It is recognized that 6 distinct 12-lead ventricular activation patterns may be seen during threshold determination. These are (1) intrinsic rhythm during loss of RV and LV capture or pacing inhibition (native QRS), (2) isolated RV stimulation, (3) isolated LV stimulation, (4) biventricular stimulation with complete capture, (5) biventricular pacing with fusion between native activation and pacing capture, (6) biventricular stimulation with anodal capture.

Ventricular pacing thresholds should ideally be performed independently and in the VVI mode at a rate exceeding the prevailing ventricular rate so as to obtain continuous ventricular capture without fusion. Alternately, thresholds can be performed in the VDD or DDD mode at very short AV delays to ensure full ventricular capture without fusion. In general, it is advisable to initiate threshold determinations at maximum output (voltage and pulse duration) because there is often a significant differential in capture thresholds between right ventricle and left ventricle.

In devices without separately programmable ventricular outputs, RV and LV capture can only be determined by ECG analysis during common ventricular voltage decrement. This requires inspection of a 12-lead ECG to demonstrate a change in electrical axis that confirms independent LV and RV capture.

Pacing from the RV apex produces a negative paced QRS complex in the inferior leads simply because the activation starts in the inferior part of the heart and travels superiorly away from the inferior leads (Figs. 21.16 and 21.17). The mean QRS frontal plan axis is superior either in the left or right superior quadrant. Pacing from the RV outflow tract (RVOT) produces

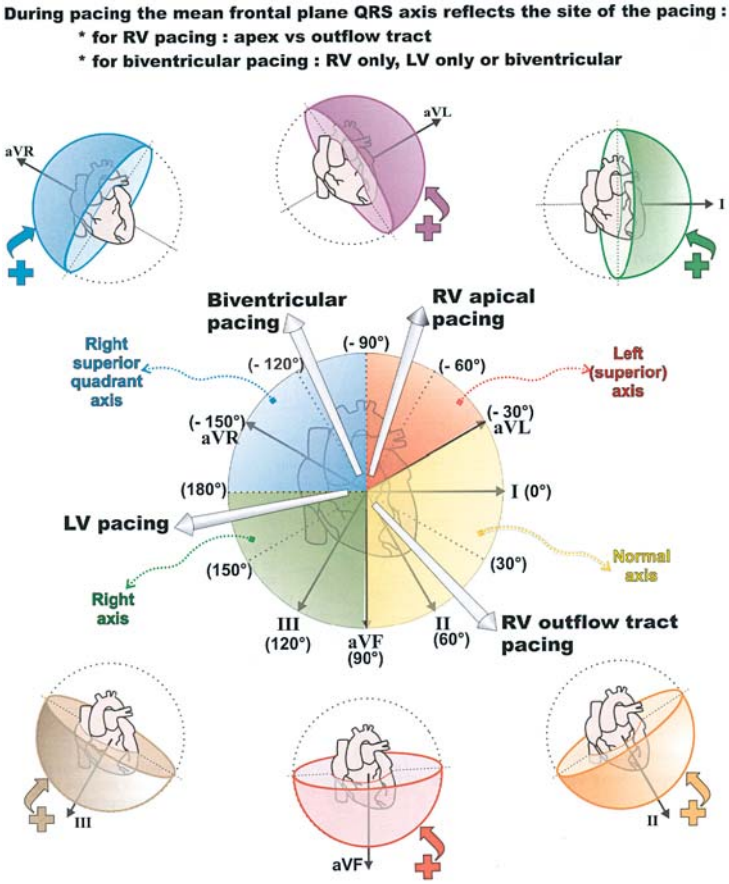


Fig. 21.16 Mean QRS axis in the frontal plane during ventricular pacing. (From Barold SS, Stroobandt RX, Sinnaeve AF. Cardiac Pacemakers Step by Step: An Illustrated Guide. Malden, MA: Blackwell; 2004.)

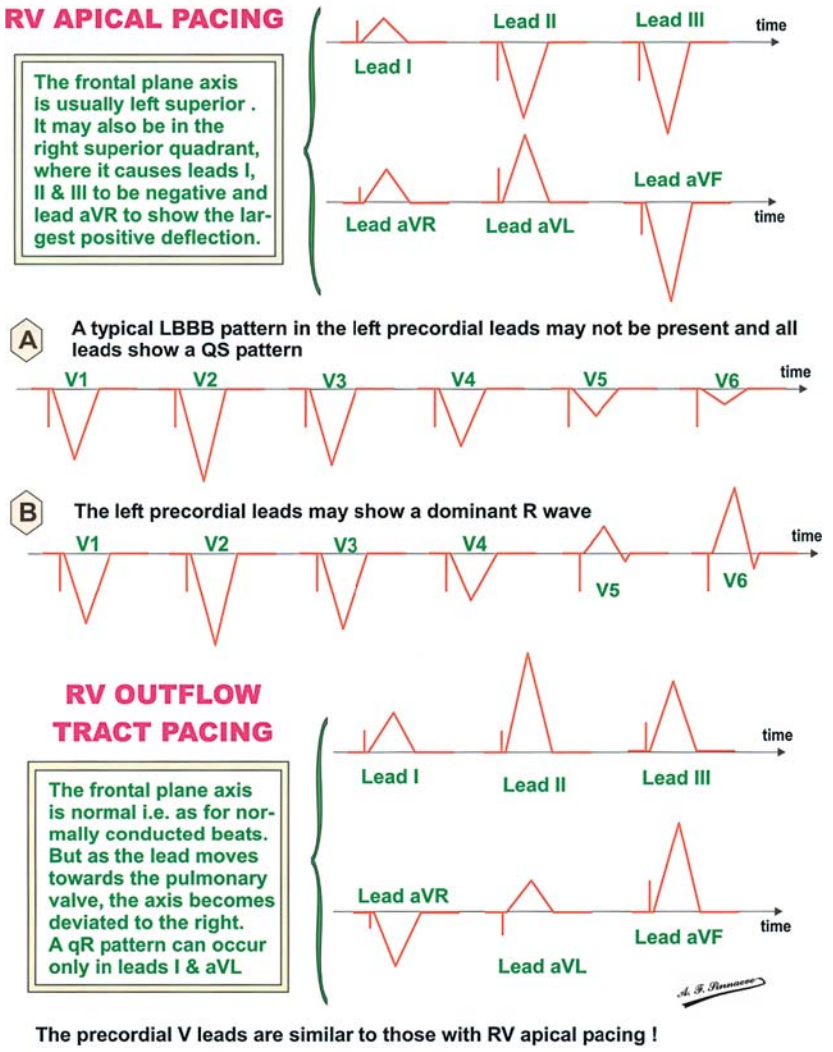


Fig. 21.17 ECG QRS patterns during RV pacing from different sites. (From Barold SS, Stroobandt RX, Sinnaeve AF. Cardiac Pacemakers Step by Step: An Illustrated Guide. Malden, MA: Blackwell; 2004.)

a frontal plane axis that is "normal," meaning inferiorly directed (positive QRS in inferior leads) (Fig. 21.17). Isolated LV pacing produces a rightward axis, similar to maximal ventricular preexcitation over a left-sided accessory pathway (Fig. 21.18). Biventricular pacing (RV + LV) produces a right superior axis as a result of fusion of RV and LV electrical axes. A qR or Qr complex in lead I is rare in uncomplicated RV apical pacing. It is present in 90% of cases of biventricular pacing. In biventricular pacing, loss of the q or Q wave in lead I is 100% predictive of loss of LV capture (Fig. 21.19). Examples of the effects of univentricular and biventricular stimulation on the 12-lead ECG are shown in Figure 21.20.

The majority of current cardiac resynchronization therapy pacing (CRTP) and defibrillation (CRTD) systems use a dual cathodal pacing configuration.

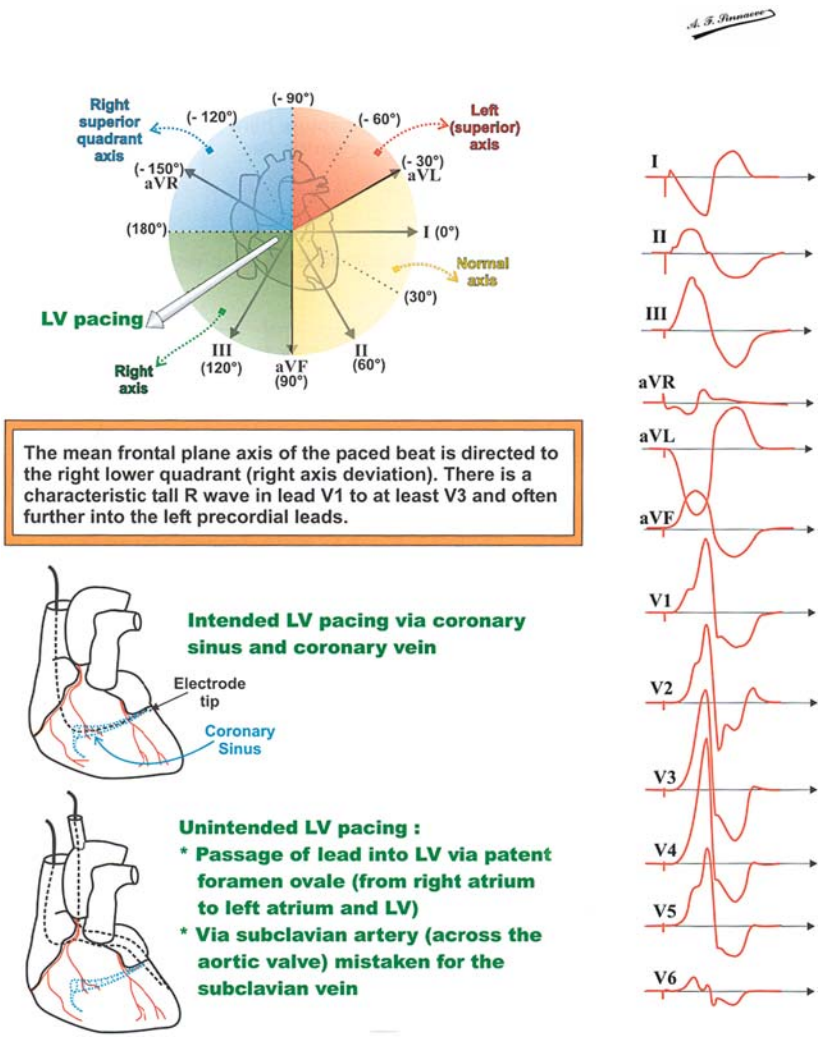


Fig. 21.18 ECG QRS patterns during LV free wall pacing. (From Barold SS, Stroobandt RX, Sinnaeve AF. Cardiac Pacemakers Step by Step: An Illustrated Guide. Malden, MA: Blackwell; 2004.)

Anodal capture refers to the situation when myocardial capture occurs at the RV anode. This could theoretically occur in isolation with the LV cathode but most commonly occurs with both RV and LV cathodes and is referred to as *triple site* pacing. Anodal capture is more common at high voltage output and with true bipolar RV leads due to the small surface area and higher current density of the ring electrode, as opposed to the larger surface area and lower current density of the coil electrode in integrated bipolar leads.

Anodal capture results in a distinct change in activation pattern compared with biventricular pacing that can only be appreciated on the 12-lead ECG (Fig. 21.21). The electrical axis is shifted leftwards and the QRS duration may be shorter as a consequence of increased ventricular fusion. The change in QRS morphology related to loss of anodal capture as voltage output is

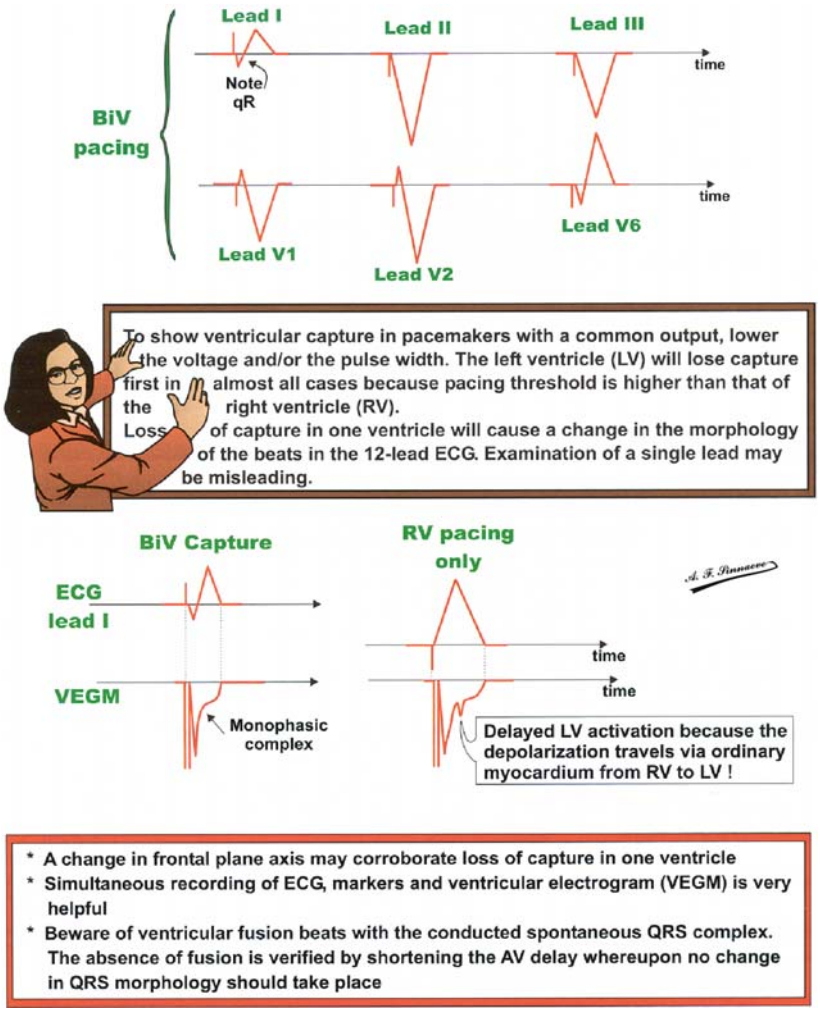


Fig. 21.19 Analysis of ECG QRS patterns to ascertain RV and LV capture in CRT systems without separately programmable ventricular outputs. (From Barold SS, Stroobandt RX, Sinnaeve AF. Cardiac Pacemakers Step by Step: An Illustrated Guide. Malden, MA: Blackwell; 2004.)

decremented during a temporary threshold test using a single ECG lead may be misinterpreted as loss of LV capture and result in erroneous overestimation of the LV threshold.

The physiologic consequences of anodal capture are uncertain. One study demonstrated that anodal capture might be advantageous during CRT by counteracting the regional activation delay located at the inferior wall of the left ventricle and improving regional measures of intraventricular dyssynchrony [43].

Programming Pacing Outputs

It is critically important that voltage output be adjusted to exceed ventricular capture threshold for left ventricle and right ventricle in common cathodal

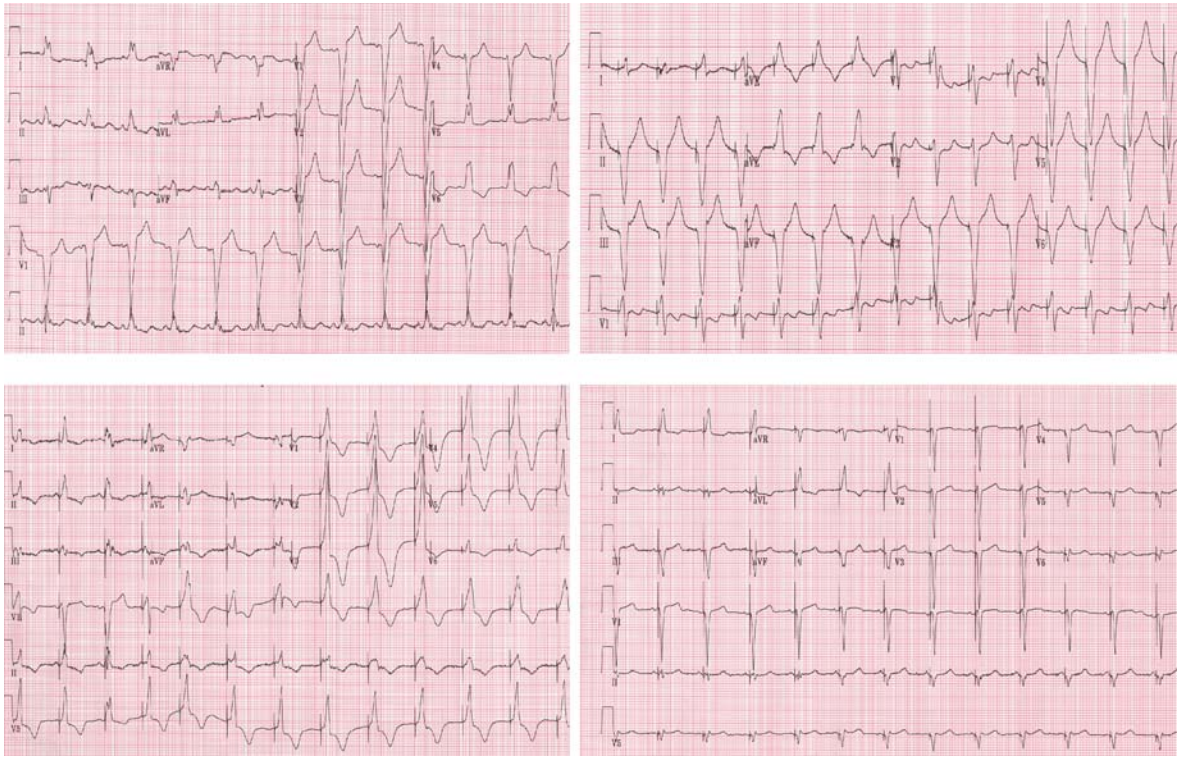


Fig. 21.20 QRS morphologies during biventricular stimulation. VVI mode is used to exclude the possibility of fusion with native ventricular activation. *Top left:* Intrinsic ventricular activation (LBBB). *Top right:* RV only pacing. *Bottom left:* LV only pacing. *Bottom right:* Biventricular pacing.

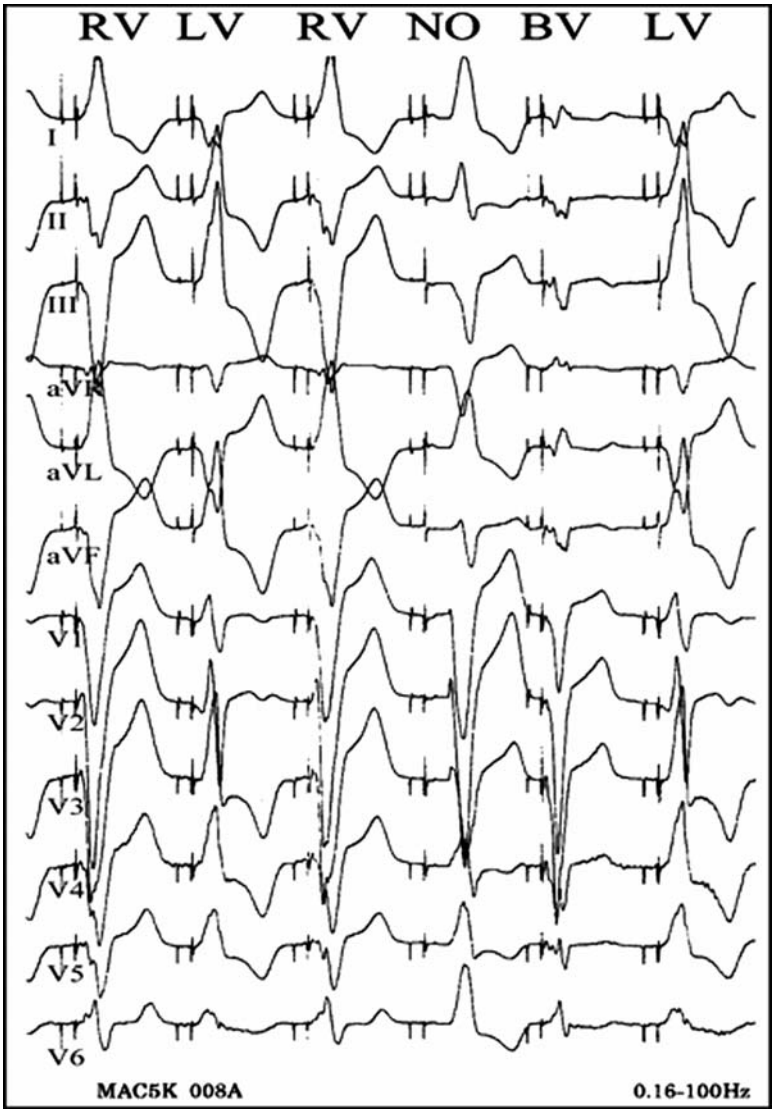


Fig. 21.21 Anodal capture during CRT. Note narrower QRS duration in V1 during complex 5. (From Thibault B, Roy D, Guerra PG, et al. Anodal right ventricular capture during left ventricular stimulation in CRT-implantable cardioverter defibrillators. Pacing Clin Electrophysiol 2005;28(7):613–619.)

devices. Because there are commonly differences in capture thresholds between ventricular chambers, this means that the voltage output must exceed capture threshold in the chamber with the highest threshold (usually the left ventricle). Newer pulse generators that permit independent programming of ventricular outputs provide greater flexibility in this regard. Similarly, RV and LV voltage outputs may be separately programmable in the situation where a standard DDD device is used to provide RV and LV stimulation in the DVI mode for CRT in permanent AF (see above).

AV Optimization

AV optimization is important for maximal hemodynamic response to CRT but not essential, as ventricular pumping function can be improved by CRT even in the presence of permanent AF. Nonetheless, acute hemodynamic studies have consistently demonstrated that AV optimization "re-times" the left atrial–left ventricular relationship and can result in 15–40% improvement in indices of left ventricular systolic performance acutely. Furthermore, small changes in AV delay may nullify hemodynamic benefit of CRT.

AV Optimization Using Invasive Hemodynamic Monitoring (Fig. 21.22)
Techniques for AV optimization using invasive left ventricular pressure monitoring have been described [20,21,22]. The optimal AV delay is assumed to be the value that yields at least a 5% increase in aortic pulse pressure or LV +dP/dt$_{max}$ compared with baseline. These indices are useful because they correlate with stroke volume and global contractile function. However, pulse pressure and LV +dP/dt can be confounded by changes in preload and arterial impedance (afterload). Though this technique is useful for assessing the effects of acute manipulations of AV delay, ventricular stimulation sites, and ventricular sequencing on LV pumping function, this is an impractical approach for routine clinical care. Furthermore, there is some evidence that

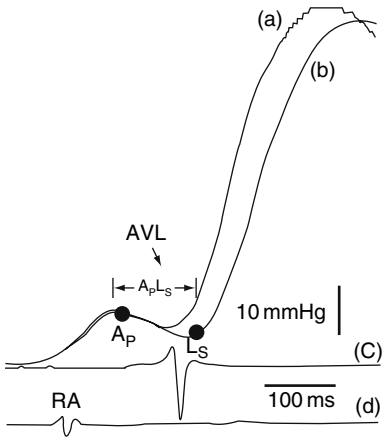


Fig. 21.22 AV optimization using invasive hemodynamic monitoring. Example of systolic left ventricular (LV) pressure during pacing (**a**) and intrinsic condition (**b**), intrinsic LV electrogram (**c**) and intrinsic right atrial (RA) electrogram (**d**) recorded from one patient. Also shown here is the presystolic peak (AP) due to atrial contraction and the start of pressure development in the LV (LS), the latter obtained as the point that first attained a slope >10% of maximum rate of increase of LV pressure. The interval (APLS) between AP and LS is defined as atrioventricular mechanical latency (AVL). When the ventricle is preexcited with pacing, the LS point moves to the left, as shown here in curve **a**. To obtain the LS point in paced condition, the pressure curves in pacing and intrinsic condition are aligned at the right atrium electrical activation (RA). Thereafter, the difference between the two curves is obtained. The LS is the first point on the difference curve at which the slope is 10% of the maximum slope. (From Auricchio A, Stellbrink C, Sack S, et al., Pacing Therapies in Congestive Heart Failure (PATH-CHF) Study Group. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. J Am Coll Cardiol 2002;39(12):2026–2033.)

acute hemodynamic response is not highly correlated with long-term clinical response including reverse ventricular remodeling.

AV Optimization Using Conventional Echocardiography

Several methods of AV optimization using echo-guided pulsed Doppler analysis of transmitral blood flow velocities to approximate an optimal timing relationship between atrial systole and ventricular filling have been described. The goal is manipulation of the AV delay until the end of the untruncated A-wave occurs coincident with mitral valve closure, which represents the onset of ventricular contraction. The common assumption of these methods is that this optimized AV delay will yield the longest diastolic filling time and best acute LV pumping function.

According to the method of Ritter et al. [44,45], optimal sensed AV (SAV) delay can be stated algebraically as $SAV_{optimal} = SAV_{short} + d$, where $d = (SAV_{long} + QA_{long}) - (SAV_{short} + QA_{short})$, Q = ventricular pacing stimulus, and A = termination of A-wave. This process is performed in three steps. First, the SAV_{long} and QA_{long} are determined by programming a "long" sensed AV delay (SAV_{long}). The AV delay should be long enough to maintain full ventricular capture but allow spontaneous closure of the mitral valve prior to aortic outflow (Fig. 21.23). QA_{long} is then measured as the time from the ventricular pacing stimulus to the end of the A-wave. Second, the SAV_{short} and QA_{short} are determined by programming a "short" sensed AV delay (SAV_{short}) that results in forced closure of the mitral valve (Fig. 21.24). QA_{short} is then measured as the time from the ventricular pacing stimulus to the end of the A-wave. Caution must be applied to not extrapolate to the end of the A-wave but to use the observed end of the A-wave. Third, AV optimization is confirmed by noting the return of normal E- and A-wave separation indicating improved diastolic filling time and optimized AV timing relationship (Fig. 21.25).

This is a rather tedious process and highly operator dependent, as visualization of the terminal portion of the A-wave is often difficult and subjective. A potentially more critical limitation is that the basis for the technique was

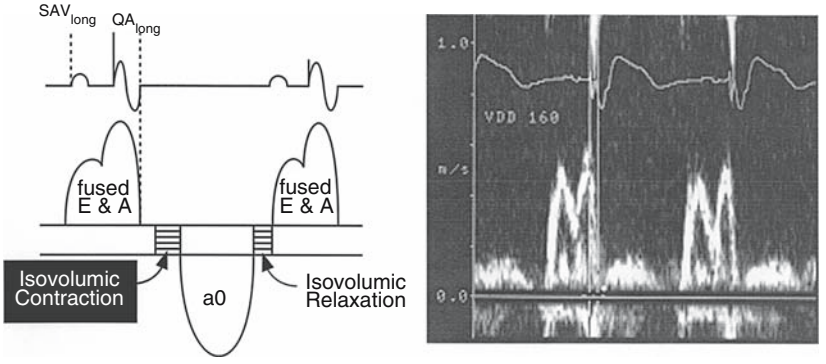


Fig. 21.23 AV optimization using Doppler mitral inflow. Determining $SAV_{lon}g$ and QA_{long}. (**a**) To determine SAV_{long}, a long sensed AV delay that maintains ventricular preexcitation, yet allows spontaneous closure of the mitral valve prior to aortic ejection (e.g., 150 ms), is programmed. Next, the time from V-pace to the end of the A-wave is measured. This is QA_{long}, which refers to the QA distance measured when a "long" SAV is programmed. (**b**) Doppler echo of transmitral blood flow with a long AV delay.

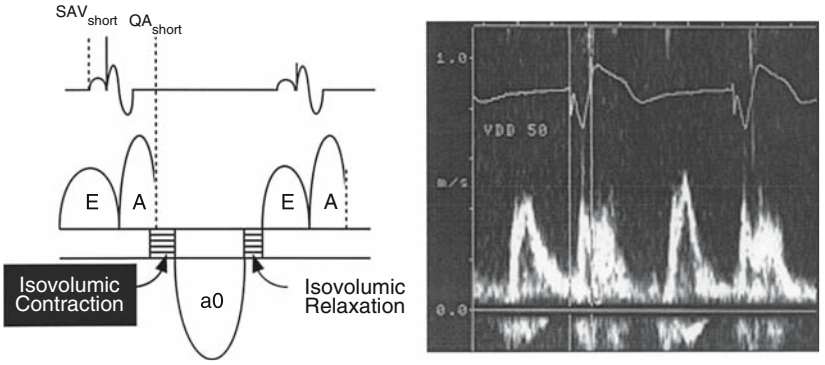


Fig. 21.24 Determining SAV_{short} and QA_{short}. (**a**) To determine SAV_{short}, a "short" sensed AV delay that results in premature closure of the mitral valve (e.g., 50 ms) is programmed. The time from V-pace to the premature end of the A-wave is measured. This is QA_{short}. (**b**) Doppler echo of transmitral blood flow with a short AV delay.

derived from studies of patients with permanent AV block and conventional dual-chamber pacing with RV apical stimulation. This may be physiologically unsound in CRT where LV pacing modifies the interventricular and intraventricular delay caused by RV only pacing.

A simplified approach to AV optimization guided by analysis of transmitral blood has been described by Meluzin et al. [46]. This approach requires two steps. A "long" AV delay is programmed to achieve full ventricular capture but to allow spontaneous closure of the mitral valve prior to aortic outflow. The time between the end of the A-wave (representing the end of the diastolic filling period) to the time of onset of high-velocity systolic mitral regurgitation (representing the onset of ventricular contraction) is then recorded. The time from the end of the A-wave to the onset of the low velocity of diastolic mitral regurgitation is denoted as t1. The optimal AV delay is then calculated as the "long" AV delay minus t1 (in milliseconds). This approach accurately predicted the optimal AV delay based on simultaneous invasive hemodynamic measurements in 78% of patients. Potential limitations include

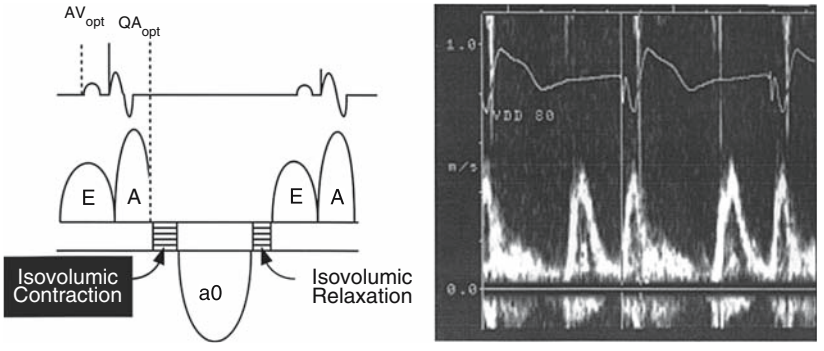


Fig. 21.25 Optimized AV delay. AV optimization is confirmed by noting the return of normal E- and A-wave separation on Doppler echo of transmitral blood flow. Note the improvement in transmitral blood flow and the increase in LV diastolic filling time, which help increase cardiac output.

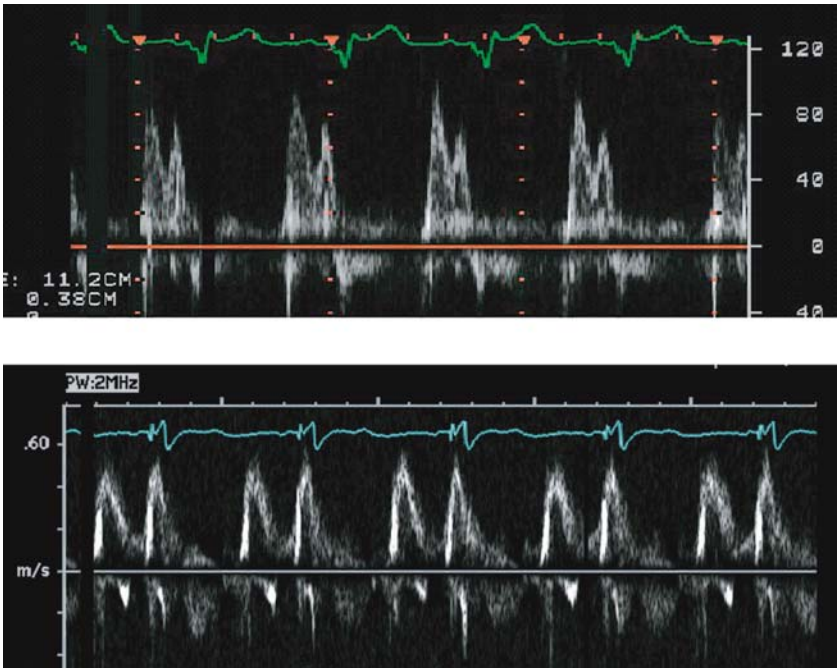


Fig. 21.26 Estimated optimal AV delay using intrinsic AV intervals . In this example, As-Vs = 200 ms, QRSd = 170 ms, therefore estimated optimal AV delay = 100 ms (see text).

a requirement for at least mild mitral regurgitation and difficulty discerning the termination of the A-wave and the transition between diastolic and systolic mitral regurgitation.

AV Optimization Using Intrinsic AV Intervals (Fig. 21.26)

Another approach to AV optimization for maximal positive change in LV +dP/dt is derived from the intrinsic AV interval measured from the local right atrial and RV endocardial electrograms (EGMs) using two linear equations [47]. If the native QRSd is >150 ms, then estimated optimal AV delay (EOAVD) = 0.7 × AVI (ms) – 55 ms and for native QRSd 120–150 ms EOAVD = 0.7 × AVI (ms). These regression formulas can be very closely approximate by the following simple rules: the estimated optimal programmed AV delay for patients with QRSd >150 ms is 50% of the intrinsic AV interval and 75% for QRSd of 120 to 150 ms. This strategy was used in the study design of the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial [48] that showed significant reductions in mortality and heart failure hospitalizations with CRT at 1 year.

AV Optimization Using Noninvasive Hemodynamic Monitoring (Fig. 21.27)

Recently, finger photoplethysmography (FPPG) has been investigated as a noninvasive tool for hemodynamic optimization of the AV delay during CRT [49]. FPPG correctly identified positive aortic pulse pressure responses with 71% sensitivity and 90% specificity and negative aortic pulse pressure responses with 57% sensitivity and 96% specificity. The magnitude of FPPG

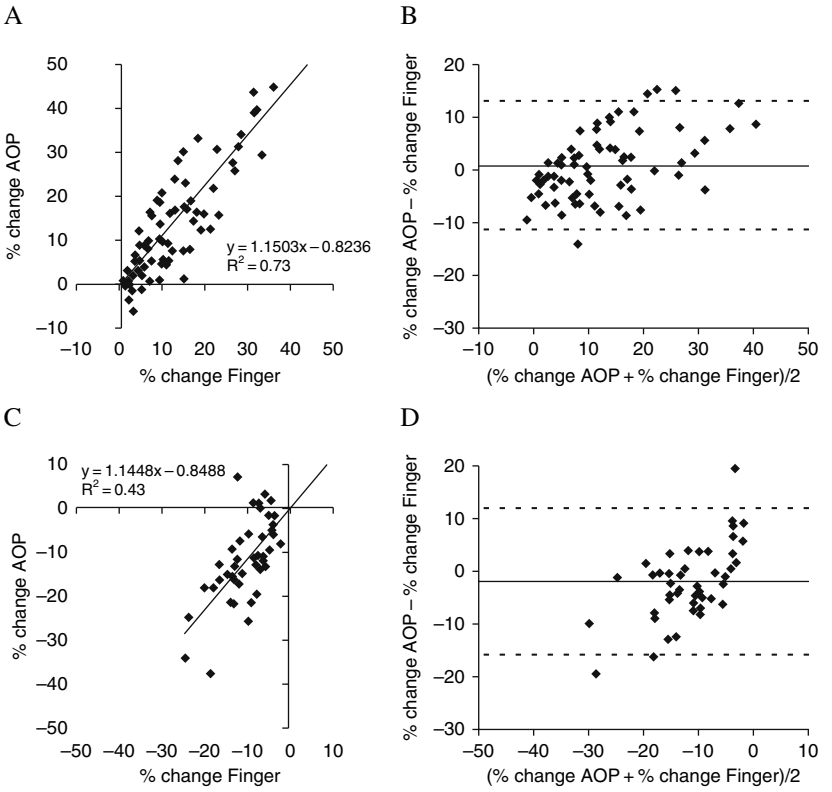


Fig. 21.27 AV optimization using finger plethysmography. Correlation of aortic pulse pressure change versus finger pulse change and the corresponding Bland–Altmann plots. (**A**) Correlation for significantly positive finger responses. (**B**) Bland–Altmann plot for significantly positive finger responses. (**C**) Correlation for significantly negative finger responses. (**D**) Bland–Altmann plot for significantly negative finger responses. (From Butter C, Stellbrink C, Belalcazar A, et al. Cardiac resynchronization therapy optimization by finger plethysmography. Heart Rhythm 2005;1:568–578.)

changes was well correlated with positive aortic pulse pressure changes (R^2 = 0.73). However, the correlation with negative aortic pressure changes was poor (R^2 = 0.43). FPPG identified 78% of the patients having positive aortic pulse pressure changes to CRT and identified the AV delay giving maximum aortic pulse pressure change in all selected patients. This approach has not been clinically validated but offers the appeal of a quick, noninvasive measure for correlating changes in AV delay with some meaningful measure of cardiac output.

Clinical Experience with AV Optimization

Previous studies have emphasized the importance of a short AV delay during standard dual-chamber pacing in patients with HF to optimize the acute hemodynamic response when native AV conduction is prolonged [50, 51]. However, in another study, the same benefit could not be documented [52]. It is now recognized that the acute hemodynamic benefit of AV optimization in conventional dual-chamber pacing is negated by the chronic adverse effects of

ventricular desynchronization on LV pump function due to RV apical pacing, particularly among patients with systolic heart failure.

However, because biventricular pacing overcomes the problem of ventricular desynchronization caused by RV only pacing, AV optimization has been incorporated into RCTs of CRT. Using variations on the method of Ritter et al. [44] or invasive hemodynamic monitoring, the optimized AV delay in studies of CRT is almost invariably in the range 80–110 ms regardless of other considerations [20,21,48,53,54]. Because of this, some have argued empiric programming of the AV delay at ~100 ms. It is almost certainly true that the optimal AV delay will likely differ as heart rate and cardiac loading conditions change, such that the optimal AV delay at one point in time may not be optimal under other conditions. Furthermore, the importance of AV delay optimization at rest for chronic clinical and hemodynamic effect remains to be shown. It has also become clear that optimal ventricular synchronization is far more important than AV optimization. The atrial contribution to ventricular filling is probably minimal when the left ventricle is operating at persistently elevated diastolic pressures and atrial mechanical transport is diminished due to myopathic processes.

Recently, Sawhney et al. [55] reported a randomized, prospective, single-blind trial of echo-guided AV optimization using the aortic velocity–time integral (VTI) versus an empiric AV delay at 120 ms in 40 CRT patients. Optimal AV delay was defined as the AV delay that yielded the largest mean aortic VTI at one of eight tested AV intervals (between 60 and 200 ms). A small improvement in ejection fraction was demonstrated in the VTI-optimized group compared with the empiric AV delay group immediately after implementation of CRT. After 3 months, modest improvements in New York Heart Association (NYHA) functional class and standardized quality of life scores were observed in the VTI-optimized group. Not unexpectedly, the mean optimized AV delay program and empiric AV delay were almost identical (119 vs. 120 ms, respectively). The authors speculated that individual patient variation accounted for the slight differences in outcomes between groups. However, due to the large range of optimal AV delays observed (60–200 ms), many patients in the empiric AV delay group had an AV delay that was significantly different than their optimized AV delay. This data, though of interest, is insufficient to recommend AV optimization in all patients who receive CRT.

Interventricular Timing Considerations

First- and second-generation CRTP and CRTD systems delivered simultaneous biventricular stimulation, even when RV and LV stimulation outputs were separately programmable. Simultaneous biventricular stimulation has reproducibly been shown to be effective in the majority of patients in RCTs of CRT. However, despite similar prolongation of the QRS duration and morphology of LBBB, considerable heterogeneity in the location of regional mechanical dyssynchrony has been revealed by sophisticated echocardiographic techniques [27,56,57]. For example, the posterobasal left ventricle most commonly shows the greatest electromechanical delay in LBBB associated with nonischemic DCM (NDCM). However, the greatest electromechanical delay occurs in the interventricular septum (paradoxical

septal contraction) in some patients with LBBB and NDCM. The situation is even more complex in ischemic cardiomyopathy where regional electromechanical delays are influenced by infarct location. It is therefore reasonable to hypothesize that timed stimulation of different left regions might be necessary for optimal resynchronization therapy. In practical application, RV stimulation serves as a surrogate for septal stimulation, but this may be influenced by RV lead position (RV apex [RVA] vs. septum).

Logically, enhancements to biventricular pacing systems might permit tailoring of ventricular stimulation by site and timing to optimally address the diversity of electromechanical phenomenon observed between individual patients. In third-generation systems, the relative timing of RV and LV stimulation can be varied. This requires separately programmable RV and LV stimulation outputs and circuitry to permit timing delay between outputs by stimulation site (V-V timing). The goal of V-V timing is site-selective, sequential ventricular stimulation. Theoretically, V-V timing could be achieved with unipolar or dual cathodal electrode configurations. From a practical perspective, unipolar pacing is inapplicable in CRTD, and anodal capture at high outputs with dual cathodal electrode configurations results in unintended biventricular stimulation and could disrupt V-V timing. This is probably only relevant when RV stimulation precedes LV stimulation, as RV capture will render the local myocardium refractory and anodal capture during high-output LV stimulation will not occur. Accordingly, the use of V-V timing where RV precedes LV stimulation with dual cathodal electrode configurations mandates exclusion of anodal capture by 12-lead electrocardiography at programmed outputs (see above). Therefore, V-V timing is optimally delivered with true bipolar (RV and LV) electrode configurations.

Interventricular Timing Operation

Interventricular timing operation in the Medtronic InSync III CRTP system is shown in Figure 21.28. Nominally, selection of biventricular (RV + LV) pacing results in delivery of a pacing stimulus to the other chamber after a 4-ms delay. However, the first chamber paced and delay interval of a paced stimulus to the first and second chamber are separately programmable. The V-V Pace Delay parameter sets the amount of time that elapses between delivery of a stimulus to the first ventricle paced and delivery of a stimulus to the other ventricle. This can be varied between 4 and 80 ms. The V-V Pace Delay parameter necessitates timing interactions to guarantee proper operation of Ventricular Safety Pacing and Ventricular Sense Response. When these are enabled, paces generated in response to a ventricular sense will be delivered at the minimum (4 ms) V-V delay.

Clinical Experience with Sequential Versus Biventricular Stimulation

The long-term clinical experience with sequential biventricular stimulation is limited, and no RCTs have reported on outcomes based on the use of this potential enhancement to CRT. Sogaard et al. [27] used tissue tracking to quantify regions of delayed longitudinal contraction and three-dimensional echocardiography to measure the effects of sequential ventricular stimulation in 21 patients with systolic heart failure and LBBB and QRSd <130 ms. After AV optimization using the Ritter method [44] and simultaneous

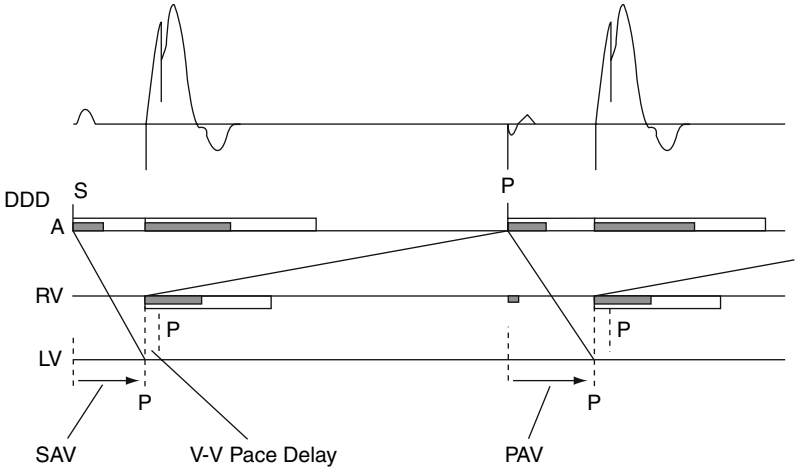


Fig. 21.28 Interventricular timing operation (Medtronic).

biventricular pacing, the number of regions displaying delayed longitudinal contraction was reduced and ejection fraction increased in all patients. These measurements were then repeated at five different interventricular delay intervals(12,20,40,60,and 80ms) with either LV or RV preactivation. Optimized sequential ventricular stimulation caused further reductions in regions displaying delayed longitudinal contraction and increases in ejection fraction, which were sustained for at least 3 months. Additionally, sequential ventricular stimulation increased diastolic filling time by about 7% even after AV optimization.

An interesting observation was that the location of myocardial regions displaying delayed longitudinal contraction varied between patients despite similar patterns of LBBB on the surface ECG. Although not uniformly observed, in most patients with nonischemic DCM (NDCM), the delayed regions were located in the posterobasal LV (Fig. 21.29), whereas in ischemic DCM the delayed regions were more frequently in the interventricular septum and inferior wall (Fig. 21.30). Correspondingly, optimal sequential ventricular stimulation was achieved with LV preexcitation when the posterobasal region was delayed and with RV preexcitation when the inferoseptal region was delayed. These beneficial effects were observed over a short range of ventricular timing intervals (±20 ms) and further increases in interventricular delay, or preexcitation of already early activated regions, resulted in worsened mechanical dyssynchrony and reduced pumping function.

Similar benefits of optimized sequential biventricular stimulation were observed by Bordachar [57]. Using combined measures of LV diastolic filling time, cardiac output, mitral regurgitant volume, and effective regurgitant orifice surface area (Fig. 21.31), systolic dyssynchrony index using tissue Doppler imaging, and extent of myocardium displaying delayed longitudinal contraction (tissue tracking), simultaneous biventricular pacing was the optimal stimulation configuration in only 15% of patients. LV preexcitation was optimal for 61% of patients with V-V interval ranging between 12 and 40 ms, whereas RV preexcitation was optimal in 24% patients with V-V interval ranging between 12 and 20 ms. All patients demonstrated clinical

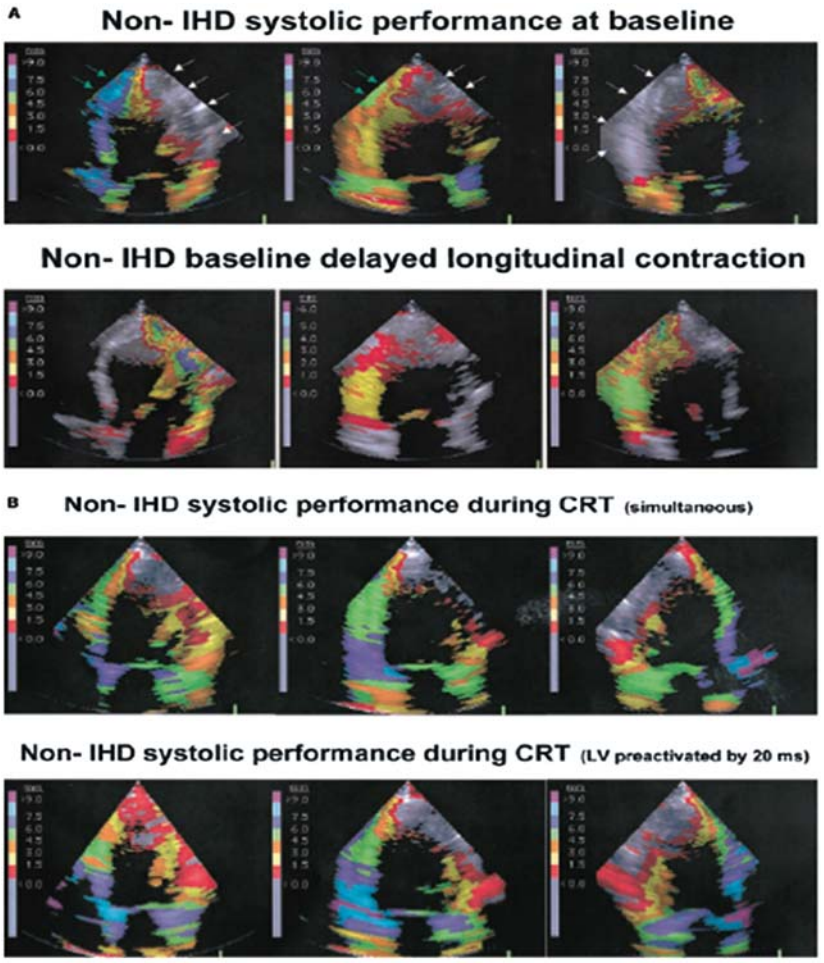


Fig. 21.29 Effect of sequential ventricular stimulation on LV systolic shortening. Color-coded scaling at left side of each image indicates regional motion amplitude. (**A**) *Top:* Baseline tissue tracking images in apical four-chamber, two-chamber, and long-axis views during systole in a patient with idiopathic dilated cardiomyopathy. Note lack of systolic motion in lateral wall, posterior wall, and distal parts of anterior wall, denoted by gray color and white arrows. Mechanical function of interventricular septum and inferior walls is abnormal, with greater motion amplitude in segments adjacent to apex (green arrows). *Bottom:* Extent of myocardium (colored segments) with delayed longitudinal contraction in diastole (mitral valve open). DLC is present in lateral, posterior, and inferior walls. Note that remaining part of LV is gray, indicating either no motion or motion toward base of heart (relaxation). (**B**) Same patient and views as in (**A**) (systole). *Top:* Simultaneous CRT resulting in contraction of larger proportion of lateral wall and posterior wall. In addition, each segment shows improved systolic shortening as seen from color coding. Abnormal distribution of myocardial motion in interventricular septum has been normalized. *Bottom:* Impact of sequential CRT with LV activated by 20 ms before RV. Compared with simultaneous CRT, sequential CRT yields further improvement in overall proportion of contracting myocardium in lateral and posterior walls. In addition, each segment shows further improvement in systolic shortening amplitude. (From Sogaard P, Egeblad H, Pedersen AK, et al. Sequential versus simultaneous biventricular resynchronization for severe heart failure: Evaluation by tissue Doppler imaging. Circulation 2002;106:2078–2084.)

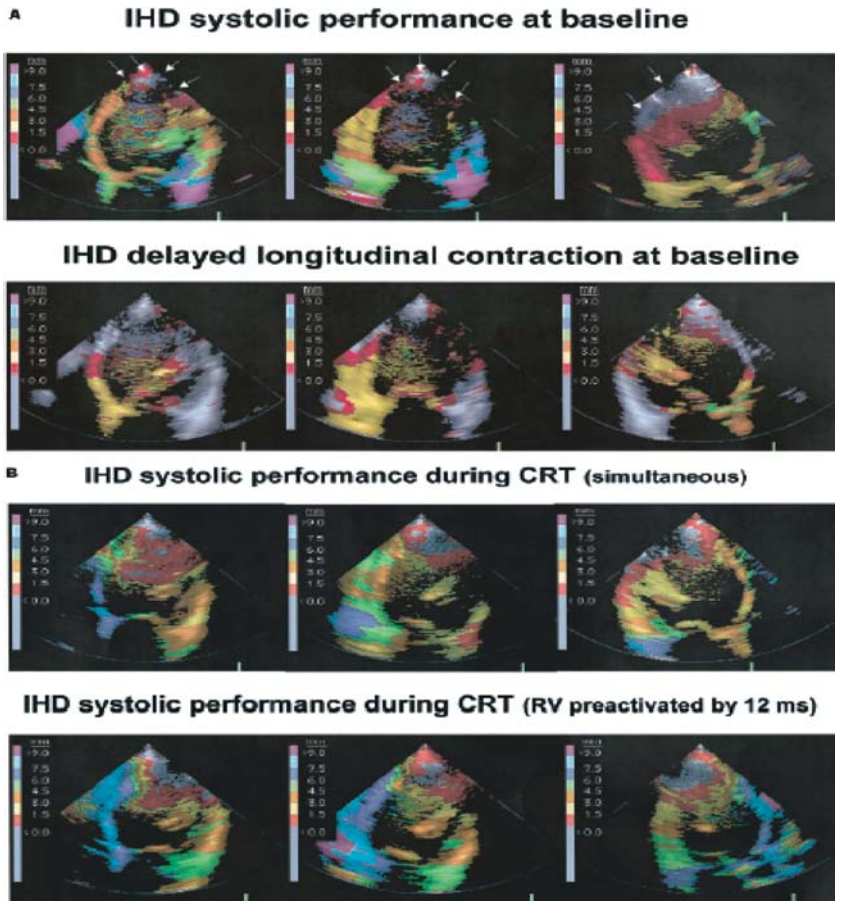


Fig. 21.30 Effect of V-V sequential ventricular stimulation on LV systolic shortening. (**A**) *Top:* Baseline tissue tracking images in apical four-chamber, two-chamber, and long-axis views during systole in a patient with idiopathic ischemic cardiomyopathy. Tissue tracking and strain rate analysis indicated apical infarct (*arrows*). *Bottom:* Extent of myocardium (colored segments) with delayed longitudinal contraction in interventricular septum and anterior and inferior walls (diastole). Extent of myocardium displaying delayed longitudinal contraction is less than that in patient with idiopathic dilated cardiomyopathy. (**B**) *Top:* Same patient as in (**A**) during simultaneous CRT, resulting in overall improvement in regional systolic shortening. *Bottom:* Impact of sequential CRT with RV lead activated 12 ms before LV lead. Compared with simultaneous CRT, sequential CRT yields further improvement in systolic contraction amplitude. (From Sogaard P, Egeblad H, Pedersen AK, et al. Sequential versus simultaneous biventricular resynchronization for severe heart failure: Evaluation by tissue Doppler imaging. Circulation 2002;106:2078–2084.)

responsiveness (improved NYHA class, quality of life, and 6-min hall walk) and evidence of reverse remodeling (improved ejection fraction, decreased LV end systolic and end diastolic volumes) at 3 months.

It is currently unclear what chronic benefit on a population scale, if any, manipulation of interventricular timing would provide during biventricular pacing. This is highlighted by the emerging evidence that univentricular left ventricular pacing is probably either equivalent or superior to biventricular pacing acutely and chronically (see below).

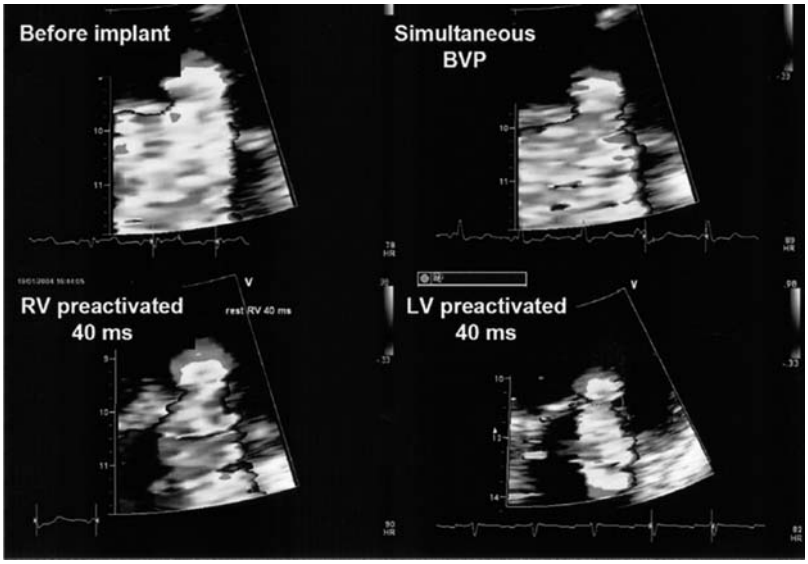


Fig. 21.31 Reduction of mitral regurgitation with optimized sequential biventricular pacing. Preimplant effective regurgitant orifice area (EROA): 31 mm^2; simultaneous BVP EROA: 22 mm^2; sequential BVP with right ventricular (RV) preactivation of 40 ms EROA: 21 mm^2; optimized sequential BVP with left ventricular (LV) preactivation of 40 ms EROA: 10 mm^2. (From Bordachar P, Lafitte S, Reuter S, et al. Echocardiographic parameters of ventricular dyssynchrony validation in patients with heart failure using sequential biventricular pacing. J Am Coll Cardiol 2004;44:2157–2165.)

Programming Ventricular Therapies in CRTD

An unresolved issue is optimal application of ventricular therapies in different ICD patient populations. Differences in the incidence of specific ventricular rhythms (ventricular tachycardia [VT], fast VT [FVT], and ventricular fibrillation [VF]), response to therapy (antitachycardia pacing [ATP] or shocks), and susceptibility to spurious therapies due to supraventricular tachycardia (SVT) by substrate and indication are incompletely characterized. This is an increasingly important consideration in view of recent expanded coverage for primary prevention ICD therapy. Using currently accepted implant criteria [58], about 30–40% of these expanded indication primary prevention patients will be candidates for CRTD.

The majority of patients who will receive CRTD systems will never have had spontaneous sustained ventricular arrhythmia. Furthermore, it can be inferred from the enrollment characteristics of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) [59] that at least 50% of CRTD patients will have NDCM. Compared with the several decades of experience with ICD therapy for ischemic cardiomyopathy, relatively little is known regarding ICD therapies in NDCM. Because the mechanisms of spontaneous ventricular arrhythmia are more diverse and less well understood in NDCM, there could be important differences in optimal programming of ventricular therapies.

Monomorphic VT associated with chronic ischemic heart disease is most commonly due to classic reentry in regions of scar interlacing with viable myocardium and is therefore highly susceptible to termination by critically

time pacing stimulation (ATP). Numerous older studies have consistently demonstrated that ATP can reliably terminate ~85–90% of slow VT (cycle lengths [CL] <300–320 ms) with a low risk of acceleration (1–5%) [60]. More recently, similar high success and low acceleration rates for fast VT (CL 320–240 ms) have been demonstrated. These observations have repositioned the ICD as primarily an ATP device with defibrillation backup only as needed and has been recently reviewed [61]. However, the majority of these studies have been performed in patients with ischemic heart disease.

Sustained monomorphic VT due to classic reentry is relatively rare in NDCM. Autopsy series have demonstrated visually evident left ventricular scars in 14% of 152 patients with NDCM [62]. The degree of replacement fibrosis has been shown to correlate with clinical severity of heart failure [63]. Interlacing of replacement fibrosis and viable myocardium can produce fractionated, broad, low amplitude, endocardial electrograms compatible with slow conduction zones as seen in chronic myocardial infarction [64]. These are capable of sustaining reentry [65]. However, most patients with NDCM have relatively normal endocardial activation and electrograms, not significantly different than normal individuals. The most common abnormality in endocardial electrograms is a prolonged duration. Only those rare patients with nonischemic dilated cardiomyopathy and sustained monomorphic VT have fractionated endocardial electrograms [66].

Experimental evidence shows that other mechanisms of VT are important in NDCM. Ventricular premature beats and nonsustained VT induced by programmed stimulation were found to arise primarily in the subendocardium by a focal mechanism without evidence of macroreentry [67]. These sites of initiation were consistently distant from zones of functional conduction delay and block that did not contribute to VT initiation. The histologic appearance of the sites of focal initiation were undistinguished from other sites throughout the explanted heart. The investigators hypothesized that focal initiation of VT could be due to triggered activity (delayed afterdepolarizations [DADs] or early afterdepolarizations [EADs]) citing the observation that triggered activity can be initiated in the myocardium of NDCM [68]. Changes at the cellular level in end-stage heart failure might favor triggered activity [68]. Prolongation of action potential duration and alterations in cellular calcium levels could contribute to EADs and DADs, respectively [68].

These fundamental differences in arrhythmic substrate between ischemic and nonischemic DCM may have important implications for programming optimal ventricular therapies and patient acceptance of ICD therapy. Because non-reentrant VT would not be expected to respond to ATP, the high success rates for painless termination of VT in ischemic heart disease may not be reproduced in NDCM. Although ICD therapy is generally well tolerated by most patients, approximately 30–50% experience some degree of psychological distress after implantation [69]. One of the principal limitations of ICD therapy is the discomfort associated with high-voltage shocks. Several studies have noted a direct correlation between poor quality of life (QoL) scores and the experience of ICD shocks [70, 71, 72, 73]. It has recently been shown that reduction in painful shocks with ATP may improve QoL [74] and may extend ICD pulse generator longevity. Whether these benefits of painless ventricular therapy are transferable to NDCM patients who receive CRTD has not been demonstrated.

Ventricular Therapies in Primary Versus Secondary Prevention Patients

In general, secondary prevention patients have a greater frequency of spontaneous ventricular arrhythmia than primary prevention patients. Several retrospective analyses have preliminarily addressed these issues. It is important to note there have been no prospective, randomized clinical trials of specific empiric programming of ventricular therapies by ICD indication or substrate.

Wilkoff et al. [75] analyzed the frequency and characteristics of spontaneous VT and VF between patients with a primary versus secondary prevention indication for ICD therapy in the MIRACLE ICD study of CRTD. Primary prevention patients had a lower frequency of appropriate VT and VF episodes (0.12 vs. 0.53 episodes/month) at significantly faster CLs (303 ± 53 ms vs. 367 ± 54 ms, $p < 0.0001$). Primary prevention patients also had a significantly higher percentage of device-classified VF (40% vs. 14%, $p < 0.0001$). The absolute rate of inappropriate detections in the primary prevention group was lower but constituted a much higher portion of all episodes for that group (32% vs. 14% for the secondary prevention group). Most inappropriate detections in the primary prevention group were due to rapidly conducted SVT with 1:1 AV relationship (sinus tachycardia or atrial tachycardia) and were treated as VT.

Russo et al. [76] examined spontaneous therapies in primary prevention patients. Over 21 ± 18 months, 23% patients had appropriate therapies and 14% had inappropriate therapies for SVT. Clinical VT rates were higher than SVT rates (211 ± 38 bpm vs. 179 ± 14 bpm). Only 10% of the patients with appropriate therapies had VT rates <190 bpm. The authors concluded that although there was some overlap in VT and SVT rates, VT rates less than 190 bpm were uncommon and avoidance of programming to nominal VF detection rates may reduce inappropriate shocks for SVT.

These preliminary observations provoke examination of tachyarrhythmia detection and therapy programming based on indication for ICD therapy. "Overtreatment" in primary prevention patients is an important concern, potentially at the cost of spurious therapies for inappropriate ventricular detections due to SVT. A more detailed analysis of the incidence of appropriate therapies for specific ventricular rhythms, inappropriate ventricular therapies, quality of life, and mortality was recently performed in the PainFREE RX II Trial study population [77]. Appropriate therapies for specific ventricular rhythms and inappropriate therapies for SVT, quality of life, and mortality were compared in 582 patients (primary prevention = 248; second prevention= 334). ICDs were identically programmed with three zones (VT <188 bpm; FVT = 188–250 bpm; VF >250 bpm) but randomized to ATP or shock as initial therapy for FVT. All treated episodes with electrograms were adjudicated. Primary prevention patients had lower ejection fractions and were more likely to have ischemic cardiomyopathy, however, beta-blockers, antiarrhythmic drugs, and follow-up duration were similar. Over 11 ± 3 months, 1563 treated episodes were classified as 740 VT, 350 FVT, 77 VF, and 396 SVT. The distribution of VT, FVT, and VF was not different between primary and secondary prevention (VT 52% vs. 54%; FVT 35% vs. 35%; VF 14% vs. 10%). More secondary prevention patients had appropriate therapies (26% vs. 18%, $p = 0.02$), but among these patients, median episodes/patient was similar. Inappropriate therapies occurred in 15% of both groups and

accounted for similar proportions of all detected and treated episodes. Quality of life improved modestly in both groups, and mortality was similar.

Because the relative frequency of specific ventricular rhythms is similar between primary and secondary prevention patients, an equivalent efficacy of ATP could be anticipated assuming similar arrhythmia substrate (i.e., reentrant VT). Therefore, it is reasonable to conclude that if any VT therapy is to be prescribed in either group, it should include ATP with the expectation that 70–90% of episodes will be painlessly terminated. The more difficult issue is whether *any* slow VT therapy should be prescribed in primary prevention patients, particularly those in who programmed stimulation has not been performed. Elimination of slow VT detection might reduce spurious therapies for some specific SVTs (such as sinus tachycardia) but might not be as effective for others, such as atrial fibrillation with a rapid ventricular response. The zeal for reducing the probability of spurious therapies by eliminating a slow VT detection zone must be balanced against the risk of failing to treat unanticipated VT. This issue was indirectly addressed by a retrospective study by Bansch et al. [78]. The risk of VT above the VT detection interval ranged between 2.7% and 3.5% per year during the first 4 years after ICD implantation. Fifty-four (88.5%) of the VT episodes above the VT detection interval were associated with significant symptoms, and 10% of patients had to be resuscitated. Risk factors for VT above the initial VT detection interval were heart failure, lower EF, spontaneous or inducible monomorphic VT, and use of class III antiarrhythmic drugs. The risk of recurrent VT above the VT detection interval was 11.8%, 12.5%, and 26.6% during the first, second, and third year after the first occurrence above the VT detection interval. This suggests that elimination of a slow VT zone in some patients will result in clinically consequential undertreatment of slow VT.

RV only, LV only, or Biventricular ATP in CRTD

An interesting recent development in the clinical application of ATP is stimulation site of origin. It is important to note that the pathophysiologic mechanism of reentrant VT is not dependent on, or influenced by, site of origin of the VT circuit. From a practical perspective, site of origin might be very important because the majority of VT circuits arise in the left ventricle, and pacing stimuli are conventionally delivered from the right ventricular apex. Because distance and conduction time between stimulation site and site of origin affect the ability of pacing stimuli to interact with the reentrant circuit, ATP delivered from the left ventricular pacing lead or biventricular pacing leads in CRTD might improve efficacy compared with right ventricular ATP.

Scientific evidence regarding the relative differences between RV, LV, or biventricular ATP for terminating monomorphic VT is limited. In the Ventak CHF/CONTAK CD study [79], all ATP among patients randomized to CRT was delivered simultaneously from right ventricle and left ventricle (biventricular ATP). Monomorphic VT was successfully terminated in 927 of 1053 (88%) episodes. Though this is in alignment with success rates for ATP delivered from the RV apex in other studies [60,80,81,82,83,84,85,86,87], no comparison was made between biventricular ATP and RV only ATP (i.e., patients randomized to no CRT).

The relative efficacy of right ventricular versus biventricular ATP was evaluated in the InSync ICD OUS (Outside United States) Study [88]. ATP

termination success was 2.4 times greater with biventricular versus right ventricular ATP and appeared to be associated with fewer accelerations for both slow VT and fast VT. A similar result was observed in the MIRACLE ICD study that randomized RV versus biventricular ATP for monomorphic VT induced during implantation. Biventricular ATP had a higher efficacy than RV ATP (622/658 [95%] versus 297/336 [88%] episodes, respectively, $p < 0.001$). A preliminary report from the VENTAK CHF/CONTAK CD study also showed that biventricular ATP was more successful in patients randomized to CRT pacing therapy [89]. This effect was influenced by left ventricular pacing lead location (improving in lateral locations, worsening in anterior locations) and improved over time in the patients who were receiving CRT.

These data are insufficient to support definitive conclusions regarding the role of alternate site ATP for terminating VT. Due to technical limitations, the CRTD ICDs in both studies were only capable of right ventricular or biventricular stimulation and therefore provide no insights on a possible role for isolated left ventricular stimulation. From a theoretical perspective, it is not immediately obvious that left ventricular stimulation should improve ATP success in coronary artery disease, as many reentrant VT circuits arise in the interventricular septum, closer to a RV stimulation site than a left ventricular free wall stimulation site. Conduction delay out of left ventricular stimulation sites due to interposed infarction and fibrosis might modify any advantage related to proximity to site of VT origin, and this effect may be different in the right ventricle. How these and other factors might influence the relative efficacy of left ventricular ATP is unknown.

Summary of Ventricular Therapy Programming in CRTD

Antitachycardia pacing reliably terminates ~85–90% of slow VT (cycle lengths [CL] <300–320 ms) with a low risk of acceleration (1–5%). Similar high success and low acceleration rates for fast VT (CL 320–240 ms) have recently been demonstrated. These results are probably consistent across different substrates (ischemic versus nonischemic DCM) when the common mechanism of VT is reentry. Therefore, ATP should be routinely applied in CRTD regardless of substrate.

Some general recommendations on programming ATP schemes are possible. For VT CL >300–330 ms, burst and ramp pacing are equivalently effective for terminating VT and equivalently low risk for causing acceleration. For VT CL <300–330 ms, burst pacing is more effective and less likely to result in acceleration than ramp pacing. In either case, the risk of acceleration is inversely related to the VT CL. "Less aggressive" burst stimulation (e.g., 91% of VT CL vs. 81% of VT CL) is more effective and causes less acceleration, especially for fast VT (CL <320 ms) [90]. "Tailoring" of ATP to specific induced VTs is not necessary in most situations.

Loss of CRT: Causes and Corrective Actions

Optimal CRT operation requires continuous delivery of ventricular pacing. In practical experience, 100% ventricular pacing is difficult to achieve. A reasonable goal is 90–95% cumulative ventricular pacing with verified left

ventricular capture. A retrospective analysis of the VENTAK CHF/CONTAK CD Biventricular Pacing Study revealed that CRT is interrupted transiently in 36% if patients and permanently in 5% within 2 years of follow-up and the causes are diverse [91]. Restoration of CRT can usually be accomplished noninvasively and less commonly requires surgical intervention.

Loss of CRT Related to Pacing Operation

Obviously, programming parameters during CRT operation should reflect the goal of continuous ventricular pacing. Therefore, any parameter choice that might reduce the frequency of ventricular pacing should be avoided. The consequence of programmed parameters on continuous delivery of CRT is influenced by the patient's AV conduction status. The majority of patients who receive CRT have reliable AV conduction, and therefore any programming choice that permits the emergence of native ventricular activation will reduce delivery of CRT. In dual-chamber CRT systems, examples include pacing modes that do not synchronize ventricular pacing to atrial activity (such as DDI or VVI), inappropriately long AV delays or use of automatic AV interval extension, or any parameter that compromises continuous atrial tracking (true undersensing or pseudo-undersensing due to a long postventricular atrial refractory period [PVARP], automatic PVARP extensions, or a low upper tracking rate). In single-chamber CRT systems among patients with permanent AF, the lower rate should be programmed to continuously exceed the spontaneous ventricular rate. The absence of AV conduction renders loss of CRT due to poor programming choices unlikely because ventricular pacing cannot be inadvertently minimized by competition with native ventricular activation; however, considerations regarding optimal AV delay still apply. Even when these recommendations are implemented, loss of CRT can occur due to the complex interplay between spontaneous electrical activity and inviolable elements of timing cycle operation.

Pseudo-atrial Undersensing

A reduction in ventricular pacing due to loss of atrial tracking at high sinus rates (*pseudo-atrial undersensing*) is common. In this circumstance, high sinus rates and first-degree AV block (AVB), which are common in heart failure patients, displace the P-wave into the PVARP resulting in simultaneous loss of atrial tracking and synchronous ventricular pacing. This situation is commonly triggered by automatic PVARP extensions after a premature ventricular contraction (PVC) or other circumstances intended to prevent pacemaker-mediated tachycardia [92]. Spontaneous AV conduction occurs in the form of a preempted upper rate Wenckebach response (Fig. 21.32).

Though not required for pseudo-atrial undersensing, double counting (see below) of the native ventricular electrogram often participates in the initiation and maintenance of the phenomenon in nondedicated (Y-adaptors) or first-generation dual cathodal CRTP/CRTD systems where pacing and sensing from the right ventricle and left ventricle occurs simultaneously (Fig. 21.33). When spontaneous conduction with LBBB (or any form of ventricular conduction delay) emerges, the LV EGM may be sensed sometime after detection of the RV EGM if the LV signal extends beyond the relatively short ventricular blanking period initiated by RV sensing. The LV signal

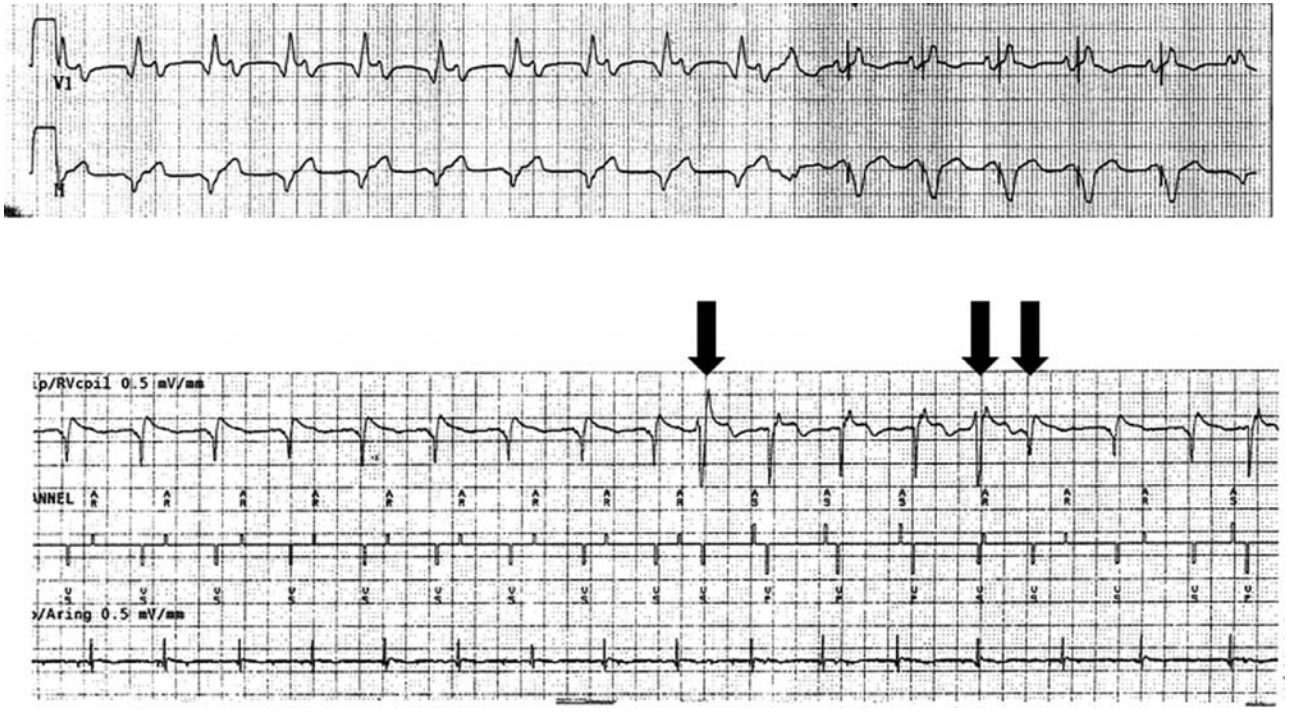


Fig. 21.32 Loss of CRT due to pseudo-atrial undersensing. *Top:* Telemetry strip. Note sinus tachycardia with marked first degree AV block (PR 400 ms) and loss of atrial synchronous biventricular pacing on left. Note restoration of atrial synchronous biventricular pacing after PVC (*arrow*) on right. *Bottom:* Same patient. Sinus rate exceeds the programmed upper rate limit, displacing P-waves into the PVARP (marked as AR). Spontaneous AV conduction occurs in the form of a preempted Wenckebach upper rate response. First PVC resets PVARP and restores atrial tracking. Second PVC (*arrow*) occurs coincident with sinus event, which falls into the post-ventricular atrial blanking period (PVAB). Third PVC (*arrow*) resets PVARP and reinitiates pseudo-atrial undersensing. Atrial tracking is restored when sinus rate slows slightly at the end of the strip.

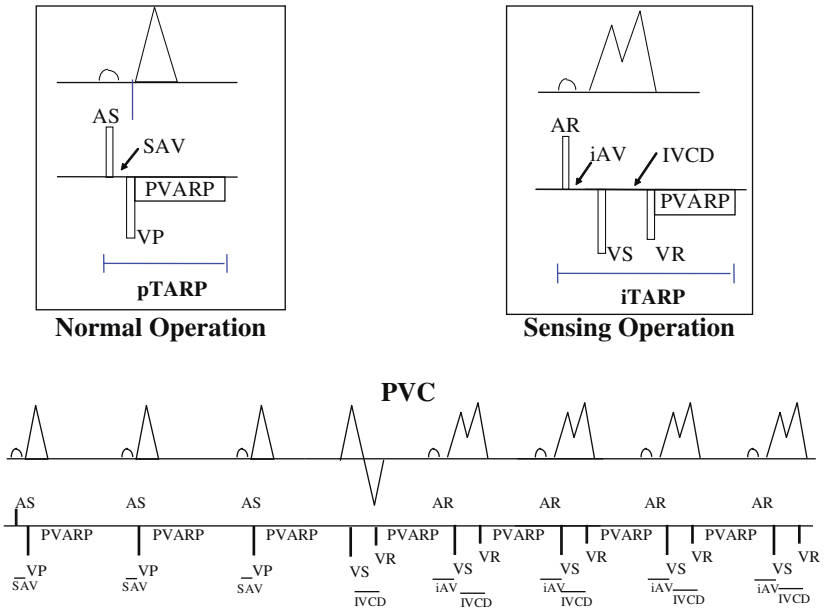


Fig. 21.33 Loss of CRT due to pseudo-atrial undersensing and ventricular double counting with implied total atrial refractory period. Premature ventricular contraction (PVC) is double counted; second component resets the PVARP, which initiates pseudo-atrial sensing. Loss of CRT results in emergence of spontaneous AV conduction. Double counting of the native ventricular electrogram continuously resets the PVARP, perpetuating pseudo-atrial sensing. Implied total atrial refractory period = SAV + PVARP + interventricular conduction delay.

continuously resets the PVARP resulting in an "implied total atrial refractory period (iTARP)" conflict and maintenance of pseudo-atrial undersensing.

Failure to deliver CRT at high sinus rates can be minimized by shortening the PVARP, increasing the upper tracking limit, and deactivating the PVC response in the DDD mode. Newer CRT systems minimize ventricular double counting by employing an interventricular ventricular refractory period (IVRP). Ventricular sensed events (i.e., LV sensing) during the IVRP do not reset the PVARP and eliminates the "implied TARP" conflict (Fig. 21.34). Another method for dealing with disruptions to CRT delivery when PVCs cause the following atrial events to fall into the PVARP is Atrial Tracking Recovery (Medtronic, Inc., Minneapolis, MN, USA) (Figs. 21.35–21.37). Atrial Tracking Recovery operates in the DDD/R mode when a mode switch episode is not in effect. Under certain conditions, Atrial Tracking Recovery temporarily shortens PVARP to reduce the intrinsic TARP. The device monitors for eight consecutive pacing cycles where all the following occur: (1) the current ventricular event is sensed, not paced, (2) the last ventricular interval contains exactly one refractory atrial event, (3) the last two atrial intervals vary from each other by less than 50 ms, (4) the last atrial interval is longer than the upper tracking rate (UTR) interval by at least 50 ms, (5) the last atrial interval is greater than current SAV plus current PVARP, (6) the last VS-AR interval (from the previous ventricular event to the atrial refractory event) is greater than Post Ventricular Atrial Blanking (PVAB).

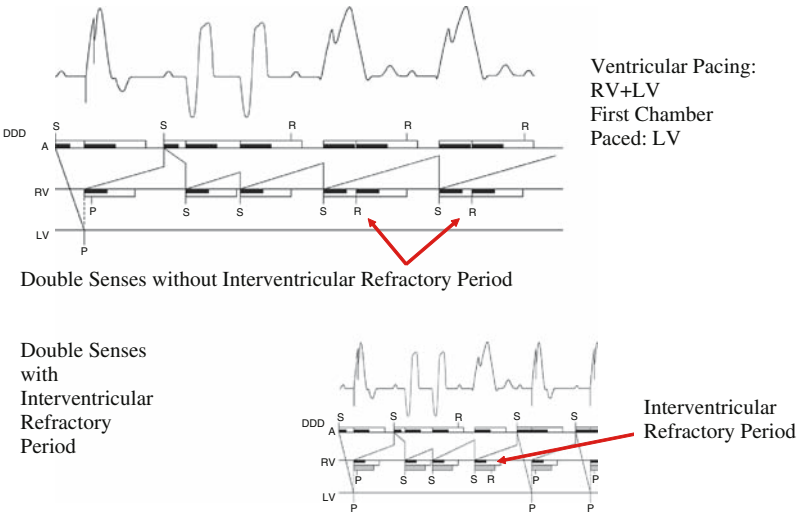


Fig. 21.34 Role of interventricular refractory period to eliminate implied total atrial refractory period and reduce loss of CRT due to pseudo-atrial undersensing.

To start or continue an ATR intervention, the device sets a temporary truncated PVARP equal to the last VS-AR interval minus 50 ms. If this computed value is shorter than the programmed PVAB, then the PVAB value is used. On subsequent pacing cycles during ATR intervention, the device recalculates the temporary PVARP. ATR intervention ends when the

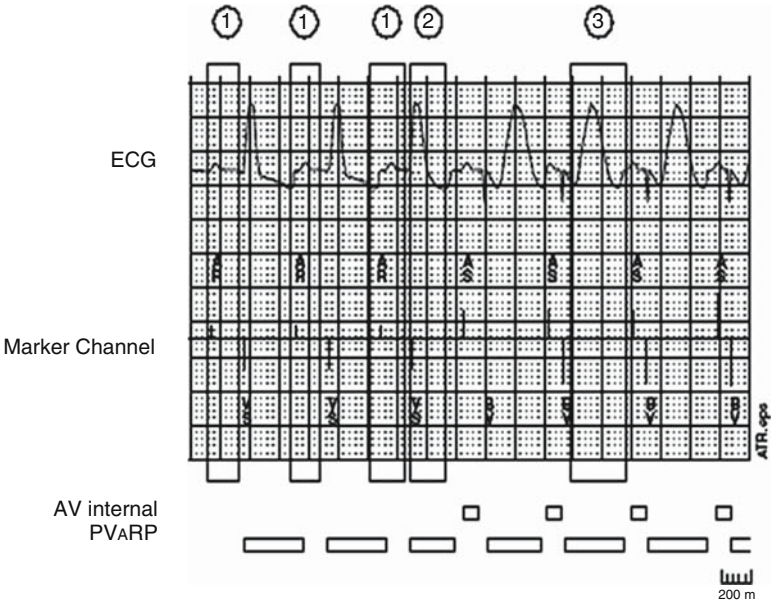


Fig. 21.35 Atrial Tracking Recovery. **(1)** Atrial events occur during PVARP and are not tracked. **(2)** After eight qualifying AR-VS cycles, Atrial Tracking Recovery intervenes to break the cycle. PVARP is shortened. **(3)** The intervention continues until proper AV tracking at the programmed SAV resumes.

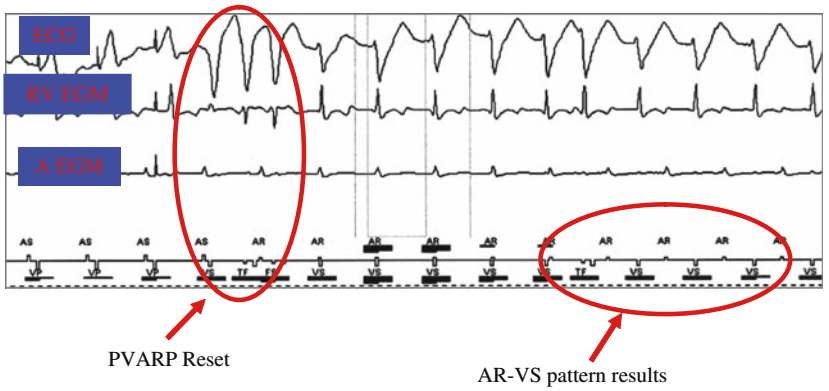


Fig. 21.36 Ventricular premature beats causing loss of CRT due to implied total atrial refractory period and pseudo-atrial undersensing.

ventricular pace occurs at the scheduled SAV interval, or when the computed temporary PVARP is no longer shorter than the otherwise indicated PVARP. If the pacing pattern is interrupted, for example by a ventricular sensed event, the intervention aborts.

Tracking Preference is a similar but less ornate approach used in Guidant (Guidant Corporation, St. Paul, MN, USA) pulse generators (Fig. 21.38). This is designed to maintain atrial-tracked ventricular pacing in DDD(R) and VDD(R) modes at high sinus rates. Tracking Preference temporarily shortens the PVARP to reestablish atrial-tracked ventricular pacing inappropriately lost due to atrial events occurring in PVARP (pseudo-atrial undersensing).

Atrial Oversensing

Automatic mode switching is intended to prevent undesirable rapid ventricular pacing due to tracking of atrial tachyarrhythmias during DDD operation. Detection of atrial tachyarrhythmias results in reversion to a nontracking mode (DDI or VDI). Spurious mode switching is a common problem and can result in loss of atrial synchronous ventricular pacing during CRT. The dominant cause of spurious mode switching is oversensing of far-field R-waves (FFRW) [93,94,95,96,97]. This can be recognized on stored marker channels or EGMs

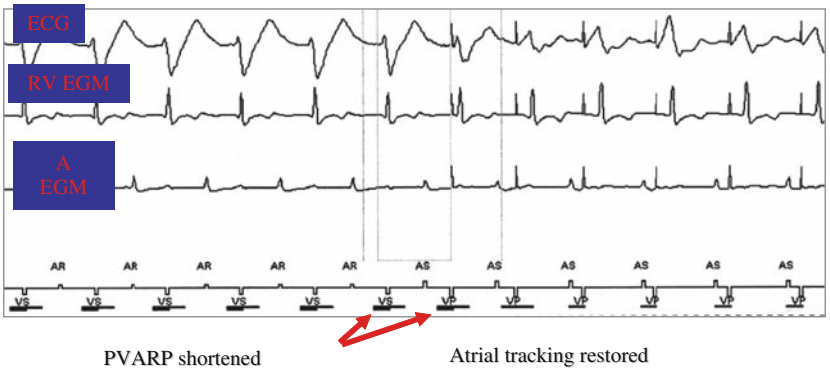


Fig. 21.37 Atrial Tracking Recovery operation.

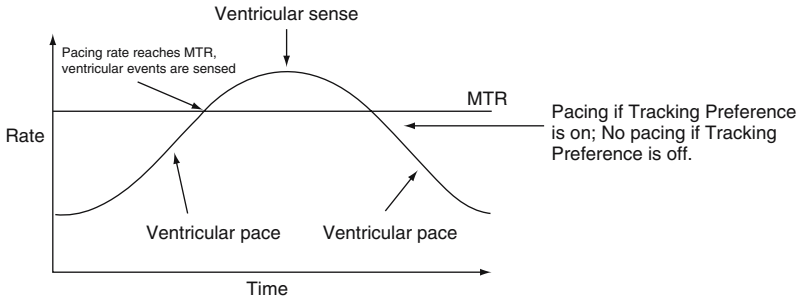


Fig. 21.38 Atrial Tracking Preference (Guidant).

by an alternating pattern of atrial cycle lengths with one signal timed close to the ventricular EGM. Less common causes of spurious mode switching include "near-field" or "early" R-wave oversensing (atrial R-wave sensing prior to arrival of the depolarization wavefront at the ventricular pacing lead position) and oversensing of the paced atrial depolarization during the AV interval [97, 98]. Spurious mode switching can usually be eliminated by the use of bipolar atrial pacing leads, extending the postventricular atrial blanking period (PVAB) or reducing atrial sensitivity so as to reject far-field signals without compromising atrial sensing.

Loss of CRT Due to Prevention of Pacing on the T-wave

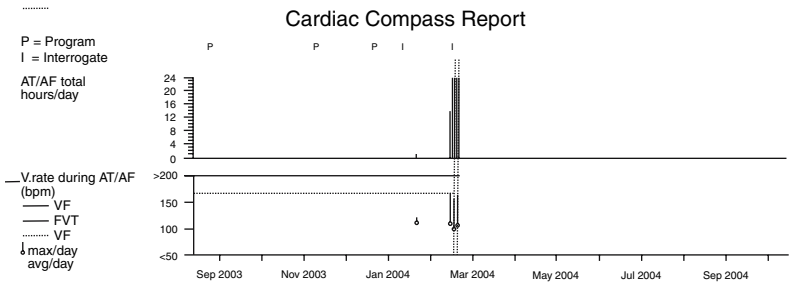
Theoretically, conduction delay could prevent a PVC initiated in the left ventricle from reaching the RV electrode (univentricular sensing) and inhibiting the scheduled biventricular pace triggered by a sensed (or paced) atrial event. In this situation, lack of LV sensing could result in competitive ventricular pacing outside the absolute myocardial refractory period. To prevent competitive pacing during the LV vulnerable period (including the T-wave), some Guidant CRTD systems incorporate a Left Ventricular Protection Period (LVPP). The LVPP is defined as the period after a left ventricular event, either paced or sensed when LV pacing is inhibited, and is programmable between 300 and 500 ms. The LVPP reduces the maximum LV pacing rate and theoretically could disrupt CRT by preventing LV stimulation when preceded by RV stimulation, depending on the programmed interventricular delay and the conduction time from the RV to LV electrode.

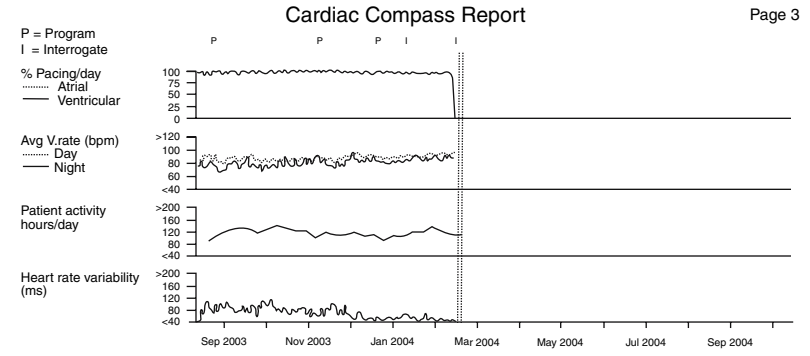
Loss of CRT Due to Competition with Native Ventricular Activation

Any situation that permits competition between the delivery of continuous ventricular pacing and native ventricular activation will degrade CRT efficacy. This is far more likely to occur among patients with intact AV conduction.

Atrial Tachyarrhythmias with Rapid Ventricular Conduction

Atrial tachyarrhythmias are the common cause of loss of CRT, accounting for 18% of all therapy interruptions in one study [91]. Paroxysmal AF in patients with dual-chamber CRT systems results in appropriate mode switching and loss of atrial synchronous ventricular pacing (see above). In the absence of mode switching, native ventricular activation due to rapidly conducted





Pacing	Feb 19, 2004	Aug 14, 2003	
AS-VS	99.1 %	4.3 %	4.3 %
AS-VP	0.7 %	95.6 %	95.6 %
AP-VS	<0.1 %	<0.1 %	<0.1 %
AP-VS	0.2 %	0.1 %	0.1 %
Additional Counters			
Single PVCs	880	104346	104346
Runs of PVCs	104	16684	16684
V.Rate Stabilization Pacos	0	0	0
Runs of V.Rate Stab. Pacos	0	0	0

Fig. 21.39 Loss of CRT due to atrial fibrillation. Note high % ASVP counter prior to onset of atrial fibrillation. Onset of atrial fibrillation with rapid AV conduction results in sudden loss of CRT, indicated by high %ASVS counter.

paroxysmal AF may compete with continuous ventricular pacing (Figs. 21.39 and 21.40). Management should focus on pharmacologic suppression of AF and control of the conducted ventricular response.

The importance of rate control and regularization of the ventricular response during AF should not be underestimated. Historically, symptoms during AF have been attributed to a combination of loss of AV synchrony and rapid ventricular response (RVR), which may result in significant reductions in cardiac output. More recently, the independent effect of ventricular cycle length irregularity on adverse hemodynamic performance during AF has been recognized [99, 100, 101]. One study demonstrated acute improvement in hemodynamic performance and long-term improvement in symptoms and QoL among patients with chronic AF and a controlled ventricular response after AV junction ablation and VVIR pacemaker implantation [99].

These benefits were attributed to an independent effect of ventricular rate regularization, because loss of AV synchrony was constant and rapid ventricular rates were excluded by study design. These results contribute to the interpretation of prior studies that reported DDDR pacing with mode

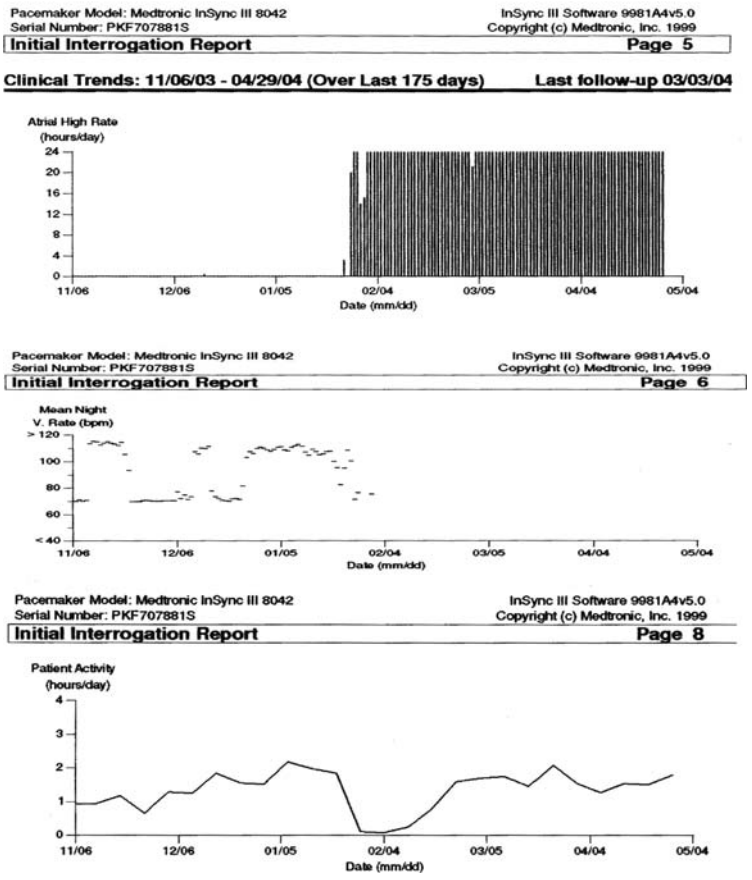


Fig. 21.40 Loss of CRT due to atrial fibrillation. *Top:* Onset of persistent AF in late January 2004. Note histogram showing 24 h/day of AF. *Middle:* Increase in mean ventricular rate at night corresponding with onset of AF. *Bottom:* Abrupt decline in patient activity hours/day corresponding with onset of persistent AF.

switching is preferred to VVIR pacing among patients who have undergone AV junction ablation for uncontrollable ventricular response during paroxysmal AF [102,103,104,105]. Such patients are rendered incapable of a rapid ventricular response during paroxysmal AF via mode switching; therefore, the symptomatic benefits are not surprising.

The importance of rate control and regularization of the ventricular response during AF to optimize CRT response should not be underestimated. For example, the relatively neutral effect of biventricular versus RVA pacing immediately after AV junction ablation among patients with systolic heart failure suggests that the benefits of rate control in AF are so large that it conceals the effect of asynchronous ventricular activation [6]. In patients with permanent AF and single-chamber CRT systems, continuous delivery of ventricular pacing and optimal CRT response may require ablation of the AV junction.

Specific features of pacing operation may increase the percentage of ventricular pacing during rapidly conducted AF and thereby prevent

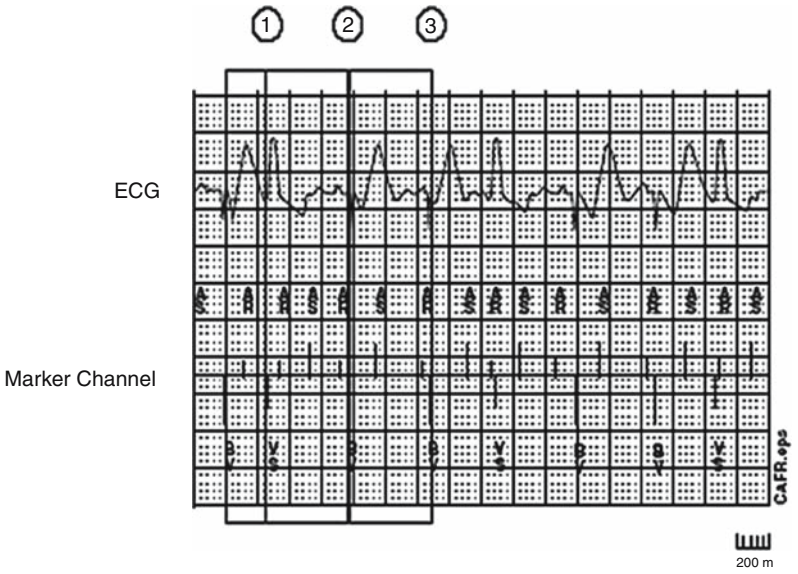


Fig. 21.41 Conducted AF Response (Medtronic). **(1)** BS-AR-VS sequence causes pacing rate to increase by 1 beat/min. **(2)** VS-BV sequence causes pacing rate to remain unchanged. **(3)** BV-BV sequence causes pacing rate to decrease by 1 beat/min.

disruptions to CRT. Conducted AF Response (Medtronic) increases the ventricular pacing rate in alignment with the native conducted ventricular response (Figs. 21.41–21.43). The intent is to regularize the ventricular rate by increasing the overall percentage of ventricular pacing while minimizing the increase in overall heart rate. This is achieved by adjusting the pacing escape interval after each ventricular event. The escape interval increases or decreases based on a contextual analysis of the preceding events. For example, a BV-AR-VS sequence will increment the pacing rate by 1 beat/min, whereas a BV-BV sequence will decrement the pacing rate by 1 beat/min. The result is a higher percentage of ventricular pacing at an average rate that closely matches the patient's own ventricular response. The maximum rate for Conducted AF Response pacing is programmable. The minimum rate derives from the otherwise-indicated (sensor rate, mode switch, or lower rate) pacing interval. When the otherwise-indicated pacing rate is faster than the programmed maximum rate, this feature is suspended and the device operates at the otherwise-indicated pacing rate. The use of Conducted AF Response necessitates interactions with other device operations. For example, in DDD and DDDR modes, Ventricular Rate Stabilization and Conducted AF Response cannot operate at the same time. When both are enabled, VRS operates only when the device is not mode switched. Conducted AF Response operates only in nontracking modes. Therefore, when DDD or DDDR mode is programmed, Conducted AF Response operates only during a mode switch. Conducted AF Response is suspended during automatic tachyarrhythmia therapies, arrhythmia inductions, manual therapies, and emergency fixed burst, cardioversion, and defibrillation.

Ventricular Rate Regulation (VRR; Guidant) is designed to reduce V-V cycle length variability during conducted atrial arrhythmias by moderating the

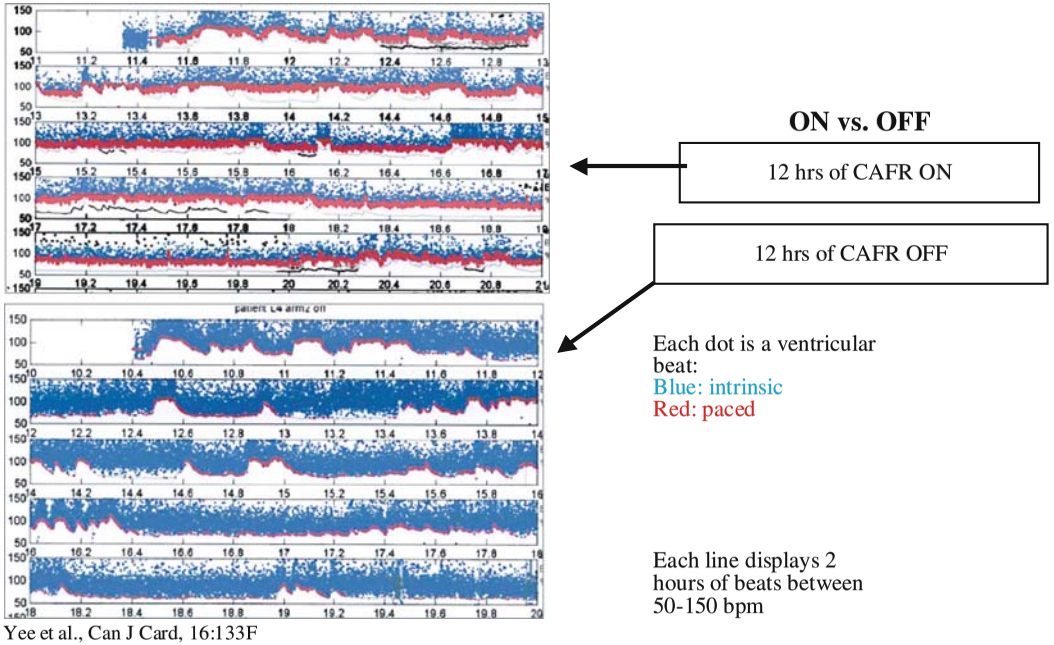


Fig. 21.42 Conducted AF Response (Medtronic). Plot of ventricular beats derived from Holter monitor of a patient with permanent AF. Top four lines show effect of CAFR therapy; bottom four lines show VVIR pacing (no CAFR therapy). Ventricular paced beats are shown in red; ventricular sensed beats in blue. Note the greater amount (and higher rate) of pacing (red dots) but also the apparent decrease in fast ventricular beats (blue dots) during CAFR operation. (From Yee et al. Can J Cardiol 16:133F.)

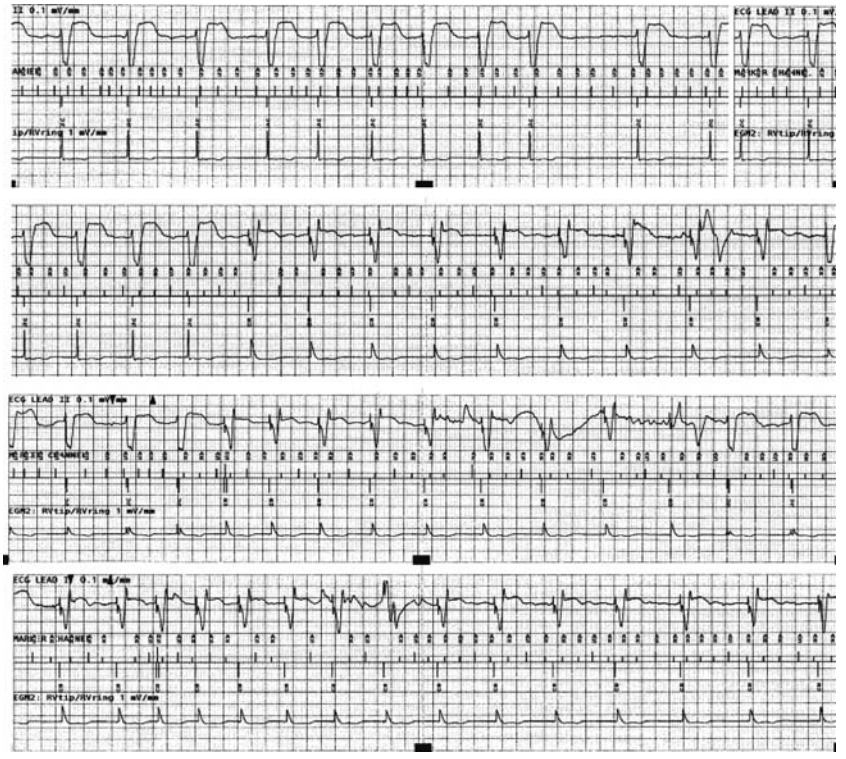


Fig. 21.43 Effects of Ventricular Sense Response and Conducted AF Response on ventricular pacing during AF with intact AV conduction. (**A**) Programmed mode is VVI 30 bpm. Note AF with intact AV conduction and absence of ventricular pacing. (**B**) Programmed mode is VVI 30 bpm with Ventricular Sense Response ON. Note delivery of biventricular pacing without any increase in ventricular rate. (**C**) Programmed mode is DDD 30 bpm with Conducted AF Response ON. Note increase in ventricular pacing rate immediately after mode switch (MS marker) occurs, which initiates Conducted AF Response operation. (**D**) Programmed mode is DDD 30 bpm with Ventricular Sense Response and Conducted AF Response ON. Note increase in ventricular pacing rate immediately after mode switch (MS marker) occurs, which initiates Conducted AF Response operation and also Ventricular Sense Response pacing during PVC (eighth complex from the left).

ventricular pacing rate based on a previous V-V average (Figs. 21.44–21.46). VRR provides ventricular regulation during conducted atrial arrhythmias, whereas Rate Smoothing (Guidant) is typically more useful for reducing pauses after PVCs. VRR operates in the DDD/R mode only during an AT/AF mode switch episode but is available all the time in the single-chamber VVI/R modes.

Unlike Rate Smoothing where changes are based on the most recent V-V interval, VRR uses a weighted ventricular average based on cycle lengths during the mode switch episode. This weighted average is made up of two parts: (1) the most recent V-V interval multiplied by 1.1 (if the most recent ventricular event was sensed) or 1.2 (if the event was paced). This calculation provides 6% of the next calculated VRR pacing rate value. (2) The calculated VRR interval value just prior to the most recent V event. This calculation provides 94% of the next calculated VRR pacing rate value. Therefore, the

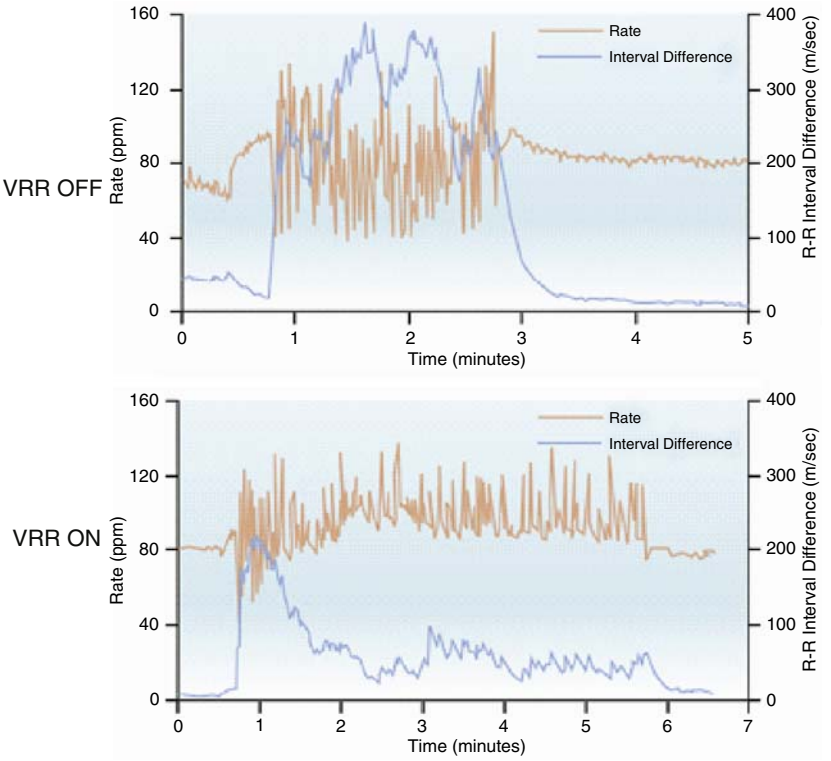


Fig. 21.44 Ventricular Rate Regularization (Guidant). Note reduction in ventricular interval variation but increase in pacing rate during VRR operation ON (*bottom*) versus VRR operation OFF (*top*).

next VRR pacing rate interval = 0.07 (recent V-V interval × 1.2 or 1.1) + 0.93 (previous VRR interval calculation). The calculated rates based on the weighted average yields a pacing rate that still adjusts on a cycle-by-cycle basis, but in much smaller increments than observed during Rate Smoothing. The frequency of VRR pacing is directly related to ventricular cycle length variability (i.e., pacing frequency increases with ventricular cycle length variability).

The use of VRR necessitates interactions with other device operations. The maximum VRR pacing rate is programmable between pacing rate and is limited between 60 and 150 beats/min. In dual-chamber modes, Rate Smoothing is temporarily disabled when VRR is active.

Frequent Ventricular Premature Beats

Frequent VPDs may disrupt CRT. Ventricular sense response (VSR; Medtronic) is intended to provide CRT when ventricular sensing occurs. Each right ventricular sensed event triggers a pace in one or both ventricles, as programmed.

When VSR is enabled in a nontracking or single-chamber pacing mode, a sensed ventricular event triggers an immediate ventricular pace. VSR pacing is delivered in one or both ventricles, according to the programmed ventricular pacing pathway. When VSR is enabled in an atrial tracking mode, a sensed ventricular event during the AV interval triggers an immediate pacing output

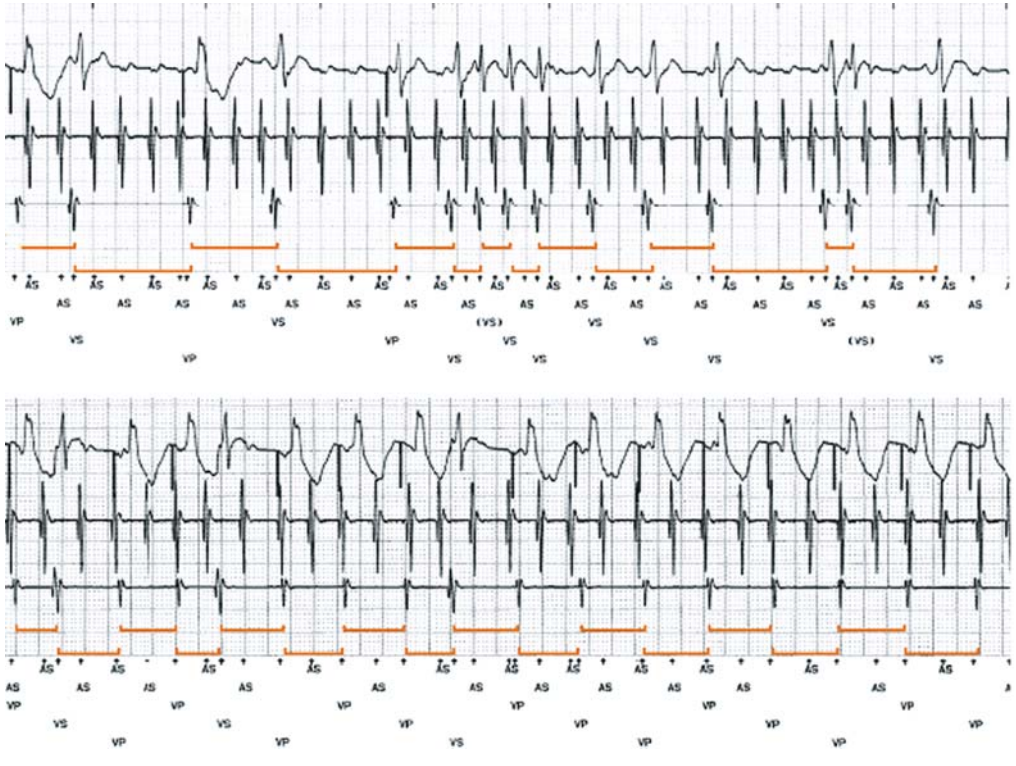
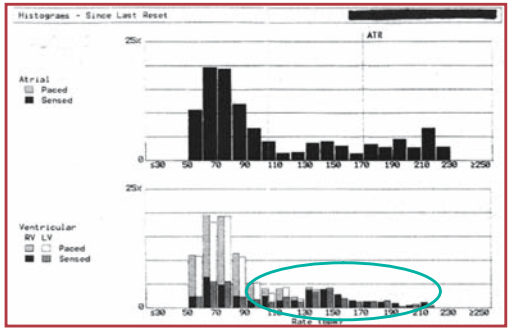


Fig. 21.45 Ventricular Rate Regularization (Guidant). *Top:* VRR OFF. Mean ventricular rate 167 ± 49 beats/min. Note wide ventricular interval variation (*horizontal bars*). *Bottom:* VRR ON. Mean ventricular rate 138 ± 37 beats/min. Note increase in ventricular pacing and reduction in ventricular interval variation (*horizontal bars*).

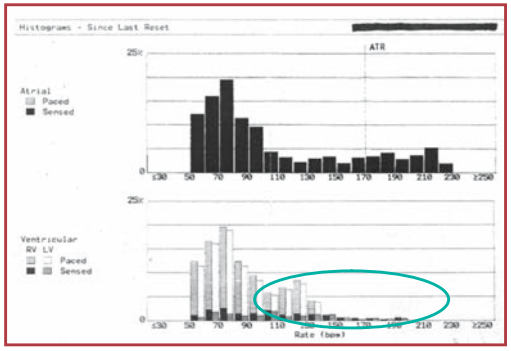
Without VRR



Previous Histograms without VRR

Right Ventricular		
Ventricular Tachy Detections		0
Right Paced	60%	780K
Tracked	63%	491K
Device Determined	37%	289K
Right Sensed	40%	520K
Left Ventricular		
Left Paced	67%	771K
Tracked	65%	501K
Device Determined	35%	270K
Left Sensed	33%	380K

With VRR



Final Histograms with VRR on at Med

Right Ventricular		
Ventricular Tachy Detections		0
Right Paced	83%	605.9K
Tracked	66%	399.9K
Device Determined	34%	206.0K
Right Sensed	17%	124.1K
Left Ventricular		
Left Paced	85%	552.5K
Tracked	67%	370.2K
Device Determined	33%	182.3K
Left Sensed	15%	97.5K

Fig. 21.46 Comparison of percent ventricular pacing histograms with VRR OFF (*top*) and VRR ON (*bottom*). VRR results in significantly higher frequency of ventricular pacing during AF with rapid ventricular conduction.

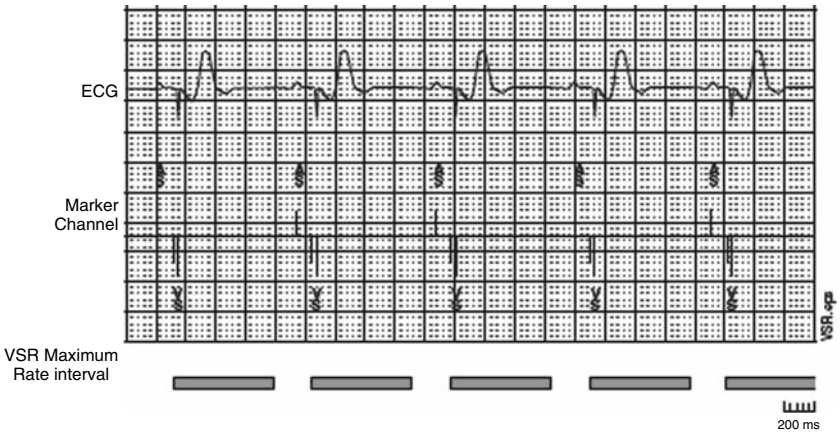


Fig. 21.47 Ventricular Sense Response (Medtronic).

to both ventricles (Fig. 21.47). The triggered output is rendered ineffectual in the chamber where sensing occurred due to ventricular refractoriness. Therefore, the triggered output "resynchronizes" ventricular activation by stimulating the chamber opposite the sensed event.

Some timing rules apply to prevent disruption of normal device operation. VSR pacing stimuli are delivered 1.25 ms after the ventricular sensed event only if the triggered pace does not violate the programmed VSR Maximum Rate. If the ventricular interval measured from the preceding ventricular event is shorter than the VSR Maximum Rate interval, no VSR pacing pulse is delivered. Ventricular sensing for VSR operation occurs via only the RV lead. Operating features of such algorithms designed to maximize cardiac resynchronization therapy such as VSR may result in pacing that occurs after QRS onset on surface ECG (Fig. 21.48).

VRS operation necessitates interactions with other device operations. When both VSR and Ventricular Safety Pacing (VSP) are enabled, VSP operation takes precedence during the VSP interval. If a ventricular event is sensed during the VSP interval, the device performs a safety pace at the end of the VSP interval. After the VSP interval expires, Ventricular Sense Response remains active for the remainder of the Paced AV interval. VSR pacing pulses are not considered in interval calculations for arrhythmia detection or pacing. VSR pacing pulses are not considered in the counts of consecutive sensed and paced events that define the beginning and end of ventricular sensing episodes storage. VSR operation is suspended during automatic tachyarrhythmia therapies, EP Study inductions, manual therapies, and emergency fixed burst, cardioversion, and defibrillation.

Loss of CRT Due to Differential LV Capture Threshold Rise

The principal limitation of the transvenous approach is that the selection of sites for pacing is entirely dictated by navigable coronary venous anatomy. A commonly encountered problem is that an apparently suitable target vein delivers the lead to a site where ventricular capture can be achieved at only very high output voltages or not at all. This presumably relates to the presence of scar on the epicardial surface of the heart underlying the target vein or

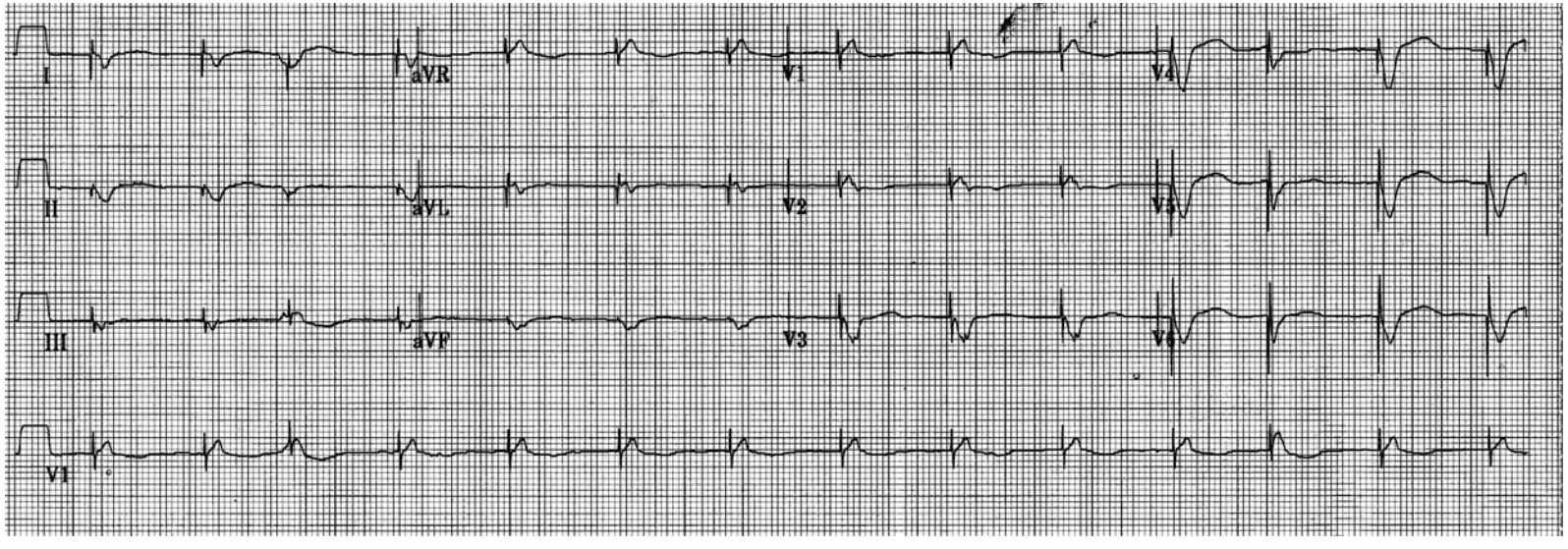


Fig. 21.48 Ventricular Sense Response operation. Third QRS complex (*arrow*) is a left ventricular PVC (note QS in lead I) that triggers VSR pacing. Note ventricular pacing stimulus is delivered nearly 100 ms after onset of QRS.

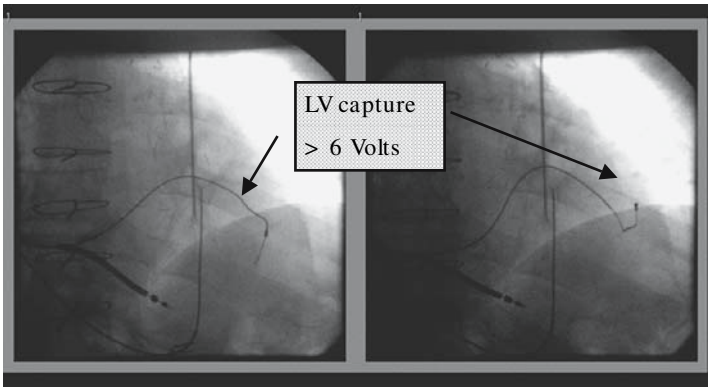


Fig. 21.49 High LV stimulation thresholds due to epicardial scar at multiple sites within distal portion of lateral coronary vein.

inadequate contact with the epicardial surface and cannot be anticipated by fluoroscopic examination a priori (Fig. 21.49). In some instances, this can be overcome by mapping a more proximal or distal site within the same vein but may require an alternate lead design to achieve mechanical stability (Fig. 21.50). If this is not successful, surgical placement of LV leads permits more detailed mapping of viable sites in the anatomic region of interest (Figs. 21.51 and 21.52).

There is relatively limited data on long-term pacing thresholds with transvenous or thoracotomy leads for LV pacing. Loss of ventricular capture occurred in 10% of patients in the VENTAK CHF/CONTAK CD study and was the second most common cause of interrupted CRT [91]. Three quarters of these cases were due to gross dislodgment of the LV lead, whereas 23% were due to chronic pacing threshold elevation that was overcome by increasing voltage output in the majority of cases. A comparison of thoracotomy and transvenous lead system performance in 87 patients who received CRTD systems between 1998 and 2001 reported no significant differences in chronic

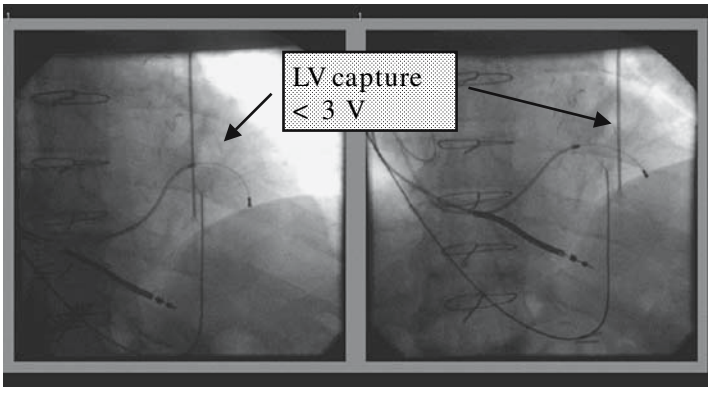


Fig. 21.50 Resolving high LV stimulation thresholds with alternate lead design and position. Same patient as in Figure 21.49. The use of a different lead design permitted more proximal positioning with the same lateral coronary vein where acceptable LV stimulation thresholds were obtained.

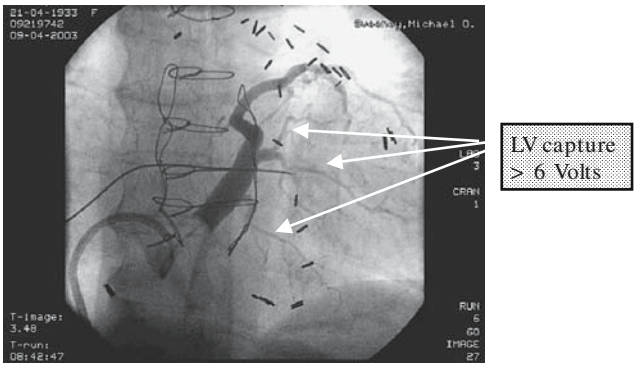


Fig. 21.51 High LV stimulation thresholds due to epicardial scar in a patient with ischemic heart disease and prior coronary bypass grafting. All coronary veins serving the posterobasal LV were mapped. LV stimulation threshold exceeded 6 V in all locations.

thresholds with either approach, which on average were between 1.5 and 2.0 V up to 30 months after implant [106] (Fig. 21.53). Similarly, there were no chronic threshold differences between transvenous lead designs (over-the-wire versus preformed shape). An interim progress report of the InSync Registry Post-Approval Study [107] in 903 patients showed similar range and stability of LV thresholds (mean 1.88 ± 1.44 V) with two different preformed transvenous lead designs at 6 months that was retained at 36 months. In this same report, epicardial voltage thresholds were similarly stable but slightly higher (2.42 ± 0.74 V) at 12 months, though data was available on a much smaller number of patients.

A particularly difficult problem with chronic epicardial leads is exit block, which in some instances results in voltage thresholds that exceed pulse generator output and results in permanent loss of CRT. Though this is infre-

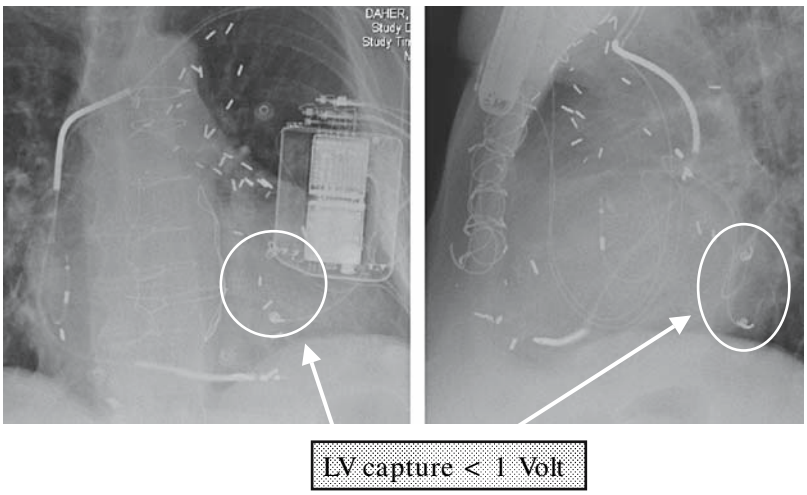


Fig. 21.52 Resolving high LV stimulation thresholds with surgical placement of epicardial leads. Same patient as in Figure 21.50. Epicardial mapping during left lateral thoracotomy permitted identification of sites with acceptable LV stimulation thresholds.

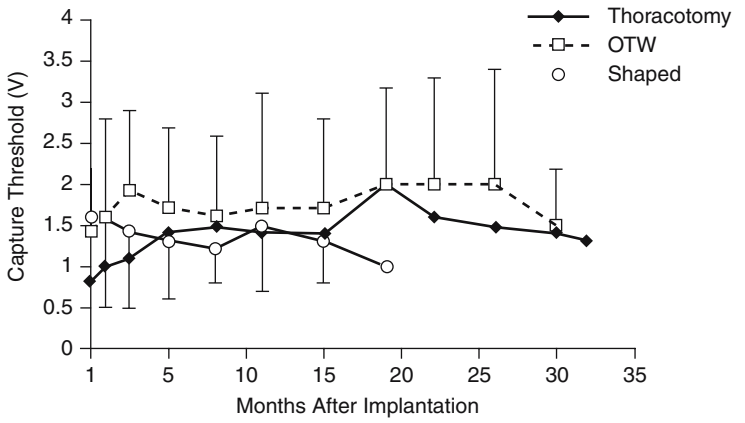


Fig. 21.53 Chronic thresholds with different LV lead designs. (From Daoud E, Kalbfleisch FJ, Hummel JD, et al. Implantation techniques and chronic lead parameters of biventricular pacing dual-chamber defibrillators. J Cardiovasc Electrophysiol 2002;13(10):964–970.)

quent, it is a devastating problem for the patient, because the epicardial approach is usually taken only when the transvenous approach fails. Several factors contribute to this problem relating to lead design and surgical technique. The most commonly used epicardial pacing lead is a fixed helix mechanism without steroid, and chronic doubling of the implant threshold is common. Furthermore, this situation is made worse by multiple applications of the helix and incautious use of suturing, which increase local tissue trauma and the subsequent inflammatory response.

Loss of CRT Due to Phrenic Nerve Stimulation

A second common problem is that the target vein delivers the lead to a site that results in phrenic nerve stimulation and diaphragmatic pacing. This can be difficult to demonstrate during implantation when the patient is supine and sedated but may be immediately evident when the patient is later active and changes body positions, even in the absence of lead dislodgment. Many experienced implanters recognize that once phrenic nerve stimulation is observed acutely (during implantation), it is almost invariably encountered during follow-up despite manipulation of output voltages, and therefore alternative site LV pacing is sought. As with high LV capture thresholds, phrenic nerve stimulation can often be overcome by repositioning the LV lead more proximally within the target vein (Fig. 21.54). Occasionally, if there is a significant differential in the capture thresholds for phrenic nerve stimulation versus LV capture, this can be overcome by manipulation of LV voltage output in CRTP or CRTD systems that permit separate RV and LV outputs. More recently, some LV leads have $\geq$2 electrodes that permit selection of specific LV sites for dual cathodal biventricular stimulation, biventricular stimulation with true bipolar LV stimulation, or true bipolar LV only univentricular stimulation. It has not been convincingly demonstrated that true bipolar LV stimulation does not seem to reliably overcome phrenic stimulation compared with dual cathodal or unipolar LV pacing. On the other hand, selecting alternate LV electrodes for dual cathodal biventricular stimulation

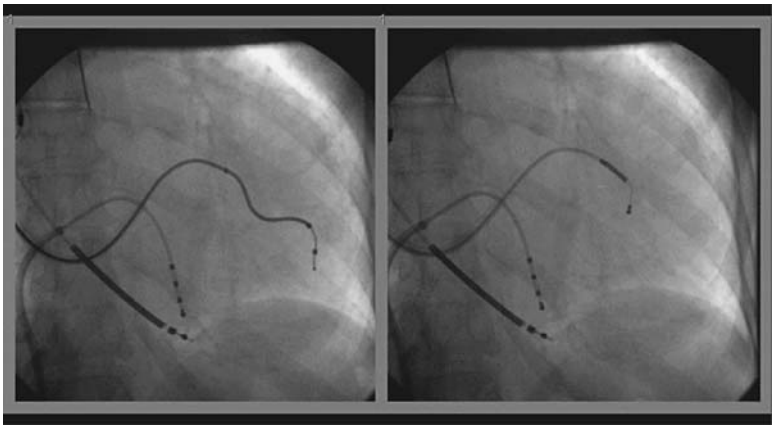


Fig. 21.54 Overcoming phrenic stimulation with alternate lead design and position. Distal locations within the lateral coronary vein resulted in phrenic nerve stimulation. The use of a different lead design permitted more proximal positioning with the same lateral coronary vein where phrenic nerve stimulation was avoided.

may occasionally overcome phrenic stimulation by altering the LV-RV pacing vector. This can be achieved noninvasively using some Guidant CRTP and CRTD generators and is referred to as "Electronic Repositioning." In either case, the problem of phrenic nerve stimulation is more reliably addressed by LV lead repositioning at implant. Chronic development of phrenic nerve stimulation results in permanent loss of CRT in about 1–2% of patients [91].

Loss of CRT Due to Lead Dislodgment

Acute dislodgment of right atrial and right ventricular electrodes is uncommon, particularly with active fixation leads. The incidence of LV lead dislodgment is considerably higher and has a reported incidence of 5–10% in larger studies [48, 53, 108]. This relates to implanter experience and other technical factors such as the lack of fixation mechanisms and stresses placed on the proximal portion of the lead at the junction of the right atrium and CS ostium. Lead dislodgments are readily identified by chest radiography but usually suspected on the basis of device interrogation that discloses a significant decline in local signal amplitude and/or change in pacing capture threshold. Typically, right atrial leads dislodge onto the floor of the right atrium and right ventricular leads dislodge toward the inflow of the right ventricular. LV leads typically dislodge into the main body of the coronary sinus and less commonly into the right atrium.

Ventricular Oversensing

Inappropriate Ventricular Therapies and Misclassification of True Ventricular Rhythms Due to Ventricular Double Counting

Conventional pacemaker and ICD generators have been adapted for atrial-synchronous biventricular pacing. The single ventricular output must be divided to provide simultaneous stimulation of the right ventricle and left ventricle (dual cathodal system with parallel outputs). First-generation multisite pacing pulse generators similarly provided a single ventricular output

for simultaneous RV and LV stimulation, however, two separate ventricular channels internally connect in parallel. This connection is made for both the lead tip and ring connections and eliminates the need for a Y-adaptor. However, this configuration still provides simultaneous RV and LV sensing with associated limitations.

The common consequence of simultaneous RV and LV sensing is double counting of the prolonged native ventricular electrogram [109, 110]. During pacing, RV and LV depolarization is synchronized and refractory periods prolonged, preventing double counting. Any situation that inhibits ventricular pacing and permits emergence of the prolonged native ventricular electrogram (e.g., ventricular premature beats, loss of atrial tracking during sinus tachycardia, rapidly conducted AF, nonsustained or sustained ventricular tachycardia) may cause ventricular oversensing due to double counting.

In all of these situations, sensed events in the LV and RV are "merged" into a single recording channel in parallel dual cathodal systems. The degree of temporal displacement between sensed RV and LV events depends on the interventricular conduction time and lead position. If the interventricular conduction time during bundle branch block exceeds the relatively short ventricular blanking period initiated by sensing, a single ventricular depolarization may be counted twice. This yields a characteristically oscillating interval plot resulting from cycle to cycle variation in the ventricular cycle length. In CRTP systems, this can result in inhibition of ventricular pacing and loss of CRT and spurious high-rate ventricular episodes (Fig. 21.55). In CRTD systems, this may result in inhibition of ventricular pacing and ventricular therapies for sinus tachycardia, rapidly conducted AF, or other SVT below

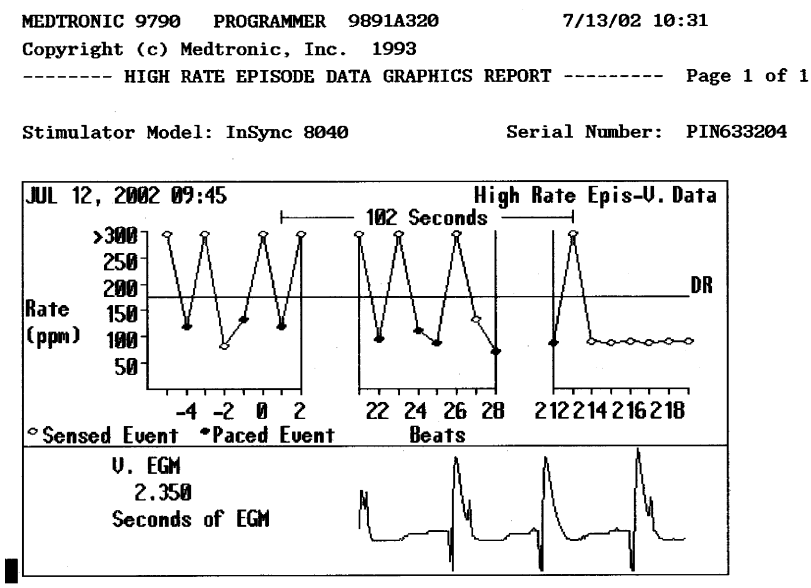


Fig. 21.55 Spurious high-rate ventricular episode with stored EGM due to loss of CRT and ventricular double counting of the native ventricular EGM in a CRT pacemaker. Note two-component of ventricular EGM (first deflection is RV activation; second deflection is LV activation). Note characteristic "W" appearance due to oscillation of cycle lengths caused by sensing of both components of the prolonged biventricular EGM.

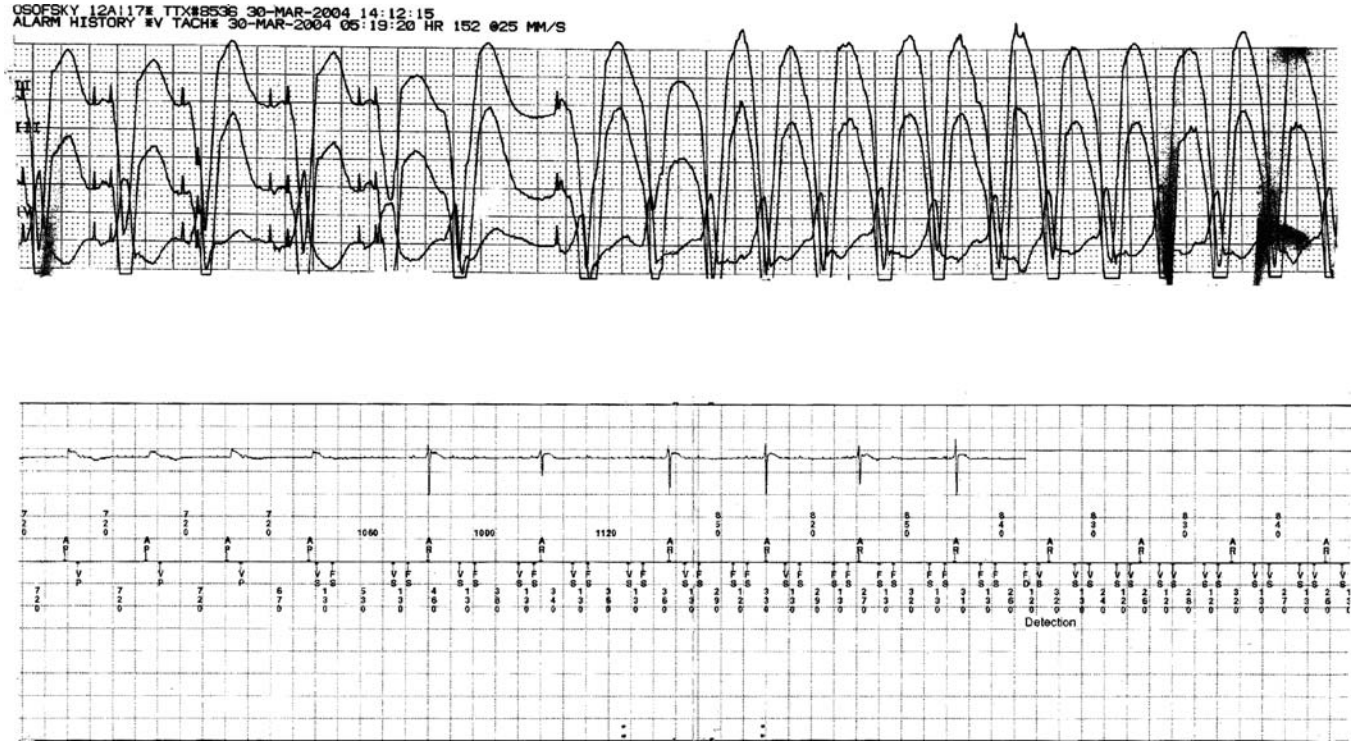


Fig. 21.56 Ventricular double counting during VT on a stored EGM in a nondedicated CRTD system. *Top:* Telemetry strip of nonsustained monomorphic VT, interrupting biventricular pacing. *Bottom:* Corresponding stored single-channel EGM and marker channel (Medtronic GEM III AT) for the same event. Note only atrial EGM is stored. Double counting of each VT event (marked as VS-FS or FS-FS) results in misclassification and detection as VF.

the programmed VT detection interval because the double counting interval exceeds the VT detection interval (Fig. 21.56). Similarly, the rate of true VT may be overestimated resulting in misclassification as VF and treatment with shocks instead of painless termination by antitachycardia pacing [111]. Similarly, nonsustained VT may satisfy VF detection criteria resulting in aborted or delivered shocks. Oversensed events due to ventricular double counting may interfere with dual-chamber detection enhancements.

Pacing inhibition and inappropriate therapies due to far-field sensing of left atrial activity by the LV lead has also been reported [112, 113, 114]. In this situation, ventricular double counting is due to sensing of the far-field atrial and near-field ventricular signals. Ventricular triple counting can also occur when the far-field atrial signal and both components of the prolonged native ventricular electrogram are sensed (Fig. 21.57). Far-field sensing of atrial activity is more likely when the LV lead is close to the AV groove, either due to coronary venous anatomy or lead displacement from a more distal position within a venous branch. Rarely, atrial oversensing from a nondisplaced integrated bipolar RV lead may cause inhibition of ventricular pacing and double counting [115].

Resolving Ventricular Double-Counting

Nondedicated CRTP/D Systems with Y-Adaptors

The options for eliminating ventricular double counting in nondedicated CRTP and CRTD systems that achieve parallel dual cathodal sensing with a Y-adaptor are limited and mostly unsatisfactory. In one small series, 36% of patients had $\geq$1 inappropriate shock (range, 1–64 per patient) due to double counting over a mean follow-up of 13 ± 7 months [42]. With the exception of misclassification of true VT as VF, double counting of the native ventricular electrogram during conducted supraventricular rhythms caused all inappropriate therapies. This could only be overcome by interrupting AV conduction with catheter ablation or disconnection of the Y-adapted LV lead because CRTD pulse generators with dedicated univentricular sensing were unavailable.

Theoretically, manipulation of the ventricular blanking period could reduce ventricular double counting in some situations with nondedicated CRTP/D systems. Manufacturer-specific differences in programmable postventricular sense blanking periods in conventional ICDs may be useful in this regard, but a common concern is true VT/VF detection failure due to pseudo-ventricular undersensing when the blanking period is maximally extended.

In some instances, decreasing the programmed ventricular sensitivity may reduce ventricular double counting if the later of the RV and LV electrograms has significantly lower amplitude than the earlier electrogram. This approach mandates validation of VF sensing and detection at the reduced ventricular sensitivity and is generally undesirable.

Second- and third-generation dedicated CRTP and CRTD generators have independent ventricular ports for differential pacing output and timing but restrict ventricular sensing to the RV or LV lead alone, depending on programmability. Removing the Y-adaptor and replacing the generator with one that uses single site (typically RV) sensing exclusively eliminates the potential complications of biventricular sensing.

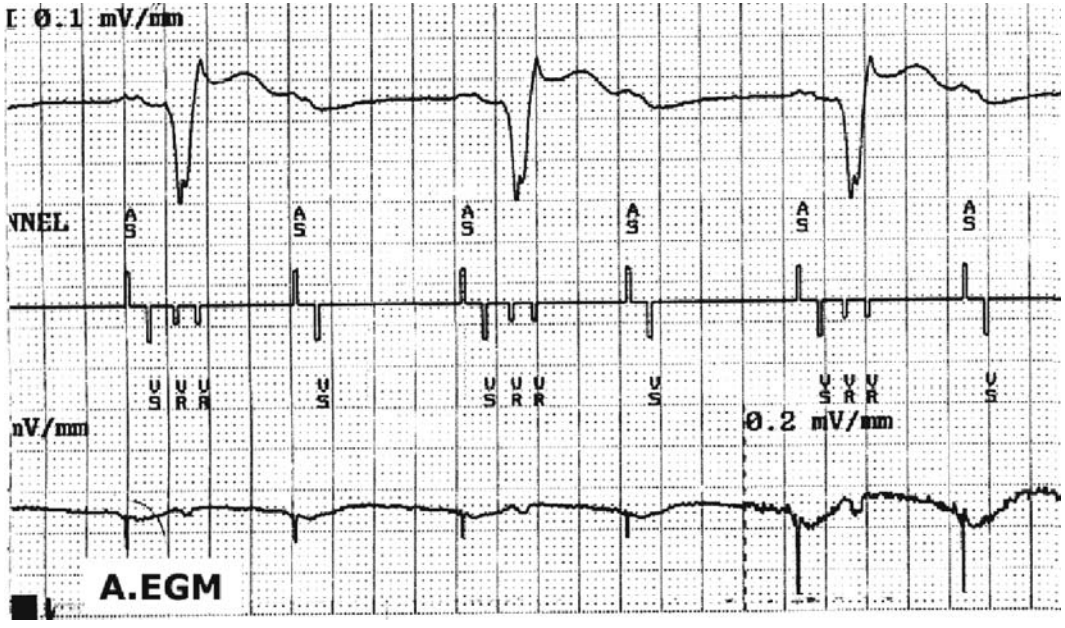


Fig. 21.57 Ventricular triple counting in a nondedicated CRTP system. Simultaneous recordings (from top to bottom) of surface ECG, marker channel, and real-time atrial EGM. The spontaneous rhythm is 2:1 AV block. The nondisplaced LV lead senses the late portion of the P-wave because of its proximity to the AV groove (note VS and AS are nearly merged) resulting in ventricular pacing inhibition. Alternating P-waves conduct resulting in emergence of the prolonged native ventricular EGM and ventricular double counting. Thus, there are three ventricular sensed events marked for each conducted sinus event: the first (VS) is the far-field atrial signal, the second (VR) and third (VR) are the two components of the "split" ventricular EGM. (From Lipchenca I, Garrigue S, Glikson M, Barold SS, Clementy J. Inhibition of biventricular pacemakers by oversensing of far-field atrial depolarization. Pacing Clin Electrophysiol 2002;25(3):365–367.)

Dedicated CRTP/D Systems with Univentricular Sensing

Double counting of the prolonged native ventricular electrogram is eliminated by univentricular sensing, which is either hardwired (RV) or programmable (RV or LV) in dedicated CRTP/D systems. Accordingly, an interventricular refractory period (see above) is not necessary though it is provided in some dedicated CRTP/D systems that permit selection of biventricular sensing. However, double counting of the far-field atrial and near-field ventricular electrogram can still occur during (univentricular) LV sensing when the LV lead is in close proximity to the AV groove due to displacement or coronary venous anatomy. In this situation, reprogramming univentricular RV sensing resolves the double counting problem but does not address LV lead displacement as the cause. Newer bipolar or dual cathodal LV leads will probably not reduce the likelihood of far-field atrial oversensing in nondisplaced leads because the proximal electrode is closer to the AV groove.

Inhibition of Ventricular Pacing and Inappropriate Therapies Due to Ventricular Oversensing of Cardiac Signals

LV lead dislodgment into the coronary sinus may result in inhibition of ventricular pacing in CRTP systems due to atrial oversensing and simultaneous inappropriate detection of atrial activity as VT/VF in CRTD systems that use RV and LV sensing even in pacemaker-dependent patients incapable of AV conduction [112, 115, 116]. In pacemaker-dependent patients, this can result in syncope followed by a high-voltage shock.

Inhibition of Ventricular Pacing and Inappropriate Therapies Due to High-Frequency, Low-Amplitude Respirophasic Noise Transients

Respirophasic oversensing is commonly provoked in ICD patients during ventricular pacing at maximum or nominal programmable sensitivities and may occur spontaneously, resulting in spurious tachyarrhythmia therapies and pacing inhibition [117]. Differences in the incidence of spontaneous and provoked oversensing between ICD systems appear to be explained on the basis of unique features of their automatic sensing systems and sensing lead design. Spontaneous and provocable oversensing is more common in male patients with ICD systems that use automatic gain control (AGC) sensing and integrated bipolar (IBP) leads. The explanation for the increased relative risk of oversensing with AGC versus automatic adjusting sensitivity (AAS) sensing devices can be rationalized by considering their respective operations. Under conditions of no pacing or continuous pacing, AGC devices attain maximum sensitivity sooner in the cardiac cycle and maintain it longer than AAS devices. This difference is most dramatic during conditions of ventricular pacing where the operational sensitivity of AGC devices is linked to the pacing interval. In contrast, the exponential increase in sensitivity of AAS devices is dissociated from the pacing interval. The large surface area of the coil and wider interelectrode spacing of IBP leads might increase the susceptibility to extraneous far-field signals, analogous to unipolar pacemaker leads. The more narrow interelectrode spacing of true bipolar (TBP) leads might increase the chance that extraneous far-field signals will arrive at each electrode simultaneously, resulting in signal averaging ("cancellation"). Sensing may

therefore be better confined to the local endocardial environment and susceptibility to oversensing reduced as with conventional bipolar pacing leads. Oversensing can be overcome in more than 50% of patients by programming a reduced sensitivity, however, this requires reconfirmation of the robustness of ventricular fibrillation detection. In selected cases, persistent oversensing despite reduced sensitivity may require implantation of a separate endocardial rate-sensing lead in the right ventricular outflow tract or use of an ICD pulse generator that does not employ AGC sensing behavior. CRTD patients may be particularly susceptible to respirophasic oversensing due to continuous ventricular pacing (Fig. 21.58).

CRT Proarrhythmia

Small studies have suggested that CRT might reduce the likelihood of inducible or spontaneous ventricular arrhythmia in susceptible patients [118, 119]. The VENTAK CHF study [120] reported a reduction in spontaneous ventricular arrhythmias during 3 months of CRT "on" versus "off" in 32 patients who served as their own controls. The short duration of follow-up, small number of patients, and stochastic nature of arrhythmia recurrence render these data inconclusive.

This concept has not been confirmed in large RCTs of CRTD where no significant difference in the incidence or frequency of ventricular

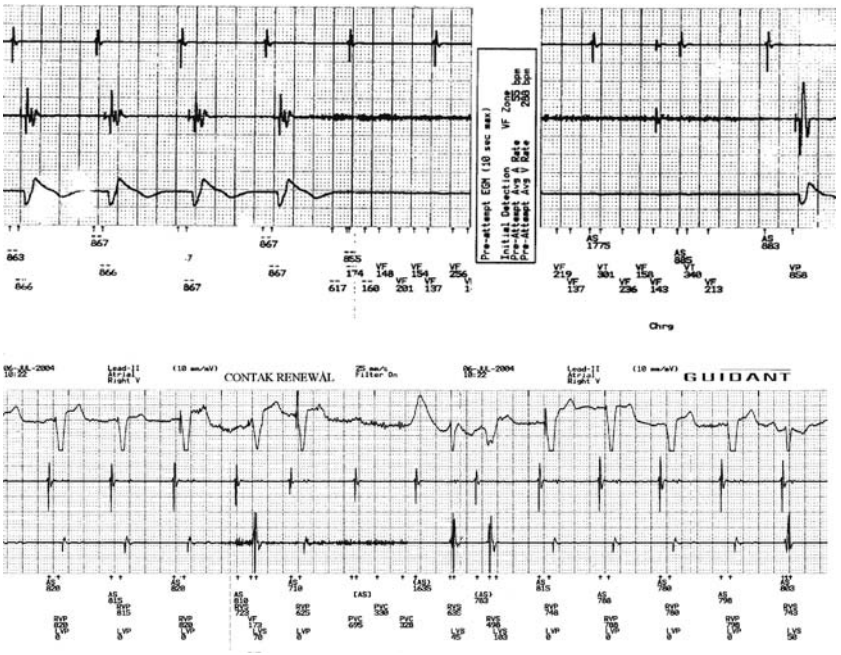


Fig. 21.58 Respirophasic ventricular oversensing resulting in loss of CRT in a pacemaker-dependent patient. *Top:* Spontaneous ventricular oversensing resulting in simultaneous ventricular pacing inhibition, syncope, and spurious VF detection denoted by capacitor charging. *Bottom:* Provoked ventricular oversensing during deep breathing at nominal ventricular sensitivity. This was not eliminated by programming a reduced ventricular sensitivity ("Less sensitive").

tachyarrhythmias between patients randomized to CRT "on" or CRT "off" was observed [48,79,108]. For example, in the VENTAK CHF/CONTAK CD study, 15% of patients randomized to CRT received appropriate therapies for VT and VF compared with 16% of patients randomized to no CRT [79]. When excluding patients who had no VT/VF episodes, those patients randomized to CRT had a median of 2.5 episodes whereas those randomized to no CRT had a median of 2 episodes during the therapy evaluation phase. During the 6-month randomization period in MIRACLE ICD, 26% of patients in the control group versus 22% in the CRT group had at least one spontaneous episode of VT or VF ($p = 0.47$) [108]. Among patients with spontaneous VT or VF, those randomized to CRT had 0.39 VT/VF episodes/month versus 0.41 episodes/month among those randomized to no CRT [108]. Additional analysis of MIRACLE ICD reinforced these observations with regard to overall detected ventricular arrhythmias [75]. There was no difference by randomization in the proportion of patients experiencing episodes or the cycle lengths of the episodes during the randomization period. For primary prevention patients, 18% of those randomized to CRT off had at least one appropriately detected episode compared with 14% with CRT on, with average cycle lengths of 285 ms and 291 ms, respectively. For secondary prevention patients, 28% of those randomized to CRT off had at least one episode compared with 27% with CRT on, with average cycle lengths of 352 ms and 361 ms, respectively.

Nonetheless, an important question is whether pacing site-specific changes in ventricular activation might facilitate the initiation of ventricular arrhythmia under certain conditions. For example, collision of site-specific stimulation wavefronts might create a favorable environment for initiation of scar-related reentry in coronary artery disease. A recent case report described the reproducible initiation of monomorphic VT by LV pacing but not RV pacing that could be reliably terminated by RV ATP but not by LV ATP [121]. This suggests the possibility that local tissue anisotropy might affect the ability of site-specific stimulation wavefronts to interact with the reentrant VT circuit.

Additionally, the sudden alteration in LV activation sequence from endocardial to epicardial and reversal of wavefront direction from left to right might affect arrhythmogenesis. Recent studies have shown that pacing site–dependent changes in ventricular activation sequence can alter ventricular repolarization and refractoriness [122, 123].

Medina-Ravell et al. [122] demonstrated that LV epicardial and biventricular pacing caused significant increases in the JT and QTc intervals, and LV pacing increased transmural dispersion of repolarization in humans with systolic heart failure. In a small number of patients, LV and biventricular pacing caused frequent R-on-T extrasystoles, leading in one instance to incessant torsades de pointes requiring multiple ICD therapies within hours of institution of biventricular pacing (Figs. 21.59–21.61). Despite more modest QTc prolongation, R-on-T extrasystoles and torsades de pointes were completely suppressed by RV endocardial pacing. In rabbit experiments, switching from endocardial to epicardial pacing resulted in prolongation of the QTc and transmural dispersion of repolarization.

These observations were extended by Fish et al. [123] using arterially perfused canine LV wedge preparations. The QT interval and transmural dispersion of repolarization increased as pacing was shifted from endocardium

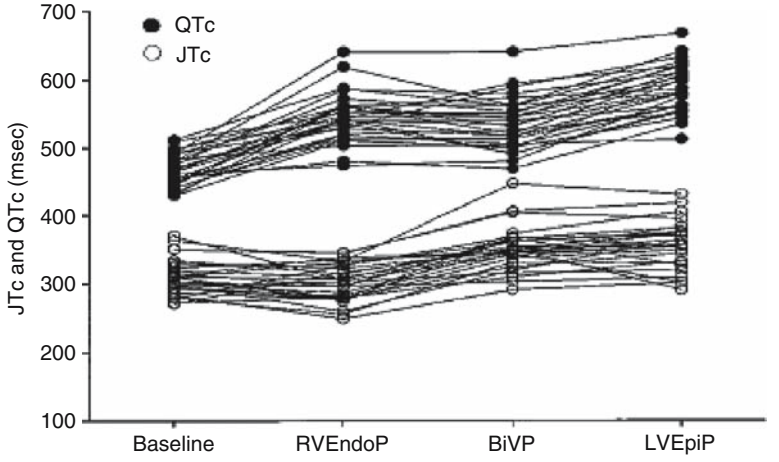


Fig. 21.59 Effect of biventricular and left ventricular pacing on QTc Interval. (From Medina-Ravell VA, Lankipalli RS, Yan GX, et al. Effect of epicardial or biventricular pacing to prolong QT interval and increase transmural dispersion of repolarization. Circulation 2003;107:740–746.)

to epicardium. In the presence of rapidly activating delayed rectifier potassium current blocker, these changes were accentuated and torsades de pointes arrhythmias could be induced during epicardial, but not endocardial, pacing. The authors concluded that sudden reversal of the direction of activation of the LV wall, as occurs during biventricular pacing, leads to increases in QT and transmural dispersion of repolarization as a result of earlier repolarization of epicardium and delayed activation and repolarization of the mid-myocardial M cells. This facilitates the development of torsades de pointes under long QT conditions.

Other Unusual Complications of CRT

The additional timing cycle complexities of nondedicated and dedicated CRT systems have introduced new forms of "pacemaker-mediated" tachycardias. Barold et al. described a "cross-ventricular" endless loop tachycardia in a conventional dual-chamber pacemaker pulse generator used for CRT during permanent AF with the RV lead in the ventricular port and the LV lead in the atrial port [124]. In the VVIR mode, T-wave oversensing on the LV lead (atrial channel) triggered ventricular pacing on the RV lead (ventricular channel). This could be overcome by reducing atrial channel (LV) sensitivity or using the DVIR mode, which excludes the possibility of LV sensing (atrial channel). Berruezo et al. described an unusual form of pacemaker-mediated tachycardia in a CRT system without an atrial lead because of "permanent" AF [125]. This was explained by the serendipitous occurrence of spontaneous termination of AF and dislodgment of the LV lead into the coronary sinus resulting in simultaneous left atrial and LV capture. Because AV conduction was intact, left atrial capture resulted in a RV sensed event, which triggered the VSR feature (see above), resulting in emission of a biventricular pacing stimulus, which perpetuated the phenomenon.

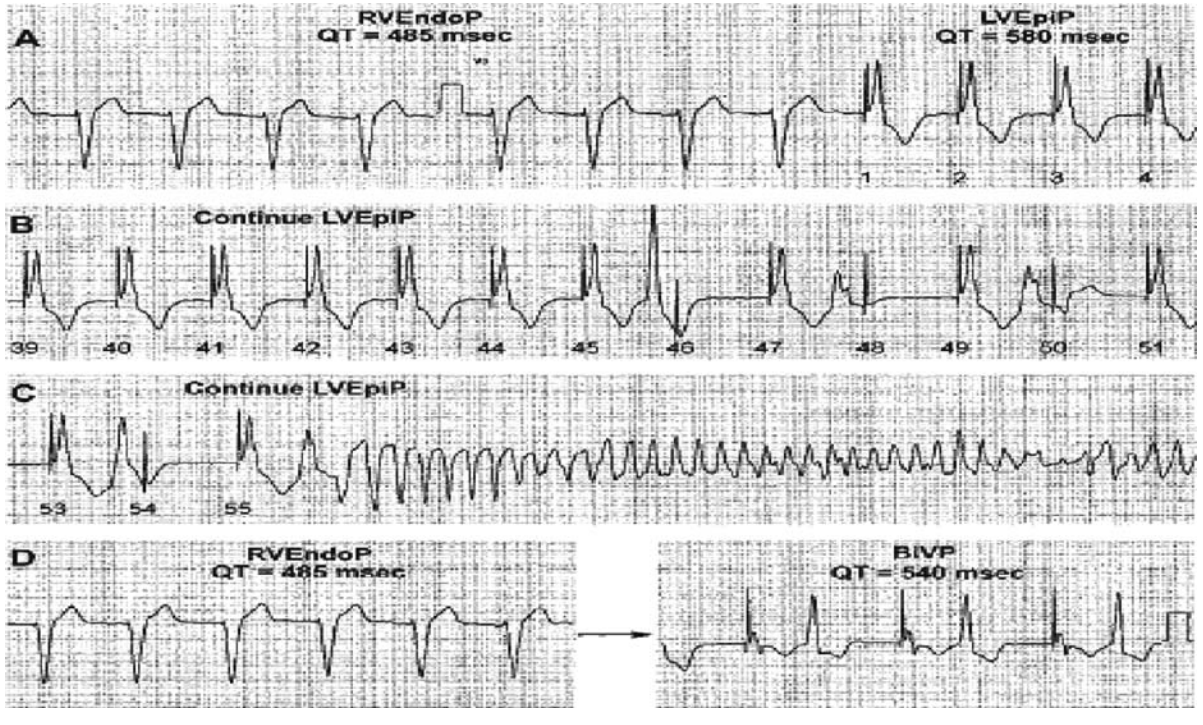


Fig. 21.60 Torsades de pointes associated with biventricular pacing. Note QT is 585 ms during LV pacing versus 485 ms during RV pacing. Polymorphic ventricular tachycardia is initiated by short–long–short sequence during LV pacing. (From Medina-Ravell VA, Lankipalli RS, Yan GX, et al. Effect of epicardial or biventricular pacing to prolong QT interval and increase transmural dispersion of repolarization. Circulation 2003;107:740–746.)

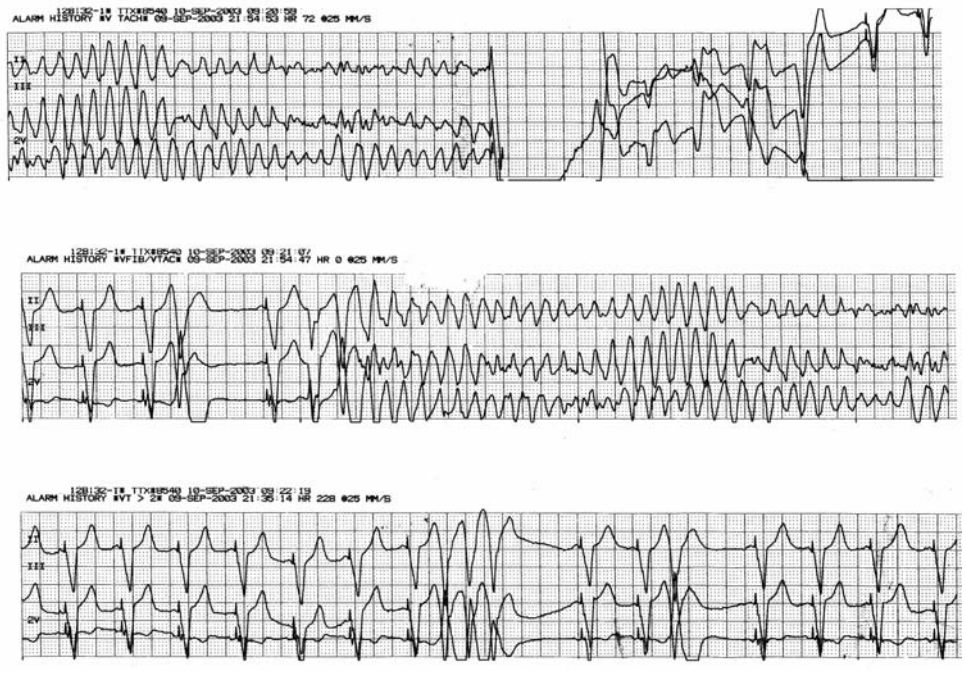


Fig. 21.61 Polymorphic ventricular tachycardia degenerating to ventricular fibrillation 6 h after initiation of CRTD. The patient was a 56-year-old woman with nonischemic dilated cardiomyopathy, left bundle branch block, and no prior history of documented ventricular arrhythmia or syncope. The two sustained events (*top and middle tracings*) occurred within 6 s of each other and were terminated by ICD shocks. Note polymorphic VT is initiated by a short–long–short sequence (*middle tracing*). Note salvos of ventricular premature beats in the bottom tracing.

CRT Responders and Nonresponders

Acute response to CRT has been defined on the basis of invasive hemodynamic measurement [20,21,126]. Patients for whom there was an increase in aortic pulse pressure with respect to their intrinsic baseline by more than 5% for any stimulation mode and AV delay combination were characterized as responders. The remaining patients were defined as nonresponders. However, there is some evidence that acute hemodynamic response may not be highly correlated with chronic clinical improvement or reverse remodeling [127,128]. This implies that the lack of an acute hemodynamic response does not preclude clinical CRT response and that the mechanisms of chronic CRT response are more complex than the effects represented by acute hemodynamic measurements.

Accordingly, randomized clinical trials (RCTs) of CRT have relied on multiple primary (NYHA class, quality-of-life score, and the distance walked in 6 min) and secondary end points (peak oxygen consumption, time on a treadmill, left ventricular ejection fraction and end-diastolic dimension, severity of mitral regurgitation), and a clinical composite response, which assigned patients to one of three response groups: improved, worsened, or unchanged [129]. The purpose of the clinical composite score is to combine changes in functional status class with the occurrence of major clinical events including episodes of clinical deterioration. Clinical deterioration is denoted by death or hospitalization or urgent care for new-onset or worsening heart failure [48]. Such clinical composite scores have been shown to be more sensitive than conventional approaches in discriminating active therapy from placebo effect in studies of drugs and electrical device therapy for heart failure [130].

Using these methods, RCTs have demonstrated that the majority of patients who meet currently accepted implant criteria [58] respond to CRT. Clinical improvement in CRT responders is modest and on average includes a 1- to 2-step reduction in NYHA class, a 1 to 2 ml kg^{-1} min^{-1} improvement in peak VO_2, a 50- to 100-m improvement in 6-min hall walk, reduced heart failure urgent care or hospitalizations, and improved quality of life by standardized measures.

Nonetheless, approximately 20–30% of patients fail to respond to CRT [53,127,131,132,133,134,135]. There is no uniform definition of CRT "nonresponse," but this is generally recognized to denote limited or lack of clinical improvement and lack of reverse ventricular remodeling. Although CRT "nonresponse" is likely a diverse phenomenon, there is emerging consensus that this can be explained on the basis of the interactive consequences of inadequate patient selection and suboptimal LV lead position. The approach to reducing "CRT" nonresponders therefore must include (1) rejection of patients who are destined not to respond (i.e., patients without mechanical dyssynchrony) and (2) maximization of LV stimulation response in patients with mechanical dyssynchrony.

Optimizing Patient Selection to Reduce Nonresponders

Intraventricular dyssynchrony is the pathophysiologic target of CRT. Techniques beyond QRS duration for selecting patients with significant ventricular dyssynchrony likely to benefit from CRT are rapidly evolving. The optimal criteria would identify all patients with a high probability of response and reject all patients with a low probability of response.

Clinical Characteristics

Numerous clinical variables have been evaluated for predicting likelihood of CRT responsiveness. Significant AV conduction delay [136], functional mitral regurgitation [132], left ventricular end-diastolic dimension >55 mm, and low baseline peak VO_2 [137] have been shown to be associated with CRT response in small studies. Baseline contractile function indexed by LV $+dP/dt_{max}$ has been shown to inversely correlate with its subsequent change during LV pacing. Heart failure functional class is positively correlated with CRT response. In several studies, equivalent benefit was observed with CRT in NYHA class III–IV patients but no significant benefit in class II [53, 108]. Left ventricular ejection fraction has not been shown to reliably correlate with likelihood of CRT response in any study. Sinus rhythm does not appear to be necessary for CRT response. Patients in permanent AF had a similar acute hemodynamic response as sinus rhythm in PATH-CHF and similar long-term function improvements in other trials [53, 126, 138, 139].

The role of myocardial substrate is an important but unresolved issue in distinguishing CRT responders and nonresponders. Some studies have suggested that ischemic DCM is less likely to respond to CRT than is NDCM [132], but not others [48,53]. However, these studies only examined outcomes on the basis of presence or absence of coronary artery disease as the cause of DCM. These studies did not consider, for example, the more specific possibility that infarct location may influence CRT response. Recently, an analysis of the MIRACLE trial reported that prior anterior infarct accompanying LBBB by ECG criteria predicted a low probability of CRT response [140]. The authors hypothesized that posterior-basal LV stimulation in this situation exaggerates systolic "bulging" of the anterior infarct segment. Another possibility is that slow conduction through a large infarct zone causing a LBBB pattern may not reflect intraventricular dyssynchrony and thus would not be expected to respond to CRT. Infarct location may influence CRT indirectly when epicardial scar results in an inability to achieve pacing capture at the optimal site for LV stimulation (below).

Baseline QRS Duration

To date, QRSd determined from the surface ECG has been most extensively evaluated as a selection criteria for CRT on the premise that electrical delay is a reliable marker for spatially dispersed mechanical activation. Numerous studies have reproducibly demonstrated that baseline QRSd is an important predictive factor of acute hemodynamic improvement with CRT. Auricchio et al. [20] showed that there was a positive correlation between the QRSd and the percentage of change in LV +dP/dt and pulse pressure during CRT. This observation was corroborated by Nelson et al. [22]. Baseline QRSd modestly predicted systolic response, as assessed by maximal rate of pressure defined as % change in LV $+dP/dt_{max} = 0.61 \times$ QRSd – 70.2. Combining baseline QRSd and LV $+dP/dt_{max}$ improved the predictive accuracy for identifying CRT clinical responders. Patients with baseline QRSd $\geq$155 ms and baseline LV $+dP/dt_{max} \leq$700 mm Hg/s consistently yielded the greatest acute hemodynamic response to CRT (% change LV $+dP/dt_{max} \geq$25%).

Prediction curves for contractile function response using baseline QRSd derived from the PATH-CHF and PATH-CHF II studies are shown in

Figure 21.62 [141]. The specificity curve indicates that 80% of CRT nonresponders had a QRSd <150 ms. The sensitivity curve indicates that 80% of CRT responders had a QRSd >150 ms. The overlap between these QRSd ranges was populated with CRT responders and nonresponders. The predictive accuracy of QRSd to separate responders from nonresponders is fairly constant around 80% with a threshold cutoff between 120 and 150 ms. If the QRSd is >150 ms, the likelihood of CRT response is greater. An important qualification is that this analysis is based on acute hemodynamic response to CRT that, as mentioned previously, may not correlate precisely with chronic clinical improvement or reverse remodeling [127]. However, these observations appear to be corroborated by the COMPANION trial, where little or no benefit of CRT or CRTD on death or heart failure hospitalization was observed among patients with baseline QRSd <150 ms [48].

In summary, 80% of patients with QRSd >150 ms will have a hemodynamic improvement with CRT, and the probability of response is positively correlated with QRSd. Patients with QRSd <150 ms are less likely to respond to CRT though this is not uniformly true. Improvements in dyssynchrony seem to be the determinant of the improvements obtained with CRT, and this may be independent of QRSd. Patients with more advanced heart failure symptoms are more likely to respond to CRT than are patients with less severe symptoms.

Pattern of Prolonged QRS Duration

Because RCTs of CRT have specified only prolonged QRS duration and not the pattern of abnormal ventricular conduction as a requirement for enrollment, patients with RBBB, LBBB, and "nonspecific" ventricular conduction delay all meet currently accepted implantation indications for CRT [58]. However, only about 10% of patients with advanced systolic heart failure and abnormal ventricular conduction have RBBB [48, 142]. Consequently,

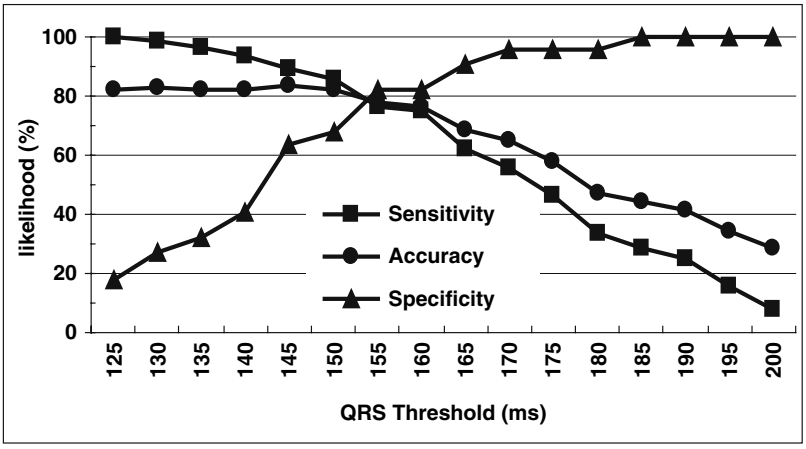


Fig. 21.62 Probability of acute hemodynamic response to CRT according to baseline QRSd. (From Kadhiresan V, Vogt J, Auricchio A, et al. Sensitivity and specificity of QRS duration to predict acute benefit in heart failure patients with cardiac resynchronization. Pacing Clin Electrophysiol 2000;23(II):555 [abstract].)

patients with RBBB have comprised a very small proportion of the enrolled population in RCTs of CRT.

Only limited data on CRT for RBBB is therefore available. Garrigue et al. reported positive clinical response to CRT after 12 months in 9 of 12 patients with RBBB [143]. Only those patients with RBBB and significant electromechanical delay in the left ventricle detected by tissue Doppler imaging responded to CRT. A retrospective analysis of 43 patients with RBBB in the MIRACLE study demonstrated a significant improvement in only NYHA functional class compared with no CRT, which led the authors to conclude that patients with RBBB have a similar intermediate-term response to CRT as patients with LBBB [144]. This was not corroborated by the much larger COMPANION study, where CRT had a neutral effect among patients with RBBB [48].

A recent study by Egoavil et al. emphasizes these uncertainties [145]. The long-term outcomes of CRT in 61 patients with systolic heart failure, prolonged QRSd with RBBB activation pattern, and persistent symptoms (>NYHA class II) despite reasonable medical therapy were pooled from two RCTs (MIRACLE [53] and CONTAK CD [79]). CRT was randomized "on" in 34 patients and "off" in 27 patients. There was no significant improvement in any outcome variables except a 1-step reduction in NYHA class, which the authors appropriately recognized as a highly subjective parameter. Further, Egoavil et al. [145] seem to have incidentally discovered a flaw in the analysis of Aranda et al. [144] that apparently misreported RBBB in 15 of 43 patients.

An important unanswered question in the analysis of Egoavil et al. [145] and others is whether the RBBB pattern was due to myocardial infarction. Some studies have suggested that ischemic DCM is less likely to respond to CRT than is nonischemic DCM [132], but not others [48, 53]. However, these studies only examined outcomes on the basis of presence or absence of coronary artery disease as the cause of systolic heart failure. These studies did not consider, for example, the more specific possibility that infarct location may influence CRT response. Recently, an analysis of the MIRACLE study reported that prior anterior infarct accompanying LBBB by ECG criteria predicted a low probability of CRT response [140].

There is reason to be circumspect regarding the applicability of biventricular pacing in RBBB. Recent studies have demonstrated that intra-LV dyssynchrony is the most potent predictor of acute and chronic response (including reverse remodeling) to CRT [56, 131, 133, 136]. Accordingly, a significant percentage of patients with LBBB may fail to respond to CRT simply because despite delayed LV electrical activation, mechanical contraction is not dyssynchronous [135, 146]. A similar situation may apply to RBBB but for different reasons. Despite prolonged QRS duration, proximal RBBB, the most commonly occurring type of chronic RBBB, does not disrupt normal LV activation [147]. Therefore, it is not clear why biventricular pacing would be helpful in chronic proximal RBBB.

However, this may be an oversimplification in patients with systolic heart failure, where abnormalities in electrical activation and mechanical contraction have been incompletely characterized in RBBB versus LBBB, and preliminary data suggest that important differences may have implications for application of CRT. A recent study using three-dimensional endocardial

activation mapping in a small cohort of patients with RBBB and systolic heart failure demonstrated that left ventricular endocardial activation was similarly delayed in RBBB versus LBBB and that the posterobasal left ventricle was the latest site in either situation [148]. Right ventricular endocardial activation was significantly delayed in the anterior and lateral walls in RBBB. This suggests the possibility that right ventricular stimulation in RBBB should target sites other than the apex. This may be an important qualification in the interpretation of limited clinical data on RBBB in randomized trials of CRT, as right ventricular leads were almost uniformly placed at the apex.

There is insufficient clinical evidence to reach definitive conclusions, and this will be difficult to overcome because of the underrepresentation of RBBB in systolic heart failure. This is an important matter in a larger context because approximately 20–30% of patients who meet currently accepted implant criteria fail to respond to CRT [53, 108, 131, 132, 133, 134]. Although CRT "nonresponse" is likely a diverse phenomenon, there is emerging consensus that inadequate patient selection is a key element. The approach to reducing "CRT" nonresponders therefore must include rejection of patients who are destined not to respond (i.e., patients without mechanical dyssynchrony). Furthermore, LV or biventricular pacing still results in abnormal activation patterns and may worsen ventricular pumping function in hearts without initially abnormal LV contraction patterns [149]. Thus, CRT might actually cause clinical deterioration in patients with systolic heart failure, prolonged QRSd (regardless of the pattern of abnormal ventricular conduction), but no mechanical dyssynchrony.

Echocardiographic Techniques for Selecting CRT Responders

Recognition of the potential limitations of QRSd for predicting CRT response has stimulated interest in techniques for directly measuring baseline ventricular dyssynchrony. Although preliminary results in small numbers of patients are encouraging, no RCT of CRT has reported on the use of echocardiographic techniques for patient selection.

Sophisticated Echocardiography

Intraventricular synchrony can be assessed echocardiographically from the delay between the maximal posterior displacement of the septum and the maximal displacement of the LV posterior wall measured from an M-mode short-axis view of the LV (septal–posterior wall delay; SPWD). Pitzalis et al. [136] found that the mean SPWD improved from 192 ms to 14 ms after 1 month of CRT and was the only echocardiographic marker (including interventricular delay, ejection fraction, mitral regurgitant duration, and mitral regurgitant area) associated with a favorable response to CRT, defined as a greater than 15% improvement in LV systolic volume index. The mean SPWD was >130 ms in all responders and was significantly longer in responders versus nonresponders (246 $\pm$ 68 ms vs. 110 $\pm$55 ms).

Tissue Doppler Imaging, Tissue Synchrony Imaging, Tissue Tracking, Strain and Strain Rate

Another promising echocardiographic technique to identify dyssynchrony and target patients for CRT is myocardial tissue imaging. This utilizes tissue Doppler signals to quantify time to peak systolic velocity or rate of regional

myocardial deformation (strain), providing a sensitive estimate of regional myocardial shortening and lengthening that correlates with LV +dP/dt and systolic function in healthy and diseased hearts [150]. In LBBB, Doppler strain imaging demonstrates maximal septal contraction occurring before aortic valve opening and accompanied by lateral wall lengthening, consistent with studies in animal model [12]. The septum then lengthens after aortic valve opening and does not contribute to ejection. Peak lateral wall contraction is observed very late in systole and persists into the postsystolic period. During CRT, systolic contraction can be demonstrated to occur simultaneously in both septal and lateral walls, contributing equally to ejection [23]. The utility of this technique in patient selection for CRT remains to be defined in clinical trials, but preliminary results appear encouraging. Ventricular dyssynchrony detected by tissue Doppler imaging has been shown to predict acute and chronic response (including remodeling) to CRT in several studies [56, 131, 151, 152, 153].

Limitations of QRS Duration for Selecting CRT Responders: Insights from Echocardiographic Techniques for Assessing Intraventricular Dyssynchrony

There are several reasons why QRSd may not reliably predict CRT response. QRSd reflects both right and left ventricular activation. In many patients with LBBB, the delay in ventricular activation resides entirely within the left ventricle, as anticipated. However, in some patients with LBBB, delayed right ventricular activation accounts for a significant proportion of electrical delay manifest on the surface ECG [17].

More notably, studies with sophisticated echocardiographic techniques have yielded the critically important observation that prolonged QRSd, which is a measure of delayed electrical activation, correlates poorly with mechanical dyssynchrony. This has been convincingly demonstrated using simple [136, 154] and sophisticated echocardiographic techniques [135, 146]. Yu et al. [135] used a dyssynchrony index (Ts-SD) derived from the standard deviation (SD) of the maximal difference in time to peak myocardial systolic contraction (Ts) of 12 LV segments to assess intraventricular dyssynchrony relative to QRSd. When a dyssynchrony index of >32.6 ms (+2 SD of normal controls) was used to define significant intraventricular dyssynchrony, it was present in only 64% of patients with prolonged QRSd (>120 ms) (Fig. 21.63). Bleeker et al. [146] reported that severe left ventricular dyssynchrony, defined as an electromechanical delay using tissue Doppler imaging between the septal and lateral wall (septal–lateral delay >60 ms), was present in only 60% of patients with LBBB and QRSd 120–150 ms and 70% with QRSd >150 ms. Thus, similar to the observations of Yu et al. 2003 [135], about 40% of patients with prolonged QRSd did not have significant intraventricular dyssynchrony. Though the proportion of patients with severe intraventricular dyssynchrony increased with increasing QRSd, linear regression failed to show any significant correlation between QRSd and dyssynchrony (Fig. 21.64).

These observations are critically important and likely explain a significant portion of the CRT nonresponse phenomenon in RCTs as recent studies have conclusively demonstrated that intraventricular dyssynchrony is the most potent predictor of acute and chronic response (including reverse remodeling) [29, 56, 131, 136, 151]. Accordingly, a significant percentage

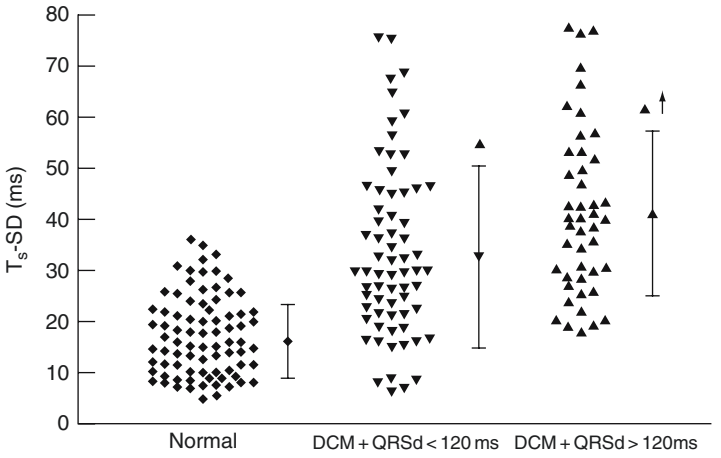


Fig. 21.63 Dyssynchrony index (derived from tissue Doppler imaging) relative to baseline QRSd groups. (From Yu CM, Lin H, Zhang Q, Sanderson JE. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. Heart 2003;89:54–60.)

of patients with prolonged QRSd may fail to respond to CRT simply because despite delayed electrical activation, mechanical contraction is not dyssynchronous. Furthermore, LV or biventricular pacing with an LV lead on the posterior or posterolateral basal LV wall still results in abnormal activation patterns in hearts without initially abnormal mechanical dyssynchrony [149]. Left ventricular pacing may worsen ventricular pumping function if ventricular contraction is not dyssynchronous. Thus, CRT might actually cause clinical deterioration in patients with systolic heart failure, prolonged QRSd, but no mechanical dyssynchrony. This may account for the observation that some patients in the MIRACLE trial actually disimproved during CRT.

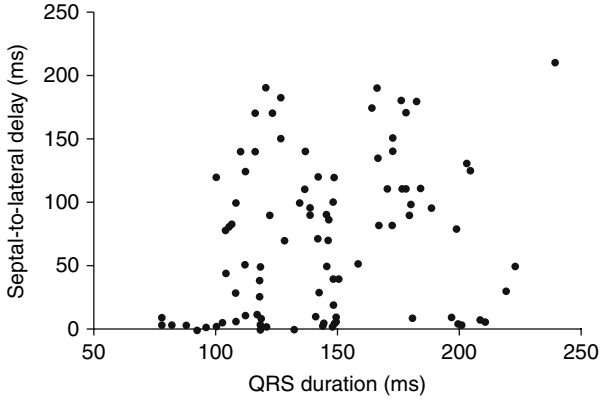


Fig. 21.64 Lack of correlation between QRSd and intraventricular dyssynchrony. (From Bleeker GB, Schalij MJ, Molhoek SG, et al. Relationship between QRS duration and left ventricular dyssynchrony in patients with end-stage heart failure. J Cardiovasc Electrophysiol 2004;15(5):544–549.)

CRT Responders with Normal QRS Duration

Further complicating the matter of patient selection for CRT is the fascinating observation that some patients with DCM and normal or near-normal QRSd have significant mechanical dyssynchrony [146, 155, 156, 157, 158]. Such patients are systematically excluded from CRT using existing implantation guidelines but have been shown to demonstrate similar responses to CRT in terms of clinical improvement and reverse ventricular remodeling as patients with prolonged QRSd and mechanical dyssynchrony [156, 159].

Management of CRT Nonresponders

Once a patient is identified as displaying a limited or absent response to CRT, a systematic search for reversible causes should be undertaken in order to guide potentially corrective interventions that may improve outcomes. This search can be partitioned into three interdependent phases: system-related, patient-related, and patient-system interface (Table 21.1).

Table 21.1 Identifying correctable causes of CRT nonresponse

Problem	Solution
SYSTEM RELATED	
Atrial undersensing	
True undersensing	Increase atrial sensitivity, reposition atrial leadShorten
Pseudo-undersensing	PVARP, deactivated PMT and PVC response, increase upper tracking limit, add interventricular refractory period
Atrial oversensing	
Far-field R-waves causing inappropriate switching to nontracking mode	Reduce atrial sensitivity, increase PVAB
Ventricular oversensing	
Inhibition of ventricular pacing	Reduce ventricular sensitivity, reposition RV or LV lead if dislodged, eliminated nondedicated CRT/CRTD system if appropriate
Loss of left ventricular capture	
True loss of capture	Increase voltage output, reposition LV leadUse sequential
Functional loss of LV capture	ventricular stimulation (V-V timing)
PATIENT RELATED	
Atrial fibrillation	
AV conduction absent	Antiarrhythmic drug for AF suppressionAntiarrhythmic
AV conduction present	drug for AF suppression, control ventricular rate with drugs or AV junction ablation, use AF response algorithms
Atrial pacing	
Disruption of optimal left-sided AV coupling	Reduce lower rate, use VDD mode. Reevaluate AV delay using echocardiography or other hemodynamic measures.
Ventricular conduction delay	Try LV only or sequential biventricular stimulation
Absence of mechanical dyssynchrony	Abandon CRT, minimize any ventricular pacing if possible
PATIENT–SYSTEM INTERFACE	
Suboptimal AV coupling	Reevaluate AV delay using echocardiography or other hemodynamic measures
LV lead position	If anterior vein site, reposition LV lead at lateral vein site (cardiac surgical approach if no venous targets or technically insurmountable)

System-Related Causes of CRT Nonresponse

The approach to troubleshooting CRTP and CRTD systems must consider both electrical operation and the effect of various parameter settings on left ventricular pumping function.

The six basic electrical problems of all cardiac pacing systems are (1) undersensing, (2) oversensing, (3) noncapture, (4) loss of output, (5) unanticipated alterations in programmed parameters, [3] undesirable side effects of programmed parameters. Reprogramming is the most desirable outcome for electrical problems, as it is painless, risk-free, and inexpensive and spares the patient a potentially morbid procedure.

Atrial Undersensing

Atrial undersensing may result in loss of atrial synchronous ventricular pacing and delivery of CRT. Atrial undersensing can be divided into true undersensing due to a mismatch between endocardial signal amplitude and programmed sensitivity or functional undersensing due to atrial events falling in refractory periods (see above). This can usually be modified by reprogramming of atrial sensitivity or refractory periods but occasionally requires surgical repositioning of the atrial lead (e.g., in the circumstance of lead dislodgment).

Atrial Oversensing

Atrial oversensing (most commonly due to far-field R-waves) may result in spurious mode-switching (in the DDD/R or VDI/R mode) resulting in reversion to a nontracking mode with loss of atrial synchronous ventricular pacing and CRT (see above). Spurious mode-switching can usually be minimized by reducing atrial sensitivity and modifying the postventricular atrial blanking period.

Ventricular Oversensing

Ventricular oversensing may result in inhibition of ventricular of ventricular pacing and loss of CRT, as well as spurious detections resulting in misdiagnosis of ventricular tachyarrhythmias. Though this can be addressed by reduction of ventricular sensitivity, caution must be applied to guarantee robustness of VF detection at reduced ventricular sensitivity.

Noncapture

Noncapture is defined as the emission of an atrial or ventricular pacing stimulus without capture. Atrial noncapture results in simultaneous loss of atrial pacing support and AV synchrony in patients with significant sinus bradycardia. In this situation, when AV conduction is intact, biventricular pacing may result in ventriculo-atrial synchrony and pacemaker syndrome.

Loss of ventricular capture is the most common reason for a CRT responder to experience a clinical decline after a period of sustained improvement. Ventricular noncapture results in nondelivery of CRT and is more common on the LV lead due to higher chronic pacing thresholds and lead dislodgments. Sudden and complete loss of LV capture is often a dramatic event and is almost always due to lead dislodgment. Lead dislodgment is readily identified by radiography, though "microdislodgments" resulting in sudden rises in capture threshold are more difficult to discern. Loss of LV capture may be gradual due to exit block. The 12-lead ECG remains a critically

important tool for evaluating LV capture even among second- and third-generation devices with separately programmable ventricular outputs for threshold testing. This can only be recognized in many instances by analysis of the ventricular activation pattern on the surface ECG. Noncapture can be successfully overcome by redetermining the single-chamber capture threshold and modifying programmed outputs accordingly in some situations.

Unanticipated Alteration in Programmed Parameters

Unanticipated alteration in programmed parameters refers to device timing cycle operation that is different from that programmed. This situation is most commonly encountered when the pulse generator has reached elective replacement status and the basic pacing mode has been automatically modified (i.e., VVI mode) to conserve battery life until replacement can be achieved. This results in instantaneous and simultaneous loss of AV and ventricular synchrony and may precipitate heart failure decompensation in some CRT patients.

Undesirable Side Effects of Programmed Parameters

Undesirable side effects of programmed parameters refers to a broad range of situations where programmed settings, despite normal operation, inadvertently impose clinical consequences on the patient. The common example during CRT is phrenic nerve stimulation during LV pacing. Approaches to preventing and overcoming phrenic nerve stimulation have been discussed.

Patient-Related Causes of CRT Nonresponse

Any interruption of ventricular pacing may reduce CRT response. As noted previously, a reasonable goal is >90% cumulative percent ventricular pacing based on device diagnostics. By far, the most common cause of loss of CRT pacing is AF with rapid AV conduction. This results in simultaneous loss of AV synchrony and ventricular synchrony combined with the adverse effects of a rapid, irregular ventricular rate on pumping function. AF and resultant consequences are readily recognized by device diagnostics. The approach here should be aggressive use of drugs to slow AV conduction or restoration of sinus rhythm if possible. Recent evidence suggests that ablation of the AV junction may be necessary to achieve optimal CRT response among patients with permanent AF and intact AV conduction.

Other causes of disruptions to ventricular pacing have been discussed previously. Specific device algorithms intended to maximize ventricular pacing during conducted AF, sinus tachycardia with loss of atrial tracking, or high-frequency ventricular premature beats should be exploited.

Patient–System Interface Causes of CRT Nonresponse

The interaction between the patient and the CRT system presents a complex array of potential causes of CRT nonresponse that is often difficult to discern and not easily resolved. Troubleshooting these causes of CRT nonresponse assumes that [1] electrical operation is normal and [2] patient factors that degrade CRT response independent of electrical operation have been optimized.

Role of Atrial Pacing

A high frequency of atrial pacing may compromise CRT response by disrupting optimal left-sided AV coupling. Programmed paced AV (PAV) delays differ significantly from sensed AV (SAV) delays during sinus rhythm. This is because of (1) latency in atrial capture and sensing, (2) interatrial conduction delay, (3) latency in ventricular capture, and (4) interventricular conduction delay. The situation is made even more complex because all four elements are influenced by atrial and ventricular lead positions.

Capture latency refers to the delay between emission of the right atrial pacing stimulus and atrial contraction (Fig. 21.65). Sensing latency refers to the delay between the onset of atrial depolarization and the time at which the local endocardial signal is sensed (Fig. 21.65). Because of latency in atrial capture and sensing, the optimal AV delay for sensed and paced P-waves may differ. During sinus rhythm, the programmed SAV delay begins when the native P-wave is sensed but the physiologic AV interval, which begins with atrial depolarization and the onset of mechanical contraction, may be delayed due to sensing latency. The mean latency between the beginning of atrial depolarization and the time of atrial sensing is 30–50 ms. Thus, the physiologic AV interval is longer than the programmed SAV delay. The opposite situation occurs during atrial pacing. The programmed AV delay begins with emission of the atrial pacing stimulus, but the physiologic AV interval begins with atrial depolarization and mechanical contraction. The mean latency between atrial output and capture is reported to be 30–50 ms, however it may be >300 ms (Figs. 21.66 and 21.67). The physiologic AV interval is therefore shorter than the programmed PAV delay. The magnitude of atrial capture and sensing latencies varies among patients and is influenced by many factors including lead design, sensing circuitry, amplitude and rate of stimulation, and characteristics of the local endocardial atrial electrogram.

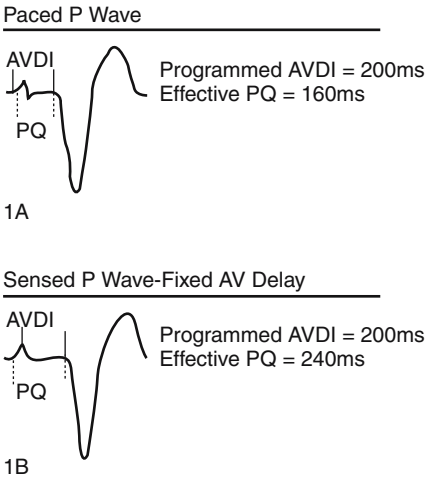


Fig. 21.65 Effect of atrial capture and sensing latency on the physiologic AV interval. (Adapted from Ellenbogen KA, Kay GN, Lau C-P, Wilkoff BL. Clinical Cardiac Pacing, Defibrillation, and Resynchronization Therapy. Philadelphia: Saunders; 2007.)

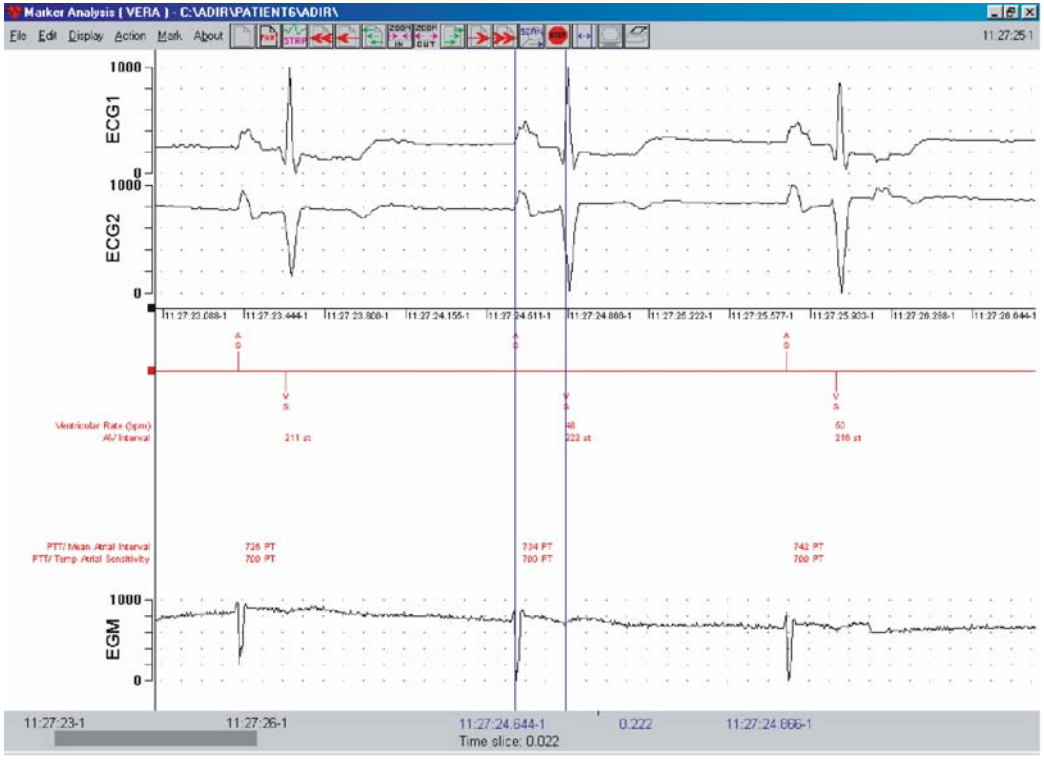


Fig. 21.66 AV intervals during atrial sensing. AS and VS occur at the start of the P- and R-waves, and the AS-VS time of 222 ms corresponds well with the surface ECG P-Q time measured by the cursors.

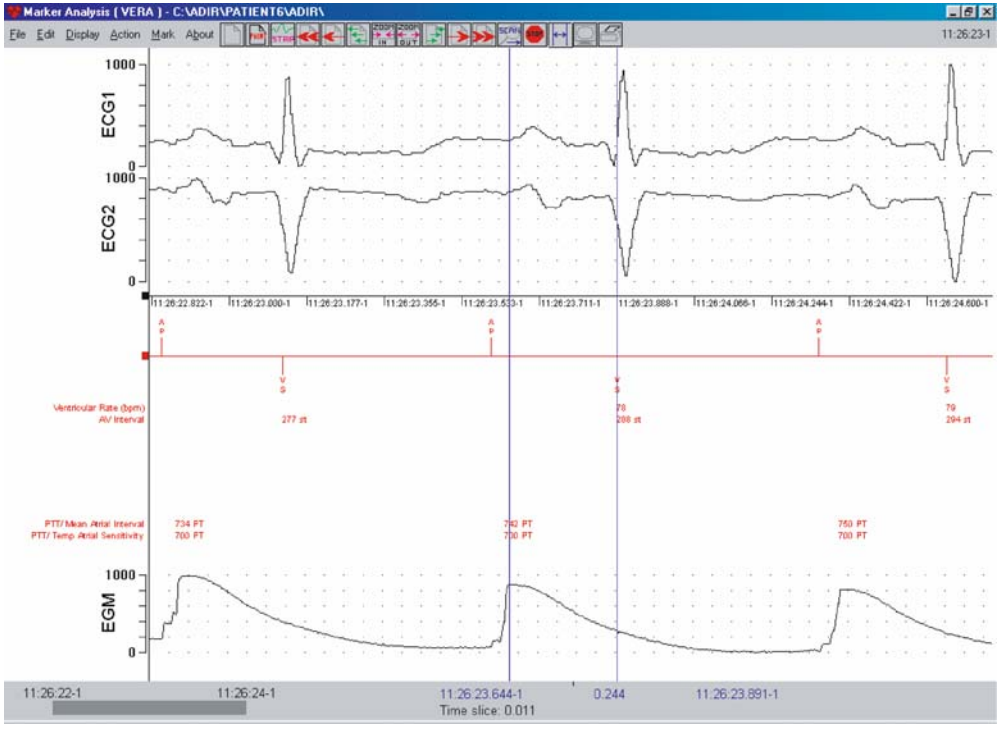


Fig. 21.67 Effect of atrial capture latency on AV interval during atrial pacing. AP occurs sooner than the P-wave is seen on the surface ECG. The AP-VS time is measured at 288 ms, but the time from the start of the P-wave–VS time is nearer to 244 ms. Thus, the AP-VS time is overreported by the device, versus the surface ECG.

Further complicating matters is the effect of autonomic innervation of the AV node during atrial pacing. Atrioventricular intervals during atrial pacing shorten during exercise and lengthen by as much as 150% in the standing or supine position [160]. A mismatch between the lower pacing rate and autonomic balance may contribute to this situation. For example, patients with a relatively high lower rate programmed (i.e., 70 or 80 beats/min) often experience significant AV interval extensions during atrial pacing while sleeping due to parasympathetic predominance (Figs. 21.68 and 21.69).

Additionally, significant interatrial conduction delays may arise due to cardiomyopathy and atrial enlargement, antiarrhythmic drugs, and other causes. Interatrial conduction delays are common during right atrial pacing and are influenced by pacing lead position (Figs. 21.70 and 21.71). Right atrial pacing from the regions of Bachmann's bundle, the fossa ovalis, and the coronary sinus ostium result in less delayed left atrial activation compared with other common pacing sites such as the right atrial appendage).

The common consequence of these effects is that the optimized AV delay is already in progress before left atrial contribution to ventricular filling has begun (Figs. 21.72 and 21.73). In this situation, the optimized AV delay during sinus rhythm may be too short during atrial pacing with adverse effects on left ventricular pumping function.

Atrial pacing should be minimized or avoided altogether if possible. Programming approaches include reducing the lower pacing rate, eliminating sensor-modulated pacing (if active), or choosing an atrial synchronous ventricular pacing mode that does not provide atrial pacing (i.e., VDD at a low programmed rate). If atrial pacing cannot be avoided because of sinus bradycardia, the paced AV delay should be reoptimized using techniques previously described.

Role of Ventricular Conduction Delay

The mere demonstration of ventricular capture on a single-lead ECG strip while pacing the LV does not guarantee that the ventricular activation sequence has been changed. "Functional" loss of LV capture may occur during synchronous biventricular pacing when there is significant latency from the LV pacing site due to epicardial scar. In this situation, LV activation may be dominated by the electrical wavefront caused by RV pacing, despite an adequately programmed LV output. This phenomenon can only be recognized using a 12-lead ECG. This problem can be overcome with the use of V-V timing as previously discussed (Figs. 21.74–21.77).

Whether or not individually optimized sequential biventricular pacing can reduce the number of CRT "nonresponders" is uncertain. Though small studies have shown that sequential ventricular stimulation can reduce intraventricular dyssynchrony [27], increase diastolic filling time [27, 161], reduce functional mitral regurgitation [161], and increase LV +dP/dt and cardiac output [161, 162], this has not been validated in RCTs. Complicating matters is the consistent observation in all of these studies that the individual response to sequential ventricular stimulation is heterogeneous and unpredictable.

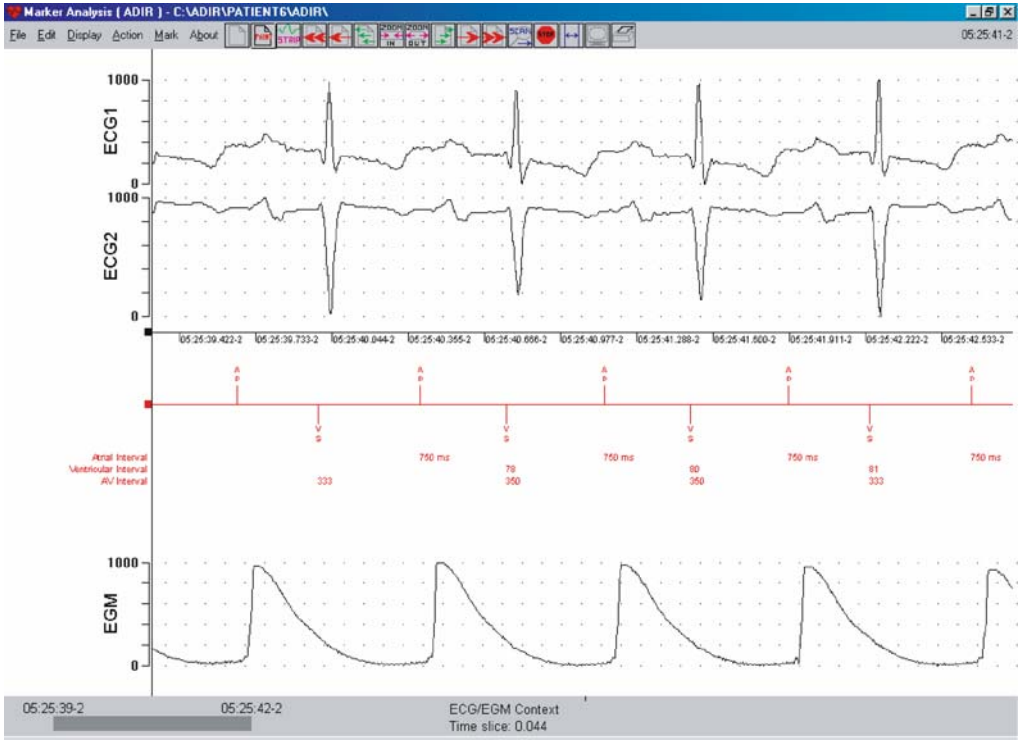


Fig. 21.68 Combined effect of atrial capture latency and increased parasympathetic tone during sleep on AV interval during atrial pacing.

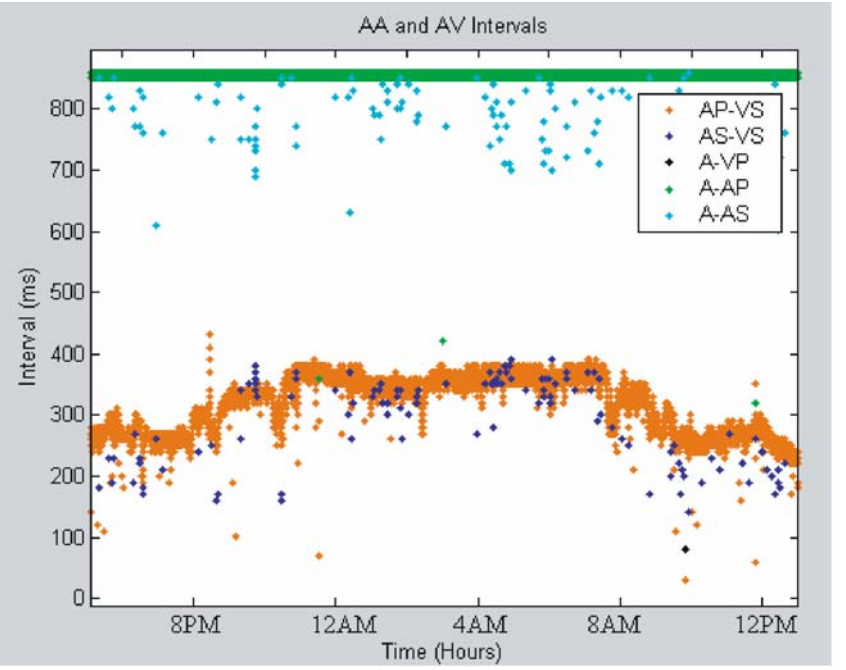


Fig. 21.69 Nocturnal response of AV conduction during atrial pacing. AP-VS time during sleep increases to 350 ms or greater.

Role of LV Stimulation Site for Optimal CRT Response

Overview

The optimal site for LV pacing is an unsettled and complex consideration. It is probably true that the optimal site varies between patients and is likely to be modified by venous anatomy, regional and global LV mechanical function, myocardial substrate, characterization of electrical delay, and other factors. In patients with abnormal ventricular conduction due to LBBB and systolic heart failure, the stimulation site influences the response to LV pacing. The success of resynchronization is dependent on pacing from a site that causes a change in the sequence of ventricular activation that translates to an improvement in cardiac performance. Such systolic improvement and mechanical resynchronization does not require electrical synchrony [6] and explains the lack of correlation between change in QRSd and clinical response to CRT [163]. Ideally, the pacing site or sites that produce the greatest hemodynamic effect would be selected.

Current clinical evidence permits some generalizations regarding LV pacing site selection for optimal acute hemodynamic response. Multiple independent investigations comparing the acute and chronic effects of different pacing sites in similar DCM populations have reported concordant evidence that stimulation site is a primary determinant of CRT hemodynamic benefit.

Auricchio et al. [164, 165] showed a positive correlation between the magnitude of pulse pressure and LV +dP/dt increases and left ventricular pacing site. The percent increases in pulse pressure and LV +dP/dt averaged over all AV delays were significantly larger at midlateral free wall LV

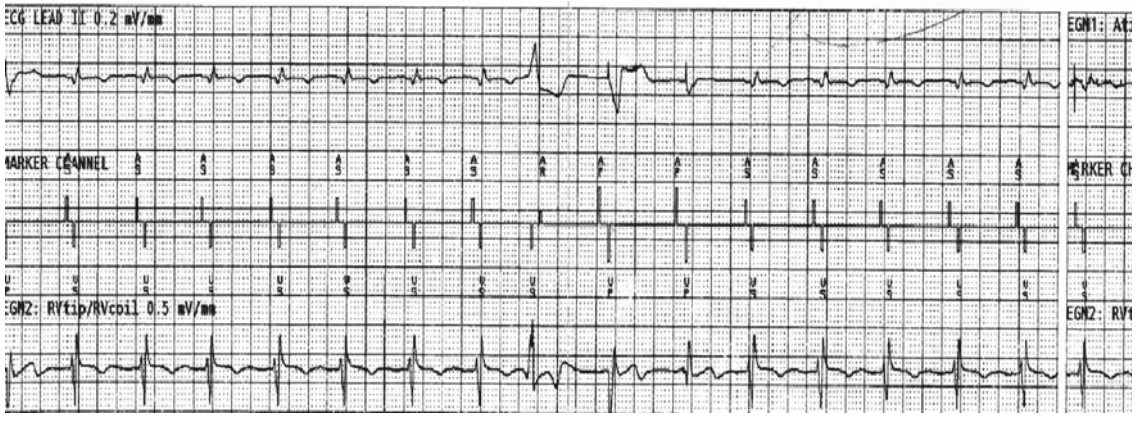


Fig. 21.70 Example of significant interatrial conduction delay during pacing from the right atrial appendage and sensing from the left atrial epicardium. The patient had single-chamber ICD from left superior transvenous approach. Antiarrhythmic drug therapy resulted in symptomatic sinus bradycardia. An attempt to add an atrial lead from the left superior approach failed due to an occluded axillary-subclavian vein. A separate single-chamber atrial pacing system was implanted via the right superior transvenous approach. Subsequently, epicardial left atrial and left ventricular pacing leads were placed for CRT. Left atrial activation is tremendously delayed during sinus rhythm. Note that left atrial activation (AS) occurs almost simultaneously with the preceding RV activation (VS), which is delayed due to first-degree AV nodal block. As a result, no CRT is delivered.

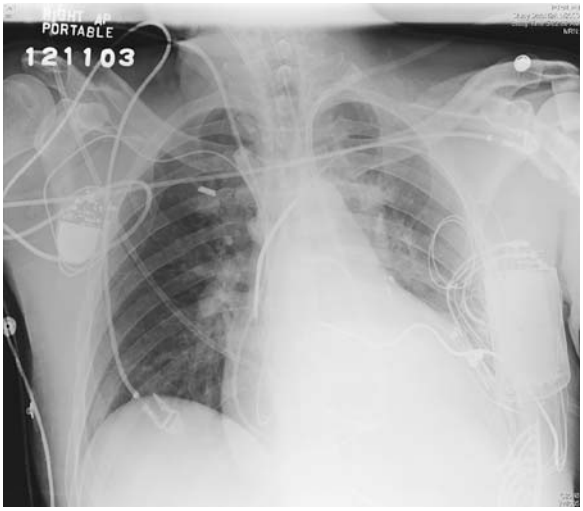


Fig. 21.71 Chest radiograph showing right atrial endocardial and left atrial epicardial lead positions in the patient of Figure 21.70.

epicardial pacing sites compared with any other sample left ventricular region. Furthermore, increases at the midanterior sites were smaller than all other sites.

These observations were extended in an analysis of 30 patients enrolled in the PATCH-CHF II trial (Fig. 21.78) [166]. Left ventricular stimulation was delivered at the lateral free wall or midanterior wall. Free wall sites yielded significantly larger improvements in LV +dP/dt and pulse pressure than anterior sites. Furthermore, in one third of patients, stimulation at anterior sites worsened acute LV hemodynamic performance, whereas free wall stimulation improved it, and the opposite pattern was never observed. This difference in acute hemodynamic response correlated with intrinsic conduction delays (Fig. 21.79). This may be interpreted as evidence that stimulating a later-activated LV region produces a larger response because it more effectively restores regional activation synchrony. Thus, the negative effect of anterior wall stimulation at all AV delays in some patients may be due to preexcitation of an already relatively early-activated site thereby exaggerating intraventricular dyssynchrony [167].

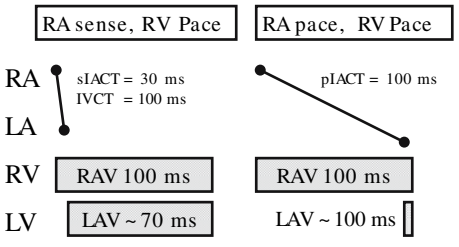


Fig. 21.72 Effect of right-sided AV delays on left-sided AV coupling during DDD pacing. iACT, intrinsic interatrial conduction time; pACT, paced interatrial conduction time; iVCT, interventricular conduction time.

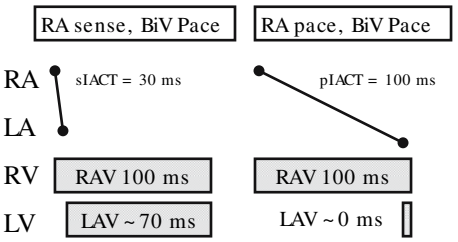


Fig. 21.73 Effect of right-sided AV delays on left-sided AV coupling during simultaneous biventricular pacing. iACT, intrinsic interatrial conduction time; pACT, paced interatrial conduction time; iVCT, interventricular conduction time.

Stimulation at the latest electrically activated (most delayed) region of the LV is associated with greatest hemodynamic response. This is usually on the posterior or posterolateral-basal wall as demonstrated by endocardial voltage mapping [17, 168, 169] and tissue Doppler imaging [170, 171]. CRT with stimulation at a LV free wall site consistently improves short-term systolic function more than stimulation at an anterior site does. Lateral or posterolateral LV vein lead positions are associated with acute improvements in +dP/dt and pulse pressure [164, 166] and significant chronic improvements in functional capacity and ventricular function [172] and possibly mortality [173] compared with anterior vein sites.

It is likely, then, that inadequate LV lead positions contribute significantly to CRT nonresponse. In the MIRACLE study, a lateral or posterolateral vein site was obtained in only 77% of patients, whereas the anterior interventricular vein or middle cardiac vein were used in 19.5% and 4.5% of patients, respectively. A similar situation was reported in the VENTAK CHF/CONTAK CD study where a lateral or posterolateral vein site was obtained in 67% of patients and an anterior interventricular vein site in the remaining 33% [79]. Furthermore, even among patients in whom the transvenous approach failed, necessitating surgical placement of LV leads, a lateral or posterolateral site was obtained in only 34%, whereas the remaining 66% were placed in the anterior or apical LV positions [79]. Thus, even in RCTs of CRT, as many as 23–33% of patients receive LV stimulation from a suboptimal site. It is conceivable that some of these patients were actually made worse by CRT due to LV pacing in the anterior vein, particularly those with relatively narrow QRSd (less than 150 ms) [166]. These differences in LV stimulation sites may partly account for the varied results and large individual difference observed among clinical studies.

Interestingly, in PATH-CHF a very small number of patients with heart failure and LBBB achieved optimal hemodynamic improvement with RV versus LV or biventricular pacing [21]. Electroanatomic mapping has demonstrated that the RV apex is frequently delayed in LBBB, and in select patients, LV preexcitation can be achieved by RV apical pacing due to early breakthrough into the left ventricle at this site (A. Auricchio, personal communication).

Methods for identifying the best site during implantation are not yet of proven clinical benefit. Furthermore, even if optimal LV pacing sites could be identified a priori, access to such sites is potentially constrained by variations in coronary venous anatomy. Despite rapid evolution of implantation techniques including guiding sheaths and catheters and over-the-wire delivery

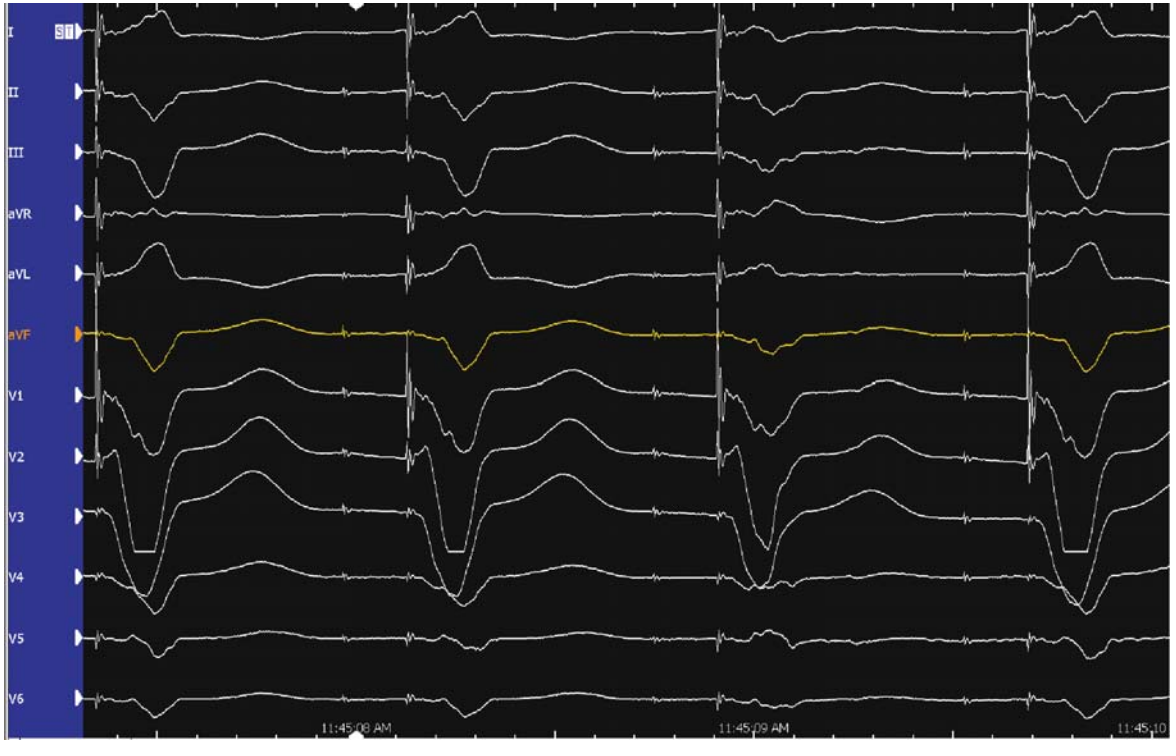


Fig. 21.74 Simultaneous biventricular pacing. Note the pattern of RV apical stimulation; there is no evidence of left ventricular capture based on the paced QRS morphology.

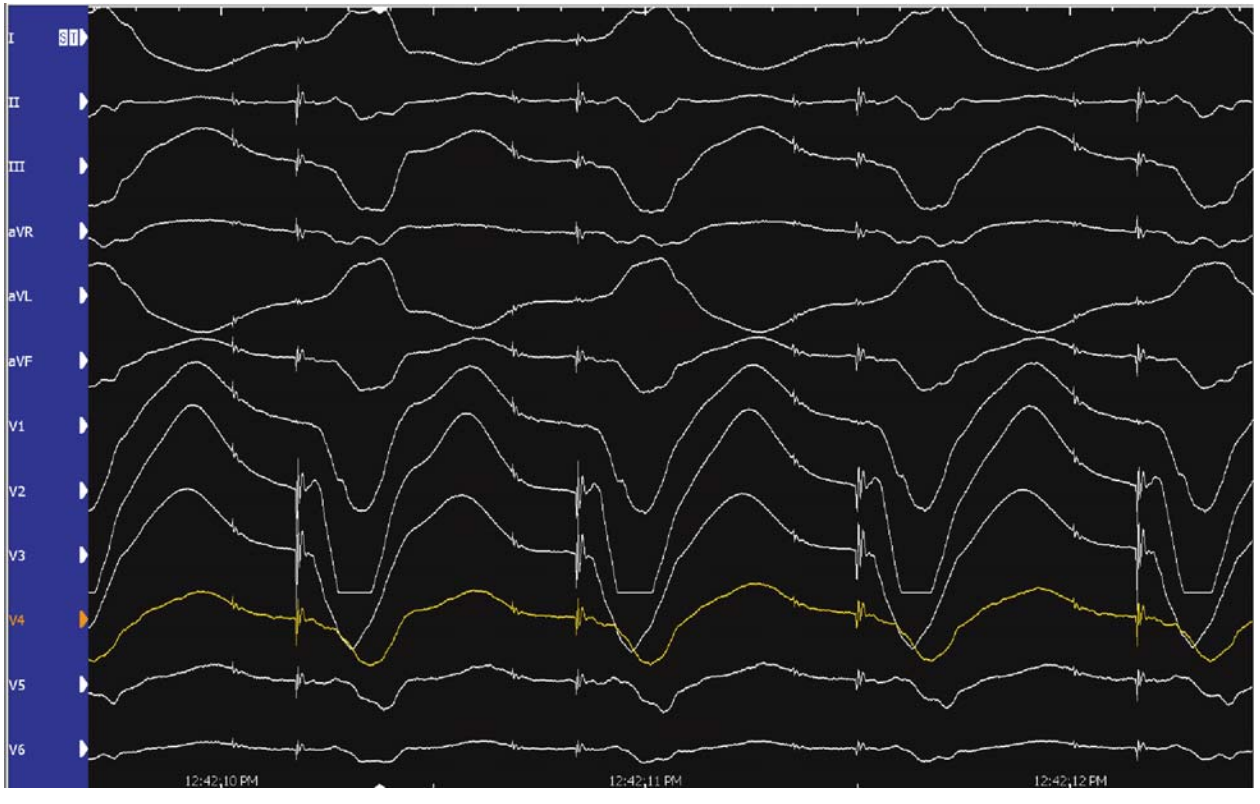


Fig. 21.75 RV only pacing in the patient of Figure 21.74. Note the pattern of RV apical stimulation.

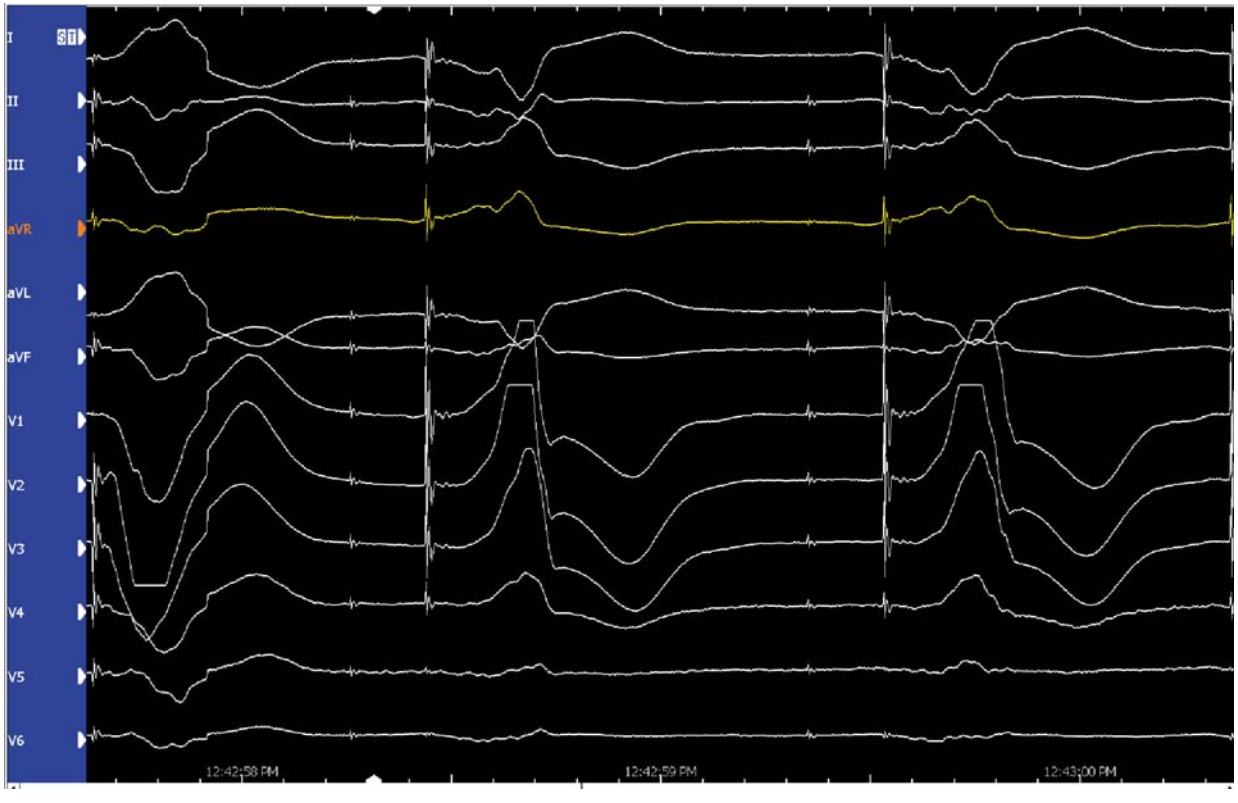


Fig. 21.76 LV only pacing in the patient of Figure 21.74. Note the pattern of LV free wall stimulation.

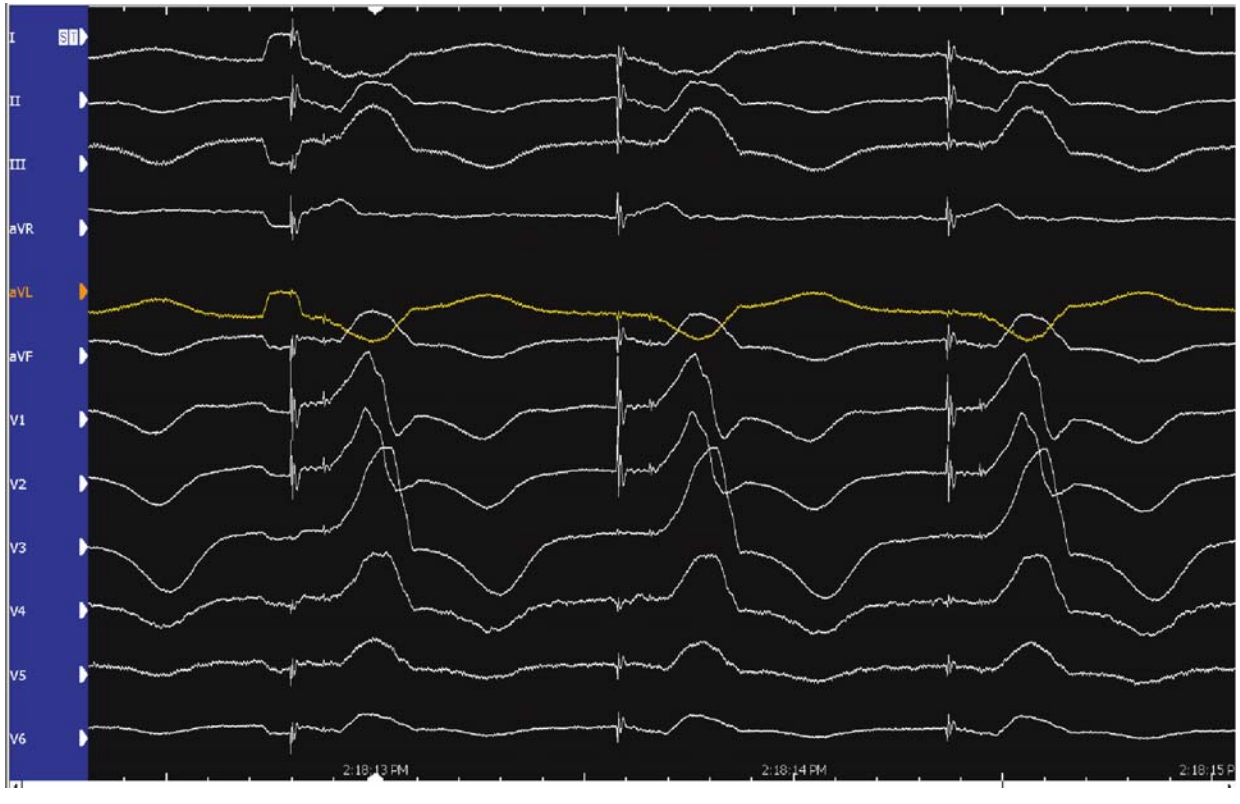


Fig. 21.77 Sequential ventricular stimulation with 80-ms offset (LV > RV). Note restoration of biventricular activation.

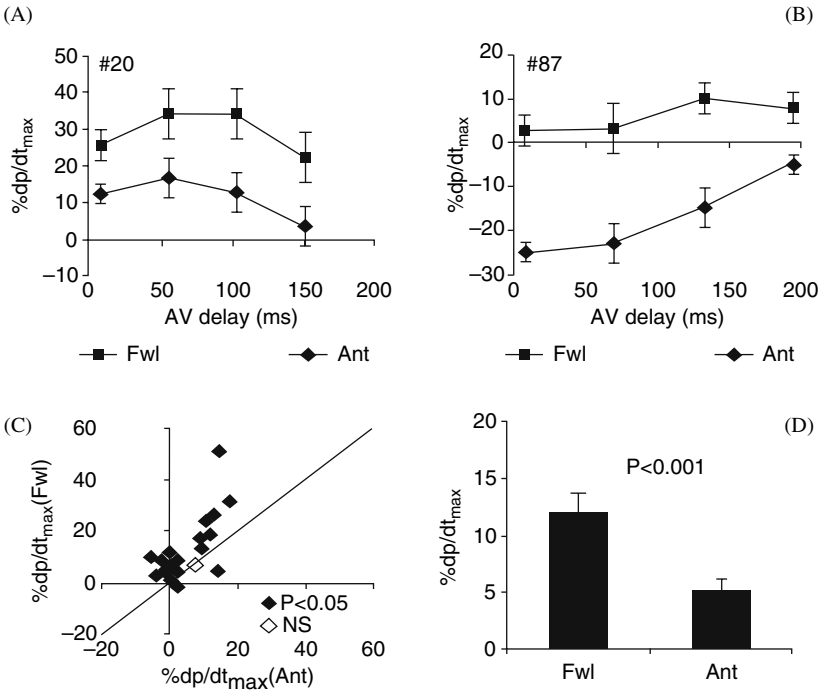


Fig. 21.78 Effect of CRT stimulation site on acute hemodynamic response to CRT. LV stimulation at free wall (FWL) sites yielded significantly larger LV +dP/dt and pulse pressure than anterior (ANT) sites. In one third of patients, stimulation at ANT sites worsened hemodynamic function, whereas FWL stimulation improved it. The opposite pattern was never observed. See text for details. (From Butter C, Auricchio A, Stellbrink C, et al., for the Pacing Therapy for Chronic Heart Failure II Study Group. Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. Circulation 2001;104(25):3026–3029.)

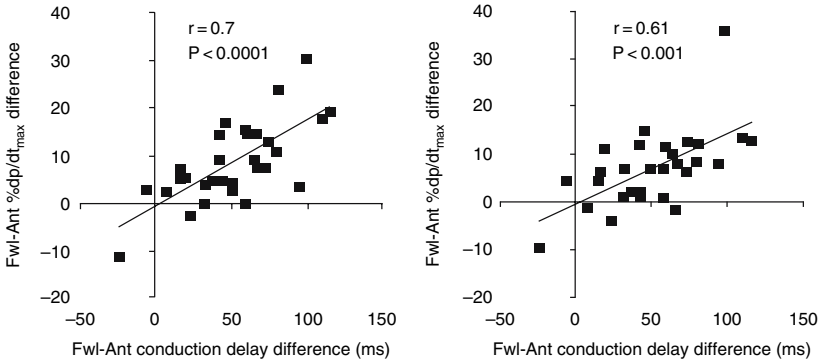


Fig. 21.79 Correlation between free wall (FWL) and anterior wall (ANT) intrinsic conduction delay differences and the LV +dP/dt$_{max}$ response differences during FWL and ANT stimulation for LV CRT (**A**) and BV CRT (**B**). Positive conduction delay differences correspond with more delayed FWL activation. Positive LV +dP/dt$_{max}$ differences correspond with a larger FWL stimulation response (percentage change from baseline). (From Butter C, Auricchio A, Stellbrink C, et al., for the Pacing Therapy for Chronic Heart Failure II Study Group. Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. Circulation 2001;104(25):3026–3029.)

systems, a suitable pacing site on the LV free wall cannot be achieved in 5–10% of patients. Even when the coronary venous anatomy is suitable and navigable, some free wall sites are rejected due to unacceptably high pacing thresholds related to epicardial scar or unavoidable phrenic nerve stimulation. Surgical placement of epicardial LV pacing leads or endocardial LV stimulation [174] are options when the coronary venous approach fails.

Approach to Avoiding or Correcting a Suboptimal LV Lead Position

Ideally, a suboptimal LV lead position should be identified and rejected at the time of implantation. The most common mistake of the uninformed or uncommitted implanter is to place the LV lead in the anterior vein and "see how the patient does." An example of the consequences of this thinking is shown in Figures 21.80 to 21.82. If a patient is not responding to CRT and the LV lead is in the anterior vein, an attempt to reposition the LV lead (or a different lead) in a lateral vein should be made. If this is not possible because of limitations in coronary venous anatomy or other insuperable technical obstacles (see below), the patient should be referred for surgical placement of the LV lead in an optimal location.

Experienced implanters using currently available tools and techniques can achieve optimal LV stimulation using a postero-basal or lateral coronary vein in >90% of cases. The techniques for transvenous delivery of CRT have been previously described [175]. However, some technical aspects merit special mention in order to increase the probability of achieving an optimal LV stimulation site.

Retrograde venography is essential to delineate optimal target veins for LV stimulation. Care must be taken to achieve a good seal within the main body of the coronary sinus in order to obtain maximal opacification of the distal vasculature. Underfilling the coronary venous system is a common mistake

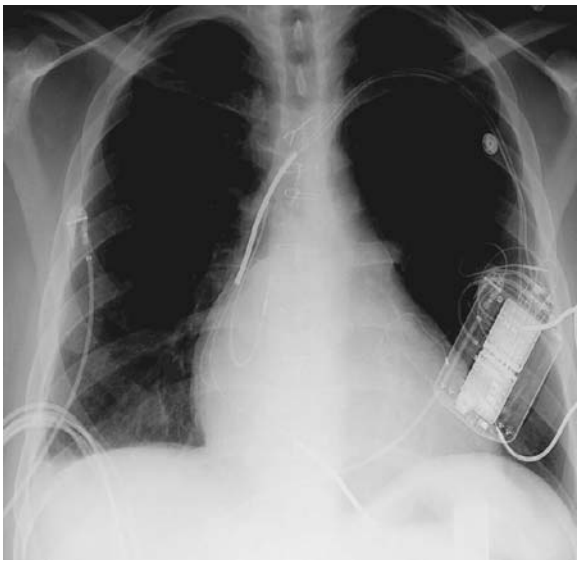


Fig. 21.80 CRT "nonresponder." The patient was a 35-year-old man with nonischemic dilated cardiomyopathy and LBBB in whom a CRTD was implanted February 5, 2002. Note position of LV lead in anterior interventricular vein.

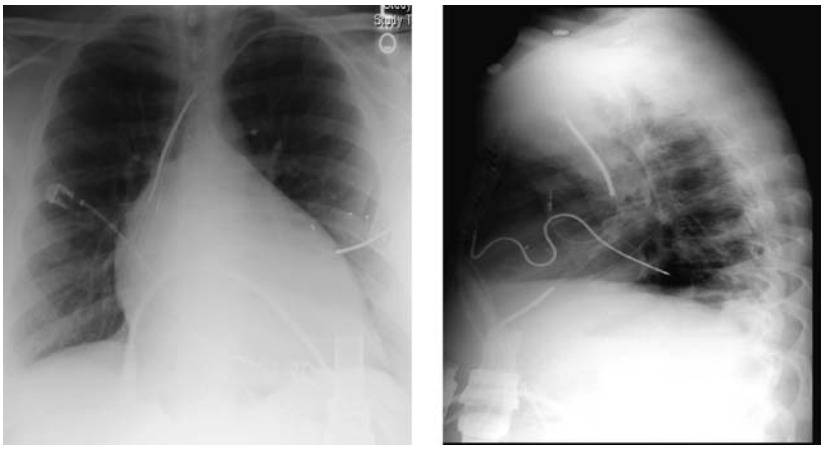


Fig. 21.81 Same patient as in Figure 21.80. The patient deteriorated subsequent to CRT and was rehospitalized on February 10, 2003, in cardiogenic shock, at which time a LVAD was implanted.

that may result in failure to identify potentially suitable targets for LV pacing lead placement. Occasionally, the inflated balloon will occlude the ostium of a suitable branch vessel for LV lead placement, therefore occlusive venography at multiple levels within the main CS are advisable.

Factors Limiting Optimal LV Lead Placement

Complex and unpredictable anatomic and technical considerations may preclude successful delivery of the LV lead to an optimal pacing site.

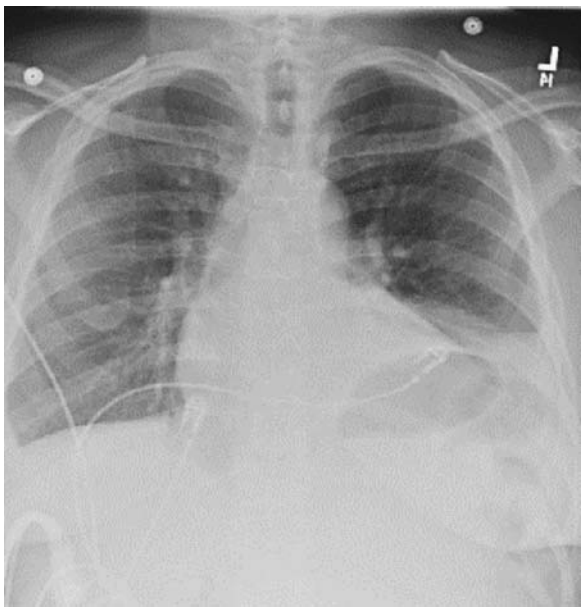


Fig. 21.82 Same patient as in Figures 21.80 and 21.81. Orthotopic heart transplant was performed on July 11, 2004.

Inability to Cannulate the Coronary Sinus

It is difficult to estimate the true percentage of cases in which the coronary sinus cannot be cannulated because this is clearly influenced by operator experience. It is probably in the range 1–5%. When the coronary sinus cannot be located by the superior approach, an adaptation of the inferior approach described for complex electrophysiology procedures is often successful in localizing the CS ostium.

Coronary Venous Anatomy: Absent or Inaccessible Target Veins

The coronary venous circulation demonstrates considerably more variability than the parallel arterial circulation. Careful studies of retrograde coronary venography have revealed that the anterior interventricular vein is present in 99% of patients and the middle cardiac vein is present in 100%. These veins are generally undesirable for LV preexcitation because they do not reach the late-activated portion of the LV free wall. Unfortunately, approximately 50% of patients have only a single vein serving the LV free wall. Anatomically, this is a lateral marginal vein in slightly more than 75% and a true posterior vein that ascends the free wall in approximately 50% of patients [176]. Thus, as many as 20% of patients may not have a vein that reaches the optimal LV free wall site for delivery of CRT. In some instances, target veins are present but too small for cannulation with existing lead systems or paradoxically too large to achieve mechanical fixation with reduced-diameter LV leads that rely primarily on "wedging" the lead tip into a distal site within the target vein for fixation such that the outer diameter of the lead closely approximates the inner luminal diameter of the vein.

Newer lead designs incorporate various self-retaining bends or cants that compress the distal segment of the lead against the outer wall of the vein and the epicardial surface of the heart. This permits fixation in larger-diameter veins and may be particularly useful for overcoming phrenic nerve stimulation or high pacing thresholds that would otherwise render optimal target veins unsuitable for use (see below).

Coronary Venous Tortuosity and Stenoses

Another commonly encountered difficulty in transvenous LV lead placement is tortuosity of the target vessel take-off or main segment. These anatomic constraints can be extremely difficult to overcome and often require the use of multiple LV lead designs and delivery systems. Larger-diameter stylet-driven leads are likely to fail in this situation unless they can be delivered with an inner guiding sheath that selectively cannulates and straightens the proximal segment of the tortuous target vein. Another approach utilizes coronary, renal, or other angiography catheters to selectively cannulate the small and tortuous target vein. A guide wire can then be placed deep into the target vein permitting delivery of an over-the-wire LV lead. In many instances, the guide wire itself will straighten the tortuous segment of the target vein permitting navigation of the LV lead. If significant resistance to lead advancement persists despite a guide wire, a second guide wire placed alongside the first ("buddy wire technique") may sufficiently straighten the vein to permit lead advancement.

Biventricular or LV Only Stimulation: Role in CRT Nonresponders?

It is important to note that uncertainty about the requirement of RV stimulation during CRT, uneasiness about long-term LV lead performance, and

unavailability of pacing systems with separately programmable ventricular outputs influenced the use of biventricular pacing, as opposed to left univentricular pacing, in large RCTs. A particular concern is LV lead dislodgment that has a reported incidence of 5–10% in larger studies [48, 53, 108] and would impose risk for potentially lethal bradycardia. However, there is some scientific evidence that RV stimulation might not be necessary for optimal CRT response or even that LV pacing alone might be superior to biventricular pacing in some patients.

Left univentricular pacing alone has acute hemodynamic effects that are similar or superior to those achieved with biventricular pacing in some patients [27, 159, 177, 178, 179]. Blanc and co-workers recently extended these observations [180]**.** Functional capacity (6-min walk and maximal O_2 uptake), ventricular size and function, and blood norepinephrine levels prior to and after 12 months of left univentricular pacing were evaluated in 22 patients with dilated cardiomyopathy, LBBB NYHA class III or IV heart failure. The LV lead was placed in a lateral coronary vein when possible, and all patients had sinus rhythm to allow atrial synchronous left univentricular pacing with an AV delay initially programmed to 100 ms. Significant improvements in functional capacity, echocardiographic mitral regurgitation, and LV end diastolic diameter were observed with favorable trend toward improvement in EF. Thus, these results are encouraging and support persistent benefit (at least to 1 year) of left univentricular pacing in some patients.

Both LV and biventricular pacing synchronize LV contraction. This "retiming" effect was initially attributed to "preexcitation" of the delayed LV segments. However, insights from tissue Doppler studies have revealed that LV pacing from a late-activated site achieves synchronous contraction by simultaneously delaying all LV segments [56,161]. This is a potentially critical observation because LV pacing reverses electrical activation and abolishes intraventricular dyssynchrony but with the result of a marked increase in LV activation time compared with biventricular pacing [6]. The consequences are a greater delay in RV contraction [159] and a shortened diastolic filling time that may have implications for ventricular pumping function, particularly at higher heart rates [161, 181].

Thus, it is theoretically possible that LV only pacing may achieve superior hemodynamic performance compared with biventricular pacing in some patients. For this reason, LV only pacing should probably be considered in the management of CRT nonresponders initially treated with biventricular pacing. This could be easily achieved noninvasively in the situation where a true bipolar LV lead is used with a pulse generator capable of separately programmable ventricular outputs. A similar effect could be achieved in the case of a unipolar LV lead (dual cathodal configuration) by programming RV output below the capture threshold. This could not be achieved in a dual cathodal configuration without separately programmable ventricular outputs unless the LV threshold was significantly lower than the RV threshold. In any event, it is not currently possible to identify patients who will respond better to LV alone compared with biventricular pacing.

Absence of Ventricular Mechanical Dyssynchrony

Finally, the lack of response to CRT may be due to the absence of intraventricular dyssynchrony despite patient selection according to existing guidelines

(see above). The most critical realization is that the electrical and mechanical synchrony achieved with the "infinite electrode" of the specialized conduction system cannot be duplicated with any pacing technique *(* except His bundle pacing*).* Alternate site or biventricular pacing in hearts *without abnormal ventricular conduction* still results in abnormal activation patterns, albeit less than during RVA pacing [149]. In this situation, LV or biventricular pacing will cause a dyssynchronous ventricular contraction that may worsen pumping function. Therefore, if no other correctable causes of CRT nonresponse are identified, an echocardiographic evaluation for intraventricular dyssynchrony should be performed during inhibition of ventricular pacing. If the underlying native ventricular contraction is synchronous, ventricular pacing in any form should be eliminated. If bradycardia support is necessary, this should be provided in an atrial-based mode.

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22

The Standard Electrocardiogram During Cardiac Resynchronization

S. Serge Barold, Michael Giudici, and Bengt Herweg

The "low-tech" paced 12-lead surface ECG has fallen into disuse for routine pacemaker evaluation because it adds expense that is not usually reimbursed and requires an additional piece of hardware [1]. However, the advent of cardiac resynchronization therapy (CRT) has made the 12-lead ECG an essential part of device evaluation and troubleshooting [2, 3, 4, 5, 6, 7]. This discussion deals mostly with depolarization during biventricular pacing. The important effect of left ventricular and biventricular pacing on repolarization (QT interval and related phenomena) is described in another chapter.

Dominant R-wave of the Paced QRS Complex in Lead V_1 During Conventional Right Ventricular Pacing

The introduction of left ventricular (LV) and biventricular pacing has increased the diagnostic importance of a dominant R-wave of paced beats in lead V_1 during right ventricular (RV), LV, and biventricular stimulation.

A dominant R-wave in V_1 (R/S >1) during RV pacing has been called a right bundle branch block (RBBB) pattern of depolarization, but this terminology is potentially misleading because this pattern may not be related to RV activation delay (Table 22.1). In our experience, a dominant R-wave of a paced ventricular beat in the right precordial leads (V_1 and V_2 recorded in the 4th intercostal space) occurs in approximately 8–10% of patients with uncomplicated RV apical pacing [8,9,10,11]. The position of precordial leads V_1 and V_2 should be checked, because a dominant R-wave can sometimes be recorded at the level of the 3rd or 2nd intercostal space during uncomplicated RV apical pacing. The pacing lead is almost certainly in the RV (apex or distal septal site) if leads V_1 and V_2 show a negative QRS complex when recorded one space lower (5th intercostal space). However, a dominant R-wave may not be always eliminated at the level of the 5th intercostal space if RV pacing originates from the midseptal region [3]. Furthermore, in the normal situation with the ventricular lead in the RV, the RBBB pattern from pacing RV sites results in a vector change from positive to negative by lead V_3 in the precordial sequence. Therefore, a tall R-wave in V_3 and V_4 signifies that

Table 22.1 Causes of a dominant R-wave in lead V_1 during conventional right ventricular apical pacing.

• Ventricular fusion
• Pacing in the myocardial relative refractory period
• Left ventricular pacing from the coronary venous system
• Left ventricular endocardial or epicardial pacing
• Lead perforation of the right ventricle or ventricular septum with left ventricular stimulation
• Uncomplicated right ventricular pacing (lead V_1 recorded too high or in the correct place)

a pacemaker lead is most probably not in the right ventricle after excluding ventricular fusion from spontaneous AV conduction. However, LV pacing (endocardial or from the coronary venous system) that generates a positive complex in lead V_1 may not necessarily be accompanied by a positive QRS complex in leads V_2 and V_3.

RV outflow tract pacing does not cause a dominant R-wave in lead V_1 despite the following statement, which appeared in a recent book on resynchronization [3]: "Right ventricular leads placed in the right ventricular outflow tract, particularly in more leftward locations, produce a right bundle branch pattern because the right ventricular outflow tract is located on the left side of the body … ." Also: "… the relatively leftward location of a pacing site in the right ventricular outflow tract produces a positive deflection or right bundle branch block." RV outflow or septal pacing invariably generates a left bundle branch block (LBBB) pattern in the precordial leads. We have never seen a so-called RBBB pattern (defined as a dominant R-wave) in lead V_1 during RV outflow tract or septal pacing and it has never been reported so far. In this context, it is important to remember that right axis deviation of the ventricular paced beats in the frontal plane with a deep S-wave in leads I and aVL does not constitute a RBBB pattern without the presence of a dominant R-wave in lead V_1 [3].

Significance of a Small r-wave in Lead V_1 During Uncomplicated RV Pacing

A small early (r) wave (sometimes wide) may occasionally occur in lead V_1 during uncomplicated RV apical or outflow tract pacing. There is no evidence that this r-wave represents a conduction abnormality at the RV exit site. Furthermore, an initial r-wave during biventricular pacing does not predict initial LV activation [3].

Left Ventricular Endocardial Pacing

Passage of a pacing lead into the LV rather than the RV occurs usually via an atrial septal defect (patent foramen ovale) or less commonly via the subclavian artery [12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27]. The diagnosis of a malpositioned endocardial LV lead will be missed in a single-lead ECG. The problem may be compounded if the radiographic malposition of the lead is not obvious or insufficient projections are taken. A 12-lead paced ECG

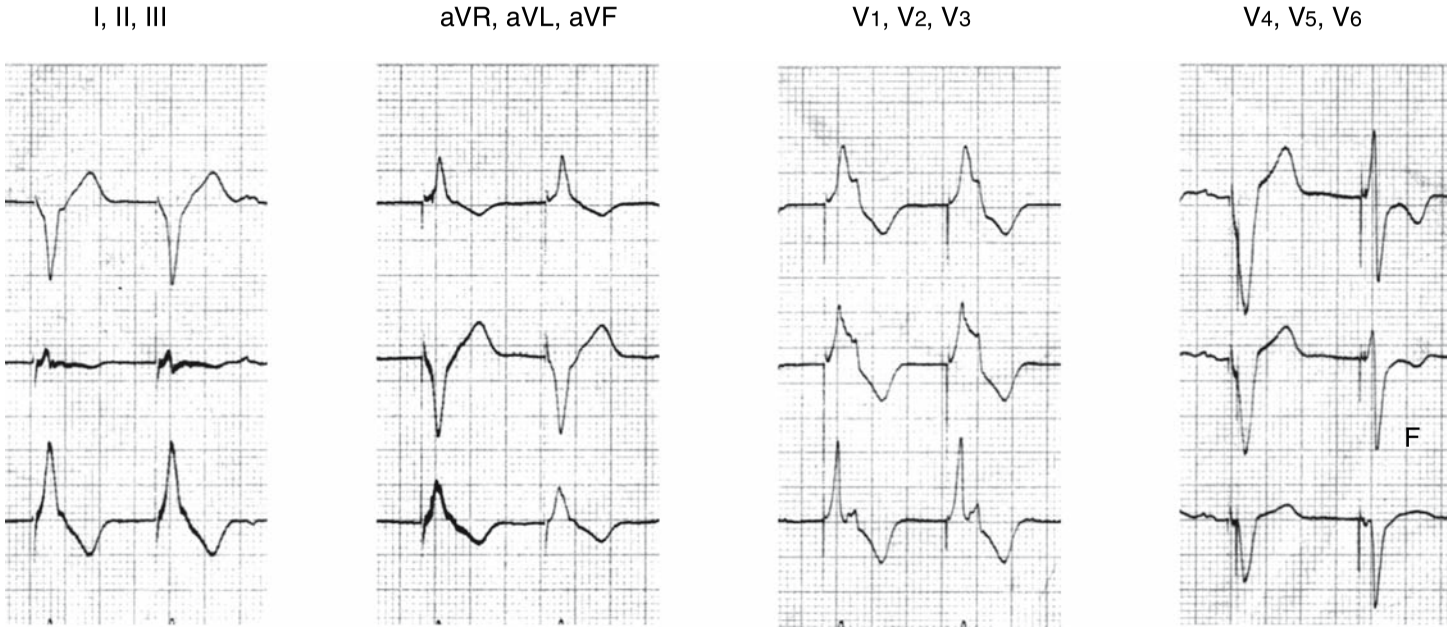

Fig. 22.1 Left ventricular endocardial pacing. ECG of a patient who received a dual-chamber pacemaker for sick sinus syndrome. Three years after pacemaker implantation, he presented with several transient ischemic attacks (TIAs). An ECG taken when the pacemaker was programmed to the VVI mode showed ventricular paced beats with a dominant R-wave in leads V_1–V_3 and right axis deviation in the frontal plane. There was a ventricular fusion beat in leads V_4–V_6. A transesophageal echocardiogram confirmed the position of the ventricular lead in the left ventricle passing from the right atrium to the left atrium and crossing the mitral valve. The lead was successfully extracted percutaneously without complications using a modified technique to prevent embolization. A new lead in the right ventricle produced ventricular paced beats with the typical left bundle branch pattern and left superior axis deviation in the frontal plane. (Reproduced with permission from Barold SS, Giudici MC, Herweg B, Curtis AB. Diagnostic value of the 12-lead electrocardiogram during conventional and biventricular pacing for cardiac resynchronization. Cardiol Clin 2006; 24:471–490).

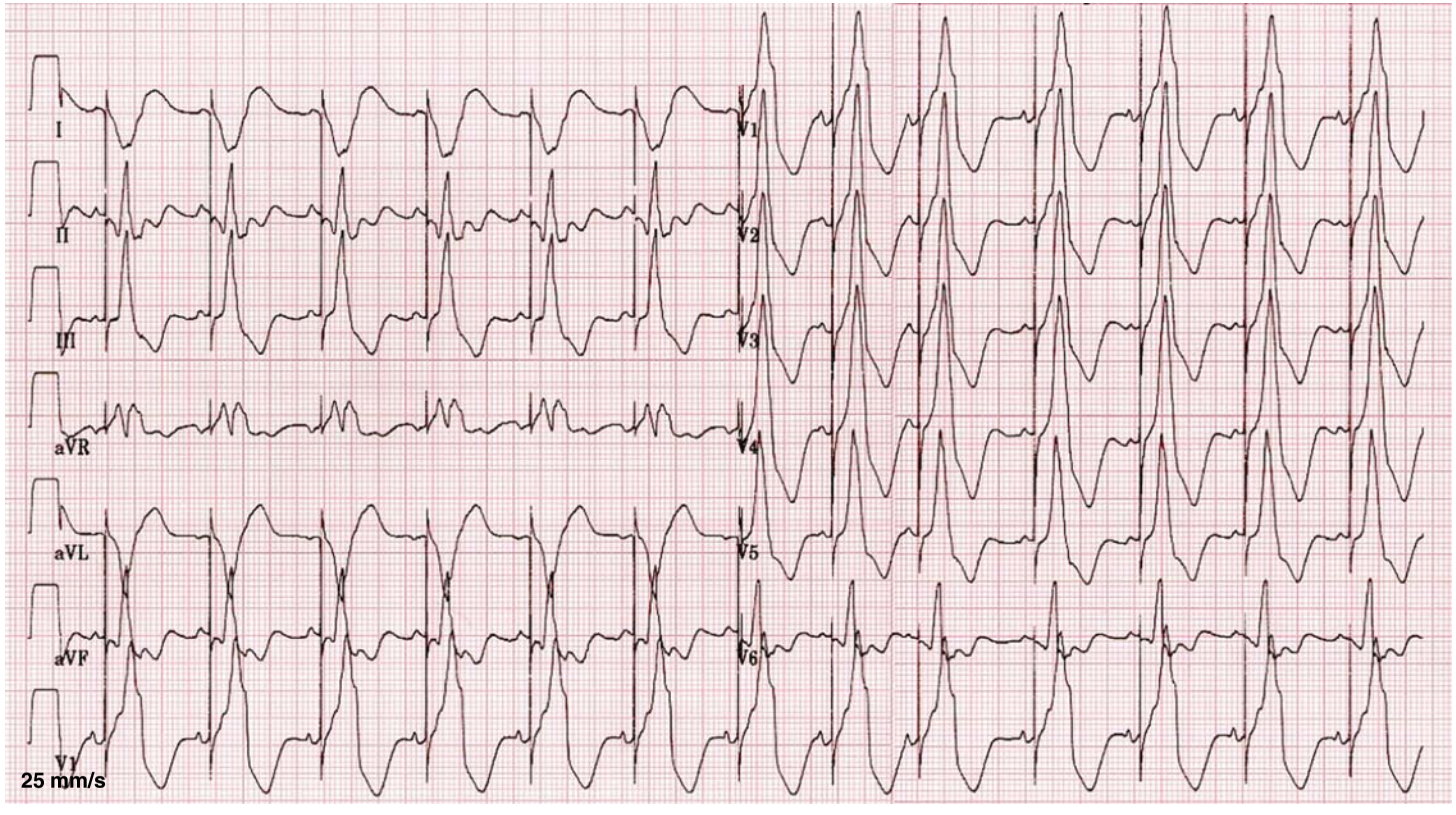

Fig. 22.2 Twelve-lead ECG showing monochamber LV pacing from the coronary venous system. There is typical right bundle branch pattern and right axis deviation. Note the dominant R-wave from V_1 to V_6 consistent with basal LV pacing. LV pacing shown in all the subsequent figures was performed from the coronary venous system. (Reproduced with permission from Barold SS, Herweg B, Giudici M. Electrocardiographic follow-up of biventricular pacemakers. Ann Noninvasive Electrocardiol 2005;10:231–255).

will show a RBBB pattern of paced ventricular depolarization, commonly with preserved QRS positivity in the right precordial leads or at least V_1 (Fig. 22.1). The positive QRS complexes are unaltered when leads V_1 and V_2 are recorded one intercostal space lower. During LV pacing, the frontal plane axis of paced beats can indicate the site of LV pacing, but as a rule with a RBBB configuration, the frontal plane axis cannot differentiate precisely an endocardial LV site from one in the coronary venous system. The diagnosis of an endocardial LV lead is easy with transesophageal echocardiography. In the usual situation, it will show the lead crossing the atrial septum then passing through the mitral valve into the LV.

ECG Patterns Recorded During LV Pacing from the Coronary Venous System

Pacing from the lateral or posterolateral vein invariably produces a RBBB pattern in a correctly positioned lead V_1 [2, 3, 4, 5, 7, 29] (Fig. 22.2). Leads V_2 and V_3 may or may not be positive. With apical sites, leads V_4–V_6 are typically negative. With basal locations, leads V_4–V_6 are usually positive as with the concordant positive R-waves during overt preexcitation in left-sided accessory pathway conduction in the Wolff–Parkinson–White syndrome [3]. During pacing from the correct site in the coronary venous system, the frontal plane axis often points to the right inferior quadrant (right axis deviation) and less commonly to the right superior quadrant. In an occasional patient with uncomplicated LV pacing with a typical RBBB pattern in lead V_1, the axis may point to the left inferior or left superior quadrant. The reasons for these unusual axis locations are unclear.

Pacing from the proximal part of the middle cardiac vein or the great (anterior) vein may produce a RBBB pattern, but stimulation from a more distal site yields a LBBB configuration. [28, 29, 30, 31, 32, 33, 34, 35, 36] (Fig. 22.3).

Negative QRS Complex in Lead V_1

When lead V_1 shows a negative QRS complex during LV pacing, one should consider incorrect ECG lead placement (lead V_1 too high as in Fig. 22.4), location in the middle or great (anterior interventricular) cardiac vein, or an undefined mechanism requiring elucidation [2].

Negative QRS Complex in Lead I

During RV apical pacing, the frontal plane axis points superiorly mostly to the left but occasionally to the right (superior quadrant). In the latter case, lead I shows a negative QRS deflection. This negativity (which is normal) has been erroneously interpreted as representing left-sided pacing [1].

ECG Patterns and Follow-up of Biventricular Pacemakers

So far, evaluation of the overall ECG patterns of biventricular pacing has focused mostly on simultaneous RV and LV stimulation [2, 5, 7, 37–40]. A baseline 12-lead ECG should be recorded at the time of implantation during

A

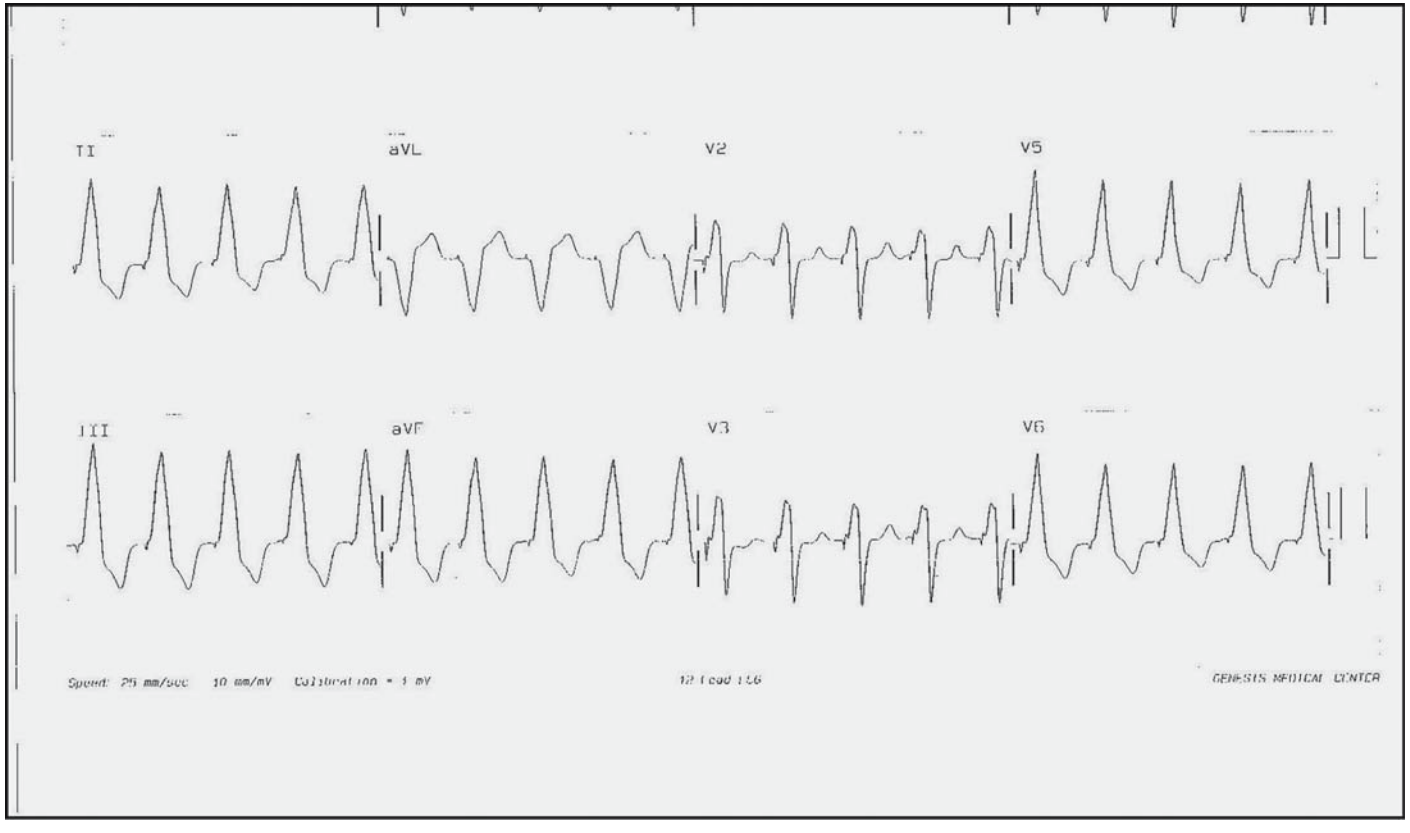

Fig. 22.3 (**A**) ECG during pacing the proximal part of the great cardiac (anterior interventricular) vein showing a RBBB pattern.

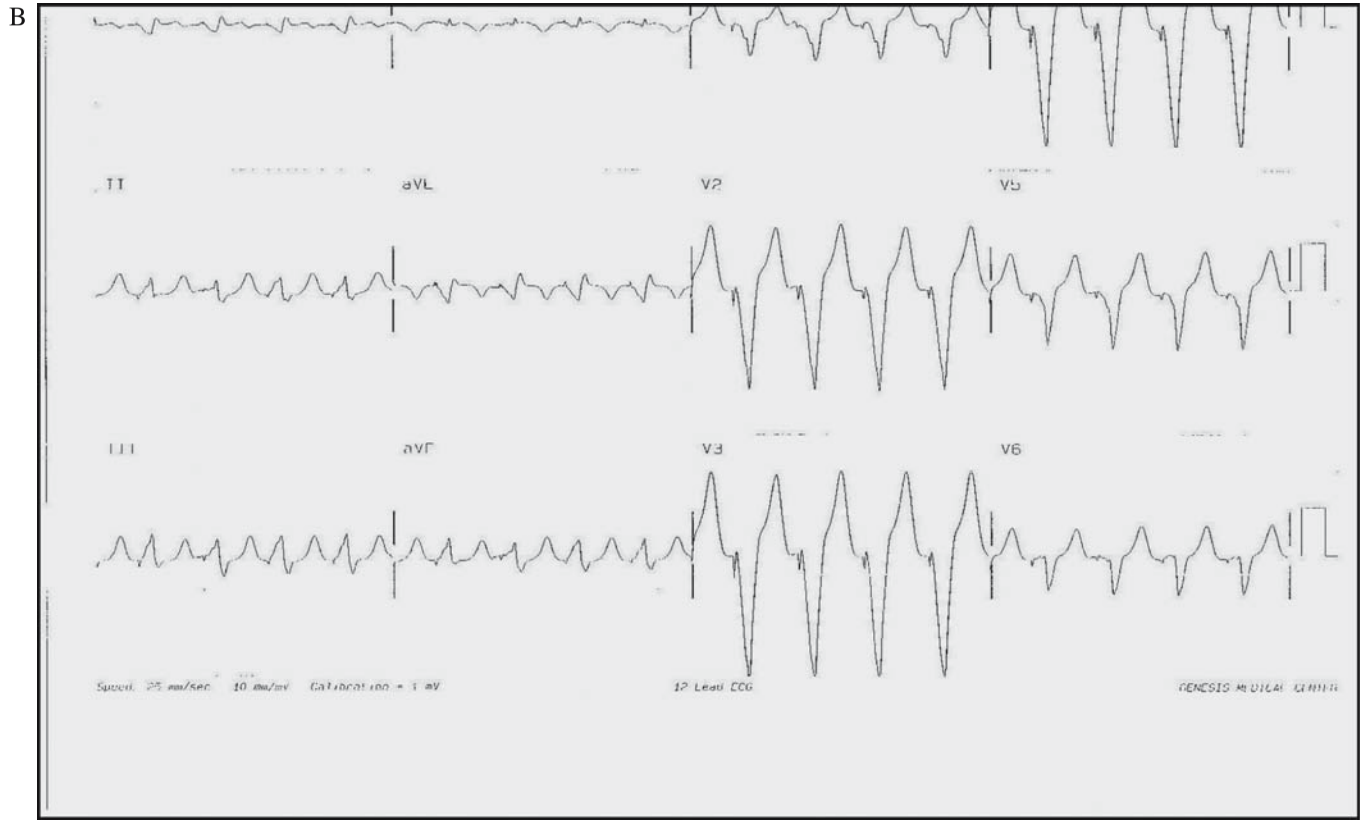

Fig. 22.3 (**B**) The ECG shows a LBBB pattern during pacing more distally in the great cardiac vein.

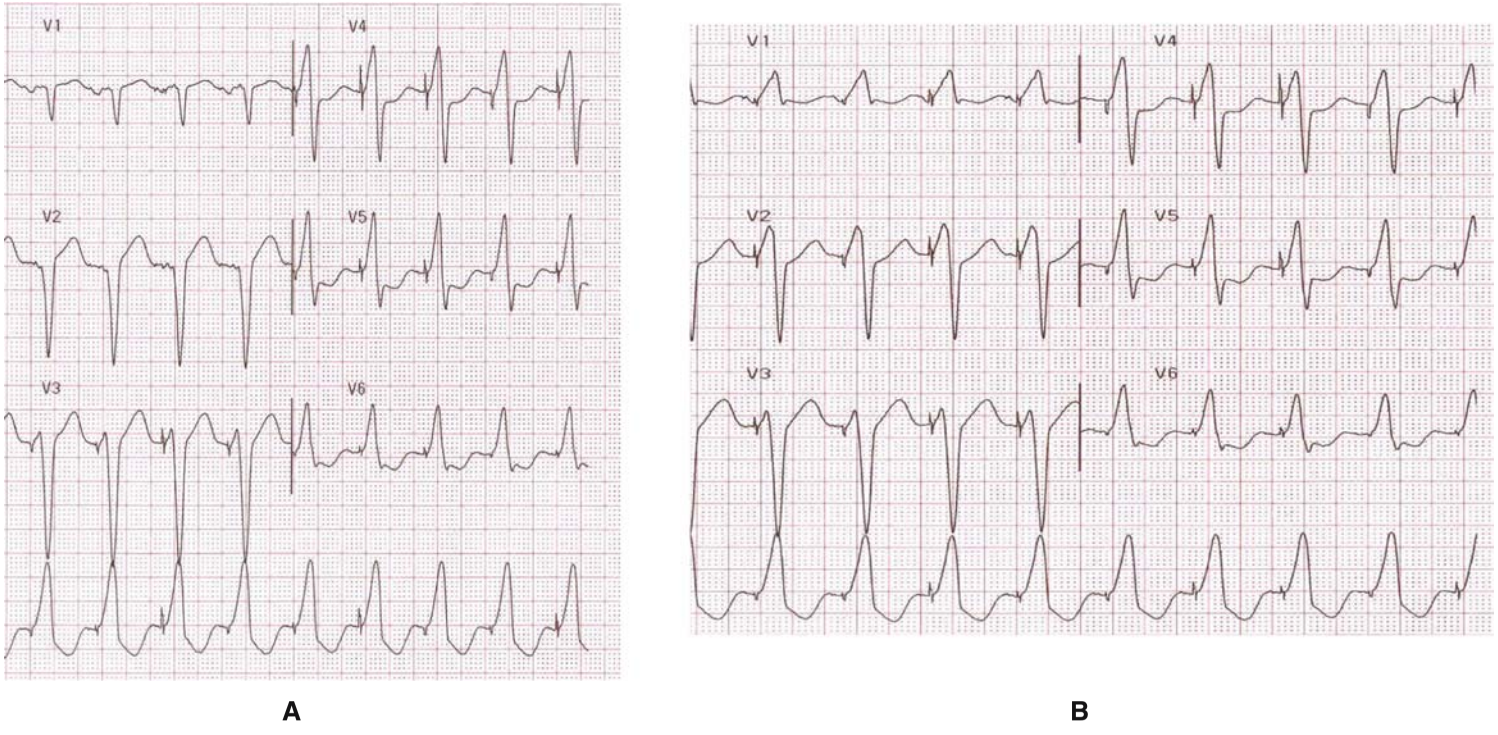

Fig. 22.4 (**A**) Twelve-lead ECG recorded during LV pacing with leads V_1 and V_2 placed at the level of the second intercostal space in a thin patient with an elongated chest. There is no dominant R-wave in lead V_1. Biventricular pacing also failed to show a dominant R-wave in V_1 at the same intercostal space. (**B**) The dominant R-wave in V_1 during LV pacing becomes evident only when lead V_1 is recorded in the 4th intercostal space. The R-wave in V_1 recorded in the 4th intercostal space during biventricular pacing also became dominant. (Reproduced with permission from Barold SS, Giudici MC, Herweg B, Curtis AB. Diagnostic value of the 12-lead electrocardiogram during conventional and biventricular pacing for cardiac resynchronization. Cardiol Clin 2006;24:471–490).

assessment of the independent capture thresholds of the right ventricle and left ventricle to identify the specific morphology of the paced QRS complexes in a multiplicity of leads [1]. This requires having the patient connected to a multichannel 12-lead ECG during the implantation procedure. A total of four 12-lead ECGs are required: [1] intrinsic rhythm and QRS complex prior to any pacing; [2] paced QRS associated with RV pacing; [3] paced QRS associated with LV pacing; [4] paced QRS associated with biventricular pacing. The four tracings should be examined to identify the lead configuration that best demonstrates a discernible and obvious difference between the four pacing states (inhibited, RV only, LV only, and biventricular). This ECG lead should then be used as the surface monitoring lead for subsequent evaluations. Loss of capture in one ventricle will cause a change in the morphology of ventricular paced beats in the 12-lead ECG similar to that of either single-chamber RV pacing or single-chamber LV pacing. A shift in the frontal plane axis may be useful to corroborate loss of capture in one of the ventricles [2,3,6,7]. If both the native QRS and the biventricular paced complex are relatively narrow, then a widening of the paced QRS complex will identify loss of capture in one chamber with effectual capture in the other.

Paced QRS Duration

The paced QRS during biventricular pacing is often narrower than that of monochamber RV or LV pacing. Thus, measurement of QRS duration during follow-up is helpful in the analysis of appropriate biventricular capture and fusion with the spontaneous QRS [3,4,7]. If the biventricular ECG is virtually similar to that recorded with RV or LV pacing alone and no cause is found, one should not automatically conclude that one of the leads does not contribute to biventricular depolarization without a detailed evaluation of the pacing system.

There is no correlation between QRS narrowing after ventricular resynchronization and the clinical response [41, 42, 43]. In some cases, the QRS complex after CRT may actually lengthen or remain unchanged despite substantial improvement in mechanical LV dyssynchrony. Increased QRS duration with CRT does not necessarily reflect the presence of ventricular areas with slow conduction resulting in more heterogeneous myocardial activation. With monochamber LV pacing, there is an obvious discrepancy between QRS duration (compared with baseline) and hemodynamic and clinical improvement [43]. Some patients with monochamber LV pacing exhibit an equal or superior degree of mechanical resynchronization compared with biventricular pacing despite a very wide paced QRS complex [44]. Thus, in CHF patients, the paced QRS duration cannot be assumed to reflect a more heterogeneous propagation pattern of LV activation and prolonged duration of mechanical activation.

Usefulness of the Frontal Plane Axis of the Paced QRS Complex

Table 22.2 and Figure 22.5 show the importance of the frontal plane axis of the paced QRS complex in determining the arrangement of pacing during testing of biventricular pacemakers [2,5,7]. The shift in the frontal plane QRS axis during programming the ventricular output is helpful in determining the

Table 22.2 Change in frontal plane axis of paced QRS when programming from biventricular to monochamber left ventricular and right ventricular pacing.

Pacing site	QRS in lead I	QRS in lead III	Axis shift
BiV → RV	Greater positivity	Greater negativity*	Clockwise
BiV → LV	Greater negativity	Greater positivity	Counterclockwise

BiV, biventricular; RV, right ventricle; LV, left ventricle.
*QRS in lead III is more negative than in lead II.

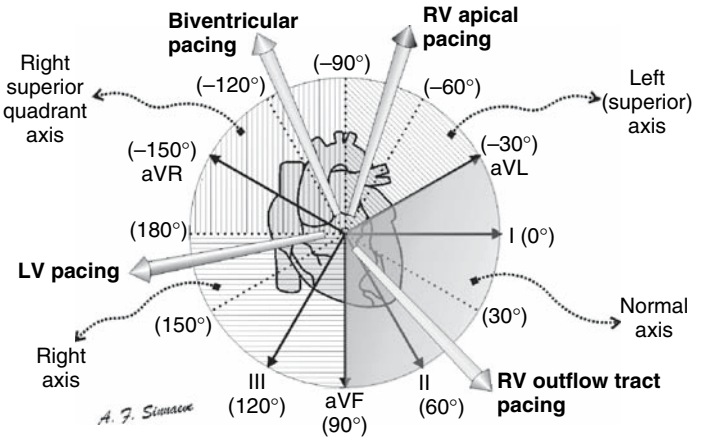

Fig. 22.5 Diagram showing the usual direction of the mean frontal plane axis during apical RV pacing, RV outflow tract pacing, LV pacing from the coronary venous system, and biventricular pacing with LV from the coronary venous system + RV from the apex. The axis during biventricular pacing from the LV from the coronary sinus + RV outflow tract usually points to the right inferior quadrant (right axis) as with monochamber LV pacing. (Reproduced with permission from Barold SS, Stroobandt RX, Sinnaeve AF. Cardiac Pacemakers Step By Step. An Illustrated Guide. Malden, MA: Blackwell-Futura; 2004).

site of ventricular stimulation in patients with first-generation devices without separately programmable RV and LV outputs (Table 22.2).

Biventricular Pacing with the RV Lead Located at the Apex

The frontal plane QRS axis usually moves superiorly from the left (RV apical pacing) to the right superior quadrant (biventricular pacing) in an anticlockwise fashion if the ventricular mass is predominately depolarized by the LV pacing lead [2, 3, 6, 7] (Fig. 22.6). The frontal plane axis may occasionally reside in the left superior rather than the right superior quadrant during uncomplicated biventricular pacing.

The QRS is often positive in lead V_1 during biventricular pacing when the RV is paced from the apex (Fig. 22.6). A negative QRS complex in lead V_1 may occur under the following circumstances: incorrect placement of lead V_1 (too high on the chest), lack of LV capture, LV lead displacement or marked latency (exit block or delay from the stimulation site, an important but poorly studied phenomenon with LV pacing) associated with LV stimulation,

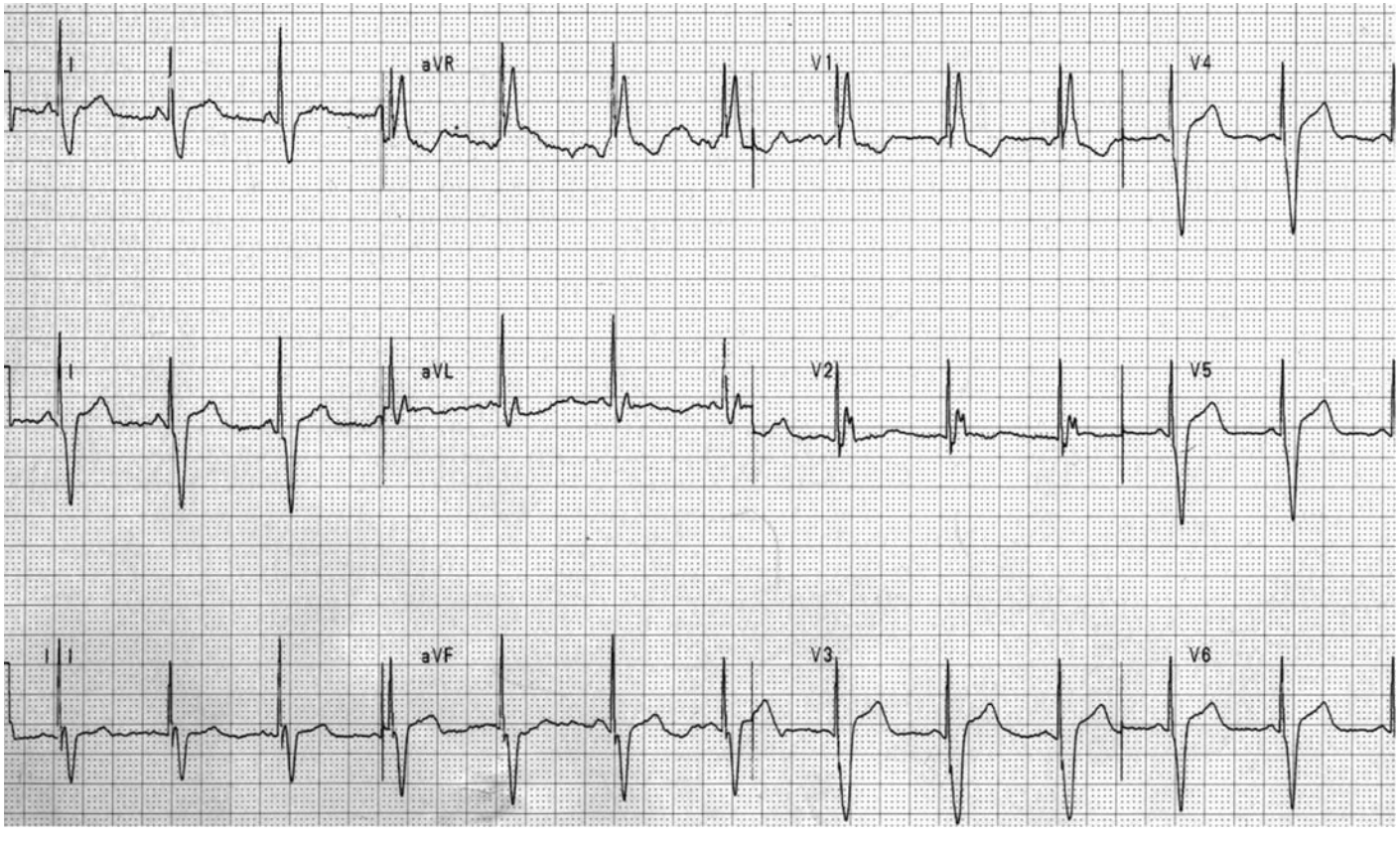

Fig. 22.6 ECG during biventricular pacing with the right ventricular lead at the apex. There is a dominant R-wave in V_1 and a right superior axis in the frontal plane. The QRS complex is relatively more narrow (170 ms) than during single-chamber right ventricular or left ventricular pacing.

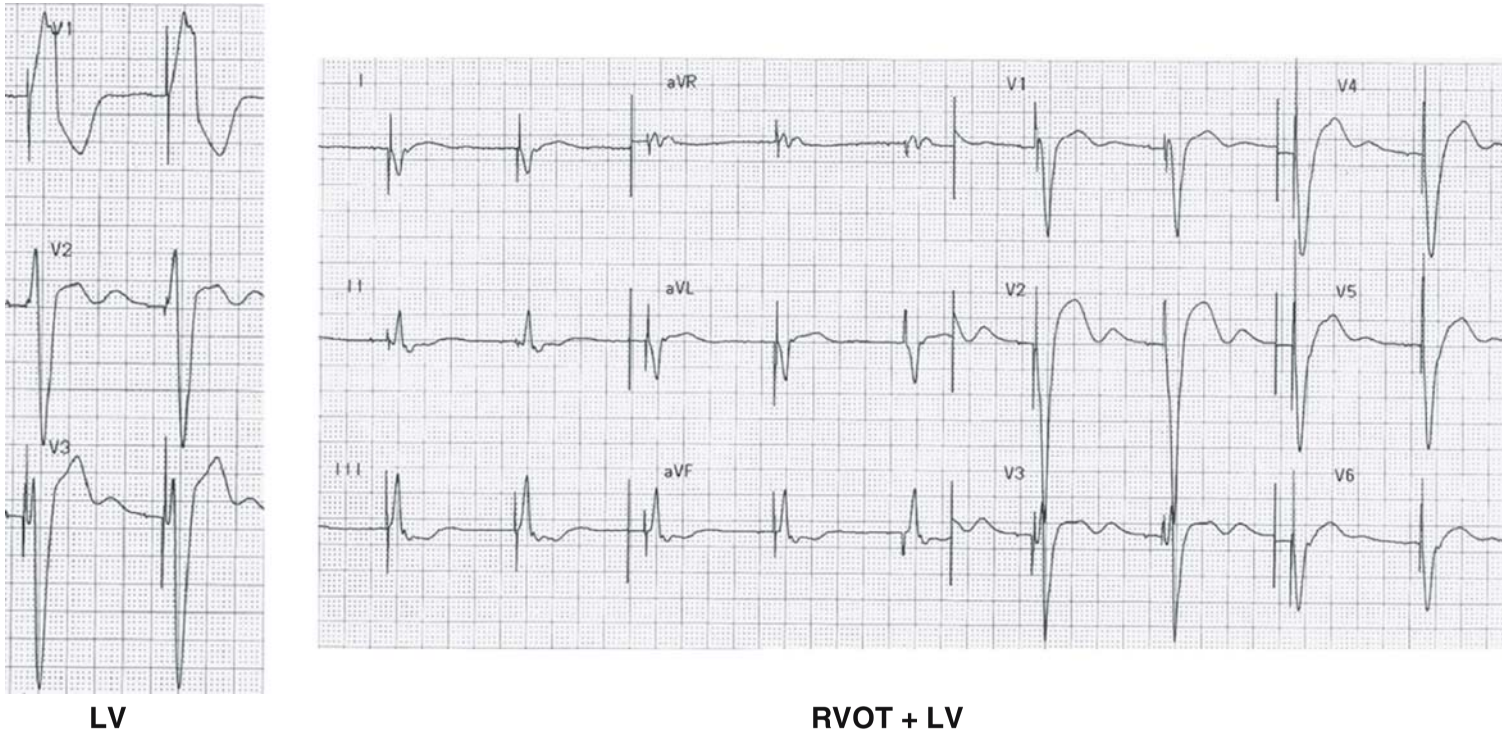

Fig. 22.7 Biventricular pacing with the RV lead in the outflow tract. There was a very prominent R-wave in lead V_1 during monochamber left ventricular pacing. Note the typical absence of a dominant R-wave in lead V_1 and the presence of right axis deviation, an uncommon finding during biventricular pacing with the RV lead at the apex. The presence of ventricular fusion with the spontaneous conducted QRS complex was ruled out. (Reproduced with permission from Barold SS, Giudici MC, Herweg B, Curtis AB. Diagnostic value of the 12-lead electrocardiogram during conventional and biventricular pacing for cardiac resynchronization. Cardiol Clin 2006;24:471–490).

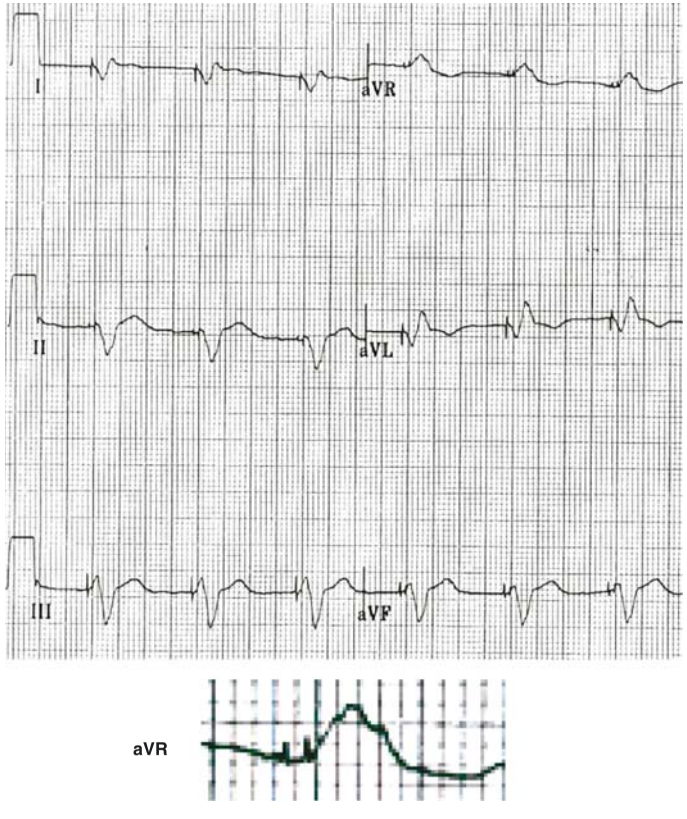

Fig. 22.8 *Top*: Uncomplicated biventricular pacing (right ventricular lead at the apex) in a patient with nonischemic cardiomyopathy. The interventricular (V-V) interval is 40 ms with left ventricular activation first. The 6-lead ECG shows a Qr complex in lead I and a QR complex in lead aVL. This pattern does not indicate an old myocardial infarction. The frontal plane axis lies in the right superior quadrant as expected with this pacing arrangement. *Bottom*: Magnified lead aVR showing separate right and left ventricular stimuli. (Reproduced with permission from Barold SS, Giudici MC, Herweg B, Curtis AB. Diagnostic value of the 12-lead electrocardiogram during conventional and biventricular pacing for cardiac resynchronization. Cardiol Clin 2006;24:471–490).

ventricular fusion with the conducted QRS complex, coronary venous pacing via the middle cardiac vein (also the anterior cardiac vein), or even unintended placement of two leads in the right ventricle [45]. A negative QRS complex in lead V_1 during uncomplicated biventricular pacing probably reflects different activation of a heterogeneous biventricular substrate (ischemia, scar, His–Purkinje participation in view of the varying patterns of LV activation in spontaneous LBBB, etc.) and does not necessarily indicate a poor (electrical or mechanical) contribution from LV stimulation.

Biventricular Pacing with the RV Lead in the Outflow Tract

In our experience, we have found that during biventricular pacing with the RV lead in the septal area or outflow tract, the paced QRS in lead V_1 is often negative and the frontal plane paced QRS axis is often directed to the right inferior quadrant (right axis deviation) (Fig. 22.7). The ECG pattern may resemble that of simple monochamber RV septal or outflow tract pacing with a LBBB pattern and right frontal axis deviation mimicking loss of LV pacing.

Q, or q and QS Configuration in Lead I

Georger et al. [39] observed a q-wave in lead I in 17 of 18 patients during biventricular pacing (Fig. 22.8). As indicated previously, a q-wave in lead I during uncomplicated RV apical pacing is rare, and these workers observed it in only one patient. Loss of the q-wave in lead I was 100% predictive of loss of LV capture [39]. It therefore appears that analysis of the Q/q wave or a QS complex in lead I may be a reliable way to assess LV capture during biventricular pacing. A Q/q wave may also occur during right ventricular septal or outflow tract RV pacing in the absence of myocardial infarction.

Ventricular Fusion Beats with Native Conduction

In patients with sinus rhythm and a relatively short PR interval, ventricular fusion with competing native conduction during biventricular pacing may cause misinterpretation of the ECG, a common pitfall in device follow-up (Figs. 22.9 and 22.10). QRS shortening mandates exclusion of ventricular fusion with the spontaneous QRS complex especially in the setting of a relatively short PR interval. The presence of ventricular fusion should be ruled out by observing the paced QRS morphology during progressive shortening of the AS–VP (atrial sensing–ventricular pacing) interval in the VDD mode or the AP–VP (atrial pacing–ventricular pacing) interval in the DDD mode. It is important to remember that a very narrow paced QRS complex may represent ventricular fusion (possibly associated with a suboptimal hemodynamic response) with the conducted QRS complex rather than near-perfect electrical ventricular resynchronization. In this respect, remarkable narrowing of the paced QRS complex occurs with triventricular pacing (two RV sites + LV), advocated by the French group for heart failure patients who have become refractory to conventional biventricular pacing [46].

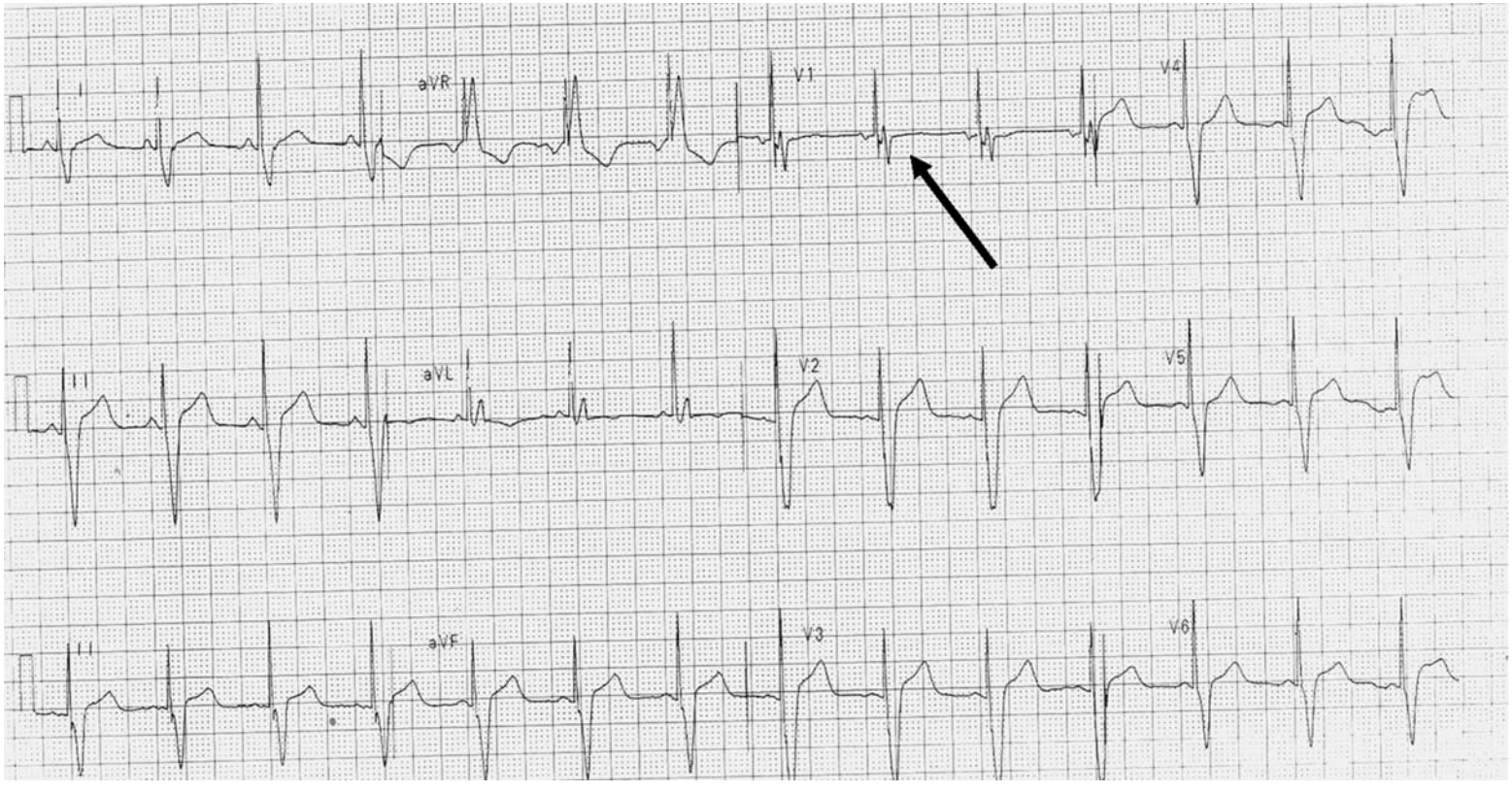

Fig. 22.9 Twelve-lead ECG showing ventricular fusion. There is narrowing of the paced QRS complex (well seen in V_1) due to ventricular fusion with the spontaneous conducted QRS complex. This ECG was the initial recording taken upon arrival to the pacemaker follow-up center. AV delay = 100 ms. The marked narrowing of the QRS complex in lead V_1 suggests ventricular fusion rather than QRS narrowing from satisfactory biventricular pacing. (Reproduced with permission from Barold SS, Giudici MC, Herweg B, Curtis AB. Diagnostic value of the 12-lead electrocardiogram during conventional and biventricular pacing for cardiac resynchronization. Cardiol Clin 2006;24:471–490).

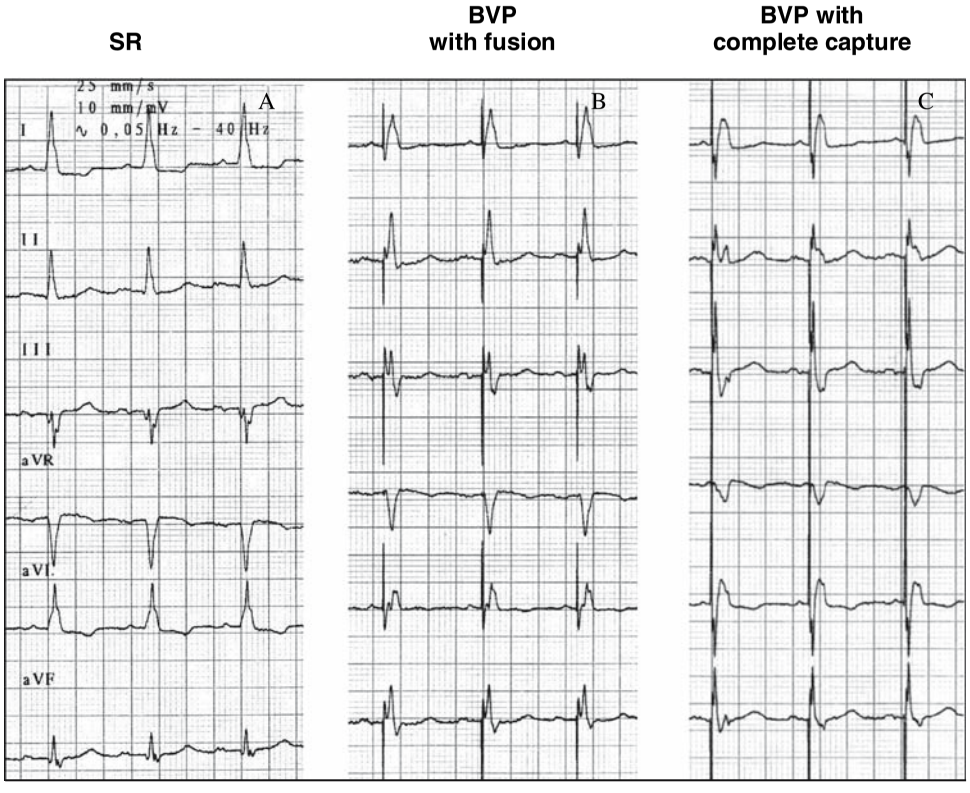

Fig. 22.10 Biventricular pacing with subtle electrocardiographic manifestations of **v**entricular fusion with the conducted QRS complex. during biventricular pacing (BVP). (**A**) Spontaneous ventricular depolarization. Surface ECG from a patient with severe congestive heart failure showing sinus rhythm, complete left bundle branch block, and QRS duration of 125 ms. (**B**) Ventricular fusion. ECG from the same patient after receiving a biventricular device. The AV delay was fixed at 120 ms and the paced QRS shortened to 115 ms. The slight change in QRS morphology strongly suggests a fusion phenomenon with spontaneous ventricular depolarization. (**C**) Pure biventricular depolarization. The atrioventricular delay was programmed to 80 ms resulting in a longer QRS duration of 130 ms. The QRS morphology is different from that in (**B**) and similar to that obtained with biventricular VVI pacing, confirming complete biventricular capture. The shorter AV delay therefore eliminated ventricular fusion with spontaneous ventricular depolarization. (Reproduced with permission from Garrigue S, Barold SS, Clémenty J. Electrocardiography of multisite ventricular pacing. In: Barold SS, Mugica J, eds. The Fifth Decade of Cardiac Pacing. Elmsford, NY: Blackwell-Futura; 2004:84–100).

Fusion with Spontaneous Ventricular Activation: Beneficial or Harmful?

Van Gelder et al. [47] recently investigated the effect of intrinsic conduction over the right bundle branch (causing fusion) on the LV dP/dt_{max} index. LV pacing (biventricular activation with LV monochamber pacing) was compared with biventricular pacing in 34 patients with New York Heart Association (NYHA) functional class III or IV, sinus rhythm with normal AV conduction, left bundle branch block, QRS >130 ms, and optimal medical therapy. LV dP/dt_{max} was measured invasively during LV and simultaneous biventricular pacing. The AV interval was varied in four steps starting with an AV interval 40 ms shorter than the intrinsic PQ time and decreased with 25% for each step with ventricular fusion caused by intrinsic activation. LV dP/dt_{max} was higher with LV than biventricular pacing provided that LV pacing was associated with ventricular fusion caused by intrinsic activation via the right bundle branch.

The clinical implications of the study of Van Gelder et al. [47] are unclear. It is impossible to obtain sustained LV stimulation with fusion of right bundle branch depolarization because of variability of the PR interval related to autonomic factors. At present, it is best to program the AV delay to avoid all forms of ventricular fusion with spontaneous ventricular activity until more data are available, and a reliable way is found to synchronize right bundle branch activity (unpaced RV) with LV stimulation.

Influence of First-Degree AV Block

Pires et al. [48] studied the predictors of a CRT response in patients from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) and MIRACLE-ICD trials. Patients with an improvement of $\geq$1 NYHA class from baseline to the 6-month follow-up were considered responders, and those who had no change or worse NYHA class or died were classified as nonresponders. Based on improvement of $\geq$1 NYHA class, less than two thirds of patients enrolled in the MIRACLE or MIRACLE-ICD trials responded to CRT. One hundred forty-three (64%) of 224 and 190 (61%) of 313 patients in the MIRACLE and MIRACLE-ICD trials, respectively, responded to therapy. Using stepwise logistic regression methods, the study identified several differing factors that predicted CRT response in the two trials. One of these factors was the absence of first-degree AV block which was associated with a response to CRT ($p = 0.005$). Tedrow et al. [49], who evaluated 75 consecutive CRT patients, also found that patients with first-degree AV block have a poorer outcome than patients with a normal PR interval though the data were not quite statistically significant (hazard ratio = 1.01, $p = 0.0650$).

Enhanced hemodynamic response in patients with normal AV conduction by concealed resynchronization or fusion was suggested by Kurzidim et al. [50]. These workers studied 22 CHF patients, all in sinus rhythm with temporary multisite pacing prior to implantation of a CRT system. LV systolic function was evaluated invasively by the maximum rate of LV pressure increase (dP/dt_{max}). Sequential biventricular pacing was performed with preactivation of either ventricle at 20–80 ms. In 60% (6/10) of patients with a normal PR interval ($\leq$200 ms), right atrial–triggered LV pacing produced a hemodynamic response superior to that of optimized sequential biventricular pacing and was equivalent to that of simultaneous biventricular pacing in

the remaining (4/10) patients. This was not the case in any patient with a prolonged PR interval or AV block of any degree. The baseline PR interval of patients showing a superior response with LV pacing was significantly shorter than that of the remaining patients (179 ± 14 ms vs. 252 ± 64 ms, $p < 0.001$). In this group with normal AV conduction, the baseline PR interval was very similar to the optimal AV delay determined for LV pacing (178 ± 13 ms). Ventricular activation in patients with a normal PR interval may have resulted from fusion of electrical wavefronts coming from the right bundle branch and the impulse initiated by the LV electrode. The hemodynamic response may thereby be superior because the detrimental effects of RV apical stimulation are avoided. Kurzidim et al. believe that the wider QRS width observed during biventricular pacing in patients with a long PR interval supports their hypothesis.

Mechanism of Altered CRT Response in Patients with First-Degree AV Block

It is unclear why CRT patients with first-degree AV block do not fare as well as those with normal AV conduction. Several mechanisms may be involved: (1) The long PR interval may be a marker of more advanced heart disease. (2) Patients with first-degree AV block may have experienced more episodes of undetected electrical desynchronization precipitated by functional atrial undersensing (to which they are predisposed) induced by devices without appropriate restorative algorithms. (3) Enhanced hemodynamic response in patients with normal AV conduction by "concealed resynchronization" or fusion as suggested by Kurzidim et al. [50]. Similar hemodynamic benefit by producing fusion with right bundle branch activation was demonstrated Van Gelder et al [47]. Finally, it is possible that RV pacing during CRT may have a detrimental hemodynamic effect. In this respect, the prolongation of the monochamber RV paced QRS complex with the passage of time may be a marker of RV dysfunction.

Intra- and Interatrial Conduction Delay

Interatrial conduction block is characterized by a wide and notched P wave (>120 ms) traditionally in ECG lead II, associated with a wide terminal negativity in lead V_1. The latter is commonly labeled *left atrial enlargement* though it reflects left atrial conduction disease. Interatrial conduction time is also measured as the activation time from the high right atrial activation to distal coronary sinus (60–85 ms) [51]. In the presence of interatrial conduction delay with late left atrial activation, left atrial systole occurs late and even during LV systole [52]. Consequently, the need to program a long AV delay to overcome delayed left atrial systole can preclude ventricular resynchronization because the lack of AV conduction disease permits the emergence of a conducted QRS complex. The incidence of interatrial conduction delay in patients who are candidates for CRT is unknown. In this respect, Daubert et al. [51] have suggested it might be about 20%. When the ECG suggests interatrial conduction delay, it would be wise to look for delayed left atrial activation at the time of CRT implantation by showing that the conduction time from the right atrium to the left atrium is longer than the conduction

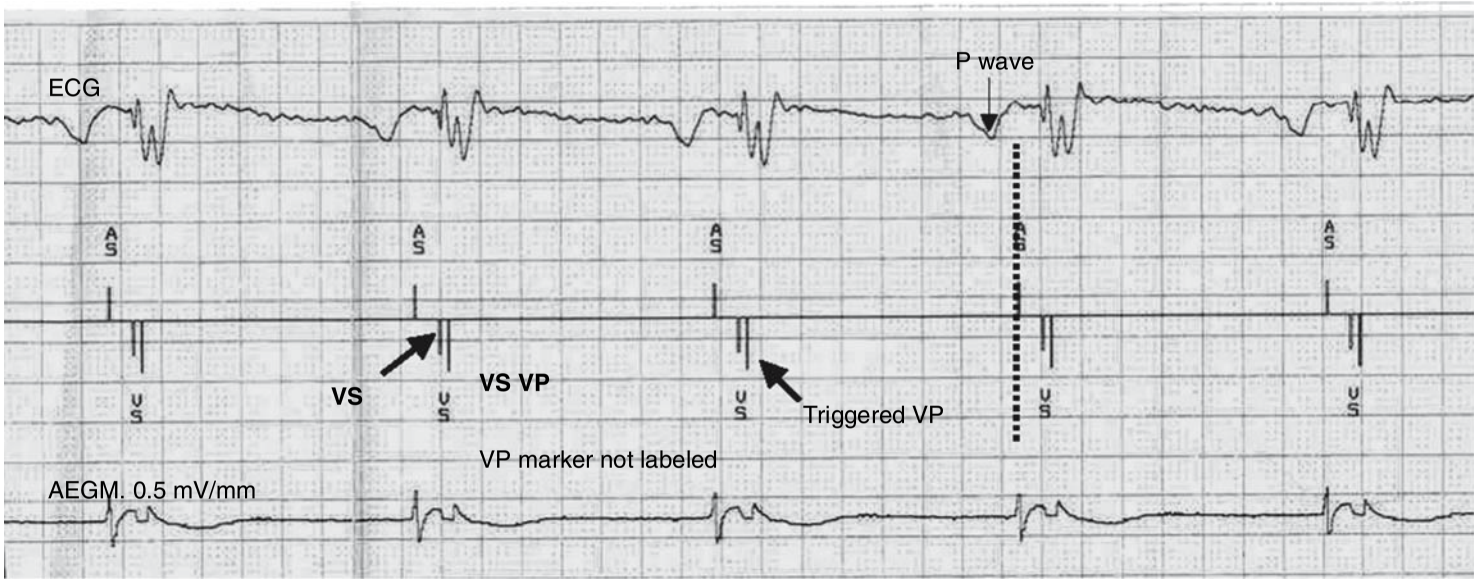

Fig. 22.11 Marked shortening of the AV delay due to late or delayed right atrial sensing. Intraatrial conduction delay causes impaired conduction from the sinus node to the electrode in the right atrial appendage where atrial sensing occurs. The ECG is on *top*, the marker channel in the *middle*, and the atrial electrogram (*AEGM*) is at the *bottom*. The timing of the atrial electrogram is so delayed that the device senses atrial activity beyond the P-wave on the surface ECG. The ventricular marker channel displays a ventricular sensing event (first downward deflection *VS*), followed by a second larger deflection representing triggered biventricular stimulation, which the marker channel does not label as a ventricular paced event (*VP*) because it is too close to the preceding marker. The pacemaker sees an AS–VS interval of 60 ms. This problem was solved by allowing biventricular triggering within 4 ms of a sensed ventricular event within the programmed AV delay. The patient's hemodynamic status improved presumably because of a well-timed important contribution by left ventricular pacing, which cannot always be guaranteed with this arrangement. In difficult cases, AV nodal ablation is required to ensure cardiac resynchronization. Paper speed = 50 mm/s.

time from right atrium to the QRS complex [52]. In the presence of interatrial conduction delay, one should consider placing the atrial lead in the interatrial septum where pacing produces a more homogeneous activation of both atria and abbreviates total atrial conduction time judged by a decrease of P-wave duration [53,54]. In the presence of established CRT with an atrial lead in the right atrial appendage, restoration of mechanical left-sided AV synchrony requires simultaneous biatrial pacing performed by the implantation of a second atrial lead either in the proximal coronary sinus or low atrium near the coronary sinus to preempt left atrial systole [55,56]. Difficult cases can be managed by AV nodal ablation to permit extension of the AV delay to promote mechanical left-sided AV synchrony, though biventricular ICDs may limit the maximum programmable AV delay.

Late Atrial Sensing (Intraatrial Conduction Delay)

In some patients with right intraatrial conduction delay, conduction from the sinus node to the right atrial appendage (site of atrial sensing) is delayed without significant conduction delay to the left atrium. In this situation, left atrial activation may take place or may even be completed by the time the device senses the right atrial electrogram (Fig. 22.11). In these circumstances, it may be difficult or impossible to program an optimal delay with CRT in the absence of ventricular fusion. A trial of ventricular-triggered biventricular pacing upon sensing the spontaneous QRS complex may be worthwhile.

Long-term ECG Changes

Many studies have shown that the paced QRS duration does not vary over time as long as the LV pacing lead does not move from its initial site [6,41,57]. Yet, surface ECGs should be performed periodically because the LV lead may become displaced into a collateral branch of the coronary sinus. Dislodgment of the LV lead may result in loss of LV capture with the ECG showing an RV pacing QRS pattern with an increased QRS duration and superior axis deviation. Ricci et al. [57] suggested that variation of the QRS duration over time may play a determinant role if correlated with remodeling of the ventricles by echocardiography. Finally, the underlying spontaneous ECG should be exposed periodically to confirm the presence of a LBBB type of intraventricular conduction abnormality. In this respect, turning off the pacemaker could potentially improve LV function and heart failure in patients who have lost their intraventricular conduction delay or block through ventricular remodeling. In other words, a spontaneous narrow QRS is better than biventricular pacing.

Anodal Stimulation in Biventricular Pacemakers

Although anodal capture may occur with high-output traditional bipolar RV pacing, this phenomenon is almost always not discernible electrocardiographically. Biventricular pacing systems may use a unipolar lead for LV pacing via a coronary vein. The tip electrode of the LV lead is the cathode and

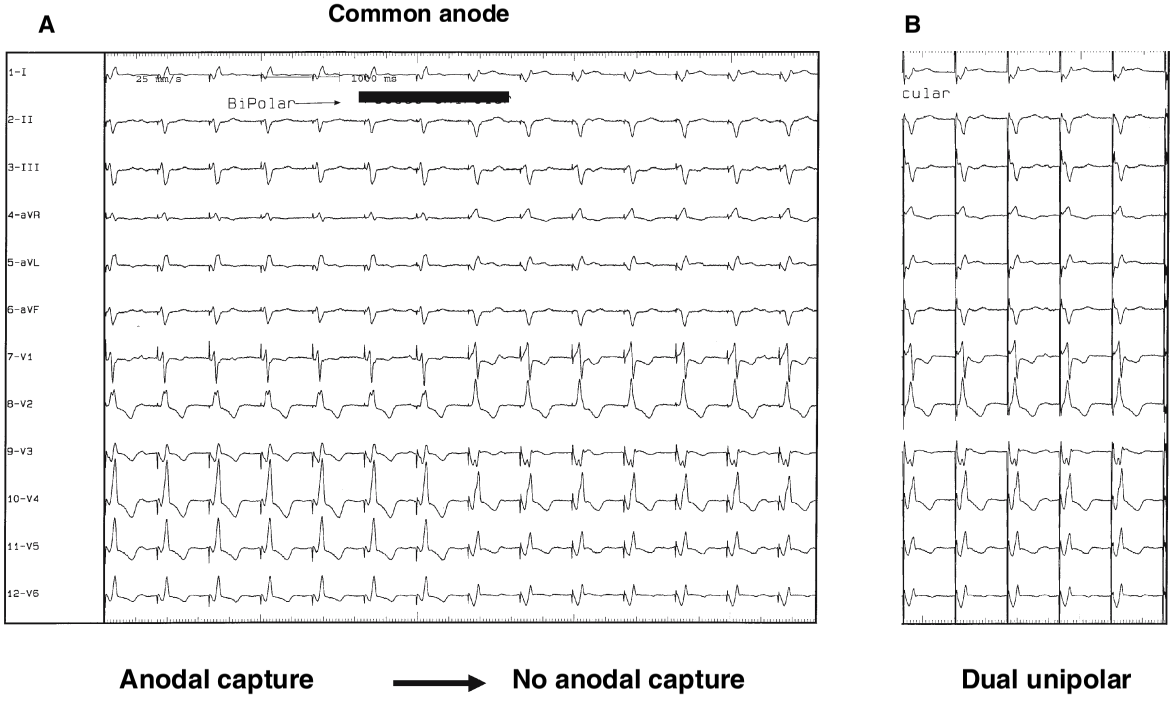

Fig. 22.12 (**A**) On the left there is RV anodal capture during simultaneous biventricular pacing with a unipolar left ventricular lead in the coronary venous system and a bipolar RV lead. The proximal electrode of the RV lead provides a common anode. RV anodal capture disappears when the left ventricular output voltage is decreased. Note the change in QRS configuration when RV anodal capture is eliminated by reducing the left ventricular output on the right of the panel. (**B**) Same patient as in (**A**). Programming dual unipolar simultaneous biventricular pacing fails to produce RV anodal stimulation despite a high left ventricular output because the RV anode is now excluded from the circuit. Consequently, the ECG in (**B**) becomes identical to that in (**A**) on the right where there is no RV anodal capture.

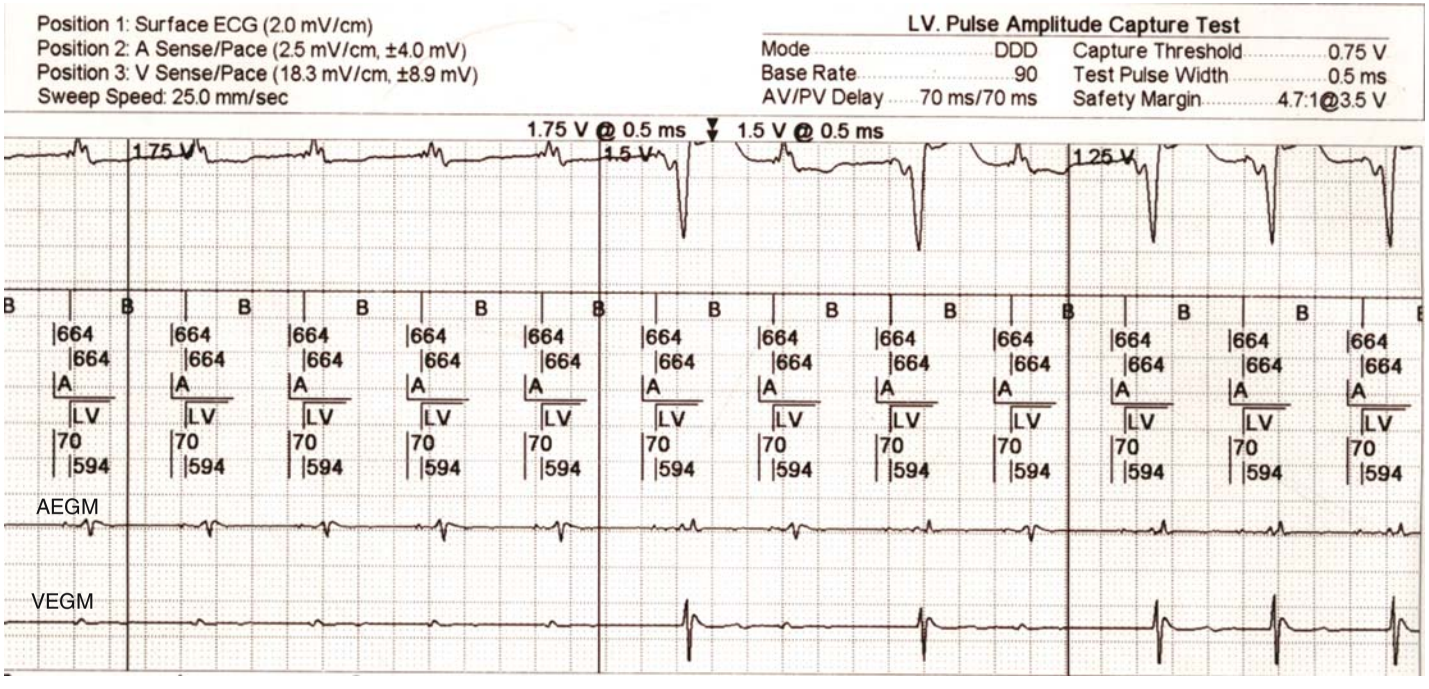

Fig. 22.13 Anodal pacing during monochamber left ventricular pacing. The left side shows the paced QRS morphology during monochamber LV pacular pacing. This was identical to the pattern previously recorded with pure biventricular pacing. This response was due to ventricular capture at the common anodal site (proximal or ring electrode of the right ventricular lead) in the right ventricle with consequent capture of both the left ventricle and the right ventricle simultaneously. Intermittent capture of the isolated left ventricle occurred only when the left ventricular output fell to 1.5 V at 0.5 ms. Monochamber left ventricular pacing became continual at 1.25 V and 0.5 ms. Thus, the threshold for anodal capture was 1.75 V at 0.5 ms. In other words, anodal capture disappeared at an output <1.75 V at 0.5 ms. *A*, atrial paced event; *LV*, LV paced event. P = atrial sensed event, BV = biventricular pacing.

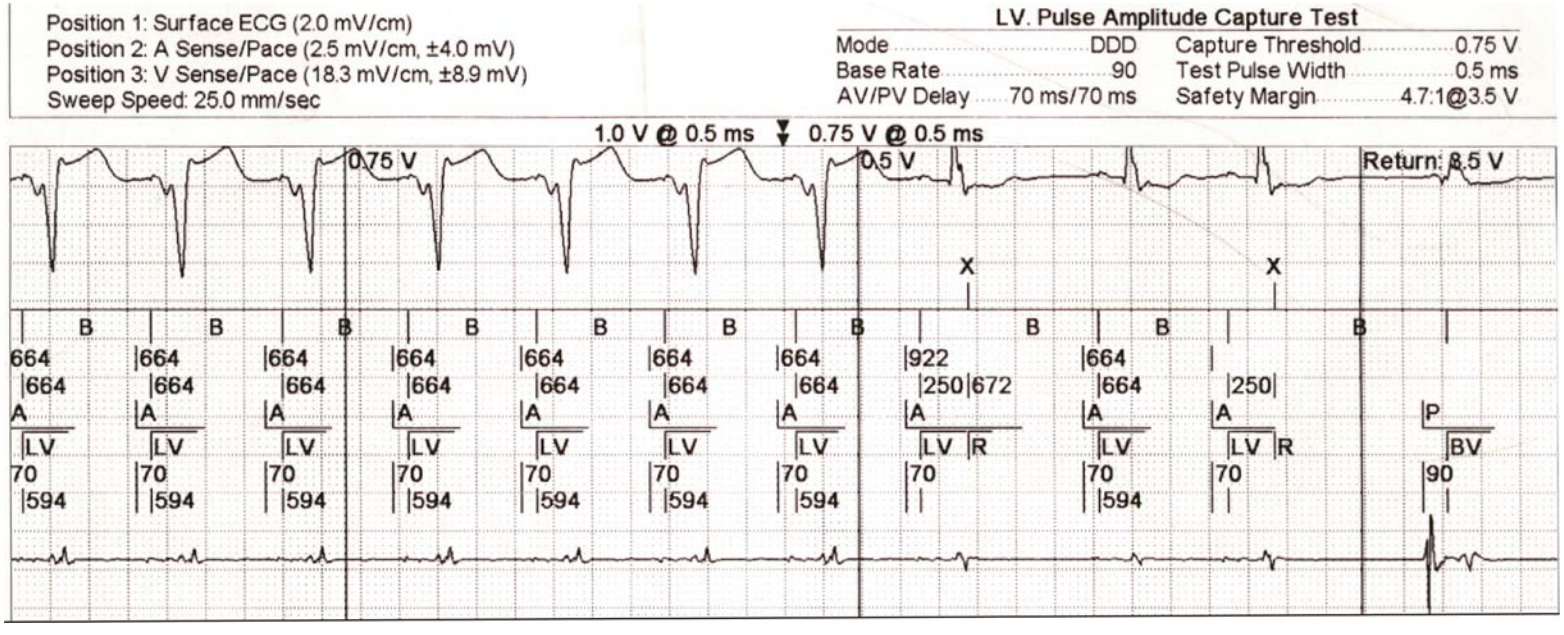

Fig. 22.14 Continuation of threshold testing from Figure 22.13. There was loss of LV capture at 0.5 V and 0.5 ms with emergence of the spontaneous rhythm. The first spontaneous QRS complex was sensed after an ineffectual LV stimulus and depicted as "R." This sensed event reset the timing cycle of the pacemaker. The second spontaneous QRS complex was unsensed because it fell into the postventricular blanking period initiated by the preceding ineffectual LV stimulus. The third spontaneous QRS complex behaved like the first one. *A*, atrial paced event; *LV*, LV paced event.

the proximal electrode of the bipolar RV lead often provides the anode for LV pacing. This arrangement creates a common anode for RV and LV pacing. A high current density (from two sources) at the common anode during biventricular pacing may cause anodal capture manifested as a paced QRS complex with a somewhat different configuration from that derived from pure biventricular pacing [58, 59] (Fig. 22.12). Anodal capture creates three distinct pacing morphologies exclusive of fusion with the spontaneous QRS complex: biventricular with anodal capture (at a high output), biventricular (at a lower output), and RV (with loss of LV capture) or rarely LV (with loss of RV capture).

A different form of anodal capture involving the ring electrode of the bipolar RV lead can also occur with contemporary biventricular pacemakers with *separately programmable ventricular outputs* (Figs. 22.13 and 22.14). During monochamber LV pacing at a relatively high output, RV anodal capture produces a paced QRS complex identical to that registered with biventricular pacing [60, 61]. Occasionally, this type of anodal capture prevents electrocardiographic documentation of pure LV pacing if the LV pacing threshold is higher than that of RV anodal stimulation. Such anodal stimulation may complicate threshold testing and should not be misinterpreted as pacemaker malfunction. Furthermore, if the LV threshold is not too high, appropriate programming of the pacemaker output should eliminate anodal stimulation in most cases. The use of true bipolar LV leads eliminates all forms of anodal stimulation.

Effect of Interventricular V-V Timing on the Electrocardiogram of Biventricular Pacemakers

The electrocardiographic consequences of temporally different RV and LV activation with programmable V-V timing in the latest biventricular devices have not yet been studied in detail (Fig. 22.15). Contemporary biventricular devices permit programming of the interventricular interval usually in steps from +80 ms (LV first) to –80 ms (RV first) to optimize LV hemodynamics. In the absence of anodal stimulation, increasing the V-V interval gradually to 80 ms (LV first) will progressively increase the duration of the paced QRS complex, alter its morphology with a larger R-wave in lead V_1 indicating more dominant LV depolarization [62] (Fig. 22.15). The varying QRS configuration in lead V_1 with different V-V intervals cannot be correlated with the hemodynamic response.

RV anodal stimulation during biventricular pacing interferes with a programmed interventricular (V-V) delay (often programmed with the LV preceding the RV) aimed at optimizing cardiac resynchronization because RV anodal capture causes simultaneous RV and LV activation (The V-V interval becomes zero) (Fig. 22.16). In the presence of anodal stimulation, the ECG morphology and its duration will not change if the device is programmed with V-V intervals of 80, 60, and 40 ms (LV before RV). The delayed RV cathodal output (80, 60, 40 ms) then falls in the myocardial refractory period initiated by the preceding anodal stimulation. At V-V intervals $\leq$20 ms, the paced QRS may change because the short LV–RV interval prevents propagation of activation from the site of RV anodal capture in time to render the

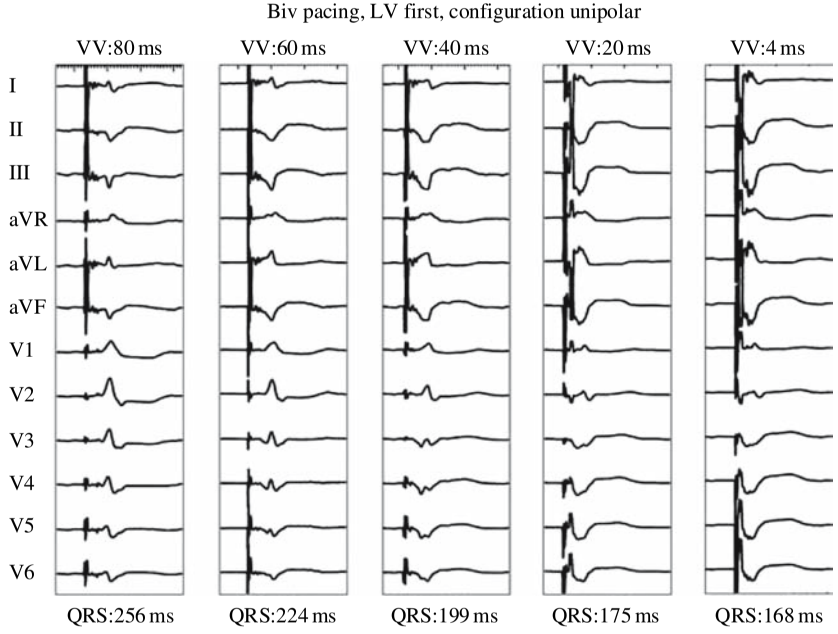

Fig. 22.15 Sequential biventricular pacing in a unipolar left ventricular configuration with varying V-V intervals. There is a gradual change in the morphology of the QRS complex, which is best reflected in the precordial leads. (Reproduced with permission from van Gelder BM, Bracke FA, Meijer A. The effect of anodal stimulation on V-V timing at varying V-V intervals. Pacing Clin Electrophysiol 2005;28:771–776).

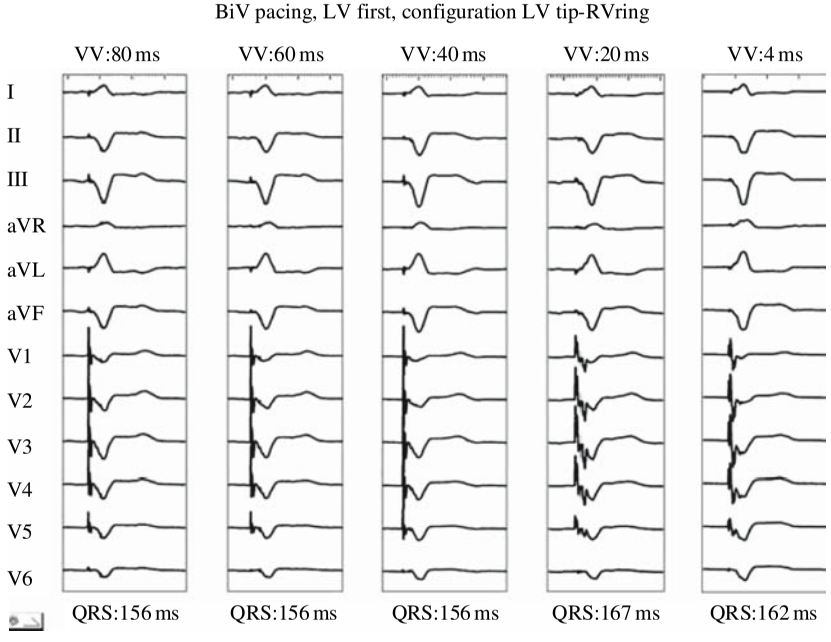

Fig. 22.16 Sequential biventricular pacing (LV first) with V-V intervals varying from 80 to 4 ms. The LV pacing configuration is LV tip to RV ring with anodal capture at the RV ring electrode. There is an identical morphology of the QRS complex at V-V intervals of 80, 60, and 40 ms, which then changes after shortening the V-V interval to 20 and 4 ms. *BiV*, biventricular; *LV*, left ventricular; *RV*, right ventricular. See text for details. (Reproduced with permission from van Gelder BM, Bracke FA, Meijer A. The effect of anodal stimulation on V-V timing at varying V-V intervals. Pacing Clin Electrophysiol 2005;28:771–776).

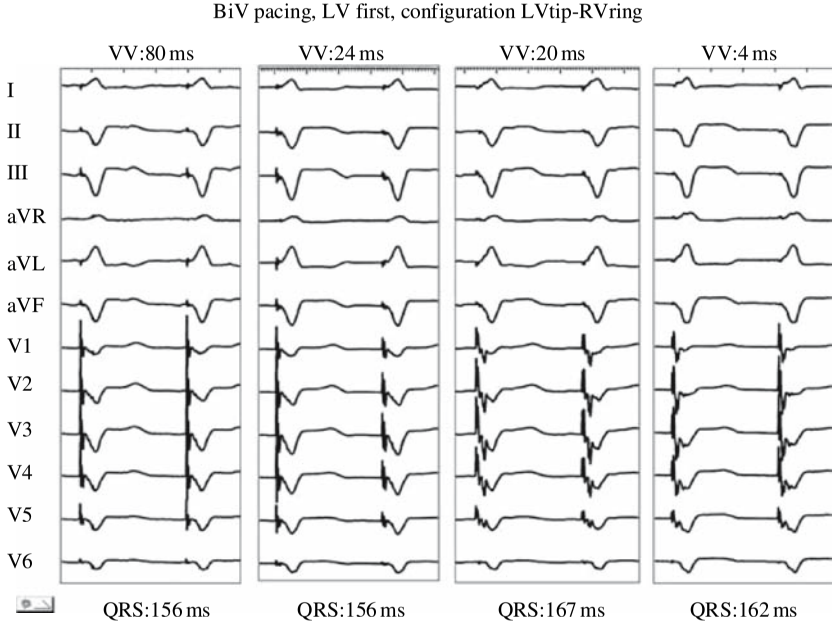

Fig. 22.17 Right ventricular anodal capture during biventricular pacing showing an abrupt change in QRS morphology when programming the V-V interval from 24 to 20 ms. (Reproduced with permission from van Gelder BM, Bracke FA, Meijer A. The effect of anodal stimulation on V-V timing at varying V-V intervals. Pacing Clin Electrophysiol 2005;28:771–776).

cathodal site refractory (Fig. 22.17). Thus, the cathode also captures the RV and contributes to RV depolarization, which then takes place from two sites: RV anode and RV cathode [62, 63].

Electrocardiography During Exercise

Exercise testing in CRT patients is technically difficult and inconvenient but helpful in the overall evaluation of CRT particularly in patients with a suboptimal CRT response where no obvious cause is found at rest [7]. An exercise test may reveal loss of capture, atrial undersensing, various arrhythmias, and the development of spontaneous AV conduction indicating that the upper rate should be reprogrammed to ensure consistent biventricular capture with effort. Exercise testing is important in patients with permanent atrial fibrillation who have not undergone ablation of the AV junction to determine the status of spontaneous AV conduction.

If the spontaneous PR interval on exercise becomes shorter than the programmed AV (atrial sensed–ventricular paced), CRT will be lost. There is preliminary evidence in acute studies suggesting that the short AV delay at rest should be prolonged during exercise to achieve optimal LV systolic performance [64]. This is in contrast with the proven benefit of programming rate-adaptive shortening of the AV delay in patients with conventional DDDR pacemakers. The dynamic changes of LV dyssynchrony on exercise may partially explain what appears to be paradoxical behavior of the AV delay on exercise in CRT patients [65]. If confirmed by other studies, it would be desirable to provide CRT devices with dynamic lengthening of the AV delay on exercise. In the meantime, it might be wise to program CRT devices without dynamic shortening of the AV delay in patients with normal sinus node function unless it is shown to be beneficial during an exercise study. At present, there are no chronic data available that provide insight regarding the optimal AV interval during activity states.

In CRT patients with severe chronotropic incompetence (defined by the failure to achieve 85% of the age-predicted heart rate (determined as 220 – the patient's age), rate-adaptive pacing DDDR with a rate-adaptive AV delay may provide incremental benefit on exercise capacity [66]. Therefore, an exercise test would be desirable to demonstrate the effect of a rate-adaptive AV delay if atrial pacing is likely to occur on exercise.

Latency

The delay from the pacing stimulus to the onset of ventricular depolarization is called *latency*. An isoelectric onset of QRS complex in one or only a few leads can mimic latency. Consequently, latency requires a 12-lead ECG taken at fast speed for diagnosis. In biventricular pacing, latency related to LV pacing may produce suboptimal hemodynamics associated with an ECG showing the pattern of RV pacing because LV depolarization is delayed and overshadowed by RV stimulation [67]. The electrical and hemodynamic problem can often be corrected by advancing LV stimulation by programming the interventricular (V-V) delay, a feature available only in contemporary devices as discussed in a special chapter on latency in this book.

Biventricular Pacing with a Conventional DDD Pacemaker

Some patients with permanent atrial fibrillation undergo CRT with conventional DDDR pacemakers. The "atrial" channel usually paces the left ventricle and the ventricular channel paces the right ventricle [68]. Two ventricular stimuli are often seen because such devices do not usually permit programming an AV interval of zero. The device is usually programmed to the DVI to prevent far-field atrial sensing by the ventricular lead.

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Cardiac Arrhythmias After Cardiac Resynchronization

S. Serge Barold and Bengt Herweg

Patients with devices for cardiac resynchronization therapy (CRT) can develop a variety of atrial and ventricular arrhythmias predominately related to poor left ventricular (LV) function. Less commonly, CRT patients may exhibit specific (long QT) ventricular proarrhythmias linked to altered ventricular repolarization resulting from reversed ventricular activation delivered by biventricular or left ventricular pacing.

Atrial Fibrillation

Atrial fibrillation/flutter occurs in up to 30% of patients with congestive heart failure and can be an important cause of decompensation after CRT. Atrial fibrillation (AF) interferes with the optimal delivery of CRT because the ventricular rhythm inhibits CRT or by the unfavorable hemodynamics associated with a fast ventricular rate. AV nodal ablation should always be considered in permanent AF but also in paroxysmal or persistent AF when it becomes troublesome and difficult to control [1].

In AF, some CRT devices provide some degree of ventricular resynchronization by attempting regularization of the paced beats up to the programmed maximum tracking rate. The overall ventricular rate remains undesirably high despite the automatic adjustment of the lower rate interval. Activation of this algorithm does not result in control of the ventricular rate and should not be a substitute for ablation of the AV junction in patients with substantial periods of drug-refractory rapid ventricular rates.

Impact of CRT on Incidence of Atrial Fibrillation

Despite reverse remodeling of the ventricle and left atrium provided by CRT together with its significant clinical benefit, the impact of CRT on the incidence of AF remains unclear because only a few studies have so far addressed this issue.

In one study, 84 CRT patients were assessed at baseline and at 3 months follow-up for AF burden (defined as time of AF per day, AF >30 s) [2]. AF was continuously measured by the device. In patients with AF episodes, the overall burden of AF was 9.88 ± 12.61 h/day in the first month of CRT

and 4.20 ± 9.24 h/day in the third month of CRT ($p = 0.001$). The overall number of patients with AF also was significantly reduced from 26 of 84 (31%) patients in the first month to 18 of 84 (21%) patients in the second month and to 13 of 84 (15%) patients in the third month ($p < 0.001$, first vs. third month). One third of the patients were free of episodes although they had a history of AF before implantation. In contrast, half of the patients who presented with AF in the first 3 months of CRT had no prior history of AF, possibly due to asymptomatic episodes of AF before device implant. The study therefore showed a significant gradual reduction in AF burden and the number of patients experiencing AF episodes during CRT.

In the CArdiac REsynchronization in Heart Failure (CARE-HF) trial, 813 patients were randomly assigned to pharmacological therapy alone or with the addition of CRT [3]. The incidence of new-onset AF was assessed by adverse event reporting and by ECGs during follow-up at 1, 3, 6, 9, 12, and 18 months and every 6 months thereafter, or documented as a serious adverse event or during hospitalization. By the end of the study (mean duration of follow-up 29.4 months), AF had been documented in 66 patients in the CRT group compared with 58 who received medical therapy only [16.1% vs. 14.4%; hazard ratio (HR), 1.05; 95% confidence interval (CI), 0.73–1.50; $p = 0.79$]. There was no difference in the time until first onset of AF between groups.

Fung et al. [4] followed 36 consecutive patients (the CRT group) in sinus rhythm at baseline and no history of AF and a matched control group. Patients in the two groups were regularly seen every 6 to 8 weeks. Holter and event recorder examinations were performed if clinically indicated in the two groups. The detection of AF relied on electrocardiography, strips from event recorders, and 24-h Holter examination. After a follow-up of 3 years, three patients in the CRT group and 11 in the control group developed AF. The annual incidence of AF was 2.8% in the CRT group and 10.2% in the control group ($p = 0.025$). Two patients in the CRT group and seven in the control group had paroxysmal AF, and one patient in the CRT group and four in the control group had permanent AF. The mechanisms of the lower incidence of AF in the CRT group may be related to the significant improvement in LV systolic function and reduction in mitral regurgitation.

In a study from Leiden (The Netherlands), 74 consecutive CRT patients and AF (20 persistent and 54 permanent) were evaluated before and after 6 months of CRT for the restoration of sinus rhythm [5]. During implantation, 18 of 20 (90%) patients with persistent AF were cardioverted to sinus rhythm. At follow-up, 13 of 18 (72%) cardioverted patients had returned to AF; thus, only 5 of 74 patients (7%) were in sinus rhythm as none of the patients with permanent AF converted spontaneously to sinus rhythm.

Impact of CRT on Ventricular Tachyarrhythmias

CRT appears to produce favorable electrophysiologic benefits (electrical remodeling) that might diminish the susceptibility of potentially life-threatening ventricular arrhythmias. In this respect, Higgins et al. [6] first suggested that CRT may reduce antitachycardia therapy in patients with a CRT-D (D = defibrillator) device, though no reduction in mortality was found in this early study. Since then, a number of reports have provided

growing evidence that CRT may indeed be antiarrhythmic and may prevent sudden death especially in association with an implantable cardioverter-defibrillator (ICD).

Does CRT Without an ICD Reduce All-Cause Mortality but Not Sudden Death?

In an extension of the of the already reported open-label randomized Cardiac Resynchronization–Heart Failure (CARE-HF) trial [7], the mean follow-up was 37.4 months (median, 37.6; interquartile range (IQR), 31.5–42.5; range, 26.1–52.6 months) [8]. There were 154 deaths (38.1%) in 404 patients assigned to medical therapy and 101 deaths (24.7%) in 409 patients assigned to CRT (HR, 0.60; 95% CI, 0.47–0.77; $p < 0.0001$) without evidence of heterogeneity in prespecified subgroups. A reduction in the risk of death due to heart failure (64 vs. 38 deaths; HR, 0.55; 95% CI, 0.37–0.82; $p = 0.003$) and sudden death was observed (55 vs. 32 sudden deaths or 4.3 vs.2.5% per annum hazard ratio 0.54, 95% CI 0.35–0.84; $p = 0.005$). The extended study highlighted that the prognostic benefits of CRT are maintained or increased with longer-term follow-up and are due to reductions in sudden death and death due to worsening heart failure in roughly equal proportion [8].

The influence of CRT alone on sudden death requires further investigation in view of a recent meta-analysis of a number of randomized controlled studies evaluating the effects of CRT (without an ICD) in patients with advanced heart failure and a depressed LV systolic performance [9]. Five studies met the criteria for inclusion, the Multisite Stimulation in Cardiomyopathies Study (MUSTIC), the Multicenter InSync Randomized Clinical Evaluation (MIRACLE), the MUSTIC AF, the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) (CRT alone and control arms only), and the CARE-HF trials in its original form not involving the extended phase of this trial. Trials that did not independently report data on CRT alone or had a follow-up period of less than 3 months, were excluded. They included a total of 2,371 patients: 1,028 controls and 1,343 CRT-treated patients. Pooled analysis demonstrated that CRT alone, compared with optimal medical therapy, significantly reduced all-cause mortality by 29% [16.9% vs. 20.7%; odds ratio (OR), 0.71; 95% CI, 0.57–0.88] and mortality due to progressive heart failure by 38% (6.7% vs. 9.7%; OR, 0.62; 95% CI, 0.45–0.84). No effect on sudden cardiac death was observed with CRT (6.4% vs. 5.9%; OR, 1.04; 95% CI, 0.73–1.22).

Do CRT and ICD Reduce Mortality?

COMPANION trial

In the COMPANION trial, with regard to the all-cause mortality end point alone after 1 year of follow-up, CRT patients had a 24% risk reduction ($p = 0.060$), and CRT-ICD patients experienced a risk reduction of 36% ($p < 0.003$) when compared with optimal medical therapy [10]. Although COMPANION showed the impact of cardiac resynchronization plus ICD therapy in reducing early mortality in CRT patients, the mortality at 24 months of follow-up was the same in CRT alone patients vs. CRT- ICD patients.

VENTAK CHF and CONTAK CD trials

In the VENTAK CHF/CONTAK CD trial, 501 of the 581 patients enrolled received a CRT device [11]. Clinical characteristics included spontaneous or inducible (primary prevention, MADIT patient profile) sustained ventricular tachyarrhythmias and New York Heart Association (NYHA) class II (33%), III (58%), or IV (9%) congestive heart failure (CHF) symptoms. During 6 months of follow-up, 73 of 501 (14%) patients received an appropriate ICD therapy. Two independent predictors of appropriate therapy were identified: a history of a spontaneous, sustained ventricular arrhythmia (HR, 2.05; 95% CI, 1.31–3.20; $p = 0.002$) and NYHA class IV CHF (HR, 1.81; 95% CI, 1.10–2.96; $p = 0.019$). When patients with NYHA class II were excluded from analysis, a history of a sustained ventricular arrhythmia and the presence of NYHA class IV CHF symptoms remained as independent predictors of appropriate ICD therapy. Appropriate ICD therapy delivery was significantly greater in patients with NYHA class IV symptoms. Approximately one quarter of the patients with NYHA class IV CHF who received a CRT-D device received an appropriate ICD therapy within 3 months after implantation. The study found that patients with a prior history of spontaneous, sustained ventricular arrhythmias were twice as likely to receive an appropriate defibrillator therapy compared with patients who received a defibrillator for primary prevention [11].

MIRACLE Trial

In a retrospective review of 978 CRT-ICD patients of the MIRACLE-ICD (Multicenter InSync Implantable Cardioversion Defibrillation Randomized Clinical Evaluation) trial, it was reported that 28% of the secondary prevention patients experienced an appropriate shock at 12 months follow-up compared with only 14% of the primary prevention patients [12]. In other words, patients with a primary prevention indication for an ICD had a significantly lower incidence of appropriate ICD therapies (0.09 vs. 0.43 episodes/month) compared with patients with a secondary prevention indication. The appropriate use of the ICD in CRT patients with a primary ICD indication suggests that this arrangement may be potentially beneficial in such a patient population susceptible to life-threatening ventricular tachyarrhythmias.

Leiden Trial

A total of 191 consecutive patients with advanced heart failure, left ventricular ejection fraction (LVEF) <35%, and a QRS duration >120 ms received CRT-ICD device [13]. Seventy-one patients had a history of ventricular arrhythmias (secondary prevention); 120 patients did not have prior ventricular arrhythmias (primary prevention). During follow-up (18 ± 4 months), primary prevention patients experienced less appropriate ICD therapies than secondary prevention patients (21% vs. 35%, $p < 0.05$) [13]. Multivariate analysis revealed, however, no predictors of ICD therapy. Furthermore, a similar, significant, improvement in clinical parameters was observed at 6 months in both groups. Also, the mortality rate in the primary prevention group was lower than in the secondary prevention group (3% vs. 18%, $p < 0.05$).

The results obtained in the primary prevention group are in line with the results of the MADIT II (Multicenter Automatic Defibrillator Implantation) study (26% ICD therapy in ischemic cardiomyopathy patients, LVEF <30%) [14]. Also, the SCD-HeFT study (LVEF <35%, ischemic and nonischemic

heart disease patients) reported an incidence of 21% ICD therapy, though the follow-up period was longer in the SCD-HeFT study [15].

Other Studies with CRT-D Devices

A number of smaller studies of patients with CRT-D devices have also confirmed that CRT reduces the need for ICD-delivered antitachycardia therapy (shocks) suggesting but not proving that ICD therapy prevent sudden arrhythmic deaths [16, 17].

Effect of Upgrading the Pacing Mode in ICD Patients with Ventricular Tachyarrhythmias

Eight consecutive ICD patients who underwent an upgrade to CRT-ICD were followed during two time periods: 47 ± 21 months (range, 24 to 70 months) before and 14 ± 2 months (range, 9 to 18 months) after CRT upgrade [18]. At time of upgrade, patient age was 69 ± 11 years and ejection fraction was 21 ± 8%. During conventional ICD treatment, antitachycardia pacing was applied in 10 of 18 (56%) patients compared with 1 of 18 (3%) after CRT-ICD placement. Similarly, the number of patients receiving ICD shocks diminished after CRT. The frequency of shocks was 0.048 ± 0.085 episodes/month per patient with the conventional ICD versus 0.003 ± 0.016 episodes/month per patient after CRT-ICD ($p = 0.05$).

Inducibility of Ventricular Tachyarrhythmias

Three small studies involving 13 patients in two acute studies, and 15 patients with a CRT device in a long-term study suggest that biventricular pacing can prevent in about 60–80% of cases sustained monomorphic ventricular tachycardia (VT) that is inducible during right ventricular (RV) stimulation [19, 20, 21] (Table 23.1).

Table 23.1 Inducibility of sustained monomorphic ventricular tachycardia during biventricular pacing.

Reference	Year	Acute vs. chronic BiV pacing*	VT, no pts RV stim.	LVEF %	Testing stimulation	% noninducible VT
Zagrodzky et al. [19]	2001	Acute. CAD, old MI	7	<35	BiV drive, RV extrast	71% (5 pts), $p < 0.05$
Kowal et al. [20]	2004	Acute. CAD	6	30	BiV drive, RV extrast	80% (5 pts), $p < 0.01$
Kies et al. [21]	2005	7.1 ± 0.8 mths after CRT	15	I: 21 ± 4 NI: 24 ± 8	RV drive at apex	60% (9 pts), $p < 0.01$

CAD, coronary artery disease; MI, myocardial infarction; VT, sustained monomorphic ventricular tachycardia; RV, right ventricle; LVEF, left ventricular ejection fraction; BiV, biventricular; I, patients with inducible VT; NI, patients with noninducible VT; Stim, stimulation; extrast (premature), extrastimulation; CRT, cardiac resynchronization therapy; pts, patients; mths, months.

*Acute testing was performed in patients without an implanted device. Chronic testing involved patients with an implanted CRT device.

Proarrhythmic Effects of CRT

CRT Causes No Proarrhythmia in Two Major Trials

Of 1,041 subjects entering two trials, (CONTAK CD and InSync-ICD), 880 were randomized to CRT (N = 439) or control (N = 441). The data included 840 electrograms in 150 patients with ventricular tachyarrhythmias including 678 monomorphic VT episodes and 162 polymorphic VT episodes [22]. CRT was not found to be associated with a measurable increase in the incidence of polymorphic VT or in a reduction in monomorphic VT in the combined populations.

Despite the above negative studies, isolated cases of CRT-induced proarrhythmia have been reported because biventricular or LV pacing influences the myocardial electrophysiology in a way that may occasionally result in malignant ventricular arrhythmias.

Disturbed Myocardial Electrophysiology by CRT

The ventricular myocardium is not uniform and exhibits electrical heterogeneity in that it comprises three electrophysiologically distinct cell types, epicardial, endocardial, and M (mid-myocardial) cells differing mainly with respect to repolarization characteristics [23, 24, 25, 26, 27]. The hallmark of M cells is the tendency for their action potentials to prolong disproportionately compared with epicardium or endocardium during bradycardia or in the presence of QT prolonging drugs or in response to agents that normally prolong the action potential. Hence, M cells (which have a different ionic basis) are thought to play an important role in delayed ventricular repolarization as in the long QT syndrome.

Normally, ventricular activation starts with the endocardium via a subendocardial Purkinje network and spreads across the ventricular wall. Although the epicardium is activated last, it repolarizes first because of its shorter action potential duration, producing a repolarization sequence opposite to activation. On the ECG, such an activation and repolarization sequence produces an upright T-wave with the same polarity as the QRS. In other words, the QT interval is normally determined by the myocardial layers with the longest action potential duration located in subendocardium or endocardium. Full repolarization of the epicardial action potential coincides with the peak of the T-wave and repolarization of the M cells is coincident with the end of the T-wave. It follows that the duration of the M-cell action potential determines the QT interval, whereas the duration of the epicardial action potential determines the QT_{peak} interval [23, 24, 25, 26, 27]. Because QRS duration determines QT interval duration, the QT interval should be interpreted cautiously during RV endocardial pacing and LV epicardial pacing when it is longer than during biventricular pacing.

The T_{peak}–T_{end} interval on the surface ECG may not be absolutely equivalent to transmural dispersion of repolarization (TDR), but this interval provides an index of TDR (electrical heterogeneity) if the measurements are limited to precordial leads [23, 24, 25, 26, 27]. A great deal of evidence has accumulated in support of the concept that amplification of TDR rather than QT prolongation underlies the substrate responsible for the creation of reentry and the development of polymorphic VT or torsades de pointes (TdP). Thus, TDR may be prognostic of arrhythmic risk under a variety of conditions.

Enhanced TDR increases the risk for the development of TdP, probably via two mechanisms. It facilitates early afterdepolarization (EAD) propagation leading to R-on-T ventricular extrasystoles capable of initiating TdP, and it could serve as a reentrant substrate for the maintenance of TdP.

Amplification of the TDR does not cause monomorphic VT because of different underlying mechanisms [23, 24, 25, 26, 27]. Most monomorphic VT can be initiated by any type of ventricular beat and can be maintained via a fixed reentrant circuit, for example, ventricular scar. Polymorphic VT or TdP from increased TDR is often initiated by an R-on-T extrasystole in the setting of a functional reentrant circuit. However, not all agents that prolong the QT interval increase TDR. Amiodarone is rarely associated with TdP. Chronic administration of amiodarone produces a greater prolongation of action potential duration (APD) in epicardium and endocardium, but less of an increase, or even a decrease at slow rates, in the M region, thereby reducing TDR.

Experimental Considerations

Using arterially perfused rabbit LV wedge preparation, transmembrane action potentials were recorded simultaneously from several sites using separate intracellular floating microelectrodes [28,29]. A transmural ECG was recorded concurrently. Action potential duration was measured at 90% repolarization. TDR was defined as the difference between the longest and shortest repolarization times across LV wall, which closely approximated T_{peak}–T_{end} interval. Shifting the stimulation site from endocardium to epicardium resulted in a change in activation sequence between epicardium and endocardium with delayed activation and repolarization of the M cells coupled with earlier activation of repolarization of epicardial cells. This was associated with an increase in QT interval and TDR and T_{peak}–T_{end} interval without a parallel increase in endocardial and epicardial transmembrane action potential duration (Fig. 23.1). Although reversal of the direction of activation causes a substantial increase in TDR in both the canine and rabbit LV wedge models under control conditions, this increase is not enough to permit the development of TdP (Fig. 23.2). However, an increase in TDR facilitates the occurrence of polymorphic VT under conditions that prolong ventricular repolarization. Thus, under long QT conditions (class III agent), the shift from endocardial to epicardial pacing at the same cycle length was sufficient to increase the TDR (T_{peak}–T_{end} interval) to the threshold for reentry (which in the canine ventricular wedge is approximately 90 ms) and the resultant development of polymorphic VT with the application of an epicardial extra stimulus with a short coupling interval.

Clinical Evidence

Medina-Ravell et al. [28] measured the TDR in 29 CRT patients during RV endocardial (Endo) pacing and LV epicardial (Epi) pacing but not during biventricular (BiV) pacing (P) because of flattened T-waves in most of the patients. TDRc (c = corrected) was significantly greater during LV epicardial pacing than during RV endocardial pacing (197 ± 26 vs. 163 ± 25 ms, n = 29, $p < 0.01$). In 4 of 29 patients, BiVP/LVEpiP, which caused a marked increase in TDR (149 ± 19 ms in RVEndoP vs. 220 ± 33 ms in LVEpiP) resulted in frequent R-on-T ventricular extrasystoles (presumably phase 2

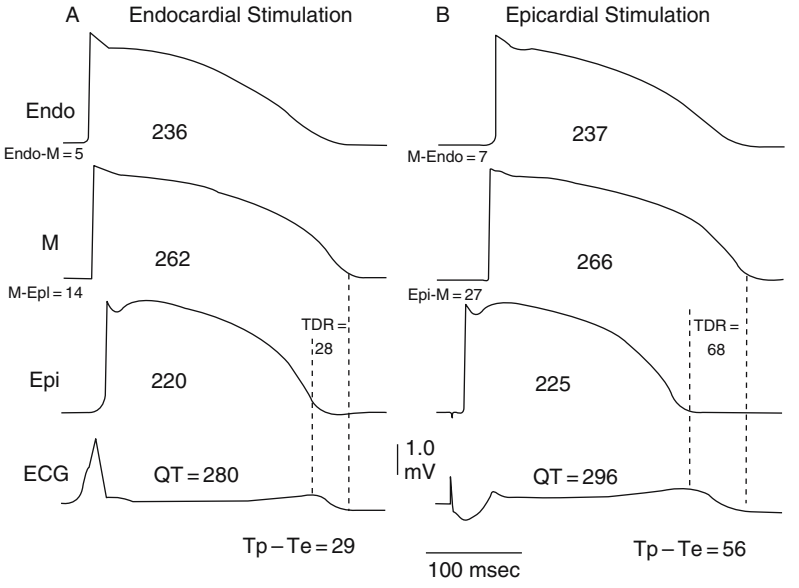

Fig. 23.1 Effect of reversal of transmural sequence of activation in canine left ventricular wedge preparation. Epicardial (*Epi*), endocardial (*Endo*), and M cell action potentials and a transmural ECG were simultaneously recorded during endocardial (**A**) and epicardial (**B**) pacing at a basic cycle length of 2,000 ms. All numbers are in milliseconds. (Reproduced with permission from Fish JM, Brugada J, Antzelevitch C. Potential proarrhythmic effects of biventricular pacing. J Am Coll Cardiol 2005;46:2340–7).

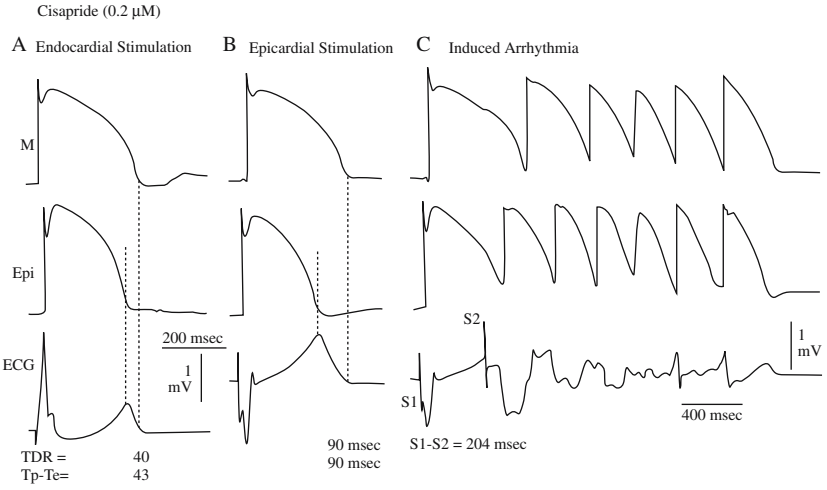

Fig. 23.2 Cisapride [(0.2 μmol/L), a drug with a propensity to cause torsades de pointes because it blocks Ikr] the rapid-delayed rectifying potassium current] induces torsades de pointes during epicardial (*Epi*) but not endocardial stimulation in a LV wedge preparation. Epicardial and M-cell action potentials and a transmural ECG were simultaneously recorded during endocardial (**A**) and epicardial (**B**) pacing of the canine LV wedge preparation at a basic cycle length of 2,000 ms. A polymorphic ventricular tachycardia was induced by an extrastimulus delivered to epicardium at an S_1–S_2 interval of 204 ms (**C**). (Reproduced with permission from Fish JM, Brugada J, Antzelevitch C. Potential proarrhythmic effects of biventricular pacing. J Am Coll Cardiol 2005;46:2340–7).

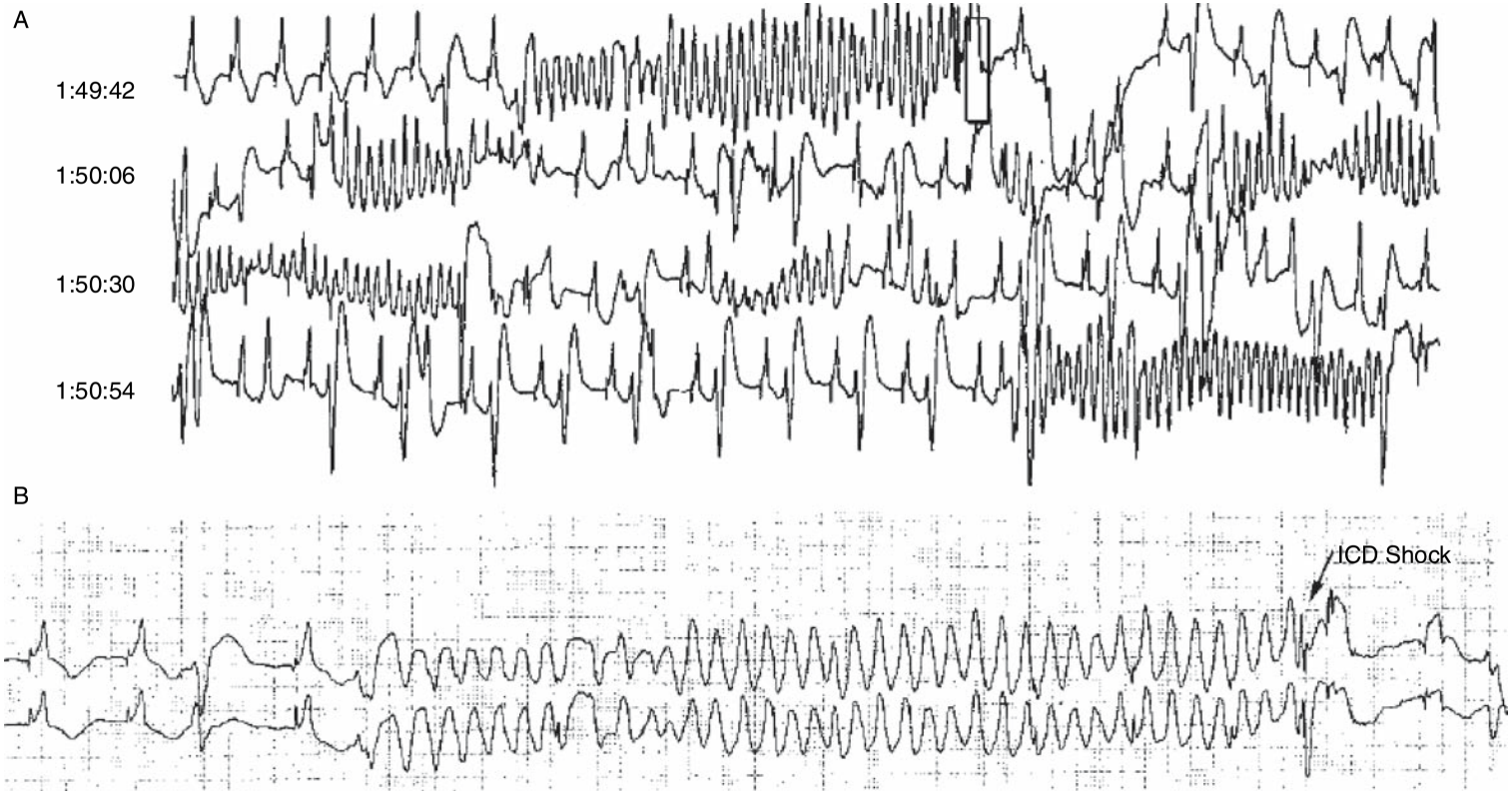

Fig. 23.3 (**A**) Incessant R-on-T ventricular ectopic beats and torsades de pointes (TdP) were observed in a patient 3 to 4 h after biventricular pacer implantation. Note that R-on-T extrasystoles were adequately sensed by the device. (**B**) Typical episode of TdP during biventricular pacing that was terminated by an ICD shock. (Reproduced with permission from Medina-Ravell VA, Lankipalli RS, Yan GX, et al. Effect of epicardial or biventricular pacing to prolong QT interval and increase transmural dispersion of repolarization: does resynchronization therapy pose a risk for patients predisposed to long QT or torsade de pointes? Circulation 2003;107:740–6).

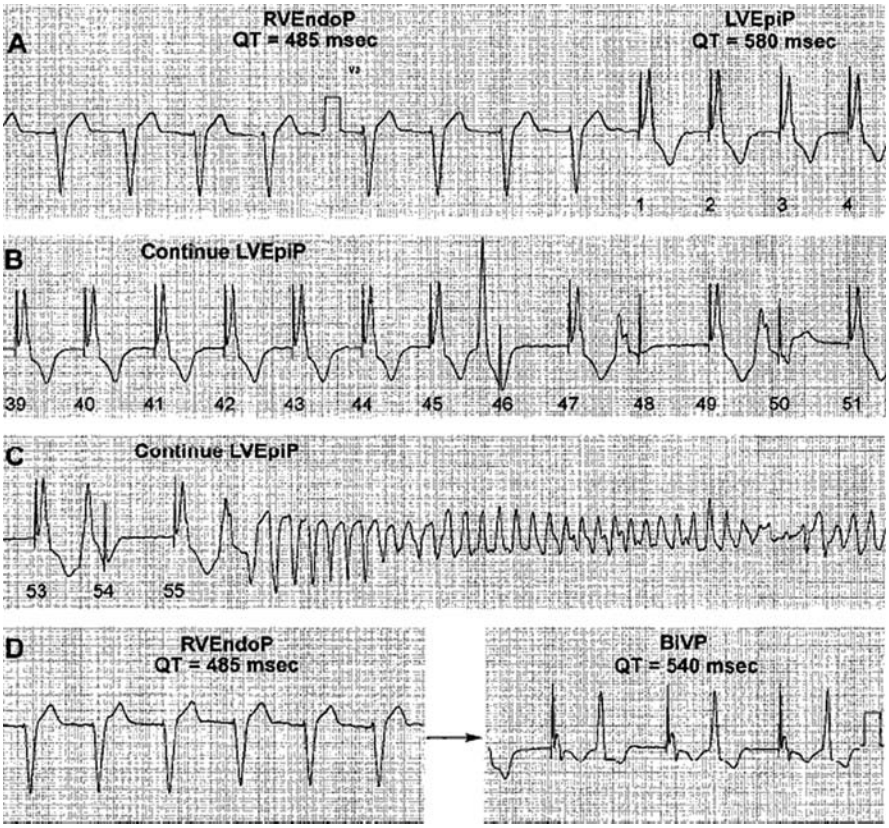

Fig. 23.4 Pacing site–dependent changes in QT interval, R-on-T ventricular extrasystoles, and the onset of torsades de pointes (TdP). Right ventricular (RV) endocardial pacing (RR interval of 840 ms) yielded a QT interval of 485 ms. Immediately after switching to left ventricular (LV) epicardial pacing (mode VOO), the QT interval increased to 580 ms (**A**). Ventricular extrasystoles started at the 46th beat of LV epicardial pacing (**B**) and initiated one episode of TdP at the 55th beat (**C**) that was terminated by an ICD shock. Switching from RV endocardial pacing to biventricular pacing resulted in an increase in QT interval by 55 ms accompanied by R-on-T ventricular extrasystoles (**D**). (Reproduced with permission from Medina-Ravell VA, Lankipalli RS, Yan GX, et al. Effect of epicardial or biventricular pacing to prolong QT interval and increase transmural dispersion of repolarization: does resynchronization therapy pose a risk for patients predisposed to long QT or torsade de pointes? Circulation 2003;107:740–6).

early after depolarizations) that were completely inhibited by RVEndoP. One developed recurrent nonsustained polymorphic VT, another suffered incessant TdP requiring multiple electrical shocks (Figs. 23.3 and 23.4). No new episodes of TdP occurred overnight during RVEndoP. BiVP was resumed the next morning after an event-free night. Numerous episodes of sustained TdP and nonsustained TdP reoccurred 4 h later. Again, switching to RVEndoP completely and immediately suppressed TdP and extrasystoles. The patient was then discharged from the hospital with RVEndoP and returned for follow-up 10 days later without any TdP events. When the device was reprogrammed from RVEndoP to BiVP and to LVEpiP, marked QT prolongation occurred and frequent R-on-T extrasystoles, leading to the development of TdP.

Table 23.2 CRT and proarrhythmia.

Reference	No pts	Previous smVT	Type VT after CRT	VT control
DiCori et al. [30]	1	No	smVT	D/C LV pacing
Guerra et al. [31]	1	VT ablation No VT in 3 mths	smVT	BiV pacing + amiodarone
Mykytsey et al. [32]	1	VT suppressed by drugs	smVT	D/C LV pacing
Bortone et al. [33]	1	No	smVT	D/C LV pacing
Medina-Ravell et al. [29]	1	Yes	TdP	D/C LV pacing
Turitto et al. [34]	1	No	TdP	D/C LV pacing
Rivero-Ayerza et al. [35]	1	No	TdP	BiV pacing induced no TdP
Shukla et al. [36]	5	Yes in all 5 pts	smVT in 4, polymVT in 1	Temporary control: D/C BiV or LV pacing Long-term control: ablation, amiodarone and resumption of BiV pacing

VT, ventricular tachycardia; smVT = sustained monomorphic VT; TdP, torsades de pointes; LV, left ventricular; BiV, biventricular; pts, patients; mths, months; D/C, discontinuation; polym, polymorphic.

Table 23.2 outlines the documented cases of CRT ventricular proarrhythmia that presented either as sustained monomorphic VT or polymorphic VT (torsades de pointes) precipitated by mainly by epicardial LV and to a lesser degree biventricular pacing [28,30,31,32,33,34,35,36] (Figs. 23.5 and 23.6). VT induced by LV pacing alone could be eliminated by turning off LV pacing, but some cases of LV-induced VT failed to occur during biventricular pacing. The opposite situation was reported by Tanabe et al. [37], who controlled an electrical storm in an ICD patient (with right bundle branch block) by upgrading the system to biventricular pacing.

In some patients, the induction of monomorphic VT by LV or biventricular pacing represents an exacerbation of a previously controlled arrhythmia but in others it appears de novo. The mechanism may involve the early arrival of LV wavefront at a site of slow conduction with resultant unidirectional block, and initiation of reentry. The prevention of VT by biventricular pacing in some cases may be due to the collision of two wavefronts preventing penetration of the reentrant circuit. In contrast, TdP is caused by a different mechanism related to amplified transmural dispersion of repolarization.

Transmural Dispersion of Repolarization Harada et al. [38] showed in man that epicardial LV pacing produces a pronounced prolongation of JTc (interval from the end of depolarization to the end of repolarization in the ventricle) and with a parallel prolongation of $Tc_{peak-end}$ interval. The increases in JTc and $Tc_{peak-end}$ intervals were similar to the enhancement of transmural dispersion of repolarization demonstrated in the experimental studies using LV wedge

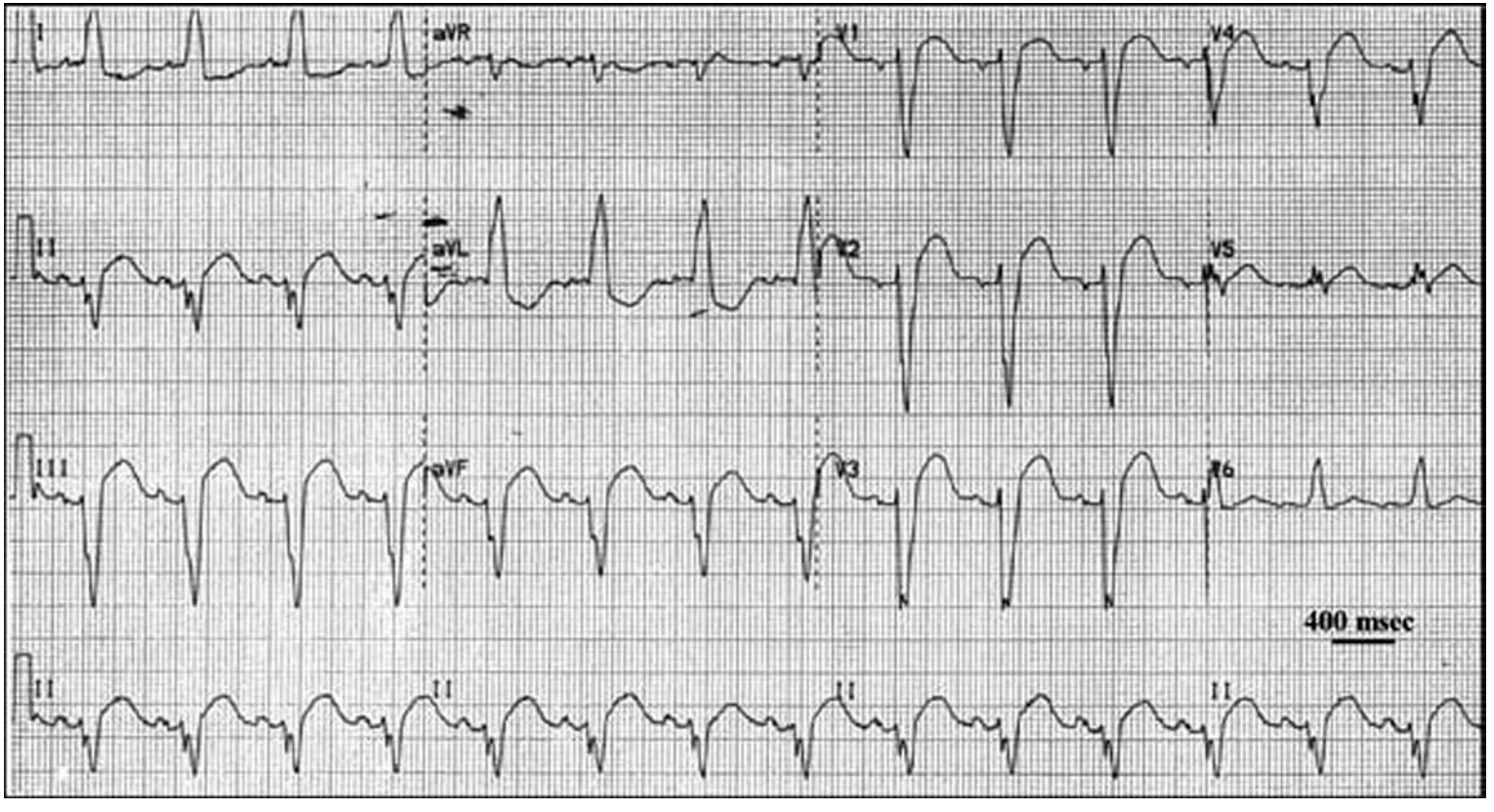

Fig. 23.5 ECG before implantation of a biventricular pacing system (see Fig. 23.6). Heart rate, 92/min; QRS duration, 150 ms; QT interval, 414 ms; corrected QT interval, 468 ms. (Reproduced with permission from Turitto G, Haq S, Benson D, El-Sherif N. Torsade de pointes: an electrophysiological effect of cardiac resynchronization? Pacing Clin Electrophysiol 2006;29:520–2).

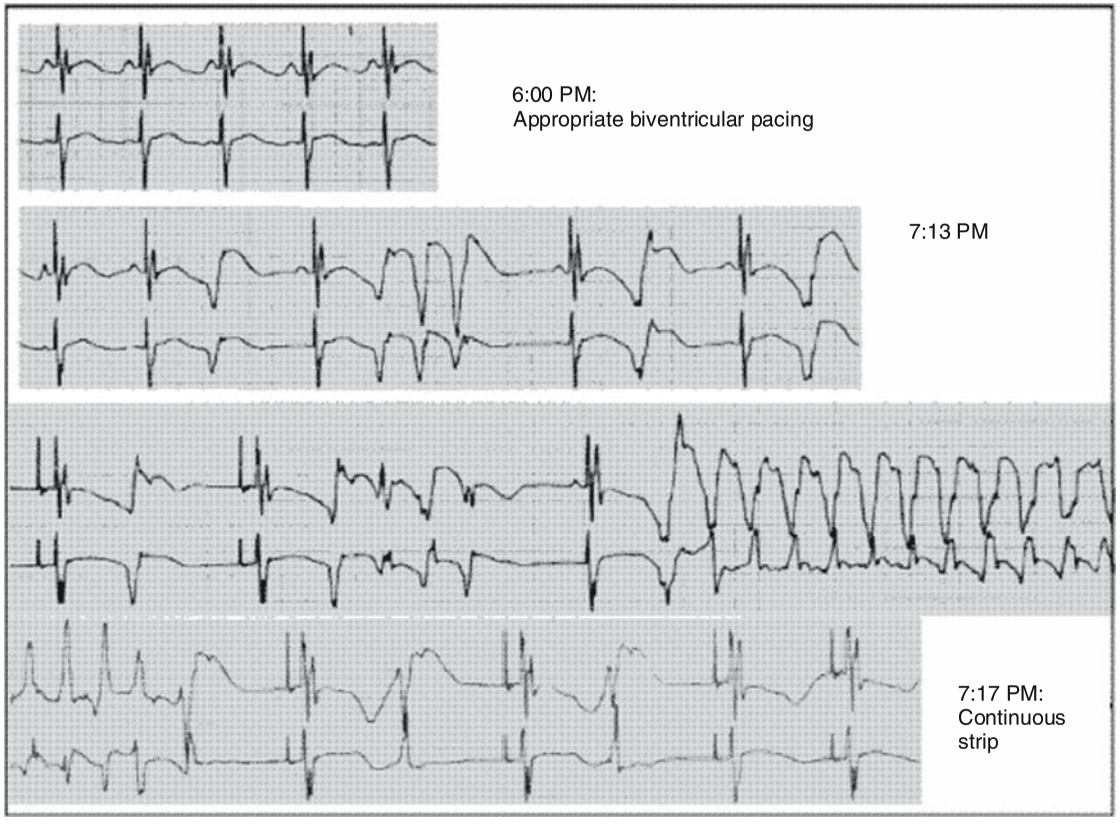

Fig. 23.6 Marked QT prolongation and malignant ventricular tachyarrhythmias a few hours after implantation of a biventricular pacing system in the patient whose preoperative ECG is shown in Figure 23.5. (Reproduced with permission from Turitto G, Haq S, Benson D, El-Sherif N. Torsade de pointes: an electrophysiological effect of cardiac resynchronization? Pacing Clin Electrophysiol 2006;29:520–2).

preparations. Perturbations of ventricular repolarization induced by epicardial LV pacing were minimized with BiVP. During RV endocardial pacing, JTc and $Tc_{peak-end}$ intervals were prolonged only slightly possibly because a physiologic LV activation sequence from endocardium to epicardium was preserved. These observations are consistent with those of Mediana-Ravell et al. [29] who reported larger prolongation of JTc during $LV_{epi}P$ than during $RV_{end}P$ and than those of Bai et al. [39]. Berger et al. [40] also reported that $LV_{epi}P$ increased QTc and $Tc_{peak-end}$, whereas BiVP did not affect QTc and decreased $Tc_{peak-end}$. These findings are concordant with the concept that BiVP is superior to $LV_{epi}P$ in minimizing ventricular dispersion of repolarization. In contrast, van Huysduynen et al. [41] found in 28 patients that the TDR during LV and biventricular pacing is not longer than the TDR during RV endocardial pacing. The reasons for such disparate results need further investigation.

Chalil et al. [42] conducted a study to determine whether CRT by biventricular pacing alters the QT interval (QT_c) and QT dispersion (QTD), which is the difference between the longest and shortest measured QT interval. The QT_c and QTD were measured before and 48 days after CRT in 75 patients to determine whether such changes related to the risk of developing major arrhythmic events (MAEs) over a period of 807 days (range, 93 to 1,543 days). Eleven patients had a MAE. The QT_c at follow-up was higher in MAE patients compared with no-MAE patients (35.9 ± 14.2 ms vs. 0.52 ± 6.0 ms; $p = 0.0323$). Similar differential responses for QTD were observed (46.4 ± 13.5 ms in MAE vs. −5.1 ± 4.1 ms in no MAE, $p < 0.0001$). Thus, patients who exhibit an increase in QTD after CRT are at increased risk of MAE compared with those who exhibit a decrease. Changes in the T_{peak}–T_{end} interval, however, failed to emerge as a significant predictor of MAE.

Increase in QT and TDR intervals during LV epicardial pacing and to a lesser extent biventricular pacing may be a potential risk for the development of TdP in a subset of patients. The overall incidence of TdP during these pacing modes appears low. This is because a change in pacing sites may facilitate the development of TdP only under conditions in which a trigger (e.g., EAD) and enhanced TDR are present.

Antitachycardia Pacing

Several clinical studies and one experimental investigation have suggested that biventricular antitachycardia pacing (ATP) is more effective than right ventricular ATP for the termination of VT [43, 44, 45]. Biventricular ATP was investigated in a total of 490 CRT patients with an indication for an ICD who participated in the VENTAK CHF/CONTAK CD study, a single-blind, randomized, placebo-controlled study [46]. ATP efficacy was evaluated in patients with or without CRT. ATP was always given simultaneously via both left and right leads (i.e., biventricular ATP). During follow-up, 32 patients received ATP: 15 with CRT and 17 without. In the 15 CRT patients, 221 episodes of tachycardia were treated by ATP. The sinus rhythm conversion rate was 90.5%. In patients not receiving CRT, there were 139 episodes of tachycardia and the sinus rhythm conversion rate was 69.1%. The sinus rhythm conversion rate in the CRT group was significantly higher than that

in the control group ($p < 0.0001$). Moreover, ATP pacing efficacy improved with time in the whole study population.

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24

Advances in CRT Device Diagnostics

Jeffrey Wing-Hong Fung and Cheuk-Man Yu

Introduction

In recent years, several large-scale randomized controlled trials have confirmed the beneficial role of cardiac resynchronization therapy (CRT) in improving the symptoms, exercise capacity, functional class, left ventricular (LV) systolic function, and in reducing heart failure–related hospitalization and mortality rates in patients with systolic heart failure and a wide QRS complex [1, 2, 3, 4]. The guideline for management of chronic heart failure has been updated, and CRT is now a standard treatment for patients with LV ejection fraction less than 35%, New York Heart Association (NYHA) class III or IV, and QRS complex duration more than 120 ms [5]. It is expected that the number of patients receiving the device will be increased substantially. The indication, patient selection, implantation techniques, troubleshooting, and other related issues have been discussed elsewhere in this book, and this chapter will focus on the advances in device diagnostic.

The primary purpose of follow-up in these CRT recipients is to (i) monitor heart failure symptoms and disease progression; (ii) ensure device integrity and optimal biventricular pacing; (iii) to predict and/or prevent heart failure decompensation or hospitalization; and (iv) provide prognostic information and identify high-risk patients who may require aggressive intervention. With advances in technology and increased storage capacity in the device, several diagnostic parameters can provide valuable information to individualize the management to these patients with severe heart failure. Three main areas will be explored in detail including heart rate variability (HRV), activity status, and intrathoracic impedance.

Heart Rate Variability

Heart rate control is a dynamic process affected by autonomic and neurohormonal systems and serves to meet the physiologic needs (e.g., exercise). The predominant mechanism of heart rate control is under the influence of sympathetic and parasympathetic innervation at the sinoatrial node [6]. The afferents from the cardiopulmonary and baroreceptors would induce autonomic modulation and subsequently modify sinoatrial nodal depolarization rates.

Parasympathetic nervous system mediates its chronotropic effect by acetylcholine release from the postganglionic neurons arising from the vagus nerve. Its effect is mainly on increasing the beat-to-beat cycle length in response to cardiopulmonary afferents via the respiratory center. The strong vagal input accounts for the high-frequency cyclic fluctuations in heart rate during ventilations [7]. In addition to positive chronotropic effect, sympathetic stimulation would increase cardiac inotropy by stimulating beta-adrenergic receptors. However, sympathetic stimulation would preferentially induce a low-frequency effect on heart rate and eventually reduce HRV [8]. The observed heart rate changes are the balance between these two autonomic systems. Apart from the autonomic modulation, HRV, especially the circadian changes during day and night, is also mediated through a complex and poorly understood neurohormonal mechanism (e.g., angiotensin II) [9].

The balance between the sympathetic and parasympathetic systems can be measured by the heart rate changes over certain period of time (i.e., HRV). It reflects the response of the neural control on the cardiovascular system when facing physiologic stress (e.g., myocardial infarction or heart failure exacerbation). There is a shift of HRV to an increase in sympathetic input and/or parasympathetic withdrawal in the presence of stressors. As a matter of fact, HRV has been evaluated in large-scale clinical trials and was a predictor of mortality after myocardial infarction and heart failure [10, 11, 12].

In simple terms, HRV can be arbitrarily classified as high or low. A low HRV usually refers to the condition of sympathetic predominance and represents the presence of stress, and indicates a high risk of lethal events. Patients are in relatively higher heart rate with little change over time. A high HRV is characterized by strong vagal tone and usually associates with lower risk of death or significant arrhythmia. However, acute changes in HRV can be a response to physiologic condition (e.g., exercise and posture). Therefore a continuous recording of heart rate changes over time is necessary to avoid these acute influences. The most common method to collect heart rate changes is a 24-h recording by Holter, and the ways to quantify HRV would include time domain, frequency domain, geometric, and nonlinear methods. There are obvious limitations to collect HRV information from 24-h Holter. It requires the clear acquisition of R-R interval by surface ECG in order to calculate time domain HRV. ECG with poor quality would definitely limit its utility. Moreover, HRV is a dynamic process and does not just vary over a 24-h period of time but rather over days or weeks indeed. A snapshot of HRV in 1 day may not be precise enough to predict an acute event, for example, heart failure decompensation, which is considered an important objective in heart failure management nowadays. A continuous monitoring is the most desirable method. However, it is not practical to ask the patients to have repeated daily measurement. HRV measurements based on intracardiac electrograms recorded in an implantable device seem to be the solution to the limitation by Holter recording. The R-R or P-P intervals (i.e., time domain analysis of HRV) can then be retrieved from the device for further analysis. In a CRT device, P-P interval obviously is the parameter of choice to determine continuous HRV in these patients with advanced heart failure.

Time Domain Analysis of HRV

In time domain analysis, the intervals of adjacent normal R-waves (NN interval) are measured over a period of time. In CRT, the intrinsic or sensed

P-waves would be used instead as continuous biventricular pacing is necessary for obvious reasons. A variety of statistical variables can be calculated from these NN intervals and other parameters can then be derived from the differences between these intervals.

SDNN, the standard deviation of measured NN interval over period of time, is the most commonly used time domain measure of HRV in general. Accurate measurements of SDNN require vigorous editing to exclude artifacts, ectopic or missed beats. Otherwise, SDNN may be substantially increased by these events. It is probably not the most appropriate and convenient parameter to reflect device-based HRV assessment. The SDANN, the standard deviation of average intrinsic interval over 5-min [13], and SDAAM, the standard deviation of the 5-min median A-A interval [14], are the two more practical and useful parameters to assess device-based HRV. They smooth out the acute changes and minimize the adverse effect of artifacts or ectopic beats on estimated HRV.

Effect of CRT on HRV

The recipients of CRT are, in general, in the advanced stage of heart failure with worse functional class and low LV ejection fraction. Diminished HRV and high mean heart rates in these patients were associated with poor prognosis [15,16]. Previous beta-blocker trials in patients with severe heart failure have shown that the time domain parameters of HRV and the mean heart rates were improved together with the prognosis [17]. It is of great clinical interest to know whether a comparable change in HRV or autonomic control can be observed in these patients after CRT.

The standard deviation of the atrial cycle length using 10 beats/min device-based histogram resolution over a 2-month period was used in early study to assess HRV in patients with CRT [18]. In the pilot phase of the Multicenter InSync Randomized Clinical Evaluation trial [1], patients were randomized to pacing therapy ON and OFF mode and the time domain parameters of HRV were compared between the two groups. The HRV in those randomized to pacing ON group was significantly higher than that of the pacing OFF group. Furthermore, the mean atrial cycle length had no difference between the two groups suggesting that CRT favorably shifted the cardiac autonomic balance toward less sympathetic dominance. This is the first study measuring HRV from the data collected via CRT in patients with severe heart failure. This study also formed the basis for HRV assessment in CRT device to delineate autonomic control over cardiovascular system in high-risk patients. However, the parameter chosen in this study may not be sensitive enough in recording small but meaningful changes of mean heart rates and time domain parameters of HRV. Moreover, it only reflected the early changes in HRV by CRT but did not provide any information about long-term effect and prognostic value of device-based HRV.

With advances in technology and increased storage capability, continuous sampling of heart rate changes and automatic calculation of time domain parameters of HRV become feasible in the recent generation of CRT devices. The SDANN of the 288 5-min segments of a day and heart rate profiles in 113 patients with CRT devices were evaluated in a long-term study [13]. The results confirmed that CRT induced a reduction of minimum and mean heart rates and an increase in SDANN at 3 months time. Interestingly, the

improvement in SDANN reached a plateau at an earlier stage than those of mean and minimum heart rates. The most salient finding of this particular study was that lack of HRV improvement as early as 4 weeks after the implantation could identify patients at higher risk for major cardiovascular events. The 2-year event-free survival rate for those with improved or no change in SDANN was 94% compared with 62% in those with worsened SDANN. When classifying responders to CRT as those with favorable SDANN changes, those with an increase in HRV were associated with significant improvement in peak oxygen consumption, LV ejection fraction, and LV end-diastolic diameter. In other words, HRV changes showed a strong and significant correlation with the structural and physiologic improvements in these patients with advanced heart failure after CRT (Fig. 24.1).

Prognostic Value of HRV in CRT

It is well-known that patients with severe heart failure are associated with significant morbidity and mortality. Apart from the high mortality due to pump failure or ventricular arrhythmic events, these patients also had frequent cardiovascular or heart failure–related hospitalizations. Prevention of hospitalization due to decompensation is one of the many goals in heart failure management nowadays. In fact, among the huge health-care burden for the management of heart failure, more than two-thirds of the expenses were spent on the treatment of acute heart failure exacerbation [19]. Hospital admission does not only increase the health care cost but, most importantly, also adversely affects the quality of life and possibly results in a worse long-term outcome. Therefore, when determining the prognostic value of certain parameters, they can grossly be divided into short-term and long-term, which represent the predictability of acute decompensation (e.g., hospitalization) and significant cardiovascular events (e.g., death), respectively.

As mentioned in previous section, Fantoni et al. reported the long-term prognostic value of device-based HRV in identifying patients at higher risk for major cardiovascular events [13]. Patients with lack of favorable changes in SDANN at 4 weeks after implantation were at significant risk of all-cause mortality, cardiovascular hospitalization, and heart transplantation than those with improved or no change in SDANN. Adamson et al. also reported the usefulness of SDAAM from the device to predict long-term prognosis [14]. The parameter was collected as an average over 4 weeks time 1 month after the implantation. Of the 397 patients in the clinical trial, those with SDAAM <50 ms had significantly higher all-cause and cardiovascular mortality with a hazard ratio of 3.2 and 4.43, respectively. When averaging the SDAAM from week 5 to 52 after device implantation, patients who died or were hospitalized had lower SDAAM than those with minor or no clinical events. It is now quite clear that the continuous or long-term autonomic assessment by HRV derived from CRT device can provide valuable information about the neural control on the cardiovascular system and should be considered as a clinical tool helping to risk-stratify patients with end-stage heart failure. In patients with persistently low HRV after CRT, repositioning of suboptimal LV lead [13] or other methods to optimize the resynchronization therapy, aggressive intervention, or early planning for heart transplantation are deemed appropriate.

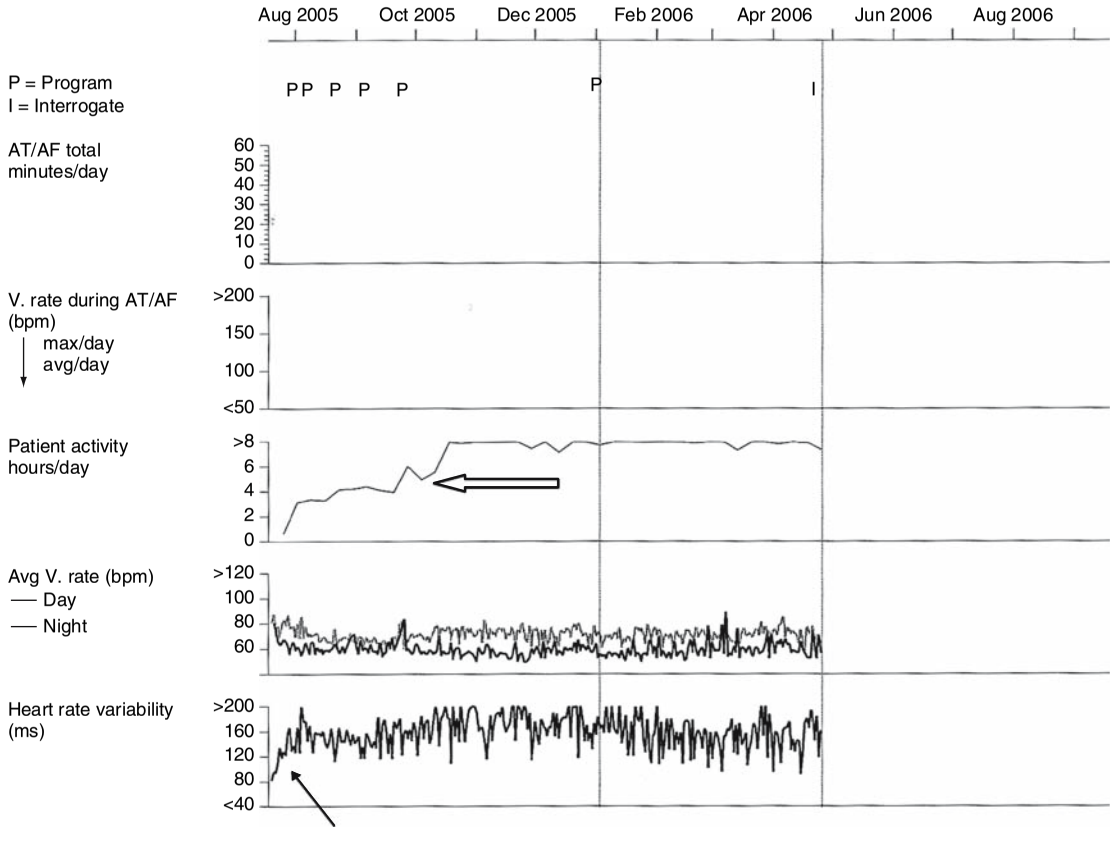

Fig. 24.1 The short- and long-term changes of heart rate variability (HRV) and activity log in a patient with CRT-D are shown. The patient was 56-year-old male with the device implanted in July 2005. There was a gradual increase in HRV as early as 4 weeks after the procedure (*arrow*) from 80 ms to 160 ms in August 2005. Parallel improvement in activity log (*open arrow*) was also observed with a plateau reached 3 months after CRT-D. The patient had no hospitalization or major cardiovascular events throughout the 7-month period. Echocardiographic examination showed significant improvement in ejection fraction, and the patient was a responder to CRT.

Determining short-term prognosis for heart failure hospitalization or precise prediction of upcoming heart failure decompensation is a clinical challenge. However, the clinical benefit of such prediction is obvious and valuable as early and appropriate intervention, for example, titrating up the dose of diuretic, may be able to abort symptomatic heart failure decompensation or even hospitalization. It does not only improve the morbidity but also potentially helps to reduce health care cost. HRV may have an important role in predicting such events. There was a significant decline in SDAAM in 34 patients who were hospitalized during the study period from 76 ± 27 ms to 64 ± 26 ms at the time of hospitalization [14]. The change in SDAAM was apparent around 3 weeks before hospital admission. With a threshold of 200 ms day, a 70% sensitivity rate was associated with a 2.4 false-positive events per patient-year follow-up. In addition, the true positive detection was not affected by the use or not of beta-blockers. Night heart rate changes (75 ± 11 bpm to 78 ± 11 bpm) were also observed in this study, but the magnitude of changes and estimated sensitivity were not comparable with that of SDAAM. It seems that continuous HRV assessment from the device is able to provide early warning signs to clinicians for more frequent follow-up and volume management in these high-risk patients. However, its role in preventing hospitalization or improving morbidity is still not clear, and whether its predictability for heart failure decompensation is comparable with other established parameters (e.g., intrathoracic impedance or central hemodynamic sensors) remain undetermined. A prospective clinical trial is needed to determine the role of HRV in preventing hospitalization in the future.

Limitations of Device-Based HRV

Device-based HRV assessment requires detection of intrinsic or sensed P-wave for calculation. A minimum of 20% of sinus rhythm over a 24-h period of time is required for estimation of SDAAM. Therefore, the most obvious limitation of its application is in those with atrial fibrillation and atrial pacing dependence. A lower atrial pacing rate (e.g., 40 bpm) is necessary in the MIRACLE trial in order to collect meaningful HRV data. Around 15–30% of patients with severe dilated cardiomyopathy were in atrial fibrillation [20], and the use of beta-blockers in heart failure may further aggravate the issue of atrial pacing dependency. Other parameters apart from HRV are needed to risk-stratify these patients.

Summary of Clinical Utility of Device-Based HRV

Device-based HRV is an important marker of autonomic condition in patients with severe heart failure. The short- and long-term prognostic value of device-based HRV in these patients is well established. It can help identify patients at significantly higher risk for major clinical events or even mortality. Furthermore, HRV can provide early warning signs and help to determine how intensively the patients should come back for clinical assessment and receive appropriate interventions. Continuous HRV now becomes feasible due to technological advances. Transmission of HRV data via the Internet may provide additional clinically relevant information to facilitate decision-making even when patients are staying at home. Appropriate interventions based on

this information may help to reduce the probability of frequent hospitalization so that the morbidity of patients can be improved substantially and the health care cost may be reduced.

Activity Status

Exercise intolerance is a common feature in patients with heart failure. Various tests to assess the exercise tolerance in a laboratory-controlled setting have confirmed their prognostic value in patients with systolic heart failure. Six-minute corridor walking distance and exercise capacity measured as metabolic equivalent by modified Bruce protocol during treadmill tests are valuable tools to assess submaximal exercise tolerance in these patients with advanced heart failure. Interestingly, the severity of heart failure as measured by LV ejection fraction had little correlation with maximal exercise capacity [21], and changes in maximal exercise tolerance also did not have any relationship with the changes in quality of life in patients receiving specific heart failure treatment [22]. Perhaps tests in which patients decide their own workload can reflect the degree of symptomatic impairment. Normal daily activity levels measured by pedometers were dramatically reduced in patients with chronic heart failure and were predictive of mortality [23]. In this early study, patients were requested to wear the pedometers around the hips. These pedometers were designed to display output as proportional to the movements of a vertically placed pendulum. The output measured by the pedometers represented the cumulated number of footsteps by the patients. Reduced levels of daily activity measured by the pedometers were even more predictive of death in chronic heart failure than the conventional exercise tolerance parameters. Although the role of daily activity to predict survival in these patients is established, the implication of this parameter for heart failure exacerbation is still unclear. Theoretically, patients with upcoming heart failure decompensation should have reductions in daily activity, and it may be a useful early warning sign for necessary intervention. However, such hypothesis has not been evaluated in a prospective trial.

Nowadays, patients' activity level can be measured by an activity sensor or accelerometer sensors in an implanted device. Rather than measuring number of footsteps, a mean daily physical activity (MDPA) index was established to measure the time in minutes per day with physical activity greater than 70 steps per minute walk rate. A sustained increase in MDPA was observed in a clinical trial assessing the effect of CRT on this index in 56 patients with NYHA class II to IV [24]. There was significant improvement in daily activity levels irrespective of baseline NYHA class after CRT. The most dramatic improvement, however, was observed in those with baseline NYHA class II patients as early as 2 weeks after CRT. The results were not entirely unexpected as the other parameters evaluating the exercise tolerance of these patients have already confirmed the beneficial of role of CRT in this aspect. More importantly, the MDPA index retrieved from the device correlated with the improvement in heart failure and may have the potential to monitor patients' response to the therapy received (Fig. 24.1). This measurement may also be applicable in other devices (e.g., conventional pacemaker or defibrillators) as well.

As mentioned, it is even more beneficial for any parameters that are predictive of upcoming heart failure decompensation or hospitalization. The role of MDPA index to predict such events has been evaluated and compared with SDAAM, the time domain measure of HRV, and the nigh heart rate changes in one study [14]. MDPA decreased significantly from 188 ± 109 to 164 ± 118 min/day at the time of hospitalization. However, the sensitivity of MDPA was lower than that of SDAAM to predict hospitalization over the entire range of false-positive rates. Its role in predicting heart failure exacerbation is probably complementary to other parameters (e.g., HRV or intrathoracic impedance).

Intrathoracic Impedance

Heart failure exacerbation and hospitalization accounts for a significant proportion of health care budget and adversely affects quality of life in patients with systolic heart failure. Factors leading to heart failure decompensation are diverse (e.g., progression of the disease, suboptimal medical therapy, drug noncompliance, failure or inability to detect worsened heart failure). Symptoms of heart failure exacerbation include shortness of breath, ankle edema, paroxysmal nocturnal dyspnea and orthopnea, and so forth, and pulmonary congestion is one of the important clinical features. Prevention of heart failure hospitalization is one of the many goals in current heart failure management. In theory, early and accurate prediction of upcoming deterioration and delivery of appropriate intervention may be able to reverse the decompensation and abort the hospitalization. Monitoring of symptoms, volume status, body weight, or change in ventricular performance by means of frequent visit and physical examination for heart failure patients is recommended as part of the management program. However, none of these measures showed promising impact on heart failure morbidity [25,26]. In addition, both symptoms and physical signs are not reliable or early enough for prediction of heart failure exacerbation [27,28]. Search for other parameters is necessary for precise prediction and prevention of hospitalization.

In general, fluid accumulates when heart failure decompensation is developing. Elevated left atrial pressure would lead to pulmonary interstitial congestion and eventually pulmonary edema. As the conductance of fluid is much higher than air in the alveoli, the transthoracic impedance would decrease as heart failure worsens. As a result, measurement of transthoracic impedance may be able to detect early stage of heart failure exacerbation. This concept was first evaluated by the noninvasive transthoracic setting in animal studies [29, 30]. Preliminary data showed that such measurement was proportional to the degree of pulmonary congestion and confirmed its feasibility. In human studies, the transthoracic impedance correlated well with the changes in clinical and radiologic evidence of pulmonary edema [31]. It has also been suggested that transthoracic impedance measurement can be a valuable tool in the emergency department for diagnosis of fluid overload [32]. However, transthoracic impedance measured transcutaneously has several limitations including lack of reproducibility, poor sensitivity and specificity, unpredictable effect of different skin impedance with different electrode placements, and so forth [33, 34].

Feasibility of Intrathoracic Impedance Measurement

Intrathoracic measurement may circumvent the limitations by transcutaneous route. Intrathoracic impedance measured by implanting a modified pacemaker in a heart failure canine model correlated well with the level of pulmonary congestion and hemodynamic parameter [35]. An implantable cardioverter-defibrillator (ICD) lead was positioned into the right ventricle and connected to a modified pacemaker capable of measuring impedance. Impedance was measured from the ICD lead using the pathway of right ventricular (RV) ring electrode to device case for current stimulation and RV coil to device case for voltage measurement. The LV end-diastolic pressure in the canine was measured by the pressure sensor lead in the left ventricle, which was connected to an implantable hemodynamic device. Both the intrathoracic impedance and LV end-diastolic pressure data were collected before, during, and after heart failure as induced by rapid RV pacing. There was a significant correlation between the measured intrathoracic impedance and the hemodynamic parameters in all phases, confirming the feasibility of such measurement in an animal setting and the potential role in detecting pulmonary congestion in early stage of exacerbation.

Prediction of Heart Failure Exacerbation

The relationship between measured intrathoracic impedance and degree of pulmonary congestion in humans was assessed in a clinical trial with 34 patients who were in NYHA functional class III or IV with a history of recurrent heart failure hospitalization [36]. Similar to the animal study, a conventional ICD lead was inserted transvenously to the RV apex and was connected into a modified pacemaker. A constant current was sent via the RV coil electrode to the device case, and the voltage was then measured to calculate the intrathoracic impedance. Instead of direct measurement of LV end-diastolic pressure, pulmonary capillary wedge pressure was determined by transvenous Swan–Ganz catheter once patients were hospitalized for decompensated heart failure. There were a total of 24 hospitalizations in 9 patients in this study. Intrathoracic impedance started to decrease and provided early warning with a mean lead time of 18 days prior to admission while the symptom onset occurred only 3 days before hospitalization (Fig. 24.2). A significant reduction of impedance from the reference baseline was noted on the day before hospitalization. During the hospitalization period, the intrathoracic impedance correlated significantly with the pulmonary capillary wedge pressure and net fluid loss with diuretic therapy. The device-measured intrathoracic impedance may also serve as a surrogate measure of pulmonary fluid status in heart failure patients. Using 60 Ω-day as the nominal threshold, the device has a sensitivity of 76.9% at the cost of 1.5 false-positives per patient-year of monitoring and gives an early warning of 13.4 ± 6.2 days before heart failure hospitalization.

This is the first landmark study confirming the strong relationship between intrathoracic impedance measurement and degree of pulmonary congestion and its predictive potential for heart failure decompensation. A 13.4-day early warning by intrathoracic impedance monitoring ahead of the symptom onset for heart failure hospitalization may allow clinical intervention such as fluid restriction or medication adjustment to prevent hospital admission. Furthermore, the measurement may act as a guide to therapy

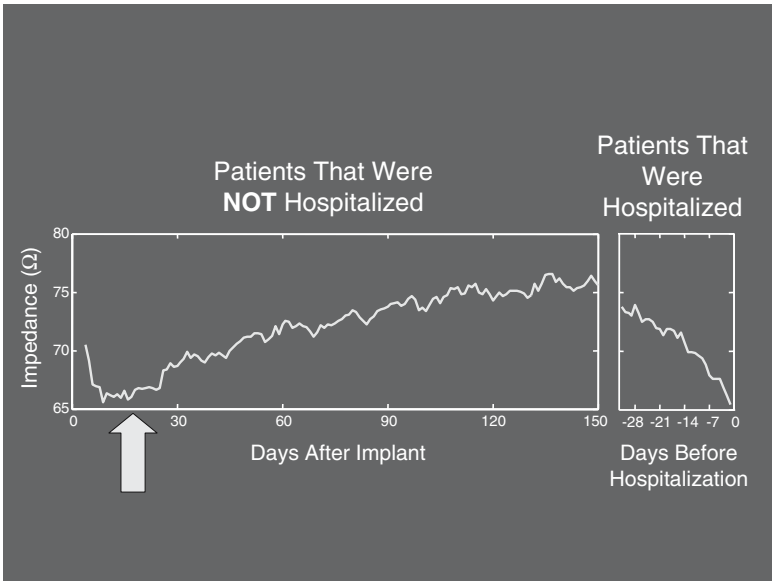

Fig. 24.2 The mean changes in intrathoracic impedance between the patients hospitalized or not are shown [36]. For those without hospitalization (*left*), there was a drop in the impedance measured right after the implantation due to pocket edema (*arrow*). It rose above 70 Ω 30 days after the procedure. The mean changes in impedance 28 days before the hospitalization are shown on the *right* side. At around 14 days before hospitalization, the mean impedance dropped below 70Ω

after hospitalization to ensure optimal volume status and avoid overdiuresis (Fig. 24.3). From the technical point of view, the intrathoracic impedance can be measured via the conventional ICD or CRT system without the need of additional lead implantation. The latter issue seems to be superior to the central hemodynamic monitor [37].

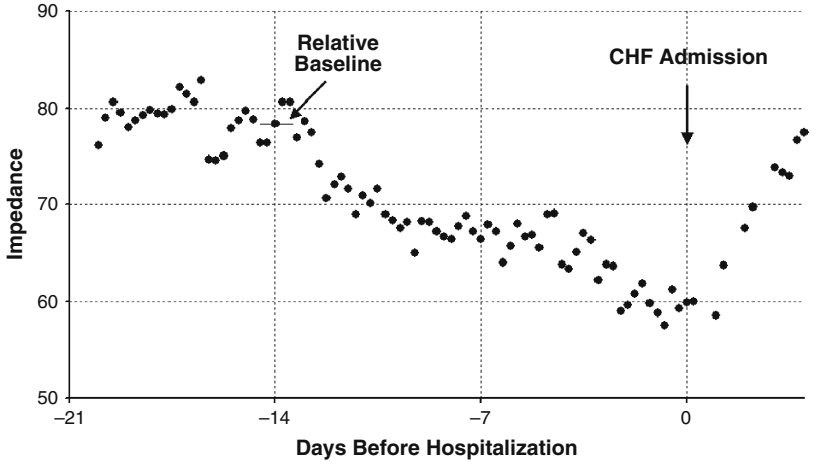

Fig. 24.3 An example of the changes in intrathoracic impedance around 14 days before heart failure hospitalization is shown. With diuretic therapy and resolution of pulmonary edema, the impedance was gradually increased back to the baseline reference.

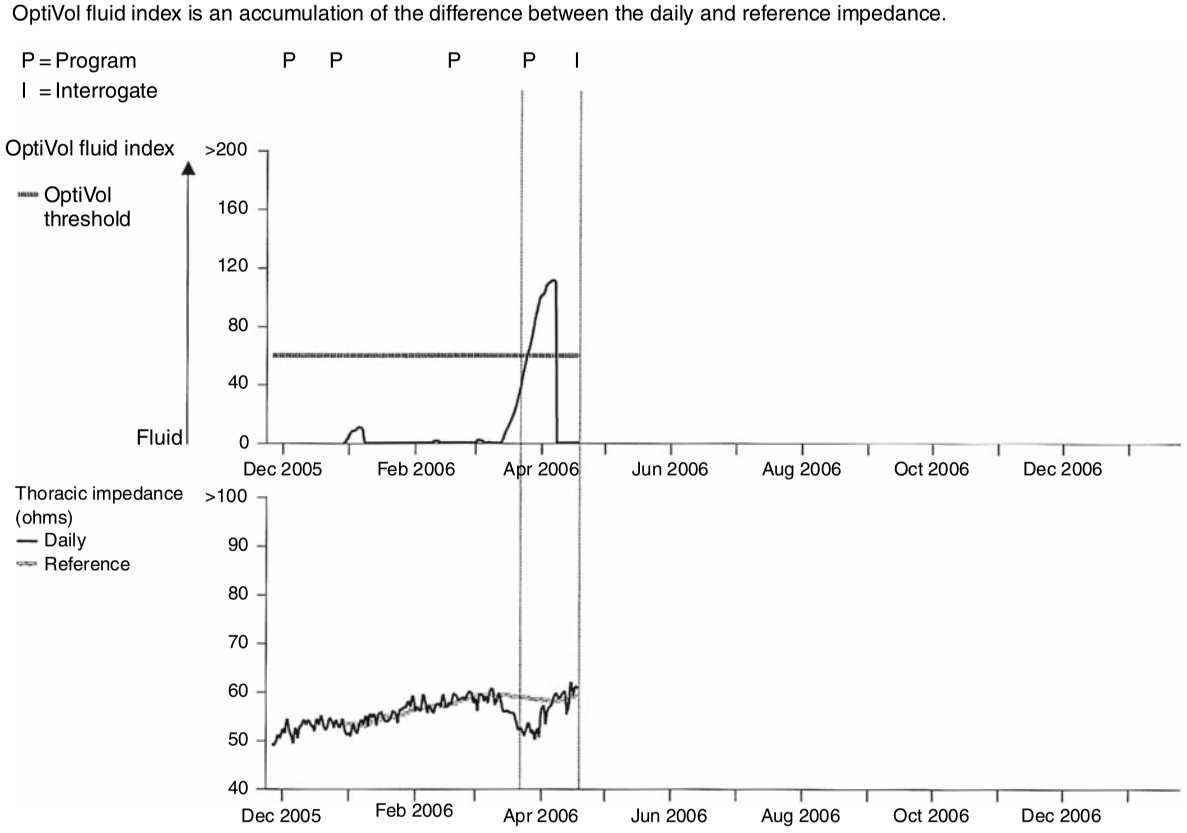

Fig. 24.4 The changes in fluid index and thoracic impedance in a 70-year-old male with CRT-D are shown. The patient received the device in November 2005. There was an episode of heart failure hospitalization in April 2006. A dramatic increase in fluid index above the threshold (60 Ω·days) was noted. The fluid index and the measured intrathoracic impedance returned to baseline or reference ranges after diuretic therapy.

The intrathoracic impedance measurement is now one of the key diagnostic parameters in the recent generation of CRT with defibrillator function (CRT-D). A *reference impedance* value was established as the average of daily impedance measurements. The reference impedance was used to quantify the magnitude and duration of any transient impedance reductions leading up to hospitalization. An automated algorithm for detection of transient decreases in impedance prior to heart failure admission was developed. On days when the measured impedance was less than the reference impedance, the difference between the measured impedance and the reference impedance was accumulated to produce the output of the algorithm, the *fluid index* (Fig. 24.4). Although this index has now been incorporated in daily use when interrogating the device, its value in aborting heart failure hospitalization by appropriate intervention has not yet been tested in prospective clinical trials. There are at least two multicenter clinical trials planned to recruit more than 1,000 patients to assess the efficacy of intrathoracic impedance monitoring with the alert algorithm on the prediction of heart failure events in patients with ICD indication.

Limitations of Intrathoracic Impedance

There are several conditions other than pulmonary congestion that would lead to a decrease in intrathoracic impedance measured by the device (i.e., false-positive events). As the measured impedance reflects the conductivity of the tissue between right ventricle and the device case, conditions that change the conduction property would potentially affect this diagnostic parameter. Thus, chronic lung disorder, chest infection, pocket infection, or even pulmonary embolism in patients may cause erroneous measurement. Cautious interpretation and careful consideration of a patient's coexisting medical condition is necessary in order to make a correct diagnosis. However, not all of the false detections occurred in the absence of the need for intervention. Anecdotally, "false-positive" detections by diuretic changes, pneumonia, and dietary noncompliance may in fact be worthy of medical attention.

Summary of Device Diagnostics

The relative merits and limitations of the three diagnostic parameters in CRT devices are displayed in Table 24.1. The mean and night heart rates are also the diagnostic features of CRT devices that may be able to monitor heart failure progression though their specificity and sensitivity are still not satisfactory. It is apparent that intrathoracic impedance and HRV can provide relatively reliable and early warning parameters to alert clinicians for upcoming heart failure exacerbation or hospitalization. The window provided by both parameters is sufficiently early to allow appropriate intervention to abort the deterioration, though data from prospective clinical trials are still pending. On the other hand, the sensitivity of activity log seems to be suboptimal. With regard to guiding therapy after heart failure hospitalization, supporting data by impedance method is available while HRV may have a potential role. It is very unlikely that activity log plays a key role in this particular aspect during the inpatient period. However, HRV has the most convincing data to support

Table 24.1 Summary of merits and limitations of the three diagnostic parameters in CRT.

	Heart rate variability	Activity log	Intrathoracic impedance
Parameters measured	SDAAM/SDANN	MDPA measured as time (min) per day with walk rate >70 steps/min	Intrathoracic impedance between RV apex and left pectoral device case across the left lung
Measuring tools	Sensed P-wave by atrial lead	Accelerometer sensor	Conventional ICD RV lead
HF exacerbation detection performance (per patient-year follow up)	70% sensitivity/2.4 false-positive events	50% sensitivity/approx. 2.2 false-positive events	77% sensitivity/1.5 false-positive events
Early alert capability	Median of 16 days [14]	NA	15.3 ± 10.6 days [36]
Conditions other than HF that may potentially affect the measurement	Any physiologic stress, e.g., major cardiovascular events, sepsis	Any conditions resulting in impairment in physical activity, e.g., major cardio/cerebrovascular or respiratory disorders	Chronic lung disorder, chest infection, pocket infection, pulmonary embolism
Guide for therapy after HF hospitalization	NA, possible	NA, but unlikely	Yes
Monitor response to CRT	Yes	Yes	NA, but unlikely
Long-term prognostic value after CRT	Yes	NA	NA

SDANN, the standard deviation of average intrinsic interval over 5-minute; SDAAM, the standard deviation of the 5-min median A-A interval; MDPA, mean daily physical activity; RV, right ventricle; HF, heart failure; ICD, implantable cardioverter-defibrillator; NA, not available.

its role as a long-term prognosticator after CRT. It may even be a significant marker of response to CRT [13].

Device Diagnostics in Clinical Practice

Care of heart failure patients is never an easy task. The disease itself is a complex and dynamic condition characterized by marked morbidity and mortality. Even though proven pharmacological therapy has been available for a long time, underuse of these medications in the community is still rather common [38]. It has been shown that patients with suboptimal medical therapy were associated with less improvement by CRT [39]. Poor drug and fluid compliance, natural progression of the disease, development of atrial or ventricular arrhythmia, and exacerbation of other comorbid conditions

are some of the common causes leading to decompensation or hospitalization. Failure to reduce hospitalization rates was still observed despite adopting a structured community-based heart failure program [40]. Methods to closely monitor, predict, and prevent heart failure exacerbation are imminently necessary to reduce the hospitalization, morbidity, or even mortality in these high-risk patients. As a matter of fact, the concepts of predicting the deterioration and long-term prognosis by heart rate changes, physical activity, or lung impedance are not really contemporary issues. The major limitation is how to provide a convenient, safe, and reliable platform for continuous monitoring. CRT does not just open a new treatment area for a subset of heart failure patients with significant electromechanical dyssynchrony but also, as an implantable device, provides such a platform to capture, analyze, and transfer this vital information for better patient care.

Apart from conventional device interrogation to ensure its integrity, follow-up visits for every CRT patient become more complex than ever due to advances in technology and device diagnostics. Cumulative data on HRV or activity log can help to monitor the response to CRT in addition to NYHA class assessment, symptom score, and echocardiographic examination. Lack of improvement in HRV and other parameters should alert the clinician to the possibility of suboptimal LV placement/performance or RV-LV timing in the device. Proper interventions (e.g., LV lead reposition or epicardial placement) should be considered accordingly. For those at ultrahigh risk as suggested by lack of sustained HRV improvement, early revision of aggressive therapy or even heart transplantation should also be considered. Detection of both symptomatic and asymptomatic arrhythmic events is also part of device interrogation nowadays. Development of atrial fibrillation (AF) is a common cause of hemodynamic deterioration in these patients (Fig. 24.5). Even though the incidence of AF appears lower in patients with CRT [41], proper treatment especially anticoagulation is absolutely necessary to prevent thromboembolism. In addition, monitoring the response to therapy for AF (e.g., antiarrhythmic drugs or ablation) can now also be retrieved from the device, the so-called AF burden.

Although detectable changes in device-derived HRV and intrathoracic impedance monitoring have been shown to occur around 2 weeks before hospitalization, the ways to alert physicians is a particular challenge. In other words, transmission of these continuously collecting data to clinicians' attention is necessary in order to decide the nature of the events and delivery of appropriate intervention to prevent the exacerbation. Telemonitoring via Internet is now the working direction. The idea of home telemonitoring allows frequent assessment of patients' clinical status and provides diagnostic information. Early signs of heart failure exacerbation may be detected by telemonitoring. The mean duration of hospital stay has been shown to be reduced by this approach in a recent study [42]. Application of this remote patient management by modern technology may further enhance the efficacy of hemodynamic and impedance monitoring systems in these implantable devices to improve the quality of life, reduce hospitalization and even mortality rates in patients with heart failure. Such application has been tested in the implantable hemodynamic monitoring system. The stored hemodynamic data in the device was read-out by radiofrequency transmission to a secure centralized server where data are maintained and reviewed by

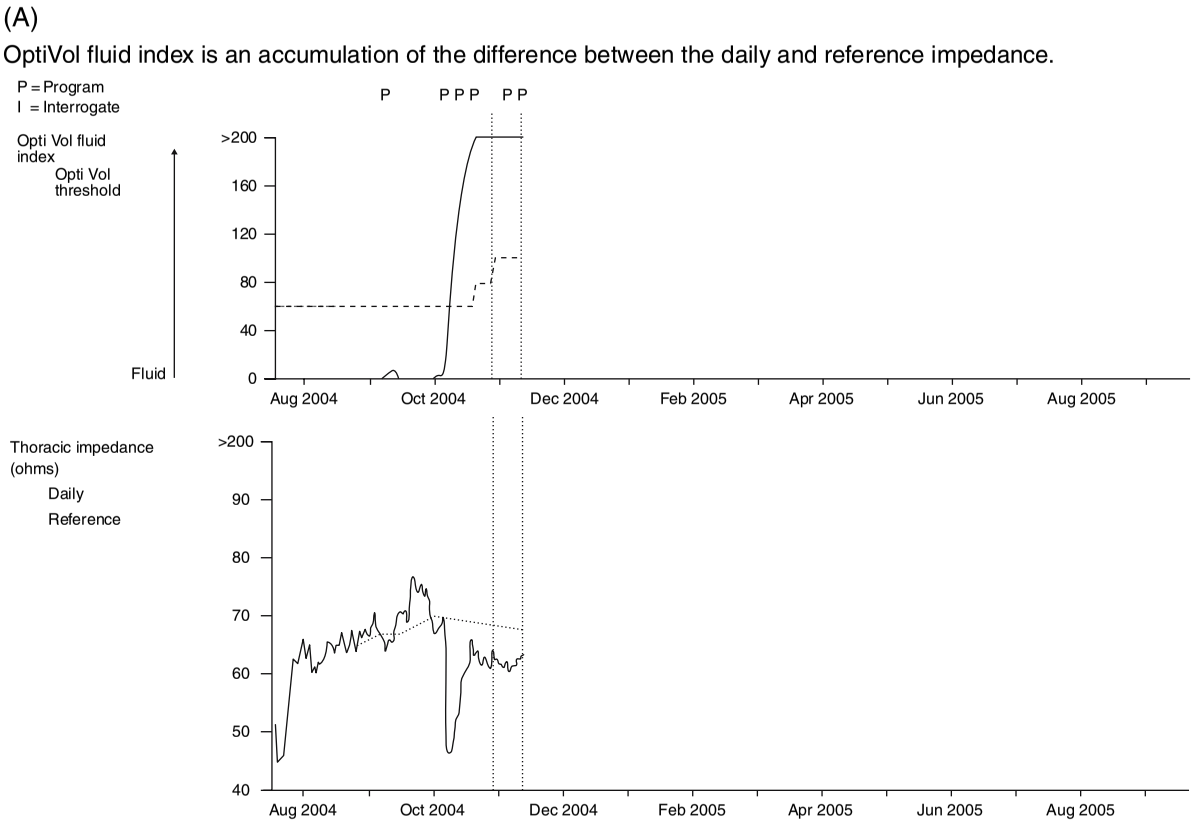

Fig. 24.5 An episode of heart failure exacerbation due to development of atrial fibrillation. There was surge in fluid index over 200 Ω·days in October 2004 (**A**). The cause of decompensation and pulmonary edema was due to the episode of atrial fibrillation and fast ventricular response, as shown in (**B**). Note there was a corresponding decrease in activity level during the exacerbation.

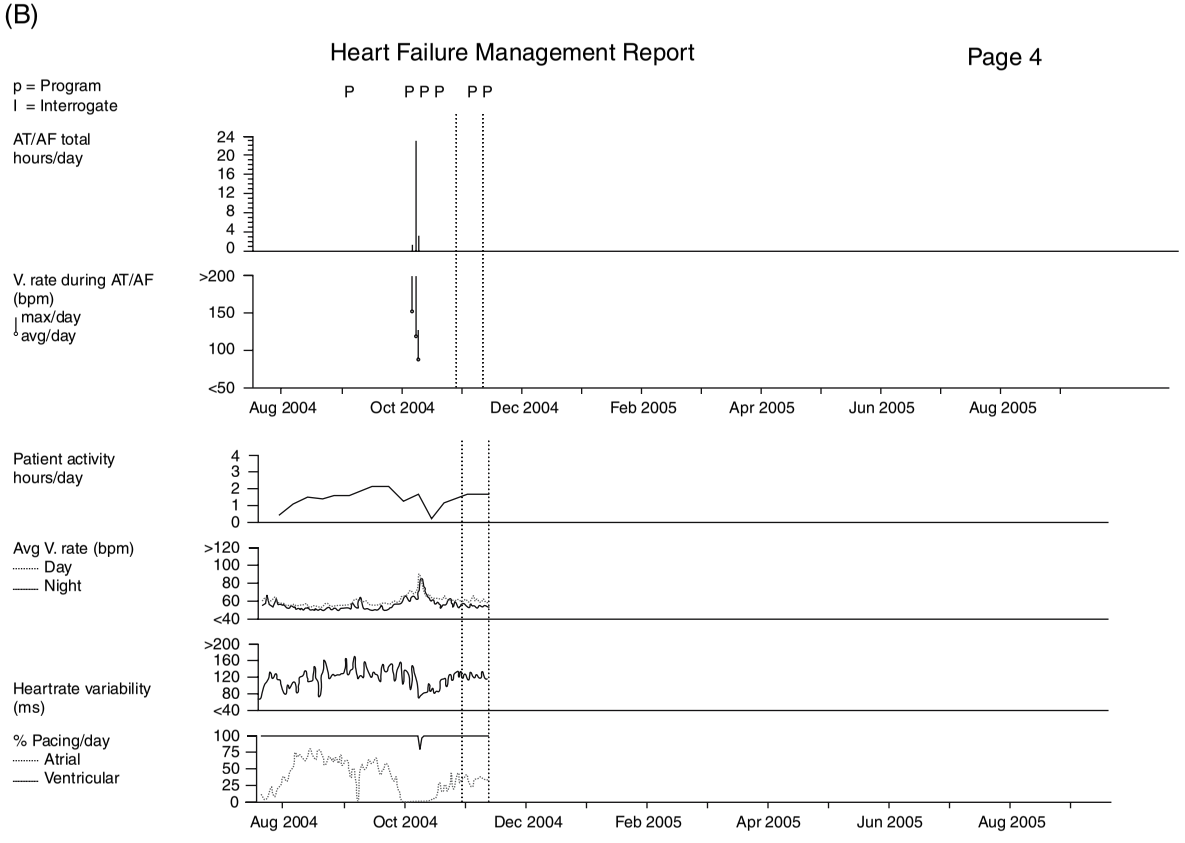

Fig. 24.5 *(Continued)*

clinicians through the Internet [43]. Further exploration and evaluation of applying the telemonitoring concept in impedance monitoring for heart failure management program is warranted.

With telemonitoring via the Internet, HRV may have a role to determine the frequency of follow-up [44]. For those with high HRV, clinic visit once in 3–4 months is acceptable with remote monitoring. In those with HRV less than 50 ms, close monitoring in 2–4 weeks time is needed. In case there is a persistent decline in HRV for a week, patients should be called back, and adjustment of the medical therapies may be necessary. Similarly, when the intrathoracic impedance drops below the reference baseline or the fluid index is persistently above 60 Ωdays, patients should come back for detailed assessment. Furthermore, the impedance derived from the device can also act as a guide to titrate the dose of diuretic therapy to relieve pulmonary congestion and minimize the risk of overdiuresis or even to help decide the proper date of discharge in addition to clinical assessment.

Conclusion

Device diagnostic parameters from the cutting-edge CRT have revolutionized the management program for patients with advanced heart failure. Continuous HRV, activity log, and intrathoracic impedance monitoring provide the opportunity to monitor patients' heart failure status, determine the response to CRT, detect significant arrhythmic events, predict upcoming heart failure hospitalization, guide medical therapy to relieve decompensation, and estimate the long-term prognosis in these high-risk patients. Telemonitoring via the Internet makes the idea of home monitoring feasible. With advances in technology, comprehensive assessment of autonomic status, accurate measurement of pulmonary congestion, and devotion of all health care providers, an even better care for these unfortunate patients is expected in the very near future.

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Complex Issues in the Follow-up of CRT Devices

Lieselot van Erven, Claudia Ypenburg, and Martin J. Schalij

Introduction

Cardiac resynchronization therapy (CRT) has proved to be a useful therapy in patients with advanced heart failure and ventricular conduction delay [1, 2, 3, 4, 5]. The first CRT pacing devices implanted were standard dual-chamber pacemakers connecting the two ventricular leads to the right ventricular (RV) pacing port of the pacemaker through a Y-connector [1]. Consequently, whereas programming of different pacing and timing parameters was possible, RV and left ventricular (LV) sensing, output and timing values could not be programmed independently. This approach, although effective in most patients, resulted in serious sensing problems in some patients because of fusion of RV and LV signals. Only in case of permanent atrial fibrillation could the LV lead be connected to the atrial port and the RV lead to the ventricular port of the DDD (dual chamber) pacemaker thereby enabling, to a certain extent, independent programming of sensing and pacing levels.

The introduction of pacemakers with specific ports for each individual lead and the possibility of independent programming of nearly all RV and LV parameters solved most of these problems. Furthermore, as CRT optimization may include sequential timing of RV and LV stimuli, most current CRT devices have the possibility to influence the V-V time (the time difference between the RV and LV stimulus).

The current generation of CRT pacemaker (CRT-P) devices combines sophisticated pacing features with multiple monitoring tools and even telemetric monitoring options reflecting the functional status of the patient. As both atrial and ventricular arrhythmias are frequently observed in heart failure patients, current CRT-P devices also incorporate arrhythmia monitoring tools. Ventricular arrhythmias are a serious threat to heart failure patients and several studies have shown that in patients with a low ejection fraction, mortality can be lowered by implanting a cardioverter-defibrillator (ICD) [2, 3, 4, 5]. However, until now no randomized studies have been performed demonstrating an additional effect of CRT-D over CRT-P only.

All pacing and monitoring features incorporated in the current CRT devices offer the unique opportunity to closely follow patients with advanced heart

failure, and data collected by the device may serve as early warning signals triggering interventions before actual deterioration of the clinical situation occurs. It can be expected that future devices will evolve into multimodality treatment and monitoring platforms and that more monitoring-only systems will become available for patients without an indication for CRT.

Thus, since the introduction of CRT, now more than 10 years ago, significant technical progress has been achieved in implantation tools and device technology [1]. However, with the increasing complexity of the devices and the growing number of heart failure patients receiving these devices, follow-up and monitoring of the technical and clinical status has become a challenging task. In this overview, some of the most important device-related issues encountered during CRT follow-up are addressed.

Device Programming

Lower and Upper Rate Programming

Although atrial pacing has potential beneficial effects on stabilizing atrial rhythm, the hemodynamic effects of atrial pacing may be unfavorable [6, 7]. Because of the intraatrial conduction delay, left atrial activation may be delayed, with consequent adverse hemodynamic effects on diastolic left ventricular filling. Therefore, programming a low lower rate to avoid atrial pacing seems reasonable, unless the patient is chronotropic incompetent.

The upper rate should be programmed higher than the maximum sinus rate to ensure tracking with biventricular pacing at high intrinsic sinus rates. In CRT-D devices, the upper rate will be limited by the cutoff value programmed for detection of ventricular arrhythmias in the lowest ventricular tachycardia zone, as current devices do not incorporate the possibility of bradycardia pacing in the ventricular tachycardia zone(s).

In order to achieve optimal resynchronization therapy, the percentage of ventricular pacing should be maximized. However, the percentage pacing provided by the device counters and the resulting histograms may not reflect the real percentage of ventricular pacing, due to intrinsic conduction, which may cause fusion and pseudo-fusion ventricular stimulation. The location of the RV lead influences the timing of ventricular sensing. To ensure early sensing by the RV lead, the lead should be placed in a more proximal position than the RV apex. Such a proximal position may decrease the amount of fusion/pseudo-fusion pacing and may contribute to a better outcome [8].

Atrioventricular Delay

It is well recognized that the programmed atrioventricular delay (AV delay) of crucial importance in optimizing the benefit of CRT [9]. Several studies have demonstrated that relatively short AV delays should be programmed to improve LV systolic function. Because CRT patients usually have intact intrinsic AV conduction, short AV delays may help to increase the percentage of biventricular pacing and to decrease the number of fusion beats. However, a short AV delay may also have a negative effect on cardiac performance. Although a short AV delay permits enough time for diastolic filling, the active filling phase may be terminated prematurely thus leading to a suboptimal preload of the LV (Fig. 25.1). Right to left intraatrial conduction

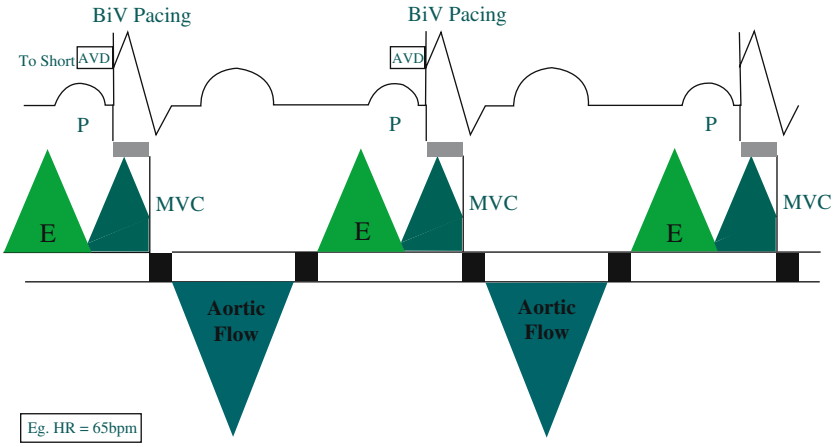

Fig. 25.1 Programming a short AV delay advances the mitral valve closure (*MVC*) and terminates the active filling phase prematurely, resulting in a suboptimal preload of the left ventricle.

time varies between patients but the impact of sensed versus paced atrial rhythms on intraatrial conduction time may be even more pronounced. AV offset programming, which increases AV delay during atrial stimulation, compensates for this phenomenon, but augments the possibility of fusion beats. Automatic shortening of the AV delay is programmed in regular DDD pacemakers because of the positive effect on upper rate programmability. In CRT patients, this feature overcomes the inherent shortening in rate-dependent intrinsic AV conduction time and thus has a positive effect on the percentage of biventricular pacing. However, in a recent publication, Scharf et al. demonstrated that lengthening of the AV delay during exercise led to a more favorable LV systolic performance at higher atrial rates [10]. In summary, optimizing the AV delay in CRT patients is a complex issue in which pacemaker parameters, intrinsic conduction and conduction times, and hemodynamic effects are intricately linked.

Ventricle-to-ventricle Timing

Because transvenous positioning of the LV lead is limited by the anatomy of the coronary sinus and the venous system of the heart, the final LV pacing site may be suboptimal with respect to the hemodynamic effects. Optimization ventricle-to-ventricle (V-V timing) is therefore usually desirable to compensate for these anatomical limitations and may enhance the clinical outcome of CRT. Optimization of V-V timing has been shown to have beneficial acute effects on dyssynchrony, systolic function, ejection fraction, and mitral regurgitation, although no chronic effects have been demonstrated [9, 11, 12]. The optimal sequence of right and left ventricular stimulation and the optimal V-V delay vary widely between individual patients, and lead positions and may change over time due to LV reverse remodeling induced by CRT [13]. Several noninvasive methods have been proposed of which the aortic velocity-time interval (VTI) may be the method of choice [14].

The relationship between V-V and AV delay is complex, because programming the V-V delay has a direct effect on the right versus the left

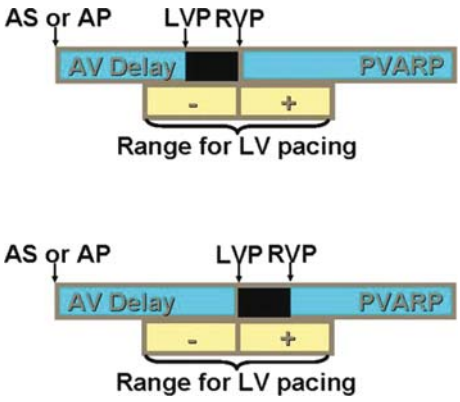

Fig. 25.2 The effect of programming the V-V delay on the AV delay varies between device manufacturers. *Upper panel*: Programming the left before right shortens the effective left-sided AV delay (Guidant). *Lower panel*: Programming of left before right increases the right-sided AV delay (Medtronic).

AV delay and is further complicated by the fact that different manufacturers offer different tools to handle this issue. For example, programming the left before right may shorten the effective left-sided AV delay (Boston Scientific) or increase the right-sided AV delay (Medtronic) (Fig. 25.2).

When programming left before right, unintentionally occurring anodal stimulation of the RV may abolish the programmed V-V delay. Anodal stimulation most commonly occurs at higher output settings when the RV lead serves as the anode, especially in case of a small anodal surface area and thus a higher currency density. Therefore, when the RV ventricular lead anode is used in the pacing circuit, one should be aware of the possible presence of anodal stimulation and this should be evaluated before optimizing the V-V delay.

Arrhythmias

Atrial Arrhythmias

Atrial fibrillation (AF) is the most common atrial arrhythmia in heart failure patients, occurring in 20–40% of patients with a significant correlation with the severity of the heart failure [15]. The loss of AV synchrony, the irregular ventricular rate causing varying left ventricular filling times, and a decrease in biventricular stimulation during atrial fibrillation may lead to a deteriorating functional status. In a subanalysis of the MUSTIC-AF study, the importance of a high percentage of biventricular pacing was demonstrated [16]. Patients with >95% biventricular pacing showed significantly more improvement of clinical parameters and a reduction of the number of all-cause and heart failure–related hospitalizations than those with a low percentage (<50%) of biventricular pacing. A subanalysis of the CARE-HF study reported that although CRT improved the outcome of the patient regardless of whether AF developed, CRT per se did not reduce the incidence of AF [17].

Algorithms used to increase the percentage of biventricular pacing during AF like ventricular rate regulation may be helpful (Fig. 25.3). The effect of RV sensed-triggered pacing warrants further investigation.

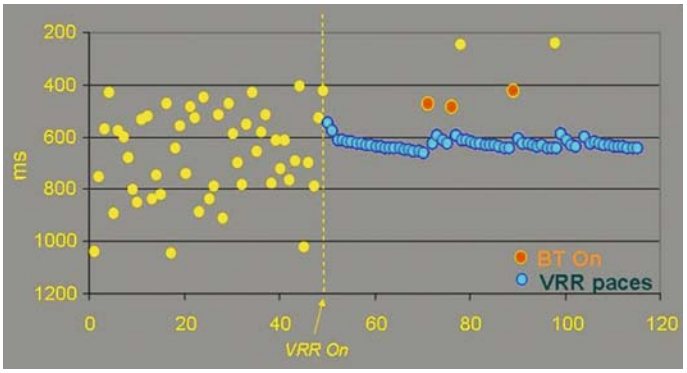

Fig. 25.3 Variation in V-V intervals during atrial fibrillation before (*left*) and after (*right*) switching on the "Ventricular Rate Regularization" (*VRR*) algorithms. VRR stabilizes the ventricular rate during atrial fibrillation.

Although modern mode switch algorithms are well capable of recognizing atrial fibrillation and react appropriately by switching to a nontracking mode, regular atrial tachycardias can lead to intermittent underdetection caused by unfortunate timing relations (Fig. 25.4).

In patients with therapy resistant or permanent atrial arrhythmias in whom rate control by drugs is not sufficient to achieve a high percentage of biventricular pacing, AV node ablation should be considered without reluctance [18]. In patients with paroxysmal AF, all efforts should be directed to maintain sinus rhythm.

Ventricular Arrhythmias

The increased risk of ventricular arrhythmias and sudden death is well recognized in patients with LV dysfunction and low ejection fraction (LVEF) [2, 3, 4, 5, 19, 20]. Several large, randomized trials demonstrated that implantation of an ICD in patients with a low LVEF has a positive effect on all-cause mortality [3, 19, 20]. Recently, the SCD-HeFT trial demonstrated that ICD therapy in patients with symptomatic heart failure and a low LVEF, regardless of the underlying cause, has a positive effect on all-cause mortality [3].

It is therefore challenging to speculate that combining CRT with ICD therapy may have a significant additional mortality effect and should be considered in all patients with a depressed LV function [5]. However, until now no large, randomized trials comparing the efficacy of CRT only with CRT-D have been conducted. Although the COMPANION trial reported only a significant mortality effect in the CRT-D group compared with optimal medical therapy, the difference between CRT-D and CRT-P patients was not significant [4].

Ventricular arrhythmias with a cycle length of <500 ms are also relatively common in patients with low ejection fraction, especially when antiarrhythmic drugs such as amiodarone are used (Fig. 25.5). In the current ICD generation, no overlap between bradycardia and tachycardia zones is allowed. Consequently, this results in limited possibilities to program the upper tracking rate and the lowest tachycardia rate.

The choice of antitachycardia therapy, antitachycardia pacing only, or antitachycardia pacing followed by shocks is ambiguous. Antitachycardia

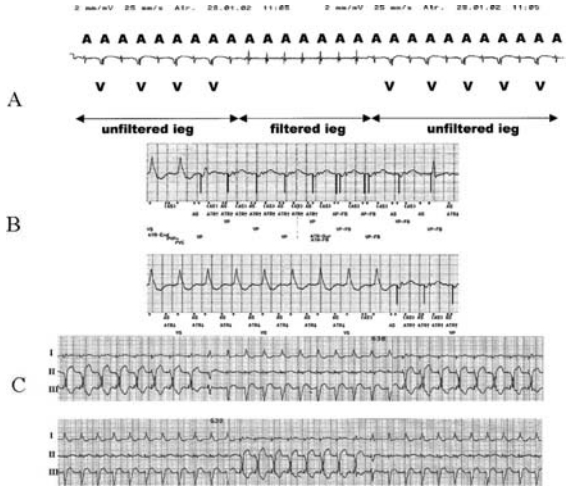

Fig. 25.4 **(A)** Intracardiac atrial electrocardiogram, unfiltered and filtered, as recorded by an external recording system. The atrial electrogram (*A*) reveals an atrial tachycardia. Far-field R-waves (*V*) can be discerned in the unfiltered parts of the registration. Note the simultaneous occurrence of every second atrial deflection with the far-field ventricular signal. **(B)** Pacemaker tracing (continuous): surface ECG lead I and marker annotations. Note the cyclic character of the tracing. After two intrinsic beats, nine ventricular beats are paced in DDD mode with tracking of the atrium in a 2:1 fashion. Sensing of the atrial tachyarrhythmia is reflected in the marker annotations as (*as*) and as, referring to an atrial sensed event or not in the postventricular atrial refractory period (PVARP). The markers show *ATR*↑, reflecting the process of counting up until the programmed number of atrial deflections fulfill the onset criteria for atrial tachycardia (programmed to 8). When the duration is also reached (*ATR-Dur*), pacing in the fallback mode is started (*ATR-FB*). The pacemaker now switches to DDI pacing in the fallback mode, slowly decelerating to its programmed rate (similar to rate smoothing), with dynamic AV delay on. The first two beats in the fallback mode show atrial pacing (*AP-FB*) as well as ventricular pacing (*VP-FB*), because the sensed atrial events fall in the PVARP [(*as*)]. The fourth *VP-FB* is a fusion beat of ventricular pacing and intrinsic conduction and therefore has a different configuration. From that beat on, the intrinsic rate is higher than the pacemaker rate, inhibiting DDI pacing. The atrial rhythm is misinterpreted as sinus rhythm, because due to their nearly simultaneous occurrence, every second flutter wave falls in the blanking period of the ventricular deflection. The other atrial deflections are sensed and followed by the ventricle (*Vs*). The marker channel shows *ATR*↓ representing the counting down of atrial deflections, after which sinus rhythm is supposedly present (*ATR-End*). Inappropriate back switching to the DDD mode occurs during which the atrial tachyarrhythmia is sensed again (*ATR*↑). **(C)** Surface ECG leads I, II, and III. This continuous tracing illustrates the unusual cyclic character of repeatedly mode switching. After appropriate mode switching, the atrial tachyarrhythmia was conducted to the ventricle in a 2:1 fashion. Due to simultaneous occurrence of each second atrial flutter wave and the intrinsic ventricular deflection, the atrial channel was blanked at the second flutter wave. The atrial rate was interpreted by the pacemaker as being below the cutoff rate for mode switching. This led to inappropriate mode switching to DDD mode after at least eight conducted beats. (Adapted from van Erven L, Molhoek SG, van der Wall EE, Schalij MJ. Cyclic appropriate mode switching and inappropriate back switching of a biventricular pacemaker during atrial tachycardia. Pacing Clin Electrophysiol 2004;27:249-51).

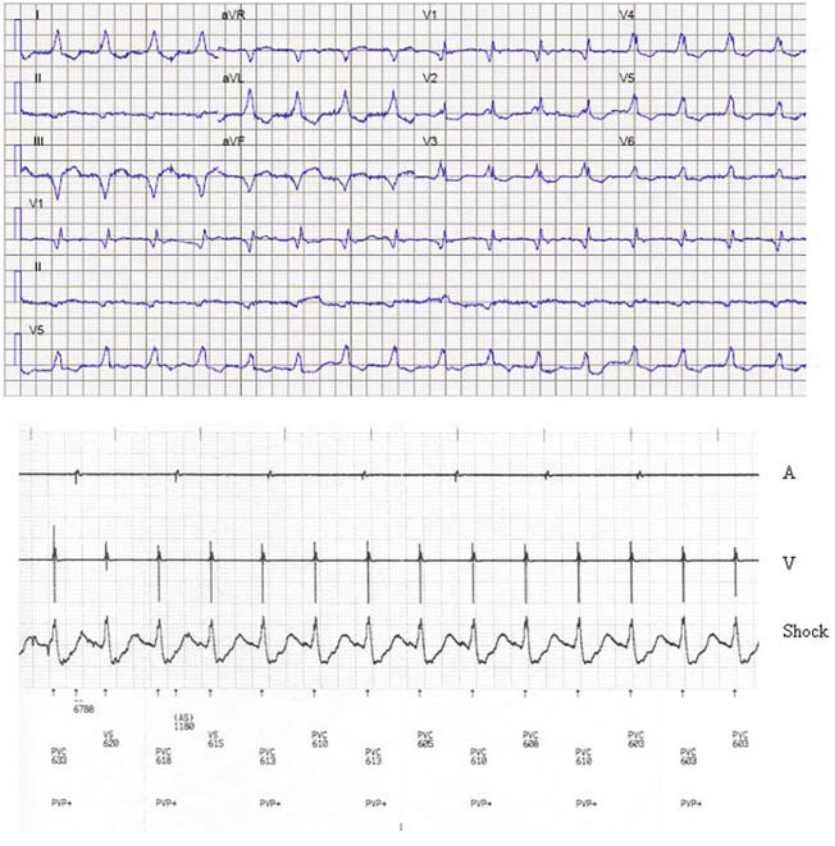

Fig. 25.5 Twelve-lead ECG (*upper panel*) and ICD tracing of intracardiac electrograms and annotations of a CRT-D device (*lower panel*), showing a very slow VT of less than 100 bpm. *A*, atrial electrogram; *V*, ventricular electrogram; *Shock*, shock electrogram.

pacing may be ineffective or may accelerate the slow VT, whereas shock therapy may be troublesome for the patient. In some cases, catheter ablation of the slow VT may be necessary to allow optimization of the device settings.

Device- and Lead-Related Issues

Pacemaker-Mediated Tachycardia

CRT patients are prone to the occurrence of pacemaker-mediated tachycardia (PMT) due to their often intact retrograde conduction through the AV node. A PMT can be initiated by retrograde activation of the atrium that occurs beyond the PVARP (Post Ventricular Atrial Refractory Period). The presence of slow intrinsic retrograde conduction, amplified by drugs used for heart failure, may result in a slow PMT that may be difficult to discriminate from sinus rhythm with the use of intracardiac signals and device annotations. PMT exhibits relatively stable heart rates (within the boundaries of lower and upper rate limits). The surface ECG may be helpful, as during PMT the P-wave axis is changed compared with regular sinus rhythm (Fig. 25.6).

In CRT patients, the effects of PMT are often more dramatic than in the normal bradycardia pacing population. During a PMT, the patient suffers from a nonphysiologic high heart rate, loss of normal AV synchrony, and reversed atrial activation. In combination with the already compromised left ventricular systolic function, this may lead to worsening symptoms of heart failure. PMT break algorithms are indispensable but are limited by their PMT recognition possibilities, which vary from manufacturer to manufacturer. Because in most devices, PMT break algorithms operate at a rate near the programmed upper tracking rate, underdetection of PMT by the device may occur especially in case of a relatively slow PMT.

Phrenic Nerve Stimulation

Phrenic nerve stimulation (PNS) is one of the most common complications of CRT, with an important impact on the patient's well-being. The inadvertent manifestation of PNS in relation to the target vessel during implant cannot be predicted, although some efforts have been made [21], and may necessitate relocation of the electrode. On the other hand, the absence of PNS during implant does not ensure the nonappearance during daily life because a significant postural-dependency may exist. Phrenic nerve stimulation has been reported to occur in up to 12% of the patients during follow-up in earlier studies. PNS can often be resolved noninvasively. Some newer devices have the possibility of programming a different vector, using either the LV tip or the LV ring electrode as a cathode either or not in combination with different anode poles [22]. This "electronic repositioning" of the vector and/or the pacing site may be successful in the majority of the patients. Programming the output closer to the LV threshold may also be of help but compromises the threshold margin with its possible negative effects on the percentage of effective biventricular pacing. Widening the pulse width is another method to lower the amplitude threshold, thereby compensating for the decreased threshold margin.

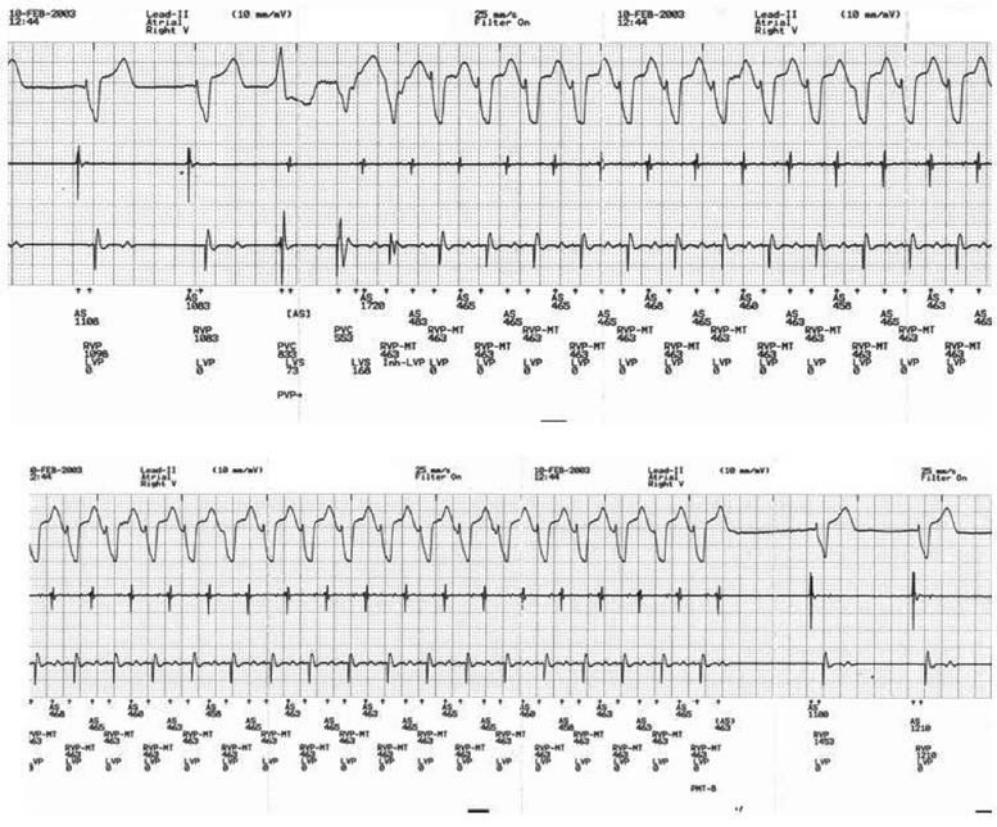

Fig. 25.6 Pacemaker mediated tachycardia in a CRT device. *Upper panel*: After two sinus beats, two PVC occurred. Retrograde atrial activation followed after the second PVC, starting the PMT. *Lower panel*: The PMT was ended with a PMT-break (PMT-B) algorithm, which prolonged the PVARP; the atrial activity falls in the refractory period [annotated as *(AS)*] and was therefore not followed by a ventricular paced event.

LV Lead Failures

Mechanical lead problems like lead fractures or insulation defects occur both in LV and RV pacing leads [21]. However, long-term LV lead performance data are not available yet due to the relatively short period of time these leads are used. Lead dislocation is a more common problem, with a reported incidence of 4–10%. In our own series of >500 patients, lead dislodgment occurred in 3% of patients, whereas a significant rise in pacing threshold up to submaximal levels, suggesting microdislocation, occurred in another 1.5%. In our series, we observed significant increases in pacing threshold up to 4 years after implantation, whereas macrodislocations of the LV lead were observed up to 10 months after implantation. Endovascular repositioning of the LV lead was successful in 87% of these cases. This suggests that epicardial lead placement in case of endovascular LV lead dysfunction should not be the first-choice solution for these problems in most patients.

Conclusion

Since the introduction of cardiac resynchronization therapy, technical progress has been impressive. With all options offered by the current devices, patient-tailored therapy has become possible. It can be expected that CRT devices will evolve into multimodality diagnostic and therapeutic platforms offering the possibility to detect and treat a variety of different cardiac conditions. However, the complexity of the current CRT devices requires profound knowledge and comprehension of all technical aspects. Furthermore, it is of importance to understand the possible effects of different settings on cardiac performance.

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26

Recurrent Heart Failure and Appropriate Evaluation After Cardiac Resynchronization Therapy

Juan M. Aranda, Jr.

Introduction

Heart failure (HF) continues to be a significant cause of morbidity and mortality in the United States with an estimated 5 million patients now affected [1]. Despite the advancement of neurohormonal blockade with angiotensin-converting enzyme (ACE) inhibitors, beta blockade, and aldosterone antagonists [2, 3, 4], more than 271,000 patients with HF in the United States have received cardiac resynchronization therapy (CRT) since 2001 when the U.S. Food and Drug Administration approved this therapy for moderate to severe HF [5].

Indications for the use of CRT have included New York Heart Association (NYHA) functional class III or IV HF refractory to pharmacologic therapy, QRS duration greater than 120 ms, left ventricular (LV) ejection fraction less than or equal to 35%, and LV end-diastolic dimension greater than or equal to 55 mm (level of evidence IIA). These indications are reviewed and emphasized in the guidelines of the American College of Cardiology, American Heart Association, and Heart Rhythm Society published in 2001 [6].

There are now seven major randomized trials of CRT involving more than 3,000 patients with HF of both ischemic and nonischemic origins [6, 7, 8, 9, 10, 11, 12, 13]. These trials have consistently shown improvement in functional class, exercise capacity, ejection fraction, and LV systolic and diastolic volumes in the presence of CRT. They have also shown a reduction in hospitalization and mortality with CRT. The benefits of CRT have been shown to occur as early as 1 month after initiation of CRT and to continue for as long as 18 months [7, 12].

The nonresponder rate for this therapy has been reported to be as high as 30% [15]. This is a subjective number that is derived from several clinical trials that showed that about 30% of patients failed to reduce their functional class by at least one class. There is no standardized definition of who should be considered a true CRT nonresponder, only various interpretations accounting for lack of improvement in functional class or exercise capacity. Nevertheless, the 30% nonresponder rate brings up the issue that we can have continued

HF in patients who received CRT and recurrent HF in patients who had a previous response to CRT.

The purpose of this chapter is to review and describe clinical and device issues that can contribute to early nonresponse to CRT or later reoccurrence of HF in those patients who had initially benefited from this therapy.

Clinical Expectations After CRT

After a patient with HF receives CRT, a series of hemodynamic and clinical events can be expected over the next several months (Table 26.1). These clinical and hemodynamic events must be recognized because they can be used to further optimize medical therapy that may help prevent the reoccurrence of HF during long-term follow-up after CRT. Immediately after implant—assuming adequate lead position and device function—systolic blood pressure, cardiac output, and dp/dt usually increase while end-systolic volume, pulmonary capillary wedge pressure, and mitral regurgitation usually decrease [16, 17]. This improvement in cardiac function is the result of correction of ventricular dyssynchrony. The change in hemodynamic parameters is important to recognize because it may require reduction in diuretics. Failure to reduce diuretics in a HF patient receiving CRT with optimal filling pressure may result in prerenal azotemia, masking or delaying the symptom improvement related to CRT. After CRT, diuretic adjustment is required both early on and during long-term follow-up as this device is maintaining ventricular synchrony and improving cardiac function. Volume status is a continuous variable, which depends on diet and compliance to medical regimen among other factors. Volume status can be independent of adequate device function and requires chronic assessment to avoid dehydration or reoccurrence of HF symptoms caused by increased filling pressures.

As the clinical benefits unfold during the first year after CRT, other interventions can be performed to decrease the chances of HF reoccurring. These interventions involve the optimization of neurohormonal blockade. After CRT, systolic blood pressure increases and continues to increase during many months of follow-up [11, 12]. This increase offers a unique opportunity to optimize neurohormonal blockers to evidence-based clinical trial

Table 26.1 Clinical and hemodynamic changes after CRT therapy.

Early response
1. Improvement in systolic blood pressure, cardiac output, and dp/dt
2. Reduction in mitral regurgitation
3. Improvement in exercise capacity and NYHA function class
4. Improvement in quality of life
Late response
1. Reduction in hospitalization and mortality
2. Improvement in ejection fraction
3. Reduction in left ventricular systolic and diastolic volume
4. Reverse cardiac remodeling

doses. Pharmacologic therapy with beta-blockers and ACE inhibitors has dramatically reduced HF mortality, sudden death, and HF hospitalizations [2, 3, 18, 19]. Despite these benefits, the use of beta blockade in recent randomized clinical trials is only around 60% to 70%. Doses of beta-blockers are often subtherapeutic. Many physicians hesitate regarding initiation of beta-blocker therapy or aggressive up-titration of beta-blocker therapy because of hypotension, bradycardia, and worsening HF [20]. CRT improves HF symptoms and systolic blood pressure while correcting ventricular dyssynchrony by pacing both ventricles. Therefore, the clinical problems that are related to beta-blocker administration are decreased by CRT. Several small retrospective analyses demonstrate that beta-blocker dose can be increased after CRT [21, 22]. We have demonstrated that beta-blocker therapy can be reinitiated after CRT in 50% of patients with a history of intolerance to these drugs [22]. The issue of device therapy and beta blockade cannot be overemphasized. Both CRT and defibrillator HF trials have shown that device use with concomitant beta-blocker therapy leads to better outcomes compared with device use without beta-blocker therapy [11, 23]. Beta-blockers can reduce the incidence of atrial fibrillation and ventricular arrhythmias. These arrhythmias can alter or reduce device function and increase antitachycardiac right ventricular (RV) pacing and defibrillator shocks, which can worsen HF. The combination of CRT and enhanced medical management may provide synergistic effects regarding reverse LV remodeling and improved systolic and diastolic function. This may prevent or reduce the reoccurrence of HF far beyond the follow-up periods currently reported in CRT trials.

Reoccurrence of Heart Failure

The reoccurrence of HF after CRT can be divided into patients who had an initial response to CRT and now have reoccurring HF and those patients who have simply not improved after CRT (nonresponders). It is important to note that when it comes to reoccurrence of HF in a patient who previously responded to CRT, we simply do not know how long this benefit lasts. Published reports have shown the benefit of CRT up to 18 months after implantation [12]. We have all had clinical experiences of patients receiving benefit long after the first 18 months of CRT, and we have all had individual patients who required advanced HF management after CRT. Systolic HF secondary to ischemic heart disease is a progressive disease that may improve with CRT. However, recurrent cardiac ischemia or myocardial infarction may cause HF symptoms to reoccur in the presence of CRT. Although initial nonresponders and patients who have reoccurrence of HF after an initial response may be considered two separate patient populations, several clinical events must be investigated in both types of patients. Table 26.2 describes clinical and mechanical issues that could affect device function and cause recurrent or continued HF early or late after CRT therapy.

We have previously described a potential troubleshooting algorithm that takes into account common problems that occur in HF and can effect CRT device function [24]. This algorithm describes the process of advanced HF management after CRT. The first step in evaluating worsening HF in a patient with CRT involves interrogating the device for adequate function. Is the device providing biventricular pacing 100% of the time? Is there loss of RV

Table 26.2 Clinical and device issues that can contribute to reoccurrence of heart failure after CRT.

A. Cardiac resynchronization therapy device function
1. Loss of right ventricular capture
2. Loss of left ventricular capture
B. Clinical issues affecting device function
1. Development of atrial fibrillation
2. Pre-renal azotemia (volume status)
3. Cardiac ischemia (patients with ischemic cardiomyopathy)
4. Mitral regurgitation
C. Evaluation of atrioventricular–interventricular delay
D. Presence of dyssynchrony after cardiac resynchronization therapy

or LV capture that could account for worsening or reoccurring HF? The rate of lead dislodgment in CRT trials is about 5%, but this involves 6 months to 1 year of follow-up. Although the chance of lead dislodgment decreases over time, its presence should be ruled out early in the troubleshooting process.

If there is adequate device function, then clinical issues that frequently occur in HF and can affect device function should be ruled out. Is the patient having intermittent atrial fibrillation affecting the ability of the device to maintain 100% biventricular pacing? It is known that patients with permanent atrial fibrillation benefit from CRT [25]. However, if the device is not programmed correctly with optimal mode switching and adequate rate control not exceeding the upper pacing rate of the CRT device, atrial fibrillation can affect device function leading to less CRT and worsening or reoccurring HF. Many of these devices provide downloadable summary cardiac reports that give an analysis of the number of episodes of atrial fibrillation, ventricular rates, duration of atrial fibrillation, and percent of biventricular pacing during episodes of atrial fibrillation. As we enter the era of chronic hemodynamic monitoring and diagnostic utilities provided by these devices, we are starting to find out that atrial fibrillation is extremely common in our HF population and can affect the function of an incorrectly programmed device.

If atrial fibrillation is ruled out, volume status should be addressed. As mentioned previously in this chapter, volume status reflecting filling pressures is a continuous variable that can be affected by many other issues regardless of adequate device function. Both prerenal azotemia (low filling pressures) and volume overload can cause the same constellation of HF symptoms. Simple management of diuretic agents may solve the immediate problem, but a search for the underlying reason (diet, compliance, cardiac ischemia, atrial fibrillation) should be performed. The important message is that advanced HF management is required and should be continued after CRT, especially as our patients live longer and pass the follow-up periods that have been reported in CRT trials.

Patients with ischemic cardiomyopathy present interesting problems. Up to 50% of patients enrolled in CRT trials have ischemic heart disease as the etiology of their HF. Ischemic heart disease is a progressive disease. We are

introducing the CRT device in a heart that has scar tissue with complete or incomplete revascularization. Some of the CRT trials have shown that patients with ischemic cardiomyopathy did not show as much improvement in HF symptoms and exercise capacity as patients with nonischemic cardiomyopathy [8]. This may be one of the issues regarding initial nonresponder rates. In a patient with ischemic cardiomyopathy who develops recurrent HF after initial response to CRT, cardiac ischemia or myocardial infarction can develop, potentially altering the ventricular dyssynchrony pattern that was being corrected by the CRT device. Reoccurrence of HF after CRT in a patient with ischemic cardiomyopathy should lead to consideration and reevaluation of the patient's ischemic heart disease.

The presence of mitral regurgitation (MR) continues to be problematic in our HF population. Causes of functional MR can be multifactorial. There is evidence to suggest that CRT can reduce MR [26, 27]. Correction of ventricular dyssynchrony results in earlier activation of the posterior medial papillary muscle, thus reducing MR. However, if the mechanism of MR is not caused by ventricular dyssynchrony (i.e., cardiac ischemia or enlarged mitral annulus restricting leaflet motion), then the continued presence or progression of MR can mask the effects of CRT and cause reoccurrence of HF.

There is much work on atrioventricular (AV) and interventricular (V-V) optimization in the early management of the CRT patient to improve hemodynamics and maintain adequate device function. Optimal AV intervals may vary among HF patients and may improve hemodynamic effects of the device [28]. Optimization of RV and LV activation is a new feature of CRT devices. Most of the CRT clinical trials have provided simultaneous RV–LV pacing. RV–LV optimization can further improve dp/dt and has recently been shown to provide greater exercise capacity compared with simultaneous CRT pacing [29, 30].

There are several important observations that should be considered regarding RV–LV optimization that have clinical relevance to the reoccurrence of HF after CRT. Optimal sequence of CRT may be difficult to predict in some individuals and may vary according to the etiology of HF. Patients with ischemic cardiomyopathy may require longer RV–LV intervals necessitating more preexcitation of the left ventricle due to the presence of scar tissue resulting in slower conduction velocities [31]. RV and LV delays are currently being optimized to improve device function and responder rates despite a lack of long-term follow-up data on the association between these intervals and the reoccurrence of HF. Although there is no clinical evidence to support it, AV and RV–LV delays should be considered in the evaluation of a patient with late reoccurrence of HF after CRT. Progression of ischemic heart disease can easily affect RV–LV delays, which may necessitate the reprogramming of the CRT device in order to provide optimal ventricular activation.

The presence of ventricular dyssynchrony prior to implant of a CRT device is currently one of the best predictors of response to CRT [32,33]. Ventricular dyssynchrony should decrease after CRT. In the MIRACLE study, interventricular dyssynchrony was reduced by 19 ms. In CARE-HF, interventricular dyssynchrony was reduced from 50 to 29 ms after 18 months of follow-up. The presence of significant ventricular dyssynchrony in an early CRT nonresponder indicates inadequate lead placement [32]. We can only

speculate about the reoccurrence of significant ventricular dyssynchrony in an initial responder who now has reoccurring heart failure. In the presence of adequate device function, reoccurrence of ventricular dyssynchrony may represent disease progression regardless of the etiology of HF. There is still much about chronic CRT that we simply do not know. As we continue to follow CRT patients for longer periods, clinical experience will help clarify these issues.

Conclusion

The use of CRT has developed and helped solve electrical mechanical issues that can affect cardiac function and cause progression of HF. Most of the clinical trials of CRT have evaluated the sole effect of restoring ventricular synchrony on clinical outcomes without significant change or intervention on other clinical issues that can affect CRT function. As our HF patients feel better and live longer with CRT, we are quickly passing the follow-up periods that are provided in the current evidence-based clinical trials.

The CRT device has been introduced in a clinical HF syndrome that includes many factors that can affect device function. Reoccurrence of HF symptoms after CRT is the last clinical manifestation of subclinical HF events (atrial fibrillation, cardiac ischemia, volume overload, noncompliance, or inadequate device function) leading to elevated filling pressures. Whether in an initial nonresponder or a responder who has reoccurring HF, an integrated approach between the HF specialist and the electrophysiologist will be needed to develop new strategies and algorithms to reduce the chance of reoccurrence of HF after CRT [34].

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