

Up-to-date cardiac resynchronization therapy

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Abstract

Cardiac resynchronization therapy (CRT) has been first reported more than 10 years ago as a therapy for patients with severe chronic heart failure. The efficacy of CRT has been proven in many studies that it improves not only quality of life but also the prognosis of the patients. Its indication has been expanded for patients with mild heart failure. On the other hand, some patients cannot receive enough benefit through CRT. The position of the left ventricular lead is limited due to the anatomy of coronary sinus branches, pacing threshold of the myocardium, phrenic nerve stimulation, and so on. Also, the right selection of the candidates for CRT is critical to receive the most benefit of this therapy. The target of this review article is to describe the efficacy and the indication of CRT, which can be of any help to enroll more patients with heart failure who are likely to get benefits through CRT.

KEYWORDS

cardiac resynchronization therapy, CRT, indication, review

1 | INTRODUCTION

The concept of cardiac resynchronization therapy (CRT), resynchronizing the dyssynchronous wall motion of the left ventricle by pacing in patients with severe systolic heart failure (HF), has been studied for many years.^{1,2} The benefit of CRT has been reported in many clinical studies that it can improve the prognosis of the HF patients as well as the quality of life (QOL).^{3,4} It is also important to prevent sudden cardiac death due to lethal arrhythmias in HF patients, and CRT with defibrillators (CRT-D) has been applied in most cases. The indication for CRT or CRT-D is decided based on the guideline on nonpharmacotherapy for arrhythmias by Japanese Circulation Society and Japanese Heart Rhythm Society published in 2011.⁵ However, many clinical studies have been demonstrating new evidences on CRT every year and we need to keep up the latest evidences to provide best treatment for the patients.^{6,7} This review article describes on the history, advancement, indication, current limitations, and the future of CRT. To recognize the position of CRT as one of the established treatments for HF is important for the doctors who are involved in primary care medicine to foresee the treatments which should be provided for the patients with HF.

2 | IMPROVEMENT OF SURVIVAL AS WELL AS QOL

Many of the patients with severe systolic HF present left bundle branch block (LBBB) pattern on their electrocardiogram (ECG) (Figure 1, left panel) and dyssynchronous wall motion of the left ventricle often accompanied by mitral regurgitation on echo cardiography. Considering this situation, the concept of CRT that pacing both right and left ventricles regardless of the indication of pacemaker for bradycardia might reduce the dyssynchronous wall motion of the ventricle and improve the efficacy of contraction and cardiac output has been proposed. Cardiologists were used to place a catheter and pace in the coronary sinus (CS) and got an idea to place a pacing lead in a branch of CS instead of pacing the left ventricle using an endocardial lead which has a risk of arterial thromboembolism. As shown in Figure 2, three leads are usually placed in the heart transvenously; one in the right atrium, one in the right ventricle, and the other one in the CS branch for left ventricular pacing. The QRS width on ECG can be narrow by biventricular pacing (Figure 1, right panel). Initial studies on CRT reported

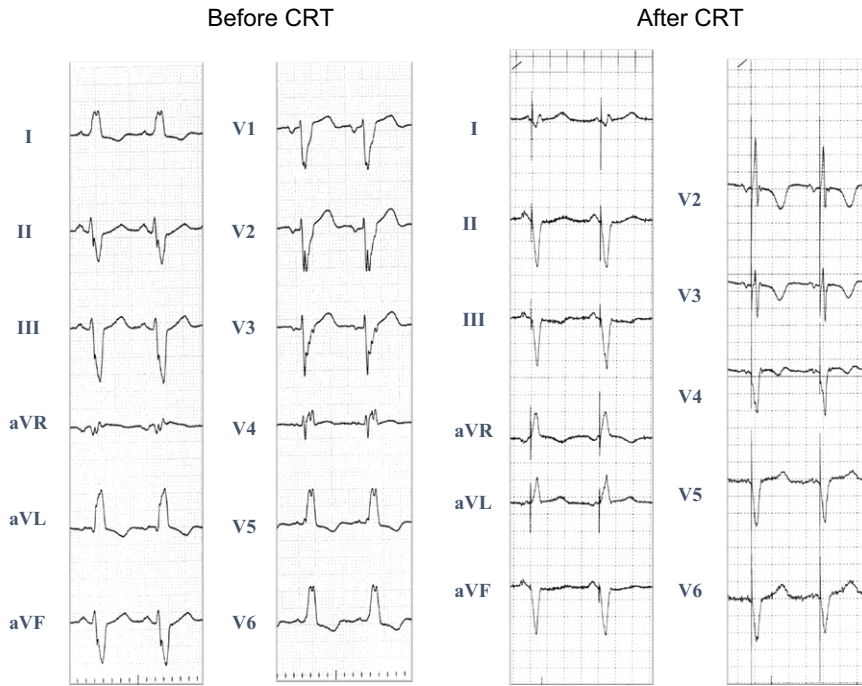


FIGURE 1 Change in QRS width by cardiac resynchronization therapy (CRT). Electrocardiogram before (left panel) and after (right panel) CRT. Many of the patients with severe systolic heart failure present left bundle branch block pattern and QRS width can be narrow by CRT

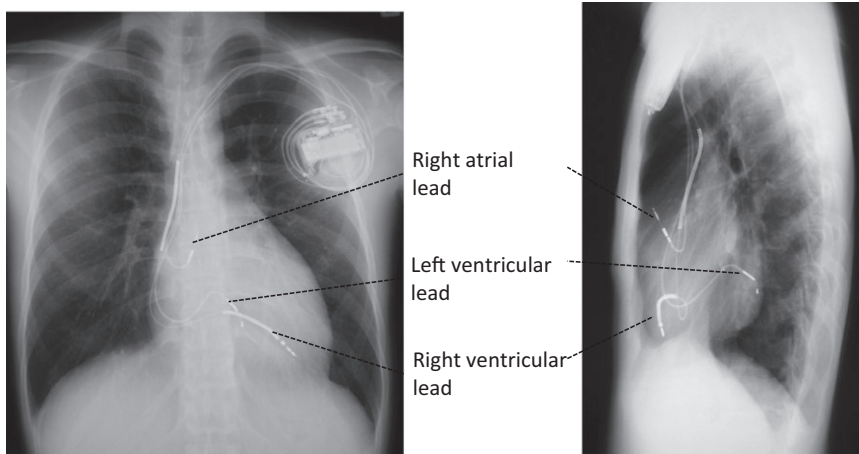


FIGURE 2 Chest x-ray after implantation of defibrillator with cardiac resynchronization therapy (CRT-D). Three leads are placed in the heart transvenously. Left ventricular lead is placed in the coronary sinus branch

its efficacy to improve QOL of severe HF patients. MIRACLE study¹ which has been published in 2002 enrolled patients with New York Heart Association (NYHA) function class III or class IV heart failure, QRS width on ECG ≥ 130 ms, and ejection fraction (EF) of left ventricle (LV) $\leq 35\%$ and showed that CRT improved 6-minute walking distance and QOL score in this patient group. On the other hand, it has been well known that severe HF patients have higher risk of sudden death due to lethal arrhythmias and prophylactic implantation of an implantable cardioverter defibrillator (ICD) has been proven to improve the prognosis of HF patients.^{8,9} Most of the patients receiving CRT can also be a candidate of ICD, and once CRT-D was launched, CRT-D has been mainly used instead of CRT pacemaker. COMPANION study⁴ published in 2004 randomized patients with NYHA class III or IV, QRS width ≥ 120 ms, and EF $\leq 35\%$ into three groups; pharmacotherapy, CRT, and CRT-D. This study showed that CRT and CRT-D decreased all-cause mortality and rehospitalization for HF compared with

pharmacotherapy. The patients with severe symptoms, NYHA class III or IV, in addition to presenting wide QRS duration on ECG were the targets for CRT or CRT-D in the beginning of CRT. Supported by the evidences of many clinical trials, CRT has established its status as one of the important therapies for HF patients.

3 | EXPANDING INDICATION FOR CRT

How much we can expand the indication of CRT was the next issue. One of the targets was HF patients with mild symptom. REVERSE trial¹⁰ published in 2008 enrolled patients with NYHA class I and II heart failure patients, QRS width ≥ 120 ms, EF $\leq 40\%$ and revealed that CRT not only prevented the re-admission due to heart failure but brought remodeling of cardiac dilatation and improved EF of LV. Also, MADIT-CRT¹¹ published in 2009 focused on patients with NYHA class

I or II heart failure and proved the efficacy of CRT-D in this patient group. RAFT trial¹² which enrolled NYHA class II or III heart failure patients showed no statistical difference on the effect of CRT between NYHA classes and established the efficacy of CRT in patients with early stage HF. As shown in Table 1 and Table 2, the current Japanese indications of CRT or CRT-D are based on the nonpharmacotherapy of arrhythmia by Japanese Society of Cardiology revised in 2011.⁵ Although the indications for NYHA class II heart failure patients are partially indicated in this guideline, the indications of CRT therapy will expand furthermore in the future based on the recent evidences.

4 | CAN WE PREDICT THE EFFECT OF CRT?

Despite the expanding indication of CRT for patients with CHF, around 30% of the patients who receive CRT do not get enough benefit through the therapy, so-called nonresponder. Predicting the patients who respond to CRT has been one of the issues of CRT to be solved. Although the parameters based on the echo cardiography had been most anticipated, PROSPECT trial¹³ which was performed aiming to determine echo parameters to predict responders and non-responders of CRT failed to find any parameters. On the other hand, subanalysis of major trials including COMPANION,⁴ MADIT-CRT,¹⁴ or REVERSE¹⁵ revealed that the patients with QRS width ≥ 150 ms were

TABLE 1 Indication of CRT Pacemaker (CRT-P) from JCS Guideline 2011 (Ref. ⁵)

Class I:
1. CRT-P is recommended in chronic HF patients with LVEF $\leq 35\%$, QRS duration ≥ 120 ms, in sinus rhythm who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment.
Class IIa:
1. CRT-P should be considered in chronic HF patients with LVEF $\leq 35\%$, QRS duration ≥ 120 ms, with atrial fibrillation who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment.
2. CRT-P should be considered in chronic HF patients with LVEF $\leq 35\%$ who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment and when a pacemaker has been already implanted or planned to be implanted and also when frequent ventricular pacing is expected.
Class IIb:
1. CRT-P may be considered in chronic HF patients with LVEF $\leq 35\%$ who remain in NYHA functional class II despite adequate medical treatment and when a pacemaker has been planned to be implanted and also when frequent ventricular pacing is expected.
Class III:
1. CRT-P is not indicated in asymptomatic patients with reduced LVEF and when pacemaker is not indicated.
2. CRT-P is not indicated in patients whose physical activity is limited due to chronic diseases other than heart failure or when life expectancy ≥ 12 mo is not expected.

TABLE 2 Indication of CRT with defibrillator (CRT-D) from JCS Guideline 2011 (Ref.⁵)

Class I:
1. CRT-D is recommended in chronic HF patients with LVEF $\leq 35\%$, QRS duration ≥ 120 ms, in sinus rhythm who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment and when ICD is also indicated.
Class IIa:
1. CRT-D should be considered in chronic HF patients with LVEF $\leq 35\%$, QRS duration ≥ 120 ms, with atrial fibrillation who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment and when ICD is also indicated.
2. CRT-D should be considered in chronic HF patients with LVEF $\leq 30\%$, QRS duration ≥ 150 ms, in sinus rhythm who remain in NYHA functional class II despite adequate medical treatment and when ICD is also indicated.
3. CRT-D should be considered in chronic HF patients with LVEF $\leq 35\%$ who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment and when an ICD has been already implanted or planned to be implanted and also when the patient is dependent on ventricular pacing or frequent ventricular pacing is expected.
Class IIb:
1. CRT-D may be considered in chronic HF patients with LVEF $\leq 35\%$ who remain in NYHA functional class II despite adequate medical treatment and when an ICD has been planned to be implanted and also when frequent ventricular pacing is expected.
Class III:
1. CRT-D is not indicated in asymptomatic patients with reduced LVEF and when ICD is not indicated.
2. CRT-D is not indicated in patients whose physical activity is limited due to chronic diseases other than heart failure or when life expectancy ≥ 12 mo is not expected.

likely to receive most benefit of CRT and LBBB pattern seemed to have better outcome than right bundle branch block or nonspecific block pattern. QRS width ≥ 150 ms was also an important predictor for responders in RAFT trial.¹² QRS width should be carefully monitored in enrolling patients for CRT.¹⁶

On the other hand, we had been still anticipating that the patient with dyssynchrony on echo cardiography can get benefit from CRT even if QRS width is not wide enough. However, EchoCRT study¹⁷ which enrolled patients with NYHA class III or IV heart failure patients who presented QRS < 130 ms but presented apparent dyssynchrony on echocardiography resulted in presenting no benefit of CRT. To consider indications of CRT, careful discussion based on evidence is important.

5 | HOW TO REDUCE NONRESPONDER? IMPORTANCE OF APPROPRIATE LV PACING SITE

Patients with heart failure often accompany with atrial fibrillation, which makes bi-ventricular pacing difficult due to increased intrinsic

heart rate. Although the efficacy of CRT in patients with atrial fibrillation has been reported, it is important to inhibit intrinsic heart rate by beta-blocker or ablation of atrioventricular node, otherwise the benefit of CRT cannot be fully utilized.¹⁸

Also, lead position of the left ventricular lead is also important, although it is limited by the anatomy of coronary sinus branches in individual patients, pacing threshold of myocardium and phrenic nerve stimulation.^{19,20} Subanalysis of MADIT-CRT²¹ demonstrated that the apical position of left ventricular lead was associated with worse outcome. Similar result was confirmed in the subanalysis of REVERSE trial.²² To reduce the number of patients who do not respond for CRT, the operator should avoid apical LV lead position as possible. The use of quadripolar LV lead (Figure 3) may be helpful to avoid apical pacing as well as to avoid phrenic nerve stimulation.^{23,24}

6 | FUTURE OF CRT

Further advances of technology will overcome the current problems of CRT and change the standard. Wireless pacing of left ventricle using ultrasound transmission is one of them. Technically it is possible to place a small electrode in the endocardium of LV through atrial septum wall and mitral valve, which does not limited the electrode position for left ventricular pacing. Although this technology is accompanied with the risk of thrombosis, it might be the standard of CRT in the future.^{25,26} Also, leadless pacemaker which serves as an independent pacemaker and does not require any lead has been already introduced for right ventricular pacing.^{27,28} If several tiny leadless pacemakers can communicate with each other, completely leadless endocardial CRT pacing may be possible in the future.

On the other hand, we need to think about the cost of CRT-Ds. Although ICD can prevent sudden cardiac death due to lethal arrhythmia, heart failure has been the majority of causes of death in patients receiving CRT-Ds. It is reported that when compared with CRT-D patients, excess mortality in CRT pacemaker recipients was mainly due to

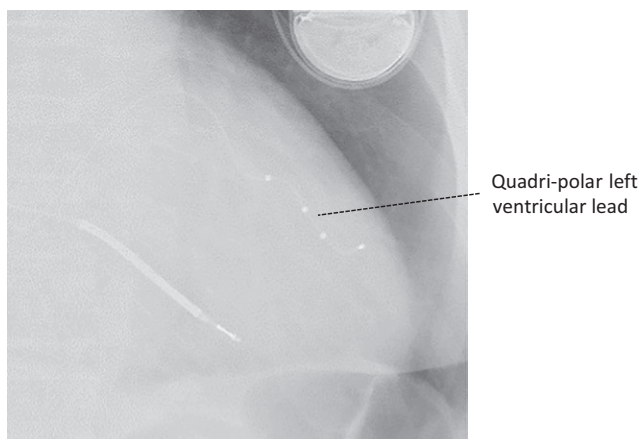


FIGURE 3 Quadripolar left ventricular lead. This lead is useful to avoid apical pacing and can change the pacing site noninvasively when phrenic nerve stimulation is observed

nonsudden death.²⁹⁻³¹ It is the time to consider how to select patients who should be treated with a defibrillator and who should be treated with a pacemaker.

7 | CONCLUSION

CRT is one of the established treatments of CHF supported by enough evidences and brings huge benefit for the patients when accompanied with adequate pharmacotherapy, cardiac rehabilitation, patient education, and so on. Patients with NYHA class II or III heart failure who present reduced EF \leq 35%, QRS $>$ 150 m with left bundle branch block are likely to well respond to this therapy. On the other hand, we need to discuss on the indication of CRT for patients with narrow QRS considering the nonresponder rate and adverse effect of CRT. Appropriate understanding of this therapy by the doctors who are involved in primary care medicine is important because it is critical to introduce CRT for adequate patients in good timing.

CONFLICTS OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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