ECHOCARDIOGRAPHIC EVALUATION OF VENTRICULAR DYSSYNCHRONY IN PATIENTS WITH LBBB

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A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE RULES AND REGULATIONS FOR THE AWARD OF **DM(CARDIOLOGY, BRANCH-II)** DEGREE OF

THE **TAMIL NADU DR.MGR MEDICAL UNIVERSITY**

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CERTIFICATE

This is to certify that the work presented in this dissertation, in partial fulfillment of the Degree of **DM Branch-II (Cardiology)** examination of the **Dr.MGR Medical University** Chennai titled "Echocardiographic evaluation of ventricular dyssynchrony" is the bonafide work of **Dr.John Roshan**, Postgraduate student in **DM (Cardiology)**. It was prepared and carried out under my overall guidance and supervision in the department of Cardiology, **CMC Hospital, Vellore.**

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Dr.John Roshan

CONTENTS

ABSTRACT

AIM OF THE STUDY: To evaluate Tissue Doppler as a tool in detecting dyssynchrony in patients with LBBB.

METHODS: From an initial cohort of patients with LBBB, 38 patients with low ejection fraction ≤ 50 and 31 with normal LV systolic function, all comparable in age and sex underwent standard Doppler echo, ECG and Tissue Doppler Imaging. The precontraction time [PCTm from the beginning of Q wave of ECG to the onset of Sm] was calculated as an index of myocardial systolic activation in five different basal myocardial segments (LV anterior, inferior, septal, lateral walls –RV lateral wall). Intraventricular systolic dyssynchrony was analyzed by difference of PCTm in different LV myocardial segments. Interventricular activation delay was calculated by the difference of PCTm between the most delayed LV segment and RV lateral wall.

RESULTS: Patients with low LV ejection fraction showed increased qrs duration and LV end diastolic diameter. By DMI these patients showed increased intraventricular delay [p=0.03] in activation of the LV lateral wall. They also showed increased interventricular dyssynchrony [p=0.006]. By receiving operating characteristic [ROC] curve analysis, a cut off value of 48.5msec of interventricular delay showed 71% sensitivity and 65% specificity in identifying patients with impaired ejection fraction. In the overall population by use of stepwise forward multivariate linear regression analyses, LV end diastolic diameter, ejection fraction and qrs duration were the only determinants of interventricular activation delay.

CONCLUSIONS: Pulsed DMI is an effective noninvasive technique for assessing the severity of regional delay in activation of ventricular walls in patients with LBBB. The impairment of interventricular systolic synchronicity is strongly related to LV dilatation and systolic dysfunction. By knowing the exact delay in contraction of the various myocardial segments patients with dilated cardiomyopathy suitable for cardiac resynchronization therapy may be better selected.

INTRODUCTION

Left bundle branch block (LBBB) generally associated with structural heart disease is a frequent conduction disorder. In patients with LBBB and structural heart disease, overall mortality is significantly increased.[1-4] Moreover, it is also known that the incidence of cardiovascular disorders and subsequent mortality is increased in isolated LBBB[5]. In the presence of LBBB, due to delay of left ventricular (LV) mechanical activity, interventricular dyssynchrony and abnormal interventricular septal movement occurs. As a result of abnormal septal movement, stroke volume, ejection fraction (EF), and LV filling are decreased.[6-8]Recently, cardiac resynchronization therapy (CRT) is advocated in heart failure in patients with NYHA class III, IV on maximum antifailure medication with wide QRS complex (≥ 130 msec) and decreased EF (≤ 35 %). [9-11] Results from mechanistic studies, observational evaluations and randomized control trials have constantly demonstrated significant improvement in quality of life, functional status and exercise capacity in patients with New York Heart Association (NYHA) class III and IV heart failure who are assigned to active resynchronization therapy. The studies in such patient population have revealed the presence of intraventricular dyssynchrony among various LV segments together with interventricular dyssynchrony.[12-16] Furthermore different trials suggest that this treatment modality yields the best hemodynamic benefits in patients with documented intraventricular dyssynchrony irrespective of the QRS duration. [12-17] Conversely no recent data is available on regional systolic dyssynchrony in patients with LBBB and normal LV ejection fraction. In our study, we looked for the presence of intra and interventricular dyssynchrony using Tissue Doppler Imaging in patients with LBBB with both normal and compromised LV function.

AIMS OF THE STUDY

1. To find out what proportion of Indian patients with congestive cardiac failure and LBBB on ECG are candidates for cardiac resynchronization therapy based on echocardiographic characteristics.

2. To evaluate the determinants of myocardial activation delay of both left and right ventricle in patients with LBBB demonstrating either normal or impaired global LV systolic function.

OBJECTIVES OF THE STUDY

The study was undertaken with the following objectives.

1. To determine the prevalence of cardiac dyssynchrony by echocardiographic evaluation in patients with LV dysfunction and LBBB.

2. To determine the prevalence of cardiac dyssynchrony by echocardiographic evaluation in patients with normal LV systolic function and LBBB.

3. To evaluate whether QRS width is a reliable method to detect dyssynchrony

4. To test whether patients with LBBB and low ejection fraction have greater dyssynchrony than those with LBBB and normal LV systolic function.

REVIEW OF LITERATURE

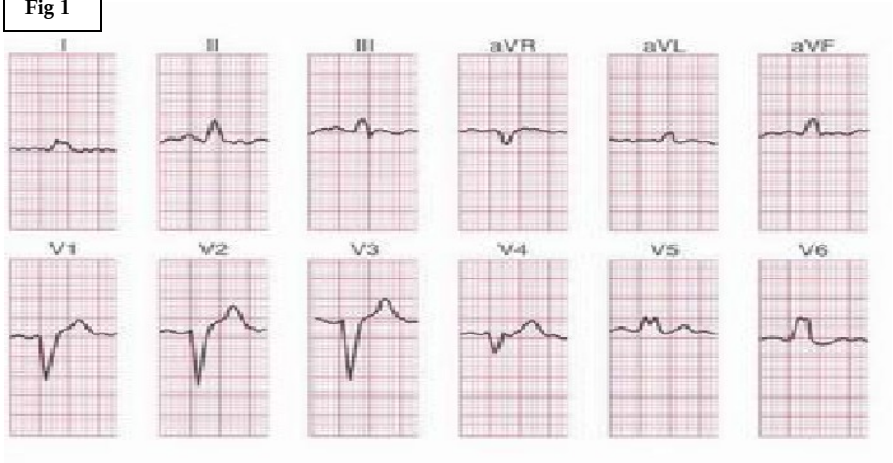
Left Bundle Branch Block

Left bundle Branch Block (LBBB) results from conduction delay or block in any of several sites in the intraventricular conduction system, including the main left bundle branch, in each of the two fascicles, or less commonly within the fibers of the bundle of His that become the main left bundle branch. The result is extensive reorganization of the activation pattern of the left ventricle.

ECG Abnormalities

LBBB produces a prolonged QRS duration, abnormal QRS complexes and ST-T wave abnormalities (Fig 1).

Fig 1



Commonly accepted diagnostic criteria are [14]

1. QRS duration ≥ 120 msec
2. Broad, notched R waves in lateral precordial leads (V_5 and V_6) and usually leads I and aV_L.
3. Small or absent initial r waves in right precordial leads (V1 and V2) followed by deep S waves
4. Absent septal q waves in left-sided leads
5. Prolonged intrinsicoid deflection (>60 msec) in V_5 and V_6

The mean QRS axis with LBBB is highly variable .It can be normal, deviated to the left, or, less often, deviated to the right. Left axis deviation is associated with more severe conduction system disease that includes the fascicles as well as the main left bundle, whereas right axis deviation suggests dilated cardiomyopathy with biventricular enlargement.

ST-T wave changes are also prominent with LBBB. In most cases, the ST wave and the T wave are discordant with the QRS complex; that is, the ST segment is depressed and the T wave is inverted in leads with positive QRS waves (leads I, aV_L, V_5 and V_6), while the ST segment is elevated and the T wave is upright in leads with negative QRS complexes (Leads V_1 and V_2)

Mechanisms of ECG abnormalities

The ECG abnormalities of LBBB result from an almost completely reorganized pattern of left ventricular activation .Initial septal activation occurs on the right (rather than on the left) septal surface, resulting in the absence of normal septal q waves in the ECG.

The excitation wave then spreads slowly, by conduction from muscle cell to muscle cell, to the left side of the septum; the earliest ventricular activation begins as late as 30 to 50 msec into the QRS complex. Endocardial activation of the left ventricle may then require an additional 40 to more than 180 msec, depending largely on the functional status of the distal left bundle and Purkinje system. Thus, the overall QRS complex is prolonged and can be very wide in patients with, for example, diffuse ventricular scarring from prior myocardial infarction.

Once left ventricular activation begins, it proceeds in a relatively simple and direct manner around the free wall, and finally, to the base of the heart. This is in contrast to the multicentric, overlapping

patterns of activation seen under normal conditions. Direct progression of activation across left ventricle projects continuous positive forces to left sided-leads and continuous negative forces to right sided-leads. Spread predominantly through working muscle fibers rather than the specialized conduction system results in notching and slurring as a consequence of discontinuous anisotropy.

The discordant ST-T wave pattern is a result of the transventricular recovery gradients referred to earlier. With LBBB, the right ventricle is activated and recovers earlier than the left, so recovery vectors or dipoles are directed toward the right and away from the left. Hence, positive ST-T waves will be registered over the right ventricle and negative ones over the left ventricle.

Clinical significance

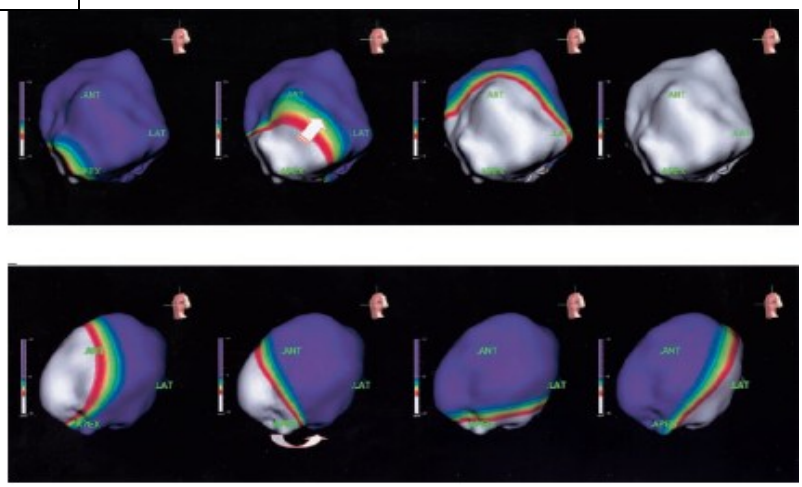
LBBB usually appears in patients with underlying heart disease .It is associated with significantly reduced long term survival and with 10 year survival rates as low as 50 percent, probably reflecting the severity of the underlying cardiac disease. Among patients with coronary artery disease, the presence of LBBB correlates with more extensive disease, more severe left ventricular dysfunction and reduced survival rates. The duration of the QRS complex in LBBB correlates inversely with left ventricular ejection fraction. Patients with associated left or right axis deviation have more clinical manifestations.

In addition to the hemodynamic abnormalities produced by these underlying conditions, the abnormal ventricular activation pattern of LBBB itself induces hemodynamic perturbations, including abnormal systolic function with dysfunctional contraction patterns, reduced ejection fraction, lower stroke volumes and abnormal diastolic function; reversed splitting of the second heart sound and functional mitral regurgitation are common.

Ventricular Dyssynchrony: A pathophysiological cause or contributor to heart failure

Patients with left ventricular (LV) systolic dysfunction and dilation, with or without clinical signs or symptoms of heart failure, frequently have ventricular conduction delays. Approximately one third of patients with systolic heart failure have a QRS duration greater than 120 ms, which is most commonly seen as left bundle-branch block (LBBB). In LBBB, the left ventricle is activated belatedly through the septum from the right ventricle, resulting in a significant delay between the onset of left ventricular (LV) and right ventricular contraction.[6] Activation of the anterior septum precedes inferoseptal activation, with the latest activation occurring in the inferior and lateral aspects of the left ventricle. (Fig 2)

Fig 2



The interventricular septum exhibits a normal (early) contraction resulting in paradoxical septal motion. LBBB is associated with significantly later aortic opening, aortic valve closure, and mitral valve opening but does not affect the timing of right ventricular events. The delay in aortic valve closure leads to a relative decrease in the duration of LV filling. In patients with LBBB, delayed depolarization or abnormal repolarization can result in regional myocardial contraction into early diastole, causing a delay of mitral valve opening and also shortening LV filling time.[6]

Patients with LBBB commonly have abnormal ventricular septal motion, which is related to the

interventricular dyssynchrony and the resulting abnormal pressure gradient between the left and right ventricles.[6] Because of the abnormal septal motional end-systolic diameter is increased and regional septal ejection fraction is decreased in patients with LBBB. LBBB patients with or without cardiac disease can reduce global LV ejection fraction (LVEF) and decrease cardiac output, mean arterial pressure, and dp/dt. [15] Moreover with ventricular dyssynchrony, mitral valve closure might not be complete because atrial contraction is not followed by a properly timed ventricular systole. If the time lag is long enough, a ventricular-atrial pressure gradient can develop and cause diastolic mitral regurgitation.[16]

The abnormal activation sequence induced by spontaneous LBBB or by right ventricular (RV) pacing generates changes in regional ventricular loading conditions, possibly redistributes myocardial blood flow[17] and creates a regional non uniform myocardial metabolism.[18] These effects of ventricular dyssynchrony might contribute to disease progression in LV systolic dysfunction patients . For example, studies in experimental heart failure induced by rapid ventricular pacing showed regional differences in the extent of ventricular hypertrophy with an apicobasal and septolateral-oriented gradient.[19] Moreover, experimentally induced LBBB has demonstrated a large effect on the expression of regional stress kinases and calcium-handling proteins.[20] Preliminary evidence suggests that the expression of p38-MAPK(a stress kinase) is significantly elevated in the endocardium of the late-activated region, whereas phospholamban is significantly decreased.[19] In addition, sacro(endo)plasmic reticulum Ca^{2+}-ATPase is decreased in the region of early activation.

In patients with LV dysfunction, ventricular dyssynchrony places the already failing left ventricle at an additional mechanical disadvantage. Ventricular dyssynchrony appears to have a deleterious impact on the natural history of heart failure, as a wide QRS complex has been associated with increased mortality in patients experiencing heart failure.[21] On the basis of these observations, investigators

hypothesized that patients with LV dysfunction and delayed ventricular conduction would benefit from pacing at sites that achieve a more rapid ventricular depolarization and thus a more synchronous contraction, or result in a more favorable contraction pattern, and correct interatrial and/or interventricular conduction delays to maintain optimal atrial-ventricular (AV) synchrony. Shortening activation might also prolong the time available for myocardial perfusion. In the mid-1990s, such notions led to the evaluation of atrial synchronized biventricular pacing as a means to resynchronize ventricular contraction and thus improve the function of the heart as a pump.

The meaning of such complex interactions between changes in regional loading conditions, blood flow distribution, regional myocardial metabolism, and gene and protein expression induced by an abnormal activation sequence is not fully understand. However, it is likely that these consequences of ventricular dyssynchrony lead to rearrangement of both contractile and noncontractile cellular elements and perhaps the extra cellular matrix in the heart, thus stimulating the process of ventricular remodeling. Thus, it is inconceivable that dyssynchrony represents a newly appreciated pathophysiological process that directly depresses the ventricular function and ultimately leads to ventricular dilatation and heart failure. Evidence from recent clinical trials comparing RV pacing versus either no pacing or atrial pacing in patients with LV systolic dysfunction supports this notion. In the dual chamber and VVI implantable defibrillator (DAVID) trial, RV pacing was associated with heart failure disease progression, including an increased incidence of worsening heart failure. [22]

Mechanisms of action of CRT

At the present time, we recognize 4 levels of electromechanical abnormalities that may be treated by CRT.

1) Atrioventricular delay
2) Interventricular delay

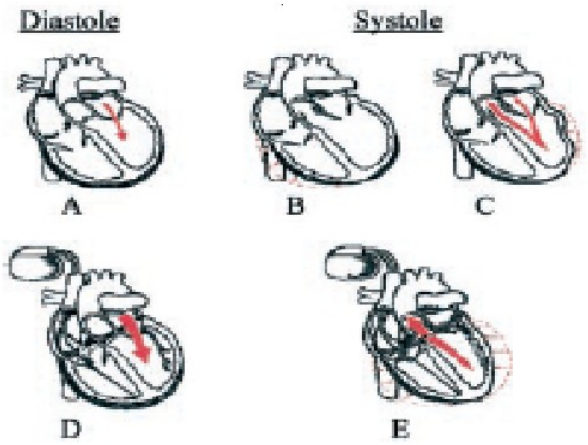
3) Intraventricular delay
4) The most recently described [23] intramural delay

Although the effect of CRT on the intramural delay has not been full investigated, the effect on interventricular delay probably plays a second role after the correction of both atrioventricular and intraventricular delay. The mechanisms by which cardiac resynchronization therapy improves mechanical LV function in patients with heart failure and ventricular dyssynchrony are not completely understood. Electrical resynchronization can reduce the LBBB-induced mechanical interventricular dyssynchrony between the right and the left ventricle and the intraventricular dyssynchrony within the left ventricle.

Preexcitation of the LV lateral wall with atrial synchronous left or biventricular pacing in heart failure patients with ventricular conduction delay can resynchronize the ventricular activation pattern by acting as an electrical bypass, thus restoring a more coordinated ventricular contraction. This novel approach to treat heart failure is called CRT. Minimizing intraventricular dyssynchrony has been shown to improve global LV function; i.e. cardiac resynchronization therapy increases LV filling time, decreases septal dyskinesis and reduces mitral regurgitation, thus improving hemodynamics (Fig 3). Shortening or optimizing the atrioventricular interval necessary to resynchronize lateral-septal wall contraction also improves atrioventricular mechanical synchrony by abolishing the late diastolic ventriculoatrial gradient and so called “presystolic” mitral regurgitation, which is seen in association with ventricular dyssynchrony, and prolongs ventricular filling time. Pacing for the left lateral wall especially from the proximity of

the posterior papillary muscle produces early activation of the papillary muscle region and can decrease systolic mitral regurgitation.

Fig 3



Optimization of ventricular loading conditions as provided by CRT improves myocardial efficiency and increases systolic function and LV contractibility with a neutral or moderately positive effect on diastolic function. When combined, these various mechanical effects of CRT improve the function of the heart as a pump.

Cardiac resynchronization therapy can improve the deranged neurohormonal milieu associated with chronic heart failure. There is increasing evidence from unpublished investigations suggesting improvement of brain natriuretic peptide and a variety of other neurohormones in more recent studies. There is also an indication that cardiac resynchronization therapy restores autonomic balance in heart failure. In 2 prospective studies, biventricular pacing resulted in a significant improvement in heart rate variability, suggesting a decrease in cardiac adrenergic activity or an increase in parasympathetic activity, or a combination of both.[24,25]

Clinical Studies of cardiac Resynchronization Therapy

Although early biventricular pacing studies used epicardial leads to pace the left ventricle, later studies used market-available transvenous leads that could be inserted into a distal cardiac vein through the coronary sinus to pace the LV free wall. This approach eliminates the need for general anesthesia and

thoracotomy to place an epicardial lead and, thus could be safer for fragile patients experiencing heart failure. As a result of the favorable outcomes of these early observational studies, randomized controlled trials to evaluate the long-term subjective and objective results of biventricular pacing have been performed. Several trials have been recently completed; others are currently underway (Table 1). These studies include the pacing therapies in congestive Heart Failure (PATH-CHF) trial, the Multisite Stimulation in Cardiomyopathy (MUSTIC) study, the MIRACLE trial, MIRACLE ICD, the VENTAK-CHF/CONTAK CD trial, the Cardiac Resynchronization in Heart Failure (CARE HF) trial, and the comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial.

Table 1. **Randomized, Controlled Trials of Cardiac Resynchronization Therapy in Heart Failure**

Study	Design	Patients	Results
PATH-CHF[24]	Single-blind, randomized, crossover, controlled	42 patients with idiopathic or ischemic dilated cardiomyopathy and NYHA class III/IV heart failure	Interim analysis (spring 1998) showed a trend toward an improvement in all primary and Secondary end points with biventricular pacing.
MUSTIC[26]	European randomized, crossover Study	Group I: 47 patients with NYHA class III heart failure, Normal sinus rhythm; group II: 41 patients with persistent atrial fibrillation and slow ventricular response	Improved exercise capacity (6-minute hall walk),NYHA class, and quality of life in normal sinus rhythm group; magnitude of improvement less in atrial fibrillation group
MIRACLE[9]	Prospective, randomized, double-blind, parallel-controlled	453 patients with idiopathic or ischemic dilated cardiomyopathy, NYHA class III/IV heart failure, LV dysfunction, and IVCD	Significant improvements in exercise capacity, NYHA class, quality of life, cardiac structure and function (by ECHO), composite clinical response, and significant reductions in worsening heart failure, and a combined measure of morbidity and mortality
MIRACLE ICD[27]	Prospective, multicenter, randomized, double-blind, parallel-controlled	560 patients with idiopathic or ischemic dilated cardiomyopathy, NYHA class II-IV heart failure, LV dysfunction, and IVCD with an indication for an ICD	Significant improvements in exercise capacity, NYHA class, quality of life, and composite clinical response, in class III-IV patients; results in class II patients have not yet been reported
CONTAK CD[28]	Prospective,	581 patients with idiopathic or	Trend toward decreased morbidity/

	randomized, crossover, and parallel-controlled	ischemic dilated Cardiomyopathy(248 in the 3-month crossover study and 333 in the 6-month parallel controlled phase),symptomatic heart failure (LVEF _35%), and IVCD with an indication for an ICD	mortality end point; improvements in exercise capacity, quality of life, and NYHA class
COMPANION[10]	Multicenter, prospective, randomized, controlled	1520 patients (planned enrollment of 2200) with dilated Cardiomyopathy, NYHA class III-IV heart failure, and an IVCD received 1 of 3 therapies: drug therapy only; drug therapy and cardiac resynchronization; or drug therapy and cardiac resynchronization/ICD	Significant reduction in primary end point of all-cause mortality plus all-cause hospitalization
CARE HF[29]	Multicenter, prospective, randomized, controlled	800 patients with idiopathic or ischemic dilated cardiomyopathy randomized to CRT device optimal medical therapy vs optimal medical therapy only	CRT was associated with a 36% reduction in the risk of mortality and a 46% reduction in the combined endpoint of death or heart failure hospitalizations

PATH-CHF

The PATH-CHF trial was a single-blind, randomized, crossover, controlled trial designed to evaluate the acute hemodynamic effects and to assess the long-term clinical benefit of right ventricular, LV and Biventricular pacing in patients with moderate-to-severe chronic heart failure and interventricular conduction block. [24] During the cross-over periods, patients were assigned to 2 different pacing modes (best univentricular versus biventricular pacing), each 4 weeks long with a 4-week control phase in between. This was followed by a chronic pacing phase. The effects of pacing on oxygen consumption at peak exercise and anaerobic threshold during cardiopulmonary exercise testing and on 6-minute hall walk distance were selected as primary end points of this study. Secondary end points were changes in NYHA class, quality of life (assessed by Minnesota Living with Heart Failure questionnaire), and hospitalization frequency. Changes in LVEF, cardiac output, and filling pattern were also assessed by echocardiography.

Forty-two patients were enrolled. Aortic pulse pressure and dp/dt were measured at baseline and during acute pacing. Acutely, biventricular and LV pacing increased dp/dt and pulse pressure more than right ventricular pacing ($p<0.01$). Chronic results were encouraging, with a tend toward improvement in all primary and secondary endpoints during pacing being noted.[24] However, the results are weakened by the small number of patients studied, the single-blind design, and the observation that functional end points did not return to baseline during the "pacing-off" control or washout period. However with chronic pacing, statistically significant reductions in end-systolic and end-diastolic volumes were also demonstrated.

MUSTIC

The MUSTIC trial was also a single-blind, randomized, crossover evaluation of cardiac resynchronization therapy.[26] Sixty seven patients were enrolled, 58 were randomized, and 47 completed both study phases of the study. Inclusion criteria were normal sinus rhythm, no indication for pacing, NYHA class III congestive heart failure, optimized drug therapy, LVEF <35%, LV end-diastolic dimension >60 mm, intraventricular conduction defect (IVCD) (QRS >150 ms), and 6-minute walk <450 m. Each phase of the study then lasted 3 months. Patients were randomized to active cardiac resynchronization or to no pacing and then crossed over to the alternative study assignment. The primary end point was the change in distance walked in 6 minutes, and secondary end points included change in quality of life, NYHA class, peak $V\dot{}O_2$, hospital admissions, worsening heart failure, total mortality, and patient preference for pacing mode. Significant improvement was shown in all of these end points. For example, during the active pacing phase, the mean distance walked in 6 minutes was 23% greater than during the inactive pacing phase ($P<0.001$).

A "second" MUSTIC (MUSTIC-AF) trial evaluated similar end points in heart failure patients with atrial fibrillation and ventricular dyssynchrony resulting from a paced QRS duration of >200 ms.[30]

Although the number of patients completing the MUSTIC AFIB trial was smaller, significant improvements were seen in the primary and secondary end points.

MIRACLE

MIRACLE was the first prospective, randomized, double-blind, parallel-controlled clinical trial designed to validate the results from previous cardiac resynchronization studies and to further evaluate the therapeutic efficacy and mechanisms of potential benefit of cardiac resynchronization therapy.[9] Primary end points were NYHA class, quality-of-life score (using the Minnesota Living with Heart Failure questionnaire),
and 6-minute hall walk distance. Secondary end points included assessments of a composite clinical response, cardiopulmonary exercise performance, neurohormone and cytokine levels, QRS duration, cardiac structure and function, and a variety of measures of worsening heart failure and combined morbidity and mortality.

The MIRACLE trial began in October 1998 and was completed late in 2000. Four hundred fifty-three patients with moderate to severe symptoms of heart failure associated with LVEF <35% and a QRS duration >130 ms were randomized (double-blind) to cardiac resynchronization (n=228) or to a control group (n=225) for 6 months, whereas conventional therapy for heart failure was maintained.[9] Compared with the control group, patients randomized to cardiac resynchronization demonstrated a significant improvement in quality of life score (-18.0 versus -9.0 points, P=0.001), 6-minute walk
distance (+39 versus +10 meters, P=0.005), NYHA functional class ranking (-1.0 versus 0.0 class, P<0.001), treadmill exercise time (+81 versus +19 seconds, P=0.001), peak $\dot{V}O_2$ (+1.1 versus+0.1 mL/ kg per minute, P<0.01), and LVEF (+4.6% versus
-0.2%, P<0.001). Patients randomized to cardiac resynchronization therapy demonstrated a highly significant improvement in a composite clinical heart failure response end point compared with control

subjects, suggesting an overall improvement in heart failure clinical status.

By intention-to-treat, there were 16 deaths in the control group and 12 deaths in the resynchronization group (P=not significant). When compared with the control group, fewer patients in the cardiac resynchronization group required hospitalization (8% versus 15%) or intravenous medications (7% and 15%) for the treatment of worsening heart failure (Figure 4). In the control group, there were 50 hospitalizations for heart failure in 34 patients for a total of 363 heart failure hospital days during the 6-month period of double-blind follow-up. In patients randomized to cardiac resynchronization, there were 25 hospitalizations for heart failure in 18 patients for a total of 83 heart failure hospital days (P=0.015 for the difference in risk of hospitalization, P=0.012 for the difference in hospital days), resulting in a 77% decrease in total days hospitalized over 6 months compared with the control group. Implantation of the device was unsuccessful in 8% of patients.

Fig 4

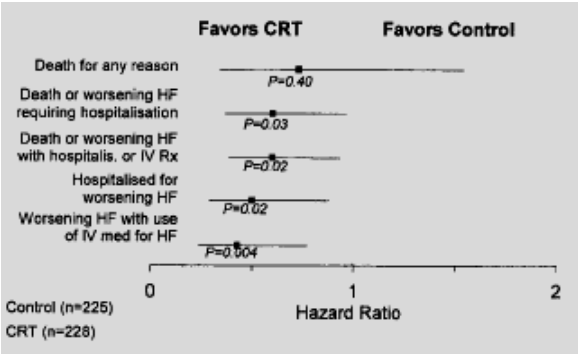


Figure 4. Effect of cardiac resynchronization therapy on morbidity and mortality in MIRACLE. Although underpowered to evaluate mortality alone, the MIRACLE trial demonstrated statistically significant reduction in measures of heart failure morbidity (hospitalization for worsening heart failure and worsening heart failure requiring treatment with an intravenous medication) and combined morbidity and mortality favoring cardiac resynchronization therapy compared with controls. The figure represents mean patient estimates ± 95% confidence intervals.

VENTAK-CHF/CONTAK-CD

The VENTAK-CHF/CONTAK-CD study was also a randomized, controlled, double-blind study comparing active cardiac resynchronization therapy versus no pacing.[31]The initial design was that of a 3-month crossover trial; this was later changed to a 6-month parallel control study design. The device used in the study combines ICD capabilities with biventricular pacing. Patients included had NYHA

functional class II–IV heart failure, LVEF ≤35%, QRS duration >120 ms, and an accepted indication for an ICD. The primary end point was a composite of mortality, hospitalizations for heart failure, and episodes of ventricular tachycardia or ventricular fibrillation.

A total of 581 patients were randomized, 248 into the 3-month crossover study and 333 into the 6-month parallel Controlled trial. For the primary composite end point, the study demonstrated an insignificant trend favoring the resynchronization group. However, peak $V\dot{}O_2$, 6-minute hall walk distance, quality of life, and NYHA class were significantly improved in the active pacing group compared with inactive control subjects, particularly in the NYHA class III–IV subgroup of patients. For example, in class III–IV patients randomized to active resynchronization therapy, peak $V\dot{}O_2$ improved by 1.8 mL/kg per minute compared with no improvement in the control group (P=0.003). There was also a reduction in LV end-systolic and end-diastolic dimensions seen in the VENTAK-CHF/CONTAK-CD trial.

MIRACLE ICD

The MIRACLE ICD study was designed to be nearly identical to the MIRACLE trial. MIRACLE ICD was a prospective, multicenter, randomized, double-blind, parallel-controlled clinical trial intended to assess the safety and clinical efficacy of another combined ICD and cardiac resynchronization system in patients with dilated cardiomyopathy (LVEF≤ 35%, LV end-diastolic diameter>55 mm), NYHA class III or IV heart failure (a cohort of class II patients was also enrolled), IVCD (QRS >130 ms), and an indication for an ICD. Primary and secondary efficacy measures were essentially the same as those evaluated in the MIRACLE trial, but also included measures of cardioverter–defibrillator function (including the efficacy of antitachycardia therapy with biventricular pacing).

Of 369 patients receiving devices and randomized, 182 were control subjects (cardioverter defibrillator

activated, cardiac resynchronization off) and 187 were in the resynchronization group (cardioverter defibrillator activated, cardiac resynchronization on). At 6 months, patients assigned to cardiac resynchronization had a greater improvement in median quality of life score (-17.5 versus -11.0, P=0.02) and functional class (-1 versus 0, P=0.007) than control subjects, but were no different than control subjects in the change in distance walked in 6 minutes (+55 meters versus +53 meters, P=0.36).[27] Peak oxygen consumption increased by 1.1 mL/kg per minute in the cardiac resynchronization group versus 0.1 mL/kg per minute in control subjects (P=0.04), whereas treadmill exercise duration increased by 56 seconds in the resynchronization group and decreased by 11 seconds in control subjects (P=0.0006). The magnitude of improvement was comparable to that seen in the MIRACLE trial, suggesting that patients experiencing heart failure with an ICD indication benefit as much from cardiac resynchronization therapy as those patients without an indication for an ICD. Interestingly, the efficacy of biventricular antitachycardia pacing was significantly greater than that seen in the univentricular (right ventricular) configuration. This observation suggests another potential benefit of a combined ICD plus resynchronization device in such patients. Finally, no proarrhythmia was observed, and arrhythmia

termination capabilities were not impaired by the addition of resynchronization therapy.

COMPANION and CARE-HF

Begun in early 2000, COMPANION was a multicenter, prospective, randomized, controlled clinical trial designed to compare drug therapy alone to drug therapy in combination with cardiac resynchronization with or without an ICD in patients with dilated cardiomyopathy, an IVCD, NYHA class III or IV heart failure, and no indication for a device.[10] The trial design called for randomization of 2200 patients into 1 of

3 treatment groups: group 1 (440 patients) receiving optimal medical care only, group II (880 patients) receiving optimal medical care and the Guidant CONTAK TR (biventricular pacing alone), and group

III (880 patients) receiving optimal medical care and the CONTAK CD (combined heart failure/ bradycardia /tachycardia ICD device). The primary end point of the COMPANION trial was a combination of all-cause mortality and all-cause hospitalization. Secondary end points included a variety of measures of cardiovascular morbidity as well as all-cause mortality alone.

After randomization of 1520 patients, the COMPANION trial was terminated prematurely in November 2002 at the recommendation of an independent data and safety monitoring board. COMPANION was designed as an event-driven study (target >950 primary events). As reported by the lead investigators (A.M. Feldman and M.R. Bristow during a late-breaking session at the 52nd Annual Scientific Sessions of the American College of Cardiology in Chicago, April 2003), 1000 events had occurred by November 18, 2002, resulting from a higher-than-expected event rate. The number of patients randomized to each treatment group was 308 to medical therapy alone, 617 to medical therapy plus resynchronization therapy, and 595 to medical therapy plus cardiac resynchronization and an ICD. The average age of patients was 66 years and 68% were men. The mean LVEF was 23% and 85% of the patients were in NYHA class III. At baseline, angiotensin-converting enzyme (ACE) inhibitors (or angiotensin receptor blockers) were taken by 90% of patients, ß-blockers by 68%, and spironolactone by 55%. Compared with control patients (group 1), the primary end point was significantly reduced in both resynchronization groups, by 18.6% in group 2 and by 19.3% in group 3 patients (P=0.015 and 0.005, respectively). All-cause mortality was also reduced by resynchronization therapy: group 1 versus group 2 by 24% (P=0.12); group 1 versus group 3 by 43% (P=0.002).

Another randomized, controlled morbidity and mortality trial is CARE-HF. This study compares optimal medical therapy alone with optimal medical therapy plus cardiac resynchronization (without an ICD) in 800 patients with NYHA class III or IV systolic heart failure and ventricular dyssynchrony

determined by either electrocardiographic (QRS duration ≥ 150 ms) or echocardiographic (QRS duration ≥ 120 and <150 ms plus echocardiographic evidence of dyssynchrony) criteria.[29] CARE-HF was fully enrolled as of March 2003. The CARE-HF trial was one of the first trials that documented a mortality benefit from CRT. At 2 years, the use of CRT was associated with a 37% reduction in the trial's primary endpoint (the composite of all-cause mortality or unplanned hospitalization for a cardiovascular event) compared with control. In addition, CRT was associated with a 36% reduction in the risk of mortality and a 46% reduction in the combined endpoint of death or heart failure hospitalizations. The results of the study remained consistent across various subgroups, including patients with and without ischemic heart disease.

CRT Induces Reverse Ventricular Remodeling

The benefits of reverse ventricular remodeling have been demonstrated by pharmacological agents, such as ß-blockers and angiotensin-converting enzyme (ACE) inhibitors, which improve ventricular geometry and function and reduce morbidity and mortality in heart failure patients.[32,33] Acting through several mechanisms, including

redistribution of regional ventricular loading, reduction or abolition of mitral regurgitation, reduction of sympathetic activity, increase of parasympathetic activity, and others, CRT also induces reverse remodeling of the failing left ventricle. Hence, the left ventricle gets smaller and contractility is improved after a period of CRT. Moreover,

as mentioned above, functional mitral regurgitation is reduced acutely and chronically during CRT. The effects of CRT on reverse ventricular remodeling have been consistently demonstrated in all randomized prospective controlled studies and in smaller mechanistic studies. Although Yu et al have demonstrated both an onset as well as an offset of the favorable remodeling effects of CRT, it is not known whether reverse remodeling will sustain over the long term. Of note, CRT has mostly been implemented in addition to optimal medical therapy for heart failure (ACE inhibitors, ß-blockers,

diuretics, and in many cases spironolactone); however, recent data from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study have shown that reverse remodeling during CRT can also take place in patients not receiving ß-blocking agents. Another important issue—whether patients with different degrees of electrical or mechanical abnormality will show similar degrees of reverse remodeling - is still unclear.

Clinical Implications of Cardiac Resynchronization Therapy Data

Although clinical application of cardiac resynchronization therapy is still in its early years, some clinical guidelines can be suggested on the basis of data to date. Cardiac resynchronization therapy should be considered only in patients who remain symptomatic despite a stable and optimized medical regimen for heart failure. Unless patients are intolerant, that medical regimen should include an ACE inhibitor or ACE inhibitor substitute and a ß-blocker with a diuretic and digitalis as needed. Resynchronization therapy should not be seen as an alternative to medical therapy. Other criteria for cardiac resynchronization include QRS duration $\geq$ 120 ms, LVEF $\leq$ 35%, and LV dilation.

At this point, cardiac resynchronization is appropriate for patients with NYHA functional class III or IV functional limitation. Not enough data are available in patients with
NYHA class II heart failure to routinely recommend it, although the application of resynchronization therapy at an earlier stage could theoretically prevent late heart failure related complications or slow disease progression. In addition, initial Food and Drug Administration labeling does not specify approval for cardiac resynchronization for patients in atrial fibrillation. Early data support its efficacy in the atrial fibrillation population; however, definitive data are lacking. Many such questions remain unanswered. Paramount among these is whether prospective predictors of response
exist to further guide patient selection. To date, the benefits of cardiac resynchronization therapy have been seen regardless of baseline QRS duration (>120 ms), bundle-branch

block pattern, and etiology of the heart failure. Very recent data suggest that resynchronization therapy could yield improvement in the patient with intraventricular dyssynchrony despite a normal QRS duration.[34]

If ventricular dyssynchrony is proven to be the best predictor of response to cardiac resynchronization therapy, the electrocardiographic morphology of the conduction delay could become less significant in patient selection. Specifically, the question of whether patients with right bundle branch block (RBBB) morphology will respond must be addressed. In small subsets of patients in both the MIRACLE and CONTAK-CD trials, patients with RBBB appeared to do as well as patients with LBBB. Other investigators have also shown a response to therapy in patients with a RBBB, but only when associated with intraventricular dyssynchrony. Future studies could help refine the indication in NYHA class III–IV patients, whereas other studies could expand the indication to those with milder forms of heart failure or lesser degrees of ventricular dyssynchrony. Information is emerging regarding the outcomes of biventricular versus LV pacing only. At this point, the results are indefinite and further investigations are warranted. Another obvious question is whether routine LV or biventricular pacing rather than traditional right ventricular apical pacing should be used once coronary sinus lead technology, implantation techniques, speed, and complication rates are similar to those of right ventricular endocardial leads.

As resynchronization therapy becomes more commonly used, clinicians should be aware that pacing nomenclature originally established in 1974 was updated recently to include a "generic code" for multisite pacing therapy. The fifth position of the code is now used to indicate whether multisite pacing is present in (0) none of the cardiac chambers, (A) 1 or both atria, (V) 1 and both ventricles, or (D) any combination of atria and ventricles. To describe a patient with a DDDR (dual-chamber rate-adaptive) pacemaker with biventricular stimulation, the code

would be DDDRV.

Limitations and Pitfalls of Cardiac Resynchronization Therapy

The success rate for placement of a transvenous cardiac resynchronization system has ranged from approximately 88% to 92% in clinical trials.[35] This means that 8% to 12% of patients undergoing an implant procedure will not attain a functioning system using this approach. Patients with failed implants must then settle for either another attempt at transvenous placement of the LV lead or epicardial placement of the lead, or they must resign themselves to no cardiac resynchronization therapy. Implant-related complications are similar to those seen with standard pacemaker and ICD technologies, with the additional risk of dissection or perforation of the coronary sinus. Although rare, this event could lead to substantial morbidity and even mortality in patients experiencing heart failure.

In addition to satisfying the clinical criteria already discussed, the patient should be given some basic information before referral. Although it is healthy for the patients to be optimistic about the potential improvement from cardiac resynchronization therapy, caregivers must provide realistic information. Although most patients respond favorably to Abraham and Hayes Cardiac Resynchronization 2601 biventricular pacing, patients should understand that just like the experience with any medication or any other therapeutic modality for heart failure and despite clinical trials data demonstrating significant improvement, not every patient has a subjective and/or objective response to resynchronization therapy. Finally, if the patient obtained subjective and objective clinical improvement after implantation of a resynchronization device, worsening of the patient's heart failure symptoms suggests worsening of the primary pathologic process or loss of resynchronization, or both. Loss of resynchronization can be manifested as frank worsening of heart failure, or it could be more occult and appear as vague weakness or fatigue. A specific programming sequence should be performed in the clinic to determine

capture thresholds and document that LV capture is present. It is possible that LV pacing thresholds are fine but resynchronization is lost for other reasons.

Anything that frequently or consistently inhibits LV stimulation can lead to “desynchronization.” If the AV interval is too long and the patient’s intrinsic PR conduction inhibits biventricular pacing, deterioration can occur. The AV interval could have been programmed appropriately, but accelerated intrinsic AV conduction could result in loss of effective biventricular pacing. Frequent premature ventricular contractions can also inhibit ventricular pacing output. In this case, the etiology of the increasing ventricular ectopy should be determined. Management can require an alteration in the medical regimen for heart failure, specific antiarrhythmic therapy, or an ICD, depending on the amount of ectopy and whether ventricular tachycardia is nonsustained or sustained.

Despite these potential concerns, follow-up of the device itself and battery life are similar to that seen for contemporary dual-chamber pacemakers and ICDs. Optimal hemodynamic response from resynchronization will depend not only on the site of LV stimulation, but also on optimization of the atrioventricular interval and the timing between the right and left ventricle. Best techniques to achieve such optimization are still being defined.[16] Another clinical problem that could result in new symptoms of heart failure is chronotropic incompetence, or inappropriate rate acceleration for a given physiological activity. In the patient with heart failure, this is probably less likely as a result of progression of intrinsic sinus node dysfunction than a change in medical regimen. If the heart failure management team has altered ß blocker therapy or any other medication, the result could be limitation of the patient’s chronotropic response

Recent data have demonstrated that mechanical dyssynchrony is not necessarily related to electrical dyssynchrony [36] and that the presence of substantial left ventricular (LV) dyssynchrony is a major

predictor of response to CRT. Indeed, some patients with a wide QRS complex do not exhibit LV dyssynchrony, whereas some patients with a narrow QRS complex may demonstrate LV dyssynchrony [37]. These considerations suggest that the surface electrocardiogram may not be the optimal marker to select candidates for CRT. New imaging techniques, in particular various echocardiographic approaches, may be superior to select potential responders to CRT.

Echocardiographic Approach to alleviate mechanical dyssynchrony

Atrioventricular (AV) dyssynchrony

Atrioventricular dyssynchrony may be related to the dysfunction of both the sinus node and the AV node. While sinus node dysfunction induces chronotropic incompetence, abnormal conduction of the AV node results in:

- a delay between atrial and ventricular contraction ("AV dyssynchrony");
- mitral valve incompetence with occurrence of late diastolic regurgitation;
- shortened ventricular filling time, limiting net diastolic stroke volume;
- atrial systole often occurs simultaneously with early passive filling, hence reducing LV filling [38].

Interventricular dyssynchrony

Dyssynchronous electrical activation of the ventricles, as during left bundle branch block, is associated with the right ventricular events preceding those of the LV, locally different contraction patterns, abnormal distribution of mechanical work in the LV, deficiencies in regional perfusion, and, therefore, decreased mechanical performance. The delay in onset of LV contraction and relaxation produces interventricular dyssynchrony and affects mainly the interventricular septal motion and its contribution to LV ejection. Earlier onset of right ventricular contraction results in right ventricular ejection

occurring during LV end-diastolic period. The higher pressure within the right ventricle reverses the transseptal pressure gradient and, therefore, displaces the septum into the LV [6].

Intraventricular dyssynchrony

Coordinate LV contraction depends on normal ventricular activation. When a portion of the LV is prematurely activated, it generates regions of both early and delayed contraction that will contribute to altered LV performance [39]. Early shortening or late shortening results in wasted work. The early contraction occurs when pressure is low and does not lead to ejection. The late contraction occurs at higher stress and results in paradoxical stretch of early contracting segments. The net result is a decline in systolic performance, an increase in end-systolic volume and wall stress, a delayed relaxation, and a decline in efficiency.

It is currently unclear to what extent each of these different forms of dyssynchrony contributes to the severity of heart failure. Crucial, however, is that all different dyssynchronies are assessed to identify patients with a high likelihood of response to CRT.

Echocardiographic assessment and quantification of dyssynchrony

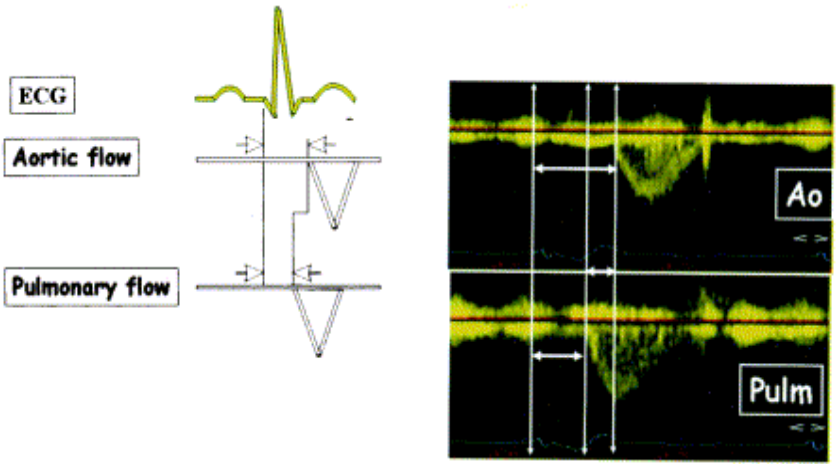
Conventional echocardiography

The AV dyssynchrony can be assessed from conventional echocardiography by evaluating the mitral inflow duration; to date, there are no specific criteria for AV dyssynchrony in the literature.

Interventricular dyssynchrony can be evaluated by assessing the extent of interventricular mechanical delay (IVMD), defined as the time difference between left and right ventricular pre-ejection intervals

Fig 5

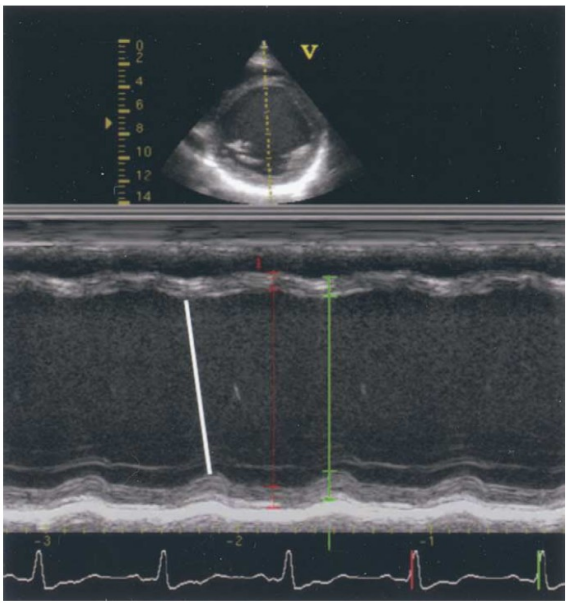
(Fig 5). An IVMD ≥40 ms is considered indicative of interventricular dyssynchrony [40].



Measurement of the interventricular mechanical delay (IVMD) by Doppler echocardiography: the right ventricular and left ventricular (LV) preejection intervals are measured from the onset of the QRS on the electrocardiogram (ECG) to the onset of pulmonary (Pulm) (RV-PEI) and aortic (Ao) (LV-PEI) outflow; IVMD is calculated by subtracting the RV-PEI from the LV-PEI.

M-mode echocardiography may be useful for assessing intraventricular dyssynchrony [12]. Using an M-mode recording from the parasternal short-axis view (at the papillary muscle level), the septal-to-posterior wall motion delay (SPWMD) can be obtained (Fig 6), and a cut-off value ≥130 ms was proposed as a marker of intraventricular dyssynchrony. However, frequently the SPWMD cannot be obtained, either because the septum is akinetic after extensive anterior infarction or because the maximal posterior motion is ill-defined. In addition, it is often not possible to obtain perpendicular M-mode sections of the proximal LV.

Fig 6

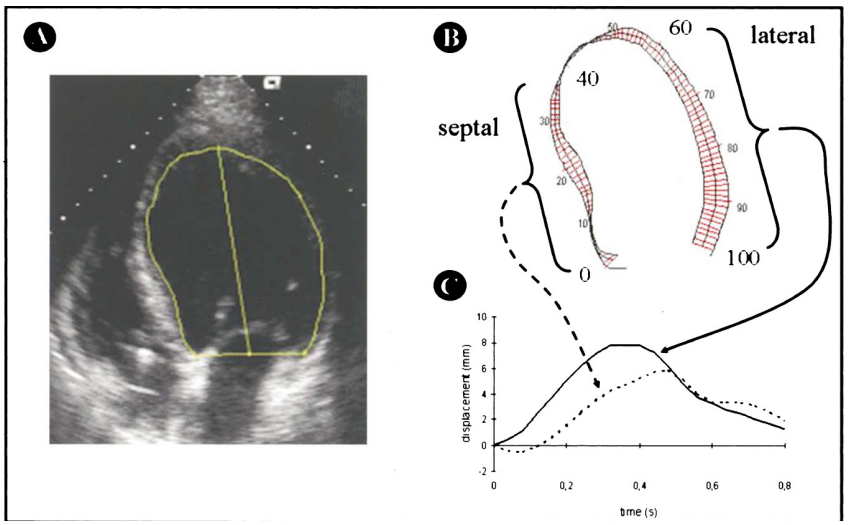


Parasternal M-mode recording in a heart failure patient with left bundle branch block. The left ventricular cavity is dilated and shows severely reduced systolic function. A clear delay between peak systolic septal and posterior wall inward motion is observed

Newer echocardiographic methods

Two newer methods have been described, both addressing intraventricular dyssynchrony. Breithardt et al[41] evaluated 34 patients undergoing CRT using a semiautomatic method for endocardial border delineation. The degree of LV dyssynchrony was quantified in two-dimensional echocardiographic sequences from the apical four-chamber view, focusing on the septal-lateral relationships. Computer-generated regional wall movement curves were compared by a mathematical phase analysis, based on Fourier transformation (Fig. 7). The resulting septal-lateral phase angle difference is a quantitative measure for intraventricular (dys)synchrony.

Fig 7



(A) **End-diastolic still frame image in the apical four-chamber view with a semiautomatically drawn left ventricular endocardial contour tracing.** (B) **Left ventricular wall motion displacement (between end-diastole and end-systole) for 100 endocardial segments determined with the centerline method.** (C) **Averaged septal** (dashed line) **and lateral** (solid line) **wall motion from 40 adjacent septal and lateral segments and three to seven cardiac cycles displayed as displacement (mm) over time (s). The** "shift" between the curves **indicates the degree of regional dyssynchrony and can be expressed quantitatively by the regional phase angle difference**

Kawaguchi et al. [42] studied 10 patients with and without CRT, and, to optimize endocardial LV border detection, echocardiography contrast (Optison, Mallinckrodt, Hazelwood, Missouri) was used; the contrast-enhanced images were processed using a technique referred to as cardiac variability imaging. On the four-chamber images, the endocardial border was outlined manually and regional fractional area changes were determined and plotted versus time, yielding displacement maps. From these maps, the dyssynchrony between the septum and lateral wall was determined.

Both methods are restricted by the use of a single imaging plane. Any dyssynchrony in other walls will be overlooked, and, thus, the precise extent of dyssynchrony cannot be measured. Three-dimensional echocardiography, with the better spatial resolution, may potentially overcome this limitation. An example of this approach is shown in Figure 8. However, the clinical feasibility of real-time three-

Fig 8

dimensional echocardiography still has to be proven.

Quantification of regional wall motion from real-time three-dimensional echocardiographic data. After semiautomatic segmentation of the left ventricular chamber (upper left), the extent and timing of regional wall motion is analyzed in a 16-segment model (lower left) and in this example expressed as regional ejection fraction over time. There is clear regional dyssynchrony between the inferoseptal and the anterolateral segments during left bundle branch block (LBBB) (lower middle), which improves immediately after initiation of cardiac resynchronization therapy (CRT) (lower right).

Tissue Doppler Imaging (TDI), strain and strain rate, tissue tracking (TT)

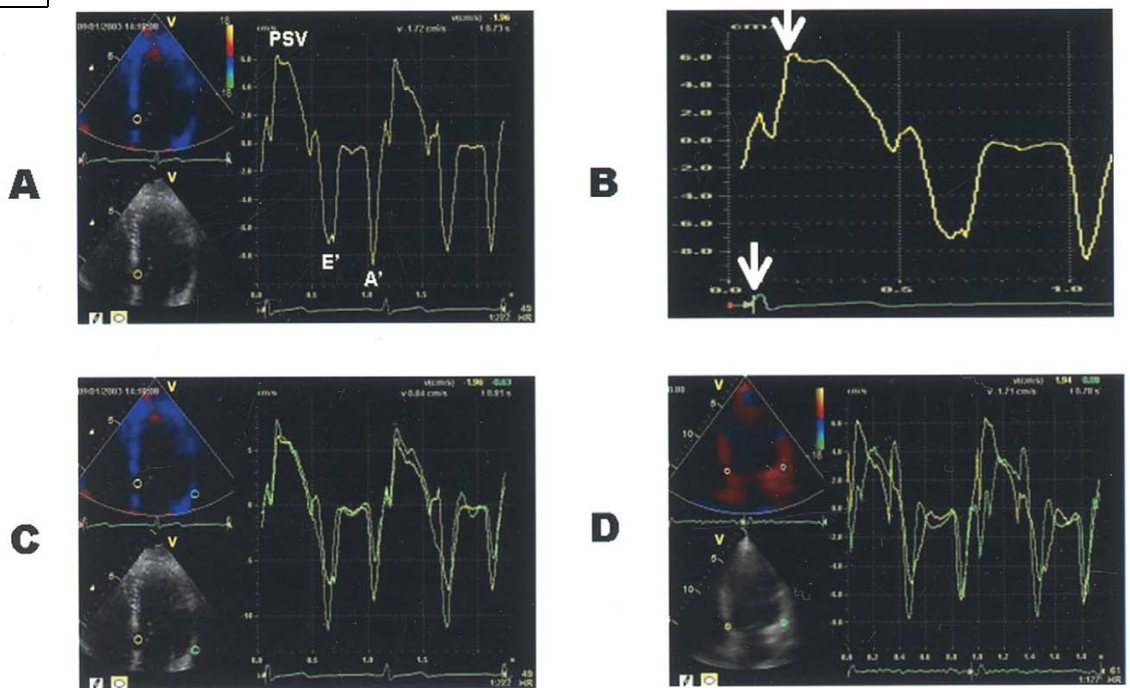
Tissue Doppler Imaging allows measurement of peak systolic velocity of different regions of the myocardium, and timing of peak systolic velocity in relation to electrical activity (QRS complex). Based on these variables, TDI can provide accurate information on electromechanical coupling, and also assess interventricular and intraventricular dyssynchrony (Fig 9). In addition, information on diastolic function can be obtained. Different groups have subsequently used TDI to assess dyssynchrony before CRT. Interventricular dyssynchrony was evaluated by Rouleau et al. who studied 35 patients with dilated cardiomyopathy. Using TDI, the authors demonstrated an excellent agreement between QRS duration and interventricular dyssynchrony. Yu et al. used TDI to assess intraventricular[34] dyssynchrony in 88 normal individuals, 67 patients with heart failure and a narrow QRS complex (≤120 ms), and 45 with a wide QRS complex (>120 ms). In this study, 12 sample volumes were placed in the myocardium, and for each sample the time from onset of QRS complex to peak systolic velocity was measured. From these data, two parameters indicating intraventricular dyssynchrony were derived:

1. The maximal difference between peak systolic velocities of any 2 of the 12 segments (intraventricular dyssynchrony defined as a difference >100 ms); and
2. The SD of all 12 time intervals measuring time to peak systolic velocity (intraventricular dyssynchrony defined as a standard deviation of 33 ms, also referred to as dyssynchrony index).

The authors demonstrated absence of substantial intraventricular dyssynchrony in normal individuals, whereas 73% of the patients with a wide QRS complex had substantial intraventricular dyssynchrony. Of interest, 51% of the patients with a narrow QRS complex also exhibited substantial intraventricular dyssynchrony.

In other studies, intraventricular dyssynchrony was measured by placing two sample volumes (on the basal parts of the septum and lateral wall), and a delay ≥ 60 ms between peak systolic velocities of the septum versus lateral wall (referred to as "septal-to-lateral delay") was used as an indicator of the substantial intraventricular dyssynchrony.[43] Using the digitally stored color-coded tissue Doppler images, further extended off-line analysis can be performed (i.e., strain and strain-rate analysis). Strain analysis allows direct assessment of the degree of myocardial deformation during systole and is expressed as the percentage of segmental shortening or lengthening in relation to its original length [44] ; it provides important information on the timing of onset and peak of myocardial contraction, permitting measurement of (dys)synchrony. Compared with TDI, the main advantage of strain rate imaging resides in the better differentiation between active systolic contraction and passive displacement, which is of particular importance in ischemic patients with scar tissue.

Fig 9



(A) The typical Tissue Doppler Imaging tracings (peak systolic velocity [PSV], diastolic velocities [E' and A']) obtained in the septum of a normal individual. (B) Illustration of assessment of timing from onset of QRS to peak systolic velocity. (C) Evaluation of intraventricular (dys)synchrony by placing sample volumes on the septum (yellow curve) and lateral wall (green curve). Data from a normal individual showing complete intraventricular synchrony. (D) Severe intraventricular dyssynchrony between the septum (yellow curve) and lateral wall (green curve).

The degree of systolic segmental shortening can be obtained with color-coded TDI by calculating the instantaneous regional velocity gradient (i.e., the strain rate, s^{-1}) and integrating this information over time (strain, %). Recent studies have focused on the application of strain and TT for the detection of mechanical intraventricular dyssynchrony in patients considered for CRT, and particular attention was paid to events that occurred late in systole extending into the isovolumetric relaxation phase and diastole. In a typical patient with left bundle branch block and delayed lateral wall activation, a delay in the onset of lateral wall shortening (as compared with the septum) can be observed. However, the clinical applicability of strain rate imaging is still limited by artefacts and a poor signal-to-clutter ratio, which renders the image acquisition and analysis process time-consuming and tedious. Moreover, the technique is operator-dependent, which limits reproducibility and widespread use.

Determinants of dyssynchrony in patients with LBBB

Chronic heart failure (CHF) is an active disease process characterized by progressive remodeling of the ventricles, even in patients with stable symptoms, and by progression within the conduction system. In fact, in approximately 30% of patients, CHF not only determines impaired cardiac systolic function, but also affects the conduction pathways causing a delay in the onset of both right (RV) and left (LV) ventricular systole. Such dyssynchrony is visible on the electrocardiogram as a QRS interval lasting more than 120msec.[6]

Several authors have reported that this intraventricular delay may further impair the ability of the failing heart to eject blood and enhance the severity of mitral valve regurgitation.[6,40] In addition, such prolongation of QRS duration in patients with left bundle branch block (LBBB) on the ECG has been described as an index of increased risk of mortality.[3] Devices using atrial-synchronized biventricular pacing to coordinate LV and RV contraction have been developed. Several recent studies have suggested that cardiac resynchronization can improve cardiac function, enhance the quality of life and reduce all-cause mortality.[26]

Pulsed Doppler myocardial imaging (DMI) extends Doppler applications beyond the analysis of cardiac blood flows to the measurement of myocardial wall motion. Several recent reports have documented the usefulness of DMI in assessing the severity of LV dyssynchrony in patients with LBBB and CHF, as well as in evaluating the pacing effects on long-axis function in these patients. Conversely, no recent data is available on regional systolic dyssynchrony in patients with LBBB and normal LV ejection fraction. On these grounds, the aim of the present study is to evaluate the determinants of myocardial activation delay of both left and right ventricle in patients with LBBB demonstrating either normal or impaired global LV systolic function.

MATERIALS AND METHODS

Study Design

This was a prospective descriptive trial performed over a 1 year period from October 2005 to October 2006.

Setting

CMC Vellore is a 2000 bedded tertiary care teaching hospital. Patients were recruited from the outpatient department.

69 consecutive patients with LBBB on ECG were enrolled for the study.

Subjects

Inclusion Criteria

1. LBBB on baseline ECG

Exclusion Criteria

1. Patients on CRT/Pacemaker
2. Atrial fibrillation with fast ventricular rate
3. Unwillingness of the patient to be enrolled
4. Poor acoustic window

Clinical Assessment.

All patients were interviewed individually. Their history, duration and severity of the symptoms were ascertained. They were therafter subjected to a thorough clinical examination and signs of failure checked for. The drugs they were on and duration of therapy was noted. An ECG was done at the time of recruitment and this was used to determine the electrocardiographic variables.

Patients were diagnosed to have ischemic cardiomyopathy if they had history of a prior MI, diagnosed by standard criteria or angiographic evidence of significant coronary artery disease. The patients who did not satisfy the criteria for ischemic cardiomyopathy but had global hypokinesia with EF<40% were diagnosed to have non ischemic dialted cardiomyopathy.

Echocardiographic Protocol

After a standard echocardiographic study, these patients eligible for inclusion were informed about the study and informed consent was obtained. Standard Doppler echocardiography and Tissue Doppler Imaging were performed with the subjects in partial decubitus, by Acuson Sequoia ultrasound system equipped with Doppler myocardial imaging capabilities. A frequency transducer of 4 MHz was used for two dimensional, M-mode and Doppler imaging. All the measurements were obtained by taking the average of ≥ 3 cardiac cycles.

2D Echo

LV Ejection fraction was measured using a commercially available software program that applied modified Simpson's rule on this chamber and four chamber views.

M-Mode

The septum to posterior wall return delay was ascertained using the M-Mode short axis view taken at the level of the papillary muscles. It was obtained by measuring the shortest interval between the maximal posterior displacement of the septum and the posterior wall. A SPWMD longer than 130

milliseconds was considered as an interventricular dyssynchrony marker.

Standard Doppler

Using Pulsed Doppler time from the Q wave to the start of RV ejection as assessed at the level of the RV outflow tract from a short axis parasternal view was measured. The time from the q wave to the start of LV ejection as assessed by pulsed Doppler at the level of the LV outflow tract from a 4-chamber view was found out.

Interventricular Dyssynchrony Assessment

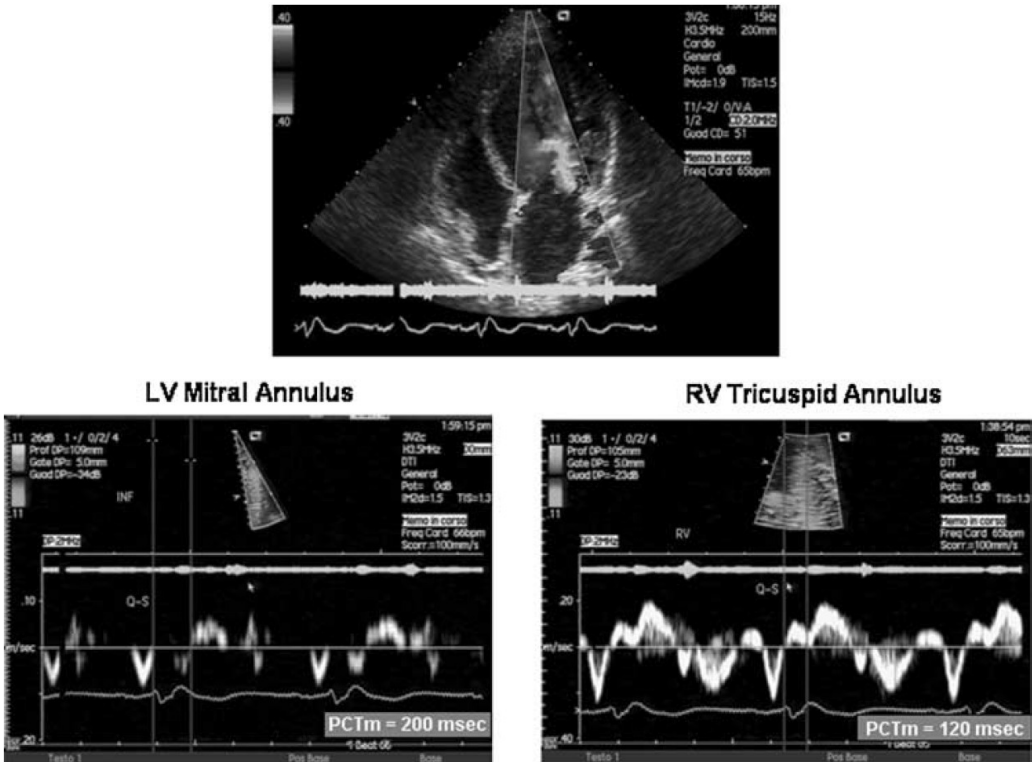
The difference between the time for LV activation (Q- A_0) and time for RV activation (Q-pulm) determined the doppler interventricular delay. A valve > 40 msec was considered an indication of dyssynchrony.

Pulsed Doppler Myocardial Imaging

Pulsed DMI was performed by spectral pulsed Doppler signal filters , bypassing high pass filter ; adjusting Nyquist limit to 15-20 cm/sec (close to myocardial velocities), and using the minimal optimal gain. In apical 4- Chamber and 2 chamber views, a 5mm pulsed Doppler sample volume was subsequently placed at the level of 5 different basal myocardial segments. LV posterior septum , LV inferior wall , LV anterior wall, LV lateral wall (at the level of mitral annulus) and RV lateral wall (at the level of tricuspid annulus). The apical view was chosen to obtain a qualitative assessment of the longitudinal regional wall motion at most simultaneous to Doppler inflow and outflow and to minimize the incidence angle between Doppler beam and longitudinal wall motion. By use of DMI the index of myocardial systolic activation in five different basal myocardial segments was calculated: Precontraction time (PCTm) (from the beginning of Q wave of ECG to the onset of Sm); intraventricular systolic synchrony was analysed by the difference of PCTm between the most delayed

LV segment and RV lateral wall.(Fig10)

Fig 10 INTERVENTRICULAR MYOCARDIAL DYSSYNCHRONY IN PATIENTS WITH LBBB



DMI PCTm of LV mitral annulus and of RV tricuspid annulus in a patient with dilated cardiomyopathy and LBBB. Interventricular delay (difference between the two parameters) was 80 msec. PCTm = myocardial precontraction time; LV = left ventricle; RV = right ventricle.

Statistical Methods

Determination of sample size

In order to determine the sample size a similar study done by Pio Caso et al [45] was chosen. One of the major outcomes of the study was a parameter called the intraventricular delay. The mean value of the intraventricular delay in those with normal ejection fraction was 20.8 ± 17.3 and in those with low ejection fraction was 35.6 ± 18.2. Based on this information we calculated the sample size of our study for two sample comparison of means by STATA software. Considering a 5% α error with a 2-sided test and 80% power we obtained a sample size of 23 in each arm.

Analyses

All the analyses were performed by SPSS for windows release 14.0 (Chicago, Illinois, USA). Variables

were presented as mean ± SD. T test for unpaired data and analysis of variance (ANOVA) test with Scheffe correction estimated differences among the groups. Linear regression analyses and partial correlation test by Pearson's method were done to assess univariate relations. Receiver operating characteristic (ROC) curve analysis was performed to select optimal cut off values of DMI measurements. A 2 x 2 table was made for each of the parameters like LV dyssynchrony, RV-LV dyssynchrony , APED and a Pearson Chi square test was performed. Differences were significant at $p<0.05$

RESULTS

During the period October 2005 to October 2006, 69 patients with LBBB on ECG were included in the study. Of these 38 patients – Group I had an ejection fraction less than 50% and 31 patients – Group II had a normal ejection fraction ≥ 50% (Table II). The two groups were comparable in age (57.5 ± 12.48 in the low EF vs 59.03 ± 11.58 in the normal EF), sex male prevalence (24/38 in low EF vs 20/31 in normal EF).There were 25 female (36.2%) and 44 male (63.8%) subjects. 56 subjects (81.2%) were euthyroid , 10 (14.5%) were hypothyroid and 3 (4.3%) were hyperthyroid. 44 subjects (63.8%) were diabetic , 41 (59.4%) were hypertensive and 49 (71%) were dyslipidemic. 25 (36.2%) individuals suffered from ischemic heart disease. 19 (27.5%) were smokers and 5 (7.2%) were alcohol consumers.

The qrs width was significantly greater in those patients with LBBB who had a low EF. However it was not found to correlate well with the ECHO parameters evaluating dyssynchrony Of the 69 patients, 10 individuals satisfied the ECHO criteria that deemed that they would benefit by resynchronization therapy (SPWMD > 130 msec, IVMD> 40 msec, APED > 140 msec, intraventricular activation delay > 65 msec and interventricular activation delay > 55 msec). 9 of these individuals had a ejection fraction less than 50% [Table III]. When compared to the Echo criteria, the ECG criteria (qrs ≥ 140 msec) to select patients who would benefit from CRT was only 88.9% sensitive and 41.4% specific. There was only an 18% agreement between the ECG and Echo criteria in selecting patients for CRT that occurred beyond chance [Table IV]. This proved beyond doubt that ECG criteria was grossly inadequate in selecting patients with dyssynchrony who would benefit from CRT.

The two groups were comparable in heart rate – 84.82 ± 15.12 in those with low EF versus 82.58 ±

18.768 in those with normal EF. The qrs duration was significantly greater in those with low EF (Mean = 148.53 ± 18.557) versus those with normal EF (Mean = 135.71 ± 11.725 p value 0.001). The mean LVIDd in those with low EF was 62.68 ± 9.355 which was significantly greater than those with normal EF (48.35 ± 5.919 $p<0.001$). The individuals with low EF had significantly higher LVIDs (51.5 ± 8.7 versus 35.5 ± 9.3 $p<0.001$), EDV (188.97 ± 59.89 versus 108.39 ± 30.177 $p<0.001$) and ESV (126.05 ± 51.6 versus 47.35 ± 13.5) [Table II].

TDI analyses showed a prolonged precontraction time at the level of the LV lateral wall in those with low EF [Table VI]. The PCTm of the LV anterior wall was almost significantly higher in the group with low EF. The PCTm for the RV lateral wall, LV inferior wall and LV septum were not significantly different between the two groups [Table V]. Individuals of both groups showed a significant delay in activation of the LV lateral wall with consequent prolonged intraventricular delay [Fig 10]. The group with normal EF were found to have significantly less interventricular myocardial activation delay ($p= 0.006$ Table XII); intraventricular mechanical delay ($p=0.007$ Table XIII); aortic pre ejection delay ($p=0.002$ Table XIV); intraventricular myocardial activation delay ($p=0.03$ Table XI). The septum to posterior wall motion delay was not significantly different between the 2 groups ($p=0.07$) [Table XV].The sensitivity and specificity of DMI measured time intervals was determined [Table XVI]. By ROC curve analysis, a cut off value of 48.5 msec of interventricular delay showed 71% sensitivity and 65% specificity in identifying patients with impaired EF [Fig 11] .

In the overall population by use of stepwise forward multivariate linear regression analyses, LV end diastolic diameter (ß coefficient = 1.408; $p<0.01$) , Ejection fraction (ß coefficient = -1.05; $p<.015$) and qrs duration (ß coefficient = .753; $p<.02$) were the only independent determinants of interventricular activation delay [Table XVII].

Table II

Parameter	Group I Low EF ≤ 50	Group II Normal EF > 50	P value
Ejection Fraction	34.71 ± 6.2	55.9 ± 2.7	
Age	57.5 ± 12.48	59.03 ± 11.58	0.6
Pulse Rate	84.82 ± 15.12	82.58 ± 18.77	0.586
QRS Duration	148.53 ± 18.56	135.71 ± 11.73	0.001
LVIDd	62.68 ± 9.36	48.35 ± 5.92	<0.001
LVIDs	51.5 ± 8.77	35.5 ± 9.33	<0.001
EDV	188.97 ± 59.89	108.39 ± 30.18	<0.001
ESV	126.05 ± 51.6	47.35 ± 13.5	<0.001
Q to Basal Lateral	127.03 ± 49.41	103.16 ± 46.01	0.043
Q to Basal Anterior	97.71 ± 37.64	79.61 ± 37.83	0.052
Q to Basal Inferior	83.03 ± 41.21	73.23 ± 35.72	0.301
Q to Basal Septal	79.13 ± 33.93	65.55 ± 35.09	0.108
Q to RV Lateral	57.81 ± 21.76	58.61 ± 32.33	0.913
Interventricular Delay	74.68 ± 43.90	47 ± 35.52	0.006
Intraventricular Delay	68.82 ± 40.68	47.06 ± 32.64	0.03

Applying CRT eligibility ECHO criteria to the data [those with interventricular dyssynchrony >55msec, intraventricular dyssynchrony >65msec, interventricular mechanical delay > 40msec, Aortic pre ejection delay >140msec and septum to posterior wall delay > 130msec] there were 9 individuals in the low EF group and 1 in the normal EF group who had dyssynchrony and would benefit from CRT(Table III)

Table III

	ELIGIBLE FOR CRT BY ECHO CRITERIA	NOT ELIGIBLE FOR CRT BY ECHO CRITERIA	TOTAL
Low EF	9	29	38
Normal EF	1	30	31
Total	10	59	69

Table IV

COMPARING THE ECG CRITERIA [QRS >140 MSEC] WITH ECHO CRITERIA FOR DYSSYNCHRONY

		ECHO		
		ABNORMAL CASES	NORMAL CASES	TOTAL
QRS DURATION ON ECG	>=140	8	12	20
	<140(NORMAL-ECG)	1	17	18
	TOTAL	9	29	38

Sensitivity = 88.9%, specificity = 41.4%

Positive predictive value = 32%, negative predictive value = 92%

Prevalence = 24% , kappa = 0.188

Only 18% agreement beyond chance, between ECG and ECHO in diagnosing dyssynchrony

Table V

THE ISOVOLUMIC CONTRACTION TIME WAS GREATER FOR THOSE WITH LOW EJECTION FRACTION IN ALL SEGMENTS

(HOWEVER IT WAS NOT STATISTICALLY SIGNIFICANT)

ISOVOLUMIC CONTRACTION TIME(PCTm)	EJECTION FRACTION	N	MEAN	STD. DEVIATION	STD. ERROR MEAN	P Value
Q to RV Lateral	<=50	38	57.89	21.76	3.53	
	>50	31	58.61	32.33	5.81	.91
Q to Basal Septal	<=50	38	79.13	33.93	5.50	
	>50	31	65.55	35.09	6.30	.11
Q to Basal anterior	<=50	38	97.71	37.64	6.11	
	>50	31	79.61	37.83	6.79	0.05
Q to Basal inferior	<=50	38	83.03	41.21	6.68	
	>50	31	73.23	35.72	6.42	0.3

Table VI

T-TEST SHOWING SIGNIFICANT DIFFERENCE IN THE PCTm FOR THE BASAL LATERAL SEGMENT OF THE LV BETWEEN THE LOW AND NORMAL EF GROUPS (P=0.04)

EJECTION FRACTION	N	MEAN	STD. DEVIATION	STD. ERROR MEAN
Q to Basal Lateral <=50	38	127.03	49.41	8.02
>50	31	103.16	46.01	8.26

Fig 10

THE LV BASAL LATERAL SEGMENT HAD DELAYED CONTRACTION COMPARED TO ALL OTHER SEGMENTS

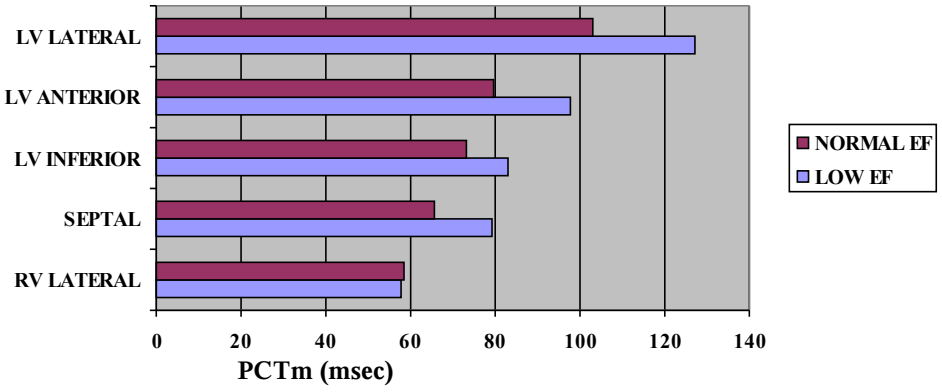


Table VII

IN THE LOW EF GROUP THE LV BASAL LATERAL SEGMENT IS SIGNIFICANTLY DELAYED COMPARED TO ALL THE OTHER BASAL SEGMENTS

Basal Segment	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean	
					Upper Bound	Lower Bound
RV	38	57.89	21.76	3.53	50.74	65.05
Sep	38	79.13	33.93 49.41	5.50	67.98	90.28
Lat	38	127.03 97.71	37.64	8.01	110.79	143.27
Ant	38	83.03 88.96	41.21 43.96	6.10	85.34	110.08
Inf	38			6.68	69.48	96.57
Total	190			3.19	82.67	95.25

RV - Right ventricle free wall ; Sep - Septum ; Lat - Lateral ; Ant - Anterior ; Inf – Inferior

Table VIII

COMPARING DYSSYNCHRONY BETWEEN VARIOUS SEGMENTS IN LOW EF GROUP

Basal Segment	Mean Difference	Std. Error	Sig.	95% Confidence Interval for Mean	
				Lower bound	Upper Bound

RV	Sep	-21.24	8.69	.155	-45.94	3.46
	Lat	-69.13*	8.69	.000	-93.83	-44.43
	Ant	-39.82*	8.69	.000	-64.52	-15.12
	Inf	-25.13*	8.69	.043	-49.83	-0.43
Sep	RV	21.24	8.69	.155	-3.46	45.94
	Lat	-47.89*	8.69	.000	-72.59	-23.20
	Ant	-18.58	8.69	.339	-43.28	6.12
	Inf	-3.89	8.69	1.000	-28.59	20.80
Lat	RV	69.13*	8.69	.000	44.43	93.83
	Sep	47.89*	8.69	.000	23.20	72.59
	Ant	29.32*	8.69	.009	4.61	54.02
	Inf	44.00*	8.69	.000	19.30	68.70
Ant	RV	39.82*	8.69	.000	15.12	64.52
	Sep	18.58	8.69	.339	-6.12	43.28
	Lat	-29.32*	8.69	.009	-54.01	-4.62
	Inf	14.68	8.69	.929	-10.01	39.38
Inf	RV	25.13*	8.69	.043	.43	49.83
	Sep	3.89	8.69	1.000	-20.80	28.59
	Lat	-44.00*	8.69	.000	-68.70	-19.30
	Ant	-14.68	8.69	.929	-39.38	10.02

*** The mean difference is significant at the .05 level**

Table IX

IN THE NORMAL EF GROUP THE LV BASAL LATERAL SEGMENT IS DELAYED WHEN COMPARED TO THE BASAL SEPTAL, BASAL INFERIOR AND RV BASAL LATERAL SEGMENT

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean	
					Upper Bound	Lower Bound
RV	31	58.61	32.33	5.80	46.75	70.47
Sep	31	65.55	35.09	6.30	52.68	78.42
Lat	31	103.16	46.01	8.26	86.28	120.04
Ant	31	79.61	37.82	6.79	65.74	93.49
Inf	31	73.23	35.72	6.41	60.12	86.33
Total	155	76.03	40.23	3.23	69.65	82.42

Table X

COMPARING DYSSYNCHRONY BETWEEN VARIOUS SEGMENTS IN NORMAL EF GROUP

Basal Segment		Mean Difference	Std. Error	Sig.	95% Confidence Interval for Mean	
					Lower bound	Upper Bound
RV	Sep	-6.93	9.57	1.00	-34.21	20.34
	Lat	-44.55	9.57	.00	-71.82	-17.28
	Ant	-21.00	9.57	.298	-48.27	6.27
	Inf	-14.61	9.57	1.00	-48.88	12.66
Se	RV	6.93	9.57	1.00	-20.33	34.20
	Lat	-37.61	9.57	.001	-64.88	-10.34
	Ant	-14.06	9.57	1.00	-41.33	13.20
	Inf	-7.68	9.57	1.00	-34.94	19.39
Lat	RV	44.55	9.57	.000	17.28	71.81
	Se	37.61	9.57	.001	10.34	64.88
	Ant	23.55	9.57	.150	-3.72	50.81
	Inf	29.93	9.57	.021	2.66	57.20
Ant	RV	21.00	9.57	.298	-6.27	48.27

	Se	14.06	9.57	1.00	-13.20	41.33
	Lat	-23.55	9.57	.150	-50.81	3.72
	Inf	6.39	9.57	1.00	-20.89	33.66
Inf	RV	14.61	9.57	1.00	-12.66	41.88
	Se	7.68	9.57	1.00	-19.59	34.95
	Lat	-29.93	9.57	.021	-57.20	-2.66
	Ant	-6.39	9.57	1.00	-33.66	20.88

Table XI

COMPARING THE INTRAVENTRICULAR MYOCARDIAL ACTIVATION DELAY BETWEEN THE LOW AND NORMAL EF GROUPS SHOWING A SIGNIFICANTLY GREATER DELAY IN THE LOW EF GROUP (P = 0.03)

EJECTION FRACTION	N	MEAN	STD. DEVIATION	STD. ERROR MEAN
LV Dyssynchrony <=50	38	68.82	40.69	6.60
>50	31	47.06	32.64	5.87

Table XII

COMPARING THE INTERVENTRICULAR MYOCARDIAL ACTIVATION DELAY BETWEEN THE LOW AND NORMAL EF GROUPS SHOWING A SIGNIFICANTLY GREATER DELAY IN THE LOW EF GROUP (P = 0.008)

	RVLV DELAY		TOTAL
	NORMAL	ABNORMAL	
Low EF	13	25	38
Normal EF	21	10	31
Total	34	35	69

Table XIII

THE INTERVENTRICULAR MECHANICAL DELAY IS SIGNIFICANTLY GREATER FOR THE LOW EF GROUP THAN THE NORMAL EF GROUP (P=0.008)

	INTERVENTRICULAR MECHANICAL DELAY		TOTAL
	NORMAL	ABNORMAL	
Low EF	11	27	38
Normal EF	19	12	31
Total	30	39	69

Table XIV

THE AORTIC PREEJECTION DELAY IS SIGNIFICANTLY GREATER FOR THE LOW EF GROUP THAN THE NORMAL EF GROUP (P=0.003)

	AORTIC PRE EJECTION DELAY		TOTAL
	NORMAL	ABNORMAL	
Low EF	8	30	38
Normal EF	18	13	31
Total	26	43	69

Table XV

THERE IS NO SIGNIFICANT DIFFERENCE BETWEEN THE SEPTUM TO POSTERIOR WALL MOTION DELAY BETWEEN THE LOW AND NORMAL EF GROUPS (P=0.124)

	SEPTUM TO POSTERIOR WALL MOTION DELAY		TOTAL
	NORMAL	ABNORMAL	
Low EF	22	16	38

Normal EF	24	7	31
Total	46	23	69

Table XVI

A CUT OFF POINT OF INTERVENTRICULAR DELAY >48.5 msec

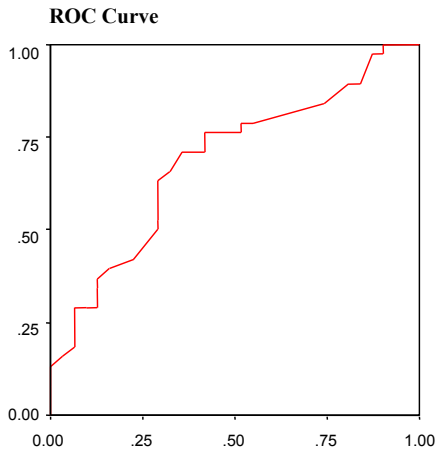
Coordinates of the Curve

Test Result Variable(s): RVLV Delay

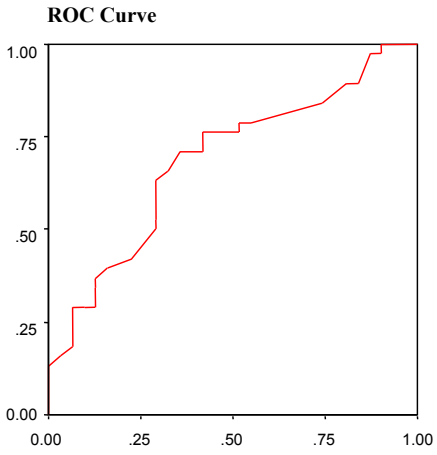
Positive if Greater than or equal to	sensitivity	1-specificity
-1.00	1.000	1.000
1.50	1.000	.903
5.00	.974	.903
10.00	.974	.871
14.00	.895	.839
17.50	.895	.806
25.00	.842	.742
31.50	.789	.548
35.00	.789	.516
38.50	.763	.516
43.00	.763	.419
46.50	.711	.419
48.50	.711	.355
53.50	.658	.323
58.50	.632	.290
63.00	.526	.290
68.00	.500	.290
75.00	.421	.226
85.00	.395	.161
92.50	.368	.129
97.50	.342	.129
101.50	.289	.129
104.00	.289	.097
107.50	.289	.065
115.00	.184	.065
125.00	.158	.032
131.50	.132	.000
139.50	.105	.000
148.00	.079	.000
155.00	.026	.000
161.00	.000	.000

Fig 11

ROC CURVE ANALYSIS OF INTERVENTRICULAR DELAY



Diagonal segments are produced by ties.



Diagonal segments are produced by ties.

Table XVII

MULTIVARIATE LINEAR REGRESSION ANALYSIS SHOWING LVIDd , EF AND QRS DURATION BEING THE ONLY INDEPENDENT DETERMINANTS OF RVLV DELAY

VARIABLE	ß COEEFICIENT	P VALUE	95% CONFIDENCE INTERVAL	
			LOWER BOUND	UPPER BOUND
Dyspnea	7.4	.57	-18.77	33.60
Diabetes	2.08	.84	-19.27	23.43
Pulse Rate	.452	.141	-0.154	1.059
TR Severity	2.5	.67	-9.33	14.48
QRS Duration	.753	0.02	.121	1.38
EF Value	-1.05	.015	-1.9	-0.21

Fig 12

SCATTER PLOT SHOWING THAT INERVENTRICULAR DYSSYNCHRONY IS INVERSELY RELATED TO THE EJECTION FRACTION

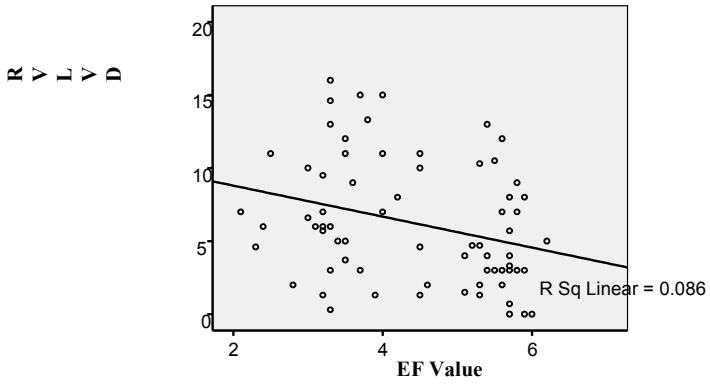


Fig 12

SCATTER PLOT SHOWING THAT INTERVENTRICULAR DYSSYNCHRONY IS DIRECTLY RELATED TO THE LV INTERNAL DIAMETER IN DIASTOLE

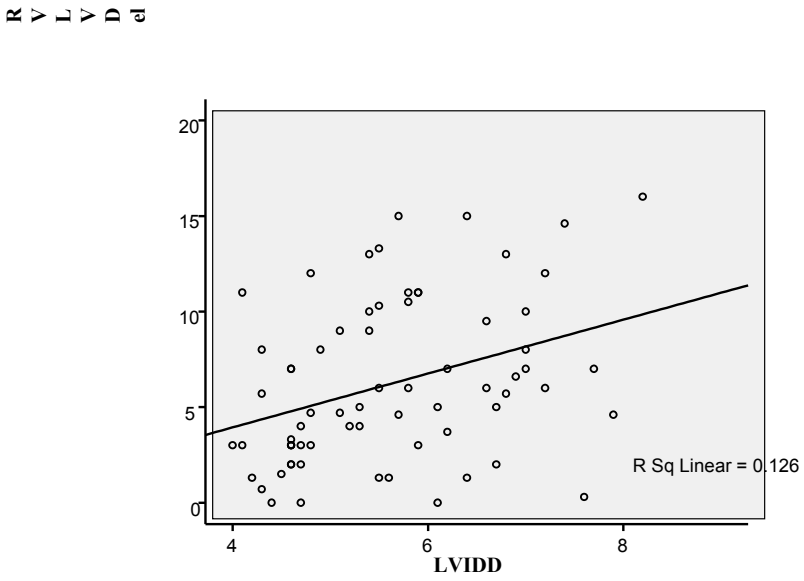


Fig 13

SCATTER PLOT SHOWING THAT EJECTION FRACTION IS INVERSELY RELATED TO THE LV INTERNAL DIAMETER IN DIASTOLE

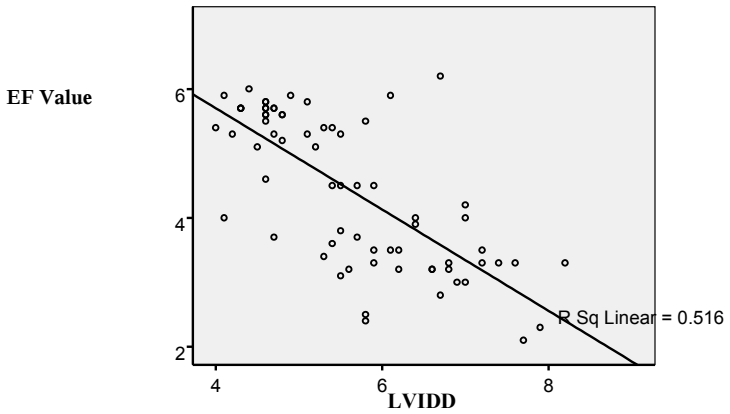
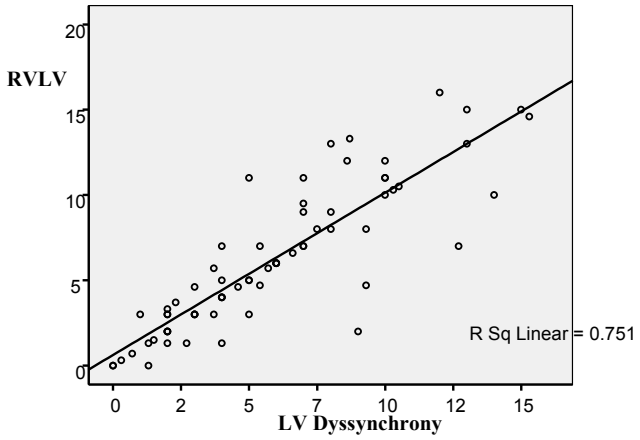


Fig 14

SCATTER PLOT SHOWING THAT INERVENTRICULAR DYSSYNCHRONY IS DIRECTLY RELATED TO INTRAVENTRICULAR DYSSYNCHRONY



DISCUSSION

The present study demonstrates the usefulness of Tissue Doppler in analyzing patterns of myocardial systolic activation of both left and right ventricle in patients with LBBB. To the best of our knowledge, this is the first Indian report comparing regional systolic dyssynchrony between patients with LBBB with either normal or impaired LV global systolic function.

In our study protocol, we evaluated three useful indices of interventricular delay in patients with LBBB:

(1) QRS width by surface ECG

(2) (Q-Ao)-(Q-Pulm) by standard echo- Doppler [IVMD];

(3) InterVentricular Delay by TDI.

ECG, Doppler and TDI assessment **:**

The IVMD and interventricular delay by TDI were significantly more in those patients with LBBB who had low EF proving beyond doubt that of LBBB patients those with low EF had greater interventricular dyssynchrony. The qrs width was also significantly greater in those patients with LBBB who had a low EF. However it was not found to correlate well with the ECHO parameters evaluating dyssynchrony. In fact, no significant correlation was observed (Pearson correlation of 0.374) between TDI Interventricular delay and qrs duration. This result confirms that, despite similar qrs morphology, patients with CHF and LBBB may present heterogeneities of myocardial electromechanical coupling and different locations of mechanical dyssynchrony consequent to myocardial disease or subendocardial ischemia. There was only a 18% agreement beyond chance between ECG [qrsd >140msec] and Echo criteria in selecting patients for CRT. Though the ECG was reasonably sensitive it was far less specific in identifying patients with dyssynchrony. Thus Tissue

Doppler Echo will help us in better selection of those cases that would benefit most from CRT.

***TDI – to measure intraventricular dyssynchrony* :**

In our study intraventricular dyssynchrony as assessed by M mode echo - septum to posterior wall motion delay was not significantly different between the low and normal EF groups. Our results are consistent with published literature suggesting that it is a measurement associated with a lot of subjective error and hence may be regarded as an unreliable method to assess intraventricular dyssynchrony.[47]

Tissue Doppler assessment of intraventricular dyssynchrony showed there was significantly longer isovolumic contraction time to the LV basal lateral wall in patients with LBBB. This delay was much longer in those with low EF when compared to those with normal EF. The shortest and the longest ICTm were measured in the basal septal and lateral segments, respectively, thus resulting in 43 msec of delay between the LV septum and lateral wall. This data diverts from the normal, in the sense that the last segment to contract is the basal lateral, whereas it is the posterior segment in normal subjects. Normally, LV contraction occurs without significant delay almost simultaneously in every LV segment that results in synchronous contraction.[36] However, in patients with LBBB, contraction is delayed far more than the normal range.

TDI –RV basal lateral to LV basal lateral :

In patients with LBBB there was a marked difference in the RV basal free wall to LV basal lateral wall in both the low and normal EF groups. This suggests that all patients with LBBB have some amount of inter and intraventricular dyssynchrony, those with low ejection fraction having greater dyssynchrony. These findings translated to a greater number of individuals with lower ejection fraction satisfying the echo criteria for cardiac resynchronization therapy; 9 out of 38 as against 1 out of 31 with normal ejection fraction. This suggests that in LBBB patients significant dyssynchrony

could occur though it is much less frequent in those with normal ejection fraction.

In individuals with LBBB, the uncoordinated systole worsens the workload and the stress of the left ventricle. The interventricular septum, which is usually activated first, develops a small pressure load with low wall stress, and contributes minimally to intraventricular pressure increase. On the other hand, the LV lateral free wall is activated late, has a high presystolic stress, and is therefore affected by unbalanced load and stress. The final result is a worsening of LV global work with, with prolongation of presystolic ventricular time (i.e, PCTm), delay in the onset of LV systole, shortening of LV ejection and filling time, and further depression of LV ejection fraction.

Multivariate analysis provided further information about this association by adjusting for several confounders, chosen according to the heart physiology and the presence of intraventricular conduction abnormalities. By this model, LV dilatation, ejection fraction and qrs duration were the only independent determinants of TDI InterVentricular delay. In addition, an InterVentricular delay >48.5 msec (a cut-off value selected by ROC curve analysis) identified patients with impaired LV global systolic function with a sensitivity of 71% and specificity of 65%.

Why TDI is better? :

Our findings are consistent with several recent reports emphasizing the usefulness of TDI to support cardiac resynchronization therapy in patients with severe CHF and LBBB. In particular, as reported by Ansalone et al [46], the extent of myocardium with asynchronous contraction at the LV base predicted the improvement in LV systolic performance and reversion of LV remodeling during short- and long-term biventricular pacing. Furthermore, individual tailoring of the pacing site, with accurate preactivation of myocardial regions showing mechanical dyssynchrony, produced a significant reduction of the extent of InterVentricular delay, and consequent significant improvement of LV EF%. In other words, the delayed longitudinal contraction assessed by TDI represents mechanical LV dyssynchrony and thus a

contractile reserve, which can be recruited by means of optimized cardiac resynchronization therapy It was also shown that after CRT, the delay between the contraction of septal and lateral walls was diminished. CRT improves coordination of contraction among LV segments due to homogeneous activation and serves to restore synchronous contraction. TDI enables the quantification of systolic and diastolic functions of separate LV segments and thus help us in appropriately planning the position of the coronary sinus lead and timing the activation of the different myocardial segments.

Study limitations :

1. The major limitation of our study is the Doppler technique used. It is angle dependent.
Also there is the possible presence of artifacts. However we tried to overcome this by taking a minimum of 3 measurements for each parameter and calculating an average of the same.
2. Sample size :The number of subjects studied is only 69. A larger study needs to be done to confirm our findings.

CONCLUSIONS

The main findings of our study are

1) The criteria for cardiac resynchronization therapy was satisfied by 9 out of 38 patients with LBBB on baseline ECG and low ejection fraction on Echo.

2) The prevalence of cardiac dyssynchrony in patients with LBBB on baseline ECG and LV dysfunction was 23.6%.

3) The prevalence of cardiac dyssynchrony in patients with LBBB on baseline ECG and normal LV function was 0.03%.

4) Patients with LBBB and low ejection fraction had greater dyssynchrony than those with LBBB and normal ejection fraction .

5). Tissue Doppler is a better technique than ECG in detecting dyssynchrony.

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ANNEXURE

T-TEST : AGE DISTRIBUTION VERSUS EJECTION FRACTION – NO SIGNIFICANT DIFFERENCE (P=0.6)

		N	MEAN	STD. DEVIATION	STD. ERROR MEAN
Age	low EF	38	57.50	12.483	2.025
	Normal EF	31	59.03	11.580	2.080

SEX DISTRIBUTION

		FREQUENCY	PERCENT
Valid	Female	25	36.2
	Male	44	63.8
	Total	69	100.0

SEX VERSUS EJECTION FRACTION- NO SIGNIFICANT DIFFERENCE (P=1)

	Female	male	TOTAL
Low EF	14	24	38
Normal EF	11	20	31
Total	25	44	69

PRESENCE OF Thyroid dysfunction AMONG SUBJECTS

	FREQUENCY	PERCENT
Euthyroid	56	81.2
Hypothyroid	10	14.5
Hyperthyroid	3	4.3
Total	69	100.0

DISTRIBUTION OF DIABETES AMONG PATIENTS

		FREQUENCY	PERCENT
Diabetes	Absent	25	36.2
	Present	44	63.8
	Total	69	100.0

DISTRIBUTION OF HYPERTENSION AMONG PATIENTS

		FREQUENCY	PERCENT
Hypertension	Absent	28	40.6
	Present	41	59.4
	Total	69	100.0

DISTRIBUTION OF DYSLIPIDEMIA AMONG PATIENTS

		FREQUENCY	PERCENT
Dyslipidemia	Absent	20	29
	Present	49	71
	Total	69	100.0

DISTRIBUTION OF ISCHEMIC HEART DISEASE AMONG PATIENTS

		FREQUENCY	PERCENT
IHD	Absent	44	63.8
	Present	25	36.2
	Total	69	100.0

DISTRIBUTION OF SMOKING AMONG PATIENTS

		FREQUENCY	PERCENT
Smoking	No	50	72.5
	Yes	19	27.5
	Total	69	100.0

DISTRIBUTION OF ALCOHOL CONSUMPTION AMONG PATIENTS

		FREQUENCY	PERCENT
Alcohol Consumption	No	64	92.8
	Yes	5	7.2
	Total	69	100.0

Correlation between QRS duration and all other parameters

		QRSvalues	EF Value	Aortic Preejection Delay	Inter ventricular Mechanical Delay	RVLV Delay	LV Dyssynchrony	Septum to Posterior wall motion Delay
QRSvalues	Pearson Correlation	1	-.351**	.355**	.337**	.374**	.365**	.496**
	Sig. (2-tailed)		.003	.003	.005	.002	.002	.000
	N	69	69	69	69	69	69	69
EF Value	Pearson Correlation	-.351**	1	-.454**	-.281*	-.293*	-.290*	-.242*
	Sig. (2-tailed)	.003		.000	.019	.015	.016	.045
	N	69	69	69	69	69	69	69
Aortic Preejection Delay	Pearson Correlation	.355**	-.451**	1	.624**	.354**	.422**	.437**
	Sig. (2-tailed)	.003	.000		.000	.003	.000	.000
	N	69	69	69	69	69	69	69
Inter ventricular Mechanical Delay	Pearson Correlation	.337**	-.281*	.624**	1	.238*	.193	.389**
	Sig. (2-tailed)	.005	.019	.000		.049	.111	.001
	N	69	69	69	69	69	69	69
RVLV Delay	Pearson Correlation	.374**	-.293*	.354**	.238*	1	.867**	.302*
	Sig. (2-tailed)	.002	.015	.003	.049		.000	.012
	N	69	69	69	69	69	69	69
LV Dyssynchrony	Pearson Correlation	.365**	-.290*	.422**	.193	.867**	1	.334**
	Sig. (2-tailed)	.002	.016	.000	.111	.000		.005
	N	69	69	69	69	69	69	69
Septum to Posterior wall motion Delay	Pearson Correlation	.496**	-.242*	.437**	.389**	.302*	.334**	1
	Sig. (2-tailed)	.000	.045	.000	.001	.012	.005	
	N	69	69	69	69	69	69	69

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

TABLE THAT SHOWS A SIGNIFICANT DIFFERENCE IN THE QRS DURATION BETWEEN THE LOW AND NORMAL EJECTION FRACTION GROUPS (P=0.001) WITH NO SIGNIFICANT DIFFERENCE IN THE PULSE RATE (P=0.58)

ejection fraction		n	mean	std. deviation	std. error mean
QRS Values	Low EF	38	148.53	18.557	3.010
	Normal EF	31	135.71	11.725	2.106
Pulse Rate	Low EF	38	84.82	15.123	2.453
	Normal EF	31	82.58	18.768	3.371

T-TEST: SIGNIFICANT DIFFERENCE BETWEEN THE LVIDD IN THE LOW AND NORMAL EF GROUPS (P<0.001)

EJECTION FRACTION		N	MEAN	STD. DEVIATION	STD. ERROR MEAN
LVIDD Value	<=50	38	62.68	9.355	1.518
	>50	31	48.35	5.919	1.063

T-TEST: SIGNIFICANT DIFFERENCE BETWEEN THE LVIDS IN THE LOW AND NORMAL EF groups (p<0.001)

EJECTION FRACTION		N	MEAN	STD. DEVIATION	STD. ERROR MEAN
LVIDS Value	<=50	38	51.50	8.773	1.423
	>50	31	35.52	9.327	1.675

T-TEST: SIGNIFICANT DIFFERENCE BETWEEN THE EDV , ESV IN THE LOW AND NORMAL EF GROUPS (P<0.001)

EJECTION FRACTION		N	MEAN	STD. DEVIATION	STD. ERROR MEAN
EDV Value	<=50	38	188.97	59.892	9.716
	>50	31	108.39	30.177	5.420
ESV Value	<=50	38	126.05	51.607	8.372
	>50	31	47.35	13.502	2.425

MEAN VALUES OF ISOVOLUMIC CONTRACTION TIMES IN ALL SEGMENTS

	N	Minimum	Maximum	Mean		Std.
	Statistic	Statistic	Statistic	Statistic	Std. Error	Deviation
Q to RV Lateral	69	0	160	58.22	3.23	26.811
Q to Basal Septal	69	10	180	73.03	4.20	34.869
Q to Basal Lateral	69	47	220	116.30	5.90	49.044
Q to Basal anterior	69	30	187	89.58	4.64	
Q to Basal inferior	69	0	200	78.62	4.68	38.870

CORRELATIONS BETWEEN VARIOUS ECHO INDICES SHOWING A STRONG CORRELATION BETWEEN INTER AND INTRAVENTRICULAR DYSSYNCHRONY

Correlations

		LVIDD Value	LVIDS Value	EDV Value	ESV Value	EF Value	QRSvalues	RVLV Delay	LV Dyssynchrony
LVIDD Value	Pearson Correlation	1	.872**	.874**	.850**	-.719**	.472**	.355**	.359**
	Sig. (2-tailed)		.000	.000	.000	.000	.000	.003	.002
	N	69	69	69	69	69	69	69	69
LVIDS Value	Pearson Correlation	.872**	1	.792**	.798**	-.732**	.398**	.263*	.269*
	Sig. (2-tailed)	.000		.000	.000	.000	.001	.029	.025
	N	69	69	69	69	69	69	69	69
EDV Value	Pearson Correlation	.874**	.792**	1	.960**	-.712**	.398**	.356**	.407**
	Sig. (2-tailed)	.000	.000		.000	.000	.001	.003	.001
	N	69	69	69	69	69	69	69	69
ESV Value	Pearson Correlation	.850**	.798**	.960**	1	-.819**	.418**	.316**	.369**
	Sig. (2-tailed)	.000	.000	.000		.000	.000	.008	.002
	N	69	69	69	69	69	69	69	69
EF Value	Pearson Correlation	-.719**	-.732**	-.712**	-.819**	1	-.351**	-.293*	-.290*
	Sig. (2-tailed)	.000	.000	.000	.000		.003	.015	.016
	N	69	69	69	69	69	69	69	69
QRSvalues	Pearson Correlation	.472**	.398**	.398**	.418**	-.351**	1	.374**	.365**
	Sig. (2-tailed)	.000	.001	.001	.000	.003		.002	.002
	N	69	69	69	69	69	69	69	69
RVLV Delay	Pearson Correlation	.355**	.263*	.356**	.316**	-.293*	.374**	1	.867**
	Sig. (2-tailed)	.003	.029	.003	.008	.015	.002		.000
	N	69	69	69	69	69	69	69	69
LV Dyssynchrony	Pearson Correlation	.359**	.269*	.407**	.369**	-.290*	.365**	.867**	1
	Sig. (2-tailed)	.002	.025	.001	.002	.016	.002	.000	
	N	69	69	69	69	69	69	69	69

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

MASTER SHEET

SNO	Name	Hno	Age	sex	NYHA	D	CP	P	Fatigue	Abd_dis	Thy_dys	HT
1	Abdul Bareque Ahmed	615067C	50	1	3	1	0	0	1	0	0	1
2	Almas Begum	59346	71	0	1	1	1	0	0	0	0	1
3	Amulya	778468C	60	1	2	1	0	0	1	0	0	0
4	Amulya Ratan Paul	793950C	65	1	3	1	1	0	1	1	0	1
5	Ananda Kumar Biswas	784931C	78	1	1	1	1	1	0	0	1	1
6	Armugam	613046C	65	1	1	0	0	0	0	0	0	1
7	Arunachalam	811874C	62	1	3	1	1	0	1	0	0	0
8	Bharathi Bhowmick	656204C	53	0	1	1	0	0	0	0	1	0
9	Bimma Devi	648574C	63	0	2	1	1	0	1	0	0	0
10	Biswanath Chakraborthy	780305C	61	1	2	1	0	0	1	0	0	1
11	Chandra Babu	604888C	45	1	2	1	0	0	0	0	0	0
12	Deb Kumar Naskar	752592C	50	1	2	0	0	0	1	0	0	1
13	Dhandapani	764770C	62	1	4	1	0	0	1	0	0	1
14	Dolly Mithra	815352C	48	0	2	1	1	0	0	0	0	1
15	Durvasalu	836608C	83	1	3	1	0	0	0	0	0	0
16	Fazley Pauman	827378C	55	1	3	1	1	0	0	0	0	0
17	Ganesh Chandra Munnerje	811536C	75	1	1	0	0	0	1	0	1	1
18	Hanif Ansari	833721C	64	1	3	1	1	0	0	0	0	0
19	Harikrishnan	046099B	53	1	1	1	0	0	0	0	0	1
20	Hasna Hena Begum	559048C	49	0	2	1	1	0	0	0	0	1
21	Jinhuri Banerjee	781503C	80	1	2	1	0	0	0	0	2	1
22	Kanai Lal Giri	795826C	49	1	2	1	0	0	0	1	0	0
23	Lily Pushpam	770818C	62	0	1	0	0	0	0	0	0	1
24	M.Vedham	808691C	66	0	3	1	0	0	1	0	1	1
25	Mahalingam	179525C	52	1	1	0	0	0	0	0	0	1
26	Manglal Majui	283500B	58	1	2	0	1	0	0	0	0	1
27	Manimegalai	368822C	65	0	4	1	0	0	1	0	2	0
28	Mrinal Kanti	840005C	44	1	1	0	1	0	0	0	0	0
29	Mriwal Kanti	834970C	65	1	2	1	0	0	0	0	0	1
30	Mumzedar	805106C	60	1	2	1	0	0	0	0	0	1
31	Munnirisuna	771665C	23	1	2	0	0	1	1	0	2	0
32	Nabendu Shekar	820548C	63	1	1	1	0	0	0	0	0	1
33	Netaj ChandraSarkar	793961C	54	1	2	1	0	0	0	0	0	0
34	Panchalai	826738C	65	0	2	1	1	0	0	0	0	1

SNO	Name	Hno	DM	DL	IHD	Sm	Al	pulse	BP	JVP	S3	S4
1	Abdul Bareque Ahmed	615067C	1	1	1	0	0	80	110/60	1	1	0
2	Almas Begum	59346	0	1	1	0	0	100	170/80	0	1	0
3	Amulya	778468C	1	1	1	1	1	89	140/80	0	0	0
4	Amulya Ratan Paul	793950C	0	1	0	0	0	106	110/80	1	1	0
5	Ananda Kumar Biswas	784931C	1	1	1	0	0	70	130/90	0	1	1
6	Armugam	613046C	0	0	0	0	0	100	136/90	0	1	0
7	Arunachalam	811874C	1	0	1	1	1	85	100/60	0	1	0
8	Bharathi Bhowmick	656204C	1	1	0	0	0	72	100/70	0	0	1
9	Bimma Devi	648574C	1	1	1	0	0	84	102/60	0	0	0
10	Biswanath Chakraborthy	780305C	1	1	1	1	0	80	120/80	0	1	0
11	Chandra Babu	604888C	1	1	0	1	0	94	102/72	1	1	0
12	Deb Kumar Naskar	752592C	1	1	0	1	0	84	120/70	0	0	0
13	Dhandapani	764770C	0	1	0	0	0	80	90/60	1	1	0
14	Dolly Mithra	815352C	1	1	0	0	0	70	150/70	0	1	0
15	Durvasalu	836608C	0	0	0	1	0	97	110/70	0	0	0
16	Fazley Pauman	827378C	0	1	1	1	0	69	120/70	0	0	0
17	Ganesh Chandra Munnerje	811536C	1	1	1	1	0	56	140/80	0	0	1
18	Hanif Ansari	833721C	0	1	1	0	0	75	100/70	0	0	0
19	Harikrishnan	046099B	1	1	0	0	0	60	160/90	0	0	0
20	Hasna Hena Begum	559048C	1	1	0	0	0	80	140/80	0	1	0
21	Jinhuri Banerjee	781503C	1	1	0	1	0	65	110/70	0	0	1
22	Kanai Lal Giri	795826C	1	0	0	0	0	50	110/80	1	0	0
23	Lily Pushpam	770818C	0	0	0	0	0	65	130/80	0	0	1
24	M.Vedham	808691C	1	1	1	0	0	86	120/70	1	1	0

Name	Hno	Age	sex	NYHA	D	CP	P	Fatigue	Abd_dis	Thy_dys	HT
Poraiappan	791244C	60	1	2	1	1	0	1	0	0	0
Pown	780423C	56	0	2	0	0	0	1	0	0	1
Prabir Kumar Biswas	778635C	51	1	2	0	1	0	1	0	0	1
Prabodh Chandra Garai	344077C	46	1	1	1	1	0	0	0	0	1
Pradip Kumar	786171C	48	1	2	1	1	1	1	0	1	0
Purushothaman	291720C	65	1	2	1	1	0	1	0	0	0
Ragavan	470842C	64	1	3	1	0	0	0	0	0	1
Rai	773873C	58	1	1	1	0	0	1	0	0	0
Rajalakshmi	939143B	65	0	4	1	0	0	1	0	0	1
Rama	834511C	31	0	2	1	1	0	0	0	1	1
Ramakani Mishra	819686C	53	1	1	1	0	0	0	0	0	0
Ramanath Maity	596897C	63	1	2	1	0	1	1	0	0	0
Ramasurey Prasad	793747C	71	1	2	1	0	0	1	0	1	0
Ramchandra Phasai	794249C	52	1	3	1	0	1	1	0	0	0
Ranu Mitra	830777C	54	0	1	0	0	0	0	0	1	1
Ratan Ghosh	737499C	40	1	3	1	0	0	0	0	0	1
Ruckmani	016357C	54	0	2	1	0	0	0	0	0	1
Sabanti Saha	083349C	30	0	1	1	0	1	0	0	0	0
Sankarlal Dey	797360C	67	1	3	1	1	0	1	1	0	1
Saroja	815512C	75	0	2	0	1	0	0	0	1	0
Selvaraj	837975C	48	1	2	1	0	0	1	0	0	1
Shika Rani Chaki	313338B	61	0	3	1	0	0	0	0	0	1
Sisir Kumar Chakraborth	784071C	62	1	2	1	1	1	0	0	0	1
Sita Pyakurec	796030C	68	0	2	1	1	1	1	0	0	1
Subramani	824506C	62	1	3	1	0	0	0	0	0	1
Suchitra	394231C	35	0	2	1	0	1	0	0	0	1
Sulaja	829445C	65	0	2	1	1	0	0	0	0	1
Susama	740380C	67	0	2	1	0	1	0	0	1	1
Swapan Kumar	807934C	45	1	2	1	0	0	0	0	0	0
Tek Bahaduk Singh	731552C	69	1	1	1	0	0	0	0	0	1
Thajunnisa	866887B	60	0	3	1	0	1	1	0	0	0
Thomas	636360C	61	1	1	0	0	0	0	0	0	0
Vanitha	828803C	37	0	3	1	0	0	0	0	0	0
Vasantha	180463B	74	0	3	1	0	0	0	0	0	0
Veddaponnammal	749961A	80	0	4	1	1	0	0	0	0	1

Name	Hno	DM	DL	IHD	Sm	Al	pulse	BP	JVP	S3	S4
Poraiappan	791244C	1	0	1	0	0	84	110/70	0	0	0
Pown	780423C	1	1	0	0	0	63	140/90	0	0	1
Prabir Kumar Biswas	778635C	0	0	0	0	1	70	210/120	0	0	1
Prabodh Chandra Garai	344077C	0	1	0	0	0	78	130/80	0	0	0
Pradip Kumar	786171C	1	0	1	1	0	62	140/90	0	0	0
Purushothaman	291720C	0	1	0	0	0	105	110/70	0	0	1
Ragavan	470842C	0	0	0	0	0	100	140/80	1	0	1
Rai	773873C	1	1	0	1	0	79	160/80	0	0	0
Rajalakshmi	939143B	0	1	0	0	0	126	80/60	1	1	0
Rama	834511C	1	1	1	0	0	80	130/80	0	0	0
Ramakani Mishra	819686C	1	1	1	1	0	82	110/70	0	0	1
Ramanath Maity	596897C	1	1	1	1	0	110	140/90	0	0	0
Ramasurey Prasad	793747C	1	1	0	1	0	89	150/100	0	0	0

Ramchandra Phasai	794249C	1	1	0	0	0	100	100/70	0	1	0
Ranu Mitra	830777C	1	1	0	0	0	113	190/90	0	0	0
Ratan Ghosh	737499C	1	0	0	0	0	88	140/80	1	1	0
Ruckmani	016357C	1	1	1	0	0	76	150/100	0	1	0
Sabanti Saha	083349C	0	0	0	0	0	84	120/80	0	0	0
Sankarlal Dey	797360C	1	1	0	1	0	93	110/60	0	0	0
Saroja	815512C	0	1	0	0	0	105	110/80	0	0	1
Selvaraj	837975C	1	1	1	0	0	102	140/80	0	0	0
Shika Rani Chaki	313338B	1	1	0	0	0	75	160/90	0	0	1
Sisir Kumar Chakraborth	784071C	1	1	0	0	0	88	140/80	0	0	1
Sita Pyakurec	796030C	0	1	1	0	0	78	130/90	0	0	0
Subramani	824506C	1	1	1	1	0	76	190/100	0	0	1
Suchitra	394231C	0	0	0	0	0	82	150/80	0	0	0
Sulaja	829445C	1	1	0	0	0	81	150/70	0	0	0
Susama	740380C	0	1	0	0	0	140	150/102	0	1	0
Swapan Kumar	807934C	0	1	0	0	0	66	110/85	1	0	1
Tek Bahaduk Singh	731552C	1	1	0	0	0	81	180/98	0	0	0
Thajunnisa	866887B	1	0	0	0	0	81	130/80	1	1	0
Thomas	636360C	1	1	0	1	0	100	120/80	0	0	1
Vanitha	828803C	0	0	0	0	0	78	100/70	1	1	0
Vasantha	180463B	1	1	0	0	0	64	110/68	0	0	0
Veddaponnammal	749961A	1	0	1	0	0	96	100/70	1	1	0

Name	**Hno**	**QRS**	**LVIDD**	**LVIDS**	**EDV**	**ESV**	**EF**	**MR**	**TR**	**AR**	**APED**
Poraiappan	791244C	140	46	33	97	39	58	0	0	0	170
Pown	780423C	122	47	34	98	41	57	1	0	1	130
Prabir Kumar Biswas	778635C	144	48	33	99	43	56	0	0	0	133
Prabodh Chandra Garai	344077C	136	55	41	147	63	53	0	0	0	153
Pradip Kumar	786171C	133	61	55	185	121	35	2	1	0	130
Purushothaman	291720C	149	48	35	106	51	52	3	3	1	170
Ragavan	470842C	140	47	39	104	66	37	2	1	0	140
Rai	773873C	131	47	33	127	60	53	0	0	0	173
Rajalakshmi	939143B	149	82	68	260	174	33	3	2	0	160
Rama	834511C	124	43	29	82	34	57	0	0	0	153
Ramakani Mishra	819686C	156	70	57	179	103	42	3	3	1	155
Ramanath Maity	596897C	158	54	44	144	74	36	0	0	0	160
Ramasurey Prasad	793747C	136	49	34	128	51	59	0	0	0	153
Ramchandra Phasai	794249C	150	70	60	255	180	30	3	0	0	190
Ranu Mitra	830777C	151	58	41	165	74	55	1	0	0	120
Ratan Ghosh	737499C	150	53	43	123	81	34	0	2	0	160
Ruckmani	016357C	125	40	20	58	26	54	0	0	0	133
Sabanti Saha	083349C	154	59	46	177	97	45	2	1	0	170
Sankarlal Dey	797360C	124	46	33	99	44	56	0	0	0	150
Saroja	815512C	139	46	33	99	43	56	0	0	0	153
Selvaraj	837975C	128	58	42	105	80	24	0	0	0	93
Shika Rani Chaki	313338B	134	59	46	150	97	35	2	1	0	147
Sisir Kumar Chakraborth	784071C	122	66	55	221	151	32	3	1	0	120
Sita Pyakurec	796030C	141	55	45	149	93	38	3	0	0	200
Subramani	824506C	164	67	53	159	60	62	0	0	0	50
Suchitra	394231C	131	46	32	96	40	58	1	0	0	160
Sulaja	829445C	125	41	29	76	31	59	0	0	0	107

Susama	740380C	133	46	33	97	44	55	2	0	0	153
Swapan Kumar	807934C	162	68	57	221	147	33	0	0	0	190
Tek Bahaduk Singh	731552C	157	57	47	198	125	37	1	0	1	170
Thajunnisa	866887B	160	74	62	219	146	33	3	2	0	207
Thomas	636360C	158	51	33	63	28	58	0	0	0	153
Vanitha	828803C	136	56	48	155	106	32	2	2	0	167
Vasantha	180463B	150	70	56	259	154	40	3	0	0	180
Veddaponnammal	749961A	152	41	34	143	106	40	3	0	3	160

Name	**Hno**	**PPED**	**IVMD**	**SPMD**	**Qrl**	**Qbs**	**Qbl**	**Qba**	**Qbi**	**RVLV**	**LV DYS**
Poraiappan	791244C	113	57	280	30	40	100	30	110	70	70
Pown	780423C	90	40	100	60	60	60	60	60	0	0
Prabir Kumar Biswas	778635C	113	20	153	93	127	213	187	127	120	86
Prabodh Chandra Garai	344077C	120	33	120	67	67	170	67	100	103	103
Pradip Kumar	786171C	115	15	140	90	140	140	140	100	50	40
Purushothaman	291720C	107	63	200	40	40	87	33	40	47	54
Ragavan	470842C	100	40	90	100	130	93	93	107	30	37
Rai	773873C	113	60	107	160	180	167	90	160	20	90
Rajalakshmi	939143B	110	50	240	60	120	220	130	100	160	120
Rama	834511C	100	53	120	60	60	67	60	67	7	7
Ramakani Mishra	819686C	100	55	100	50	70	130	105	55	80	75
Ramanath Maity	596897C	100	60	300	40	50	130	120	50	90	80
Ramasurey Prasad	793747C	113	40	173	50	50	130	60	50	80	80
Ramchandra Phasai	794249C	120	70	100	100	180	200	60	200	100	140
Ranu Mitra	830777C	100	20	120	55	55	160	125	55	80	75
Ratan Ghosh	737499C	110	50	60	50	50	70	100	70	50	50
Ruckmani	016357C	93	40	113	40	50	65	70	50	30	20
Sabanti Saha	083349C	120	150	150	60	120	150	170	150	110	50
Sankarlal Dey	797360C	120	30	100	60	60	130	130	65	70	70
Saroja	815512C	107	46	120	40	40	60	60	40	20	20
Selvaraj	837975C	80	13	60	53	67	113	80	53	60	60
Shika Rani Chaki	313338B	97	50	133	40	50	150	80	147	110	100
Sisir Kumar Chakraborth	784071C	90	30	70	35	130	130	130	60	95	70
Sita Pyakurec	796030C	150	50	200	67	120	200	180	113	133	87
Subramani	824506C	20	30	100	0	10	50	30	0	50	50
Suchitra	394231C	100	60	200	50	50	80	70	60	30	30
Sulaja	829445C	80	27	60	60	73	87	90	60	30	30
Susama	740380C	100	53	200	60	60	88	90	70	30	30
Swapan Kumar	807934C	110	80	180	80	80	210	100	190	130	130
Tek Bahaduk Singh	731552C	100	70	90	30	50	180	140	50	150	130
Thajunnisa	866887B	153	54	200	67	60	213	93	133	146	153
Thomas	636360C	87	66	80	70	130	160	140	90	90	70
Vanitha	828803C	120	47	90	67	60	80	80	60	13	20
Vasantha	180463B	93	87	100	50	73	120	73	127	70	54
Veddaponnammal	749961A	130	30	93	50	60	160	40	60	110	100

ABBREVIATIONS FOR THE MASTER SHEET WITH CODING

SNO : Serial number

Hno : Hospital number

Sex : male = 1, female =2

NYHA : New York Heart Association Class from 1 to 4

D : NYHA class for dyspnoea from 1 to 4

CP : NYHA class for chest pain from 1 to 4

P : NYHA class for palpitations from 1 to 4

Fatigue : NYHA class for fatigue from 1 to 4

Abd_dis : Abdominal distension [Present +1, Absent = 0]

Thy_dys : Thyroid dysfunction [euthyroid==0,hypothyroid=1,hyperthyroid=2]

HT : Hypertension [Present +1, Absent = 0]

DM : Diabetes Mellitus [Present +1, Absent = 0]

DL : Dyslipidemia [Present +1, Absent = 0]

IHD : Ischemic heart disease [Present +1, Absent = 0]

Sm : Smoking [Present +1, Absent = 0]

Al : Alcohol consumption [Present +1, Absent = 0]

BP : Blood pressure [Present +1, Absent = 0]

JVP : Jugular venous pressure [Elevated = 1, normal = 0]

S3 : Presence of third heart sound [Present +1, Absent = 0]

S4 : Presence of fourth heart sound [Present +1, Absent = 0]

QRS : Duration of qrs in msec

LVIDD : Left ventricular internal diameter in diastole

LVIDS : Left ventricular internal diameter in systole

EDV : End diastolic volume

ESV : End systolic volume

EF : Ejection fraction

MR : Grade of MR [0=absent,1=mild,2=moderate,3=severe]

TR : Grade of TR [0=absent,1=mild,2=moderate,3=severe]

AR : Grade of AR [0=absent,1=mild,2=moderate,3=severe]

APED : Aortic preejection delay in msec

PPED : Pulmonary preejection delay in msec

IVMD : Intraventricular delay in msec

SPMD : Septum to posterior wall motion delay in msec

Qrl : Isovolumic contraction time from Q to RV basal lateral wall in msec

Qbs : Isovolumic contraction time from Q to basal septum in msec

Qbl : Isovolumic contraction time from Q to basal lateral wall in msec

Qba : Isovolumic contraction time from Q to basal anterior wall in msec

Qbi : Isovolumic contraction time from Q to basal inferior wall in msec

RVLV : Interventricular dyssynchrony in msec

LVDYS : Intraventricular dyssynchrony in msec