Ventricular Resynchronization

Current State of the Art
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Cardiac resynchronization therapy (CRT) is a new therapy that improves hemodynamics and symptoms in patients with advanced heart failure (HF). In HF, ventricular dyssynchrony results most commonly from left bundle-branch block (LBBB). Resynchronization pacing can influence hemodynamics by improving mechanical synchrony both between and within the right and left ventricles, as well as by optimizing atrioventricular synchrony. Biventricular pacing devices, first implanted in 1994, were approved by the U.S. Food and Drug Administration in 2001. Currently available devices may also have defibrillation capacity. Much of the information regarding the clinical benefits of CRT derives from clinical trials (Table) that together demonstrate that CRT improves symptoms and exercise tolerance in medically treated patients with persistent, moderate to severe symptoms of HF; poor left ventricular (LV) function; and intraventricular conduction delay. Here we review the proposed mechanisms of action, potential applicability, and cost impact of CRT of appropriately selected patients.

Pathophysiology of Dyssynchrony
Both atrioventricular and intraventricular conduction delays further impair LV function in patients with underlying cardiomyopathies. Notably, LBBB (and also possibly right bundle-branch block) changes LV contraction patterns, leading to regions of early and late contraction. This, in turn, impairs systolic function, reduces cardiac output, and increases end-systolic volume and wall stress. In addition to having mechanical consequences, there is preliminary evidence that LBBB, estimated to affect 30% to 50% of patients with advanced HF, confers an independent risk for mortality. Currently, it remains unknown whether ventricular dyssynchrony is fundamental to the pathogenesis of dysfunctional hearts. Early experimental studies demonstrate regional molecular changes in discoordinately contracting myocardium, a finding that is consistent with the idea that dyssynchrony contributes to disease pathophysiology.

Impact of CRT
Hemodynamic Studies
Biventricular or LV pacing improves hemodynamics in patients with HF and LBBB by increasing cardiac output and reducing ventricular filling pressures. The hemodynamic improvements due to CRT begin almost immediately after pacing is initiated and are reflected by the patient’s sense of well-being. In addition, CRT is associated with reduced sympathetic nervous activity, suggesting potentially favorable neurohormonal effects. Importantly, CRT improves systolic function without increasing cardiac oxygen consumption, unlike inotropic drugs that increase oxygen consumption for a given rise in contractile performance. Thus, CRT contributes to reversing mechanoenergetic uncoupling associated with HF.
Clinical Outcome Studies
To date, 3 placebo control studies have been published, as follows: PACing THERapies for Congestive Heart Failure (PATH-CHF), MultiSite Stimulation In Cardiomyopathy (MUSTIC), and Multicenter Insync RAndomized CLinical Evaluation (MIRACLE) (Table), comprising a totality of evidence from 562 patients. PATH-CHF assigned patients in single blind fashion to either a 4-week period of pacing (LV or biventricular), or a 4-week period of no pacing. The initial 4-week period was followed by a second period of active pacing, and increased exercise performance was demonstrated during the 2 active pacing periods.4 MUSTIC sinus rhythm, a crossover trial, and MIRACLE, a placebo-controlled study, both demonstrated improved New York Heart Association class, exercise tolerance (6-minute walk test and peak VO2), and quality of life (Minnesotan living with HF questionnaire) due to CRT.

Individual studies published to date have not been adequately powered to address whether CRT reduces mortality, all-cause or otherwise. To address this, Bradley and colleagues performed a meta-analysis of existing trials, including 809 patients with CRT compared with 825 without.2 This study, which included the results of the unpublished In-Sync ICD and CONTAK ICD studies, demonstrated that CRT reduced HF-associated mortality by 51% (odds ratio [OR], 0.49; 95% confidence interval [CI], 0.25 to 0.93) and hospitalization by 29% (OR, 0.71; 95% CI, 0.53 to 0.96). Neither all-cause mortality (OR, 0.77; 95% CI, 0.51 to 1.18) nor non-HF deaths (OR, 1.15; 95% CI, 0.65 to 2.02) were statistically reduced by CRT.2

Whether CRT alone, per se, reduces mortality will be difficult to address in future prospective trials because of the results of the Multicenter Automatic Defibrillator Implantation II Trial (MADIT II), which demonstrated that intracardiac defibrillators (ICDs) reduce mortality by 31% in postmyocardial infarction patients with LV ejection fraction (LVEF) <30%, an effect that was enhanced as a function of QRS duration.13 Thus, trials of CRT in the future will likely incorporate devices with ICD (CRT-D) capability, at least in patients with HF due to previous myocardial infarction, and it may be difficult to assess the relative role played by each individual therapeutic modality in patient all-cause mortality.

It is important to note that currently, it is not known whether ICDs reduce all-cause mortality in patients with nonischemic cardiomyopathy.

There are 2 current, important mortality-morbidity trials, as follows: Cardiac Resynchronization in Heart Failure Study (CARE-HF) conducted in Europe (completed in March 2003) and COmparison of Medical therapy, Pacing, ANd Defibril-lation in Chronic Heart Failure (COMPANION)14 in the US. The results of COMPANION have been announced but are currently unpublished; the study was terminated early by the Data Safety and Monitoring Board after the enrollment of 1600 patients out of the 2200 planned because of early benefit (combined endpoint of mortality and hospitalization) associated with CRT either with or without ICD, and a survival benefit with CRT-D. Like MIRACLE, this study enrolled patients with prolonged QRS durations and persistent symptoms of HF despite aggressive HF therapy. The results of this study clearly are supportive of the use of CRT in appropriate patients, and full scrutiny of this trial awaits publication.

Impact on Hospitalization
Both the MUSTIC and MIRACLE trials demonstrated reduced HF hospitalization rates after CRT. In MUSTIC, the monthly hospitalization rate was reduced to from 14% to 2% in the biventricular pacing group as compared with crossover to an inactive period (pacer off) over a period of 1 year. In the MIRACLE trial, CRT reduced the risk of hospitalization for HF from 15% to 8% and the total days hospitalized for worsening HF over 6 months from 363 to 83. As previously mentioned, the meta-analysis by Bradley and the COMPANION trial substantiate reduced utilization of hospitalization for HF.12

Impact on LV Architecture
LV remodeling is a potentially valuable surrogate marker of therapeutic response to a HF therapy. Several noncontrolled studies demonstrated reverse LV remodeling due to CRT, with a decrease in LV end-systolic and end-diastolic volumes and an increase in LVEF.15,16 These benefits are pacing dependent, however, because discontinuation of pacing resulted in the loss of the cardiac improvement.15,16 Improved LV structure and function were also observed in the 6-month MIRACLE follow-up2 and in the 1-year MUSTIC follow-up.17

### Published Controlled Studies With Permanent Cardiac Multisite Pacing

<table>
<thead>
<tr>
<th>Study Duration</th>
<th>Randomized</th>
<th>Placebo-Controlled</th>
<th>Follow-Up, Months</th>
<th>NYHA Class, Mean</th>
<th>QRS Duration, ms</th>
<th>LVEF, % LV EDD, mm</th>
<th>Clinical Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATH-CHF N=42 (4)</td>
<td>1995–1998</td>
<td>Yes</td>
<td>No</td>
<td>3</td>
<td>III/V 3.1±0.3</td>
<td>175±32</td>
<td>21±7/7±3±11</td>
</tr>
<tr>
<td>MUSTIC SR N=67 (3)</td>
<td>1998–1999</td>
<td>Yes/crossover</td>
<td>Yes</td>
<td>3/3</td>
<td>III</td>
<td>176±19</td>
<td>23±7/7±3±10</td>
</tr>
<tr>
<td>MUSTIC AF N=43 (21)</td>
<td>1998–1999</td>
<td>Yes/crossover</td>
<td>Yes</td>
<td>3/3</td>
<td>III AF</td>
<td>207±17</td>
<td>26±10/6±8</td>
</tr>
<tr>
<td>MIRACLE N=453 (2)</td>
<td>1998–2000</td>
<td>Yes/parallel</td>
<td>Yes</td>
<td>6</td>
<td>III/V 3.09</td>
<td>165±20</td>
<td>22±6/6±10</td>
</tr>
</tbody>
</table>

SR indicates sinus rhythm; AF, atrial fibrillation; NYHA, New York Heart Association; QOL, quality of life; 6WT, 6-minute walk test; LV EDD, LV end-diastolic dimension.
Complications and Technical Considerations of CRT

The technology of CRT is still evolving. With improving catheter and lead design, implantation success has risen from approximately 50% to over 90%. The major complications of LV lead implantation as reported by the MIRACLE investigators (n=453) are death (n=2); complete heart block (n=2); coronary sinus dissection (n=23) or perforation (n=12); and need to reposition (n=20), replace (n=10), or remove (n=7) pacing leads. The investigators also reported that about 8% of patients experienced failure of successful implantation. LV lead position (usually but not always in the midlateral or posterolateral LV wall) is crucial to optimize the clinical benefit of CRT. New generations of biventricular pacemakers will offer independent LV and RV ports to allow programming of an interventricular interval so as to enhance ventricular resynchronization. Finally, whether simultaneous pacing of both ventricles is necessary remains unknown, and hemodynamic studies suggest that LV pacing alone may improve mechanical synchrony even without electrical synchrony.

The Future of CRT

Case for Broadened or Refining Indications

While clinical outcome data are limited for CRT, the hemodynamic impact of the therapy has been extensively studied. The net result of these studies indicates that restoring ventricular dyssynchrony, per se, is achievable in a broader range of patients and that improved patient selection is possible. Currently patient selection is based solely on the QRS duration in patients with LV dysfunction and symptoms of HF. However, experimental and preliminary clinical studies demonstrate only a weak correlation between the QRS width (electrical dyssynchrony) and mechanical dyssynchrony.

Substantial efforts have been brought to bear to develop methods to measure mechanical dyssynchrony directly, and both Doppler-echocardiography and cardiac MRI may be used in this regard. The case for improving dyssynchrony leading to hemodynamic benefits is fairly sound, making these attempts important. Whether such criteria for dyssynchrony are translatable into clinical benefits for patients will require completion of prospective controlled trials such as the ongoing European CARE-HF trial.

There are 2 important groups of patients that require further study for CRT efficacy, those with atrial fibrillation (potentially 20% to 30% of severe HF patients) and those with dyssynchrony due to conventional right ventricular pacing. MUSTIC AF demonstrates promising, but not definitive, results of CRT in patients with atrial fibrillation (Table). With regard to the latter group, given cost implications (see below) and lack of clinical trial data, it seems critical to prove that clinical benefits derive before a widespread recommendation is made to use CRT in all patients with LV dysfunction who require conventional pacing.

Case for Limiting Indications

Although a formal cost-effectiveness analysis has not yet been performed for CRT and is beyond the scope of this article, CRT clearly is an expensive therapy, with device costs in the US ranging from $25,000 to $40,000 and total per patient charges (including hospital and professional fees) reaching $100,000 in some cases. Among HF patients, it is estimated that 10% meet current criteria for CRT, representing 500,000 patients in the United States and 50,000 in Western Europe. Given that the estimated annual cost for treating HF is $20 billion, CRT costs have the potential to increase substantially the HF budget unless balanced by major cost savings. Clearly, either CRT costs must be reduced or patient selectivity improved in order for this therapy to have widespread applicability. Moreover, CRT must be clearly established to have substantial and sustainable benefits, and to offer advantages over alternative treatment strategies.

Indeed, given these costs, it is important to consider patients eligible for CRT in the broader context of other treatment options. CRT is currently indicated only for patients who remain symptomatic despite conventional therapy. Thus, the factors that lead to ongoing symptoms warrant consideration. It is estimated that the majority of patients who remain symptomatic and require recurrent hospitalizations for HF do so for preventable reasons and can be effectively managed with so-called “disease management strategies.” These programs reduce patient symptoms, decrease hospitalizations, and, in some studies, lead to lower rates of death. It must be recognized that highly successful pharmacological strategies currently available (notably angiotensin-converting enzyme inhibitors, β-adrenergic blockers, and spironolactone) are widely underutilized and have clearly proven benefits for reducing morbidity and mortality, and that HF management clinics greatly increase their usage and lead to improved patient outcomes.

Importantly, there is no evidence that these drugs are less effective in patients with LBBB and associated ventricular dyssynchrony.

Fundamental pathophysiological questions must be answered before CRT can be more widely applied. First, it remains unknown whether dyssynchrony represents a central pathophysiological process or is a “marker” of progressing cardiac dysfunction. Although studies have demonstrated that LBBB does portend worse prognosis in populations of HF patients, it is not known whether this represents cause or effect. There is a lack of data from clinical trials regarding long-term benefits of CRT, given the short (6-month to 1-year) duration of currently published studies (Table). The ongoing COMPANION and CARE-HF studies have substantially longer follow-up durations. As previously mentioned, the COMPANION trial does provide evidence for long-term clinical benefits of CRT and CRT-D.

Summary

In summary, CRT is an extremely promising and effective strategy to improve hemodynamic performance in patients.
with HF and bundle-branch blocks. Numerous elegant studies have demonstrated that CRT can restore synchrony and improve cardiac performance without the cost of increased myocardial oxygen consumption. This hemodynamic benefit rapidly translates into improved patient well-being as evidenced by enhanced exercise capacity and reduced utilization of inpatient care. As-yet unpublished studies and meta-analyses suggest that CRT has a mortality benefit, particularly when combined with a defibrillator. Enthusiasm must be balanced by the high cost of the procedure, the relative dearth of clinical trial data (notably long-term follow-up studies powered for mortality endpoints), and very limited pathophysiological/mechanistic studies that support the idea that CRT addresses a fundamental biological process in the failing heart not otherwise addressed by conventional medical therapies. As with all new treatment strategies, the continuing conduct of new clinical trials remains a critical means by which practitioners clarify the appropriate use of the new therapy.

Our current recommendation is that CRT is appropriate in the exact scenario addressed by the MUSTIC, MIRACLE, and COMPANION trials, ie, in patients with wide QRS complexes who remain symptomatic despite optimal medical therapy. Attempts should be made to ensure that the latter is achieved, and patients should be referred for participation in HF clinics or other disease management programs. There are multiple additional scenarios in which CRT could have a potential role—less symptomatic patients, patients with atrial fibrillation, or patients with narrow QRS complexes who are given iatrogenic LBBBs as a result of right ventricular pacing for conventional reasons. To date, evidence-based medicine criteria for dyssynchrony are based on QRS duration, but we can expect that in the near future, the assessment of mechanical dyssynchrony using sophisticated imaging techniques might play an important role in the selection and follow-up of patients and the optimization of the therapy. Although we endorse the conduct of clinical trials to test these scenarios, we do not currently recommend CRT for these indications.

Acknowledgments

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References

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