Critical Appraisal of the Use of Cardiac Resynchronization Therapy Beyond Current Guidelines

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Cardiac resynchronization therapy (CRT) is an effective treatment for patients with drug-refractory, chronic heart failure. Multiple single-center and multicenter studies have shown significant reductions in left ventricular (LV) volumes and an increase in LV systolic function. More importantly, CRT reduces mortality and morbidity during long-term follow-up. Current guidelines consider CRT as a Class I indication for heart failure patients in New York Heart Association (NYHA) functional class III to IV with depressed LV ejection fraction ≤35% and a wide QRS complex (≥120 ms). However, the benefits of this therapy could possibly be extended to selected subgroups of patients who do not fulfill these criteria. These subgroups include patients with mildly symptomatic heart failure and patients with a narrow QRS complex (<120 ms). Results from recent multicenter controlled clinical trials including heart failure patients in NYHA functional class I to II or with a narrow QRS complex are equivocal. Although expanding CRT to patients with a narrow QRS complex seems currently not likely, the benefits of CRT in mildly symptomatic patients are more evident. Perhaps attenuation of disease progression will prove to be a successful new treatment strategy in heart failure patients in the future. In addition, multimodality cardiac imaging will allow optimizing responder rate in patients undergoing CRT according to current guidelines. (J Am Coll Cardiol 2010;56:754–62) © 2010 by the American College of Cardiology Foundation

CRT in Patients With Narrow QRS Complex

Prolonged QRS complex duration (≥120 ms) indicates the presence of cardiac dyssynchrony that can be corrected with CRT. The landmark trials that demonstrated the efficacy of CRT included heart failure patients with QRS complex durations >120 ms. Therefore, current guidelines recommend CRT only in heart failure patients with QRS complex duration ≥120 ms (10). However, data from the CONQUEST (Congestive Heart Failure and QRS Duration: Establishing Prognosis) study, including more than 3,000 heart failure patients, demonstrated that 42% of the patients with systolic heart failure had a QRS duration <120 ms (14). On the basis of these data and according to current guidelines, a significant percentage of heart failure patients would not be amenable for CRT. The assessment of LV mechanical dyssynchrony with different imaging modalities may identify heart failure patients who could benefit from CRT, despite having a narrow QRS complex. Indeed, several echocardiographic studies have demonstrated that 40% to 50% of heart failure patients with a narrow QRS complex...
may also exhibit LV dyssynchrony (15). This subgroup of patients with a narrow QRS complex, but with presence of LV mechanical dyssynchrony, may also benefit from CRT. To elucidate the effects of CRT on heart failure patients with a narrow QRS complex, several single-center studies were performed, providing encouraging results (Table 1) (16–19). In these trials, patients with a narrow QRS complex exhibited similar improvements in clinical parameters and LVEF as patients with a wide QRS complex. Comparable observations were made in the ESTEEM-CRT (Evaluation of CRT in Narrow QRS Patients With Mechanical Dyssynchrony From a Multicenter Study). This study included 68 patients with NYHA functional class III heart failure symptoms of QRS <120 ms, LVEF ≤35%, and LV mechanical dyssynchrony as defined by the standard deviation of time to peak systolic velocity of 12 segments (Ts-SD) >28.7 ms. All patients received CRT with defibrillator (CRT-D) and underwent invasive rate of rise in LV filling pressure testing for atioventricular optimization at implantation. Preliminary results of this trial were presented at the Heart Rhythm Society congress in 2008 (20). After 6 months of follow-up, a significant reduction in NYHA functional class (−0.7 ± 0.7; p < 0.01) was observed, accompanied by an improvement in quality-of-life score (−23 ± 21; p < 0.01). In contrast, however, no significant changes in peak VO₂ or LVEF were noted. The authors concluded from these results that patients with narrow QRS complex and LV dyssynchrony (using tissue Doppler imaging, Ts-SD) did not improve as measured by exercise performance and LV reverse remodeling.

The RethinQ (Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS) trial. The RethinQ trial is the first randomized multicenter study in patients with narrow QRS complex (<130 ms) and included a total of 172 heart failure patients in NYHA functional class III with an indication for an implantable cardioverter-defibrillator (ICD) (11). All patients showed LV mechanical dyssynchrony as assessed by echocardiographic techniques (96% as assessed with tissue Doppler imaging and 4% as assessed with M-mode echocardiography). After implantation of a CRT device with cardioverter-defibrillator capability, patients were randomized to the CRT group or the control group (no CRT). The study failed to demonstrate a significant difference in the primary endpoint (increase in peak oxygen consumption ≥1.0 ml per kilogram of body weight per minute during exercise testing at 6 months) between the CRT group and the control group. Secondary end points included change in quality-of-life score and change in NYHA functional class at 6 months of follow-up. Change in quality-of-life score was similar between the CRT group and the control group (−7 vs. −8; p = 0.91). However, at 6 months of follow-up, a significantly larger proportion of patients in the CRT group improved in NYHA functional class by ≥1 point compared with patients in the control group (54% vs. 29%; p = 0.006), although no differences in change in 6-min walk distance and LV volumes were noted between the 2 groups. When the analyses were performed according to baseline QRS complex duration, those patients with a QRS complex between 120 and 130 ms exhibited significant improvements in peak oxygen consumption and NYHA functional class, whereas those patients with a QRS <120 ms showed a significant improvement only in NYHA functional class (Fig. 1) (11).

Although RethinQ could not demonstrate conclusive evidence to support CRT in narrow QRS patients by its

<table>
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<th>Benefits of CRT on Symptomatic Heart Failure Patients With a Narrow QRS Complex: Results From Single-Center and Multicenter Trials</th>
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<td>Achilli et al. (16)</td>
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<td>Patient characteristics</td>
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<tr>
<td>No. of patients</td>
<td>14</td>
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<tr>
<td>Age (yrs)</td>
<td>68 ± 8</td>
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<tr>
<td>Male sex (%)</td>
<td>71</td>
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<td>Ischemic etiology (%)</td>
<td>29</td>
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<td>QRS duration (ms)</td>
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<td>LV dyssynchrony (ms)</td>
<td>43 ± 17</td>
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<td>Effects of CRT on clinical and echocardiographic parameters at follow-up</td>
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<tr>
<td>Reduction in NYHA functional class</td>
<td>1.6 ± 0.1</td>
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<td>Reduction in quality-of-life score</td>
<td>NA</td>
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<tr>
<td>Improvement in 6MWD (m)</td>
<td>94 ± 19</td>
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<td>Reduction in LV end-systolic dimensions</td>
<td>5.8 ± 0.2†</td>
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<td>Improvement in LVEF (%)</td>
<td>9 ± 1</td>
</tr>
</tbody>
</table>

*95% confidence intervals. †Diameter (mm). ‡Volume (ml).

CRT = cardiac resynchronization therapy; LV = left ventricular; LVEF = left ventricular ejection fraction; 6MWD = 6-min walk distance; NYHA = New York Heart Association.
primary end point of peak myocardial oxygen consumption, there was a significant improvement in NYHA functional class in the CRT group as compared with the control group. The limited benefits of CRT in patients with narrow QRS complex may be explained by the presence of short LV electrical activation delays as recently demonstrated (21,22). The time delay between onset of the QRS complex to the latest activated area of the left ventricle may indicate the amount of global LV dyssynchrony amenable to be corrected through CRT. In patients with left bundle-branch block morphology, the LV activation delays are usually longer than those observed in patients with narrow QRS complex or right bundle-branch block (RBBB). Indeed, patients with QRS duration >150 ms and left bundle-branch block morphology showed the highest response rates in recent multicenter trials (12,13). In contrast, patients with short LV activation delays or with the latest activated areas located far away from the vein targeted by the LV pacing lead (patients with RBBB or anterior myocardial scar) may show less clinical and echocardiographic improvement at mid- or long-term follow-up after CRT (23,24). In this regard, accurate identification of the latest mechanically activated areas to guide the LV lead positioning may help to improve the response rates to CRT. The use of noninvasive imaging techniques to evaluate either the electrical or mechanical substrate of LV dyssynchrony will help to identify the patients with narrow QRS complex or RBBB who will benefit from CRT.

It should be emphasized that the current 2 trials (ESTEEM-CRT and RethinQ) included few patients, had limited follow-up (up to 6 months), and did not focus on rehospitalization and long-term survival. Currently, there is a large prospective randomized trial ongoing that will focus on exactly these issues. The EchoCRT (Echocardiography Guided Cardiac Resynchronization Therapy) trial will include more than 1,000 patients, carefully selected by novel advanced echo techniques, evaluated by a single core laboratory before entrance in the study (25). Patients are randomized to CRT or no CRT, and patients in both study arms will receive an ICD. The primary end point is all-cause mortality or hospitalization for cardiovascular events during long-term follow-up.

There are several other ongoing studies evaluating the effects of CRT in heart failure patients with narrow QRS complex. The CRT-Narrow (Cardiac Resynchronization Therapy–Narrow-dp/dt) is a nonrandomized study that evaluates acute and midterm effects of CRT on LV function by invasive measures of LV performance and LV reverse remodeling (26). Finally, the EARTH (Evaluation of Resynchronization Therapy for Heart Failure) trial (27) will investigate the impact of LV mechanical dyssynchrony on clinical outcome of symptomatic heart failure patients with a narrow QRS complex (<130 ms). The results of these trials may determine the subsequent dissemination of CRT in this specific group of patients.

**CRT in Mild Heart Failure**

To date, the vast majority of patients in the large CRT trials were in NYHA functional class III and IV. The 2 largest trials that showed a survival benefit for CRT over optimal medical therapy alone included patients only in NYHA functional class III and IV. As a result, current guidelines consider CRT as a Class I indication only for heart failure patients in NYHA functional class III to IV (10). Much less is known about the effects of CRT in patients with mild symptoms of heart failure. Some studies have hypothesized that CRT in mildly symptomatic heart failure patients might prevent heart failure worsening. In the MIRACLE ICD II (Multicenter InSync Randomized Clinical Evaluation II) trial, 186 patients in NYHA functional class II with LVEF ≤35%, a QRS complex ≥130 ms, and a Class I indication for an ICD were implanted with a CRT-D device and then randomized to receive biventricular pacing (“CRT-ON,” n = 85) or no biventricular pacing (“CRT-OFF,” n = 101) (28). At 6 months of follow-up, patients in the CRT-ON group had a greater reduction in LV diastolic and systolic volumes (p = 0.04 and p = 0.01,
respectively). In addition, CRT-ON recipients showed statistically significant improvement in NYHA functional class and clinical composite (29) response (p < 0.05 and p < 0.01, respectively). There were no significant differences in improvement in peak oxygen consumption, 6-min walking distance, or quality-of-life scores (28). Similar results were reported by the CONTAK-CD (CONTAK-Cardiac Defibrillator) trial, with significant reductions in LV dimensions (5).

The results of CONTAK-CD and MIRACLE ICD II, together with the observation that LV reverse remodeling was a better predictor of long-term survival than clinical improvement (30), led to the use of LV reverse remodeling as an end point in clinical randomized CRT trials. Because patients with mild heart failure symptoms may also exhibit depressed LV function and wide QRS complex, 2 large clinical trials were conducted to investigate whether CRT could prevent or attenuate disease progression and induce LV reverse remodeling in this group (Table 2) (31,32).

The REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial. REVERSE was a randomized, double-blind trial investigating the effects of CRT in patients with asymptomatic and mildly symptomatic heart failure and a prolonged QRS interval (12). The study hypothesized that CRT might delay disease progression in heart failure patients with less severe symptoms by inducing LV reverse remodeling. Eligible patients were in NYHA functional class I or II for at least 3 months before enrollment. Patients were required to be in sinus rhythm with a QRS duration ≥120 ms, to have LVEF ≤40%, and to have an LV end-diastolic diameter ≥55 mm (Table 2).

The primary end point of the study was the heart failure clinical composite response (29). The main secondary end point was the absolute change in left ventricular end-systolic volume index (LVESVi) between baseline and 12 months of follow-up. A total of 610 patients were included between September 2004 and September 2006. After enrollment, 419 were randomized to CRT-ON and 191 were randomized to CRT-OFF. In the CRT-ON group, 16% worsened in their heart failure clinical composite response at 1 year, as compared with 21% of patients in the CRT-OFF group (p = 0.10) (Fig. 2). The LVESVi decreased significantly in the CRT-ON group (−18.4 ± 29.5 ml/m²), whereas no change in LVESVi (−1.3 ± 23.4 ml/m²) was observed in the CRT-OFF group (p < 0.0001). This decrease in LVESVi was even more evident in patients with a QRS duration ≥152 ms as compared with patients with a QRS duration <152 ms. Also, a significant increase in LVEF was observed in the CRT-ON group (+3.8%), whereas no significant change (+0.6%) was noted in the CRT-OFF group (p < 0.0001). Finally, CRT reduced the risk of heart failure hospitalization (hazard ratio [HR]: 0.46; p = 0.03).

Although REVERSE failed to show a difference in the primary end point, the results indicate that CRT can reverse LV remodeling and reduce the risk for heart failure hospi-
talization in mildly symptomatic heart failure patients (NYHA functional class I and II), thereby delaying disease progression in these patients.

Recently, Daubert et al. (33) reported the results from the 24-month follow-up of the European cohort of REVERSE. In this subgroup, the 262 European patients in REVERSE were followed for 24 months (in contrast to the 12-month follow-up in the main trial). Over this 24-month follow-up period, CRT resulted in less clinical worsening and an improvement in LV function. There was a significant reduction in the clinical composite end point in the CRT group (19% worsened in the CRT-ON group as compared with 34% of patients in the CRT-OFF group; \( p = 0.01 \)). In addition, LVESV decreased significantly in the CRT-ON group (decrease of 27.5 \( \pm \) 31.8 ml/m\(^2\) in the CRT-ON group vs. 2.7 \( \pm \) 25.8 ml/m\(^2\) in the CRT-OFF group; \( p < 0.0001 \)). Finally, a significant reduction in time to first heart failure hospitalization or death was observed in the CRT-ON group (HR: 0.38; \( p = 0.003 \)) (Fig. 3). These results provide further evidence that CRT might be useful in delaying heart failure worsening.

The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). The MADIT-CRT trial enrolled 1,820 patients between December 2004 and April 2008 (13). It was designed to determine whether CRT-D would reduce the risk of mortality and heart failure events as compared with ICD only in subjects with NYHA functional class I to II heart failure, LVEF \( \leq \) 30%, and QRS duration \( \geq \) 130 ms. Other end points included changes in left ventricular end-systolic volume (LVESV) at 1 year of follow-up, changes in LV end-diastolic volume at 1-year follow-up, and subject-specific rates of multiple heart failure events.

During follow-up, 187 of 1,089 patients (17.2%) in the CRT-D group reached the primary end point, as compared with 185 of 731 patients (25.3%) in the ICD-only group (HR: 0.66; 95% confidence interval [CI]: 0.52 to 0.84; \( p = 0.001 \)) (Fig. 4). This superiority of CRT-D over ICD only was driven by a 41% reduction in the risk of heart failure events. There was no difference in mortality between the groups, with a 3% annual mortality in both groups. Interestingly, the beneficial effect of CRT on the primary end point was greater in patients with a QRS duration \( \geq \) 150 ms than in patients with a QRS duration <150 ms (HR: 0.48, 95% CI: 0.37 to 0.64 vs. HR: 1.06, 95% CI: 0.74 to 1.52; \( p = 0.001 \) for interaction). In addition to these findings, a reduction of 52 ml in LV end-diastolic volume was observed at 1 year of follow-up in the CRT-D group, compared with a 15-ml reduction in the ICD-only group, \( p < 0.001 \) (Fig. 5). Finally, a reduction of 57 ml in LVESV was observed in the CRT-D group, as compared with 18 ml in the ICD-only group, \( p < 0.001 \) (Fig. 5). The results of MADIT-CRT provide evidence that preventive therapy...
with CRT-D in heart failure patients with minimal heart failure symptoms, but a wide QRS complex and a low LVEF, decreases the risk of heart failure events.

Currently, there is another large trial ongoing in patients with mild heart failure symptoms. RAFT (Resynchronization/Defibrillation for Ambulatory Heart Failure Trial) will include 1,800 subjects in NYHA functional class II, LVEF ≤30%, and QRS duration ≥120 ms (34). Patients will then be randomized to receive either ICD or CRT-D in a 1:1 fashion. The primary end point is a composite of total mortality and heart failure hospitalization during long-term follow-up. The results of this large randomized trial are eagerly awaited.

Future Perspective

The future of CRT might be heading toward 2 separate directions: 1) to improve the responder rate in patients undergoing CRT according to current guidelines; and 2) to expand treatment to patient groups that might also benefit from CRT.

Improving response rate. In order to optimize CRT response rate, numerous studies have focused on identifying possible responders before implantation by means of echocardiography. A recent subanalysis of the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) trial revealed that patients with more extensive LV dyssynchrony had more pronounced reduction in LVESV at 6 months of follow-up (35). This finding emphasizes the relation between pre-implantation LV dyssynchrony and outcome after CRT. Conversely, it remains currently unclear which measure of dyssynchrony should be used and which cut-off value for dyssynchrony should be considered to select patients for CRT implantation. In addition to the use of echocardiographic measurements to predict response to CRT, a more recent study identified several electrocardiography (ECG) patterns as potential determinants of CRT response (36). In particular, longer LV activation times, lower QRS scar score, and evidence of wavefront fusion after CRT initiation, as measured from the surface ECG, were potent markers of significant LV reverse remodeling at 6 months of follow-up. Using an algorithm based on these specific ECG parameters may also further optimize patient selection for CRT.

Furthermore, the extent and location of myocardial scar and the presence of a suitable venous anatomy to place the LV pacing lead at the latest activated area of the left ventricle are crucial determinants of a favorable response to CRT (37). Therefore, an integrated approach evaluating LV dyssynchrony, total myocardial scar burden, and cardiac venous anatomy may refine the selection of potential responders to CRT. Currently, magnetic resonance imaging, nuclear imaging, and multidetector-row computed tomography constitute valuable imaging techniques to evaluate all these parameters (37).

Finally, the LV pacing lead location may be of importance. Several studies have indicated that positioning the LV lead outside the region of latest activation may reduce the response rate after CRT (38,39). In addition, (transmural) scar at the location of the LV pacing lead may also result in nonresponse after CRT, making scar assessment of significant importance in ischemic heart failure patients before device implantation (40). Taking all this into consideration, an integrated approach on these factors may improve response to CRT, rather than relying on any single measure (Fig. 6) (41).

After CRT device implantation, cardiac imaging plays a central role in the evaluation of response to CRT. Among several parameters proposed to define response to CRT, reduction in LVESV ≥15% has demonstrated to be independently related to improved long-term clinical outcome.
Perhaps the most important issue raised by the results of these recent large trials is whether the current indications for CRT should be expanded. The performance of current inclusion criteria for CRT implantation may be suboptimal because they may exclude some groups of patients who may benefit from CRT. Indeed, definitions of heart failure are imprecise, and the majority includes typical symptoms and objective evidence of LV dysfunction. Currently, only heart failure patients in NYHA functional class III to IV and with LVEF ≤35% are considered candidates for CRT implantation. However, these inclusion criteria exclude patients in NYHA functional class I to II who may benefit from CRT by preventing progression of the disease, as recently observed in the MADIT-CRT and REVERSE trials (12,13).

Both trials have demonstrated the effect of CRT to improve LV function and prevent heart failure progression in mildly symptomatic heart failure patients (12,13), and expansion of guidelines for CRT selection may be considered. Perhaps attenuation of disease progression, rather than reversing severe heart failure, will prove to be a successful new treatment strategy in heart failure patients in the future, although more data on survival benefit in these patients may be needed before definitive conclusions can be drawn.

Conversely, the results from ESTEEM-CRT and RetinQ (11,20) make the expansion of CRT to heart failure patients with a narrow QRS complex currently unlikely. However, the results of the ongoing EchoCRT trial will determine whether CRT is an effective treatment option in this specific group of patients (25). The last mentioned trial will be the first to use the newly proposed speckle tracking echocardiographic technique for evaluation of LV mechanical dyssynchrony. This novel methodology permits the assessment of active myocardial deformation, provides accurate information on LV dyssynchrony, and permits identification of the area of latest mechanical activation. This more robust method of dyssynchrony assessment may improve selection of suitable candidates for CRT.

Finally, there are a few other cardiac conditions for which CRT indication is still controversial. It has been suggested that atrial fibrillation may convey a lower response rate to CRT (46,47). A recent meta-analysis including 1,146 heart failure patients compared the clinical and echocardiographic response to CRT in patients with sinus rhythm (n = 797) or atrial fibrillation (n = 367) (48). Both patient groups showed significant improvement in NYHA functional class, LVEF, and long-term survival after CRT; the need for ativoventricular junction ablation in atrial fibrillation is still not entirely clear (46,47,49).

Other clinical conditions, such as upgrading from right ventricular pacing, right-sided heart failure, and congenital heart disease, have also demonstrated clinical benefit from CRT (50–52). Patients with drug-refractory heart failure but preserved LVEF (>35%) and impaired LV filling may also benefit from CRT (53). However, more data are needed in these subpopulations.

**REFERENCES**


Key Words: cardiac resynchronization therapy • heart failure • review • outcome.