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Cardiac Resynchronization Therapy

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ABSTRACT

Systolic heart failure is a major problem for Americans today, with 550,000 new cases diagnosed per year, and ultimately contributes to 287,000 deaths annually. While pharmacologic therapy has drastically improved outcomes in patients with systolic heart failure, hospitalizations from systolic heart failure continue to increase and remain a major cost burden. In response to this unmet need, recent years have seen dramatic improvements in device-based therapy targeting one cause of systolic dysfunction: dyssynchronous ventricular contraction. Cardiac resynchronization therapy aims to restore mechanical synchrony by electrically activating the heart in a synchronized manner. This review summarizes the rationale for cardiac resynchronization therapy, evidence for its use, current guidelines, and ongoing and future directions for research.

INTRODUCTION

Systolic heart failure is a major problem for Americans today, with 550,000 new cases diagnosed per year, and ultimately contributes to 287,000 deaths annually.[1] While pharmacologic therapy has drastically improved outcomes in patients with systolic heart failure, hospitalizations from systolic heart failure continue to increase and remain a major cost burden.[2] In response to this unmet need, recent years have seen dramatic improvements in device-based therapy targeting one cause of systolic dysfunction: dyssynchronous ventricular contraction.

Ventricular dyssynchrony arises because of delayed ventricular activation and contraction of the ventricle, thereby disturbing the normally coordinated heartbeat.[3] In a dyssynchronously beating ventricle, one or more ventricular segments contract out of time with the rest of the ventricle, which reduces the heart's pumping efficiency by wasting energy and worsening valvular regurgitation. Approximately one-third of patients with systolic heart failure (HF) and New York Heart Association (NYHA) functional class III or IV symptoms suffer from dyssynchronous ventricular contraction[4] (see Table 1 for definitions of NYHA functional classifications).

Cardiac resynchronization therapy (CRT) was introduced in the 1990s and has revolutionized therapy for many patients with persistent symptoms of systolic heart failure.[2] The aim of CRT is to restore mechanical synchrony by electrically activating the heart in a synchronized manner. As detailed below, there is strong evidence from randomized controlled trials showing that CRT combined with optimal medical therapy improves HF symptoms, left ventricular ejection fraction (LVEF), and quality of life (QOL), while decreasing heart failure hospitalizations and reducing mortality.[4]

This review summarizes the rationale for cardiac resynchronization therapy, evidence for its use, current guidelines, and ongoing and future directions for research.

MARKERS OF DYSSYNCHRONY

The most readily available marker of ventricular dyssynchrony is the QRS duration (QRSd) on the surface 12-lead electrocardiogram. As the QRS complex represents ventricular depolarization, it follows that a wide QRS denotes prolonged ventricular conduction time and nonsimultaneous activation of the ventricular walls.

Thus, the rationale for using a wide QRS as an indication of dyssynchrony is that electrical conduction abnormalities contribute to mechanical dyssynchrony.[4] Mechanical dyssynchrony results in prolongation of the isovolumic contraction and isovolumic relaxation periods (during which no movement of blood occurs) and a significant decrease in left

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Table 1. New York Heart Association Functional Classifications for Patients With Heart Failure

Functional Class	Symptoms
I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

ventricular filling time. A prolonged QRS has been shown to be a marker for atrioventricular, interventricular, and intraleft ventricular dyssynchronies.[5,6] The net result of these perturbations in the timing of cardiac contraction is decreased pump function.

The American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) and Heart Failure Society of America (HFSA) guidelines for the use of cardiac resynchronization therapy use a QRS duration of more than 120 ms on the 12-lead electrocardiogram as a marker of ventricular dyssynchrony (see Table 2 for definition of classes of ACC/AHA/HRS recommendations). This has been the most consistently used parameter in clinical trials. The threshold value of 120 ms was selected primarily because this was the arbitrarily chosen QRSd criterion used in the landmark Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION)[7] and the Cardiac Resynchronization in Heart Failure (CARE-HF)[8] trials. As discussed below, QRSd is a simple and convenient marker of dyssynchrony. However, the fact that it is an imperfect marker presents an opportunity for further research.

DETAILS OF PROCEDURE

Cardiac resynchronization therapy is typically accomplished by adding a left ventricular pacing lead to a standard pacemaker or defibrillator system, which typically includes right atrial and right ventricular leads (Figures 1 and 2). Coordinated pacing of the left and right ventricles causes resynchronization of ventricular contraction.[8–10]

Table 2. Classification of Recommendations of the American College of Cardiology/American Heart Association/Heart Rhythm Society Regarding Treatment With CRT With or Without an ICD

Class I (indicated)	Means the benefit greatly outweighs the risk and that the procedure or treatment should be performed or administered.
Class IIa (reasonable)	Means the benefit outweighs the risk but additional studies with focused objectives are needed. Class IIa recommendation means that it is reasonable to perform the procedure or treatment.
Class IIb (may be considered)	Means the benefit is equal to or greater than the risk but additional studies with broad objectives are needed, and additional data registry would be helpful. Class IIb recommendation means that the procedure or treatment may be considered.
Class III (not indicated)	Means the risk greatly outweighs the benefit and that the procedure should not be performed.

CRT=cardiac resynchronization therapy; ICD=implantable cardioverter-defibrillator.

Placement of the left ventricular lead is commonly performed by using a transvenous approach via the subclavian vein and superior vena cava, which allows cannulation of the coronary sinus with specially

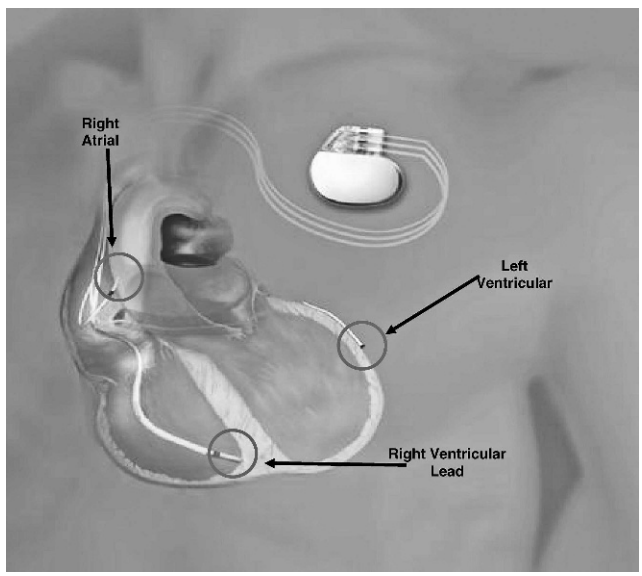

Figure 1. A typical cardiac resynchronization system. Note pacing leads in the right atrium, right ventricle, and left ventricle.

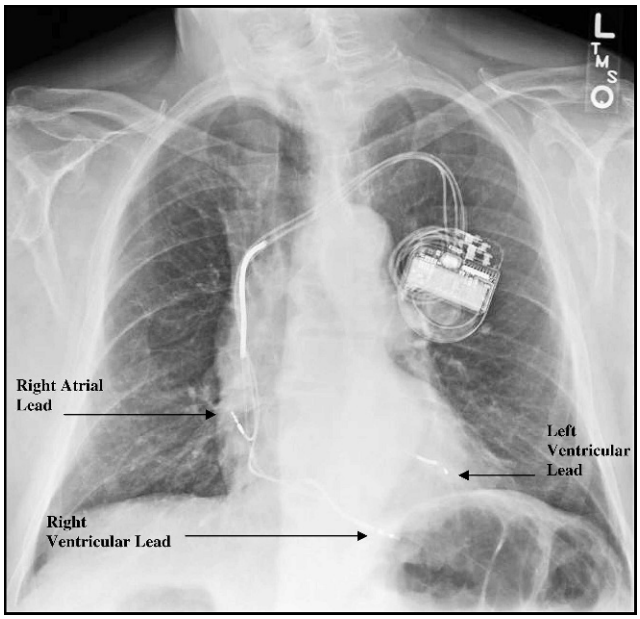

Figure 2. Chest x-ray showing pacing leads in the right atrium, right ventricle, and left ventricle.

designed sheaths.[2] After cannulation of the coronary sinus, retrograde venography is performed to identify coronary sinus anatomy. The pacing lead is then advanced into the target vein, ideally in the area of the left ventricle with the greatest delay in contraction. This additional lead is placed via the right atrium and coronary sinus into the lateral, posterolateral, or anterolateral branches of the coronary venous system. Optimal lead placement is dependent on the presence of an acceptable target vein, adequate pacing capture threshold, lack of stimulation of the phrenic nerve and/or diaphragm, and lead stability.[11]

This approach is successful for most patients. However, right heart remodeling, significant tricuspid regurgitation, and variability in coronary sinus anatomy can make it difficult to access the coronary sinus and venous tributaries, and sometimes prevents lead placement.[8] In these cases, one option is epicardial left ventricular lead placement, which is performed via minithoracotomy.

MECHANICAL BENEFITS OF CRT

Three basic types of mechanical dyssynchrony have been described.[3,12]

1. *Intra*ventricular dyssynchrony within the left ventricle, which is often most prominent between the early-activated interventricular septum and late-activated posterolateral wall.
2. *Inter*ventricular (V-V) dyssynchrony between the left and right ventricles, which is most often the result of delayed activation of the left ventricle due to left bundle branch block.
3. Atrioventricular (A-V) dyssynchrony secondary to prolonged AV nodal conduction coupled with His-Purkinje system dysfunction.

Cardiac resynchronization therapy has been shown to decrease all 3 types of dyssynchrony.[2] Another benefit of pacing from the left ventricular lateral wall is early activation of the anterolateral papillary muscle, which can decrease the severity of mitral regurgitation.[4] Mitral regurgitation also can be reduced over time because of reverse remodeling induced by CRT, which reduces left ventricular cavity size, thus reducing mitral annular diameter and allowing mitral leaflet coaptation.

IMPORTANT CLINICAL STUDIES OF PATIENTS WITH HF AND WIDE QRS COMPLEX

The Multisite Stimulation in Cardiomyopathy (MUSTIC) trial,[12] which was reported in 2001, was a single-blinded crossover study that helped pave the way for future randomized controlled trials. The study enlisted patients with NYHA class III HF with LVEF of 35% or less, left ventricular end-diastolic diameter greater than 60 mm, and QRSd of more than 150 ms. The MUSTIC investigators compared exercise tolerance and QOL during active biventricular pacing for 3 months and during backup right-ventricular-only pacing for another 3 months. The results showed a statistically significant improvement in 6-minute walking distance (the primary end point), as well as improved QOL and peak oxygen consumption. The MUSTIC trial was important because it was one of the first trials demonstrating significant clinical improvement with CRT.

The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial[9] soon followed, in which 453 patients in sinus rhythm with NYHA class III or IV HF, LVEF of 35% or less, and QRSd of more than 130 ms were randomly assigned to CRT versus control. The patients were followed up for 6 months. Hospitalizations secondary to heart failure were reduced, and there were significant improvements in 6-minute walking distance, NYHA functional class, and QOL score. A significant improvement in walking distance was noticed as early as 3 months into the period of CRT (Figure 3). In addition, the MIRACLE trial showed electrical therapy to be an effective adjunct to pharmacologic therapy in affecting major morbidity. There was a statistically significant reduction in the combined end point of heart failure hospitalization or death (Figure 4).

A topic of ongoing debate is whether every implanted device should have defibrillator capabilities. The Multicenter InSync Randomized Clinical Evaluation Implantable Cardiac Defibrillator (MIRA-

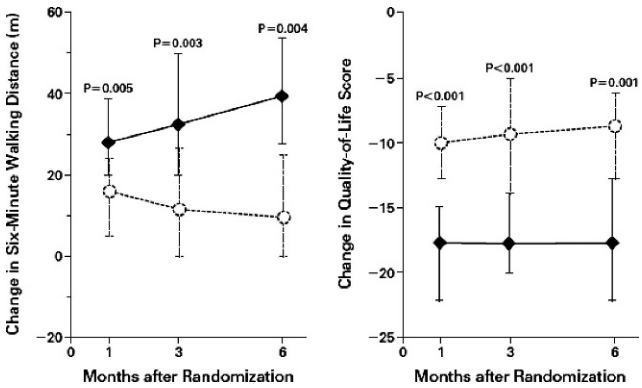

Figure 3. Change in 6-minute walking distance and quality-of-life scores in the MIRACLE trial, demonstrating significant improvements in patients receiving cardiac resynchronization therapy (CRT) (solid diamonds) when compared with those receiving no CRT (circles). Note that a more negative quality-of-life score indicates superior quality of life. (Adapted with permission from Abraham WT, Fisher WG, Smith AL, et al. *N Engl J Med.* 2002;346:1845–1853.[9])

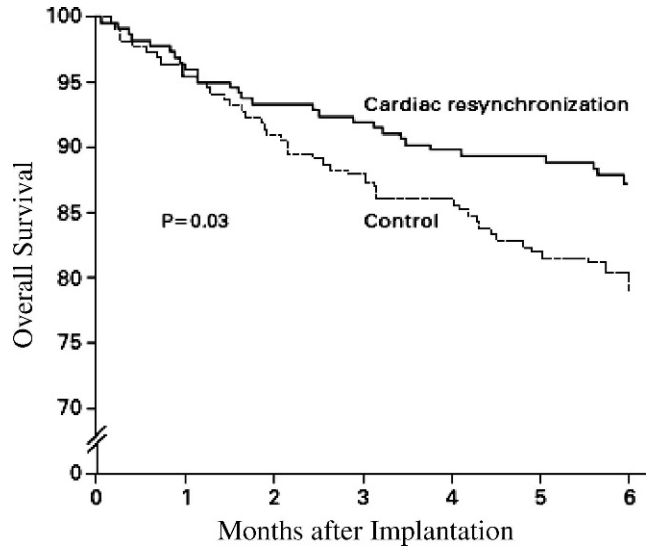

Figure 4. Kaplan-Meier estimates of the overall survival for worsening heart failure in the control and resynchronization groups in the MIRACLE trial, demonstrating a 40% decrease in the combined end point (death or hospitalization for worsening heart failure) during 6 months' follow-up. (Adapted with permission from Abraham WT, Fisher WG, Smith AL, et al. *N Engl J Med.* 2002;346:1845–1853.[9])

CLE ICD)[13] trial was the first randomized trial that evaluated the effectiveness of CRT with an implantable cardioverter-defibrillator (ICD). This study included 369 patients with LVEF of 35% or less, QRSd of more than 130 ms, and NYHA class III or IV HF. All patients received ICDs with CRT capability (CRT-D), and were randomly assigned to CRT-on versus CRT-off. After 6 months, there was statistically significant improvement in the QOL score, peak oxygen consumption, and functional capacity. The MIRACLE ICD trial also demonstrated that CRT does not interfere with cardioverter-defibrillator function: the time required for the device to detect ventricular fibrillation did not differ between the two groups. Also, CRT did not have a significant effect on the percentage of patients who suffered ventricular tachyarrhythmias or inappropriate device shocks. In part because of this trial, most patients undergoing CRT in the United States today receive a device with ventricular defibrillation capability.

The studies discussed above were pivotal in that they helped to set the stage for a randomized controlled trial that would be powered to evaluate the effect of CRT on mortality. The two largest and arguably most important randomized controlled trials examining this question were the COMPANION[7] and CARE-HF[8] trials.

The COMPANION trial[7] included 1520 patients with NYHA class III or IV HF, LVEF of 35% or less, and QRSd of more than120 ms. The trial had 3 treatment arms; patients were randomly assigned in a 1:2:2 fashion to optimal medical therapy alone (OMT), OMT plus CRT with pacing only (CRT-P), or OMT plus CRT with a pacemaker/defibrillator (CRT-D). Unlike prior trials, COMPANION was powered to evaluate a primary composite end point of time to hospitalization or death from any cause. The secondary end point was all-cause mortality. At 1 year, CRT-P showed a relative risk reduction of 19% (HR [hazard ratio], 0.81; $P=0.014$) and CRT-D had a relative risk reduction of 20% (HR, 0.80; $P=0.01$) when compared to OMT alone with regard to the composite end point. The CRT-D group, but not the CRT-P group, had a significant reduction in overall mortality as compared to the group receiving OMT alone (Figure 5). The CRT-P group barely missed statistical significance for overall mortality ($P= 0.059$). The exciting results of the COMPANION study showed that CRT-D had a mortality benefit and suggested that cardiac resynchronization therapy, even in the absence of a defibrillator, may improve mortality as well.

The COMPANION trial[7] was followed in 2005 by the CARE-HF trial,[8] which enrolled 813 patients with NYHA class III or IV HF, QRSd of more than 120 ms, and LVEF of 35% or less. A total of 404 patients were assigned to receive medical therapy alone, while 409 received medical therapy plus CRT-P. Of note, only about 8% of patients in CARE HF had QRSd between 120 and 150 ms, and these patients required echocardiographically determined mechanical dyssynchrony to be enrolled. The remaining study population had QRSd greater than150 ms. The primary end point was a composite of all-cause mortality or hospitalization for a major cardiovascular event; the secondary end point was all-cause mortality. Compared to OMT alone, CRT-P was associated with a significant

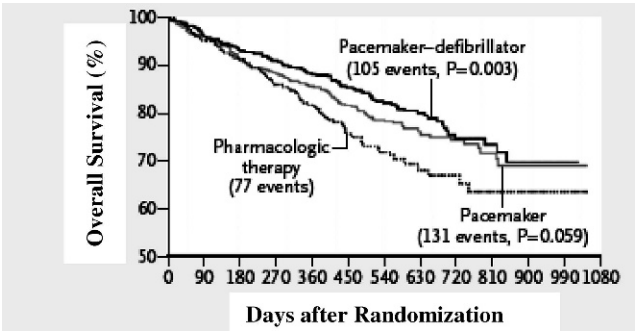

Figure 5. Kaplan-Meier curve showing overall survival in the cardiac resynchronization therapy-pacemaker (CRT-P) group, CRT-defibrillator (CRT-D) group, and control group in the COMPANION trial. The CRT-D cohort showed a significant reduction in all-cause mortality, while the CRT-P cohort barely missed statistical significance for this end point. (Adapted with permission from Bristow MR, Saxon LA, Boehmer J, et al. *N Engl J Med.* 2004;350:2140–2150.[7])

reduction in all-cause mortality and hospitalization for major cardiovascular events at 29 months (Figure 6). Most importantly, CARE-HF was the first trial to show definitively that CRT-P, even in the absence of ICD therapy, had a mortality benefit (See Table 3 for landmark trials evaluating CRT).

CURRENT ACC/AHA/HRS GUIDELINES

The 2008 ACC/AHA/HRS guidelines for cardiac resynchronization therapy are discussed below.[14] Table 2 shows an outline of guideline categories.

Class I (''Indicated'')

Treatment with CRT (with or without an ICD) is indicated for patients with sinus rhythm, LVEF of 35% or less, QRSd of 120 ms or more, and NYHA class III or ambulatory class IV HF symptoms despite optimal medical therapy.

Class IIa (''Reasonable'')

Treatment with CRT (with or without an ICD) is considered reasonable for patients with sinus rhythm, LVEF of 35% or less, and NYHA class III or ambulatory class IV HF symptoms despite optimal medical therapy, who have frequent dependence on ventricular pacing.

Class IIa (''Reasonable'')

Treatment with CRT (with or without an ICD) is considered reasonable for patients in atrial fibrillation (AF), LVEF of 35% or less, QRSd of 120 ms or more, and NYHA class III or ambulatory class IV HF symptoms despite optimal medical therapy.

Class IIb (''May Be Considered'')

Treatment with CRT may be considered for patients with sinus rhythm, LVEF of 35% or less,

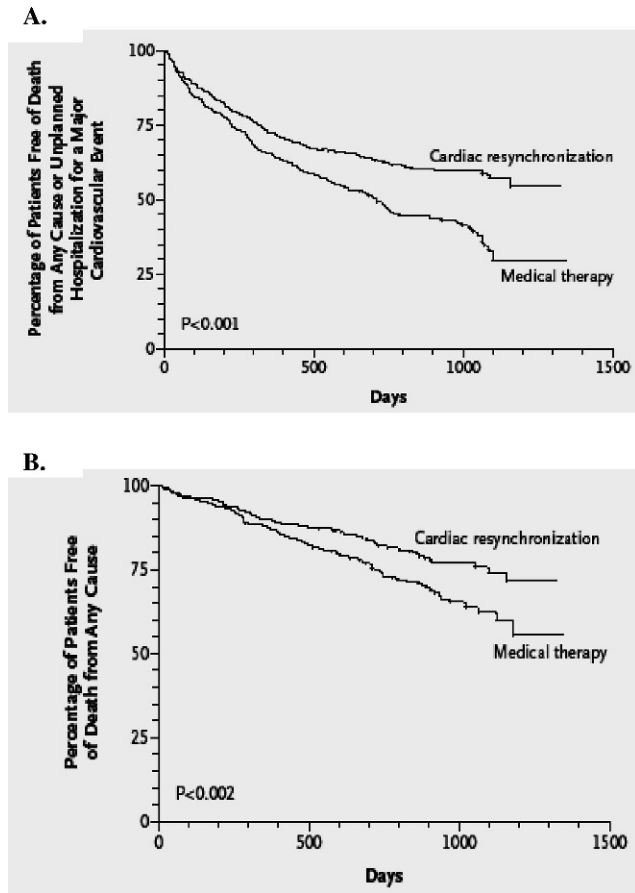

Figure 6. Kaplan-Meier survival curves from the CARE-HF trial, showing CRT's benefit both for (A) the combined end point of mortality and/or heart failure hospitalization and for (B) all-cause mortality. (Adapted with permission from Cleland JGF, Daubert JC, Erdmann E, et al. *N Engl J Med.* 2005;352: 1539–1549.[8])

and NYHA class I or class II HF symptoms, who are undergoing implantation of a permanent pacemaker/ ICD with anticipated frequent ventricular pacing.

Class III (Not Indicated)

Treatment with CRT is not indicated for asymptomatic patients with reduced LVEF in the absence of other indications for pacing, or for those whose functional status and life expectancy are limited predominantly by chronic noncardiac conditions.

REDUCING THE RATE OF CRT NONRESPONSE

Unfortunately, not every patient who undergoes CRT receives benefit. Despite randomized controlled trials showing significant average improvements in morbidity and mortality as a result of CRT, the number of patients who do not improve symptomatically remains high at 30%.[15] This highlights the need for better ways to predict which patients will respond to

Table 3. Landmark Trials Evaluating Cardiac Resynchronization Therapy*†

Study	NYHA Functional Classification	QRSd, ms	Follow-up, mo	End Points
MUSTIC[12]	III, IV	≥130	6	NYHA, QOL, 6MWD
MIRACLE[9]	III, IV	≥130	6	NYHA, QOL, 6MWD, VO_2
MIRACLE ICD[13]	III, IV	≥130	6	NYHA, QOL, 6MWD, VO_2
CARE-HF[8]	III, IV	≥120	29	Morbidity + mortality
COMPANION[7]	III, IV	≥120	12	Morbidity + mortality

* NYHA=New York Heart Association; QOL=quality of life; QRSd=QRS duration; VO_2=peak oxygen consumption; 6MWD=6-minute walking distance.

† Adapted with permission from Abraham T, Kass D, Giovanni T, et al. J Am Coll Cardiol Img 2009; 2: 486–497.[21]

CRT, while avoiding the risks associated with CRT implantation for those who will not respond.

Most importantly, for biventricular pacing to have any effect, pacing must occur. If the patient's own heart rate exceeds the device's programmed lower rate limit, pacing is inhibited and the potential benefits of resynchronization are missed completely. Biventricular pacing appears to be of greatest benefit when the ventricle is paced frequently (as close to 100% as possible).[16]

The benefits of CRT are contingent on numerous factors other than the percentage of paced beats and baseline left ventricular dyssynchrony. These factors include pacing site, ischemia and scar burden, severity of ventricular remodeling, and postimplant device optimization.[17] The presence of ischemic cardiomyopathy (rather than nonischemic cardiomyopathy) has been shown to be an independent predictor for CRT nonresponse.[18] A large scar burden with nonviable myocardium in the area of pacing, especially with a severely enlarged and remodeled ventricle, can cause high capture thresholds and can influence mechanical function.[19]

With several factors potentially responsible for a lack of response to CRT, parameters other than QRSd are being evaluated for use in improving patient selection. The use of echocardiographic measures of dyssynchrony as a superior method of patient selection has been an important area of research. However, recent trials have revealed that measuring dyssynchrony by using echocardiography can be complex, demonstrating unacceptable low reproducibility with low correlation between dyssynchrony and response to CRT. Consequently, at present, the ACC/AHA/HRS guidelines do not require echocardiographic dyssynchrony as part of the inclusion criteria. However, ongoing areas of research into advanced echocardiographic techniques, such as 2-dimensional speckle tracking and strain imaging, show promise with regard to echocardiographic assessment of dyssynchrony[20,21] Other modalities, such as cardiac magnetic resonance imaging, are being investigated as well.[22]

CURRENT CONTROVERSY AND FUTURE DIRECTIONS

In an attempt to better select patients for CRT, recent trials' inclusion criteria have been extended to 4 subgroups who previously have been excluded from many randomized controlled trials. These subgroups are as follows:

1. Patients with AF.
2. Patients with a relatively narrow QRSd (<130 ms).
3. Patients with NYHA class I and II HF (ie, asymptomatic or mildly symptomatic).
4. Patients with right bundle branch block (RBBB).

Atrial Fibrillation

The prevalence of AF increases with the severity of heart failure, affecting as many as 30% of patients with severe heart failure.[23] Despite this high prevalence, most clinical trials examining CRT have included only patients in sinus rhythm.[24–26] Thus, the question is raised: Do patients with heart failure who have AF respond as well to CRT as do patients in sinus rhythm?

A meta-analysis of prospective cohort studies (totaling 1164 patients) comparing the impact of CRT on patients in AF versus those in sinus rhythm showed similar improvement in LVEF between the 2 groups.[27] However, the benefit in functional outcome (measured by NYHA functional class, 6-minute walking distance, and Minnesota Living with Heart Failure Questionnaire score) for patients with AF was less than that for patients in sinus rhythm.

As discussed above, it has been shown that the greatest hemodynamic benefit of biventricular pacing occurs when the ventricles are paced as close to 100% of the time as possible.[17] To achieve a high percentage of biventricularly paced beats in patients with AF, often it is necessary to slow conduction through the AV node. This can be accomplished either medically with beta

blockers, calcium channel blockers, and/or digoxin, or with catheter ablation of the AV node.[26]

Narrow QRS Complex (QRSd of Less Than 120 Milliseconds)

Echocardiographic studies[28] have shown that 20% to 40% of patients with NYHA class III or IV HF and a narrow QRS (QRSd <120 ms) have intraventricular mechanical dyssynchrony and, therefore, theoretically may benefit from CRT. The Resynchronization Therapy in Narrow QRS (RethinQ) trial[29] was the first randomized controlled study to evaluate CRT in patients with a narrow QRS. This study included patients with LVEF of less than 35%, NYHA class III HF, QRSd of less than130 ms, and evidence of mechanical dyssynchrony on echocardiography. The primary end point was an increase in peak oxygen consumption at 6 months. The study failed to demonstrate an improvement in this primary end point. The RethinQ trial showed that CRT is not beneficial in patients with systolic heart failure and QRSd of less than 120 ms.

The ongoing Echocardiographic Guided Cardiac Resynchronization Therapy (EchoCRT) trial[30] is a large multicenter randomized trial that will enroll more than 1000 patients with a narrow QRS and evidence of dyssynchrony on echocardiography. In contrast to RethinQ, the primary end point is reduction of all-cause mortality or hospitalization for cardiovascular events. This trial is expected to be completed in 2012.

NYHA Functional Class I and II

As systolic heart failure progresses, a pathologic process known as ''remodeling''occurs that manifests clinically as a change in the size, shape, and function of the heart, and leads to progression of heart failure. Slowing or reversing remodeling has recently been a goal of medical therapy.[31] It has been shown that angiotensin-converting enzyme inhibitors and beta blockers reduce morbidity and mortality in systolic heart failure, partly as a result of their ability to induce reverse remodeling.[1] Interestingly, for patients with NYHA class III or IV HF and a wide QRS, CRT also has been shown to cause reverse remodeling, and this is thought to be one reason for the observed decrease in mortality seen in CRT trials.[2] An interesting question has arisen: Does CRT cause reverse remodeling in asymptomatic or mildly symptomatic left ventricular dysfunction, and thereby slow progression of disease? This was addressed in the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial.[32]

The recently published REVERSE trial[32] investigated whether CRT (with or without an ICD), combined with optimal medical therapy, can attenuate heart failure disease progression in patients with NYHA class I or II HF, LVEF of 40% or less, and a wide QRS. The primary end point was a composite of all-cause mortality, heart failure hospitalization, progression to a higher HF class, and worsening global assessment score. After 12 months, the study's North American cohort did not quite meet this end point: worsening was observed in 21% of patients in the CRT-off group versus 16% in the CRT-on group ($P=0.10$). However, follow-up of the study's European cohort was extended to 24 months, and with this extended follow-up, the study did show a statistically significant reduction in the composite end point (34% worsening in CRT-off versus 19% in CRT-on, $P=0.01$).

The recently completed Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy (MADIT-CRT) trial[33] enrolled more than 1800 patients with NYHA class I and II HF and compared CRT-D with ICD alone. The primary end point was heart failure events and mortality. In June 2009, it was reported that there was a 29% reduction in this combined end point in the CRT-D group compared to the group with ICD alone ($P= 0.003$). It is important to note that this reduction in the primary end point was driven primarily by a 41% reduction in heart failure events alone, and that there was no difference in mortality.

Thus, both the REVERSE and MADIT-CRT trials concluded that CRT may indeed be useful in slowing the progression of mildly symptomatic systolic HF.

Right Bundle Branch Block

The preponderance of data in randomized controlled clinical trials evaluating the utility of CRT in heart failure was obtained from patients with left bundle branch block. Patients with RBBB have been underrepresented.

Pure proximal RBBB, the most common type of RBBB, does not disrupt normal left ventricular activation.[34] Thus, it is intuitively unclear how the addition of a left ventricular lead could improve synchrony in patients whose *right* ventricular activation is delayed. A possible answer to the question of how CRT may be of use in RBBB may lie in the fact that RBBB can mask underlying concomitant delay in the left bundle branch.[35]

The benefit of CRT for patients with RBBB is an area of active investigation, and further analysis of a larger cohort of patients is needed. Currently, the ACC/AHA/HRS guidelines do not discriminate with regard to specific QRS morphology in their CRT recommendations.

CONCLUSIONS

Based on the results of randomized controlled trials evaluating more than 4000 patients, it has been

shown that cardiac resynchronization therapy combined with optimal medical therapy improves morbidity and mortality for patients with NYHA class III and IV HF with LVEF of 35% or less and QRSd of 120 ms or more. Furthermore, over time, CRT results in significant benefits in myocardial structure and function via improvement in left ventricular remodeling and lessening of mitral regurgitation. Ongoing and future trials will continue to investigate ways to improve the nonresponse rate of approximately 30% through improved patient selection. Unsettled issues lie mostly for patients in atrial fibrillation, narrow QRSd (<120 ms), mildly symptomatic heart failure, and right bundle branch block.

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