Potential Role of Biventricular Pacing Beyond Advanced Systolic Heart Failure

Fang Fang, PhD; John E. Sanderson, MD; Cheuk-Man Yu, MD

Cardiac resynchronization therapy (CRT) is an effective therapy for advanced heart failure (HF) patients. The indications are well defined in recent guidelines and broadly indicate that CRT is suitable for chronic HF patients with left ventricular ejection fraction (EF) ≤35% and had prolonged QRS duration ≥120 ms with left bundle branch block (LBBB) QRS morphology, or QRS duration ≥150 ms irrespective of QRS morphology (Class IIa). For patients with NYHA class II symptoms, CRT is recommended for patients with EF ≤30% and QRS duration ≥130 ms with LBBB QRS morphology (Class I, level of evidence: A), or QRS duration ≥150 ms irrespective of QRS morphology (Class IIa, level of evidence: A). However, CRT may benefit additional patients outside these criteria. In this review, we summarize the role of CRT in some subgroups, including patients with mild and moderate HF, upgrading to CRT from right ventricular (RV) pacing, bradycardia patients with routine pacing indications, congenital heart disease and specific cardiomyopathies. It is possible that CRT can give symptomatic and mortality benefits in some of these subgroups in the future and further clinical trials are warranted. (Circ J 2013; 77: 1364–1369)

Key Words: Cardiac resynchronization therapy; Heart failure; Pacing

Heart failure (HF) is an increasingly worldwide public health issue. On top of standard drug treatment, cardiac resynchronization therapy (CRT) has been widely accepted as effective device management of advanced HF patients with left ventricular ejection fraction (LVEF) <35% and had prolonged QRS duration. Early observational studies demonstrated that CRT reduces mortality and this was later confirmed by multicenter clinical trials. In addition, CRT consistently improves clinical symptoms in some patients (often dramatically), reverses LV remodeling, restores systolic synchrony and enhances both ventricular and atrial functions.

The Guidelines for Class I indication of CRT implantation are mainly for patients with severe HF and New York Heart Association (NYHA) class III–IV symptoms with LVEF <35%. However, it is becoming clear that CRT not only benefits such patients but potentially could be expanded to include a wider patient population. Most recently, some researchers have provided evidence to expand the application of CRT to include patients with mild HF, patients who require pacing with normal LV function, upgrading CRT from right ventricular (RV) pacing only, in special cardiomyopathies such as hypertrophic obstructive cardiomyopathy (HOCM) and noncompaction of ventricular myocardium, as well as in patients with congenital heart disease (CHD) who require cardiac pacing therapy. In this review article, we summarize the potential role of CRT in patients beyond those with severe HF based on recent research (Table).

CRT in Patients With Mild to Moderate HF

Although traditionally CRT has been used mainly for patients with severe HF, there has been increasing interest in whether it may also be useful for patients with mild to moderate symptoms of HF.

In the Resynchronization/defibrillation for Ambulatory heart Failure Trial (RAFT), 1,798 patients with NYHA class II or III HF and QRS duration ≥120 ms and LVEF <30% were enrolled. It was found that all-cause mortality was significantly reduced when CRT-D was compared with implantable cardioverter defibrillator alone. In the trial, 80% of patients were in NYHA class II, and further analysis stratified by NYHA class showed that hospitalization for HF or death was significantly reduced in both subgroups, but more so in those with NYHA class II. In the updated ESC guideline, if HF patients are expected to survive for >1 year, CRT is recommended for those with NYHA class II and LVEF <30% and QRS duration ≥130 ms with left bundle branch block (LBBB) QRS morphology (Class I, Level A) or QRS duration ≥150 ms irrespective of QRS morphology (Class IIa, Level A). However, it is still not known whether CRT will benefit HF patients in NYHA class I and with prolonged QRS duration. In a substudy of the REVERSE trial in which NYHA I/II HF patients were se-
Focused studies with larger sample size of NYHA class I patients are warranted to ascertain the CRT effect in these sub-

In patients with normal EF and bradycardia

In patients with normal EF and bradycardia in PACE trial at 2-year follow-up

In patients with NYHA class I or II HF with QRS duration ≥ 120 ms and LVEF < 30%

In patients with normal EF and bradycardia in PACE trial: extended result

In patients with obstructive hypertrophic cardiomyopaty: preliminary study

In patients with isolated ventricular noncompaction associated with dilated cardiomyopathy without other coexisting cardiac diseases

In patients with structural CHD and congenital AV block, dilated cardiomyopathy

In pediatric and CHD

Table. Application of CRT Beyond HF

| Study | CRT application | Results |
|-------|-----------------|---------|
| Mild or moderate HF | | |
| REVERSE trial$^{11}$ | In asymptomatic or mildly symptomatic HF patients in combination with optimal medical therapy (± defibrillator) | HF hospitalization ↓, ventricular structure and function ↑ |
| RAFT trial$^{17}$ | CRT used in addition to ICD and optimal medical therapy in mild-to-moderate HF (NYHA class II or III HF with QRS duration ≥ 120 ms and LVEF < 30%) | All-cause mortality ↓ |
| MADI trial$^{19}$ | CRT combined with ICD for mild cardiac symptoms, reduced EF < 30%, and wide QRS complex | Risk of heart-failure events ↓ |
| Normal EF with bradycardia | | |
| PACE trial$^{12}$ | In patients with normal EF and bradycardia | LVEF and volume unchanged with Biv pacing, but deteriorated with RVA pacing |
| PACE trial: extended result$^{10}$ | In patients with normal EF and bradycardia in PACE trial at 2-year follow-up | LV adverse remodeling and deterioration of systolic function continued in the 2nd year after RVA pacing, but still unchanged in Biv pacing arm |
| PREVENT-HF$^{34}$ | In patients with AV block with nearly normal EF | No LV volume differences > 12 months between RVA and Biv pacing for AV block |
| Upgrading from RVA pacing | | |
| Frohlich et al$^{13}$ | Upgrading to resynchronization therapy after chronic RV pacing | CRT reverses LV remodeling in HF patients with chronic RV pacing |
| Marai et al$^{27}$ | Upgrading of conventional to resynchronization pacemaker in those with HF | NYHA functional class ↑ and 6-min walking distance ↑ in patients with prior RV pacing with the equivalent effect with those with de novo CRT |
| Special cardiomyopathies | | |
| Lenarczyk et al$^{14}$ | In patients with obstructive hypertrophic cardiomyopathy | Outflow tract gradient ↓ and functional status ↑ after CRT |
| Bertini et al$^{15}$ | In patients with isolated ventricular noncompaction associated with dilated cardiomyopathy without other coexisting cardiac diseases | LV reverse remodeling detected greater than after CRT compared with those with dilated cardiomyopathy without noncompaction |
| CHD with pacing indications | | |
| Janousek et al$^{29}$ | In patients with structural CHD and congenital AV block, dilated cardiomyopathy | NYHA functional class ↑ |
| Dubin et al$^{36}$ | Biv CRT in those under 21 years of age, or who had CHD regardless of age | Systemic ventricular EF ↑ after CRT |
| Cecchin et al$^{31}$ | In pediatrics and CHD | Ventricular function ↑ acutely |

AV, atrioventricular; Biv, biventricular; CHD, congenital heart disease; CRT, cardiac resynchronization therapy; EF, ejection fraction; HF, heart failure; ICD, implantable cardioverter defibrillator; RVA, right ventricular apical.

It was shown that beneficial reduction of LV volume in the CRT-On arm occurred in both ischemic and non-ischemic patients. Although the MADI-CRT$^{19}$ and REVERSE trials$^{20}$ focused on mild HF, only 75 and 152 patients, respectively, were in NYHA class I. Moreover, in the REVERSE study,$^{21}$ there was a tendency for the benefit of CRT (ie, reduction of LV end-systolic volume index) to be more obvious in the NYHA class II patients than in those in NYHA class I. Focused studies with larger sample size of NYHA class I patients are warranted to ascertain the CRT effect in these subjects.

**Upgrading to Biventricular (Biv) Pacing After Chronic RV Pacing in HF Patients With Conventional Pacing Indications**

RV apical (RVA) pacing causes iatrogenic LBBB and thereby mechanical dyssynchrony (Figures 1,2). The DAVID trial confirmed that a high percentage of RV pacing was associated with a reduction of LVEF in patients with systolic HF$^{21}$ and therefore upgrading the patients who require persistent RV pacing to CRT has been attempted in a series of studies of patients with pre-existing HF. In these cohorts, the published findings suggest that CRT improved clinical symptoms, and LV global and regional performance, as well as LV remodeling, by synchronizing mechanical dyssynchrony. $^{22–27}$ Marai et al further demonstrated that the benefit of CRT upgrade from prior RV pacing was equivalent to those with HF receiving CRT for the first time.$^{27}$ The BLOCK HF trial$^{28}$ enrolled 691 patients and was designed to clarify the benefit of CRT compared with RV pacing in patients with mild to moderate HF, atrioventricular block and LVEF ≤ 50%. The results reported at the AHA Late-breaking Clinical Trials session demonstrated that CRT was substantially superior to RV pacing for mortality, urgent HF care and LV enlargement at 3-year follow-up. Although there are no randomized, controlled trials comparing CRT upgrade with continuation of RV pacing in these patients, it can be assumed to be the recommended therapy when LV systolic dysfunction develops. The improvements in cardiac function status and LV reverse remodeling after upgrading to CRT were also observed in several studies of patients with CHD who received RV-based pacing.$^{29–31}$

**CRT in Bradycardia Patients With Normal EF**

Even in those without LV systolic dysfunction, RV pacing can lead to deterioration of LV function and HF hospitalization because of the induction of LV systolic dyssynchrony in those who are dependent on continuous ventricular pacing. $^{12,32}$ Al-
The ongoing BIOPACE study, which includes 1,200 patients and has the primary endpoints of survival rate, exercise ability and quality of life, may shed light on whether the use of Biv will prevent adverse cardiac events.

Although CRT may prevent HF in those with normal EF and bradycardia with long-term use, in the real world the wider application of CRT in these patients will be limited by its cost and a lower success rate of LV lead implantation. As a result, the pre-implantation evaluation for patient selection should be performed carefully to ensure an optimum outcome. Numerous data have proved that restoration of LV systolic dyssynchrony was the principal mechanism of CRT in systolic HF, and a recent study has revealed that maintenance of intraventricular synchrony in the early stage of pacing might be linked to the unchanged LV volume and function observed with Biv pacing in patients with normal EF.

However, the PREVENT-HF study did not show any difference between the Biv and RV pacing arms in LV systolic function or LV remodeling at 1-year follow-up. This discrepancy in results might be related to the smaller sample size than in the PACE trial and the high rate of LV lead implantation failure, as well as the use of insensitive echocardiographic assessment. The ongoing BIOPACE study, which includes 1,200 patients and has the primary endpoints of survival rate, exercise ability and quality of life, may shed light on whether the use of Biv will prevent adverse cardiac events.

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**Figure 1.** Parametric imaging derived from real-time 3-dimensional imaging shows there is no systolic dyssynchrony (all green color) without right ventricular apical pacing.

**Figure 2.** Development of systolic dyssynchrony after long-term pacing as shown by the asynchronous pattern with heterogeneous color.
The potential mechanism is thought to be related to the dyssynchrony caused by CRT in HOCM and more importantly, the pre-excitation of papillary muscle by the LV lead, consequently reducing the systolic anterior mitral motion, because valve closure timing is affected by pre-excitation. However, more data from larger clinical trials are needed regarding the benefit of CRT in HOCM and the potential mechanisms of benefit warrant further evaluation.

LV noncompaction (LVNC) is a special type of cardiomyopathy, characterized by prominent trabeculations and deep intertrabecular recesses. Although the natural history of LVNC remains unclear, 3-year mortality is reported to be approximately 15% from HF, ventricular arrhythmias and embolic events. The prognosis of late-stage LVNC is similar to that for HF, and HF can occur even at young age in LVNC patients. Although there is no specific therapy for LVNC, besides drugs, device therapy might be an option. In some anecdotal case reports and observational studies with small number of patients, CRT was observed to improve clinical symptoms and the LVEF with either an epicardial LV lead or implanted via the coronary sinus. Evidence from long-term follow-up and larger sample size is necessary. However, it has been recommended that on the basis of optimal medical therapy, CRT should be considered in those with LVEF <35% and LV dysynchrony.

**CRT in CHD**

There has been considerable improvement in the survival of patients with CHD because of advances in diagnostic techniques, early awareness, the use of cardiac intervention, and better clinical care. However, HF is the main complication in this condition, especially in adulthood, and effective therapy, including CRT, could be considered. Although there have been
The main phenotypes of HF in CHD include systemic LV failure and an individualized management plan should be implemented. Moreover, the effect of CRT depends on the anatomical defect that potentially may be corrected by CRT. 

With a high survival rate (92–95%), 29,31 three published retrospective studies with relatively large sample sizes, 29–31 mid-term follow-up showed that CRT improved ventricular function and symptoms of HF in CHD patients. 

As mentioned earlier, CRT shows promise in systemic right HF and its application has been extended to this field. A small study of 7 patients with repaired tetralogy of Fallot and right bundle branch block demonstrated that CRT enhanced the cardiac index and RV dp/dt. 54 In an animal model of RV failure, the improvement in RV function could be produced by RV free wall pre-excitation. 52 An acute study of 67 patients with pulmonary artery hypertension, interventricular dyssynchrony might be related to the impaired RV function, which is very scarce. 49,50 The Karolinska-Rennes (KaRen) prospective study of dyssynchrony in HF with preserved EF is still ongoing. 

In pulmonary artery hypertension, interventricular dyssynchrony might be related to the impaired RV function, 52 which potentially may be corrected by CRT. 54 As mentioned earlier, CRT shows promise in systemic right HF and its application has been extended to this field. A small study of 7 patients with repaired tetralogy of Fallot and right bundle branch block demonstrated that CRT enhanced the cardiac index and RV dp/dt. 54 In an animal model of RV failure, the improvement in RV function could be produced by RV free wall pre-excitation. 52 An acute study of 67 patients with pulmonary artery hypertension showed enhancement of RV contractility by CRT. 55 To date, there have been very few studies of the long-term benefit of CRT in these patients and their associated response rate.

Conclusion
It appears that with recent progress in research, the clinical applications for CRT are expanding and CRT should not be limited only to severe HF patients. However, unlike the wealth of clinical trial evidence in advanced HF, there is a need for more clinical trials and in particular, randomized controlled studies, to provide stronger evidence for any potentially new indications.

Other Potential CRT Indications
Approximately half of HF patients have a normal or “preserved” EF, 46 which carries almost similar mortality to systolic HF. In addition to systolic impairment, cross-sectional study shows that long-axis systolic dyssynchrony is also prevalent, irrespective of QRS duration, in these subjects. 47,48 Recently, torsional dyssynchrony measured by speckle tracking imaging has been shown to occur during exercise and this reflects the disturbed systolic and diastolic functions, which are more apparent with exercise in this condition. 49 It has been postulated that CRT may benefit HF with preserved EF by correcting systolic dyssynchrony, though the current evidence is very scarce. 50,50 The Karolinska-Rennes (KaRen) prospective study of dyssynchrony in HF with preserved EF is still ongoing. 51

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