ABSTRACT

Congestive heart failure (CHF) remains an important and growing public health issue with a high mortality rate. Even though, advances in pharmacotherapy, mechanical assist devices and expertise in cardiac implantation is now available, these approaches are limited due to high cost and organ availability. Cardiac resynchronization therapy (CRT) seems to be an attractive option for these patients for improvement in clinical status and quality of life. But the limitation of CRT being its has a non responder rate of 20-30 %, which could be explained by suboptimal patient selection and technical difficulties. Therefore, with emphasis now shifting towards selection of potential responders before device implantation.

Cardiac resynchronization therapy (CRT), also called atrial synchronized biventricular pacing, is a new treatment modality for CHF that may relieve symptoms, improve patient quality of life, and prevent re-hospitalization. (5) In August 2001, the US Food and Drug Administration (FDA) approved the use of CRT in heart failure treatment.

CARDIAC DYSSYNCHRONY AND THE RATIONALE FOR RESYNCHRONIZATION

The heart relies on a coordinated sequence of electrical impulse generation and conduction that allows repeated filling and emptying of the atria and ventricles. When there is a delay in electrical signal transmission through the left bundle branch, this causes left bundle branch block (LBBB). Because the electrical signal to the left ventricle is delayed, the right ventricle begins to contract a fraction of a second before the left ventricle, instead of simultaneously. The result is an asynchronous, or uncoordinated contraction of the ventricles and a mis-timing in the contraction pattern of the left atrium and ventricle. Other conduction abnormalities, such as right bundle branch block (RBBB), also may contribute to less efficient contraction of the heart. This further reduces the pumping ability of the already weakened heart muscle. In the setting of CHF, the consequences of this electromechanical abnormality are abnormal ventricular filling, reduction in the left ventricular systolic output, and worsening of mitral regurgitation. (6)

Several studies have shown that intraventricular conduction delay is an independent risk factor for mortality in heart failure. (6,7) The aim of CRT is to improve electromechanical coupling in the heart by generating a more efficient sequence of impulse generation and conduction. The immediate hemodynamic benefits of the procedure include improved diastolic filling and more efficient systolic contractility. Mortality from CHF is a result of either progressive pump failure or sudden death caused by arrhythmia. CRT can slow the progression of pump failure and, when combined with an implant-able cardioverter defibrillator (ICD), prevent sudden cardiac death.

TECHNIQUE

Dual-chamber pacing is accomplished by placing pacing wires in the right atrium and right ventricle using subclavian or cephalic vein access. In CRT, an ad-ditional wire is inserted via the right atrium through the coronary sinus into a cardiac vein on the lateral wall of the left ventricle. (8) The presence of a pacemaker lead in the left ventricular free wall allows for simultaneous pacing of both ventricles and more physiologic atrioventricular timing. The result is more effective left ventricular contraction and improvement in stroke output.

INDICATIONS

The 2002 joint guidelines of the American College of Cardiology,
the American Heart Association, and the North American Society of Pacing and Electrophysiology endorse the use of CRT in patients with medically refractory, symptomatic, NYHA class III or IV disease and a QRS interval of at least 130 msec, a left ventricular end-diastolic diameter of at least 55 mm, and an LVEF of 30 percent or less. (9) Similar recommendations have been made by the Canadian Cardiovascular Society (10) and the European Society of Cardiology. (11) These guidelines were refined by an April 2005 American Heart Association Science Advisory, (12) which stated that "optimal candidates for CRT have a dilated cardiomyopathy on an ischemic or nonischemic basis, an LVEF ≤0.35, a QRS complex ≥120 ms, and sinus rhythm, and are NYHA functional class III or IV despite maximal medical therapy for heart failure."

**BENEFITS**

As shown in recent randomized controlled trials, (13-16), the benefits of CRT include the following:

- Improved cardiac contractility and increase ejection fraction
- Reduced mitral regurgitant fraction, which enhances cardiac output
- Improved exercise tolerance in the 6-minute walk test
- Improved New York Heart Association functional class
- Improved quality of life
- Reduced re-hospitalization for worsening heart failure

The role of CRT without an ICD in reducing mortality from heart failure is still unresolved. A recent meta-analysis by Bradley et al that pooled data from 4 randomized trials using CRT alone (2 trials) and CRT-ICD (2 trials) suggests that cardiac resynchronization reduces mortality from progressive heart failure by 51%. (17) Although CRT alone clearly improves symptoms of heart failure, the addition of a defibrillator appears to confer significant improvement in survival.

The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial enrolled patients to medical therapy, medical therapy plus CRT, and medical therapy plus CRT-ICD (18). This study, the first to directly compare CRT and CRT-ICD in patients without established criteria for defibrillator therapy, confirmed that the addition of a defibrillator to CRT has a significant impact on reducing heart failure-related mortality. CRT represents an important adjunct to existing medical therapies, and patients in reported trials were continued on angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers, β-blockers, diuretic agents, and aldosterone antagonists as appropriate.

The most important limitation of CRT as a modality of treatment for CHF is a relatively high nonresponder rate of around 30%. Lack of response to CRT is explained by suboptimal patient selection and technical questions relating (17) to placement of the left ventricular lead as well as timing of the atrioventricular interval delay.

Accordingly, emphasis has shifted toward selection of potential responders to CRT, before device implantation.

**CRITERIA FOR SELECTION OF RESPONDERS:**

**ECG CRITERIA FOR SELECTION:**

- **QRS Duration:**
  - In most of the trials, primary criteria for identifying interventricular dyssynchrony was QRS duration. Accordingly, patients with wide QRS were considered candidates for CRT. In general, studies used QRS duration >120 to 130 ms as a selection criterion. In addition, data from the Pacing Therapies in Congestive Heart Failure (PATH-CHF) II trial demonstrated that the benefit of CRT was most pronounced in patients with QRS duration >150 ms (as compared to patients with QRS duration 120 to 150 ms). (19)
  - However, careful analysis of the individual patients in many CRT studies demonstrated that 20% to 30% of the patients failed to respond to CRT, despite prolonged QRS duration. (20)

- **QRS Morphology:**
  - The initial studies required the presence of a left bundle branch block (LBBB) pattern on the ECG, whereas more recent studies also included patients with non-specific interventricular conduction delay (a poorly defined entity) or even right bundle branch block (RBBB) pattern. Only few studies evaluated CRT in patients with RBBB. In the CONTAK CD trial, (21) the patient subgroup with RBBB did not demonstrate a significant improvement in symptom status, heart size, or LVEF. Furthermore, a study designed to test patients with RBBB needs to be developed. In spite of no strong evidence in favor, guidelines do not differentiate between various types of conduction blocks and CRT.

**ECHOCARDIOGRAPHIC CRITERIA FOR SELECTION:**

Conventional selection criteria, which was applied in the large randomized trials, is mainly based on QRS as an identifier for cardiac dyssynchrony, but it has been demonstrated that many patients may present with areas of ventricular dyssynchrony despite a normal QRS width. In particular, patients with mild QRS prolongation between 120–150 ms may present very heterogeneously with synchronous contraction or pronounced dyssynchrony but in patients with a QRS width >150 ms, the picture appears more consistent and most patients will present with significant correctable dyssynchrony, thus requiring the need for further tests to demonstrate mechanical dyssynchrony. (20)

**Interventricular Dyssynchrony:**

As echocardiography remains a useful tool to select patients with heart failure and LV dyssynchrony, Initial CRT studies have focused on assessment of interventricular (left - right) dyssynchrony to predict response. Interventricular dyssynchrony can be evaluated by conventional pulsed-wave Doppler echocardiography and Tissue Doppler imaging as well for assessing the extent of interventricular mechanical delay. But most evidence suggests
that interventricular dyssynchrony is not useful in the prediction of response to CRT (20).

**Intraventricular Dyssynchrony**: Using an M-mode recording from the parasternal short-axis view (at the level of the papillary muscles), the septal-toposterior wall motion delay can be obtained, and a cutoff value of 130 ms was proposed as a marker of intraventricular dyssynchrony. Pitzalis et al. (22) evaluated 20 patients and reported a sensitivity and specificity of 100% and 63%, respectively, to predict response to CRT. Various new techniques like TDI, color-coded TDI, strain and strain rate analysis, three-dimensional echocardiography (3D Echo) have been tested to analyze mechanical dyssynchrony. However, no major trial has tested these new techniques.

A randomized, controlled Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (RethinQ) trial investigated the role of CRT in patients with heart failure who had mechanical dyssynchrony but a narrow QRS duration (23). At 6 months, there was no benefit from CRT on the primary end point of peak oxygen capacity or on heart-failure events. Similarly, the observational Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) trial (24) which was designed to identify echocardiographic predictors of response to CRT, revealed a low predictive accuracy for various measures of mechanical dyssynchrony. Undoubtedly, tissue Doppler will unravel more dyssynchrony than conventional Doppler. But crucial issues regarding “isolated tissue-Doppler dyssynchrony” remain like, intra- and interobserver variability, Quantification of dyssynchrony, Area of dyssynchrony versus site of LV lead (we all know how difficult it is to choose the site of LV pacing when using the transvenous route) and the area of dyssynchrony identified today may not be the same after a few months.

**ATRIAL FIBRILLATION AND RESYNCHRONISATION**

Atrial fibrillation (AF) is a frequently encountered problem in end-stage heart failure. The prevalence of AF has been reported to increase in parallel to the severity of heart failure, with 10% to 15% of patients in NYHA functional class II to III and up to 50% of patients in NYHA class IV having AF (25). Thus even if the patient today is in sinus rhythm, s/he is likely to develop AF in future. Currently, indications for CRT are limited to patients in sinus rhythm, namely because of the scarcity of data regarding the role of CRT in HF patients with AF; as well as the fact that the only randomized trial to evaluate the role of CRT in this setting (MUltisite STimulation In Cardiomyopathies-Atrial Fibrillation [MUSTIC AF]) yielded findings showing only “marginal benefit” of CRT compared with right univentricular pacing (26).

**COMPLICATIONS**

In a recent multicenter trial (the Multicenter InSync ICD Randomized Clinical Evaluation [MIRACLE ICD] trial) involving more than 400 patients, the overall complication rate was approximately 28%; however, most complications were minor and no mortality was reported. Failure of lead placement was the most frequent complication, and cardiac perforation and coronary sinus dissection were the most serious adverse events (27).

**ROLE OF CARDIAC RESYNCHRONISATION FOR PREVENTION OF HEART FAILURE EVENTS**

An argument that CRT might delay disease progression in patients with less severe symptoms through left ventricular reverse remodeling has led to a number of trials enrolling patients with New York Heart Association (NYHA) functional class I or II heart failure, including the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial (28) and the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT) (29). The results of the REVERSE trial and other smaller CRT trials involving patients with mild-to-moderate heart failure are strikingly consistent, although all the studies had a relatively short follow-up period (6 to 12 months). The trials did not show any significant improvement in functional capacity, as assessed by the 6-minute walk test or NYHA classification, and there was no improvement in quality of life. However, there was a concordant and significant reduction in the left ventricular volume and an increase in the LVEF across the trials. In addition, the REVERSE trial showed a significant reduction (53%) in the relative risk of first hospitalization for heart failure in patients receiving CRT, although there was no difference in mortality between patients who received CRT and those who received optimal medical therapy.

The recently published results of the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) (30) confirm the earlier findings. The investigators followed 1820 patients with NYHA class I or II heart failure for an average of 2.4 years. The primary end point, a composite of death from any cause or nonfatal heart failure (which was defined as the need for intravenous decongestant therapy in an outpatient regimen or an augmented heart-failure regimen during hospitalization), was significantly reduced when CRT was added to an implantable cardioverter-defibrillator (ICD), as compared with an ICD alone. Patients in the CRT-ICD group also had significant improvement in cardiac function at 1 year. The superiority of CRT was driven solely by a 41% reduction in the risk of a first heart failure event, since mortality was not influenced by the choice of device, even with an increased trial duration.

It is not completely clear how the enrolled patients differ from those in earlier CRT trials, since no objective criteria were used to classify functional status at baseline and the treatment of patients and their subsequent functional status were determined by clinicians who were aware of study-group assignments. Moreover, at least 10% of patients had NYHA class III or IV symptoms at least 3 months before randomization. It appears that MADIT-CRT enrolled patients with stage C heart failure and not patients who had always been asymptomatic (e.g., stage B). This is a critical point and would argue against the use of CRT in patients solely on the
Basis of a wide QRS duration. Given high cost of these devices, it appears prudent that any expanded indication for CRT in less symptomatic patients should be confined to patients with a QRS duration of more than 150 msec and in whom previous marked symptoms have been controlled with optimal medical therapy.

**COST EFFECTIVENESS OF CRT**

Economic considerations have not been studied from Indian perspective. A preliminary economic analysis from Germany has concluded that CRT is a cost-effective intervention (31). The modestly higher upfront cost (>22% compared with medical treatment) due to implantation of a CRT device was offset by a significant decrease in hospitalization within the first year of treatment. Longerterm data are not available, and a comparison with CRTdefibrillator (a more expensive form of implantable device therapy) has not been performed. From an Indian perspective identification of prospective responder becomes more important because of economic consideration.

**CONCLUSION**

Over the last 10 years, the rate of hospitalization for CHF has increased by more than 150% (32). This trend will most likely continue because of an aging population and increased survival after acute myocardial infarction. Currently, an estimated 10% of patients with CHF are eligible for CRT: these patients have a low ejection fraction, evidence of dyssynchrony, and severe symptoms of CHF despite optimal medical therapy (33). For a treatment modality that is free of compliance issues and appears to be well tolerated, CRT should be considered for all patients who have advanced CHF and meet existing criteria. In patients with CHF, CRT has the potential to improve exercise capacity and patient well being, reduce rehospitalization, and, most likely, reduce mortality. When combined with an ICD, CRT also reduces the risk of sudden arrhythmic death. Several ongoing large randomized trials will shed more light on patient selection, technical issues of lead placement, role of CRT in atrial fibrillation, and the long-term tolerability of CRT.

**REFERENCES**


