Congestive heart failure (CHF) is a disease process characterized by fibrosis, left ventricular (LV) dilatation and dysfunction, and adverse remodeling. Abnormalities in myocardial substrate can occur from myocardial infarction due to obstructive coronary artery disease, diffuse scarring from myocarditis, and other non-ischemic cardiomyopathies, as well as a variety of other conditions. Often, LV remodeling and dysfunction occur before significant symptoms are manifest. Conduction system disease can exacerbate this dysfunction. Almost two decades ago, early treatment with angiotensin-converting enzyme inhibitors (ACE-I) and beta-adrenergic blockers showed improvements in morbidity and mortality, as well as a variety of other conditions. Often, LV remodeling and dysfunction occur before significant symptoms are manifest. Conduction system disease can exacerbate this dysfunction. Almost two decades ago, early treatment with angiotensin-converting enzyme inhibitors (ACE-I) and beta-adrenergic blockers showed improvements in morbidity and mortality, as well as reverse cardiac remodeling among patients with chronic systolic heart failure.1–4 Many of these benefits were observed in patients with more mild to moderate CHF. Therefore, aggressive medical therapy has become the standard of care in treating patients with LV dysfunction regardless of functional status or symptoms. This strategy is underlined by the American College of Cardiology/American Heart Association staging of heart failure, which emphasizes the importance of risk factors and the presence of structural disease in addition to symptoms for the definition and treatment of CHF.5

Cardiac resynchronization therapy (CRT) has well-established benefits in the treatment of moderate to severe heart failure in selected patients, particularly those with electrical dyssynchrony as manifest by prolonged QRS duration. The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) and Cardiac Resynchronization in Heart Failure (CARE-HF) trials both showed the potential survival benefits that could be realized using CRT with or without defibrillator therapy.6,7 Other studies have shown that CRT can decrease myocardial workload and improve the efficiency of myocardial contraction.8,9 A subanalysis of the CARE-HF trial suggested that patients who reported less severe CHF symptoms (New York Heart Association (NYHA) Functional Class I or II) were just as likely to have mortality and symptomatic benefit as those with more severe symptoms in this trial.10 This suggested that it may be appropriate to use CRT to target the underlying disease process, rather than limiting its use to those with only severe symptoms refractory to medical therapy. That is, perhaps like beta-blockers and ACE-I, CRT should be used early for the primary prevention of CHF among patients with abnormal substrate.

In the past two years, this theory has been tested in two randomized controlled clinical trials, which showed that CRT has beneficial effects in mild CHF. The Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) and Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) studies showed that CRT therapy in mild CHF (NYHA Class I–II) with depressed LV ejection fractions and QRS prolongation can decrease hospitalizations and CHF “events”, as well as promote reverse remodeling with
significant reductions in LV chamber size and improvements in systolic function. Neither trial was expected nor powered to demonstrate a mortality benefit, as most of these patients were treated with implantable cardioverter-defibrillators (ICDs) for primary prevention of sudden cardiac death, and follow-up was only for several years. However, the European cohort from REVERSE who received CRT showed a trend toward improved survival that approached statistical significance (HR = 0.40, p = 0.09).

More recently, the Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) was the first trial to demonstrate that CRT in addition to ICD therapy reduced mortality in patients with mild CHF. In this study of almost 1800 patients with predominantly NYHA Class II CHF (80%) and a QRS duration of \(\geq 120 \text{ ms}\), CRT defibrillator (CRT-D) therapy was associated with a 25% relative risk reduction in death compared with ICD alone (95% CI 0.62–0.91, \(p = 0.003\)). This mortality benefit was of similar magnitude in both NYHA Class II and III patients but only reached statistical significance in the NYHA Class II group. In agreement with MADIT-CRT and REVERSE, RAFT also demonstrated that CRT was associated with decreased heart failure hospitalizations.

In selecting patients who will best benefit from CRT, in both primary and secondary prevention of CHF, several factors need to be considered. One key factor that has been associated with clinical response in all three of the major trials of CRT in mild CHF is QRS duration. Subgroup analysis in REVERSE, MADIT-CRT, and RAFT showed that patients with QRS durations \(\geq 150 \text{ ms}\) and with left bundle branch morphology on the unpaced electrocardiogram had significant improvements in clinical endpoints as well as remodeling. Preliminary data from the REVERSE study show that patients in the highest quartiles of QRS duration receive the greatest benefits, whereas those with QRS durations of 120–136 ms may have clinical deterioration with CRT and have less dramatic improvements in LV size and function (Gold et al, AHA Scientific Sessions 2009). Follow-up analyses of the REVERSE and MADIT-CRT populations have both shown that the beneficial effects of CRT on LV remodeling are associated with clinical outcomes.

As noted above, in addition to the role of QRS duration, morphology is also a key factor in CRT selection and response in mild CHF. It is important to note that most patients in these studies had left bundle branch block morphology, and it was these patients who seemed to derive the clinical benefits from CRT in subgroup analyses. Clinical response to CRT in patients with right bundle branch block and non-specific intraventricular conduction delays is less well established.

Many implanters of CRT devices feel that LV lead position also plays an important role in patient response, although recent data from the COMPANION trial imply that an anterior lead location yields similar benefits to more “optimal” lateral or posterior lead positions. The etiology of CHF may also impact the degree of response, as demonstrated in a subgroup from REVERSE. Non-ischemic patients may have a greater remodeling benefit; however, etiology does not appear to be an independent predictor of response in any of the three major trials. All these data are very similar to studies of advanced heart failure where QRS duration and morphology are also strong predictors of acute hemodynamic response, reverse remodeling, and clinical outcomes in many trials.

In conclusion, primary prevention of cardiac disease is an essential component of comprehensive cardiovascular care today. In addition to medical therapy, CRT has now been shown to have morbidity and mortality benefits in patients with less severe CHF symptoms, and its use should be expanded to this population. Although the expense of delivering this therapy is a concern, recent data suggest that CRT is a cost-effective intervention in mildly symptomatic heart failure and will quite possibly become more cost-saving over longer follow-up periods, as patients avoid hospitalizations and realize mortality benefits. Careful selection and targeting of those patients with wider QRS durations and left bundle branch block morphology should enable physicians to achieve favorable outcomes and avoid potential detrimental effects of chronic pacing.

References


