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The Emerging Role of Cardiac Resynchronization Therapy in Milder Heart Failure: Are We Implanting Too Late for Response?

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Abstract The role of cardiac resynchronization therapy in mild heart failure has become a focus of attention with the publication of recent clinical trials. We present a review of the data supporting implantation of cardiac resynchronization devices in early stage heart failure. In addition, we present evidence that may suggest patients are often implanted too late for clinical benefit, potentially contributing to the relatively high nonresponder rate seen in randomized trials and clinical practice.

Keywords Heart failure · Cardiac resynchronization · Defibrillator · Pacemaker · Remodeling · Dyssynchrony · Nonpharmacologic therapy · Biventricular pacing

Introduction

Heart failure (HF) is estimated to affect 5.8 million individuals in the United States (US) and is the cause of over one million hospital admissions annually [1]. Medical therapy has made significant advances in the treatment of HF, with β-blockers and angiotensin-converting enzyme inhibitors providing significant mortality benefit for HF patients. Yet, despite these pharmacologic advances, HF continues to be a major cause of morbidity and mortality worldwide.

Device-based therapy, specifically cardiac resynchronization therapy (CRT), was developed to provide further optimization and stabilization for HF patients. CRT was first described in 1995 by Thomas and Mower [2], with subsequent introduction in the late 1990s and approval by the US Food and Drug Administration (FDA) in 2001.

The concept in CRT is to treat the dyssynchrony between the left ventricular (LV) septum and posterolateral wall, which is commonly seen in patients with significant cardiomyopathy (CM) and associated QRS complex widening, with pacing from both the right ventricle (RV) and lateral wall of the LV (biventricular pacing). The aim of this therapy is to improve the synchronization and hemodynamic performance of the LV, and slow or reverse the pathologic remodeling of the ventricle.

Numerous large, multicenter, randomized controlled trials have demonstrated that in addition to decreasing symptoms and causing reverse remodeling, CRT improves survival in patients with New York Heart Association (NYHA) class III and IV HF and a wide QRS interval on electrocardiogram, even when these patients are on optimal medical therapy [3–8]. A meta-analysis by McAlister and colleagues [9] showed that CRT decreased hospitalization by 37% and decreased mortality by 22%.

These studies led to the current US guidelines that recommend CRT device implantation for those HF patients with ejection fraction (EF) of 35% or less, QRS interval of 120 ms or longer, and NYHA class III or IV HF symptoms [10]. All of these initial studies excluded patients with NYHA class I or II HF symptoms. Yet, there is evidence that even in patients with NYHA class III and IV HF, this treatment modality may be underused, even at major heart transplant centers [11].

Additional evidence for the benefits of CRT comes from the literature on chronic RV pacing. The Dual Chamber and VVI Implantable Defibrillator (DAVID) trial [12] demonstrated that chronic RV pacing (> 40%) led to significant LV dysfunction. This finding, and concerns that chronic RV

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pacing could result in further deterioration in patients who already had LV dysfunction, led to further investigation in trials such as the Post AV (atrioventricular) Nodal Ablation Evaluation (PAVE) and the Homburg Biventricular Pacing Evaluation (HOBIPACE), which demonstrated a symptomatic benefit for CRT, as well as improved cardiac function, in patients with baseline LV dysfunction and need for chronic pacing [13, 14].

However, despite optimal medical therapy and implantation of CRT devices, patients with advanced HF have an exceedingly high mortality. In a study of 14,946 Medicare patients implanted with CRT devices, the 1-year, 3-year, and overall mortality were 12%, 32%, and 37%, respectively [15].

With the high mortality rate and the estimated 30% nonresponder rate, an important question arises: are we implanting too late? Is a patient with late-stage CM with an LV end-diastolic dimension (LVEDD) of 7.5 cm really the best candidate? Or, should we be considering CRT therapy earlier for HF patients when they are NYHA class I or II, which could lead to reverse remodeling and longer-term benefits?

The role of CRT devices in the spectrum of CM and HF patients presents both challenges and opportunities. At one end are the patients with mild HF for whom acute CRT benefits may be subtle due to limited baseline symptoms but who will perhaps have a longer-term benefit with delayed progression of disease. This has been the impetus for recent studies such as the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial and the Multicenter Automatic Defibrillator Implantation Trial—Cardiac Resynchronization Therapy (MADIT-CRT). On the other end of the spectrum are those patients with severe, longstanding, irreversible disease who may have very limited response to CRT. Whether CRT implants earlier in disease course or limiting implants in certain severe HF patients who may be better served by cardiac transplant would optimize outcomes is a matter for debate.

Data Supporting Implantation in Mild Heart Failure

The data supporting CRT device implantation in mild HF patients is growing. The CONTAK CD (Guidant Corporation, Indianapolis, IN) trial was one of the first trials to include a group of patients with mild HF [8]. This study, published in 2003, included 490 patients (67% ischemic) with NYHA class II to IV congestive HF, EF of 35% or less, and QRS interval of 120 ms or longer. About one third of these patients had NYHA class II HF. Patients were randomly assigned to CRT with defibrillator (CRT-D) versus implantable cardioverter-defibrillator (ICD) with a composite primary end point that included worsening HF events. The subgroup of patients with NYHA class II HF did not show significant symptomatic improvements, with no change in maximal oxygen consumption (VO_2 max), 6-minute walk, or quality of life (QOL). However, there were reduced LV volumes (LVEDD and LV end-systolic diameter [LVESD]) that were statistically significant, though the relative improvement wasn't as large as in patients with more advanced HF.

The MIRACLE (Multicenter InSync Randomized Clinical Evaluation) ICD II trial [16] was published in 2004 and focused on patients with NYHA class II HF (47% ischemic CM) with EF of 35% or less, QRS interval less than 130 ms, and LVEDD of 5.5 cm or more referred for secondary prevention ICD implant. The authors compared CRT-D versus ICD with a primary end point of peak VO_2 max. The prespecified secondary end points were NYHA class, QOL score, 6-minute walk, and indices of remodeling. While the study didn't meet its primary end point, there was evidence suggesting reverse remodeling (improved EF and reduced LV end-systolic volume [LVESV] and LV end-diastolic volume [LVEDV]), but no improvement in NYHA class or QOL.

Bleeker and colleagues [17] reported a small study of 55 patients with NYHA class II HF and found that LV function significantly improved based on improved EF and reduced cardiac volumes, but NYHA class remained unchanged.

These early studies suggested the importance of measures of reverse remodeling as a secondary end point, which then were included in multicenter studies such as REVERSE and MADIT-CRT. In addition, patients with NYHA class I HF also were enrolled in these trials, which was not the case in earlier studies.

The REVERSE trial was the first randomized double-blind trial of CRT in NYHA class I and II HF. The study enrolled 610 patients from 73 centers throughout Europe, Canada, and the US from 2004 to 2006. Inclusion criteria included NYHA class I and II HF with LVEDD over 55 mm, EF less than 40%, and QRS interval over 120 ms. The mean EF in this study was 26%, with a mean LVEDD of 7.0±0.9 cm versus 6.9±0.9 cm (P=0.65, CRT off vs CRT on groups) and mean QRS interval of 154±24 ms versus 153±21 ms (P=0.41). Ischemia was the cause of CM in 51% versus 56% (P=0.22). Most patients got an ICD in addition to CRT and were assigned to CRT on or CRT off for comparison.

The primary end point was a clinical composite that included clinical events in combination with changes in NYHA class and global assessment, with a secondary end point of LVESV index (LVESVi). At 12-month evaluation, the outcomes did not meet the primary end point but did reach the secondary end point of decrease in LVESVi. There was evidence of significant reverse remodeling and delayed time to first HF hospitalization [18].

MADIT-CRT was a multicenter study with 1820 patients in the US and Europe comparing ICD alone versus CRT-ICD. Inclusion criteria were similar to the REVERSE trial but with the criterion of EF less than 30%. Ischemic patients with NYHA class I or II HF were included, but only nonischemic patients with NYHA class II HF were included. The primary end point was all-cause mortality or HF events. The secondary end point was change in LVESD. There was a 24-month minimum follow-up, with a mean of 2.4 years.

The study met the primary end point driven by a decrease in HF events (41% reduction). There was equal benefit in both patients with ischemic CM and patients with nonischemic CM. While the study included patients with a QRS interval over 130 ms, most benefit was seen in those with QRS interval over 150 ms (64.2% of patients). Significant reverse remodeling was seen, with more benefit in women than men in a retrospective analysis. Not surprisingly, patients with left bundle-branch block (LBBB) seemed to do better than non-LBBB patients [19••].

The Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) was a double-blind trial that included 1798 patients with NYHA class II or III HF, QRS interval of 120 ms or more, and EF of 30% or less. Patients were randomly assigned to ICD versus CRT-ICD. While the initial proposal involved enrolling patients with NYHA class II and III HF, the study primarily enrolled patients with NYHA class II HF because CRT implantation in patients with NYHA class III HF became part of the guidelines during enrollment. The HF etiology was ischemic in 68.7% of the patients and the mean QRS duration was 157 ms in nonpaced patients. The study did include patients with atrial fibrillation who were rate controlled (12.7% vs 12.8%; P=not significant), a patient population not included in either MADIT-CRT or REVERSE.

The study met its primary end point of HF hospitalizations or all-cause mortality (33.2% in CRT-ICD group versus 40.3% in ICD-only group; $P<0.001$). When only patients with NYHA class II HF were considered, there was a statistically significant decrease in primary end point, cardiac mortality, all-cause mortality, and hospitalizations due to HF. The mean follow-up was 40±20 months. More benefit was seen for women and those with LBBB, similar to MADIT-CRT [20••].

In 2010, Lubitz and colleagues [21] published a meta-analysis of the combined results of REVERSE and MADIT-CRT. They found a reduction in HF events and significant LV reverse remodeling, but no mortality benefit was seen. In 2011, Santangeli and colleagues [22•] published a meta-analysis of available data for CRT in mild HF. This study included results from five trials, including CONTAK-CD, MIRACLE ICD-II, REVERSE, MADIT CRT, and RAFT, for a total of 4213 patients with mild HF (NYHA class I or II). When these data were pooled, CRT appeared to reduce mortality and HF events in addition to showing significant LV reverse remodeling (based on EF and LVESVi improvements). The mortality benefit was driven by the inclusion of the RAFT trial data, which were not included in the review by Lubitz et al. [21].

Based on the definition of the American College of Cardiology/American Heart Association HF stages [23] and NYHA HF classes, these patients are asymptomatic or minimally symptomatic, and therefore, the use of clinical improvement end points may be inappropriate. In addition, these studies were never individually powered to show a decrease in mortality. However, if these studies consistently show that CRT can modify disease progression and improve parameters of LV function, size, and EF, then this may be sufficient evidence to prove the cost is worth the benefit.

The potential importance of reverse remodeling seen in these studies should not be underestimated. There is evidence that patients who show reverse remodeling are more likely to have long-term survival benefits. Specifically, decrease of LVESV of at least 10% is a strong predictor of long-term mortality [24]. This potential mortality benefit from reverse remodeling is not a new concept. Earlier studies on drug therapy have demonstrated similar benefits [25–27]. This idea makes intuitive sense and has led many to hypothesize that earlier implantation of CRT devices in HF could provide mortality benefit. While studies in early stage HF did not show consistent survival benefit, it is possible that with longer follow-up there could be a significant effect.

Additional potential benefits of CRT response with associated LV reverse remodeling were demonstrated in a retrospective analysis of patients from MADIT-CRT. When CRT responders (based on improvement in LVESV) were compared to nonresponders and ICD-only patients, there was a significant (55%) reduction in ventricular arrhythmias requiring ICD therapies. In addition, the authors found that patients with a greater degree of LV reverse remodeling had more significant reductions in ventricular arrhythmias (20% reduction in arrhythmias for every 10% decrease in LVESV). This finding is well known in the CRT literature for patients with NYHA class III and IV HF [28•, 29–32]. While a mortality benefit was seen for CRT without ICD therapy in patients with NYHA class III and IV HF in the Cardiac Resynchronization in Heart Failure (CARE-HF) study, the mechanism of this mortality benefit is not completely clear. Reduction in arrhythmia burden and the associated detrimental myocardial effects of such arrhythmias may play a role. Reduction in ventricular arrhythmias and ICD shocks is not inconsequential, as previous studies have shown not only decreased QOL, but also increased mortality in patients who receive either appropriate or inappropriate shocks [33–35].

Data Demonstrating Lack of Response in Severe Cardiomyopathy

Early studies and guidelines required a certain amount of LV enlargement to be considered for CRT. Yet, intuitively, a ventricle that has dilated beyond a certain point seems less likely to recover with resynchronization, and there is evidence to support this concept.

A recent study by Verhaert et al. [36] suggested that patients with less LV dilation may do better than those patients with more advanced dilation. There is also evidence that patients with NYHA class IV HF have worse outcomes than those with less advanced HF and show little additional benefit if on optimal medical therapy [15, 37].

In 2008, Gradaus et al. [38] published their evaluation of 122 consecutive patients with indications for CRT implantation. They found that both LVEDD and LVESD were univariate predictors of response to CRT, with LVESD found to be a multivariate predictor. Achilli and colleagues [39] followed 133 patients with NYHA class II to IV congestive HF from multiple centers. They found that a smaller LVESD was a predictor of response to CRT. Vidal and colleagues [40] followed 147 patients with NYHA class III to IV HF for 12 months. The study demonstrated that elevated LVEDV and increased mitral regurgitant orifice area at baseline were independent predictors of poor response to CRT. The responders in this study had a LVEDV of 193±67 mL compared to the nonresponders, who had a LVEDV of 208±80 mL.

In 2009, Antonio et al. [41] looked at so-called "super-responders," a term used to describe patients whose LV function and anatomy returned to near normal values. Patient with this dramatic response to CRT in their study had a shorter duration of HF symptoms and a smaller LVEDD, suggesting that longer periods of dysfunction led to less likelihood of pronounced response. The correlation of shorter duration of CM and smaller baseline LV dimension with super-response also was seen in the chronic RV pacing population upgraded to CRT [41, 42].

Other factors that may relate to more severe disease, such as development of RV dysfunction and increased infarct size, also may play a role. As patients develop progressive LV dysfunction, associated RV dysfunction also may develop. Evidence from recent studies suggests that RV dysfunction may be a further predictor of poor response to CRT [43]. Increased infarct size also may affect response, as it is known that patients with infarcted posterolateral walls have worse outcomes with CRT [44, 45]. These patients may do worse after suboptimal LV pacing sites are chosen.

Patient Selection

While the early stage patients have limited inclusion in clinical trials, many patients with disease that is potentially too advanced to benefit from CRT have been implanted. The inclusion of such end stage patients in clinical trials and real world practice may be a contributing factor to the about 30% nonresponder rate for CRT [46]. Much like valvular heart disease, there may be a point in the progression of LV dysfunction beyond which CRT will not be of benefit. Unfortunately, the data on this topic are limited. The complex substrate means there are numerous reasons patients do not respond to CRT therapy, and to date, there have been limited data to assist cardiologists in deciding which patients are most or least likely to benefit from CRT.

The use of echocardiographic dyssynchrony has largely fallen out of favor due to inconsistent findings and the results of the Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) study [47]. While the use of echocardiographic dyssynchrony is of unclear value, data available to date still suggest that electrical dyssynchrony (prolonged QRS duration) predicts greater benefit from CRT. The Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (RETHINQ) trial failed to show benefit from CRT in patients with a QRS duration less than 130 ms, even though enrollment criteria required echocardiographic evidence of dyssynchrony [48].

Based on the data from MADIT-CRT, the FDA expanded the approval for CRT devices in 2010. The new labeling includes patients with LBBB and NYHA class II HF symptoms with an EF of 30% or less and QRS of 130 ms or more. It also includes patients with NYHA class I HF who have an ischemic etiology. The American Heart Associated/American College of Cardiology/Heart Rhythm Society guidelines have not been updated since the FDA made its modification. However, the European Society of Cardiology (ESC) did expand its guidelines the same year. They were more limited in their approval, allowing only patients with NYHA class II HF with a QRS duration of 150 ms or more, and no patients with NYHA class I HF. The exclusion of patients with NYHA class I HF in the ESC guidelines was likely based on the limited number of those patients included in REVERSE and MADIT-CRT, and the fact that in retrospect, these patients did not derive a statistically significant benefit [49].

Conclusions

Device-based HF management has had significant impact on the field. The use of these devices has expanded beyond the use for pacing and tachyarrhythmia therapy. Remote monitoring and the ability to follow parameters related to fluid retention based on thoracic impedance changes (OptiVol [Medtronic Inc., Minneapolis, MN]) has allowed for remote outpatient follow-up of these patients. Other

technologies such as direct left atrial pressure sensors are also being evaluated [50]. The utility of these additional features may add further benefit to earlier implantation.

Ultimately, the physicians will have to weigh the risks and benefits of implanting a CRT device earlier in a patient's HF clinical course. A reasonable argument can be made that the addition of an LV lead to an already planned ICD implant is of limited additional risk and has the potential for significant benefit to the patient over time. However, LV lead placement is not completely benign, as MADIT-CRT did demonstrate higher complication rates in the CRT arm [19••]. In addition, an economic impact of the potentially large increase in CRT implants will have to be assessed. Continued efforts to risk-stratify patients to decrease nonresponder rates, including improved ability to determine which patients have such severe irreversible disease that they would be unlikely to benefit and perhaps should be referred directly for transplant, is also essential.

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