CARDIAC RESYNCHRONIZATION THERAPY: IMPROVING QUALITY OF LIFE AND SURVIVAL IN PATIENTS WITH HEART FAILURE

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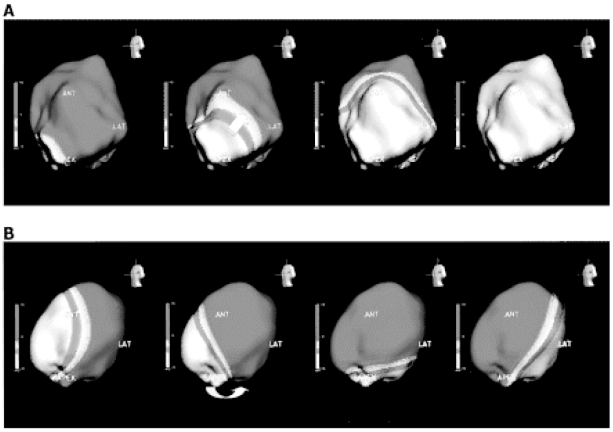
INTRODUCTION

WIDE QRS IN HEART FAILURE PATIENTS: An electrical problem with severe mechanical consequences

Just 30 years ago, the hope for survival in patients with heart failure (CHF) was dismal and centered on heart transplantation as the ultimate therapy[1]. Now, medical and device therapies are available that reduce symptoms, reverse progression of left ventricular (LV) dysfunction, and, importantly, improve long-term survival without the need for heart transplantation[1]. Between 7%-14% of all patients with dilated cardiomyopathy are candidates for Cardiac Resynchronization Therapy (CRT)[2]. Other than severe CHF these patients have wide QRS[2]. It is now known that the presence of LBBB or intra-ventricular conduction delay may cause mechanical abnormalities (or asynchrony)[3], resulting aggravation of CHF and death. CRT addresses the mechanical asynchrony caused by prolonged QRS and is turning out to be one of the most promising developments in the fight against CHF. The mechanical asynchrony results in decreased left ventricular (LV) ejection fraction[3], and increases mortality[5,6]. In fact, the QRS duration is a simple marker which has a linear correlation with higher death date[7,8]. Approximately, 20% of the heart failure patients will have prolonged QRS duration. It is vital to recognize these patients as CRT results in symptomatic relief and importantly, prolongation of their life[9]. Iatrogenic widening of the QRS such as that caused by permanent pacing also results in mechanical LV dyssynchrony and is associated with increasing frequency of heart failure admissions, and of heart failure related deaths[10].

Figure 1 shows the 3D spread of electrical activity in a patient with severe CHF and normal QRS and in the lower panel a CHF patient with a wide QRS. It is easy to visualize how an abnormal electrical spread can

Figure 1:
Ventricular activation sequence in narrow vs prolonged QRS duration failing hearts. A, 3D activation sequence recorded with 3D mapping system (EnSite 3000, Endocardial Solutions) in a patient with dilated cardiomyopathy, heart failure, and QRS duration of 95 ms. The activation breakthrough point was located in the septal region of the left ventricle. From this site, the activation immediately propagated to the anterior and lateral walls as indicated by the arrow. The basal region of the left ventricle was the last activated. B, In contrast, in a patient with a QRS duration of 179 ms, dilated cardiomyopathy, and heart failure, the propagation wave front was unable to cross from the anterior region to the lateral wall as a result of a functional line of block, but instead, rotated around the apex showing a U-shaped activation sequence. The lateral and posterolateral regions were the last activated areas of the left ventricle. Circulation. 2004; 109:300



cause an abnormal mechanical contraction of the LV. Such abnormal contraction or asynchrony results in development of mitral regurgitation, and generally ineffectual contraction of the different regions of the LV[11]. Typically, there is regional contractile phase delay between the anteroseptal and posterolateral walls of the LV (intraventricular asynchrony), and a phase delay in contraction between the right and left ventricles (interventricular asynchrony). Thus the electrical abnormalities result in 'remodeling of the LV'[12]. These mechanical asynchronies translate into abnormal myocardial metabolism, redirection of regional coronary perfusion, and cellular changes

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characterized by abnormalities in cellular calcium handling and upregulation of stress kinases[13,14].

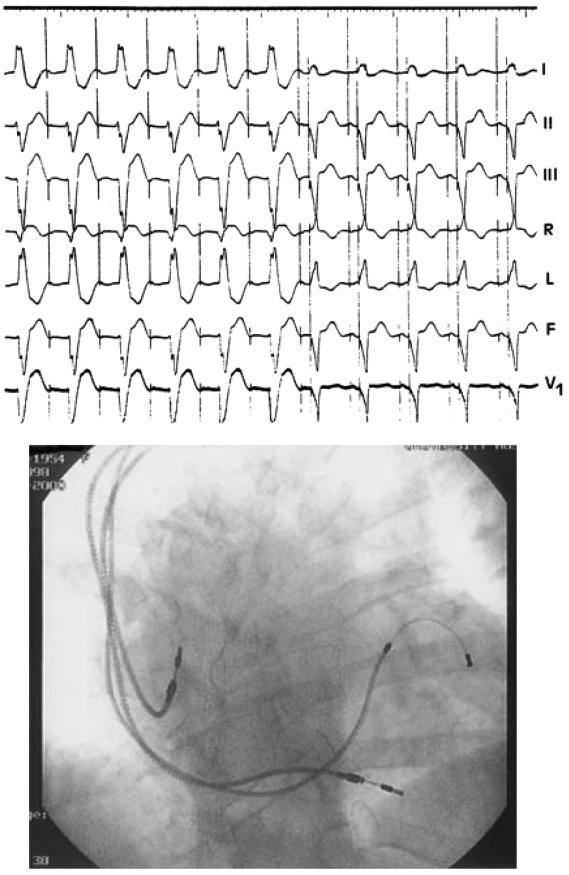
Some of the early hemodynamic studies of abnormal ventricular activation in dilated cardiomyopathy (DCM) patients were done by Xiao et al.[15,16]. In 50 DCM patients with QRS duration between normal and extremely long (190 ms), a positive correlation was found between the QRS duration and the overall duration of mitral regurgitation and LV contraction time. These data show that the wider the QRS complex, the poorer the LV systolic performance. Furthermore, prolonged isovolumic contraction and relaxation times induced a proportionate decrease in LV filling time to a critical value of 200 ms or less in patients with the longest QRS duration. The functional changes brought about by the widening of QRS can unleash a cascade of events which results in mechanical, metabolic and perhaps even molecular abnormalities[17]. It is possible that the development of wide QRS is a stage in the natural history of DCM which portends an ominous prognosis. In 1998 Wilensky et al reviewed ECG's of patients dying from DCM[18]. Eighty two per cent of patients had significant intraventricular conduction disturbances on the last ECG recorded within 60 days before death. Among the patients who presented with conduction abnormalities at baseline, 68% had progressive disturbances in the time period studied. The mean QRS duration increased from 100 ± 20 ms at the first examination to 130 ± 30 ms at the end of follow-up.

Bi-Ventricular Pacing:
Restoring Electrical Synchrony

In 1998 LeClerc and Cazeau demonstrated the acute hemodynamic effects of biventricular pacing in patients with end-stage heart failure[19]. They placed percutaneous leads in the right atrium, right ventricle (RV) and left ventricle (LV) via the coronary sinus.

Significant narrowing of the QRS associated with beneficial hemodynamic effect was shown (Figures 2, 3). Cardiac Index was significantly improved with Bi-Ventricular pacing. LeClerc et al, also showed that the posterolateral base of the LV was the last to be activated (Figure 4), thus establishing a target for the LV lead position. Pacing simultaneously from the RV and LV could narrow the delay in activation in effect resynchronize the LV. Several acute studies followed

Figure 2:
Surface ECG showing the effects on QRS duration of switching from the AAI pacing mode (left side) to the biventricular DDD pacing mode (right side) at the same pacing rate. QRS duration is decreased by 110 ms (from 240 to 130 ms). LeClerc C, J Am Coll Cardiol 1998; 32:1825-1831



and confirmed the benefits of Bi-Ventricular pacing on cardiac function and LV mechanics [20-24].

In 2001, Stellbrink et al, on behalf of PATH-CHF Investigators, reported the intermediate term effects of 6 months of Bi-Ventricular pacing or 'cardiac resynchronization'[25]. The data showed a reduction in LV volumes in the majority of patients with advanced HF and wide QRS. As there was a reversal of the remodeling which occurred with conduction delay, the authors coined the term 'reverse remodeling' to describe the effect of cardiac resynchronization therapy. The authors admitted that the mechanisms leading to this reverse remodeling effect were incompletely understood, but postulated that a reduction in regional wall stress, myocardial oxygen demand and functional mitral regurgitation may be responsible. Of note the PATH-CHF Investigators

Figure 3:
Acute hemodynamic effects of temporary biventricular DDD pacing in a class III patient with ischemic cardiomyopathy. Switching from AAI to biventricular DDD pacing at the same pacing rate produces an instantaneous decrease in pulmonary capillary wedge pressure (PCWP) (mean and systolic peak) and a 32% increase in cardiac output, while the QRS duration is decreased by 35% (200 to 130 ms). LeClerc C, J Am Coll Cardiol 1998; 32:1825-1831

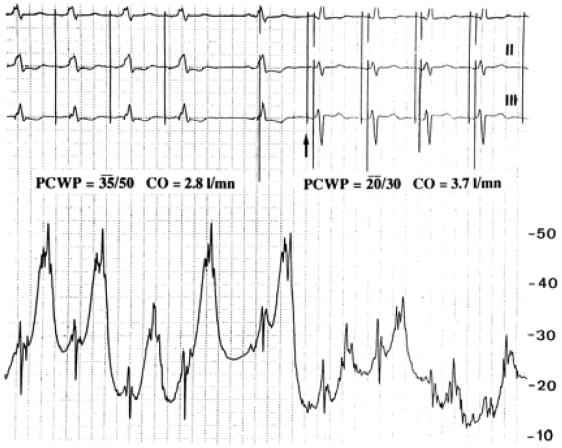
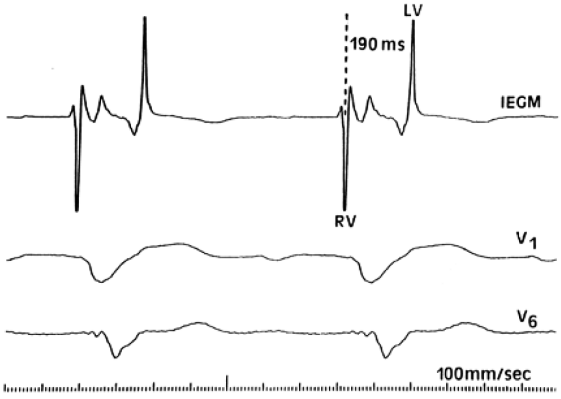


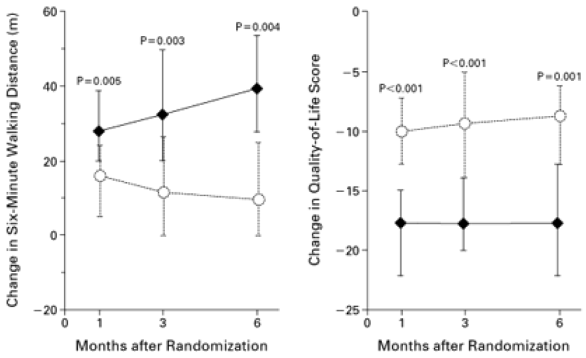
Figure 4:
Intracardiac ECG recording at the sites of the earliest (inferior base of the right ventricle close to the tricuspid annulus) and of the latest ventricular activation (posterolateral base of the left ventricle). The interventricular conduction delay is 190 ms. LeClerc C, J Am Coll Cardiol 1998; 32:1825-1831



used an epicardial 'screw-in' lead for their study.

In 2002, the results of the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) were reported[26]. Using less ambitious goals they were able to show clinically and statistically significant improvement in quality of life score and the 6-minute walk (Figure 5). The successful completion of this double-blind study of patients with moderate-to-severe heart failure and a prolonged QRS interval established cardiac resynchronization as an accepted therapy for CHF and led to the approval of the Medtronic InSync device. It also established clinical criteria for CRT i.e., 1) CHF refractory to drug therapy. 2) QRS duration >130 msec. 3) LV ejection

Figure 5:
Shown are median changes (with 95 percent confidence intervals) one, three, and six months after randomization in the control group (circles) and the cardiac-resynchronization group (diamonds). P values are for the comparison between groups. For each variable, data are shown for patients who had values at all three time points (for the six-minute walk, 196 patients in the control group and 212 patients in the resynchronization group; for the quality-of-life score, 192 patients and 211 patients, respectively). MIRACLE Study



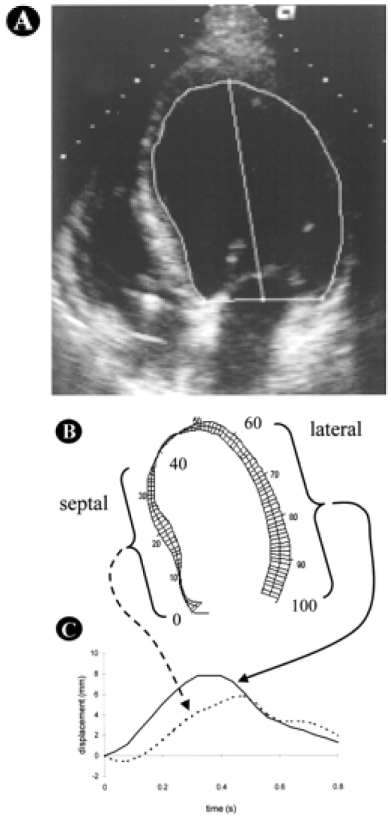
fraction <35% and 4) New York Heart Association functional class III or IV. As this was the first major trial some of the criteria were of necessity somewhat empirical. However a wealth of data was collected including an analysis of patients who responded to CRT.

Now that improvement of symptoms and exercise capacity had been demonstrated, Yu et al using tissue Doppler showed reversal of LV remodeling with chronic CRT therapy[27]. Echocardiography assumed an important role in developing CRT indications and in follow-up of these patients. Several Echocardiographic measures have been proposed to screen patients with heart failure. These parameters try to quantify asynchrony so as to identify the 'responders' to CRT. The 'paradoxical septal motion' is the primary mechanical abnormality which results from conduction disorder such as LBBB. The MIRACLE trial investigators using retrospective analysis quantified the degree of paradox which identified the responders in their study. Other use more sophisticated variations on the same theme. Breithardt et al described a technique of

Echocardiographic phase analysis of the paradoxical septal motion (Figure 6). As may be predicted by students of echocardiography, several types of wall motion patterns were described[28]. Patients with a QRS duration >150 ms could exhibit near-synchronous L-S displacements (type 1); much delayed lateral displacements (type 2) or paradoxical septal motion (type 3). The type 1 pattern with a prolonged QRS complex probably results from a symmetrical conduction delay across the septal and lateral regions. In this group, CRT did not result in improved hemodynamic function, despite the presence of wide QRS complexes and a very low baseline dP/dtmax value. Type 2 patients presented with delayed lateral wall motion and exhibited the most benefit from CRT. This included patients with QRS complexes <155 ms, who, by these criteria, would have been predicted to be acute hemodynamic CRT nonresponders, according to earlier studies. Lateral-septal synchrony improved in the majority of type 3 patients. The lesson from this study is quite clear. A wide QRS must cause mechanical dyssynchrony in order to benefit from CRT. It would also stand to reason that the LV as well as RV pacing sites will also influence the response to CRT. To wit, an anterior LV pacing site will not address a postero-basal LV delay.

Figure 6:

A. End-diastolic image (apical four-chamber view) with manually drawn left ventricular (LV) endocardial contour tracing. B. Left ventricular wall motion displacement for 100 endocardial segments determined by using the centerline method. C. Septal (dashed line) and lateral (solid line) wall motion displayed as displacement (mm) over time (s).



CRT is not all about pacing the LV

Buoyed by the gratifying observation that systolic function is influenced by pacing the posterolateral LVsite, Yu et al turned their attention to changing the timing of atrial contraction as it relates to ventricular contraction. They reported that the LV function can be further improved by modulating preload[29]. It is known that the mechanical AV delay is prolonged resulting in suboptimal LV filling in patients with heart failure[30]. Auricchio et al showed that programming an optimal AV delay in patients with Bi-Ventricular pacemaker (CRT) can increase pulse pressure. They showed that the optimal pulse pressure occurs when the peak of left atrial systole coincides with the start of LV contraction[31]. Auricchio et al had previously observed that CHF patients have heterogeneous symptoms, etiologies, and substrates, and pacing may operate through multiple mechanisms requiring individual optimization. They felt that outcome depends on pacing parameters and individual variables. 'The most important pacing parameter was pacing the LV chamber, but that AV delay significantly modulates the result'[24].

Does CRT prolong Life?

In previous trials lasting up to six months, CRT has shown decrease in symptoms and improvement in exercise capacity, quality of life, and ventricular function[19,25,26]. The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial showed that cardiac-resynchronization therapy alone or combined with an implantable defibrillator reduced the composite end point of death from any cause or hospitalization[32]; however, the decrease in the risk of death was not significant with cardiac resynchronization therapy alone (P=0.06).

Meta-analyses have been inconclusive about the effects of cardiac resynchronization on the risk of complications and death[33,34] that is up until the publication of the Cardiac Resynchronization - Heart

Failure (CARE-HF) trial. This was a multicenter, international, randomized trial specifically designed to compare the risk of death in standard pharmacologic therapy with that of the CRT. Eligible patients had CHF and were in New York Heart Association (NYHA) class III or IV, with a left ventricular ejection fraction of no more than 35 percent, and a QRS interval of at least 120 msec on the electrocardiogram. Patients with a QRS interval of 120 to 149 msec were required to meet two of three additional criteria for dyssynchrony: an aortic pre-ejection delay of more than 140 msec, an interventricular mechanical delay of more than 40 msec, or delayed activation of the posterolateral left ventricular wall (These echo parameters discussed below).

The results showed that the favorable effects of cardiac resynchronization on symptoms, the quality of life, ventricular function, and blood pressure in our trial are similar to those reported in previous trials[19,25,26,32]. However, in CARE-HF cardiac resynchronization significantly reduced the risk of death (Figure 7).

In this study, the cardiac-resynchronization group had a decreased incidence of both sudden death as well as a decreased incidence of death from worsening heart failure; both were felt to be secondary to improvement in cardiac function. The authors felt that as 29 patients (7 percent) in the cardiac-resynchronization group died suddenly, a defibrillator may have prevented these additional deaths.

Figure 7:
Kaplan-Meier Estimates of the Time to the Primary (Panel A) and the Secondary Outcome (Panel B) in the CARE-HF trial. The mortality rate in the medical-therapy group was 12.6 percent at one year and 25.1 percent at two years, as compared with 9.7 percent and 18.0 percent, respectively, in the cardiac-resynchronization group.

Is CRT cost effective?

In Pakistan the hospital 'package' for a CRT implant can range from less than Rs. 400,000 for a CRT pacemaker to Rs. 1,200,000 for CRT Pacemaker-ICD combination. In the developed countries hospitalizations for CHF have been found to constitute the major cost for society in HF management[36]. A pilot study has indicated a lesser need for hospital care after the implantation of CRT[37]. This observation was confirmed in the MUSTIC study in which found seven times less need for hospital care for CHF patients who received CRT[38]. MUSTIC study main finding was that the benefit persisted for 12 months (the period of observation), a placebo effect was also noted but this waned over time. While it may be easy to show that the more modest higher upfront cost CRT pacemaker was offset by a significant decrease in hospitalization within the first year of treatment, a similar comparison with CRT+defibrillator (a more expensive form of implantable device therapy) has not been performed[39].

CRT Experience in Pakistan

The cost often appears to an insurmountable obstacle when contemplating CRT in Pakistan. Still it is difficult to dismiss a therapy which relieves our patient's symptoms, improves LV function, and importantly reduces mortality. There may indeed be a clinical mandate for use of CRT in many patients with chronic heart failure[39]. Thus in our practice we do inform patients of this option. Contrary to our experience with implantable defibrillators where patients are content to leave the risk of sudden death

in Divine hands, candidates for CRT will often try to marshal up resources for this option. This is likely to be due to the debilitating nature of symptoms. It also helps that in Pakistan we may have some of the lowest non-device related expense.

On our part we try to minimize non-responders by requiring that mechanical dyssynchrony be demonstrated in addition to usual criteria for implant. Therefore in patients with severe CHF, wide QRS and severe LV dysfunction we will routinely perform an Echocardiographic study to specifically quantify the degree of dyssynchrony. Figures 8 and 9 show how interventricular and intraventricular dyssynchrony are measured. These variables were first noted in the MIRACLE trial[26]. We also cannulate the

Figure 8:
Measurement of the interventricular mechanical delay (IVMD) by Doppler echocardiography: the right ventricular and left ventricular (lower) pre-ejection intervals are measured from the onset of the QRS to the onset of pulmonary (RV-PEI, top panel) and aortic flow (LV-PEI, lower panel); IVMD is calculated by subtracting the RV-PEI from the LV-PEI. Interventricular dyssynchrony is defined as the time difference between left and right ventricular pre-ejection intervals. An IVMD of 40 ms is considered indicative of interventricular dyssynchrony (26).

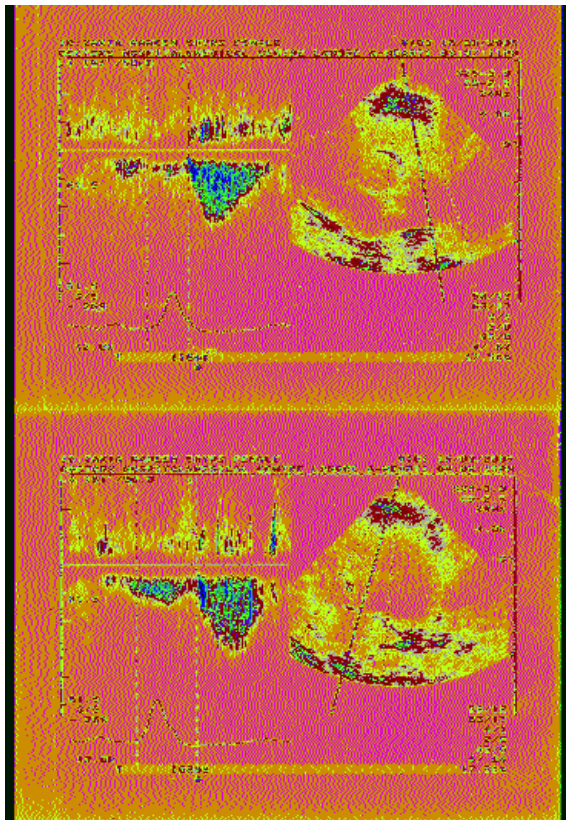


Figure 9:
The Intra-Ventricular Mechanical Delay is measured as the interval from Septum-to-Posterior Wall Motion Delay (SPWMD). An interval >130 ms is considered indicative of significant intra ventricular dyssynchrony.

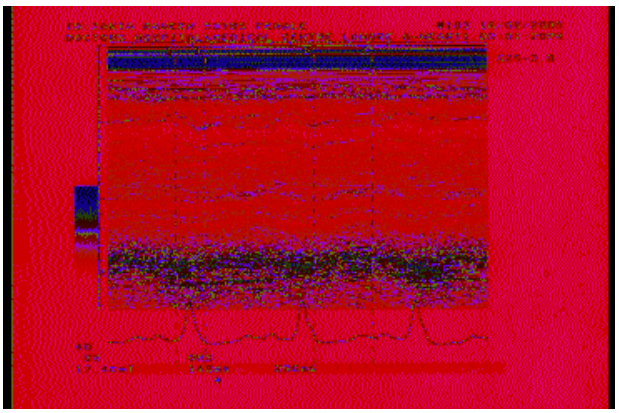
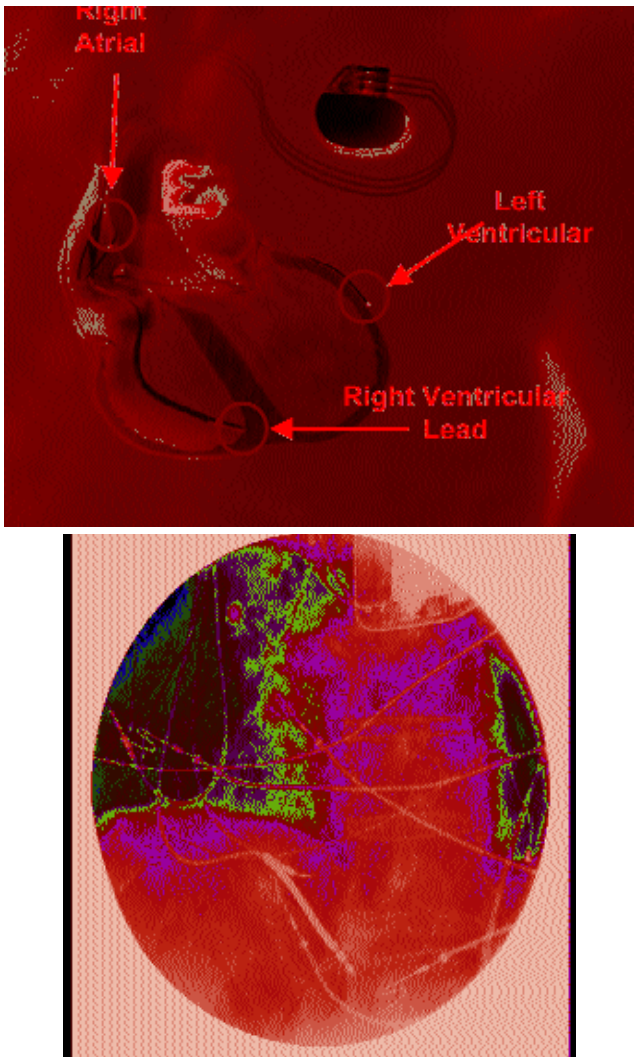


Figure 10:
A Bi-Ventricular pacemaker/ICD. Note the CS lead in the postero-lateral branch of the CS



posterolateral branch of the coronary sinus whenever possible (Figure 10). If this branch was atretic or resulted in diaphragmatic pacing another lateral branch was sought. Use of these additional criteria have been gratifying and as shown in Table 11, reverse remodeling and NYHA functional class improvement were noted in all our patients [40].

Table 11
Result in 26 Patients implanted in Pakistan

	Baseline	Follow-up
LVED mm	74±7	66±8
LEVF	20±6	33±4
MYHA	III-IV	II

LVED=Left ventricular end diastolic dimension.
LVEF=LV Ejection fraction.
NYHA=New York Heart Association Functional Class.

Practice Guidelines

The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology (ESC) recommends consideration for CRT in symptomatic patients, NYHA class III-IV, on optimum medical therapy and a wide QRS which it defines as >120 msec (Class of recommendation 1, Level of evidence A)[41]. The class of recommendation and the level of evidence are the same as that of the mainstays of CHF therapy such as ACE inhibitor and beta blocker therapy.

American College of Cardiology/American Heart Association echo the recommendation of ESC, while stating that there is strong evidence to support the use of CRT to improve symptoms, exercise capacity, quality of life, LVEF, and survival and to decrease hospitalizations in patients with persistently symptomatic HF undergoing optimal medical therapy who have cardiac dyssynchrony (as evidenced by a prolonged QRS duration)[42].

Placing this recommendation in perspective the European Society of Cardiology states that there is no data to support the use of revascularization procedures for heart failure symptoms. They therefore do not recommend the use of revascularization (Surgical or Percutaneous) in patients with CHF and coronary artery disease[41].

Procedure related morbidity and mortality

Ten studies have reported on CRT peri-implant morbidity and mortality. There were 13 deaths in 3,113 patients (0.4%). From a pooled assessment of 3,475 patients in 17 studies, the success rate of implantation was approximately 90%. Device-related problems during the first 6 months after implantation reported in 13 studies included lead malfunction or dislodgement in 8.5%, pacemaker problems in 6.7%, and infection in 1.4% of cases. These morbidity and mortality data are derived from trials that used expert centers[42]. Although our numbers are small, in Pakistan we have had none of the above mentioned complications except one patient with CS lead dislodgement requiring a repositioning.

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