



## **Cardiac resynchronization therapy in Congestive Heart Failure – a review**

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### **ABSTRACT**

**Congestive Heart Failure (CHF) incidence is increasing in contrast to incidence of coronary heart disease. Since 1992 cardiac pacing was introduced to treat heart failure. Improved modes of biventricular pacing created a milestone in treatment of CHF. Interventricular conduction delays (IVCD) are associated with adverse mechanical conditions and put CHF patients at a significant mechanical disadvantage. Apex to base contraction sequence is noted in CHF patients with IVCD. Atrial synchronized biventricular pacing or cardiac resynchronization therapy restores the base to apex contraction sequence and is shown to improve left ventricular systolic function and reversal of left ventricular remodelling. Hence, there is a promising electrical arm of therapy for CHF patients.**

*Keywords: Congestive heart failure; resynchronization; biventricular pacing.*

Epidemiological evidence show that heart failure has shown increasing incidence in contrast to coronary artery disease which is decreasing due to secondary and primary prevention. The present data show incidence for heart failure of 2% per year. 4-5 million people are newly affected by the disease. The prognosis is limited after the diagnosis is confirmed. According to US Framingham study, median life expectancy is 3.2 & 5.4 year after the diagnosis in male and female respectively. For the patients in advanced stage of the disease, mortality rate is 27% within 3 years.<sup>1</sup>

Till early nineties, cardiac pacing was mainly used to treat various forms of bradyarrhythmias. Austrian group lead by Margarete Hochleitner in 1992 introduced AV sequential pacing & has revolutionized the treatment of congestive heart failure and added an electrical arm of therapeutic options along with the drug therapy.

One third of patients with chronic heart failure have electrocardiographic evidence of a major intraventricular conduction delay, which may worsen left ventricular systolic dysfunction through asynchronous ventricular contraction.<sup>2</sup>

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Left bundle branch block (LBBB), traditionally viewed as an electrophysiologic abnormality, is increasingly recognized for its profound hemodynamic effects. Besides asynchronous myocardial activation, LBBB may trigger ventricular remodelling. Exercise nuclear studies frequently show reversible perfusion defects in the absence of obstructive coronary artery disease and some patients with intermittent LBBB develop angina coincident with the onset of LBBB. It is uncertain, however, if these phenomena are because of myocardial ischemia or ventricular asynergy. LBBB is accompanied by progressive left ventricular (LV) dilatation and mitral regurgitation. Some authors opine that it is not known whether LBBB is the cause or consequence of LV dilatation.<sup>3</sup>

But some authors have a firm belief that bundle branch block is a result of the dilatation of the myocardial fibers, death of myocardial cells which are replaced by fibrous tissue.<sup>4</sup>

AV sequential pacing or biventricular pacing or multisite pacing showed an improved LV systolic function, an improved clinical benefit in terms of New York Heart Association (NYHA) classification, an improved systolic and diastolic blood pressure reduction of the heart-chest relationship as well as a reduction in resting heart rate and the echocardiographic resting parameters.<sup>5</sup>

Toussaint *et al* conducted a study in which radionuclide angioscintigraphy with Tc99m red cell labelling was performed in 21 patients with NYHA functional class III or IV, mean QRS duration of  $180 \pm 15$  msec and

resynchronization between LV apex-base. It was shown that biventricular pacing could reduce activation delays between LV and right ventricle (RV). A close correlation was found between early apex to base resynchronization induced by biventricular pacing and late increase in LV ejection fraction ( $r=0.59$ ) parallel with its known interventricular resynchronization effect. Biventricular pacing reversed the apex to base ventricular activation sequence, causing early contraction of LV base followed by the apex. These changes persisted upto 12 months along with an improvement of LV systolic function.<sup>6</sup>

It has been shown that upto 50% of patients with chronic systolic heart failure have interventricular conduction delays, such as LBBB that result in abnormal electrical depolarization of heart. Prolonged QRS duration results in abnormal interventricular septal wall motion, decreased contractility, reduced diastolic filling time, prolonged duration of mitral regurgitation, which places the failing heart at a significant mechanical disadvantage. Prolonged QRS duration has been associated with poor outcome in heart failure patients. Atrial synchronized, biventricular pacing or cardiac resynchronization therapy optimizes atrial-ventricular delay, narrows QRS duration and seems promising in the management of advanced heart failure patients.<sup>7</sup>

Further, it has been shown that sudden cardiac death accounts for 50% of deaths in patients with congestive heart failure (CHF). The value of an implantable cardioverter

defibrillator (ICD) in secondary prevention of sudden cardiac death is well established. The use of ICD for primary prevention of sudden cardiac deaths in patients of CHF is being actively evaluated. Several large multicenter trials are underway, some combined with biventricular pacing.<sup>8</sup> The cost of ICD limits its wider application especially in developing countries like Nepal. Besides, some authors have concluded that biventricular pacing decreases the inducibility of ventricular tachycardia in patients with ischemic cardiomyopathy.<sup>9</sup> Thus raising the hope for the same results in dilated cardiomyopathy (DCM) and alleviating the need for implanting costlier ICDs

## HOW ?

Left ventricular and biventricular pacing as an adjunct therapy for chronic heart failure in selected patients use new electrode for transvenous left epicardial pacing via tributaries of the coronary sinus. Dual chamber pacemakers designed for atrial triggered biventricular pacing were implanted in conjunction with Easytrak-lead for left ventricular pacing in a coronary vein. Lead placement was achieved via subclavian vein access and a preformed guiding catheter for coronary sinus insertion.<sup>10</sup>

Before the advent of the new type of left ventricular pacing lead -- the 'side-wire' pacing lead--, LV pacing was a difficult procedure and had a high failure rate.<sup>11</sup>

Earlier, biventricular pacing was done by endocardial pacing which also appeared safe.

LV pacing lead was placed either via combined femoral and internal jugular approach or later by transseptal puncture via right internal jugular vein with a dedicated kit.<sup>12</sup>

Successful use of a new unipolar ventricular lead with a distal portion preshaped in an S curve to provide steerability within the coronary sinus in 13 patients in sick-sinus-syndrome has opened new avenue for safe and reliable permanent pacing via the coronary sinus in the majority of patients in isolation or in conjunction with right ventricular pacing for biventricular synchronization.<sup>13</sup>

## EFFECTS

Various clinical trials have shown beneficial effects of biventricular pacing.

In a study of 42 patients with NYHA class III-IV symptoms, baseline QRS complex of  $175 \pm 3$  msec, PR interval of  $196 \pm 33$  msec, mean LVEF 0.23 by Vogt *et al*, functional benefit was indicated by relative increase in peak oxygen intake ( $\text{VO}_2$ ) compared with baseline, was significantly correlated with shortening of paced QRS width (correlation coefficient,  $r=0.055$ ;  $p<0.05$ ).<sup>14</sup>

Contradicting the established concept of most of the heart therapies enhancing systolic function while concomitantly increasing myocardial oxygen consumption ( $\text{MVO}_2$ ) Nelson GS *et al* hypothesized that pacing/stimulation in contrast incurred systolic benefits without raising energy demand. Methods applied to test the hypothesis was cardiac catheterization to measure ventricular and aortic pressure,

coronary blood flow, arterial-coronary sinus oxygen difference ( $\sigma\text{AVO}_2 - \text{MVO}_2$ ). They concluded that ventricular resynchronization by left ventricular or biventricular pacing/stimulation in DCM patients with LBBB acutely enhances systolic function while modestly lowering energy cost (decrease in  $\text{AVO}_2 - \text{MVO}_2$ ) proving the valuable mode for treating DCM patients with basal dyssynchrony.<sup>15</sup>

To assess the modes of benefit by biventricular pacing noninvasively, Kim *et al* performed three dimensional echocardiography and six-minute walk tests in 15 consecutive heart failure patients (NYHA class III-IV) with an implanted biventricular pacing system after short term (2-7 days post-implant) while the patients were in sinus rhythm. Compared with baseline values, biventricular pacing significantly reduced LV end diastolic volume (EDV) and end systolic volume (ESV). Mitral regurgitation fraction was significantly reduced by 11% and forward stroke volume (FSV) increased by 13.9%. Exercise capacity was significantly improved with biventricular pacing by 43.3%. Regression analysis showed that increase in FSV independently predicted percentage improvement in walking distance. Both basal QRS duration and QRS narrowing predicted pacing efficacy, showing a significant correlation with % Delta EDV, % Delta ESV and % Delta FSV. Hence, the conclusion: Biventricular pacing induced >15% increase in FSV, predicted >25% increase in walking distance and accompanied by an immediate reduction in LV size & mitral regurgitation.<sup>16</sup>

Similar benefits of reversal of LV remodelling was found in a study conducted

by Lau *et al* up to 3 months post-biventricular pacing in CHF.<sup>17</sup>

Encouraged by the finding that acute left ventricular pacing had been associated with hemodynamic improvement in patients with congestive heart failure, wide QRS complex, Pappone C *et al* hypothesized that pacing two left ventricular sites simultaneously would produce faster activation and better systolic function than single site pacing. They selected 14 NYHA class III-IV

CHF patients in normal sinus rhythm with LBBB and QRS > 150 msec. 8 F dual micromanometer catheter was placed in aorta for measuring  $+dP/dt$ , aortic pulse pressure and end diastolic pressure. Pacing leads were positioned via coronary veins at posterior base and lateral wall. Dual site pacing increased peak  $+dP/dt$  significantly more than that observed in lateral and posterior base pacing separately. Dual site & posterior base pacing raised aortic pulse pressure significantly more than lateral pacing. Dual site pacing shortened QRS duration by 22%. Thus, dual site pacing was shown to have had improved ventricular activation synchrony and systolic function more than single site pacing. This novel approach deserves consideration for future heart failure pacing strategy.<sup>18</sup>

However, there is a divulgence of opinion regarding the mechanism of benefit in biventricular pacing. Morris-Thurgood *et al* in a study published in *Europace* demonstrated that LV pacing acutely benefited CHF patients with pulmonary capillary wedge pressure more than 15 mmHg irrespective of LBBB. They proposed that the mechanism of response

might be an improvement in LV filling rather than ventricular systolic resynchronization.<sup>19</sup>

To sum up, small uncontrolled studies which had little or no follow-up demonstrated that pacing from the left ventricle could synchronize contraction of the ventricle and improve overall performance. These encouraging reports led to a number of larger multicenter trials, which been recently reported. These trials have consistently shown improvements in such objective measurements as peak exercise oxygen consumption, ejection fraction, heart rate variability, 6-minute walk test distance and anaerobic threshold, as well as subjective improvements such as quality of life assessment. A number of large, multicenter double-blinded trials are ongoing which will seek to further assess the benefits of biventricular or multisite pacing.

Another novel mode of pacing therapy, which may be of clinical importance for a broader range of CHF patients, is **contractility modulation**, which involves subthreshold pacing to increase intracellular calcium and enhance inotropy.<sup>20</sup>

### **Trials**

Following are the list of major ongoing & near-completed trials.

The pacing therapies for congestive heart failure (**PATH-CHF**) study.<sup>21</sup>

PATH-CHF : a single-blind, randomized, crossover controlled trial. Epicardial LV electrodes in 50 patients was successfully implanted with low (2%) early mortality. Improvement in LV function in 80% (increase in dP/dt by 28%, aortic pulse pressure up to

16%, improvement in 6-min walk test distance by 60 meters, rise in peak exercise oxygen consumption by 23% )

The multicenter insync randomized clinical evaluation (**MIRACLE**).<sup>22</sup>

Large (n=500), prospective, randomized, double-blind, controlled trial Pacing therapies in congestive heart failure II (**PATH CHF-II**) study.<sup>23</sup>

Prospective, randomized cross-over study currently investigating the potential benefit of ventricular resynchronization therapy in a population with advanced heart failure, with or without an accepted indication for an implantable defibrillator.

Heart failure management using implantable devices for ventricular resynchronization : Comparison of medical therapy, pacing and defibrillation in chronic heart failure (**COMPANION**) trial. COMPANION Steering Committee and COMPANION Clinical Investigators.<sup>24</sup>

### **Objectives**

To determine whether optimal pharmacological therapy used with ventricular resynchronization therapy alone or (2)ventricular resynchronization therapy combined with cardioverter-defibrillator capability is superior to optimal pharmacological therapy alone in reducing combined all-cause mortality and hospitalization; reducing cardiac morbidity; improving functional capacity, exercise performance, quality of life and increasing total survival.

### Size of beneficiaries ?

To estimate the number of people who might benefit from ventricular resynchronization therapy, all patients admitted to a U.K. District General Hospital with the diagnosis of CHF over one calendar year were audited. The selection criteria were: severe heart failure NYHA class III or IV, CHF due to DCM, QRS >120msec or presence of BBB pattern. 1042 patients fulfilled diagnostic criteria & approximately 10% of patients were found to be appropriate for biventricular pacing.<sup>25</sup> This represents a large number of patients who might benefit from this new therapy.

Results of completed & ongoing trials would certainly throw more light on this new form of treatment.

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