Cardiac Resynchronization Therapy: Past, Present, and Future

Rahul N. Doshi, MD, Nikhil Gupta

Department of Cardiovascular Research, Anaheim Memorial Medical Center, Anaheim, CA, and Fullerton Cardiovascular Medical Group, Fullerton, CA

Cardiac resynchronization therapy (CRT) is an established treatment for patients with advanced heart failure, cardiomyopathy, and interventricular conduction delay or wide QRS complex. Use of this treatment is supported by a multitude of clinical trials that have demonstrated its benefits on clinical parameters such as exercise capacity, heart failure functional class, and quality of life. More recently, CRT has been shown to reduce total mortality rates in patients with heart failure. Many questions have yet to be answered, however, including how to better identify patients for this therapy and how to potentially expand its clinical indications to other groups of patients. This article reviews the published literature supporting the current indications and addresses some of the issues that may change how this therapy is utilized in the future.
[Rev Cardiovasc Med. *2007;8(2):69-77*]

Key words: Cardiac resynchronization therapy • Left ventricular ejection fraction • Biventricular pacing • Congestive heart failure

Cardiac resynchronization therapy (CRT) is now considered the standard of care for patients with chronic cardiomyopathy, congestive heart failure, and aberrant conduction or ventricular dyssynchrony. The deleterious effects of ventricular dyssynchrony are substantial and include abnormal filling of the left ventricle, abnormal sequence of contraction, reduced contractility, and increased mitral regurgitation. These effects are manifested by poor clinical outcomes, such as increased hospitalizations for heart failure and overall mortality. Many clinical trials have demonstrated the benefits of CRT in patient hemodynamics, patient well-being, heart failure functional classification, and exercise tolerance.[1-6] Several studies have shown benefits in "reverse remodeling," with

improvements in left ventricular ejection fraction (LVEF) and reduction in left ventricular (LV) volumes.[1,7-10] These early studies have been followed by larger, prospective studies that have demonstrated benefits in total mortality.[11-13] However, as many as one third of patients are considered "nonresponders."[1] There is also increasing evidence that QRS duration is not the ideal method for identifying candidates for biventricular pacing.[14] This article will highlight some of the published data supporting current indications for CRT. In addition, it will aim to provide a framework supporting some of the future direction for this life-saving therapy.

Studies Supporting Current Indications

The standard criteria for CRT are shown in Table 1. The following trials included patients with an LVEF at or less than 35%, LV dilation, severe symptomatic heart failure, and QRS duration of 120 ms or longer. These trials are summarized in Table 2.

PATH-CHF

The Pacing Therapies for Congestive Heart Failure (PATH-CHF) trial was a longitudinal, crossover study of 42 patients comparing biventricular (BV) pacing with right ventricular (RV) and LV pacing.[2,3] Subjects were implanted with 2 dual-chamber pacemakers. The first pacemaker utilized a traditional endocardial right atrial and RV pacing electrode. The second used an endocardial right atrial electrode and an epicardial LV lead. Of note is that in only two thirds of patients the LV lead was placed on the lateral wall; in the remainder the lead was placed on the anterior wall. The devices were programmed to an atrial synchronous tracking mode without atrial pacing (VDD). The first and third 4-week periods compared BV pacing versus the best univentricular mode, while the second 4-week period served as the control. The primary endpoints were distance on the 6-minute hall walk (6MW) and peak oxygen consumption (VO_2max) during cardiopulmonary exercise testing.

BV- and LV-based pacing showed acute improvements in contractility. There was a trend towards a benefit in the primary endpoints, and significant improvements in LVEF and LV volumes were seen. Functional class improved significantly during the second treatment period, with 63% of patients improving to New York Heart Association (NYHA) class I or II heart failure.

MUSTIC

The Multisite Stimulation in Cardiomyopathies Trial (MUSTIC) was a single-blind crossover study with a more rigorous enrollment criterion.[4] The 67 subjects had an LVEF of at least 35%, an LV end-diastolic dimension greater than 60 mm, a QRS duration of greater than 150 ms, and NYHA class III heart failure. Each phase was for 3 months, with each patient serving as his or her own control. The primary endpoint was distance on the 6MW test.

The study demonstrated a significant 23% greater distance on the 6MW test, as well as significant improvements in VO_2max, hospital admissions, and functional class. BV pacing was preferred by 85% of patients over no pacing.

MIRACLE

The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study was a large, prospective, randomized, double-blind controlled study that evaluated primary endpoints of NYHA functional class, quality of life (QoL) scores, and the 6MW test.[1] The 453 subjects experienced significant improvements in 6MW (29 meters), QoL scores, and functional class. There were also significant benefits seen on peak VO_2max, increased LVEF (4.6%), decreased mitral regurgitation, and decreased heart failure hospitalizations (77% decrease in total hospital days). The effect was not altered by cause of heart failure (ischemic vs nonischemic), type of aberrancy (right or left bundle branch block), or baseline QRS duration.

CONTAK-CD

The CONTAK-CD trial was a prospective, randomized, double-blind, controlled study that evaluated the effectiveness of CRT in combination with an implantable defibrillator.[5] It was the first study to include NYHA class II patients, who represented one third of the total patient group. The study enrolled 581 patients who were evaluated for a composite endpoint of mortality, heart failure hospitalizations, and ventricular tachycardia or fibrillation at 6-month follow-up.

The study failed to reach statistical significance for the primary endpoint, although positive trends were seen in total mortality and mortality plus heart failure hospitalizations.

Table 1
Current Indications for Biventricular Pacing

Ischemic or idiopathic cardiomyopathy, LVEF ≤ 35%
Symptomatic heart failure NYHA class III-IV
QRS duration ≥ 130 ms
LVEDD ≥ 55 mm
Optimal pharmacologic therapy

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; LVEDD, left ventricular end-diastolic dimension.

Table 2
Early Clinical Trials for Cardiac Resynchronization Therapy

Trial	Completion Date	Number of Patients	Study Type	Follow-Up Period	NYHA Class	LVEF	QRS Width	Endpoints	Results
Path-CHF[2,3]	1998	42	Longitudinal crossover design first 3 months, followed by chronic pacing phase	12 months	III-IV	≤ 35%	120 ms	Peak VO_2, 6MW	Improved exercise capacity, functional class and QoL
MUSTIC[4]	2000	67	Prospective, randomized, single-blind crossover design	3 months each arm	III	≤ 35%	> 150 ms	6MW, peak VO_2, NYHA class	Improved exercise capacity, functional class and QoL, decreased hosp, patients preferred CRT
MIRACLE[1]	2001	453	Prospective, randomized, double-blind, placebo-controlled	6 months	III-IV	≤ 35%	≥ 130 ms	NYHA class, 6MW, QoL	Improved functional class, 6MW, QoL; improvements in echo parameters (LVEF and LV volumes), reduced hosp
CONTAK-CD[5]	2001	581	Prospective, randomized, double-blind, placebo-controlled	6 months	II-IV	≤ 35%	120 ms	Composite endpoint all-cause mortality/ CHF hosp/ICD therapy	Primary endpoint not met; improved VO_2, 6MW, QoL, functional class
Path-CHF II[16]	2001	89	Crossover, randomized CRT with LV only	3 months each arm	III-IV	≤ 35%	120 ms	6MW, QoL, VO_2	Improved exercise capacity, decreased CHF hosp
MIRACLE ICD[15]	2002	364	Prospective, randomized, double-blind, placebo-controlled	6 months	III-IV	≤ 35%	130 ms	QoL, NYHA class, 6MW	Improved functional class, QoL, 6MW; improved composite endpoint (death, CHF hosp, NYHA, patient assessment)
MIRACLE ICD II[24]	2002	186	Prospective, randomized, double-blind, placebo-controlled	6 months	II	≤ 35%	≥ 130 ms	Peak VO_2, 6MW, QoL	No difference in peak VO_2, exercise capacity or QoL; improvements in LVEF and LV volumes
COMPANION[12]	2002	1520	Prospective, randomized, open-label, 3-arm study (placebo, CRT-P, CRT-D)	Stopped prematurely secondary to reaching endpoint, mean f/u 11.9-16.2 months	III-IV	≤ 35%	120 ms	Composite endpoint all-cause mortality or any-cause hosp	CRT-P and CRT-D similar benefits with composite endpoint, significant mortality reduction with CRT-D
CARE-HF[13]	2004	813	Prospective, randomized, placebo-controlled	Minimum 18 months, mean f/u 29.4 months	III-IV	≤ 35%	120 ms with interventricular delay, 150 ms otherwise	Composite endpoint all cause mortality or CV hosp	Reduction in composite endpoint, reduction in total mortality (CRT-P only)

NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; PATH-CHF, Pacing Therapies for Congestive Heart Failure; VO_2, oxygen consumption; 6MW, 6-minute hall walk; QoL, quality of life; MUSTIC, Multi-site Stimulation in Cardiomyopathies Trial; hosp, hospitalization; CRT, cardiac resynchronization therapy; MIRACLE, Multicenter InSync Randomized Clinical Evaluation; LV, left ventricular; CHF, congestive heart failure; ICD, implantable cardioverter defibrillator; MIRACLE ICD, Multisite Stimulation in Cardiomyopathies Trial of an Implantable Cardioverter Defibrillator; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; f/u, follow-up; CRT-P, drug therapy plus a biventricular pacemaker; CRT-D, drug therapy plus a biventricular defibrillator; CARE-HF, Cardiac Resynchronization Heart Failure; CV, cardiovascular.

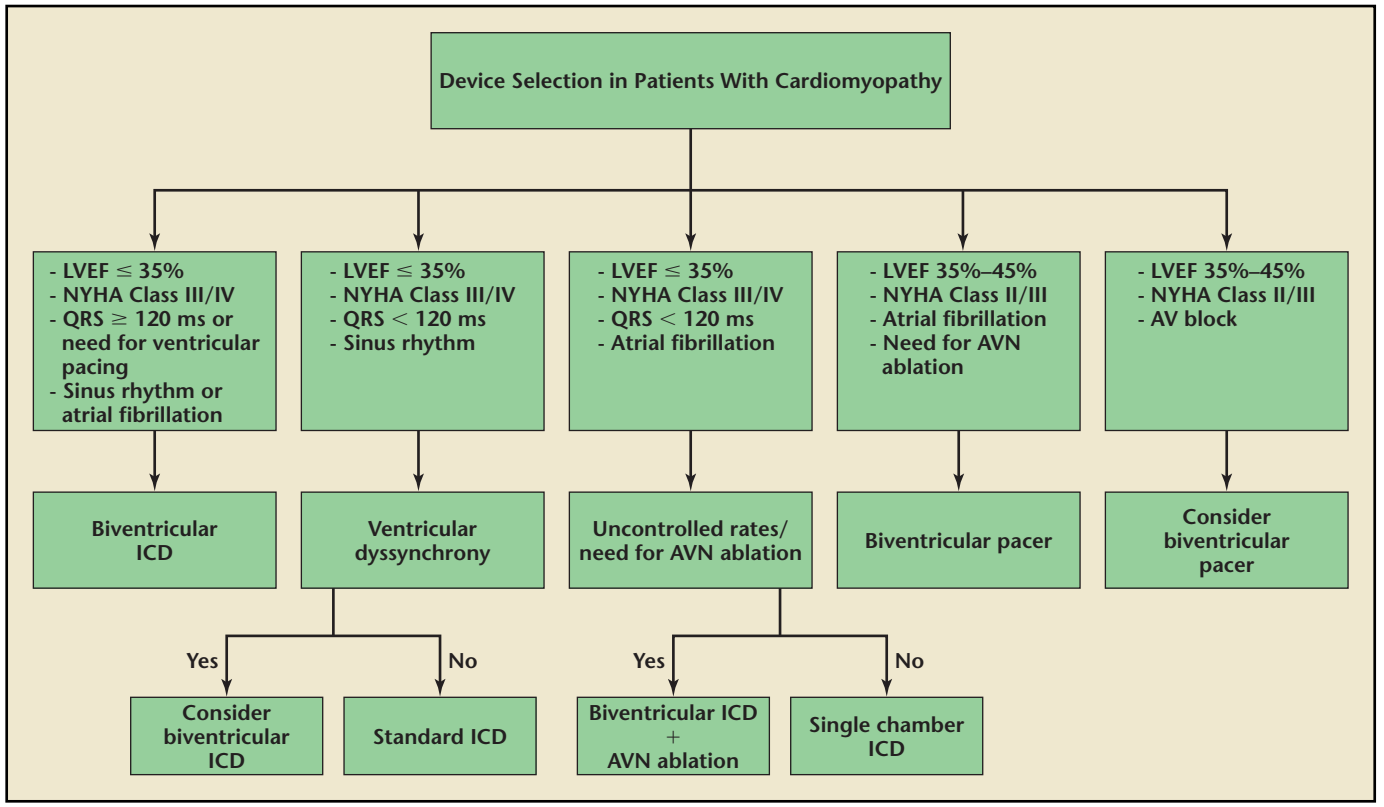

Figure 1. *Recommendations for device implantation in patients with cardiomyopathy and heart failure. LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; AVN, atrioventricular nodal; AV, atrioventricular; ICD, implantable cardioverter defibrillator.* www.medreviews.com

There were statistically significant improvements in NYHA functional class, VO_2max, 6MW distance, and QoL. LVEF and LV volumes also improved. Of interest is that within the group receiving a transvenous LV lead (89% of the total group implanted), only 54% had the lead placed on the lateral wall. Of the remaining subjects who received a transthoracic lead, only 26% had the lead placed laterally.

MIRACLE-ICD

The Multicenter InSync Randomized Clinical Evaluation of an Implantable Cardioverter Defibrillator (MIRACLE-ICD) trial was a prospective, randomized, double-blind trial examining the effects of implanting a device capable of delivering both CRT and defibrillator therapy.[15] A total of 364 patients were randomized with similar entry criteria as the CONTAK-CD trial, but only severe heart failure patients were included (NYHA class III and IV). Once again, patients at 6 months had improvements in QoL score, peak VO_2max, and exercise duration.

Trials Demonstrating Mortality Benefits

The above-mentioned trials paved the way for the larger, randomized clinical trials that have now demonstrated that CRT does result in improved total mortality in the patient population with cardiomyopathy, heart failure, and interventricular conduction delay. Bradley and colleagues[11] performed a meta-analysis examining the patient populations from the CONTAK-CD, MIRACLE, MIRACLE ICD, and MUSTIC trials. Pooled data from the patients in these trials revealed a 51% relative risk reduction in heart failure mortality. Heart failure hospitalizations were reduced by 29%. These findings set the stage for the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) and Cardiac Resynchronization Heart Failure (CARE-HF) trials.

COMPANION

The COMPANION trial began in 2000 and was completed in 2002. It was the first published trial that demonstrated a mortality benefit for CRT combined with an implantable defibrillator.[12] The trial was a prospective, randomized, controlled trial in which 1520 patients were divided into 3 groups: optimal pharmacologic

therapy alone, drug therapy plus a BV pacemaker (CRT-P), or drug therapy combined with a BV defibrillator (CRT-D). The primary endpoint was a combined endpoint of all-cause mortality or hospitalization for any reason. The trial was stopped when the predefined boundaries for efficacy were crossed by the CRT-D group. The mean duration of follow-up was 11.9 months for the drug therapy group, 16.2 months for the CRT-P group, and 15.7 months for the CRT-D group.

The risk of reaching the combined endpoint was reduced by 34% in subjects treated with a CRT-P, and reduced by 40% in subjects treated with a CRT-D. There was a 36% reduction in all-cause mortality in the CRT-D group, which was highly statistically significant ($P = .003$). However, in the CRT-P group, there was also a 24% reduction in mortality, which almost reached statistical significance ($P = .059$).

CARE-HF

The CARE-HF trial of 813 patients began in 2001 and was completed in 2004. This prospective, randomized, controlled trial compared optimal pharmacologic therapy alone versus drug therapy combined with a BV pacemaker.[13] Enrollment criteria included an LVEF at or less than 35%, NYHA class III or IV, and either a QRS that was at least 150 ms or a QRS that was at least 120 ms with evidence of ventricular dyssynchrony on echocardiography. The primary combined endpoint was all-cause mortality or cardiovascular hospitalization. The mean follow-up duration was 29.4 months. This trial was the first to allow for atrial pacing, with a minimum rate set at 60 beat/min. Previous trials had the devices programmed to track the atrium only (VDD mode).

At the end of the study, 55% of patients in the pharmacologic therapy arm reached the primary endpoint versus 39% in the group treated with CRT ($P < .001$). Mortality rates were 30% for the control group versus 20% in the group treated with CRT ($P < .01$). This study was the first to demonstrate the mortality benefit of BV pacing without a defibrillator in this patient population.

In summary, a large number of trials have been published that show clear benefits of CRT in functional classification, exercise duration, QoL, and, more recently, mortality. Despite these clear benefits, however, significant questions remain unanswered regarding this therapy.

Therapeutic Considerations

Several important aspects highlighted by the trials mentioned above include the anatomical placement of coronary leads, the effects of BV pacing in patients with AF, the effects of implementing BV pacing earlier in the treatment of patients with heart failure, and how to determine the appropriate cardiac device for therapy.

Coronary Sinus Lead Position

Most experts would agree that one must achieve lateral wall placement, and this approach is not without foundation. The PATH-CHF study, which evaluated contractility improvements acutely in patients undergoing LV lead placement, found the greatest degree of improvement on the mid-lateral wall.[2] When researchers compared anterior versus LV free-wall sites, they found that improvements in contractility and aortic pulse pressure with free-wall pacing were twice those of anterior wall pacing.[16] This finding has significant implications on the large trials already mentioned, where up to one third of patients had lead placement on the anterior wall.[1,5]

Rosillo and colleagues[17] retrospectively evaluated 233 consecutive patients undergoing transvenous LV lead placement, and divided them into an anterior/anterolateral placement (n = 66) group or a lateral/posterolateral placement (n = 167) group. The latter group showed greater improvements in NYHA functional class and LVEF, emphasizing the importance of placement. Although there may be individual differences in patients,[18] it is our recommendation that only the lateral/posterolateral position be used. If this approach is not possible, the patient should undergo surgical epicardial lead placement. Alternative approaches, such as prospectively evaluating the latest contracting segment by tissue Doppler techniques, are being evaluated.

CRT and AF

In most of the major trials that established the benefits of CRT, there was a requirement for patients to be in normal sinus rhythm. The data supporting the use of CRT in atrial fibrillation (AF) are not as extensive. One arm of the MUSTIC study did enroll patients with atrial fibrillation (MUSTIC-AF).[19] Fifty-nine patients with chronic AF, NYHA class III heart failure, and a need for pacing with a wide-paced QRS complex exceeding 200 ms were implanted with a BV pacemaker. Like the MUSTIC study, this study was a longitudinal crossover design, with each patient thus serving as his or her own control. The patients who completed the study had improved exercise tolerance and peak VO_2max. Again, patients preferred BV pacing to conventional pacing. Leon and colleagues[20] evaluated the effects of upgrading patients with cardiomyopathy who had received prior AV junctional ablation and a pacing device to a CRT system. Patients had marked improvements in NYHA functional class, LVEF, and ventricular

dimensions. Molhoek and associates[21] compared the clinical response and survival rate between patients with SR versus chronic AF in the setting of cardiomyopathy and ventricular conduction delay. They found no significant difference between the 2 groups.

Several prospective, randomized trials have now been completed that evaluated CRT in patients with AF without cardiomyopathy. It is becoming increasingly recognized that RV pacing alone can lead to detrimental long-term effects on hemodynamics and to heart failure. The Optimal Pacing Site (OPSITE) study compared 56 patients with chronic AF and rapid ventricular rates undergoing AV junctional ablation.[22] An initial 3-month phase comparing RV and LV pacing was followed by a second phase comparing RV and BV pacing. Researchers found that BV pacing was associated with modest improvements in QoL, NYHA functional class, and exercise tolerance compared to RV pacing. The Post AV Node Ablation Evaluation (PAVE) study was a randomized, controlled study comparing RV and BV pacing in 184 patients undergoing AV junctional ablation.[23] The endpoints were 6MW distance, QoL, and LVEF. At 6 months, there were significant improvements in 6MW distance and LVEF. However, when patients were stratified by LVEF, the benefit was seen in the low LVEF group (≤ 45%). Regardless, it is clear that CRT does provide a similar benefit for patients with atrial fibrillation and cardiomyopathy, with either conduction system disease or a need for permanent ventricular pacing, such as after His bundle ablation.

It is becoming increasingly recognized that right ventricular pacing alone can lead to detrimental long-term effects on hemodynamics and to heart failure.

CRT in Less Symptomatic Heart Failure

CRT has clearly been shown to provide meaningful clinical benefits in patients with advanced heart failure and ventricular conduction delay. Given these benefits, it stands to reason that CRT, if begun early in a patient's history, could halt the progression of heart failure and perhaps also result in more sustainable benefits. The MIRACLE ICD II study was the first prospective, randomized study that enrolled patients with cardiomyopathy, QRS of 130 ms or more, and NYHA class II only.[24] The 186 patients were randomized and evaluated at 6 months for peak VO_2max, 6MW distance, and QoL. There were no differences in exercise capacity at the end of the study. There were, however, improvements in LVEF and ventricular dimensions, supporting the favorable remodeling effects of CRT in this less symptomatic population. The Multicenter Automatic Defibrillator Implantation Trial with CRT (MADIT-CRT), which started enrolling patients in 2005, will address whether patients with CRT and relatively asymptomatic heart failure (NYHA class I/II) experience a benefit in long-term mortality.

Traditional RV-only pacing has been demonstrated to cause acute hemodynamic alterations and decreases in LVEF, and to precipitate heart failure. These associations are presumably because of an iatrogenic left bundle branch block that causes subsequent ventricular dyssynchrony. The recently published Homburg Biventricular Pacing Evaluation (HOBIPACE) study demonstrated that in patients with atrioventricular (AV) block and LV dysfunction with an LVEF at or less than 40%, those receiving a BV pacemaker experienced significant benefits in symptoms, LVEF, and exercise capacity compared with subjects who received traditional RV-only pacing.[25] Future investigations, such as the Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization (BIOPACE) study, will address the question of whether the prevention of desynchronization with a CRT device will translate to improved clinical status in patients with a standard pacing indication.[26] At this time, the published data would support the use of BV pacing in any patient with cardiomyopathy and a need for ventricular-based pacing, although the current treatment guidelines do not support this approach.

CRT With or Without the ICD

Most of the recently published large trials evaluating the benefits of CRT included devices that were also capable of defibrillation of ventricular arrhythmias. The CARE-HF study, however, clearly demonstrated a sustainable mortality benefit from CRT pacing alone.[13] The study results showed a decrease in the amount of sudden death in the study group treated with CRT, suggesting that the favorable remodeling effects of this therapy reduce the risk of sudden cardiac death. Although there are reports of CRT being proarrhythmic

. . .cardiac resynchronization therapy, if begun early in a patient's history, could halt the progression of heart failure and perhaps also result in more sustainable benefits.

in certain patients, the data from CARE-HF is supported by data from the CONTAK-CD trial, in which patients were also found to have less chance of ICD shock for ventricular arrhythmia.[5]

Recently, the mode of death in the COMPANION trial was evaluated.[27] Of the 313 deaths that occurred in the study, 78% were deemed cardiac. Pump failure was the most common cause (44.4%), followed by sudden cardiac death (26.5%). In the COMPANION trial, CRT combined with defibrillator therapy reduced the risk of sudden cardiac death by 56%, but CRT alone did not. Given these findings, as well as the data from primary prevention trials, most practitioners choose to implant a CRT-defibrillator device. In our opinion, the CRT-pacing device should be utilized in patients with heart failure who either have ventricular dyssynchrony or require ventricular-based pacing, and are either less symptomatic or have more preserved LVEF. This practice needs to be evaluated prospectively.

Nonresponders

Despite appropriate patient selection, there remains a sizeable percentage of patients who do not benefit from this therapy. The larger trials for CRT have demonstrated a nonresponder rate of approximately one third.[1] This number may be even larger because it had been suggested that the placebo effect of these trials is substantial.[28]

Unfortunately, post-implantation programming probably has little influence on increasing the responder rate. At many centers, an optimal AV delay is programmed in all patients or in patients who do not have an ideal clinical response. The ideal AV delay can be determined by straightforward echocardiographic techniques, such as maximizing the volume on mitral valve inflow or aortic velocity-time integral (VTI).[29] Some methods are extremely time-consuming and thus are rarely used clinically.[30] Sawhney and colleagues[31] prospectively compared AV optimization and an empiric AV delay of 120 ms in 40 patients. Although differences were seen acutely with both aortic VTI and LVEF, QoL scores were not different at 3 months. There are some significant limitations to utilizing AV delay optimization. Currently, there are no accepted criteria for AV dyssynchrony. In some patients, the ideal delay may be quite long, thus promoting intrinsic conduction and negating the benefits of BV pacing. The optimal AV delay varies tremendously among patients and is dependent on factors such as heart rate, body position, activity level, and volume status. For this reason, we choose to program a shorter AV delay to ensure BV pacing.

Many devices currently have the capability to adjust the relative timing between the right and left ventricle (VV interval). The ideal VV interval could further reduce both interventricular and intraventricular dyssynchrony. Although this feature is readily available, data are still limited regarding its clinical utility. Several authors have demonstrated benefits in measurements of dyssynchrony and mitral regurgitation[9,32] as well as in contractility.[33] However, a significant limitation of these studies is that the benefits are within the error range for making these measurements. This notion is supported by subsequent prospective evaluations that have failed to show any benefit in clinical outcomes.[34,35] Varying VV timing may provide a small incremental benefit, but has not demonstrated objective clinical benefit. It is our practice to simultaneously pace the RV and LV, with consideration for VV optimization in the nonresponders, although we have not seen meaningful improvement.

Prospective Determination of Ventricular Dyssynchrony

The high nonresponder rate and the inability to help more patients after device implantation suggest that the future of CRT may be determined by advances in determining the ideal candidates. QRS duration is not a good predictor of clinical response.[1,4,36] There is also accumulating evidence that patients with a narrow QRS and ventricular dyssynchrony benefit from CRT.[37-39]

Although there are relatively straightforward measurements of dyssynchrony on standard 2D-echocardiography,[29] tissue Doppler imaging (TDI) is the most widely used method for determining mechanical dyssynchrony. Yu and colleagues[39] have demonstrated with the use of TDI that ventricular dyssynchrony is present in 64% of patients with a wide QRS complex and 43% of patients with a narrow QRS. Thus, an alternative strategy in selecting patients for CRT would utilize methods such as TDI to prospectively identify which patients will respond. Bax and associates[40] have demonstrated that the use of TDI can accurately determine which patients will respond to CRT. Although this technology does have limitations, it is being increasingly used in clinical practice. Trials are currently evaluating the clinical use of TDI in selecting patients with a narrow QRS complex.

Conclusions

CRT provides meaningful clinical improvements in the patient population with advanced heart failure, cardiomyopathy, and interventricular conduction delay. These improvements in ventricular modeling, exercise tolerance, NYHA functional class, hospitalizations, and QoL are

extremely relevant in the treatment of these patients. In addition, we now have conclusive evidence that this therapy is life-saving. In the near future, candidates for this procedure may be identified by direct determination of ventricular dyssynchrony, such as with tissue Doppler imaging, instead of a wide QRS complex. It is hoped that this approach will decrease the number of patients who are deemed nonresponders, as well as identify a patient population that is not currently being treated. CRT with an implantable defibrillator will likely remain the mainstay of treatment for this patient population. However, in the near future, the use of CRT alone may be utilized in the less advanced patient, or potentially in any patient who requires ventricular-based pacing. ■

References

1. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002;346:1845-1853.
2. Auricchio A, Ding J, Spinelli JC, et al. Cardiac resynchronization therapy restores optimal atrioventricular mechanical timing in heart failure patients with ventricular conduction delay. *J Am Coll Cardiol*. 2002;39:1163-1169.
3. Auricchio A, Stellbrink C, Sack S, et al. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol*. 2002;39:2026-2033.
4. Cazeau S, Leclercq C, Larvergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med*. 2001;344:873-880.
5. Higgins SL, Hummel JD, Niazi IK, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J Am Coll Cardiol*. 2003;42:1454-1459.
6. Linde C, Braunschweig F, Gadler F, et al. Long-term improvements in quality of life by biventricular pacing in patients with chronic heart failure: results from the MUltisite STimulation In Cardiomyopathy Study (MUSTIC). *Am J Cardiol*. 2003;91:1090-1095.
7. Duncan A, Wait D, Gibson D, et al. Left ventricular remodeling and hemodynamic effects of multisite biventricular pacing in patients with left ventricular systolic dysfunction and activation disturbances in sinus rhythm: substudy of the MUSTIC (Multisite Stimulation in Cardiomyopathies) trial. *Eur Heart J*. 2003;24:430-441.
8. Kerwin WF, Botvinick EH, O'Connell JW, et al. Ventricular contraction abnormalities in dilated cardiomyopathy: effect of biventricular pacing to correct interventricular dyssynchrony. *J Am Coll Cardiol*. 2000;35:1221-1227.
9. Bordachar P, Garrigue S, Reuter S, et al. Hemodynamic assessment of right, left, and biventricular pacing by peak endocardial acceleration and echocardiography in patients with end-stage heart failure. *Pacing Clin Electrophysiol*. 2000;23(11 Pt 2):1726-1730.
10. St John Sutton MG, Plappert T, Abraham WT, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation*. 2003;107:1985-1990.
11. Bradley DJ, Bradley EA, Baughman KL, et al. Cardiac resynchronization and death from progressive heart failure. *JAMA*. 2003;289:730-740.
12. Bristow MR, Saxon LA, Boehmer JP, et al. Cardiac resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004;350:2140-2150.
13. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352:1539-1549.
14. Auricchio A, Yu CM. Beyond the measurement of QRS complex toward mechanical dyssynchrony: cardiac resynchronization therapy in heart failure patients with a normal QRS duration. *Heart J*. 2004;90:479-481.
15. Young JB, Abraham WT, Liem L, for the In Sync ICD Clinical Investigators. Cardiac resynchronization therapy (CRT) benefits patients with ICD indications—results of the InSync ICD trial. *Pacing Clin Electrophysiol*. 2002;26(Pt 2):694.
16. Butter C, Auricchio A, Stellbrink C, et al. Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. *Circulation*. 2001;104:3026-3029.
17. Rosillo A, Verma A, Saad EB, et al. Impact of coronary sinus lead position on biventricular pacing: mortality and echocardiographic evaluation during long-term follow-up. *J Cardiovasc Electrophysiol*. 2004:15:1120-1125.
18. Dekker AL, Phelps B, Dijkman B, et al. Epicardial left ventricular lead placement for cardiac resynchronization therapy: optimal pace site selection with pressure-volume loops. *J Thorac Cardiovasc Surg*. 2004;127:1641-1647.
19. Leclercq C, Walker S, Linde C, et al. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. *Eur Heart J*. 2002;23:1780-1787.
20. Leon AR, Greenberg JM, Kanuru N, et al. Cardiac resynchronization in patients with congestive heart failure and chronic atrial fibrillation: effect of upgrading to biventricular pacing after chronic right ventricular pacing. *J Am Coll Cardiol*. 2002;39:1258-1263.
21. Molhoek SG, Bax JJ, Bleeker GB, et al. Comparison of cardiac resynchronization therapy in patients with sinus rhythm versus chronic atrial fibrillation. *Am J Cardiol*. 2004;94:1506-1509.
22. Brignole M, Gammage M, Puggioni E, et al. Comparative assessment of right, left, and biventricular pacing in patients with permanent atrial fibrillation. *Eur Heart J*. 2005;2:712-722.
23. Doshi RN, Daoud EG, Fellows C, et al. Left ventricular-based cardiac stimulation Post AV Nodal Ablation Evaluation (The PAVE Study). *J Cardiovasc Electrophysiol*. 2005;16:1-6.

Main Points

- In a meta-analysis of clinical trials of cardiac resynchronization therapy (CRT), pooled data from 1634 patients revealed a 51% relative risk reduction in heart failure mortality. Heart failure hospitalizations were reduced by 29%.
- A large number of trials have been published that show clear benefits of CRT therapy in functional classification, exercise duration, quality of life, and, more recently, mortality.
- CRT provides a similar benefit for patients with cardiomyopathy, conduction system disease, or a need for permanent ventricular pacing.
- The larger trials for CRT have demonstrated a nonresponder rate of approximately one third.
- In the near future, candidates for CRT may be identified by direct determination of ventricular dyssynchrony, such as with tissue Doppler imaging, instead of a wide QRS complex.

24. Abraham WT, Young JB, Leon AR, et al. 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.
25. Kinderman 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.
26. Funck RC, Blanc JJ, Mueller HH, et al. Biventricular stimulation to prevent cardiac desynchronization: rationale, design, and endpoints of the 'Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization (BIOPACE)' study. *Europace*. 2006;8:629-635.
27. Carson P, Anand I, O'Connor C, et al. Mode of death in advanced heart failure: the Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) trial. *J Am Coll Cardiol*. 2005;46:2329-2334.
28. Mehra MR, Greenberg BH. Cardiac resynchronization therapy: caveat medicus! *J Am Coll Cardiol*. 2004;43:1145-1148.
29. Bax JJ, Ansalone G, Breithardt OA, et al. Echocardiographic evaluation of cardiac resynchronization therapy: ready for routine clinical use? *J Am Coll Cardiol*. 2004;44:1-9.
30. Ritter P, Dib JC, Mahaux V, et al. New method for determining the optimal atrio-ventricular delay in patients paced in DDD mode for complete atrioventricular block. *Pacing Clin Electrophysiol*. 1995;18(Pt 2):237.
31. Sawhney NS, Waggoner AD, Garhwal S, et al. Randomized prospective trial of atrioventricular delay programming for cardiac resynchronization therapy. *Heart Rhythm*. 2004;1:562-567.
32. 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.
33. Van Gelder BM, Bracke FA, Meijer A, et al. Effect of optimizing the VV intervalon left ventricular contractility in cardiac resynchronization. *Am J Cardiol*. 2004;93:1500-1503.
34. Boriani G, Muller CP, Seidl KH, et al. Randomized comparison of simultaneous biventricular stimulation versus optimized interventricular delay in cardiac resynchronization therapy. The Resynchronization for the HemodYnamic Treatment for Heart Failure Management II implantable cardioverter defibrillator (RHYTHM ICD II) study. *Am Heart J*. 2006;151:1050-1058.
35. Leon AR, Abraham WT, Brozena S, et al. Cardiac resynchronization with sequential biventricular pacing for the treatment of moderate-to-severe heart failure. *J Am Coll Cardiol*. 2005;46:2298-2304.
36. 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.
37. Achilli A, Sassara M, Ficili S, et al. Long-term effectiveness of cardiac resynchronization therapy in patients with refractory heart failure and "narrow" QRS. *J Am Coll Cardiol*. 2003;42:2117-2124.
38. Ghio S, Constantin C, Klersy C, et al. Interventricular and intraventricular dyssynchrony are common in heart failure patients, regardless of QRS duration. *Eur Heart J*. 2004;25:571-578.
39. Yu CM, Fung JW, Chan CK, et al. Comparison of efficacy of reverse remodeling and clinical improvements for relatively narrow and wide QRS complexes after cardiac resynchronization therapy for heart failure. *J Cardiovasc Electrophysiol*. 2004;15:1058-1065.
40. Bax JJ, Marwick TH, Molhoek SG, et al. Left ventricular dyssynchrony predicts benefit of cardiac resynchronization therapy in patients with end-stage heart failure before pacemaker implantation. *Am J Cardiol*. 2003;92:1238-1240.