REVIEW

Cardiac Resynchronization Therapy: Who Benefits?

Jason S. Chinitz, MD, Andre d'Avila, MD, PhD, Martin Goldman, MD, Vivek Reddy, MD, and Srinivas Dukkipati, MD

ABSTRACT

Background: Cardiac resynchronization therapy (CRT) has been well established in multiple large trials to improve symptoms, hospitalizations, reverse remodeling, and mortality in well-selected patients with heart failure when used in addition to optimal medical therapy. Updated consensus guidelines outline patients in whom such therapy is most likely to result in substantial benefit. However, pooled data have demonstrated that only approximately 70% of patients who qualify for CRT based on current indications actually respond favorably. In addition, current guidelines are based on outcomes from the carefully selected patients enrolled in clinical trials, and almost certainly fail to include all patients who might benefit from CRT.

Findings: The identification of patients most likely to benefit from CRT requires consideration of factors beyond these standard criteria, QRS morphology with particular consideration in patients with left bundle-branch block pattern, extent of QRS prolongation, etiology of cardiomyopathy, rhythm, and whether the patient requires or will eventually need antibradycardia pacing. In addition, the baseline severity of functional impairment may influence the type of benefit to be expected from CRT; for example, New York Heart Association class I patients may derive long-term benefit in cardiac structure and function, but no benefit in symptoms or hospitalizations can be reasonably expected. In contrast, certain New York Heart Association class IV patients may be too sick to realize long-term mortality benefits from CRT, but improvements in hemodynamic profile and functional capacity may represent vital advances in this population.

Conclusion: This review evaluates the evidence regarding the various factors that can predict positive or even detrimental responses to CRT, to help better determine who benefits most from this evolving therapy.

Key Words: biventricular pacing, cardiac resynchronization therapy, cardiomyopathy, dyssynchrony, heart failure, implantable cardioverter defibrillator

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INTRODUCTION

Cardiac resynchronization therapy (CRT) is an effective therapy to correct impaired ventricular electromechanical coupling, or dyssynchrony. In many, but not all, patients with heart failure (HF), it can produce benefitial hemodynamic effects and improved outcomes. Identification of the subset of patients most likely to respond favorably to CRT is the primary clinical challenge. Several large clinical trials have established the efficacy of CRT to improve peak oxygen consumption (VO_2), 6-minute walking distance (6MWD), quality of life (QoL) scores, left ventricular (LV) size and function, mitral regurgitation severity, and functional capacity in most HF patients with New York Heart Association (NYHA) class III to IV symptoms, severely impaired LV function, sinus rhythm, and significant QRS prolongation. The Comparison of Medical Therapy, Pacing, and Defibrillation on Heart Failure (COMPANION)[1] and the Cardiac Resynchronization-Heart Failure (CARE-HF)[2] trials subsequently established significant improvements in hospitalizations for HF and mortality from CRT, either alone (CRT-P) or in combination (CRT-D) with an implantable cardioverter defibrillator (ICD), in these selected patients. This overall benefit is similar to the efficacy reported for angiotensin-converting enzyme inhibitor[3] or β-blocker treatment[4] in patients with HF, and is additive to this medical therapy.

Professional societies in the United States and Europe have adopted strong recommendations in support of CRT. Both the 2008 American College of

From the Mount Sinai School of Medicine, New York, NY. Received March 7, 2013; final revision received March 12, 2014. Address correspondence to J.S.C.; e-mail: jason.chinitz@mountsinai.org

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Cardiology Foundation/American Heart Association/Heart Rhythm Society (ACCF/AHA/HRS) Guidelines for Device-based Therapy,[5] and the 2010 European Society of Cardiology (ESC) Guidelines on Device Therapy in Heart Failure,[6] gave CRT a class I indication for NYHA class III and ambulatory class IV patients in sinus rhythm, with LV ejection fraction (LVEF) ≤35% and QRS duration >120 ms. In 2012, the ACCF/AHA/HRS released a focused update modifying the class I indication for CRT only to patients with NYHA class II, III, and ambulatory class IV symptoms with left bundle-branch block (LBBB) and QRS duration ≥150 ms (Table 1).[7] However, pooled data have demonstrated that only approximately 70% of patients who qualify for CRT based on current indications actually respond favorably.[8] In addition, current guidelines are based on outcomes from the carefully selected patients enrolled in clinical trials and almost certainly fail to include all patients who might benefit from CRT. Important questions remain, such as whether less symptomatic patients respond to CRT, how QRS morphology or extent of QRS delay affects response, and the effect of tachy- and brady-arrhythmias on CRT efficacy. More recently, the effect of CRT has been evaluated in more diverse populations of patients with HF to help better appreciate the various factors that can predict positive or even detrimental responses to CRT beyond currently accepted criteria and to help better determine who benefits from this evolving therapy.

ROLE OF CRT ACCORDING TO NYHA FUNCTIONAL CLASS

NYHA Class IV Heart Failure

Although the benefit of CRT in patients with HF who have advanced symptoms has been established in multiple studies, only small numbers of patients in these trials have been classified as NYHA class IV. These highly symptomatic patients generally have limited myocardial reserve and poor survival, and thus it has been suggested that they may not realize the time-dependent benefits of CRT on cardiac function, or they may be destabilized by the implant procedure resulting in worse short-term outcomes. The COMPANION trial included 217 NYHA class IV patients (14% of the total population, mean LVEF 21%), all of whom were considered "ambulatory" in that they had no hospital admissions or vasoactive therapy in excess of 4 hours in the month before enrollment.[1] A post hoc analysis of this subset of patients revealed a significant improvement compared with that from optimal medical therapy (OMT) in time to all-cause mortality or hospitalization for both CRT-P (hazard ratio [HR], 0.64; $P = 0.02$) and CRT-D (HR, 0.62; $P = 0.01$), an improvement in QoL ($P < 0.01$), as well as a significant functional improvement (NYHA class improved in 78% in the CRT group compared with 52% in OMT; $P < 0.01$). However, only a nonsignificant trend toward benefit in all-cause mortality alone was demonstrated (HR, 0.67; $P = 0.11$ for CRT-P; HR, 0.63; $P = 0.06$ for CRT-D),[9] although no NYHA class IV patients died during the implantation hospitalization.

CRT also may provide meaningful functional and hemodynamic benefits in the sickest class IV HF patients as well. In one small cohort of 10 patients with inotrope-dependent class IV HF who successfully underwent CRT implantation, NYHA functional class improved in 9 of 10 patients, intravenous inotropes were discontinued in 9 patients 15 ± 14 days after CRT implant, mean LV end systolic volume (LVESV) decreased (from 174 to 150 mL; $P < 0.01$), and mean LVEF increased (from 23% to 32%; $P < 0.05$).[10] Another recent small study evaluated the use of temporary LV pacing for patients in acute refractory cardiogenic shock and evidence of LV dyssynchrony and found acute hemodynamic improvements in 67%, with an impressive (but statistically insignificant) reduction in in-hospital mortality (30% vs 80%; $P = 0.119$) in these "responders."[11] The 2012 ACCF/AHA/HRS guidelines include ambulatory class IV patients in the class I recommendation for CRT but note that data are few in these patients and comment that the sickest patients, who are dependent on inotropic therapy, have refractory fluid retention, or have progressive renal dysfunction, are at highest risk for complications from implantation and early mortality, and also are unlikely to benefit significantly from concomitant defibrillator therapy.[7] The 2010 ESC guidelines also support CRT in ambulatory class IV patients, but recognize that the use of CRT in these patients is supported to improve morbidity, but not mortality.[6]

CRT in NYHA Class I and II Heart Failure

Recent studies have established a role for CRT in patients with less symptomatic HF. To our knowledge, the Resynchronization Reverses Remodelling in Systolic Left Ventricular Dysfunction (REVERSE) study[12] was the first to evaluate this hypothesis and included 610 patients with NYHA class I (18%, all previously symptomatic) and NYHA class II (82%) HF symptoms. It concluded that in these mildly symptomatic patients, CRT improves LV remodeling and reduces HF hospitalizations, but does not significantly improve symptoms or exercise capacity in these patients with little functional impairment at baseline.[12] The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT)[13] expanded on the REVERSE findings and compared CRT-D with ICD alone in 1820 patients with NYHA class I and II symptoms, LVEF ≤30%, and QRS interval ≥130 ms. The executive committee stopped the trial early after a mean follow-up of 2.4 years as the primary endpoint (death from any cause or nonfatal HF event) was significantly improved by CRT-D (17.2% vs 25.3%; $P = 0.001$). This benefit of CRT in these class I