Cardiac Resynchronization Therapy for Heart Failure

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The weight of evidence supporting the routine use of cardiac resynchronization therapy, or atrial-synchronized biventricular pacing, as a treatment for patients with moderate-to-severe chronic systolic heart failure and ventricular dyssynchrony is now quite substantial. Results from mechanistic studies, observational evaluations, and randomized, controlled trials have consistently demonstrated significant improvement in quality of life, functional status, and exercise capacity in patients with New York Heart Association (NYHA) class III and IV heart failure who are assigned to active resynchronization therapy.1–3 In these patients, cardiac resynchronization has also been shown to improve cardiac structure and function while significantly reducing the risk of worsening heart failure.1,2 In 2001, the first resynchronization device became commercially available in the United States. The following year, 2 devices that combine biventricular pacing capability with implantable cardioverter defibrillators (ICDs) were approved for use by the US Food and Drug Administration. Recently updated ACC/AHA/NASPE Pacemaker and ICD Guidelines included cardiac resynchronization therapy as a class IIA recommendation for the weight of evidence supporting the routine use of cardiac resynchronization therapy, or atrial-synchronized biventricular pacing, as a treatment for patients with moderate-to-severe chronic systolic heart failure and ventricular dyssynchrony is now quite substantial. Results from mechanistic studies, observational evaluations, and randomized, controlled trials have consistently demonstrated significant improvement in quality of life, functional status, and exercise capacity in patients with New York Heart Association (NYHA) class III and IV heart failure who are assigned to active resynchronization therapy.1–3 In these patients, cardiac resynchronization has also been shown to improve cardiac structure and function while significantly reducing the risk of worsening heart failure.1,2 In 2001, the first resynchronization device became commercially available in the United States. The following year, 2 devices that combine biventricular pacing capability with implantable cardioverter defibrillators (ICDs) were approved for use by the US Food and Drug Administration. Recently updated ACC/AHA/NASPE Pacemaker and ICD Guidelines included cardiac resynchronization therapy as a class IIA recommendation for pacing. Since that time, preliminary results from another large-scale trial have suggested a significant reduction in the combined end point of all-cause mortality and all-cause hospitalization with cardiac resynchronization therapy in an advanced heart failure population.5 The present article briefly reviews the rationale for and mechanisms of cardiac resynchronization therapy in heart failure as background to a more in-depth discussion of landmark clinical trials. Patient selection and limitations/pitfalls of resynchronization therapy are also discussed.

Rationale for Cardiac Resynchronization Therapy

Approximately one third of patients with systolic heart failure have a QRS duration greater than 120 ms, which is most commonly seen as left bundle-branch block (LBBB).6,7 In LBBB, the left ventricle is activated belatedly through the septum from the right ventricle, resulting in a significant delay between the onset of left ventricular (LV) and right ventricular contraction.8,9 Activation of the anterior septum precedes inferoseptal activation, with the latest activation occurring in the inferior and lateral aspects of the left ventricle.8,9 LBBB is associated with significantly later aortic opening, aortic valve closure, and mitral valve opening but does not affect the timing of right ventricular events. The delay in aortic valve closure leads to a relative decrease in the duration of LV filling. In patients with LBBB, delayed depolarization or abnormal repolarization can result in regional myocardial contraction into early diastole, causing a delay of mitral valve opening and also shortening LV filling time.8

Patients with LBBB commonly have abnormal ventricular septal motion, which is related to the interventricular dyssynchrony and the resulting abnormal pressure gradient between the left and right ventricles.8 Because of the abnormal septal motion, LV end-systolic diameter is increased and regional septal ejection fraction is decreased in patients with LBBB. LBBB in patients with or without cardiac disease can reduce global LV ejection fraction (LVEF) and decrease cardiac output, mean arterial pressure, and dP/dt.8,10,11 Moreover, with ventricular dyssynchrony, mitral valve closure might not be complete because atrial contraction is not followed by a properly timed ventricular systole. If the time lag is long enough, a ventricular–atrial pressure gradient can develop and cause diastolic mitral regurgitation.12

In patients with LV dysfunction, ventricular dyssynchrony places the already failing left ventricle at an additional mechanical disadvantage. Ventricular dyssynchrony appears to have a deleterious impact on the natural history of heart failure, as a wide QRS complex has been associated with increased mortality in patients experiencing heart failure.13–15 On the basis of these observations, investigators hypothesized that patients with LV dysfunction and delayed ventricular conduction would benefit from pacing at sites that achieve a more rapid ventricular depolarization and thus a more synchronous contraction, or result in a more favorable contraction pattern, and correct interfibrillar and/or interventricular conduction delays to maintain optimal atrial–ventricular (AV) synchrony. Shortening activation might also prolong the time available for myocardial perfusion. In the mid-1990s, such notions led to the evaluation of atrial-synchronized biventricular pacing as a means to resynchro-
suggesting a decrease in cardiac adrenergic activity or an increase in parasympathetic activity, or a combination of both.3,21

Several studies demonstrate the beneficial effects of cardiac resynchronization therapy on LV remodeling. Yu and colleagues22 evaluated 25 NYHA class III or IV heart failure patients with baseline ejection fractions <40% and QRS durations >140 ms treated with biventricular pacing therapy. The subjects were assessed serially during 3 months of pacing and when pacing was withheld for 4 weeks. During cardiac resynchronization therapy, there was a progressive improvement in ventricular structure and function. At 3 months, significant improvements were noted in ejection fraction, dP/dt, myocardial performance index, and mitral regurgitation. LV end-diastolic and end-systolic volumes were significantly reduced (from 205±68 to 168±67 mL and from 162±54 to 122±42 mL, respectively). These benefits appeared to be dependent on continued pacing because withholding pacing resulted in a progressive but not immediate loss of effect. The authors concluded that biventricular pacing reverses the adverse LV remodeling seen in chronic heart failure and suggested that improvement of LV mechanical synchrony was the predominant mechanism.

Such observations have been confirmed in studies of hundreds of patients experiencing heart failure. In the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial, serial Doppler echocardiograms were obtained at baseline, 3, and 6 months in 323 optimally treated patients with NYHA class III and IV heart failure.1 Cardiac resynchronization therapy for 6 months was associated with reduced end-diastolic and end-systolic volumes (both \(P<0.001\)), reduced LV mass \((P<0.001)\), increased ejection fraction \((P<0.001)\), reduced mitral regurgitant blood flow \((P<0.001)\), and improved myocardial performance index \((P<0.001)\) as compared with controls.

**Clinical Studies of Cardiac Resynchronization Therapy**

Table 1 summarizes a number of observational acute and chronic studies of cardiac resynchronization in heart failure.16,17,23–29 Although early biventricular pacing studies used epicardial leads to pace the left ventricle, later studies used market-available transvenous leads and subsequently specially designed transvenous leads that could be inserted into a distal cardiac vein through the coronary sinus to pace the LV free wall. This approach eliminates the need for general anesthesia and thoracotomy to place an epicardial lead and, thus, could be safer for fragile patients experiencing heart failure. As a result of the favorable outcomes of these early observational studies, randomized, controlled trials to evaluate the long-term subjective and objective results of biventricular pacing have been performed. Several trials have recently been completed, and others are currently underway (Table 2). These studies include the Pacing Therapies in Congestive Heart Failure (PATH-CHF) trial, the Multisite Stimulation in Cardiomyopathy (MUSTIC) study, the MIRACLE trial, MIRACLE ICD, the VENTAK-CHF/CONTAK CD trial, the Cardiac Resynchronization in Heart Failure (CARE HF) trial, and the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial.
TABLE 1. Observational Trials of Cardiac Resynchronization Therapy in Heart Failure

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cazeau et al (1994)</td>
<td>Six-week technical feasibility study of 4-chamber pacing in a 54 year old</td>
<td>Yes (clinical status)</td>
</tr>
<tr>
<td>Cazeau et al (1996)</td>
<td>Eight patients with wide QRS and end-stage heart failure; compared the effect of various ventricular pacing sites</td>
<td>Yes (hemodynamics and functional status, in patients with LV or biventricular pacing only)</td>
</tr>
<tr>
<td>Blanc et al (1997)</td>
<td>Acute hemodynamic study comparing the effect of various ventricular pacing sites</td>
<td>Yes (hemodynamics, in patients with LV or biventricular pacing only)</td>
</tr>
<tr>
<td>Kass et al (1999)</td>
<td>Acute hemodynamic study comparing the effect of various ventricular pacing modes</td>
<td>Yes (hemodynamics, in patients with LV or biventricular pacing only)</td>
</tr>
<tr>
<td>Gras et al (1998)</td>
<td>(InSync Study, interim results, 3-month follow up) European and Canadian multicenter trial of biventricular pacing in 68 patients with dilated cardiomyopathy, WCD, and NYHA class III or IV heart failure</td>
<td>Yes (quality of life, NYHA class, 6-minute hall distance)</td>
</tr>
<tr>
<td>Leclercq et al (1998)</td>
<td>Acute hemodynamic study comparing single-site right ventricular DDD pacing with biventricular pacing in 18 patients with NYHA class III or IV heart failure</td>
<td>Yes (hemodynamics, for biventricular pacing only)</td>
</tr>
<tr>
<td>InSync Trial (1998)</td>
<td>(InSync Study, final analysis, long-term follow up) 117 patients (103 were successfully implanted with a CRT device) with idiopathic or ischemic dilated cardiomyopathy, NYHA class III or IV heart failure, LV dysfunction, and an VCD</td>
<td>Yes (quality of life, NYHA class, 6-minute hall distance)</td>
</tr>
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RV indicates right ventricular; RVOT, RV outflow tract.

PATH-CHF

The PATH-CHF trial was a single-blind, randomized, crossover, controlled trial designed to evaluate the acute hemodynamic effects and to assess the long-term clinical benefit of right ventricular, LV, and biventricular pacing in patients with moderate-to-severe chronic heart failure and interventricular conduction block.3,30 During the crossover periods, patients were assigned to 2 different pacing modes (best univentricular versus biventricular pacing), each 4 weeks long with a 4-week control phase in between. This was followed by a chronic pacing phase. The effects of pacing on oxygen consumption at peak exercise and at anaerobic threshold during cardiopulmonary exercise testing and on 6-minute hall walk distance were selected as primary end points of this study. Secondary end points were changes in NYHA class, quality of life (assessed by the Minnesota Living with Heart Failure questionnaire), and hospitalization frequency. Changes in LVEF, cardiac output, and filling pattern were also assessed by echocardiography.

Forty-two patients were enrolled. Aortic pulse pressure and dP/dt were measured at baseline and during acute pacing. Acutely, biventricular and LV pacing increased dP/dt and pulse pressure more than right ventricular pacing (P<0.01). Chronic results were encouraging, with a trend toward improvement in all primary and secondary end points during pacing being noted.3 However, the results are weakened by the small number of patients studied, the single-blind design, and the observation that functional end points did not return to baseline during the “pacing-off” control or washout period. However, with chronic pacing, statistically significant reductions in end-systolic and end-diastolic volumes were also demonstrated.

MUSTIC

The MUSTIC trial was also a single-blind, randomized, crossover evaluation of cardiac resynchronization therapy.2 Sixty-seven patients were enrolled, 58 were randomized, and 47 completed both study phases of the study. Inclusion criteria were normal sinus rhythm, no indication for pacing, NYHA class III congestive heart failure, optimized drug therapy, LVEF <35%, LV end-diastolic dimension >60 mm, intraventricular conduction defect (IVCD) (QRS >150 ms), and 6-minute walk <450 m. Each phase of the study then lasted 3 months. Patients were randomized to active cardiac resynchronization or to no pacing and then crossed over to the alternative study assignment. The primary end point was the change in distance walked in 6 minutes, and secondary end points included change in quality of life, NYHA class, peak Vo2, hospital admissions, worsening heart failure, total mortality, and patient preference for pacing mode. Significant improvement was shown in all of these end points. For example, during the active pacing phase, the mean distance walked in 6 minutes was 23% greater than during the inactive pacing phase (P<0.001).

A “second” MUSTIC (MUSTIC-AF) trial evaluated similar end points in heart failure patients with atrial fibrillation and ventricular dyssynchrony resulting from a paced QRS duration of >200 ms.31 Although the number of patients completing the MUSTIC AFIB trial was smaller, significant improvements were seen in the primary and secondary end points.

MIRACLE

MIRACLE was the first prospective, randomized, double-blind, parallel-controlled clinical trial designed to validate the
TABLE 2. Randomized, Controlled Trials of Cardiac Resynchronization Therapy in Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATH-CHF</td>
<td>Single-blind, randomized,</td>
<td>42 patients with idiopathic or ischemic dilated cardiomyopathy and NYHA</td>
<td>Interim analysis (spring 1998) showed a trend toward an improvement in all primary and secondary end points with biventricular pacing.</td>
</tr>
<tr>
<td></td>
<td>crossover, controlled</td>
<td>class III/IV heart failure</td>
<td></td>
</tr>
<tr>
<td>MUCISTIC</td>
<td>European randomized,</td>
<td>Group I: 47 patients with NYHA class III heart failure, normal sinus</td>
<td>Improved exercise capacity (6-minute hall walk), NYHA class, and quality of life in normal sinus rhythm group; magnitude of improvement less in atrial fibrillation group</td>
</tr>
<tr>
<td></td>
<td>crossover study</td>
<td>rhythm; group II: 41 patients with persistent atrial fibrillation and</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>slow ventricular response</td>
<td></td>
</tr>
<tr>
<td>MIRACLE</td>
<td>Prospective, randomized,</td>
<td>453 patients with idiopathic or ischemic dilated cardiomyopathy, NYHA</td>
<td>Significant improvements in exercise capacity, NYHA class, quality of life, cardiac structure and function (by ECHO), composite clinical response, and significant reductions in worsening heart failure, and a combined measure of morbidity and mortality</td>
</tr>
<tr>
<td></td>
<td>double-blind, parallel-</td>
<td>class III/IV heart failure, LV dysfunction, and ICD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>controlled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIRACLE ICD</td>
<td>Prospective, multicenter,</td>
<td>560 patients with idiopathic or ischemic dilated cardiomyopathy, NYHA</td>
<td>Significant improvements in exercise capacity, NYHA class, quality of life, and composite clinical response, in class III-IV patients; results in class II patients have not yet been reported</td>
</tr>
<tr>
<td></td>
<td>randomized, double-blind,</td>
<td>class II-IV heart failure, LV dysfunction, and ICD with an indication for</td>
<td></td>
</tr>
<tr>
<td></td>
<td>parallel-controlled</td>
<td>an ICD</td>
<td></td>
</tr>
<tr>
<td>CONTAK CD</td>
<td>Prospective, randomized,</td>
<td>581 patients with idiopathic or ischemic dilated cardiomyopathy (248 in</td>
<td>Trend toward decreased morbidity/mortality end point; improvements in exercise capacity, quality of life, and NYHA class</td>
</tr>
<tr>
<td></td>
<td>crossover, and parallel-</td>
<td>the 3-month crossover study and 333 in the 6-month parallel controlled</td>
<td></td>
</tr>
<tr>
<td></td>
<td>controlled</td>
<td>phase), symptomatic heart failure (LVEF ≤35%), and ICD with an indication</td>
<td></td>
</tr>
<tr>
<td>COMPANION</td>
<td>Multicenter, prospective,</td>
<td>1520 patients (planned enrollment of 2200) with dilated cardiomyopathy,</td>
<td>Preliminary report indicates significant reduction in primary end point of all-cause mortality plus all-cause hospitalization</td>
</tr>
<tr>
<td></td>
<td>randomized, controlled</td>
<td>NYHA class III/IV heart failure, and an ICD; drug therapy for cardiac</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>resynchronization; or drug therapy and cardiac resynchronization/ICD</td>
<td></td>
</tr>
<tr>
<td>CARE HF</td>
<td>Multicenter, prospective,</td>
<td>800 patients with idiopathic or ischemic dilated cardiomyopathy</td>
<td>Enrollment completed in March 2003; results expected late 2003 or early 2004</td>
</tr>
<tr>
<td></td>
<td>randomized, controlled</td>
<td>randomized to CRT device+optimal medical therapy vs optimal medical therapy only</td>
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</table>

ECHO indicates echocardiogram.

results from previous cardiac resynchronization studies and to further evaluate the therapeutic efficacy and mechanisms of potential benefit of cardiac resynchronization therapy. Primary end points were NYHA class, quality-of-life score (using the Minnesota Living with Heart Failure questionnaire), and 6-minute hall walk distance. Secondary end points included assessments of a composite clinical response, cardiopulmonary exercise performance, neurohormone and cytokine levels, QRS duration, cardiac structure and function, and a variety of measures of worsening heart failure and combined morbidity and mortality.

The MIRACLE trial began in October 1998 and was completed late in 2000. Four hundred thirty-six patients with moderate to severe symptoms of heart failure associated with LVEF <35% and a QRS duration >130 ms were randomized (double-blind) to cardiac resynchronization (n=228) or to a control group (n=225) for 6 months, whereas conventional therapy for heart failure was maintained. Compared with the control group, patients randomized to cardiac resynchronization demonstrated a significant improvement in quality of life score (−18.0 versus −9.0 points, P=0.001), 6-minute walk distance (+39 versus +10 meters, P=0.005), NYHA functional class ranking (−1.0 versus 0.0 class, P<0.001), treadmill exercise time (+81 versus +19 seconds, P=0.001), peak VO2 (+1.1 versus +0.1 mL/kg per minute, P<0.01), and LVEF (+4.6% versus −0.2%, P<0.001). Patients randomized to cardiac resynchronization therapy demonstrated a highly significant improvement in a composite clinical heart failure response end point compared with control subjects, suggesting an overall improvement in heart failure clinical status.

By intention-to-treat, there were 16 deaths in the control group and 12 deaths in the resynchronization group (P=not significant). When compared with the control group, fewer patients in the cardiac resynchronization group required hospitalization (8% versus 15%) or intravenous medications (7% and 15%) for the treatment of worsening heart failure (Figure 2). In the control group, there were 50 hospitalizations for heart failure in 34 patients for a total of 363 heart failure hospital days during the 6-month period of double-blind follow-up. In patients randomized to cardiac resynchronization, there were 25 hospitalizations for heart failure in 18 patients for a total of 83 heart failure hospital days (P=0.015 for the difference in risk of hospitalization, P=0.012 for the difference in hospital days), resulting in a 77% decrease in total days hospitalized over 6 months compared with the control group. Implantation of the device was unsuccessful in 8% of patients.

VENTAK-CHF/CONTAK-CD
The VENTAK-CHF/CONTAK-CD study was also a randomized, controlled, double-blind study comparing active cardiac
resynchronization therapy versus no pacing.32 The initial design was that of a 3-month crossover trial; this was later changed to a 6-month parallel control study design. The device used in the study combines ICD capabilities with biventricular pacing. Patients included had NYHA functional class II–IV heart failure, LVEF \( \leq 35\% \), QRS duration \( > 120 \) ms, and an accepted indication for an ICD. The primary end point was a composite of mortality, hospitalizations for heart failure, and episodes of ventricular tachycardia or ventricular fibrillation.

A total of 581 patients were randomized, 248 into the 3-month crossover study and 333 into the 6-month parallel controlled trial.33 For the primary composite end point, the study demonstrated an insignificant trend favoring the resynchronization group. However, peak \( \dot{V}O_2 \), 6-minute hall walk distance, quality of life, and NYHA class were significantly improved in the active pacing group compared with inactive control subjects, particularly in the NYHA class III–IV subgroup of patients. For example, in class III–IV patients randomized to active resynchronization therapy, peak \( \dot{V}O_2 \) improved by 1.8 mL/kg per minute compared with no improvement in the control group (\( P = 0.003 \)). There was also a reduction in LV end-systolic and end-diastolic dimensions seen in the VENTAK-CHF/CONTAK-CD trial.

MIRACLE ICD

The MIRACLE ICD study was designed to be nearly identical to the MIRACLE trial. MIRACLE ICD was a prospective, multicenter, randomized, double-blind, parallel-controlled clinical trial intended to assess the safety and clinical efficacy of another combined ICD and cardiac resynchronization system in patients with dilated cardiomyopathy (LVEF \( \leq 35\% \), LV end-diastolic diameter \( > 55 \) mm), NYHA class III or IV heart failure (a cohort of class II patients was also enrolled), IVCD (QRS = 130 ms), and an indication for an ICD. Primary and secondary efficacy measures were essentially the same as those evaluated in the MIRACLE trial, but also included measures of cardioverter–defibrillator function (including the efficacy of antitachycardia therapy with biventricular pacing).

Of 369 patients receiving devices and randomized, 182 were control subjects (cardioverter defibrillator activated, cardiac resynchronization off) and 187 were in the resynchronization group (cardioverter defibrillator activated, cardiac resynchronization on). At 6 months, patients assigned to cardiac resynchronization had a greater improvement in median quality of life score (\(-17.5 \) versus \(-11.0, P = 0.02\)) and functional class (\(-1 \) versus 0, \( P = 0.007 \)) than control subjects, but were no different than control subjects in the change in distance walked in 6 minutes (+55 meters versus +53 meters, \( P = 0.36 \)).34 Peak oxygen consumption increased by 1.1 mL/kg per minute in the cardiac resynchronization group versus 0.1 mL/kg per minute in control subjects (\( P = 0.04 \)), whereas treadmill exercise duration increased by 56 seconds in the resynchronization group and decreased by 11 seconds in control subjects (\( P = 0.0006 \)). The magnitude of improvement was comparable to that seen in the MIRACLE trial, suggesting that patients experiencing heart failure with an ICD indication benefit as much from cardiac resynchronization therapy as those patients without an indication for an ICD. Interestingly, the efficacy of biventricular antitachycardia pacing was significantly greater than that seen in the univentricular (right ventricular) configuration. This observation suggests another potential benefit of a combined ICD plus resynchronization device in such patients. Finally, no proarrhythmia was observed, and arrhythmia termination capabilities were not impaired by the addition of resynchronization therapy.

COMPANION and CARE-HF

Begun in early 2000, COMPANION was a multicenter, prospective, randomized, controlled clinical trial designed to compare drug therapy alone to drug therapy in combination with cardiac resynchronization with or without an ICD in patients with dilated cardiomyopathy, an IVCD, NYHA class III or IV heart failure, and no indication for an ICD.3 The trial design called for randomization of 2200 patients into 1 of 3 treatment groups: group I (440 patients) receiving optimal medical care only, group II (880 patients) receiving optimal medical care and the Guidant CONTAK TR (biventricular pacing alone), and group III (880 patients) receiving optimal medical care and the CONTAK CD (combined heart failure/bradycardia/tachycardia ICD device). The primary end point of the COMPANION trial was a combination of all-cause mortality and all-cause hospitalization. Secondary end points included a variety of measures of cardiovascular morbidity as well as all-cause mortality alone.

After randomization of 1520 patients, the COMPANION trial was terminated prematurely in November 2002 at the recommendation of an independent data and safety monitoring board. COMPANION was designed as an event-driven study (target \( > 950 \) primary events). As reported by the lead investigators (A.M. Feldman and M.R. Bristow during a late-breaking session at the 52nd Annual Scientific Sessions of the American College of Cardiology in Chicago, April 2003), 1000 events had occurred by November 18, 2002, resulting from a higher-than-expected event rate. The number
of patients randomized to each treatment group was 308 to medical therapy alone, 617 to medical therapy plus resynchronization therapy, and 595 to medical therapy plus cardiac resynchronization and an ICD. The average age of patients was 66 years and 68% were men. The mean LVEF was 23% and 85% of the patients were in NYHA class III. At baseline, angiotensin-converting enzyme (ACE) inhibitors (or angiotensin receptor blockers) were taken by 90% of patients, β-blockers by 68%, and spironolactone by 55%. Compared with control patients (group 1), the primary end point was significantly reduced in both resynchronization groups, by 18.6% in group 2 and by 19.3% in group 3 patients (P=0.015 and 0.005, respectively). All-cause mortality was also reduced by resynchronization therapy: group 1 versus group 2 by 24% (P=0.12); group 1 versus group 3 by 43% (P=0.002).

Another randomized, controlled morbidity and mortality trial is CARE-HF. This study compares optimal medical therapy alone with optimal medical therapy plus cardiac resynchronization (without an ICD) in 800 patients with NYHA class III or IV systolic heart failure and ventricular dyssynchrony determined by either electrocardiographic (QRS duration ≥150 ms) or echocardiographic (QRS duration ≥120 and <150 ms plus echocardiographic evidence of dyssynchrony) criteria. CARE-HF was fully enrolled as of March 2003. The study is expected to conclude late in 2003 or early in 2004.

**Clinical Implications of Cardiac Resynchronization Therapy Data**

Although clinical application of cardiac resynchronization therapy is still in its early years, some clinical guidelines can be suggested on the basis of data to date. Cardiac resynchronization therapy should be considered only in patients who remain symptomatic despite a stable and optimized medical regimen for heart failure. Unless patients are intolerant, that medical regimen should include an ACE inhibitor or ACE inhibitor substitute and a digitalis as needed. Resynchronization therapy should not be seen as an alternative to medical therapy. Other criteria for cardiac resynchronization include QRS duration ≥120 ms, LVEF ≤35%, and LV dilation.

At this point, cardiac resynchronization is appropriate for patients with NYHA functional class III or IV functional limitation. Not enough data are available in patients with NYHA class II heart failure to routinely recommend it, although the application of resynchronization therapy at an earlier stage could theoretically prevent late heart failure-related complications or slow disease progression. In addition, initial Food and Drug Administration labeling does not specify approval for cardiac resynchronization for patients in atrial fibrillation. Early data support its efficacy in the atrial fibrillation population; however, definitive data are lacking. Many such questions remain unanswered. Paramount among these is whether prospective predictors of response exist to further guide patient selection. To date, the benefits of cardiac resynchronization therapy have been seen regardless of baseline QRS duration (>120 ms), bundle-branch block pattern, and etiology of the heart failure. Very recent data suggest that resynchronization therapy could yield improvement in the patient with intraventricular dyssynchrony despite a normal QRS duration.

If ventricular dyssynchrony is proven to be the best predictor of response to cardiac resynchronization therapy, the electrocardiographic morphology of the conduction delay could become less significant in patient selection. Specifically, the question of whether patients with a right bundle branch block (RBBB) morphology will respond must be addressed. In small subsets of patients in both the MIRACLE and CONTAK-CD trials, patients with RBBB appeared to do as well as patients with LBBB. Other investigators have also shown a response to therapy in patients with a RBBB, but only when associated with intraventricular asynchrony.

Future studies could help refine the indication in NYHA class III–IV patients, whereas other studies could expand the indication to those with milder forms of heart failure or lesser degrees of ventricular dyssynchrony. Information is emerging regarding the outcomes of biventricular versus LV pacing only. At this point, the results are indefinite and further investigations are warranted. Another obvious question is whether routine LV or biventricular pacing rather than traditional right ventricular apical pacing should be used once coronary sinus lead technology, implantation techniques, speed, and complication rates are similar to those of right ventricular endocardial leads.

As resynchronization therapy becomes more commonly used, clinicians should be aware that pacing nomenclature originally established in 1974 was updated recently to include a “generic code” for multisite pacing therapy. The fifth position of the code is now used to indicate whether multisite pacing is present in (O) none of the cardiac chambers, (A) 1 or both atria, (V) 1 and both ventricles, or (D) any combination of atria and ventricles. To describe a patient with a DDDR (dual-chamber rate-adaptive) pacemaker with biventricular stimulation, the code would be DDDRV.

**Limitations and Pitfalls of Cardiac Resynchronization Therapy**

The success rate for placement of a transvenous cardiac resynchronization system has ranged from approximately 88% to 92% in clinical trials. This means that 8% to 12% of patients undergoing an implant procedure will not attain a functioning system using this approach. Patients with failed implants must then settle for either another attempt at transvenous placement of the LV lead or epicardial placement of the lead, or they must resign themselves to no cardiac resynchronization therapy. Implant-related complications are similar to those seen with standard pacemaker and ICD technologies, with the additional risk of dissection or perforation of the coronary sinus. Although rare, this event could lead to substantial morbidity and even mortality in patients experiencing heart failure.

In addition to satisfying the clinical criteria already discussed, the patient should be given some basic information before referral. Although it is healthy for the patients to be optimistic about the potential improvement from cardiac resynchronization therapy, caregivers must provide realistic information. Although most patients respond favorably to
biventricular pacing, patients should understand that just like the experience with any medication or any other therapeutic modality for heart failure and despite clinical trials data demonstrating significant improvement, not every patient has a subjective and/or objective response to resynchronization therapy.

Finally, if the patient obtained subjective and objective clinical improvement after implantation of a resynchronization device, worsening of the patient’s heart failure symptoms suggests worsening of the primary pathologic process or loss of resynchronization, or both. Loss of resynchronization can be manifested as frank worsening of heart failure, or it could be more occult and appear as vague weakness or fatigue. A specific programming sequence should be performed in the clinic to determine capture thresholds and document that LV capture is present. It is possible that LV pacing thresholds are fine but resynchronization is lost for other reasons.44 Anything that frequently or consistently inhibits LV stimulation can lead to “desynchronization.” If the AV interval is too long and the patient’s intrinsic PR conduction inhibits biventricular pacing, deterioration can occur. The AV interval could have been programmed appropriately, but accelerated intrinsic AV conduction could result in loss of effective biventricular pacing. Frequent premature ventricular contractions can also inhibit ventricular pacing output. In this case, the etiology of the increasing ventricular ectopy should be determined. Management can require an alteration in the medical regimen for heart failure, specific antiarrhythmic therapy, or an ICD, depending on the amount of ectopy and whether ventricular tachycardia is nonsustained or sustained. Despite these potential concerns, follow-up of the device itself and battery life are similar to that seen for contemporary dual-chamber pacemakers and ICDs.

Optimal hemodynamic response from resynchronization will depend not only on the site of LV stimulation,45 but also on optimization of the atioventricular interval12 and the timing between the right and left ventricle.46 Best techniques to achieve such optimization are still being defined.

Another clinical problem that could result in new symptoms of heart failure is chronotropic incompetence, or inappropriate rate acceleration for a given physiological activity. In the patient with heart failure, this is probably less likely as a result of progression of intrinsic sinus node dysfunction than a change in medical regimen. If the heart failure management team has altered β-blocker therapy or any other medication, the result could be limitation of the patient’s chronotropic response. Any significant change in the medical regimen should be communicated from the heart failure caregivers to the pacemaker surveillance center.

Summary
Cardiac resynchronization therapy offers a new therapeutic approach for treating patients with ventricular dyssynchrony and moderate-to-severe heart failure. Clinical trials have demonstrated that it is safe and effective, with patients achieving significant improvement in both clinical symptoms as well as multiple measures of functional status and exercise capacity. Moreover, cardiac resynchronization therapy has reduced measures of morbidity and mortality in several studies. Thus, cardiac resynchronization therapy should be routinely offered to eligible patients experiencing heart failure.

References
Cardiac Resynchronization Therapy for Heart Failure
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