Cardiac Resynchronization Therapy With and Without Implantable Cardioverter-Defibrillator

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Cardiac resynchronization therapy (CRT) is recommended to reduce morbidity and mortality in patients with New York Heart Association class III/IV, who are symptomatic despite optimal medical therapy, and who had a reduced left ventricle (LV) ejection fraction and electrical dyssynchrony. The effects of CRT are reflected mainly by the degree and location of dyssynchrony and by working in insertion of optimal LV lead site. Echocardiography and Doppler echocardiography are considered to be good tools to measure LV dyssynchrony directly. However, the large randomized trials have shown that no single echocardiographic measure of dyssynchrony is recommended to improve patient selection for CRT beyond current guidelines. There were several unsolved issues on CRT, such as patient selection, electrical or electromechanical dyssynchrony criteria to patients for CRT, indication of patients with a narrow or slightly prolonged QRS width, indication of patients with atrial fibrillation, and indication of patients with mild heart failure or asymptomatic LV dysfunction, and device selection; CRT alone (CRT-P) or CRT in combination with implantable cardioverter therapy (CRT-D). This review paper summarized the concept of therapy, the current evidence regarding the indications, effectiveness and safety of CRT-P and CRT-D in patients with LV dysfunction, and unsolved issues. (Circ J 2009; Suppl A: A-29–A-35)

Key Words: CRT; CRT-D; Heart failure

Recently, the prognosis of patients with chronic heart failure (CHF) and left ventricular (LV) systolic dysfunction had been improving by pharmacological treatment, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-adrenergic antagonist, and aldosterone inhibitors. However, unsatisfactory results remain with these treatments. Further, heart transplantation and/or implantable circulatory support are very costly and applicable for only a limited number of patients. Cardiac resynchronization therapy (CRT) has been developed as a new equipment for patients with CHF. The clinical applications of the pacing method known as CRT alone (CRT-P) began by using an epicardial lead in 1994¹ and the method using endocardial lead through coronary sinus for LV pacing were published in 1996.² Finally, CRT received US Food and Drug Administration approval for use in selected patients with LV dysfunction in 2001. Several guidelines³–⁸ have been published in Europe and USA.

However, in Japan, implantable cardioverter-defibrillator (ICD) was approved by the Japanese Ministry of Health, Labor and Welfare (MHLW) in 1996. The first guidelines for ICD were published by the Japanese Circulation Society in 2001.⁹ CRT-P and CRT with ICD (CRT-D) were also approved in 2004 and 2006, respectively. Further, new guidelines set forth by the Japanese Circulation Society were begun in 2007, and patients with left ventricular ejection fraction (LVEF) of ≤35%, drug resistant CHF (New York Heart Association (NYHA) class III/IV) and with or without a history of fatal ventricular arrhythmias, were classified as class IIa indication.¹⁰ This review paper summarized the concept of therapy and the current evidence regarding the indications, effectiveness and safety of CRT with or without ICD in patients with LV dysfunction in Western countries and Japan.

Principle of CRT

Intraventricular conduction disturbance (a QRS width ≥120 ms) is prevalent in 15% patients with CHF and in approximately 30% patients with moderate-to-severe CHF, and it correlated the prognosis of patients with CHF.¹¹ A prolongation of PR interval, as a maker of atrio-ventricular dyssynchrony, is present in up to 35% of severe heart failure (HF) patients.¹² Intraventricular conduction disturbance induces the abnormal sequence of LV contraction, causing LV wall segments to contract early or late with redistribution of myocardial blood flow, non-uniform regional myocardial metabolism and changes in regional molecular process, such as calcium handling.¹³–¹⁵ CRT improves delays of ventricular systolic time accompanied with conduction disturbance, causing the improvement of intraventricular synchrony, interventricular synchrony and atrioventricular synchrony, and finally the improvement of cardiac function.¹⁶

Acute effects of CRT were an increase of dp/dt, ejection fraction and cardiac output by effective systole. Synchronizing the contraction reduces LV end-systolic volume (LVESV), LV end-diastolic pressure and volume, mechanical mitral regurgitation and left atrial pressure. The optimization of atrioventricular delay shortened isovolumic contraction time, then increases the effective diastolic filling time and the stroke volume.¹⁷ Those effects resulted in the increase of systolic blood pressure (18.0±18.0%), the decrease of pul-
monary wedge pressure, the increase of dp/dtmax (23.7± 19.0%) and stroke work without the increase of O2 consumption. Further, sympathetic nerve activity decreased in accompany with hemodynamic improvement.

Chronic effects of CRT shoumd be considered by several multicenter trials were the improvement of symptoms, excises tolerance, quality of life (QOL) and parameters of cardiac echocardiography and the infrequent admissions for HF (Table 1). Notably, the QOL and exercise tolerance improved and then the effect of revere remodeling occurred even if acute hemodynamic improvement of CRT was not shown. The degree of improvement of LV dyssynchrony had a good correlation to the prognosis. A reduction in LVESV of 10% signifies clinically relevant reverse remodeling, which is a strong predictor of lower long-term mortality and HF events. Further, in the CARE-HF trial CRT was associated with a significant reduction of 37% in the composite end-point of total death and hospitalization for major cardiovascular events (P<0.001), and of 36% in total mortality (P<0.002). Recent meta-analysis demonstrated that CRT improved LVEF, QOL, functional status and all-cause mortality.

Indications and Several Issues Related to CRT

Indication criteria in Western countries and Japan for CRT are summarized in Table 2. CRT is recommended to reduce morbidity and mortality in patients in NYHA class III/IV who are symptomatic despite optimal medical therapy, and who had a reduced LVEF and QRS prolongation, although there are small differences in which they were proposed in years and countries. However, the condition of CHF in all patients who meets criteria is not considered to have improved. One-third of patients assigned to CRT were considered to have worsened, so called the non-responder group. The reasons of non-responder are considered as: (1) large scar tissue; (2) no dyssynchrony before CRT; (3) inappropriate placement of LV lead; and (4) setting inappropriate AV delay and/or VV delay.

Basic Heart Disease

The effect of CRT is not related to the basic heart disease; however, the degree of hemodynamic improvement was better in non-ischemic heart disease than in ischemic heart disease (Table 3). In patients with ischemic heart disease, the effect of CRT was lower in associated with larger infarction area and in a case of LV posterior and lateral infarction where it is usually the optimal LV pacing site.

Patients With Atrial Fibrillation

The effect of CRT in patients with atrial fibrillation is
questioned because of (1) no improvement of AV dyssynchrony and (2) no biventricular pacing when ventricular rate during atrial fibrillation is faster than the pacing rate. In fact, the guidelines of AHA/ACC 2005 restricted to patients in sinus rhythm (Table 2), and the multicenter studies of CRT have been almost exclusively restricted to patients in sinus rhythm (Table 1). However, the prevalence of atrial fibrillation in patients with HF varied between 30 and 40%, and that in patients with NYHA class IV was approximately half. AV junction ablation and PV ablation for atrial fibrillation are considered as methods for more effective CRT in patients with atrial fibrillation. The MUSTIC trial showed a significant functional improvement. Combining CRT with AV junctional ablation resulted in marked improvements of LV function and exercise capacity. In contrast, atrial fibrillation patients treated with CRT without AV junction ablation, in whom rate control was achieved by means of negative chronotropic drugs, performed very poorly.

**Patient Selection**

The effects of CRT are reflected mainly by the degree and location of dyssynchrony and by working in insertion of optimal LV lead site on the basis of CRT. Therefore, the prediction of CRT benefits depends on the methods of assessment on LV dyssynchrony using surface electrocardiogram (ECG), magnetic resonance imaging (MRI), echocardiography and Doppler echocardiography.

QRS width is the most simple method to assess LV dyssynchrony. At the dawn of CRT, it was reported that higher efficacy of CRT was associated with longer QRS width. However, no LV dyssynchrony is seen in some patients with wide QRS complex. In contrast, there were some patients who had high grade dyssynchrony without wide QRS complex. Those facts induce that it is impossible to predict the efficacy of CRT only by QRS width.

Next, echocardiography and Doppler cardiography are considered to be good tools to measure LV dyssynchrony directly. Several parameters, such as septal-to-posterior wall motion delay (≥130 ms) in M mode echocardiography, tissue velocity imaging, tissue synchronized imaging and speckle tracing method, have been reported as useful methods for assessment of LV dyssynchrony. The PROSPECT trial was designed to access which parameters were predictors of response to CRT. In contrary to our expectation, the ability of the 12 echocardiographic parameters to predict clinical composite score responses varied widely: no single echocardiographic measure of dyssynchrony might be recommended to improve patient selection for CRT beyond current guidelines. Further, CARE-HF sub-analysis also addressed that it was impossible to predict the effect of CRT on mortality, even if using 15 pre-specified baseline variables. The useful predictors after CRT were severe mitral regurgitation and persistently elevated NT-Pro BNP, despite 3 months treatment for CHF.

However, the mean duration of the QRS of patients actually enrolled in these studies was approximately 160 ms, far from the recommended 120 ms lower limit. No

**Table 3. Effectiveness of CRT in Comparison of Non-ICM With ICM**

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>No. of patients</th>
<th>Subjects</th>
<th>Indication criteria</th>
<th>Observation period (month)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gasparini13 (2003)</td>
<td>158</td>
<td>ICM 75, Non-ICM 83</td>
<td>NYHA II-IV, QRS &gt;110 ms, LVEF &lt;40%</td>
<td>11.2</td>
<td>Non-ICM better than ICM.</td>
</tr>
<tr>
<td>Molhoek14 (2004)</td>
<td>74</td>
<td>ICM 40, Non-ICM 34</td>
<td>NYHA III/IV, QRS &gt;120 ms, LVEF &lt;35%, LBBB</td>
<td>24</td>
<td>Non-ICM equal ICM after 6 months and 2 years.</td>
</tr>
<tr>
<td>Diaz-infante15 (2005)</td>
<td>143</td>
<td>ICM 49, Non-ICM 94</td>
<td>NYHA II-IV, QRS ≥130 ms, 6MWD ≤450 m</td>
<td>6</td>
<td>Non-ICM better than ICM.</td>
</tr>
<tr>
<td>Sutton16 (2006)</td>
<td>228</td>
<td>ICM 115, Non-ICM 113</td>
<td>NYHA III/IV, QRS ≥130 ms, LVEF ≤35%, LVEDd ≥55 mm</td>
<td>12</td>
<td>Non-ICM better than ICM. Both non-ICM and ICM were improved after 6 months. Non-ICM was improved further, but ICM returned to the condition before the implantation.</td>
</tr>
</tbody>
</table>

LBBB, left bundle brunch block. Other abbreviations see in Table 1.

**Figure.** Chest X ray in a patient with cardiac resynchronization therapy in combination with implantable cardioverter therapy. AP view in left panel and left lateral view in right panel.
study had prospectively examined the value of Doppler echocardiography to identify potential responders among patients with QRS width <150 ms. Thus, the DESIRE study identified potential long term responders for CRT on the basis of simple echo indices of dyssynchrony. In regards to the primary combined endpoint (death from any cause, HF-related hospitalizations, and improvement of NYHA class at 6 months) at 6 months, 33 patients (55%) had improved, 10 (16%) were unchanged, and 17 (29%) had deteriorated. Clinical improvement was observed in 19 of 27 dysynchrony + (70%), versus 14 of 33 dysynchrony− (42%) patients (P=0.04). Therefore, in this population of CHF patients with QRS <150 ms, the presence of mechanical dyssynchrony at baseline Doppler-echo examination, but not the QRS width, predicted 6-month clinical response to CRT.

Narrow or Slightly Prolonged QRS Complex

There still exists a substantial population of patients who have LV mechanical dyssynchrony and a narrow QRS width. Patients with mechanical dyssynchrony and a narrow QRS complex might also benefit from CRT. Tissue Doppler imaging and other such techniques have shown that some patients with narrow or slightly prolonged QRS width (<130 ms) also have mechanical dyssynchrony. These imaging techniques might be a more specific marker of regional intraventricular-conduction delay than the marker of electrical dyssynchrony on electrocardiography, as shown by a prolonged QRS width. If so, some patients with a narrow QRS complex have echocardiographic evidence of LV mechanical dyssynchrony and might also benefit from CRT. However, the CRT group and the control group (no CRT) did not differ significantly in the proportion of patients with the primary endpoint (46% and 41%, respectively) at 6 months on the basis of prospective, randomized, controlled clinical trial. Thus, patients with CHF and narrow QRS widths might not benefit from CRT.

Asymptomatic and Mild HF

Since a reverse remodeling by CRT is sustained, it is presumed that CRT confers better prognosis of long term follow-up, even in patients with NYHA class I or II. The large randomized trial was performed to solve this issue. There was no significant difference in the composite primary endpoint (all cause of mortality, hospitalization for HF and worsened HF) in CRT-ON and CRT-OFF (16% vs 21%, P=0.10). However, the LV remodeling index as the second endpoint demonstrated the superiority of CRT-ON to CRT-OFF (LVEF 3.8% vs 0.6%, P<0.0001). Although these observations indicate that CRT has a favorable impact on the LV remodeling of patients with mild HF or asymptomatic LV systolic dysfunction, CRT has a no benefit in mortality and hospitalization for HF.

Severely Advanced HF (NYHA IV)

CRT-P or CRT-D has been shown to improve exercise capacity and QOL and to reduce HF hospitalizations and mortality in patients with NYHA class III/IV. There is concern that the device procedure might destabilize very ill class IV patients. In the class IV patients of COMPANION sub-analysis to assess the potential benefits of CRT-P and CRT-D, the primary endpoint of time to death or hospitalization for any cause was significantly improved by both CRT-P and CRT-D. Time to all-cause death and HF hospitalization was also significantly improved in both CRT-P and CRT-D. Time to all-cause death trended to an improvement in both CRT-P and CRT-D. Time to sudden death appeared to be significantly reduced in only the CRT-D group. Therefore, these devices should be considered in ambulatory NYHA class IV HF patients similar to those enrolled in the COMPANION trial in order to improve time to all-cause mortality and hospitalizations in NYHA class IV patients.

CORT-D

Most of the ICD trials for primary prevention of sudden cardiac death have focused on patients with ischemic LV dysfunction. The strongest evidence exists for patients in NYHA II/III class, but the data for patients in NYHA class I is less strong. Meta-analyzes of primary prevention trials have shown that the benefit on survival with ICDs is highest in patients with ischemic LV dysfunction; however, another meta-analysis of trials enrolling only patients with dilated cardiomyopathy also showed a 25% reduction in mortality in the patients with ICDs (P=0.003). These data suggested the efficacy of the ICD alone in the primary prevention of sudden cardiac death in patients with LV dysfunction, regardless of the etiology.

In the MIRACLE-ICD trial, CRT-P demonstrated the improvement of morbidity, but not mortality. A third of death in the CARE-HF trial was caused by sudden cardiac death. These observations indicated that CRT alone could not reduce the risk for sudden cardiac death in the typical CRT patients with a high risk for sudden cardiac death. The COMPANION trial has demonstrated that CRT-D significantly reduces total mortality compared with optimal pharmacological treatment alone. Therefore, the guidelines stated that CRT-D is recommended to reduce morbidity and mortality in patients in NYHA class III/IV who are symptomatic despite optimal medical therapy, and who have a LVEF ≤35% and QRS width ≥120 ms (class of recommendation I, level of evidence A). However, the meta-analysis failed to demonstrate that CRT-D improved survival when compared with ICD alone. Therefore, the incremental benefits of CRT-D devices versus ICD devices in patients with LV systolic dysfunction remain uncertain. The DECREASE-HF trials are ongoing to resolve this issue. Further, the meta-analysis failed to demonstrate that CRT-D improved survival when compared with CRT-P. Then, the large randomized studies that compare the efficacy of CRT-D devices with CRT-P device are also necessary.

Defining Response and Defining How We Measure Response to CRT

The efficacy of CRT usually was evaluated by the time-to-event analysis after the implantation of CRT devices. A response to CRT is defined as an improvement in both symptom status as measured by NYHA class, and improvement in LVEF. In the MIRACLE trial, the only echocardiographic measure that strongly correlated with improved NYHA functional class was LVEF. Only an improvement in NYHA functional class, but not LVEF, was associated with improved survival by Cox analysis. The recent emphasis on using echocardiographic measures of dyssynchrony to sub-select patients for CRT implies that correcting dyssynchrony, again by echocardiographic measures, was central to achieving a ‘response’. However, the PROSPECTIVE and CARE-HF sub-analysis addressed that no single echocardiographic measure of dyssynchrony can be recommended.
to improve patient selection for CRT beyond current guidelines. This important question, ‘What do these data tell us about measuring response to CRT?’ remains unclear.

Problems on Defibrillation Therapy, CRT-D

A significant number of patients with ICD have experienced long-term difficulties, the prevalence of psychological disorders, such as anxiety disorders, depression adjustment disorder and anger, ranged from 15 to 60%. Those psychological problems and inappropriate shocks have caused impaired QOL in some patients with ICD. New or worsened HF requiring hospitalization was slightly more frequent in the patients with ICD than in the conventional-therapy group. Patients saved from lethal ventricular arrhythmias by the implantation of a defibrillator might live longer than conventionally treated patients or CRT-P implanted patients. Thus, they would have more time for HF to develop. In fact, in the MADIT–II trial, 11 patients had their defibrillator removed during the trial (1.5%) and 12 patients had their defibrillator deactivated during the trial, usually as a result of terminal illness. Moreover, defibrillator shocks might contribute to rehospitalization and myocardial injury. Back-up ventricular pacing might impair ventricular function.

Cost-Effectiveness Issues

Although CRT-P devices are clearly cost-effective compared with medical therapy alone in trial eligible patients, the cost-effectiveness ratios when these devices are used in clinical practice are uncertain. Clinical benefits of CRT-D are economically variable and can be achieved at a reasonable cost in most European countries, USA, and Japan. Cost-effectiveness of CRT-D compared with CRT-P is age-sensitive, and the expected longevity should help to determine whether to use CRT-P or CRT-D in the individual patients. An incremental cost-effectiveness of CRT-D versus CRT-P devices remains uncertain.

Safety of CRT

In a recent meta-analysis (6,123 patients) implant success rate was 93.0%, peri-implantation mechanical complications occurred in 4.3% of procedure, and 0.3% of patients died during implantation. During a median 11-month follow-up, 6.6% of CRT devices exhibited lead problems and 5% malfunctioned. In Japan, based on Japanese Cardiac Device Treatment Registry (JCDTR) administered by the Japanese Heart Rhythm Society from 188 facilities (1,584 patients), the incidence of complications during the ICD/CRT-D implantations, was very low and only 1 patient died during implantation of CRT. The incidence of complications was significantly higher for CRT-D than ICD implantation (4.3% vs 2.3%; P<0.03).

Relation to Surgical Therapy for End-Stage HF

CRT-P/CRT-D implantations are one of the bridge therapies for patients who have been waiting as a candidate for cardiac transplantation or the operation of LV volume reduction for the therapy of severe HF. However, it is not unclear the indication and effect of those devices to patients who have the surgical treatment for severe HF, such as Dor operation, septal-anterior ventricular exclusion (SAVE) operation, and Batista operation. CRT-P/CRT-D implantation might be useful as a combination therapy or after the operation of LV volume reduction. Shimamoto et al reported a case with end-stage non-ischemic dilated cardiomyopathy complicated with AF and LV dysynchrony, who was successfully treated with the combined use of SAVE, undersized mitral annuloplasty, left atrial Maze procedure with cryoablation, and postoperative biventricular pacing. They noted that CRT was shown to be effective in resolving residual dysynchrony between the septum and lateral wall after SAVE, wherein a firm, non-compliant Dacron patch was sutured to the septum. Nishimura et al reported a case of successful bridge recovery using CRT with a left ventricular assist system in a patient with idiopathic dilated cardiomyopathy. However, it might be not useful in cases if CRT was performed before the surgical therapy for HF, because the disease of LV muscle is progressing and the patient becomes too sick to be a potential candidate of left ventriculoplasty (personal communication from Dr. Masashi Komeda).

Current Status in Japan

ICD was first approved by the MHLW in 1996, which was 10 years behind the USA. The first CRT-D was also finally approved by the MHLW in August of 2006, which was 5 years behind the USA. The current status of those devices still remains unclear in Japan. Data from JCDTR shows a total of 1,584 patients who had LVEF ≤40% and had ICD or CRT-D, there were 42% primary and 58% secondary prevention indication. However, there were 82% primary and 18% secondary prevention indications in ICD therapy (ACT registry in the USA). Significant differences were observed in the types of indications for ICDs between ACT and JCDTR. These observations indicate a need for further investigations to determine if these differences make different QOL and clinical outcomes. Therefore, the large randomized studies are needed to resolve whether there are differences on the efficacy of CRT and ICD between the Western countries and Japan.

ICD/CRT-Ds were implanted mainly for patients with ischemic heart disease and dilated cardiomyopathy in Japan. Approximately 7% of the Japanese patients with dilated cardiomyopathy are CRT candidates. The implantation of ICD/CRT-D for secondary prevention in ischemic heart disease was significantly higher than that in dilated cardiomyopathy (48% vs 35%; P<0.0001). Inversely, the implantations of ICD/CRT-D for primary prevention in ischemic heart disease was significantly lower than that in dilated cardiomyopathy (33% vs 51%; P<0.0001). There might be several reasons why the implantation for primary prevention in patients with ischemic heart disease was lower in Japan compared with that in the USA. One of the major reasons is probably due to the different guidelines for patients with ischemic heart disease. Further, Japanese physicians believe the risk in Japanese patients with ischemic heart disease and a lower LVEF is lower than that in the USA. These differences in device utilization rates might be explained by variable factors such as acceptance of published guidelines, differences in clinical presentation of patients, access to electrophysiologists and other implanters, overall capacity of the workforce to support ICD implantation, acceptance by policymakers, cost-effectiveness financial constraints, and capitation.

References


