Review Article

CARDIAC RESYNCHRONIZATION THERAPY FOR SEVERE DRUG REFRACTORY SYSTOLIC HEART FAILURE

Deepak Natarajan

Senior Consultant (Interventional Cardiology), Indraprastha Apollo Hospitals, Sarita Vihar, New Delhi 110 076, India.

\ A substantial number of patients with severe congestive heart failure due to systolic dysfunction develop mechanical dyssynchrony of the left ventricle, which results in suboptimal filling, and contraction of this chamber and consequently reduced ejection of blood into the aorta. Furthermore the altered hemodynamics are accompanied with reduction of left ventricle ejection fraction, increased volumes of the heart, and increased morbidity and mortlity. Cardiac reysnchronization therapy using a biventricular pacemaker with three leads- the first placed in the right atrium, the second placed in the right ventricular apex and the third pacing lead positioned in a branch of the coronary sinus effectively aids the heart to pump in a synchronous fashion. Large scale randomized trials have demonstrated significant reduction in mortality and hospitalizations with this therapy in patients with severe heart failure refractory to optimal drug therapy. The reduction in mortality is preceded by significant improvement in clinical symptoms; quality of life and reverse left ventricle remodeling.

Key words: Heart failure, Systolic dysfunction, Mechanical dyssynchrony, Biventricular pace maker, Cardiac resynchronization therapy, Tissue Doppler imaging.

HEART failure is a clinical syndrome which results from structural or functional cardiac disorder that impairs the ability of the ventricle to fill up with or eject blood commensurate with the needs of the body. Heart failure may result from disorders of the myocardium, endocardium, valvular structures, great vessels of the heart, or rhythm disturbances. Heart failure, however, is usually discussed primarily in terms of myocardial dysfunction because valvular disease, pericardial disorders and rhythm disturbances are usually amenable to surgery or other definitive treatment.

Short-term hemodynamic affects of left or simultaneous right and left ventricle stimulation were first published more than 3 decades ago and clinical ramifications of the technique called as cardiac resynchronization therapy were first reported in the mid nineties of the last century. The implantation of atrio biventricular pacemakers in patients with severe congetsive heart failure, but minus the conventional indications for pacemaker, was first reported in Europe. The concept was based on the frequent manifestation of intraventricular conduction delays in patients with chronic heart failure.

Heart failure is practically divided into systolic and diastolic dysfunction and the distinction is primarily based on the left ventricle ejection fraction. In diastolic dysfunction the left ventricle ejection fraction is preserved in the presence of all the symptoms of heart failure such as dyspnoea, fatigue, fluid retention and decreased exercise tolerance. This article will mainly focus on heart failure due to systolic dysfunction.

Biventricular pacemaker (BIV) implantation has rapidly evolved as mainstream therapy for severe drug refractory congestive heart failure (CHF) because of systolic left ventricle (LV) dysfunction. This modality of treatment is also known as cardiac resynchronization therapy (CRT). This is particularly true in patients of severe CHF (almost 40% to 45%) who develop mechanical dyssynchrony. More than a third of patients with ischaemic or nonischaemic cardiomyopathy possess abnormal electrical activation in the form of left bundle branch or intraventricular blocks, which result in different parts of LV to contract at different times of the cardiac cycle resulting in intraventricular dyssynchrony. Mechanical dyssynchrony of LV causes blood contained in this chamber to slosh around, back and forth, rather than being ejected into the aorta. This mechanical dyssynchrony of the LV may manifest as prolongation of the QRS complex on the surface ECG. Most randomized studies with CRT have defined "wide QRS" as more than 120 ms, although some have used a cut off of more than 130 ms.

Many studies have suggested that electrical conduction delay is accompanied by suboptimal LV systolic function and is an important prognostic marker for morbidity and mortality in patients with severe CHF. However it has now been realized that QRS duration is an indirect marker and not a true reflection of mechanical dyssynchrony, which is the substrate causing actual decline in LV function. Recent studies have shown that LV mechanical dyssynchrony is a predictor of severe cardiac events in patients with CHF independent of surface QRS duration. In fact mechanical dyssynchrony is present in a substantial number of patients of CHF, with normal QRS duration on surface ECG. Hence an important parameter in the workup of such patients is detection of LV mechanical dyssynchrony. Luckily this can be achieved quite easily by non-invasive means and the best tool for the job is tissue Doppler imaging (TDI). This is a simple echocardiographic test to record the difference in contraction times of the various LV wall segments. The R-wave of the QRS complex is used as the reference point for measurement of time intervals, and time to peak myocardial systolic velocity (Ts) is measured in milliseconds. The sample volume is placed at the LV septal, lateral, anterior and inferior segments at both basal and mid levels using apical 2 and 4 chamber views. For the assessment of systolic dyssynchrony the standard deviation of Ts (Ts-SD) and the maximum temporal of Ts (Ts-diff) of all 8 segments are calculated. The cut off values by and large employed are Ts-SD >35 ms and Ts-diff >65 ms to detect mechanical dyssynchrony.

A variety of echocardiographic techniques have been suggested for assessment of LV dyssynchrony and prediction of response to CRT. These techniques include M-mode assessment, 2 dimensional echocardiography using phase energy or intravenous contrast, and three-dimensional echocardiography. TDI is the most extensively used technique and the majority of studies have used time to peak systolic velocity to assess LV dyssynchrony. Initially 4-chamber view was used and velocity tracing from the septal to lateral segments were obtained and a septal to lateral wall delay of 61 ms, was prediction of acute response to CRT. Subsequently 4 basal segments (septal, lateral.inferior and anterior) were used and a delay of 65 ms identified a responder, defined as 15% reduction in LV end systolic volume. Some workers use 12 segments and LV index is derived from the standard deviation of all 12-time intervals. This formula using a dyssynchrony index of >31 ms yields a sensitivity and specificity of 96% and 78% to predict LV reverse remodeling.

Intraventricular dyssynchrony can be accompanied by intraventricular dyssynchrony, which is also associated with negative clinical outcomes, because in this case the right and left ventricles are out of synch with each other and consequently there is no synchronized contraction or relaxation. Added to this there might be prolonged AV delay leading to mitral regurgitation and further exacerbation of heart failure.

In CRT a BIV pacemaker is implanted percutaneously with one atrial lead in the right atrium, and two ventricular pacing leads placed in the right ventricle apex and the other (the third lead) lead positioned in a posteriolateral branch of the coronary sinus, and this corresponds to pacing the left ventricle. The mouth of the coronary sinus lies in the right atrium.

Thousands of CHF patients have been studied in large randomized clinical trials using CRT involving low voltage stimulating pulses (typically 2 or 3 volt output.) to help the failing heart to contract in a more synchronized and effective fashion. The right ventricle and coronary sinus lead (i.e., left ventricle lead) act simultaneously to make the LV contract in a single cohesive unit. The right ventricle is also stimulated in the process and therefore right ventricle contraction is also synchronized.

Besides delivering low output pulses during pacing a large study has employed CRT systems with defibrillation capacity. These devices over and above prolonged synchronized pacing also perform as cardioverter-defibrillators (ICD's) and are termed CRT-D devices (they are also nicknamed "combo" devices).

The COMPANION study (2000-2002, published in 2004) enrolled 1520 NYHA class 111-1V patients with a QRS > 120 ms, LV ejection fraction (LVEF) of <35 % and they also had to be receiving optimal drug therapy for their condition. Patients were randomized into 3 arms: drug therapy alone, drug therapy plus CRT, and drug therapy and CRT-D. At the end of the study it was observed that CRT reduced all cause mortality by 24% ($P = 0.059$) while CRT-D reduced the risk of all cause mortality 36% ($P = 0.003$) compared with drugs alone. COMPANION, the largest CRT trial to date, demonstrated that CRT-D significantly reduced mortality in severe CHF patients already on optimal pharmacological therapy.

The other large CRT study involving 813 patients with NYHA class 111-1V CHF, LVEF < 35% and a wide QRS (>120 ms) was called CARE- HF. Similar to the

companion trial CARE_HF studied patients with severe CHF who were already on optimal medication. The major difference was that CARE did not use the CRT-D device (there was no defibrillators attached to the BIV pacemakers).

The primary composite end points in the care study were all cause mortality or first hospitalization for a major cardiovascular event. Patients in the CRT arm demonstrated 37% reduction in the composite endpoints compared with the drugs only group. Moreover all cause mortality was significantly reduced by 36% in the CRT group. The CARE trial demonstrated reduction in LV size, lessening of mitral regurgitation, and improvement in LVEF. Definite reverse remodeling of the LV was observed and this may have accounted for the significant reduction in deaths. It must be however borne in mind that one third of deaths in the CRT arm were sudden and this makes a strong case for combo devices in patients with severe CHF on optimal drug therapy.

Biventricular pacemaker implantation is slightly more complicated than conventional dual chamber pacemakers. The commonest problem is difficulty in successfully positioning the LV lead in a favorable branch of the coronary sinus. Lead dislodgement can occur in 10% cases. Other complications include coronary sinus dissection or perforation besides pacemaker pocket infection.

The earlier randomized trials of CRT were under-powered to detect reduction in mortality but did demonstrate substantial improvements in symptoms, quality of life scores, 6 minutes walking distance and LV function.

Armed with all this evidence the American College of Cardiology and the American Heart Association endorsed CRT for patients with severe CHD as early as 2002. In 2005 an American Heart Association Science Advisory stated that "optimal candidate for CRT has dilated cardiomyopathy (ischaemic or non ischaemic), an LVEF <35%, a QRS complex of 120 ms, is in sinus rhythm, and is in NYHA class 111-1V despite maximal medical therapy for heart failure".

The European Society of Cardiology in September 2007 has recommended the use of BIV pacemaker in heart failure patients who remain symptomatic in NYHA classes 111-1V despite optimal drug therapy, with LVEF <35%, LV dilatation (LV dilatation/different criteria have been used to define LV dilatation in controlled studies on CRT), normal sinus rhythm and wide QRS complex >120 ms).

In the Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) 426 patients with severe CHF were assessed for good CRT responses by a composite clinical end point that included HF-free survival, NYHA class improvement, and patient self assessment cores and also in terms of changes in left ventricular end systolic volumes as measure of reverse remodeling. By 6 months 69% of the group had improved according to the clinical criteria; the rate being 76% in patients with non- ischaemic disease and 64% in ischaemic HF patients (P = 0.01). Three Doppler measurements were significantly associated with good clinical response, and these were interventricular mechanical delay (difference between left and right pre ejection intervals); LV pre-ejection interval and changes in LV filling time relative to RR interval.

Some unresolved issues in CRT are implantation of BIV pacemakers in less symptomatic patients (NYHA class 11-111) and in patients with atrial fibrillation (AF). CRT has been shown to improve LV functions in the less symptomatic group without any reduction of mortality, which is understandable as deaths in this group of patients would be extremely low. In patients with AF it would be best to reduce the heart rate with a combination of digoxin, amiodarone and beta-blocker to ensure that there is BIV pacemaker capture more than 85% of the time.. The other approach being considered is the "ablate and pace" technique wherein the AV node is ablated and then the BIV pacemaker implanted. In CHF patients AF is present in as high as 50% of the time in class IV patients because atrial myopathy. Atrial myopathy in CHF is an early and consistent component of the HF condition and once developed heralds a worse prognosis. A recent randomized study of CRT in patients of CHF with AF suggested that the best response was obtained by the "ablate and pace" because this ensured adequate BIV pacing. Further large scale randomized studies will give definitive answers in these gray areas

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