SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

TRIVANDRUM, KERALA

PROJECT REPORT

A STUDY OF TRANSMURAL DISPERSION OF REPOLARISATION DURING BIVENTRICULAR, EPICARDIAL AND ENDOCARDIAL PACING IN PATIENTS WITH HEART FAILURE UNDERGOING CRT- A PROSPECTIVE LONGITUDINAL STUDY

Submitted during the course of

DM Cardiology

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DECLARATION

*I, **Dr Bharatraj N. Banavalikar,** hereby declare that the project in this book was undertaken by me under the supervision of the faculty, Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.*

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Thiruvananthapuram
Date 05-10-2015

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TITLE

A study of transmural dispersion of repolarisation in patients with heart failure during biventricular, epicardial and endocardial pacing- A prospective longitudinal study

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INTRODUCTION

Heart failure is a condition that has attained epidemic proportions in recent years and has become a major public health burden. Improving prognosis and survival in CHF is of utmost importance which has an estimated global burden exceeding 23 million. The prevalence of heart failure is increasing owing to aging of the population, improvements in the management of acute coronary syndromes and increased survival of patients with heart failure. Cardiac resynchronisation therapy (CRT) has been a major advancement in the therapy of patients with heart failure (HF). Intracardiac conduction disturbances especially left bundle branch block (LBBB) are commonly encountered in advanced heart disease and lead to intraventricular as well as interventricular dyssynchrony. Intracardiac conduction disturbances are observed in around one third of patients with heart failure. Most of the intracardiac disturbances is accounted by LBBB, which is seen in 25% patients with HF. CRT, by virtue of biventricular pacing ameliorates the adverse impact on hemodynamics and has a favourable long term outcome. Several randomised controlled trials have demonstrated the salutary long term effects of CRT with respect to ventricular hemodynamics (reverse mechanical LV remodelling), quality of life, mortality as well as HF hospitalisation rates.

Nevertheless, the influence of CRT on ventricular arrhythmias and sudden cardiac death is not clear and the evidence in the literature is conflicting. Initial

reports suggested CRT might facilitate ventricular arrhythmias by augmenting the dispersion of repolarisation. During CRT, activation wavefront in the LV proceeds from epicardium to endocardium whereas activation of RV occurs from endocardium to epicardium. This nonphysiological activation in the LV augments the transmural dispersion of repolarisation (TDR) which is intrinsic to the ventricular myocardium. Several studies but not all, have demonstrated that TDR is augmented with epicardial as well as biventricular pacing when compared with endocardial pacing at baseline. Howevere, TDR is a dynamic entity and demonstrates favourable modulation with response to CRT. Recent studies have demonstrated a reduced incidence of sudden cardiac death and ventricular arrhythmias in CRT responders. This implies that reverse remodelling of the left ventricle associated with CRT may have beneficial effects with respect to arrhythmic substrate and dispersion of repolarisation. Several studies have shown that the extent of reverse electrical remodelling correlates directly with reverse mechanical remodelling. To the best of our knowledge, the effects of reverse LV remodelling on transmural dispersion of repolariation has not been prospectively evaluated until now.

AIMS AND OBJECTIVES

- To compare Tpeak-Tend interval (Tp-e), a marker of transmural dispersion of repolarisation (TDR), during LV epicardial & biventricular pacing with RV endocardial pacing at baseline & at 1year follow-up
- To assess time dependent changes in transmural dispersion of repolarisation with cardiac resynchronization therapy and correlate with reverse mechanical remodeling
- To correlate Tp-e interval at baseline during biventricular pacing with VT/VF episodes in the 1-year follow-up period.

REVIEW OF LITERATURE

Heart failure is a condition that has attained epidemic proportions in recent years and has become a major public health burden. Improving prognosis and survival in CHF is of utmost importance which has an estimated global burden exceeding 23 million.[1] The prevalence of heart failure is increasing owing to aging of the population, improvements in the treatment of acute coronary syndromes and increased survival of patients with heart failure.[2] Coronary artery disease is the most common cause of systolic heart failure. Conduction disturbances including left bundle branch block (LBBB) is common in advanced heart disease and associated with increased mortality.[3]

Intracardiac conduction disturbances are observed in around one third of patients with heart failure. Most of the intracardiac disturbances is accounted by LBBB, which is seen in 25% patients with HF. LBBB causes classic type of dyssynchrony that leads to abnormal electrical activation of the left ventricle. In patients with LBBB, interventricular septum is activated early where as the posterior and lateral LV walls are activated late.[4]

Typically early septal contraction causes posterior-lateral stretching or thinning, followed by late posterior-lateral contraction causing septal stretching or thinning. Dyssynchrony results in inefficient LV systolic performance, increases

in end-systolic volume and wall stress, and delayed relaxation of the left ventricle.

LV mechanical remodelling is a dynamic process that may be triggered by pressure or volume overload, loss of cardiomyocytes owing to ischemia or other acquired causes or may be genetically programmed. LV remodelling causes progressive increase in chamber volumes, distortion of LV chamber shape and geometry, disruption of mitral valve apparatus leading to mitral regurgitation and progressive deterioration of left ventricular contractile function that eventually culminates in heart failure.[5]

Cardiac resynchronisation therapy, by virtue of biventricular pacing induces reverse remodelling of the left ventricle[6] and has demonstrated reductions in mortality and heart failure hospitalisations in advanced as well as mild to moderate heart failure.[7]

CARE-HF was a randomised, clinical trial that included 819 patients with NYHA class III/ IV heart failure, LVEF less than 35% or less and dyssynchrony, represented as QRS duration >150ms or >120ms in conjunction with echo evidence of dyssynchrony.[8] The composite of death from any cause and unplanned hospitalisation for a major cardiac event was the primary endpoint. Over an average follow-up of 29.4 months, the primary endpoint was significantly reduced by 37% in the treatment arm [CRT] compared with optimal medical therapy alone. Death occurred in 20% patients in the CRT arm

compared with 30% in the control arm, which was a 36% significant reduction in all cause mortality in the CRT group [(HR, 0.64; 95% CI, 0.48 to 0.85; $P <$ 0.002].

The COMPANION trial was multicenter randomised trial that included 1520 patients with NYHA class III/ IV heart failure and QRS duration> 120ms allocated into three treatment arms in 1:2:2 ratio.[9] Group I patients received optimal medical therapy only (308 patients), group II patients received CRT-P (617 patients) whereas group III patients were randomised to receive CRT-D (595 patients). The primary endpoint of the trial, a composite of all-cause mortality and all-cause hospitalisation was significantly reduced by both CRT-P (by 35%) and CRT-D (by 40%) compared to optimal medical therapy (both P<0.001). All-cause mortality was reduced by 24% in the CRT-P arm (p=0.06) and by 36% in the CRT-D arm (p<0.003) when compared with control group.

Several recent trials including REVERSE, MADIT-CRT and RAFT, have demonstrated beneficial effects of CRT even in mildly symptomatic patients (NYHA class I or II) with heart failure.[7]

The MADIT-CRT trial was a multi-center randomised unblinded clinical trial that comprised of 1820 patients with NYHA class I (ischemic) or II (any cause) heart failure, LVEF <30% and QRS duration >130ms, randomised to CRT-D and ICD-only respectively.[10] The average follow-up in this trial was 28 months. The primary endpoint of all-cause mortality and any heart failure event,

occurred in 17.2% of the CRT-D arm compared with 25.2% in the ICD arm, a significant relative risk reduction of 34% (HR, 0.66; 95% CI, 0.52 to 0.84; p = 0.001).

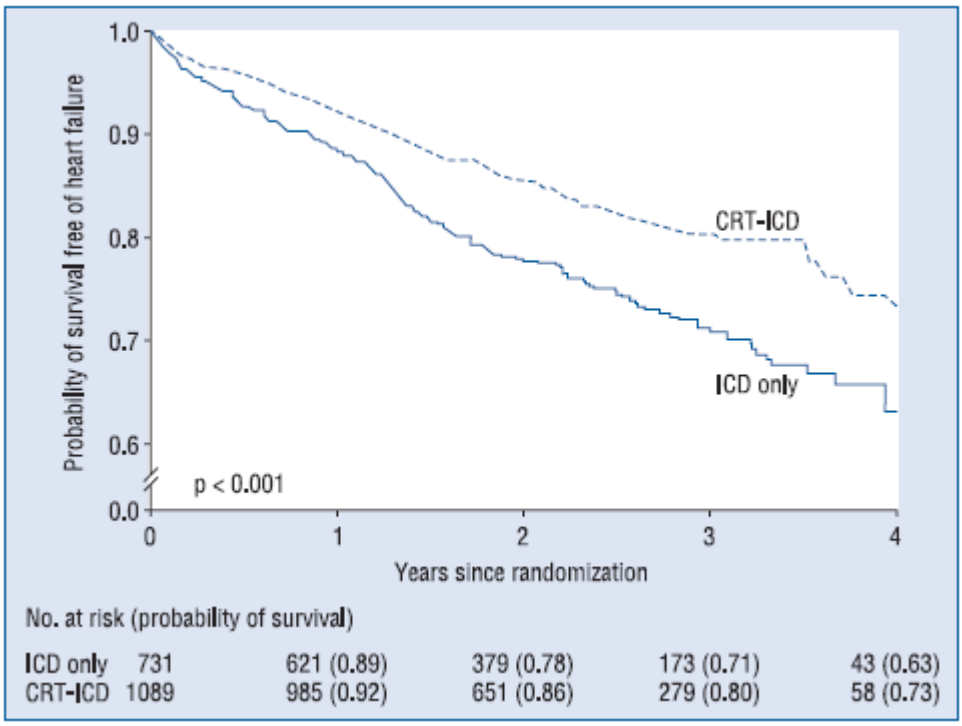

Fig 1. Kaplan-Meier estimates of survival free of HF in the CRT-D arm versus ICD arm in the MADIT-CRT trial.[10]

The electrocardiographic T wave is a manifestation of ventricular repolarisation and its electrophysiological basis has been deciphered in magnificent detail.[11-16] Several elegant studies in LV wedge preparations by Antzelevitch and co-workers have demonstrated the presence in the ventricular free wall of 3

electrophysiologically distinct cell types: epicardial cell, midmyocardial 'M' cell and the endocardial cell. Epicardial cells and M cells are characterised by a prominent phase 1 notch owing to high density of transient outward K+ channels. M cells greatly prolong their action potential duration in response to slowing of heart rate or in response to class III anti-arrhythmic drugs.[17] Differences in the temporal profile of repolarisation of these 3 myocardial cell types causes the inscription of the electrocardiographic T wave. The epicardial cell has the shortest action potential duration whereas the midmyocardial M cell has the longest action potential duration. T wave results from the currents flowing down voltage gradients on either side of the M region. The onset of the T wave is marked by the divergence of phase 2 plateau of epicardial action potentials from that of M cells. As the epicardial repolarisation progresses further, the voltage gradient increases between these two cellular layers and ultimately reaches maximum when the epicardial repolarisation is complete. This coincides with the peak of the T wave. At the opposite end of the ventricular wall, the endocardial repolarisation diverges from that of the M cell, thereby generating a voltage gradient in the reverse direction and contributing the descending limb of the T wave. The electrical gradient between the M cell and the endocardial cell becomes maximum when the endocardial repolarisation is complete. Completion of M cell repolarisation abolishes all voltage gradient across the myocardium and thus determines the end of the T wave.

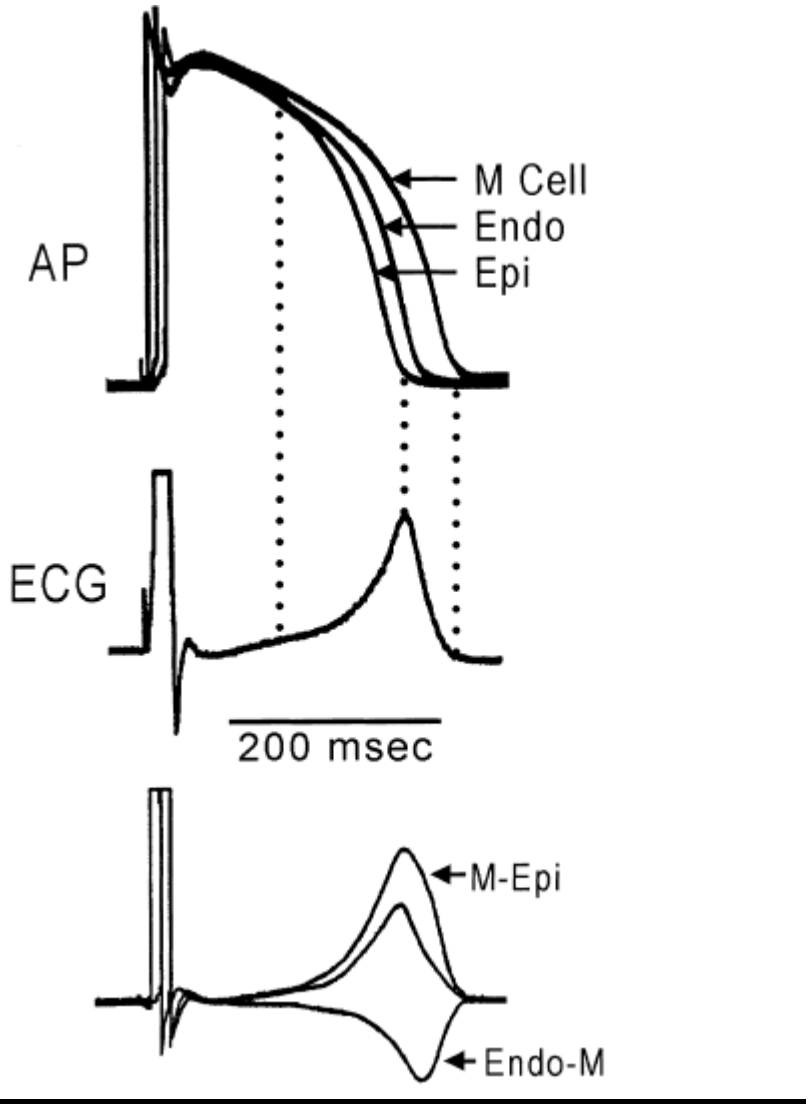

Fig 2. Action potentials in the 3 myocardial cell types and the inscription of the T wave.

As already described, the epicardial cell type is the earliest to repolarise and M cell the latest. Culmination of repolarisation in the epicardium corresponds to

the peak of the T wave whereas completion of M cell repolarisation marks the end of T wave. This implies that the interval between peak of T wave and the end of T wave is a crucial measure of transmural dispersion of repolarisation (TDR).

Transmural dispersion of repolarisation as a prognostic marker has been validated in various clinical scenarios including congenital and acquired long QT syndromes, Brugada syndrome, cardiomyopathies and acute myocardial infarction.[18]

Lubinski et al. studied 7congenital LQTS patients with Holter and reported that automatically measured mean 24hr Tp-e interval was significantly prolonged in LQTS patients than controls. Moreover, dispersion of repolarisation in LQTS was significantly prolonged during night sleep hours when compared with day hours.[19]

Castro Hevia et al. evaluated 29 patients diagnosed with Brugada syndrome and followed them for 42.65+/-24.42 months.[20] They also included 29 age and gender matched controls. They found that those with recurrences of ventricular arrhythmias on follow up had significantly higher Tp-e interval and Tp-e dispersion when compared with patients without recurrences (104.4 and 35.6 ms versus 87.4 and 23.2 ms; p=0.006 and p =0.03, respectively) or controls (90.7 and 17.9 ms; p=0.02 and p =0.001, respectively).

Yamaguchi et al. evaluated 27 patients with acquired long QT syndrome and reported that symptomatic acquired LQTS patients with torsades de pointes had significantly greater transmural dispersion of repolarisation than asymptomatic acquired LQTS patients.[21]

In a recent study,[22] Rosenthal et al. prospectively followed up 305 patients with systolic cardiomyopathy without prior ventricular arrhythmia who had ICD implanted for primary prophylaxis. They identified that baseline Tp-e interval was predictive of VT/VF risk as well as mortality during a mean follow-up of 31+/-23 months.

Although CRT has salutary effects on cardiac pump function, its role in causing ventricular arrhythmias and sudden cardiac death during long term follow up is less clear and the data in medical literature is conflicting. Several initial small studies reported increased incidence of ventricular arrhythmias after initiation of biventricular pacing.[23-26]

Medina-Ravell et al. were one of the first investigators to provide an experimental basis for the potential pro-arrhythmic effects of CRT.[27] They evaluated pacing site dependent variations in dispersion of repolarisation in 29 patients with CHF undergoing CRT implantation and reported that epicardial pacing significantly prolonged TDR compared with endocardial pacing. They

noted that QT and JT intervals were more prolonged during epicardial and biventricular pacing versus endocardial pacing. Furthermore, they also studied isolated arterially perfused rabbit LV wedge preparations and found that epicardial pacing was associated with increased TDR and QT interval but without a corresponding increase in transmembrane action potential duration. During dofetilide infusion, epicardial pacing facilitated transmural propagation of early afterdepolarisations and induction of torsades de pointes.

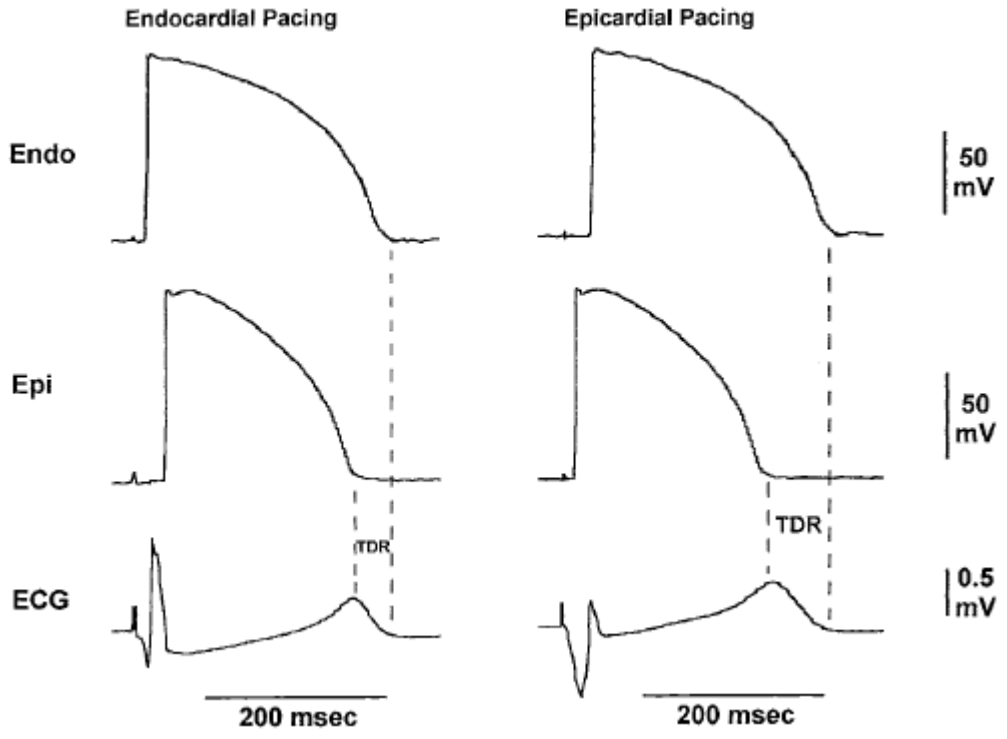

Fig 3. Pacing site dependent changes in dispersion of ventricular repolarisation[27]

Bai et al. also evaluated heterogeneity of repolarisation during pacing from different sites and reported similar findings. Compared to RV endocardial pacing, both LV epicardial pacing and biventricular pacing were associated with a prolongation of TDR, JT interval and QT interval in patients with CHF as well as in subjects without structural heart disease.[28]

In contrast, the study by Santangelo et al.[29] revealed that biventricular pacing was associated with significantly shorter TDR and QT interval compared to sinus rhythm whereas both endocardial and epicardial pacing caused prolongation of TDR and QT interval. Likewise, Huysduynen et al.[30] reported shorter Tp-e interval during biventricular pacing and epicardial pacing than endocardial pacing. They used automated software for making their measurements.

Several analyses from large clinical trials have reported that CRT induced LV reverse remodelling is associated with reduced risk of ventricular arrhythmias on long term follow up.[31-33]

Higgins et al. analysed 32 patients in a cross-over study enrolled in the Ventak CHF trial and concluded that biventricular pacing is associated with a decreased incidence of ICD therapy.[31]

Arya et al. retrospectively analysed 65 patients with ischemic or dilated cardiomyopathy of whom 31 had CRT-D whereas 34 had ICD only. During

follow-up of 11+/-8 months, 35% in the CRT-D arm received one or more appropriate ICD therapy versus 62% in the ICD-only arm. [32]

Barshashet et al. evaluated 1372 patients with mild-moderate heart failure enrolled in the MADIT-CRT trial and classified CRT-D patients into high CRT responders and low responders depending on ΔLVESV at 1yr echocardiogram (High responder: ΔLVESV >25% and low responder: ΔLVESV <25%).[33] There were 529 high responders and 220 low responders in the CRT-D arm whereas the ICD-only arm (control arm) comprised of 623 patients. During a follow-up of 2 years, the cumulative probability of ventricular arrhythmias was lowest for high responders (12%), intermediate for ICD-only patients (21%) and highest for low responders (28%). On multivariate analysis, high responders exhibited a significant 55% reduction in the risk of ventricular arrhythmias compared with ICD-only patients ($p < 0.001$) whereas there was no significant difference between ICD-only patients and low responders ($p = 0.21$). There was a trend towards higher risk of VT/VF or death among low responders compared with ICD (HR 1.34; $p = 0.08$). The investigators observed that CRT might have two opposing effects with respect to ventricular arrhythmias: an anti-arrhythmic effect in high responders owing to reverse remodelling but a predominantly proarrhythmic effect in low responders.

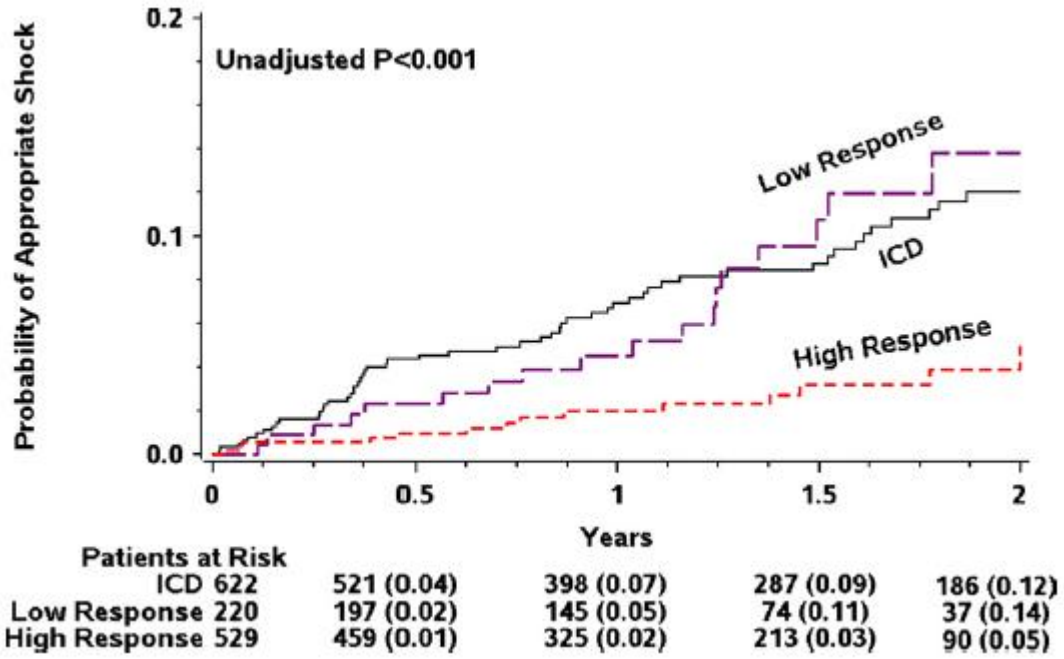

Fig 4. Kaplan-Meier probability of appropriate ICD shocks according to echocardiographic response in the MADIT-CRT trial.[33]

Several retrospective studies have shown that CRT is associated with negative electrical remodelling as assessed by QRS duration and/or TDR on long term follow-up. [34-37] The degree of reverse electrical remodelling is directly related to the extent of mechanical reverse remodelling. Kamireddy et al. analysed paced QRS duration of CRT patients at baseline and long term follow-up. They reported that paced QRS duration was significantly reduced in responders on follow-up and the magnitude of reduction was directly related to reverse remodelling (paced QRS change on F/U 11 +/-31 ms in non-responders vs -11 +/-33 ms in responders; $P < 0.001$).[34]

Lellouche et al. retrospectively analysed 45 patients with CRT-D and observed that at 1yr follow-up, CRT responders had significantly lower Tp-e interval compared with non-responders ((107+/-26 vs. 92+/-22 ms, P <0.0001). Patients with mechanical reverse remodelling had lower rate of ICD therapy (p=0.0025) on follow-up of 19 months.[35]

M.Itoh et al. retrospectively evaluated 84 patients with CRT-D and noted that CRT responders had a greater reduction of Tp–e interval at 6 and 12 months of follow-up but not at 1 month. CRT responders also had a lower rate of ventricular arhhythmias versus non-responders (log-rank test, P= 0.004).[36]

In view of these conflicting results of CRT with respect to long term ventricular arrhythmias, the present study is undertaken with the intention to delineate TDR at baseline and 1 year follow-up during pacing from different sites; and to correlate LV reverse remodelling with TDR and also VT/VF events on follow-up.

MATERIALS AND METHODS

Type of study: The present study is a prospective observational study

Study duration: September 2013 to June 2015

Study location: Department of Cardiology, SCTIMST

Inclusion criteria: All patients with heart failure undergoing CRT implantation at SCTIMST during the study period

Exclusion criteria:

a. Patients with documented myocardial infarction [MI] or revascularisation [PCI/ CABG] in the 3 months preceding CRT implantation
b. Patients in whom EKG during endocardial, epicardial and biventricular pacing was not available at baseline or if the EKG was technically inadequate.

Study subjects: A total 35 patients with CHF undergoing CRT implantation at SCTIMST were recruited for the purpose of the study. All patients had baseline EKG recordings obtained during endocardial, epicardial and biventricular pacing. Most of the patients were on standard HF medications [ACE inhibitors, Beta blockers, Aldosterone antagonists and diuretics]. Fifty-one percent of patients were on low dose Amiodarone at baseline.

Study protocol: All patients underwent detailed history and physical examination as per predesigned proforma. Routine blood investigations including complete hemogram, RFT, LFT and TFT were performed in all patients prior to CRT implantation. Six-minute walk test and NT pro-BNP measurements were performed prior to CRT implantation and also at 1 year follow-up. Each patient had a standard 12-lead EKG, recorded at a paper speed of 50 mm/s, performed at baseline in the peri-implantation period and subsequently again at the end of 1 year follow-up period (i.e 12 months after the procedure). Transthoracic echocardiogram was performed prior to CRT implantation to document LV ejection fraction (LVEF), end diastolic and end systolic volumes (EDV & ESV respectively), LA dimension and severity of mitral regurgitation. The same parameters were repeated at the end of one year. Chamber volumes(LVEDV and LVESV) and LV ejection fraction were calculated via the modified Simpson's rule as per the recommendations of American Society of Echocardiography (ASE).[38] Echocardiogram was performed by an experienced operator blinded to electrocardiographic data. Patients were classified as CRT responders if they demonstrated a decrease in ESV >15% or increase in LVEF >5% on 1 year follow-up. Responders were further classified as high responders (ΔLVESV >25%) and low responders (ΔLVESV <25%) Informed consent was obtained from all patients and the study protocol was approved by the institutional ethics committee.

Data acquisition and EKG measurements:

Standard twelve-lead electrocardiograms were recorded in all patients in the peri-implantation period (within five days of CRT implantation) and then again at one year follow-up. EKGs were recorded separately during RV endocardial, LV epicardial and biventricular pacing at a fixed rate of 80/min. Each stimulation was continued for atleast 3 minutes to permit stabilisation of action potential duration. All EKG recordings were made at a speed of 50 mm/s. QRS duration, QT interval, and Tp-e interval on the EKG were manually measured at magnification using digital calipers with a sensitivity of ~1ms. The analysis was performed by a single investigator blinded to clinical data. All measurements were made in the precordial leads V1-V6 and the maximum value was reported, which has been validated previously.[20]

The QRS interval was measured from the onset of the Q wave or, in the absence of the Q wave, from the onset of R wave to the end of S, that is to its return to the isoelectric line.

The QT interval was measured from the initial deflection of the QRS complex to the end of the T wave, which was determined by the point at which a tangent drawn to the steepest portion of the terminal part of the T wave crossed the isoelectric line.

Tp-e interval was measured as the interval from the maximum T wave amplitude to the end of the T wave. The measurements were made in the precordial leads V1-V6 only and the largest value was selected. T waves <0.15mV were excluded from analysis. Measurements were corrected for heart rate using Bazette's formula.

Follow-up: All patients were followed up in the device-clinic at SCTIMST at 1, 3, 6 and 12 months respectively. Depending on the clinical status, more frequent follow-up visits were advised if necessary. Device interrogation was performed by an experienced electrophysiologist who was blinded to clinical and electrocardiographic data. At the end of one year, transthoracic echocardiogram was performed to assess CRT response. Six-minute walk test and NT pro-BNP measurements were performed in all patients. Twelve-lead electrocardiograms were recorded during RV endocardial, LV epicardial and biventricular pacing and the same parameters were measured.

STATISTICAL ANALYSIS:

All analyses were performed using the SPSS software version 21.0. Continuous variables were expressed as mean+/- standard deviation. Categorical data were expressed as numbers or percentages. Continuous variables were compared between groups using students *t*- test. Categorical variables were compared using chi-square test or Fisher's exact test, as appropriate. Pearson correlation coefficients were calculated to determine the relationship between electrical and

mechanical remodeling. Kaplan-Meier curves were plotted to determine the cumulative probability of first VT/VF events in the high responder and the low responder groups and differences between groups were compared by a log-rank test. Univariate analysis was performed to detect predictors of VT/VF. All tests were two-tailed, and a P value <0.05 was considered statistically significant.

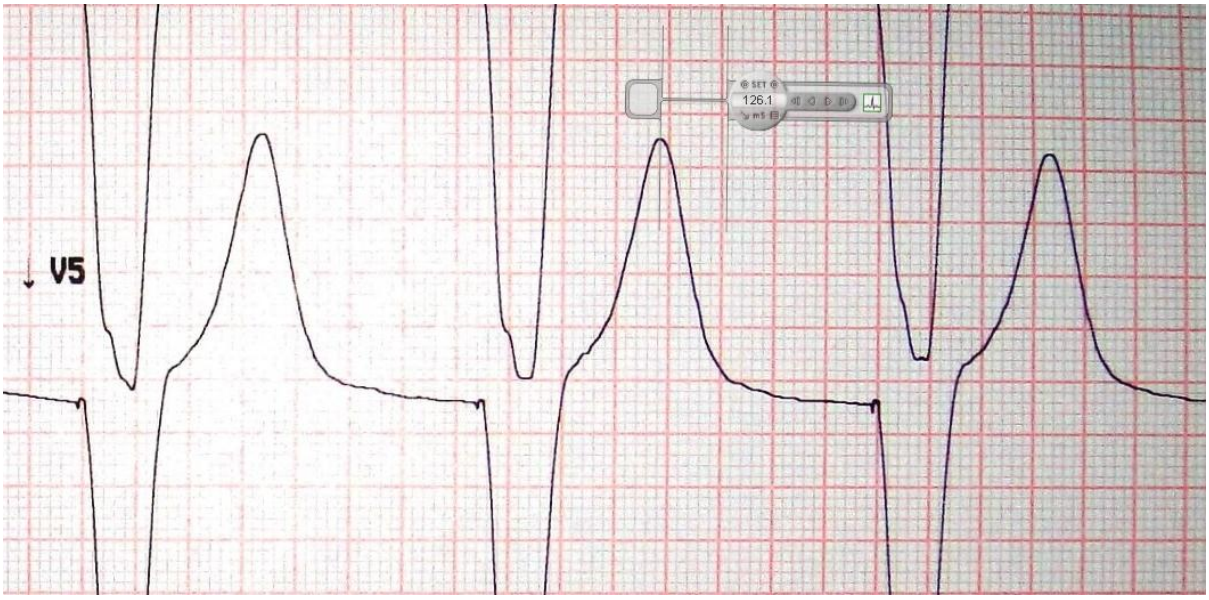

Fig 5. demonstrating measurement of Tp-e interval with digital calipers.

RESULTS

During the study period, 35 consecutive patients with CHF that underwent CRT implantation were recruited in the study. Nine patients were excluded owing to lack of adequate baseline electrographic data and two patients were excluded due to recent PCI.

Baseline characteristics: Mean age of the study population was 56.8 +/-11.09 years. Twenty five patients were males (71.43%) and the rest were females. Mean BMI was 23.62 +/-4.02 kg/m^2. Ischemic cardiomyopathy was the underlying diagnosis in 14 patients (40%) whereas non-ischemic idiopathic dilated cardiomyopathy was observed in 17 patients (48.57%). Anthracycline-induced cardiomyopathy, burnt-out hypertrophic cardiomyopathy, idiopathic restrictive cardiomyopathy and cardiac sarcoidosis accounted for one patient each (figure 6). Twenty two patients (62.85%) had h/o acute pulmonary edema in the past. NYHA class III or IV symptoms were present in 23 patients (65.7%) whereas the remaining 12 patients (34.3%) had NYHA class II dyspnea. Diabetes mellitus was present in 12 patients (34.29%), HTN in 9 patients (25.71%) and hypothyroidism in 4 patients (11.43%).

CRT implantation: A total of 35 patients who underwent successful CRT implantation were recruited as part of the study. Right atrial and right ventricular leads were positioned endocardially whereas left ventricular lead

was positioned in a posterolateral tributary of the coronary sinus. Major complications were quite rare. One patient developed pneumothorax which required chest tube insertion. Another patient had perforation of RV lead into the pericardium which required open surgical repair. No peri-procedural deaths were observed during the study period. CRT-D was implanted in 16 patients [45.72%] whereas the rest underwent CRT-P implantation.

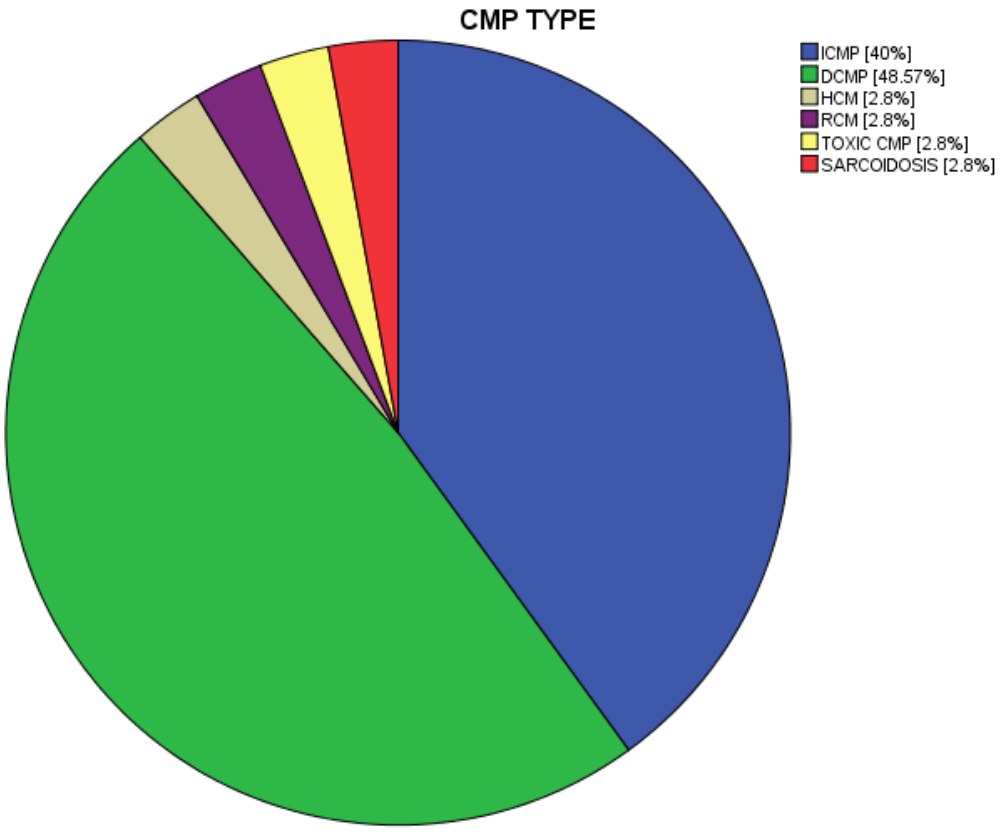

Figure 6. Frequencies of underlying cardiomyopathies

Medications: Most patients were on guideline directed medical therapy for heart failure at the time of CRT implantation. Beta blockers were prescribed in 33 patients [94.29%] whereas aldosterone antagonists were used in 31 patients [88.57%]. ACE inhibitors or ARBs were prescribed in 28 patients [80%]. Amiodarone was used in 18 patients [54.28%] at the time of CRT implantation. No other class III or class I anti-arrhythmic drugs were used in these patients.

Baseline characteristics: sinus rhythm at baseline was observed in 31patients [88.57%] whereas ectopic atrial rhythm, junctional rhythm and complete AV block was observed in one patient each. One patient also had RV paced rhythm. Baseline LBBB was observed in 26 patients [74.29%] whereas nonspecific intraventricular conduction defect was noted in 7 patients [20%]. One patient had complete AV block with wide QRS escape. Mean QRS duration was 173 +/- 22.31 ms whereas mean QRS axis was -21 +/- 47.38 degrees. Mean baseline corrected QT interval was 473.26 +/- 39.99 ms. Mean six minute walk distance was 304.69 +/- 79.88 metres. Mean NT pro-BNP was 3043.68 +/- 2850.89 ng/L.

Baseline echocardiogram: Thirty-three out of 35 patients had severe LV dysfunction. Remaining two patients had moderate LV dysfunction with complete AV block. Mean LVEF of the study population was 26.86 +/- 6.68%. Mean LV end diastolic & end systolic volumes were 215.06 +/- 63.37ml and 161.49 +/- 55.96ml respectively. Mean LA dimension was 42.57 +/- 5.95mm.

Moderate or severe MR was noted in 18 patients[51.43%]. Mean septum-posterior wall delay (SPWD), a marker of intraventricular dyssynchrony was 186.03 +/- 68.85 ms. On the other hand, mean inter-ventricular mechanical delay (IWMD) was 53.41 +/- 22.65 ms.

Table 1. Baseline patient characteristics

Baseline characteristics	
LBBB	26 [74.29%]
Non-specific IVCD	7 [20%]
CHB	1 [2.85%]
QRS DURATION	173 +/- 22.31 ms
QRS AXIS	-21 +/- 47.38 degrees
QTc	473.26 +/- 39.99 ms
6-min walk distance [m]	304.69 +/- 79.88
NT pro-BNP [ng/L]	3043.68 +/- 2850.89

Table 2. Baseline echocardiographic parameters

Echo parameter	**Pre-CRT [n=35]**
LV EDV [ml]	215.06 +/- 63.37
LV ESV [ml]	161.49 +/- 55.96
2D EF [%]	26.86 +/- 6.68%
LA [mm]	42.57 +/- 5.95
MR 3+/ 4+	18 [51.43%]
Septum-PW Delay	186.03 +/- 68.85
Q- PULM EJ	88.76 +/- 24.73
Q-Aorta EJ	141.48 +/- 28.09
IVMD	53.41 +/- 22.65

Baseline EKG analysis: QRS duration during BiVP (151.83 +/- 19.65ms) was significantly shorter than LVepiP (209.47 +/- 31.03ms) and RVendoP (203.14 +/- 31.63ms) [p<0.001 for BiVP vs RVendoP and p=0.184 for LVepiP vs RVendoP]. Likewise, QT interval was shorter during BiVP (470.06+/-51.01ms) than during LVepiP (529.01+/- 55.12ms) and RVendoP (505.81 +/- 49.65ms) [p <0.001 BiVP vs RVendoP and LVepiP vs RVendoP].

Table 3. baseline EKG parameters during pacing from different sites

	Bi-V	**EPI**	**ENDO**	**p value**
QRS [ms]	151.83 +/- 19.65	209.47 +/- 31.03	203.14 +/- 31.63	<0.001 BiV vs Endo; 0.184 Epi vs Endo
QT [ms]	470.06 +/- 51.01	529.01 +/- 55.12	505.81 +/- 49.65	<0.001 BiV vs Endo & Epi vs Endo
Tp-e [ms]	142.06 +/- 21.98	183.45 +/- 27.87	130.41 +/- 16.75	<0.001 BiV vs Endo & Epi vs Endo

However, Tp-e interval was significantly longer during BiVP (142.06+/-21.98ms) and LVepiP (183.45+/-27.87ms) compared to RVendoP (130.41 +/-16.75ms) [p <0.001 BiV vs RVendoP and LVepiP vs RVendoP pacing].

Follow-up: Data at 1yr follow-up was available for 31 patients. Out of 4 patients without follow up data, one patient expired 2 weeks after CRT implantation owing to atrial tachycardia causing cardiogenic shock. Three patients didn't appear for follow-up due to comorbid conditions.

On follow-up, there was significant improvement in echo parameters of LV function (table 4). LVEDV reduced from 215.06 +/- 63.37 to 165.32 +/- 42.8 ml (p <0.001), LVESV reduced from 161.49 +/- 55.96ml to 110.68 +/-35.29ml (p <0.001). Similarly, LVEF increased from 26.68 +/-6.68% to 33.42 +/-6.79% (p <0.001). Six-minute walk test improved significantly from 310.91 +/- 81.44 metres to 393.72 +/- 76.72 metres (p <0.001). NT pro-BNP reduced significantly from 3043.68 +/- 2850.89 ng/L to 1107.45 +/- 1652.85 ng/L (p <0.001).

All except two out of 31 patients had improvement in ΔLVESV >15% (CRT responders) at 1yr follow-up. Furthermore, based on ΔLVESV at 1yr follow-up, 22 patients were classified as high responders (ΔLVESV >25%) and 9 patients as low responders (ΔLVESV <25%). There was no significant difference in baseline characteristics between high responders and low responders (table 7).

Table 4. Echo and other parameters at baseline and follow-up.

	Pre-CRT [n=35]	At 1year F/U [n=31]	p value
LV EDV [ml]	215.06 +/- 63.37	165.32 +/- 42.8	<0.001
LV ESV [ml]	161.49 +/- 55.96	110.68 +/- 35.29	<0.001
2D EF [%]	26.86 +/- 6.68%	33.42 +/- 6.79	<0.001
LA [mm]	42.57 +/- 5.95	41.71 +/- 5.24	0.15
MR 3+/ 4+ [n / %]	18 [51.43%]	11 [35.48%]	0.179
6-min walk distance [m]	310.91 +/- 81.44	393.72 +/- 76.72	<0.001
NT pro-BNP [ng/L]	3043.68 +/- 2850.89	1107.45 +/- 1652.85	<0.001

Table 5. Follow-up EKG parameters during pacing from different sites.

	BiV	EPI	ENDO	p value
QRS [ms]	140.86 +/- 16.38	202.27 +/- 23.92	185.74 +/- 25.38	<0.001 BiV vs Endo & Epi vs Endo
QT [ms]	436.25 +/- 41.78	498.6 +/- 47.02	452.44 +/- 44.27	0.017 BiV vs Endo & <0.001 Epi vs Endo
Tp-e [ms]	117.93 +/- 15.03	158.71 +/- 24.79	118.08 +/- 15.57	0.957 BiV vs Endo & <0.001 Epi vs Endo

EKG parameters on 1yr follow-up (tables 5 & 6): During BiVP, QRS duration, QT interval and Tp-e interval were all significantly reduced compared to baseline (BiV QRS 140.86 +/-19.65ms vs 151.83 +/-19.65ms, p <0.001; QT interval 436.25 +/-41.78ms vs 470.06 +/-51.01ms, p=0.007; Tp-e interval 117.93 +/-15.03ms vs 142.06 +/-21.98ms, p <0.001). In other words, biventricular pacing was associated with significant reverse electrical remodelling. CRT high responders had significantly shorter Tp-e interval on follow-up compared with low-responders (113.16 +/- 14.3ms versus 129.59 +/- 9.75ms, p=0.004) [Table 8 and figures 7 & 8].

Table 6. Comparison of EKG parameters during BiVP at baseline & follow-up.

	BiV baseline	BiV F/U	p value
QRS	151.83 +/- 19.65	140.86 +/- 16.38	<0.001
QT	470.06 +/- 51.01	436.25 +/- 41.78	0.007
Tp-e	142.06 +/- 21.98	117.93 +/- 15.03	<0.001

Table 7. Comparison of baseline characteristics between CRT high responders and low responders.

	CRT high responders [n=22]	CRT low responders [n=9]	p value
AGE [yr]	58.41 +/- 9.84	53.44 +/- 13.98	0.269
BMI [kg/m2]	23.25 +/- 3.63	24.87 +/- 5.99	0.346
QRS DURATION [ms]	171.73 +/- 17.56	174.56 +/- 34.25	0.762
LVEF [%]	24.5 +/- 4.79	28.56 +/- 6.95	0.071
LVEDV [ml]	231.68 +/- 58.19	204 +/- 55.40	0.233
LVESV [ml]	178.73 +/- 48.24	147.78 +/- 52.73	0.125
LA [mm]	42.09 +/- 6.7	45.00 +/- 4.03	0.237
SEPTUM-PW DELAY [ms]	201.26 +/- 65.97	163.38 +/- 63.85	0.181
IVMD [ms]	56.05 +/-21.43	44.29 +/-22.46	0.232
6MWT [m]	325.52 +/- 82.57	291.88 +/- 69.67	0.317
NT PRO-BNP [ng/L]	3049 +/- 3028.68	2766.67 +/-2487.85	0.807

Table 8. Comparison of EKG parameters at baseline and 1yr follow up in high responders versus low responders.

	CRT high responders [n=22]	CRT low responders [n=9]	p value
BiV QRS [Baseline] ms	150.01 +/- 16.6	154.79 +/- 20.84	0.504
BiV QRS [F/U] ms	138.07 +/- 16.82	147.7 +/- 13.79	0.14
BiV Tp-e [Baseline] ms	141.71 +/- 21.45	148.56 +/- 21.8	0.428
BiV Tp-e [Follow-up 1yr] ms	113.16 +/- 14.3	129.59 +/- 9.75	0.004
BiV QT [Baseline] ms	430.91 +/- 45.03	449.28 +/- 30.86	0.274
BiV QT [F/U] ms	430.91 +/- 45.03	449.28 +/- 30.86	0.274

VT/ VF episodes on follow-up: Out of 31 patients, 7 pts [22.6%] had sustained VT on 1 year follow-up. This comprised of 4 out of 9 low responders (44.4%) and 3 out of 22 high responders (13.64%). Three patients had an underlying diagnosis of ischemic CMP, 2 had non-ischemic DCMP and 1 patient each had burnt out hypertrophic CMP and cardiac sarcoidosis respectively. Five patients had VT terminated by successful ICD shocks where as one patient's VT responded to anti-tachycardia pacing and one patient had a stable VT which reverted spontaneously. Baseline BiV Tp-e interval was significantly prolonged

in patients with ventricular arrhythmias on follow-up (158.19 +/- 17.59ms vs 139.72 +/- 20.94ms, p= 0.043). Kaplan–Meier event-free survival analysis (figure 9) demonstrated that the high responder group had a significantly lower rate of VT/VF episodes, compared with the low responder group (log-rank test, P= 0.043).

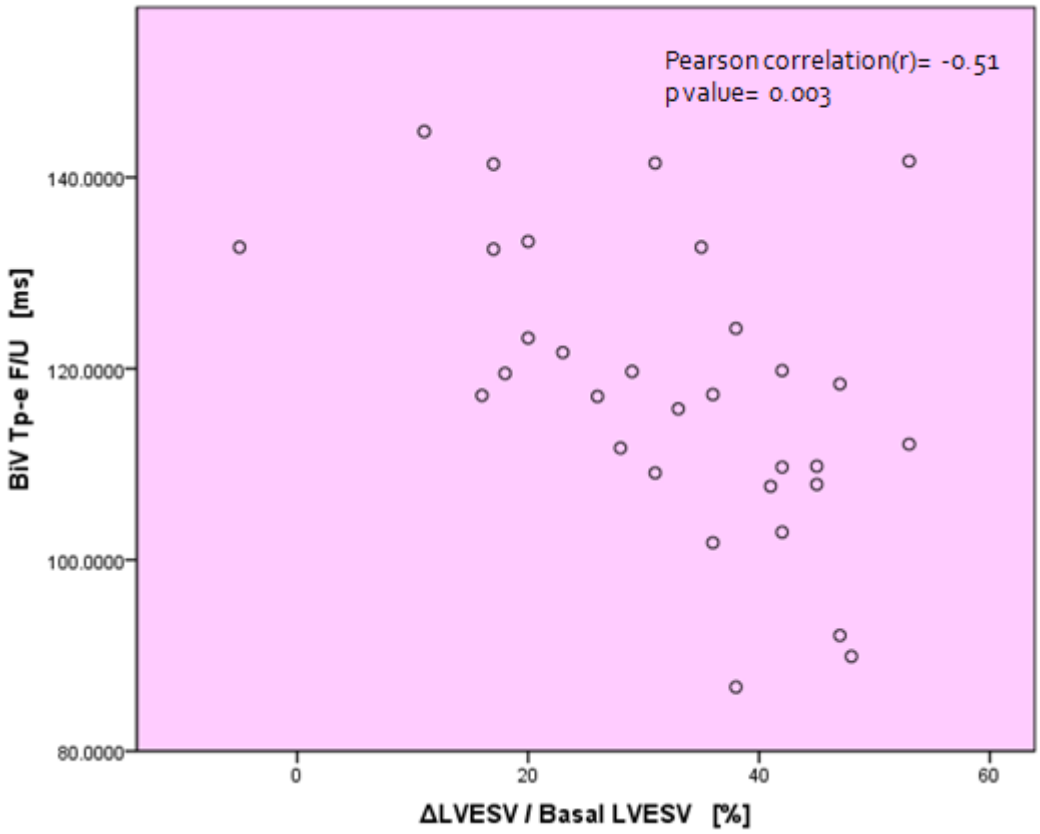

Figure 7. Scatter plot demonstrating significant correlation between reverse mechanical remodelling and Tp-e interval on follow-up.

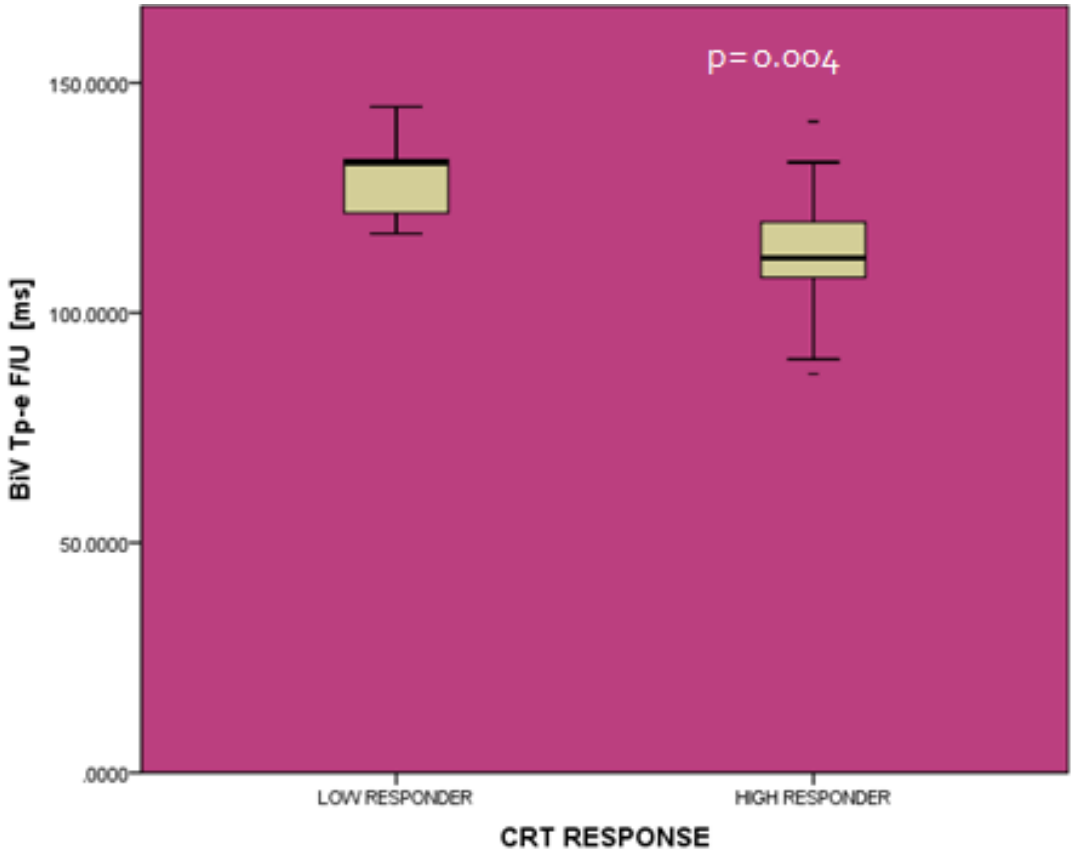

Figure 8. Box plot showing significant difference in Tp-e on follow-up in CRT high responders compared to low responders.

Table 9. Baseline characteristics in patients with and without ventricular arrhythmias on follow up.

	No VT on F/U [n=24]	VT on F/U [n=7]	p value
AGE [yr]	57.25 +/- 10.94	56.00 +/- 12.86	0.8
BMI [kg/m2]	24.00 +/- 4.64	22.75 +/- 2.61	0.505
QRS duration [ms]	171.83 +/- 21.98	175.00 +/- 28.14	0.755
LVEF [%]	24.54 +/- 4.99	29.57 +/- 6.60	0.037
LVEDV [ml]	232.21 +/- 59.86	194.29 +/- 41.51	0.129
LVESV [ml]	177.04 +/- 50.49	144.71 +/- 46.43	0.141
LA [mm]	42.71 +/- 6.61	43.71 +/- 4.46	0.709
6MWT [m]	329.96 +/- 80.69	263.67 +/- 50.49	0.06
NT PRO-BNP [ng/L]	3346.88 +/- 3125.36	1664.71 +/- 663.15	0.172

Table 10. Baseline BiVP EKG parameters in patients with and without ventricular arrhythmias on follow up.

	No VT on F/U [n=24]	VT on F/U [n=7]	p value
Basal BiV QRS [ms]	150.37 +/- 20.4	157.71 +/- 16.29	0.384
Basal BiV Tp-e [ms]	139.72 +/- 20.94	158.19 +/- 17.59	0.043
Basal BiV QT [ms]	469.04 +/- 56.51	478.87 +/- 23.08	0.659

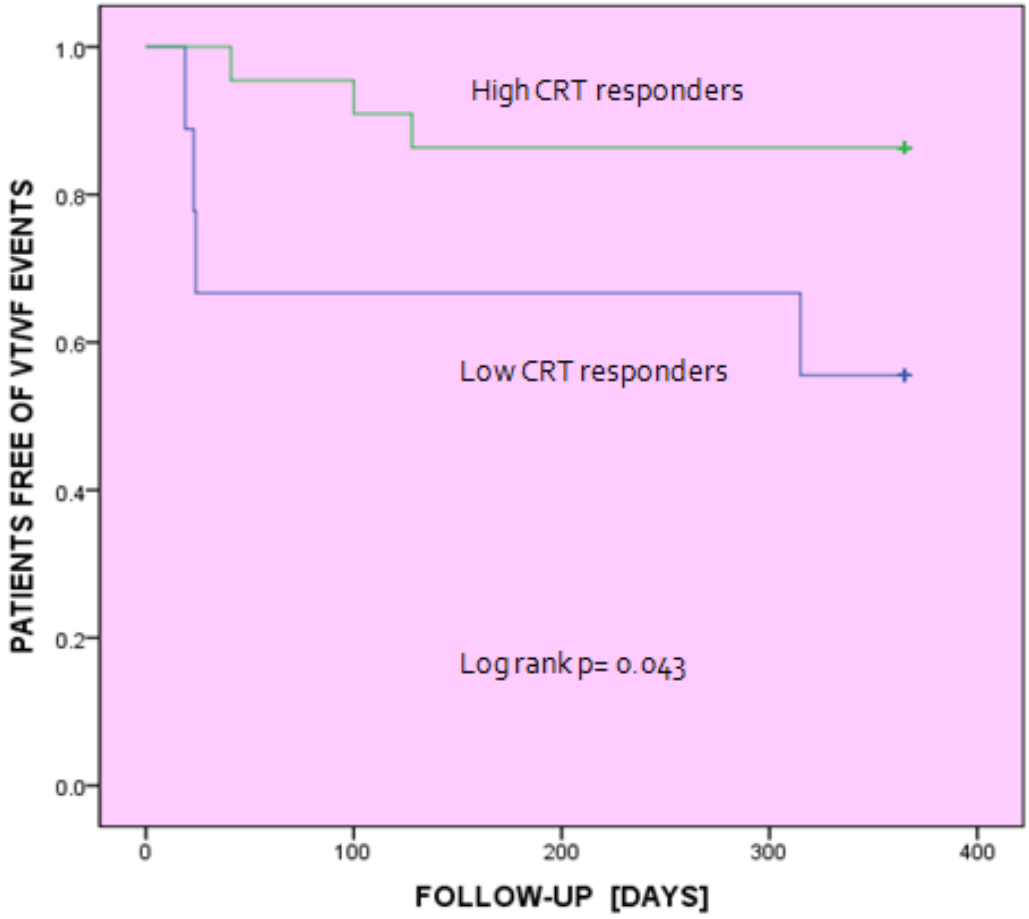

Figure 9. Kaplan-Meier estimates of cumulative VT/VF events in high responders compared with low responders.

DISCUSSION

The salient findings of the present study are that biventricular and epicardial pacing at baseline are associated with greater transmural dispersion of repolarisation than endocardial pacing. Nevertheless, reverse LV remodelling owing to CRT is associated with significant reductions in TDR on follow up. This implies that defibrillator along with CRT with the sole intention to prevent CRT associated proarrhythmia is not warranted.

High CRT responders have significantly greater reductions in TDR and lower VT/VF events during follow-up compared with low responders. Moreover, patients with ventricular arrhythmias on follow up had significantly higher baseline Tp-e interval during biventricular pacing. To the best of our knowledge, this is the first prospective study demonstrating correlation between CRT induced reverse mechanical remodelling and reverse electrical remodelling.

Table 11. Comparison of baseline Tp-e intervals during pacing from different sites between present study and previous studies.

STUDY	BiVP Tp-e (ms)	LVEpiP Tp-e (ms)	RVEndoP Tp-e (ms)	reference
Medina-Ravell et al.	NA	197 +/-26	163 +/-25	27
Bai et al.	184.89+74.08	199.7+/-62.44	146.41+/-31.06	28
Santangelo et al.	93.16+15.60	114.71+26.1	108.13+/-19.94	29
Huysduynen et al.	102 +/- 18	106 +/- 21	117 +/- 22	30
Present study	142.06+/- 21.98	183.45 +/- 27.87	130.41+/- 16.75	

Baseline TDR: The findings of present study at baseline correlates with some but not all previous studies (table 11). Medina-Ravell et al. and Bai et al. demonstrated greater dispersion of repolarisation during biventricular and epicardial pacing compared with endocardial pacing. On the other hand, the studies by Santangelo et al. and Huysduynen et al. reported shorter Tp-e intervals with biventricular pacing. Moreover, the magnitude of Tp-e interval

during pacing from various sites reported by the latter two studies was considerably shorter than the Tp-e interval from corresponding sites in the present study. This could be due to

several causes. First, due to differences in EKG acquisition. EKGs were obtained in ventricular pacing mode (VVI mode rather than DDD mode) in the present study in order to obtain fully paced complexes instead of fusion complexes. Second, due to differences in Tp-e measurement. Santangelo et al used mean Tp-e values in the precordial leads where as Huysduynen et al used automated software for EKG analysis. In the present study, Tp-e interval was measured in all the precordial leads and only the maximum value has been reported, as validated previously.[20] The differences in measurements in various studies also highlights the need for standardisation of Tp-e interval reporting. Third, the differences could be due to differing patient selection.

Reverse mechanical remodelling: Twenty nine out of 31 patients (93.54%) in the present study were CRT responders. Twenty two out of 31 patients (70.9%) were high CRT responders whereas 9 patients (29.1%) were low responders. The rate of reverse mechanical remodelling in the present study is considerably higher when compared with previous studies.[35,36,39] This isn't surprising since selection criteria for CRT was more rigid in the present study. Majority of patients had typical LBBB (74%), wide QRS (173 +/- 22.31 ms), non-ischemic dilated cardiomyopathy (48.5%) and significant dyssynchrony on

echocardiography. None of our patients had right bundle branch block at baseline, which is not associated with significant benefit with CRT.[38] Judicious patient selection for CRT assumes significance especially in developing countries where financial resources are constrained.

Reverse electrical remodeling: The present study demonstrates that CRT reduces paced QRS as well as TDR at 1 year follow up. The magnitude of reduction in TDR is significantly greater in high responders compared with low responders. High responders also have significantly lower VT/VF episodes on follow-up. The mechanism of negative electrical remodeling due to CRT has not been fully elucidated. Reduction in paced QRS duration probably reflects better cell to cell coupling rather than improved His-Purkinje system conduction. Heart failure induced ventricular remodelling involves myocyte apoptosis and inflammation[40,41] leading to an increase in ventricular fibrosis and subsequent impairment of the normal electrical conduction system. Chakir et al. demonstrated that CRT significantly shortens the AP in lateral myocytes and reduces the LV regional heterogeneity in APD. They also showed CRT reverses heart failure induced downregulation of K+ & Ca++ currents. Aiba et al. studied CRT induced reverse modelling experimentally in adult canine hearts and demonstrated that CRT partially restores DHF-induced ion channel remodeling and abnormal Ca^{2+} homeostasis and attenuates the regional heterogeneity of

action potential duration.[43] Further studies are needed to fully uncover the mechanisms of CRT induced reverse electrical remodelling.

Ventricular arrhythmias on follow-up: The present study had 7 patients with VT on follow-up. Low responders had significantly higher VT episodes compared with high responders. Six out of 7 patients had VT within the first six months after CRT implantation (4 within 2 months, 1 each in 4^{th} month & 5^{th} month) whereas one patient had ICD shock in the tenth month after CRT implantation. Thus there was a time dependent reduction in the number of VT episodes. Gold et al.[44] assessed patients enrolled in the REVERSE trial and noted that patients with reverse modelling had lower VT/VF episodes compared with non-responders ((5.6% vs. 16.3%, hazard ratio 0.31, P = .001). Similarly, Bardashet et al. evaluated patients in the MADIT-CRT trial and showed that high responders exhibited a significant 55% reduction in the risk of ventricular arrhythmias compared with ICD-only patients ($p < 0.001$) whereas there was no significant difference between ICD-only patients and low responders ($p = 0.21$).[33] Itoh et al. demonstrated time dependent reduction in ventricular arrhythmias in patients with CRT, with greater reductions in CRT responders as opposed to non-responders.[36]

Patients with VT/VF events in the present study had higher TDR during biventricular pacing immediately after CRT. This finding was also observed by Itoh et al.[36] where Tp-e interval 1 week after CRT was significantly greater.

LIMITATIONS

The present has several shortcomings that needs to be highlighted.

1. TDR during native sinus rhythm was not analysed which could have provided important insights regarding electrical remodeling.
2. Only 45% of patients had defibrillator implanted along with CRT. This might have likely underdiagnosed the number of asymptomatic VT/VF episodes.
3. Majority of patients in the present study were CRT responders. Hence alterations in TDR in CRT non-responders could not be assessed.
4. The present study had a small sample size and hence larger studies are needed to confirm these findings.

CONCLUSIONS

- Baseline transmural dispersion of repolarisation in patients with heart failure is greater during biventricular and epicardial pacing compared with endocardial pacing.
- Biventricular pacing causes negative electrical remodeling on long term follow up in CRT responders. The magnitude of reduction in TDR is greater in high responders compared with low responders.
- High CRT responders have significantly reduced VT/VF events on follow-up compared with low responders. Higher baseline TDR during biventricular pacing is a predictor of VT/VF events on follow-up.

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