



Supplement

What is Cardiac Resynchronisation Therapy and Who Will Benefit?

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Abstract

Cardiac Resynchronisation Therapy (CRT) has been used extensively over the last years in the therapeutic management of the patients with end stage heart failure based on the data of large randomized trials on CRT. CRT improves symptoms, exercise capacity, quality of life and echocardiographic indices of severe systolic heart failure besides reduction in heart failure related hospitalizations and improvement in survival. However, there may be some non-responders as well. There is on-going research, which will identify patients without conventional indications for CRT so as to improve the responder rate. Tissue Doppler Imaging (TDI) techniques will assume an important role in identifying patients for CRT. ©

INTRODUCTION

The growing incidence and prevalence of congestive heart failure (CHF) is reaching worldwide epidemic proportions. The syndrome of CHF is responsible for substantial morbidity and mortality.¹ Patients with heart failure (HF) have shortness of breath and a limited capacity for exercise, have high rates of hospitalization and re-hospitalization, and die prematurely. Although medical therapy has helped improve morbidity and mortality, the prevalence of CHF continues to increase. Unfortunately, the disease is progressive in nature and advances in medical management have not made as big of an impact as it was hoped in reversing advanced stages of the disease. Thus, despite these therapeutic advances, it is generally accepted that current therapies do not adequately address the clinical needs of patients with heart failure. Therefore, the need to develop additional strategies.

CONDUCTION ABNORMALITIES IN CHF

Approximately 20-50% of patients with cardiomyopathy have prolongation of PR interval and intraventricular conduction defects (IVCD) such as left or right bundle-branch block, leading to loss of coordination of ventricular contraction.² The prevalence of these conduction disturbances depends upon the severity of CHF. Functional NYHA class IV patients tend to have wider QRS complexes.

Wilkensky *et al*³ showed that 82% of patients had significant IVCD in the ECG recorded within 60 days before death and in 68% of these patients, the conduction abnormality was progressive. It has been shown that in CHF patients both PR interval prolongation and a wide QRS are independent predictors of mortality. The relationship of QRS duration with mortality was shown by Gottipaty *et al* in the VEST study.⁴ 3654 ECGs in patients with CHF were evaluated. The QRS duration was found to be an independent predictor of mortality as patients with a wide QRS (>200 msec) had a five times greater mortality risk than those with a normal (<90 msec) QRS duration.

The association of IVCD in patients with CHF leads to loss of coordination of ventricular contraction.² This dyssynchronous pattern of ventricular contraction is believed to contribute to the pathophysiology of heart failure reducing the already diminished contractile reserve of the heart.⁵ The dyssynchronous contraction

exacerbates inefficient use of energy by the heart, resulting in decrease in stroke volume, facilitation of MR, increased wall stress and delayed relaxation. Leclercq *C et al*⁶ showed 29% of patients had a complete LBBB and 9% had a RBBB, which was associated with left axis deviation in two thirds of these patients, indicating a probable involvement of the left bundle branch. During LBBB there is delayed activation of the lateral wall of the left ventricle (LV). LBBB has been associated with adverse haemodynamic effects. In these patients there is reversal of the normal sequence between right and left ventricular mechanical events, RV systole and diastole markedly preceding that of the LV, with LV isovolumic contraction time and relaxation phases lengthening and diastolic filling time shortening. This reversal of normal sequence between right and left ventricular mechanical events results in dynamic interventricular asynchrony with altered interventricular septal motion and reduced septal contribution to LV ejection fraction.

The primary objective of CRT is restoration of a more normal ventricular activation pattern by activating the part of LV, which was being, activated the latest. Secondly CRT allows the optimization of the atrioventricular interval for patients in sinus rhythm.

CARDIAC RESYNCHRONISATION

Early reports of Biventricular pacing involved epicardial LV leads. In 1994, Cazeau *et al*⁷ reported a patient with refractory heart failure who responded to four chamber pacing. Foster *et al*⁸ in 1995 investigated pacing following CABG, using different combinations of cardiac chambers with epicardial leads. The authors found that maximal hemodynamic benefit was derived from a combination of atrial and biventricular pacing. Daubert *et al*⁹ in 1998 reported that LV free wall could be effectively paced by a transvenous technique. Thus, it became possible to deliver the hemodynamic benefits as a permanent therapy without the morbidity associated with thoracotomy technique.

Biventricular Pacemaker

An implantable biventricular pacemaker is an advanced version of a standard implantable pacemaker. The biventricular pacemaker is implanted in the muscle tissue of the chest, below the clavicle. The biventricular pacemaker comprises three leads, one atrial and two ventricular – the right and the left ventricular leads.

The RV lead is the lead used in the conventional pacemaker, the LV lead is placed transvenously through the right atrium into the coronary sinus (CS). Once in the CS, the posterolateral or the lateral vein is the vein of choice for pacing the LV. The leads are connected transvenously to the pacemaker. In a small proportion of patients due to unsuitable coronary anatomy, unacceptable pacing thresholds or

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due to diaphragmatic pacing, one might have to resort to epicardial pacing via thoracotomy. Placement of a biventricular pacemaker can usually be accomplished under sedation. General anaesthesia is seldom needed during transvenous route, however it is during epicardial pacing that general anaesthesia is needed. Once the pacemaker is implanted, it is programmed so that both ventricles are stimulated to contract after atrial contraction with the goal of improving LV function, reducing presystolic mitral regurgitation, and improving LV diastolic filling time.

It is understood that patients with CHF, irrespective of the width of the QRS, do exhibit various forms of dyssynchrony: atrioventricular, intraventricular and intraventricular dyssynchrony. Various methods have been devised to identify the dyssynchrony- tissue Doppler imaging (TDI) being novel and the most often used modality. It is important to study the dyssynchrony in patients prior to implantation of the biventricular pacemaker so as to decrease the non-responder rate. The aim of CRT is to deliver atrial synchronized biventricular pacing so as to improve electromechanical coupling in the heart by generating a more efficient sequence of impulse generation and conduction.

HOW DOES CRT WORK?

Optimization of AV delay

CHF patients with PR interval prolongation is a subgroup who benefit from optimization of atrioventricular delay. This optimization of atrioventricular delay increases the diastolic filling period and also reduces the presystolic MR.

Reduction in systolic MR

Reduction in the MR jet area has been consistently shown in various trials. One possible explanation for this improvement in patients with functional MR may be the change in activation sequence of the LV chamber and papillary muscles. In patients with biventricular pacemaker, base contracts before the apical LV myocardium as the LV lead is close to the atrioventricular ring. This contraction pattern correlates with long-term benefits from biventricular pacing.

Increased efficiency of LV function:

Electromechanical dyssynchrony results in long delay in activation time from septal depolarization to depolarization of the LV free wall, thus contractile patterns arise where the septal muscle is starting to relax as LV free wall enters systole. This results in reduced contractile efficiency. Correction of this problem by biventricular stimulation helps in simultaneous activation of the septum and the free wall resulting in increased arterial pulse pressure and LV dp/dt .

The above hemodynamics manifest as improved quality of life, improved NYHA functional status, 6 min walk test. CARE-HF trial was powered and designed to answer the question whether there is a significant mortality benefit from biventricular pacing additional to the combined mortality benefit from optimized HF drug therapy. It showed that CRT significantly reduces mortality by 36% ($p < 0.002$) in patients with functional class III and IV heart failure and ventricular dyssynchrony, besides demonstrating reverse remodeling and improvement in myocardial performance progressively which continued for at least 18 months.

WHO ARE THE CANDIDATES FOR CRT

Approximately one-third of patients with low EF and CL III-IV symptoms of HF manifest a QRS duration > 120 msec. This is the widely accepted consensus definition of cardiac dyssynchrony although several echo cardiographic measures appear promising. Ventricular dyssynchrony has been associated with increased mortality in HF patients. The dyssynchronous contraction can be addressed by CRT. This approach to HF therapy may enhance ventricular contraction and reduce the degree of secondary mitral regurgitation^(10,11,12) and reduce mortality. So far more than 4000 HF patients with ventricular dyssynchrony have been evaluated in randomized controlled trials of optimal medical therapy (OMT) versus OMT plus CRT with or without an Implantable Cardioverter Defibrillator.

CRT when added to OMT in persistently symptomatic patients have resulted in significant improvement in quality of life, functional class, exercise capacity and exercise duration during 6 minute walk test and ejection fraction.

The metaanalysis of several CRT trials showed HF hospitalizations were reduced by 32% and all cause mortality by 25% which became apparent after 3 months of therapy⁽¹³⁾. The combination of CRT and ICD (COMPANION) significantly decreased all cause mortality by approximately 36%.

Thus, there is strong evidence to support the use of CRT to improve symptoms, exercise capacity, QOL, LVEF and survival. The use of an ICD in combination with CRT should be based on the indications for ICD therapy.¹⁴

The current indications for implantation of a CRT device are based on the presence of a prolonged QRS duration (≥ 120 ms), LV systolic dysfunction (LVEF $< 35\%$), NYHA class III-IV despite optimal medical treatment (ACE inhibitors, beta-blockers, spironolactone and diuretics) and LV end systolic dimension ≥ 55 mm. The aforementioned indications for CRT therapy addresses the core issue of choosing patients with significant atrioventricular and inter or intraventricular mechanical dyssynchrony who would benefit from CRT. Most of the CRT trials have enrolled patients with severe CHF and prolonged QRS duration.¹⁵⁻¹⁹ Although this may be generally correct there is an ongoing debate on the reliability of QRS duration as a marker of mechanical ventricular dyssynchrony. It may be worth mentioning that some patients with a narrow QRS may have significant mechanical ventricular dyssynchrony and thus be candidates for CRT. The other issues that need to be addressed before selecting patients for CRT are presence of RBBB and atrial fibrillation.

QRS Duration

There is evidence of inter or intraventricular dyssynchrony in heart failure patients with normal QRS duration. Beneficial effects of CRT have been demonstrated in such patients in a pilot study.²⁰ Similarly beneficial effects of CRT in patients with QRS duration between 120-150 ms can be expected as seen in patients with QRS duration of > 150 ms.²¹

Tissue Doppler Imaging (TDI) is a viable diagnostic modality to identify patients with mechanical ventricular dyssynchrony in the absence of electrical dyssynchrony. There is evidence of beneficial effects of CRT in such patients.²² In another study, the same group demonstrated a high prevalence of systolic and diastolic dyssynchrony in patients with HF and narrow QRS complexes (≤ 120 ms).

There is increasing evidence that QRS duration is a poor surrogate of response in individual patients. In contrast, direct measures of mechanical dyssynchrony by conventional echocardiographic imaging and TDI appear to be more precise in patient selection and to predict long-term response to CRT.

Right Bundle Branch Block

There is scarce data of CRT in patients with right bundle branch block (RBBB). The patient subgroup with RBBB, in CONTAK CD trial for unknown reasons, did not demonstrate a significant improvement in symptoms status and LVEF. Pacing from alternative stimulation sites eg RVOT might lead to better response in such patients. Beneficial effects of CRT were demonstrated in such patients in a small study.²³ It has been seen that in about two thirds of patients with RBBB there is some conduction disturbance in the LBB. Thus, the role of TDI in this sub group of patients prior to biventricular pacing.

ATRIAL FIBRILLATION

There is evidence of beneficial effects of Biventricular Pacing compared to VVIR pacing in patients with chronic AF and severe HF.^{28,29} Similar results were demonstrated in MUSTIC trial in patients with AF. There was a statistically significant increase in six-minute walk distance, peak VO_2 , quality of life and ejection fraction. On the other hand the episodes of paroxysmal AF in CRT recipients may decrease probably due to improvement in atrial loading conditions and reverse remodeling.³⁰ Based on the aforementioned evidence, patients with atrial fibrillation should not deny the benefits of CRT.

Responders : Approximately 2,70,000 Heart Failure patients have received CRT devices in United States alone but there is no consensual definition of a CRT responder as yet. A well-defined set of criteria for a positive response is needed to better identify potential candidates for CRT and to predict the long term response to CRT. Different authors have used different definitions of positive response to CRT viz-

Improved symptoms at least one NYHA class down and at least 10% increase in peak VO_2 for at least 6 months (Ansalone *et al*),²⁴ improved symptoms and NYHA class with a decrease on QOL scores (Reuter *et al*),²⁵ improved NYHA class associated with improved echocardiographically derived indices of dyssynchrony (Cazeau *et al*), improvement of more than 25% in dp/dt max. (Nelson *et al*).

As mentioned earlier QRS duration is not a reliable indicator of dyssynchrony.

As a rule larger the mechanical ventricular dyssynchrony, the greater the benefit of CRT. The direct assessment of ventricular dyssynchrony will therefore increases the accuracy of patient selection and will improve the responder rate.

A recent study²⁶ selected patients of CHF with LVEF \leq 35% NYHA functional class III and IV, despite OMT for CRT purely on the indices of mechanical ventricular dyssynchrony rather than electrical dyssynchrony. They reported encouraging results though they should be viewed cautiously until randomized prospective trials address this issue.

COST EFFECTIVENESS OF CRT

The issue of survival, hospitalization costs and incremental cost effectiveness ratio (ICER) was analysed in the COMPANION trial patient cohort³⁰. The results indicate that the clinical benefits of CRT are economically viable and can be achieved at a reasonable cost. In the seven year base case analysis, CRT alone group had an ICER of \$ 19,600 per quality adjusted life year (QALY) gained, and CRT-D (pacemaker defibrillator) had an ICER of \$ 43000 per QALY gained. However, the decision regarding the use of CRT therapy must be individualized to each patient independent of its economic impact.

To conclude, CRT is an effective device based management for heart failure patients who are symptomatic despite optimal medical treatment. It has been shown to improve symptoms, quality of life, reduction in heart failure related hospitalizations and all cause mortality. The introduction of CRT-D, to eligible patients has led to further reduction in mortality. The variable coronary sinus anatomy may be a limiting factor in these procedures but the success of optimal lead placement exceeds 90%. Further more, refinements in implantation techniques and reduction in cost should make CRT a widely accepted procedure, particularly in developing countries.

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