Recent Clinical Trials on Cardiac Resynchronization Therapy

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ABSTRACT
Cardiac resynchronization therapy (CRT) has emerged as a major therapeutic option in the management of patients with medically refractory heart failure. Its clinical application can be determined by patient’s performance, left ventricular ejection fraction (LVEF) level, degree of intraventricular conduction delay, and rhythm status. This paper reviews recent major clinical trials in the area of CRT.

Key words: heart failure, resynchronization

Introduction
The concept that ventricular dyssynchrony could start the vicious cycle of mechanical pump function and electrical conduction delay was proved in the MUSTIC and MIRACLE trials. Improved left ventricular (LV) function translated into improved mortality outcomes in the following larger clinical trials (COMPANION, CARE-HF). Cardiac resynchronization therapy (CRT) reverses the remodeling process by intervening in this vicious cycle. As a result of these large clinical trials, CRT has been emerging as a major therapeutic option in the management of patients with congestive heart failure (CHF). This paper reviews recent major clinical trials about CRT.

Summary of Recent CRT Clinical Trials
1. Benefits of CRT
The role of CRT in patients with CHF was first highlighted in the CARE-HF and COMPANION trials. The CARE-HF trial randomized 813 patients (New York Heart Association [NYHA] functional classification III–IV, left ventricular ejection fraction [LVEF] 35%, and QRS prolongation) for CRT or medical therapy. The COMPANION trial randomly assigned a similar population into 3 groups, as medical therapy, CRT alone, and CRT plus implantable cardioverter–defibrillator (ICD). These 2 studies showed significant reduction in total mortality or hospitalization rate (primary endpoint) as 20–37% of the patients who underwent CRT.
2. The role of CRT in patients with ICD indication

The indications for CRT and ICD overlap in the majority of patients with severe HF. The role of CRT in addition to ICD was demonstrated in the COMPANION trial and was confirmed in subsequent trials (RAFT, REVERSE, and MADIT–CRT) \(^{5-7}\) (Table 1). In the MADIT–CRT trial, 41% reduction in HF events was observed in patients with CRT with defibrillators (CRT–D) than in those with ICD only. In the RAFT trial, the total mortality was reduced by 29% in the ICD–CRT vs. the ICD only group.

3. The role of CRT in patients with mild to moderate HF

Early studies (CONTAKCD, MIRACLE ICDII, substudy of CARE–HF) showed that the use of CRT may extend to patients with mild HF.\(^{8}\) This concept was subsequently verified in the REVERSE–HF, MADIT–CRT, and RAFT trials.\(^{5-7}\)

MADIT–CRT tested the hypothesis that CRT might be beneficial in patients with mild HF. The study randomized 1,820 patients with LVEF <30%, QRS duration (QRSd) >120 msec, and NYHA class I or II to CRT–D or ICD alone. The primary endpoints (death or nonfatal HF) were significantly decreased in the CRT–D group. The clinical predictors of benefit from CRT–D vs. ICD alone were QRS of ≥150 msec, systolic blood pressure <115 mmHg, or left bundle branch block (LBBB) in patients with ischemic cardiomyopathy; female gender, the presence of diabetes mellitus, or LBBB predicted benefit in patients with nonischemic cardiomyopathy. This study emphasized the role of CRT intervening in the progression of LV dysfunction, even in patients with mildly symptomatic CHF and broadened the indication of CRT–D. Results from other randomized trials in patients with LVEF <40% and NYHA class I or II disease showed a mortality benefit from CRT (MIRACLE ICDII, REVERSE, MADIT–CRT, and RAFT [only NYHA class II patients]).

4. CRT in patients with right bundle branch block

Past CRT trials have mainly included patients with LBBB (right bundle branch block [RBBB] was present in only 5-13%), and thus the role of CRT in patients with RBBB is not clearly established. The current guidelines do not provide specific information on the QRS morphology. That is, CRT also can be indicated for those with RBBB as long as the QRSd criteria are satisfied. However, based on data from the Medicare ICD registry, RBBB, ischemic cardiomyopathy, NYHA class IV status, and advanced age were powerful adjusted predictors of poor outcome after CRT–D.\(^{9}\) In addition, benefit was observed only in the subgroup of patients with LBBB in the MADIT–CRT trial, and therefore, the US Food and Drug Administration (FDA) labeling limits CRT to patients with HF who have LBBB and who are belong to NYHA class I or II.\(^{7}\)

5. CRT in patients with AF

Approximately one-third of the patients with advanced HF have atrial fibrillation (AF), and the role of CRT in these patients may be disrupted by the rapid ventricular responses of AF. A meta-analysis comparing responses to CRT in patients with sinus rhythm vs. AF revealed that the NYHA functional class improved similarly for both groups, but patients with sinus rhythm showed greater relative improvement in the 6-minute walk test. Patients with AF, however, achieved a small but
Table 1. Major clinical trials

<table>
<thead>
<tr>
<th>Name</th>
<th>Population (n)</th>
<th>Inclusion</th>
<th>Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUSTIC SR</td>
<td>58</td>
<td>III, EF &lt;35%, QRS ≥ 150</td>
<td>6MWT, QoL, pVO₂, hospitalization</td>
<td>CRT-P improved: 6MWT, QoL, pVO₂, reduced hospitalization</td>
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<tr>
<td>MIRACLE</td>
<td>228-CRT</td>
<td>III-IV, EF &lt;35%, QRS ≥ 130</td>
<td>NYHA class, QoL, pVO₂</td>
<td>CRT-P improved: NYHA, pVO₂, 6MWT</td>
</tr>
<tr>
<td>(Abraham, NEJM 2002)</td>
<td>25-control</td>
<td></td>
<td></td>
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<tr>
<td>MIRACLE-ICD</td>
<td>186</td>
<td>II, EF&lt;35%, QRS ≥ 130</td>
<td>6MWT, QoL, hospitalization</td>
<td>CRT-D improved all from baseline (not ICD)</td>
</tr>
<tr>
<td>COMPANION</td>
<td>ICM NICM 1,520</td>
<td>III-IV, EF &lt;35%, QRS &gt; 120</td>
<td>All cause mortality or hospitalization</td>
<td>CRT-P/CRT-D: reduced endpoints HR 0.80 (CRT vs medical)</td>
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<td>(NEJM 2004)</td>
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<tr>
<td>CARE-HR</td>
<td>ICM NICM 813</td>
<td>III-IV, EF &lt;35%, QRS &gt; 120</td>
<td>All cause mortality or hospitalization</td>
<td>CRT-P/CRT-D: reduced endpoints HR 0.63</td>
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<tr>
<td>(NEJM 2005)</td>
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<tr>
<td>MUSTIC AF</td>
<td>59</td>
<td>III, EF &lt;35%, QRS ≥ 200</td>
<td>6MWT, QoL, pVO₂, hospitalization</td>
<td>CRT-P improved 6MWT, QoL, pVO₂, hospitalization</td>
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<tr>
<td>CONTAK-CD</td>
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<td>RAFT (Tang, NEJM 2010)</td>
<td>1,798</td>
<td>II, III, EF &lt;30%, QRS ≥ 120</td>
<td>death from any cause or hospitalization for HF</td>
<td>The addition of CRT to an ICD reduced rates of death and hospitalization for HT</td>
</tr>
<tr>
<td>REVERSE</td>
<td>610</td>
<td>I-III, EF &lt;40%, QRS ≥ 120</td>
<td>(i) % worsened by clinical composite endpoint, (ii) LVESVi, (iii) HF hospitalization, (iv) all-cause death</td>
<td>Primary endpoint NS; CRT-P/CRT-D reduced (i) and (iii) hospitalization but not (ii)</td>
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<td>(Linde, JACC 2008)</td>
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<tr>
<td>MADIT-CRT</td>
<td>ICM NICM 1,820</td>
<td>I-II, EF &lt;30%, QRS ≥ 130</td>
<td>(i) HF event or death, (ii) All-cause death, (iii) LVESV</td>
<td>CRT-D reduced (i) and (iii) but not (ii)</td>
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<td>(Moss, NEJM 2009)</td>
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<tr>
<td>MIACL-ICD II</td>
<td>186</td>
<td>II, EF &lt;35%, QRS ≥ 130</td>
<td>VE/CO₂, pVO₂, NYHA, QoL, 6MWT, LV volumes, LVEF</td>
<td>CRT-D improved: NYHA, VE/CO₂, volumes, LVEF</td>
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<tr>
<td>(Abraham, Circulation 2004)</td>
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CRT: cardiac resynchronization therapy, CRT-D: CRT-defibrillator, CRT-P: CRT-pacemaker, EF: ejection fraction, HF: heart failure, HR: heart rate, HT: hypertension, ICD: implantable cardioverter-defibrillator, ICM NICM: ischemic or nonischemic cardiomyopathy, LV: left ventricular, LVEDD: left ventricular end diastolic dimensions, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, pVO₂: peak oxygen uptake, QoL: quality of life, VE/CO₂: the slope of the ventilatory response to carbon dioxide, 6MWT: 6 minute walk test.
There were no significant differences of mortality from CRT in patients with AF or sinus rhythm at 1 year.\textsuperscript{10, 11}

Overall, CRT is a class IIa indication in patients with AF. The benefit of CRT appears to be similar for those with AF and those with sinus rhythm. However, this occurs only when 100% biventricular pacing is achieved, and AV junctional ablation is crucially important to maximize the effects of CRT.

6. CRT in patients with pacemakers

Chronic right ventricular (RV) pacing induces dyssynchrony and may worsen cardiac function. CRT may prevent this RV pacing–induced LV dysfunction and HF. In the HOBIPACE trial, a randomized crossover study of 30 patients with LV systolic dysfunction, patients with CRT showed reverse cardiac remodeling, improvements in LVEF, and fewer HF symptoms compared with baseline measures or results of RV pacing.\textsuperscript{12} Thus, for patients with LV systolic dysfunction who require pacemakers for standard bradycardic indications, prophylactic implantation of a CRT system may be beneficial.

Furthermore, the PACE trial evaluated the effect of biventricular pacing vs. conventional RV pacing in 177 pacemaker candidates with normal LVEF (≥ 45%). After implantation of a biventricular pacing system, patients were randomly assigned to either biventricular or RV apical pacing. At 12 months, patients with RV pacing showed significantly lower LVEF levels and significantly higher LV end-systolic volume than patients with biventricular pacing.\textsuperscript{13}

Summary

CRT has been emerging as an important therapeutic option in the management of patients with HF and ventricular dyssynchrony. A favorable outcome is expected in patients with severe LV dysfunction (LVEF of <35%), moderate to severe (NYHA III, ambulatory IV) symptoms of HF, and a marked (>150 msec) prolongation of QRSd. In patients with less QRS prolongation (120–150 msec), CRT should be considered for those with LBBB, but other therapies should be considered for those with RBBB because of the possibility of a poor outcome in these patients. In patients with NYHA class III, IV HF symptoms, the presence of RBBB or AF is not a contraindication to ICD implantation, but these factors may predict poorer outcome than that in patients with LBBB or sinus rhythm.

In patients with mild or no HF symptoms (NYHA I, II), CRT can be indicated for patients with LVEF <30%, QRSd >150 msec, sinus rhythm, and LBBB.

References


