COMPARISION OF CLINICAL AND ECHOCARDIOGRAPHIC PARAMETERS IN PATIENTS UNDERGOING CRT AND LEFT BUNDLE OPTIMISED CRT IN HEART FAILURE WITH REDUCED EJECTION FRACTION

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MD/DM/MCh THESIS

Year 2021

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND

TECHNOLOGY, TRIVANDRUM

An Institution of National Importance established by an Act of the Indian Parliament
(Act No.52 of 1980)

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TABLE OF CONTENTS

DECLARATION BY THE STUDENT i
CERTIFICATE BY THE RESEARCH GUIDE ii
ACKNOWLEDGEMENTS.. vi
TABLE OF CONTENTS vii
LIST OF FIGURES viii
LIST OF TABLES ix
LIST OF ABBREVIATIONS (Optional)...x
SYNOPSIS xii
1 INTRODUCTION..1
2 LITERATURE REVIEW...13
3 MATERIAL AND METHODS...20
4 RESULTS ……………………………………………………………………………. 29
5 DISCUSSION ……………………………………………………………………….38
6 LIMITATIONS ……………………………………………………………………...44
7 SUMMARY AND CONCLUSION ……………………………………………………45
8 ANNEXURES

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DECLARATION BY THE STUDENT

CERTIFICATE

I, Dr. Pooja Prasad, hereby certify that I had personally carried out the work in the thesis titled.

'COMPARISION OF CLINICAL AND ECHOCARDIOGRAPHIC PARAMETERS IN PATIENTS UNDERGOING CRT AND LEFT BUNDLE OPTIMISED CRT IN HEART FAILURE WITH REDUCED EJECTION FRACTION'

Before this date, no part of this thesis has been submitted for the award of any other degree or diploma.

Pooja Prasad.

Signature

Date: 29/08/2023

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The thesis entitled "COMPARISION OF CLINICAL AND ECHOCARDIOGRAPHIC PARAMETERS IN PATIENTS UNDERGOING CRT AND LEFT BUNDLE OPTIMISED CRT IN HEART FAILURE WITH REDUCED EJECTION FRACTION" was carried out under my direct supervision. Before this date, no part of the thesis was submitted for awarding any degree or diploma.

*Clearance was obtained from the Institutional Ethics Committee for carrying out the study.

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APPROVAL OF THE THESIS

The thesis entitled

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Submitted by

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DM Cardiology

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Dr. Narayanan Namboodiri.

ACKNOWLEDGEMENT

It has been a great pleasure and privilege to undertake this study and work on this topic for the dissertation. The knowledge and insight gained during this period, both with respect to the subject studied as well as the complexities of the procedure and the steps involved in completion of a study have been enlightening and inspiring.

I wish to acknowledge the Institute, Sree Chitra Tirunal Institute of Medical Sciences and Technology, Trivandrum, under whose wings we are nurtured and have learnt to spread our wings. The support provided in terms of the infrastructure and the system has been instrumental.

I wish to acknowledge my guide, Dr Narayanan Namboodiri, whose constant support and encouragement has been the driving force for this study. The commitment towards the subject, towards patient care as well as his keen aptitude towards research and furthering developments in the speciality is truly inspiring.

I wish to acknowledge my Co Guide, Dr Arun Gopalakrishnan, for his support and guidance, and take inspiration from his keen interest in pursuing research activities that have a meaningful impact on patient care and practice. His knowledge and experience in research work and the support has been instrumental.

I wish to acknowledge all my teachers in the Department of Cardiology, for their constant guidance, support and encouragement.

The Technical staff and nursing staff at the Cardiac catheterization Lab as well as all the staff involved in patient care have also been valuable, without whose support this study could not be done.

I would also wish to acknowledge my seniors in the department for guiding me and helping me along the way, with valuable inputs to enrich the study. Particular mention to Dr Sai Kiran, for being patient and offering valuable guidance throughout.

I thank my colleagues and juniors for the support, and for making the environment conducive to bring out my best.

I thank my family, my parents Dr Venkatesh Prasad and Arathi Prasad, who have been of tremendous support and have always been the backbone of strength through this period. My husband Dr Sreenath, whose support and encouragement has brought me where I stand today

LIST OF FIGURES

Figure No	Figure Caption	Page No
1	AHA Classification of heart failure	2
2	AHA classification of heart failure according to Ejection fraction	3
3	Assessment of Deptal to posterior wall motion delay with M mode echocardiography and tissue doppler imaging	7
4	M mode parasternal long axis and demonstration of the Septal to posterior wall motion delay.	8
5	Septal flash on M mode echocardiography	8
6	Chest X ray PA view showing the CRT pulse generator and the position	10
7	Showing the conduction system of the heart, and the mechanism of activation using the pacing leads in CRT- The RV and LV leads which pace near simultaneously- to achieve electrical synchrony Figure 7. B. Chart showing the effects of CRT, and the final pathway of reverse cardiac remodelling, that contributes to the morbidity and mortality benefit of CRT in heart failure.	11
8	Sites for Conduction system pacing that can be explored In CRT.	15
9	A timeline of the Studies for alternate conduction system pacing sites in CRT	18
10	Latest APHRS guidelines outlining the definitions of the different modalities of pacing and CRT.	19

11	Speckle tracking using Philips EPIQ softw25are- apical 3 chamber view	24
12	The different views used in strain imaging and the corresponding myocardial segments29	24
13.	Apical 2 chamber view assessment in strain imaging	25
14	The Bull's eye plot , showing the Global and segmental myocardia strain values, in a normal patient.	25
15	A box plot showing the age distribution of patients. 1- BiV CRT 2. LOT-CRT	29
16	Bar Diagram showing the gender distribution. Geen= female and red= male, 1- BiV CRT and 2- LOT CRT	29
17	Scatter drop chart showing the distribution of Longitudinal strain	33

LIST OF TABLES

Table No	Table Caption	Page No
1	A Comparison of early clinical Trials studying CRT and their outcomes	14
2	The symptomatology of patients enrolled for the study	30
3	. Preprocedure heart failure medication use in patients enrolled	31
4	Baseline demographic parameters of patients enrolled for the study.	31
5	Baseline echocardiographic parameters of patients enrolled for the study.	32
6	Baseline strain echocardiography and dyssynchrony parameters	33
7	Post procedure clinical parameters and Pro-BNP	34
8	Post procedure echocardiography parameters	34
9	Post procedure strain and dyssynchrony parameters.	35
10	Post procedure values of Global Longitudinal Strain.	35
11	A comparison of the pre and post values of Septal to Posterior wall delay, and the quantified improvement post procedure	36

LIST OF ABBREVIATIONS

S No	Abbreviation	Full Form
1.	HF	Heart Failure
2	HFrEF	Heart failure with reduced ejection fraction
3	CRT	Cardiac Resynchronization Therapy
4	LBBB	Left bundle branch block
5	BiV CRT	Biventricular CRT
6	LOTCRT	Left bundle optimized CRT
7	EF	Ejection fraction
8	GLS	Global longitudinal strain
9	PW	Posteriro wall
10	SD	Standard Deviation
11	CSP	Conduction System pacing
12	NYHA	New York Heart Association
13	QRSD	QRS Complex duration
14	ms	Milliseconds
15	CS	Coronary sinus

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INTRODUCTION

Heart Failure

Heart failure is a multifactorial clinical syndrome occurring as a result of impairment of ventricular filling or ejection of blood. Itis estimated to affect 26 million people worldwide, and it id disabling and deadly disease with an annual hospitalization of approximately one million US adults and a 1 year mortality of 23.6% in patients hospitalized with acute HF in high-income setting.

ACC/ AHA has defined heart failure, and divided it into stages, based on the symptoms and clinicoetiological profile of patients.

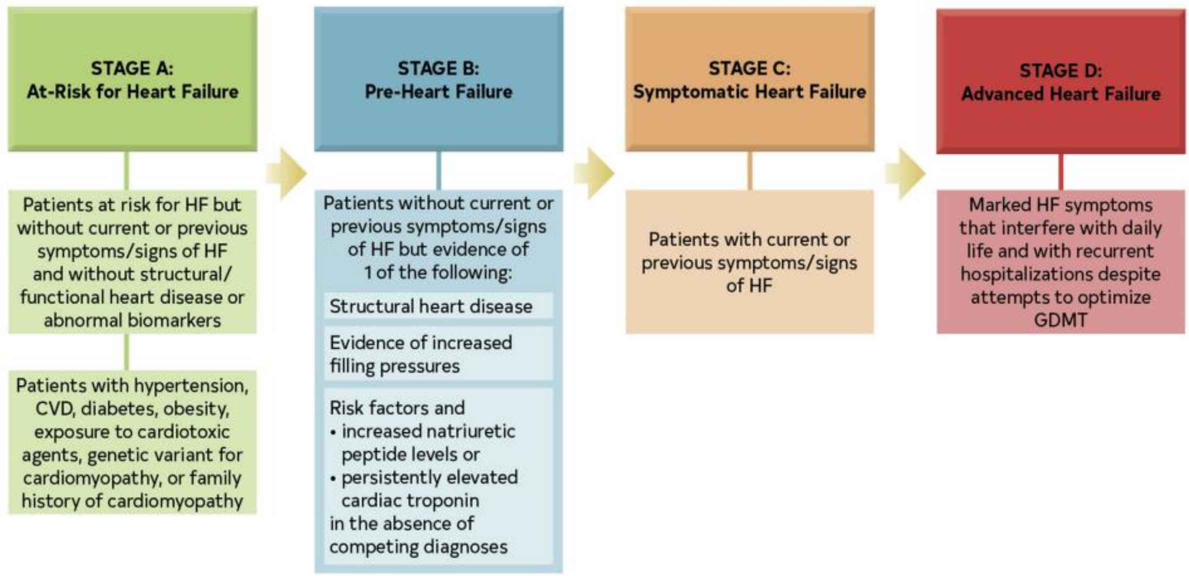


Figure 1. AHA Classification of heart failure

Therapeutic interventions in each stage aim to modify risk factors (stage A), treat risk and structural heart disease to prevent HF (stage B), and reduce symptoms, morbidity, and mortality (stages C and D)

Left Ventricular Ejection Fraction (LVEF) is used to classify patients of Stage B, C and D heart failure, because of differing prognosis and response to treatments.

Type of HF According to LVEF	Criteria
HFrEF (HF with reduced EF)	■ LVEF ≤40%
HFimpEF (HF with improved EF)	■ Previous LVEF ≤40% and a follow-up measurement of LVEF >40%
HFmrEF (HF with mildly reduced EF)	■ LVEF 41%-49% ■ Evidence of spontaneous or provokable increased LV filling pressures (e.g., elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)
HFpEF (HF with preserved EF)	■ LVEF ≥50% ■ Evidence of spontaneous or provokable increased LV filling pressures (e.g., elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)

Figure 2. AHA classification of heart failure according to Ejection fraction

Dilated cardiomyopathy is defined as left ventricular (LV) or biventricular dilatation with systolic dysfunction in the absence of coronary artery disease or abnormal loading condition.

The relationship between left bundle branch block (LBBB) and dilated cardiomyopathy is well known. The prevalence of LBBB in the general population is between 0.2% and 1.1%

Conduction abnormalities may develop in ischemic/nonischemic cardiomyopathy due to degeneration and fibrosis of the conduction system, adverse ventricular remodeling, or ischemia. In patients with HF with reduced ejection fraction, the presence of LBBB is associated with increased mortality.

Left Bundle Branch Block(LBBB) is an abnormality of the conduction system of the heart, affecting the left bundle branch, leading oo selective transmission of cardiac electric impulse via the right bundle brach, which then goes on the activate the left ventricle via delayed myocyte to myocyte tranfer of impulse, giving rise to the wide QRS on ECG- Suggesting delayed condution.

In Dilated cardiomyopathy, Structural and morpho-functional ventricular remodeling is often associated with delayed electrical activation and prolongation of QRS, ultimately leading to left bundle branch block (LBBB)

LBBB has been largely associated with higher morbidity and mortality in DCM.

DCM predominantly affects younger adults and is the most frequent indication for cardiac transplantation. The condition has a nonspecific phenotype and represents l common response of myocardium to genetic and environmental insults or toxins like alcohol.

A large number of patients with heart failure appear to have substantial LV dyssynchrony, which is usually most prominent between the interventricular septum posterolateral LV wal- the site of latest activation of the LV in patients with LBBB

The etiology/ basis of LV dyssynchrony is complex -related to several pathophysiologic mechanisms. For example, LV dyssynchrony could be the result of an abnormal electrical activation of the left ventricle, due to underlying damage to the Purkinje system, resulting in LV activation through the slower conducting myocardium

Abnormal electrical activation of the left ventricle resulting in LV dyssynchrony is frequently called electrical dyssynchrony, and this is different from LV dyssynchrony as a result of abnormal LV contraction caused by diffuse tissue damage or nonuniform wall structure, for example due to areas of scar tissue secondary to previous myocardial infarction, which prohibits normal LV activation known as mechanical dyssynchrony. Thus LV electrical synchrony and LV mechanicl synchrony are both factors that may be dysfunctional, leading to heart failure.

The LV dyssynchrony reflects an imbalance of foce and stress, the region that is activated early being unable to withstand the stress generated by the late-activated LV segments.

The regional wall contractions are not effectively converted to pressure build-up in the left ventricle, but rather cause substantial blood volume shifts within the LV cavity. The overall result is a decrease in LV pumping efficiency, because the ejection fraction is reduced despite maintained, or even increased, energy demand, in an attempt to improve the efficacy of pumping.

Other effects of LV dyssynchrony include mitral valve dysfunction due to a lack of coordination of the papillary muscles that may result in hemodynamically significant Mitral regurgitation This may also cause an impairment of LV diastolic function related to the late systolic stretch and consequent delayed muscle relaxation.

The loss of a nearly simultaneous LV contraction in patients with typical left bundle branch block and left ventricular dyssynchrony is associated with the presence of early septal activation, starting at low LV pressure, which does not contribute to LV ejection and stretches the lateral wall. The stretch of the lateral wall further delays shortening and causes a vigorous activation against a locally increased preload. This leads to a peculiar septal motion called the septal flash, and this has been diescribed as one of the echo screening parameters that predict a super response to Left bundle pacing / CRT

This alternation of activation and stretch of opposite LV walls seen in the dyssynchronous heart promotes local modifications of the LV function at the molecular and cellular level., which are later corrected and the normalisation of these molecular functions contributes to the delayed benifitd of CRT including reverse cardiac remodelling.

Intra-ventricular mechanical dyssynchrony is a term used to describe the presence of abnormal timing of motion within the LV. In the normal heart, the different myocardial segments demonstrate onset of motion and peak motion that is highly synchronized in longitudinal, radial, and circumferential planes. This motion can be measured as tissue velocity, displacement, or strain,

Cardiac resynchronization therapy (CRT) creates simultaneous or near simultaneous biventricular stimulation aimed at correcting the lack of ventricular synchrony found in some patients with congestive heart failure and, most commonly, those with left bundle branch block. CRT is among the most important contemporary advances in the treatment of heart failure.

Several randomized clinical trials have demonstrated benefits in survival, hospitalizations for heart failure, functional capacity and improvement in left ventricular function and architecture among patients with advanced systolic dysfunction and QRS duration equal or greater to 120 milliseconds. The benefit is additional to that of optimal medical therapy for heart failure.

The QRS duration as a measure of electrical dyssynchrony and the pattern of the left bundle branch block, suggest the presence of mechanical dyssynchrony and are often associated with it. However, the delay in conduction, as might be inferred, does not necessarily correspond consistently with the measures of mechanical dyssynchrony obtained with imaging modalities.

Imaging Modalities for assessment of Synchrony

A number of techniques have been proposed for quantifying mechanical dyssynchrony. Echocardiography is a practical and cost- effective tool that has become widely used for this purpose. In particular, tissue Doppler imaging (TDI) and, more recently, speckle tracking echocardiography (STE) have emerged as robust techniques for quantifying mechanical LV dyssynchrony

M-mode images of the parasternal long-axis view can be used to measure mechanical dyssynchrony using standard ultrasound equipment without more advanced motion quantification software. A difference of more than 130ms between the maximal inward movements of the basal septal and posterior walls has been used to identify dyssynchrony. This is known as the septal to posterior wall delay.

The septal flash that is a sudden jerky movement as the interventricular septum at the beginning of systole, corresponds to isovolumic systole and can be easily detected by M-mode parasternal long-axis view.

These are the specific features f dyssynchrony that can be used in M mode echocardiography, but these parameters have their limitations due to poor reproducibility of the echo-derived analysis of dyssynchrony parameters, and the inability to differentiate the complex pattern of contraction and area of latest activation of LV.

M mode in addition is important to identify septal scarring, which may be the result of ischemia, which may preclude the use of LBB are pacing when planning CRT. Some subtle specific features like basal septal thing on M mode may point towards specific underling etiology like sarcoidosis, and prompt further evaluation.

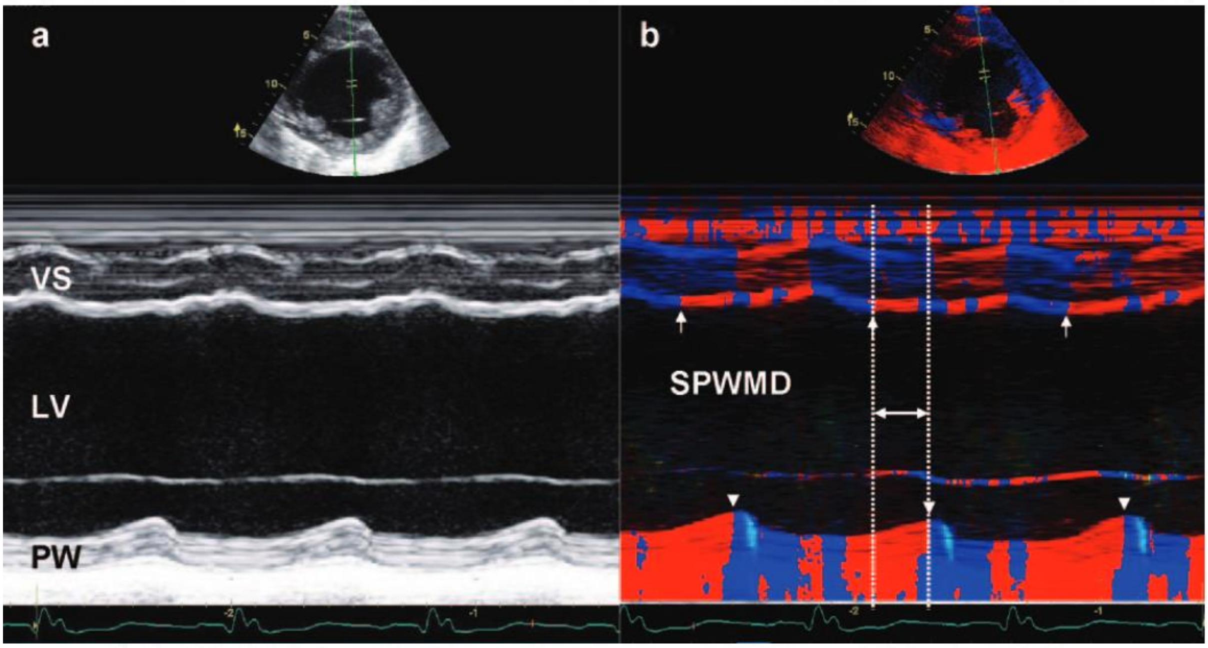


Figure 3. Assessment of Septal to posterior wall motion delay with M mode echocardiography and tissue doppler imaging

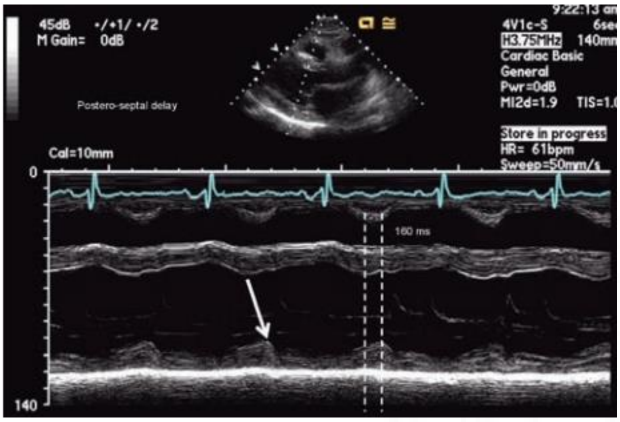


Figure 4. M mode parasternal long axis and demonstration of the Septal to posterior wall motion delay.

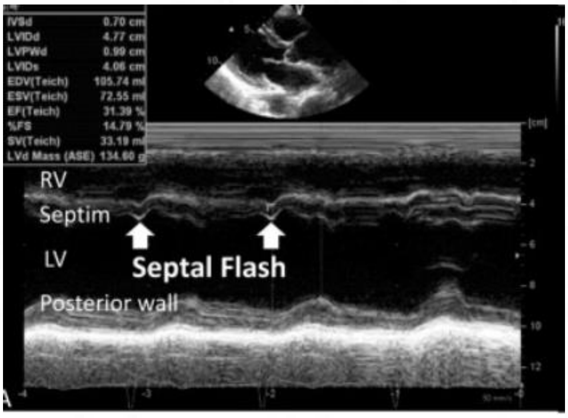


Figure 5. Septal flash on M mode echocardiography

TISSUE DOPPLER IMAGING

Longitudinal and radial shortening velocities can be recorded with tissue Doppler in different segments from different windows to assess the time of contraction of each segment and quantify the difference among individual segments. Time intervals are measured in reference to the electrocardiogram using the beginning of the QRS complex and the peak systolic velocity recorded in selected regions of interest on basal and mid segments of opposing walls wherever the maximal systolic velocity is found to be stable.

Assessment of Dyssynchrony by tissue doppler tales the peak velocities of the LV septal and lateral basal segments in the apical four-chamber view. Dyssynchrony is defined when the delay in activation of opposite walls is more than 65 msec. The dyssynchrony index that incorporates measurements in 12 segments in all three standard planes of the apical window (basal anterior, inferior, septal and lateral in the two and four chamber and longitudinal views can also be used.

Strain Imaging

Strain can be measured by TDI or by 2-dimensional speckle tracking and since it is less affected by tethering or translation induced by unbalanced rocking motion, this is a better and more reproducible method of assessment of LV mechanical property

Multicentre study using strain delay index for predicting response to cardiac resynchronization therapy (MUSIC) study showed that in the case of preserved contractility and significant dyssynchrony, LV segments that contract late present a higher difference between the peak and end systolic strain, which is a measure of segmental wasted energy. The global LV wasted energy is referred to as strain delay index (SDI) and has been shown to predict CRT response with an AUC of 0.88, a sensitivity of 92% and a specificity of 65%. This method of assessment of strain is not routinely feasible.

Other components in strain imaging include Longitudinal strain, which uses speckle tracking in the apical 2, 3 and 4 chamber views for a global assesment of LV myocardial velocities. This is the mist commonly employed modality of strain imaging, and the necessary software is now readily available, making this a feasible method of echo assessment of dyssynchrony, and LV function.

CRT- Cardiac Resynchronization Therapy.

Cardiac resynchronization therapy (CRT) is one of the most exciting recent advancements in heart failure (HF) treatment. By targeting ventricular dyssynchrony, which affects as many as one third of patients with highly symptomatic systolic Heart failure. CRT attempts to give the failing heart a mechanical advantage that can substantially improve symptoms and mortality,

CRT is typically accomplished by adding a left ventricular (LV) pacing lead to a standard pacemaker or defibrillator system that generally includes only a right ventricular (RV) lead and possibly a right atrial lead The RV lead most often rests in the apex of the right ventricle. The LV lead is placed through the coronary sinus onto the lateral or posterolateral wall of the left ventricle. When the 2 leads are activated, coordinated pacing of the left ventricle and right ventricle results.

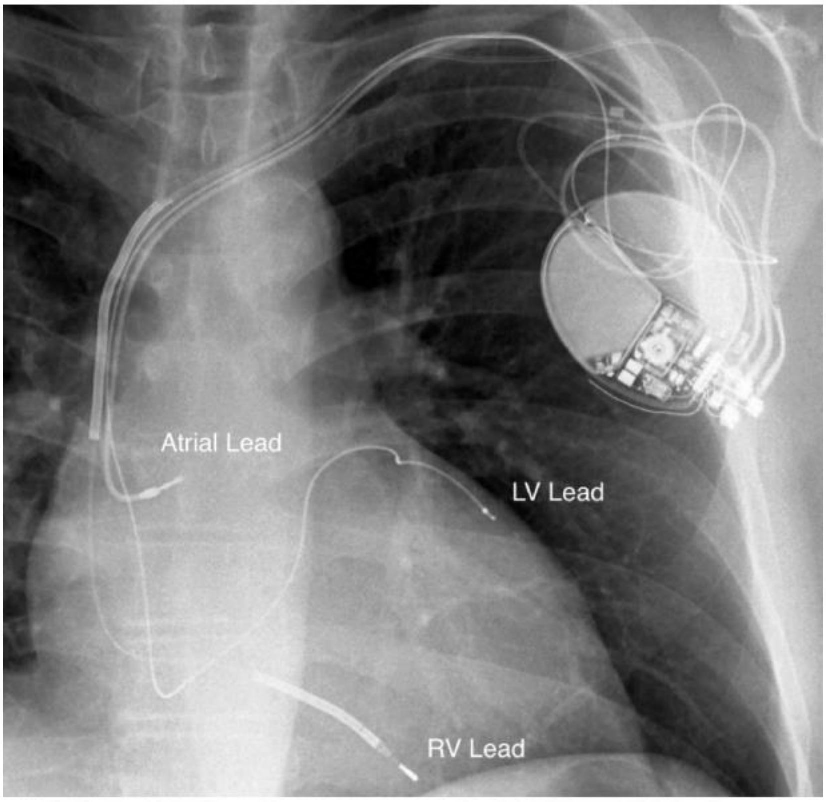


Figure 6. Chest X ray PA view showing the CRT pulse generator and the position

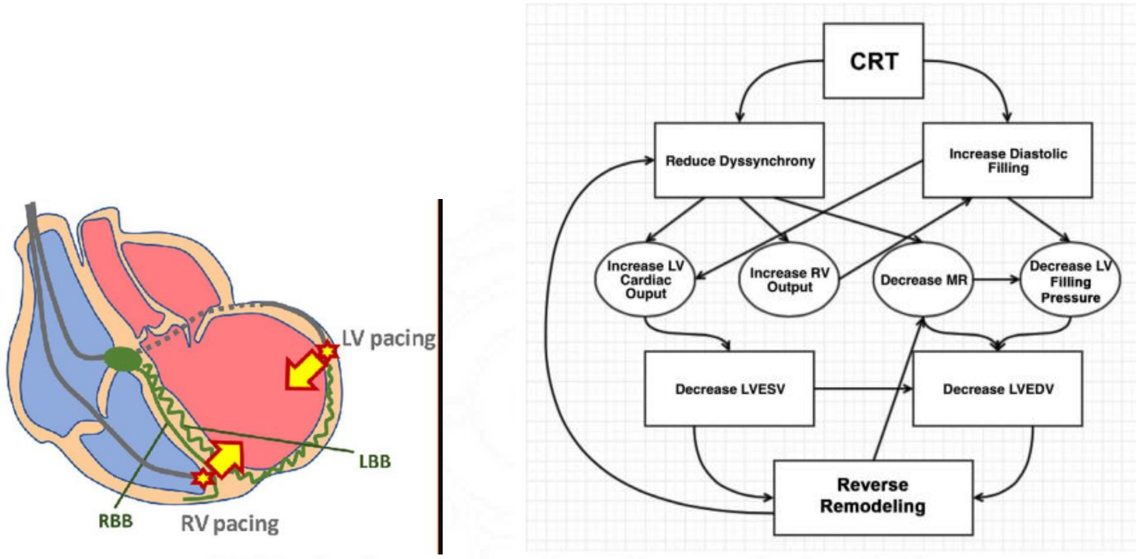


Figure 7. A. Showing the conduction system of the heart, and the mechanism of activation using the pacing leads in CRT- The RV and LV leads which pace near simultaneously- to achieve electrical synchrony

Figure 7. B. Chart showing the effects of CRT, and the final pathway of reverse cardiac remodelling, that contributes to the morbidity and mortality benefit of CRT in heart failure.

Coordinated contraction of the ventricles gives the previously dyssynchronous heart an instant mechanical advantage that augments cardiac output. In addition to the immediate hemodynamic benefits, CRT leads to further improvement in the structure and function of the heart over long term- with benefit seen in 3-12 months.

These long-term changes are known collectively as reverse remodeling that evident by a reduction in LV size and an improvement in LV function. Reverse remodeling is a consistent finding in CRT-treated patients with baseline symptomatic HF and long QRS duration at baseline, which significantly narrowed immediately post procedure.

The resultant geometric changes may also lead to less dilatation of the mitral annulus and thereby to a decrease in the severity of Mitral regurgitation, also contributing to Symptomatic and hemodynamic benefit.

At the cellular level, CRT improves sarcomere shortening via increased peak calcium levels that improve cardiac contractility and systolic function

REVIEW OF LITERATURE:

Multisite Stimulation in Cardiomyopathy (MUSTIC) Trial, published in 2001, was the first large trial demonstrating the clinical benefits of CRT

It was a single-blind crossover study that enrolled patients with New York Heart Association (NYHA) class III HF, LVEF 35%, left ventricle end-diastolic diameter >60 mm, and QRS duration >150 ms. They compared exercise tolerance and quality of life during active biventricular pacing for 3 months to exercise tolerance and quality of life during right ventricle–only backup pacing for a separate 3 months. The trial showed a statistically significant improvement in 6-minute walk distance (, as well as improved quality of life and peak oxygen consumption following CRT.

Tthe MIRACLE trial showed that resynchronization therapy is an effective adjunct to pharmacologic therapy in reducing the secondary combined endpoint of HF hospitalization or death, and this study paved the way for the imclusion of CRT in the armamentarium of heart failure management strategies.

Comparison of Medical Therapy, Pacing, and Defibrillation in HF (COMPANION) Trial. included 1,520 patients and was the first trial able to detect improvement in the primary combined endpoint of hospitalization or death from any cause. ardiac-resynchronization therapy with a pacemaker decreased the risk of the primary end point (hazard ratio, 0.81; P=0.014), as did cardiac-resynchronization therapy with a pacemaker–defibrillator (hazard ratio, 0.80; P=0.01). The risk of the combined end point of death from or hospitalization for heart failure was reduced by 34 percent in the pacemaker group (P<0.002) and by 40 percent in the pacemaker–defibrillator group (P<0.001 for the comparison with the pharmacologic-therapy group)

In 2005, the CARE-HF trial attempted to clarify the mortality benefit of CRT independent of the mortality benefit of defibrillation

This trial enrolled 813 patients with NYHA class III-IV HF, QRS duration ‡120 ms, echocardiographic dyssynchrony, and LVEF 35%. Compared to OMT alone, CRT-P was associated with a significant (26%) reduction in all-cause mortality and hospitalization for major cardiovascular events at 29 months. Most important, CARE-HF was the first trial to show definitively that CRT-P had a mortality benefit, even in the absence of implantable cardioverter defibrillator (ICD) therapy

	Patients Enrolled	Inclusion Criteria	Comparison	Significant Findings
MUSTIC[19]	131	LVEF ≤35% LVEDD >60 mm NYHA class III 6-min walk test <450 m QRS >150 ms ***or*** Paced QRS >200 & persistent AF	OMT vs OMT + CRT-D ***or*** RV pacing in persistent AF vs OMT + CRT-D	Improvement in 6-min walk test Peak VO_2 Quality of life NYHA class
MIRACLE[20]	453	LVEF ≤35% LVEDD >55 mm NYHA class III/IV QRS ≥130 ms	OMT vs OMT + CRT-D	Decrease in HF hospitalizations Improvement in 6-min walk test Ejection fraction Mitral regurgitation Quality of life NYHA class
COMPANION[21]	1,520	LVEF ≤35% NYHA class III/IV QRS >120 ms	OMT vs OMT + CRT-P vs OMT + CRT-D	Decrease in combined endpoint of hospitalizations or death for CRT-P and CRT-D Decrease in mortality for CRT-D
CARE-HF[22]	813	LVEF ≤35% LVEDD >30 NYHA class III/IV QRS ≥150 ms ***or*** *QRS* ≥120 ms and echo dyssynchrony	OMT vs OMT + CRT-P	Decrease in combined endpoint of hospitalizations or death for CRT-P Decrease in mortality for CRT-P
MADIT-CRT[15]	1,820	LVEF ≤30 NYHA class I/II QRS ≥150 ms	OMT + ICD vs OMT + CRT-D	Decrease in combined endpoint of hospitalization for HF or death
RAFT[23]	1,798	LVEF ≤30 NYHA class II/III QRS ≥120 ms ***or*** paced QRS ≥200 ms	OMT + ICD vs OMT + CRT-D	Decrease in death or hospitalization from HF

Table 1. A Comparison of early clinical Trials studying CRT and their outcomes.

SITES FOR CARDIAC PACING IN CRT

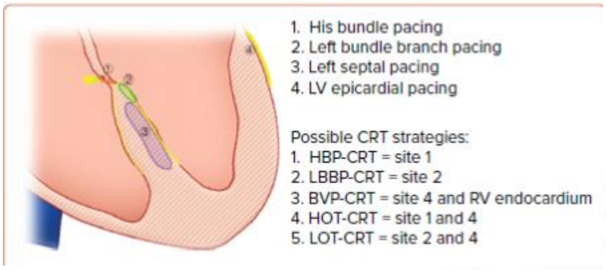


Figure 8. Sites for Conduction system pacing that can be explored In CRT.

Left bundle branch area pacing (LBBAP) is a promising physiological pacing technique with potential for application in both patients with bradyarrhythmia and those with heart failure. The extension of the Left bundle branch area pacing along with the LV pacing via CS lead constitutes Left budle optimised pacing i.e LOT-CRT.

The Proximal left bundle branch (LBB) pacing is inherently limited in its ability to restore physiological activation of the lateral wall of the left ventricle (LV) in patients with distal conduction delay in the distal LBB, LV Purkinje network, or myocardium. In the initial few studies/ series on LBBAP, in a significant percentage of patients in whom LBBAP was attempted, only left ventricular septal (LVS) myocardial capture was obtained, resulting in a small but potentially important nonphysiological delay in LV lateral wall activation. Thus the concept of Left bundle branch area pacing came into being, which includes both selective left bundle capture wherein the Left bundle branch is directly captured, and the non selective Left bubdle capture, where the initial LV septal myocardium is captured, and then the conduction system is captured.

The difference in time in the above 2 methods has been found to be insignificant, and both ethods of capture are effective.

Conventional cardiac resynchronization therapy (CRT) using biventricular (BiV) pacing based on right ventricular (RV) pacing and coronary venous (CV) pacing is also limited in its ability to fully restore physiological activation of the LV. Limitations of BiV-CRT are

- the potentially desynchronizing impact of myocardial pacing with the RV lead
- single area nonphysiological epicardial LV pacing
- latency,
- suboptimal LV lead position (paraseptal/ apical) due to the unfavorable anatomy of the cardiac veins and/or LV scars, which may reduce the benefit.

Combining LBBAP and BiV pacing might address some of the above-mentioned limitations of both techniques, providing narrower QRS complex and a more efficient form of CRT, especially in challenging cases and patients with more advanced heart failure.

The major rationale behind replacing the RV lead with the LBBA lead was to obtain greater electrical synchrony due to

(1) direct depolarization of the LV conduction system

(2) bypass the slow cell-to-cell conduction from the right to the left side of the interventricular septum.

Although LBBAP alone can achieve electrical synchrony of the LV, delayed activation of the lateral wall of the LV in patients with heart failure might results not only from discrete lesion in LBB that can be bypassed by LBB pacing but also from widespread and/or distal delay in the conduction system. Electrical uncoupling, myocardial scars, or functional conduction block can lead to delay in LV lateral wall activation as well.

Such conduction abnormality can be corrected by the Coronary sinys pacing pacing but not LBBAP. There is often a coexistence of both mechanisms (focal lesion and distal delay) in some patients with LBBB and wider QRS complex on ECG and advanced heart failure., thus the rationale for using the LV epicardial/ coronaruy sinus elad in addition to the septal lead in LOT-CRT.

The area of conduction system pacing and CRT is relatively recent, and initial studies in 2017, a study by Vijayaraman et al postulated that His bundle pacing i.e HOT-CRT can ben alternative to achieve greater electrical resynchronization in patients with advanced conduction disease and severe heart failure. This was limited by higher pacing thresholds and the problems of loss of capture, and thus the area of Left bundle are pacing was explored, with initial studies being done in 2017 and 2018.

In LOT-CRT, the quadripolar LV lead can be used with the option of multipoint pacing if necessary and ventricular sensing/arrhythmia detection is normal.

LBBAP provides additional LV resynchronization by early LV septal endocardial activation in addition to conduction system capture. Furthermore, HBP is often associated with higher pacing thresholds and potential risk of late rise in capture thresholds. LBBAP has consistently been shown to achieve low and stable capture thresholds with high R-wave amplitudes, as demonstrated in future studies where LBBAP was explored.

Initial investigators studied the utility of alternate / non conventional pacing sites as an adjunct to the CRT procedure, wherein instead of pacing the Right ventricle, they placed the leads to ensure capture of the conduction system, resulting theoretically in more physiological pacing, with narrower QRS duration and quasi normal synchrony.

His optimised CRT(HOT-CRT) was studied initially, and showed good results in terms of narrower QRSd and electrical synchrony, however the procedure was limited by higher pacing thresholds and potential risk of late rise in capture thresholds.

A study by the international LBBAP collaborative group, studied Left bundle area pacing CRT(LOT-CRT) and compared it to conventional CRT in patients with LBBB and Heart failure. They found that

LOT-CRT was successful in 91 of 112 patients (81%). LOT-CRT resulted in significantly greater narrowing of QRS complex from 182 6 25 ms at baseline to 144 6 22 ms (P , .0001) than did BiV-CRT (170 6 30 ms; P , .0001) and LBBAP (162 6 23 ms; P , .0001). At follow-up of 3 months, the ejection fraction improved to 37% 6 12%, and Clinial improvement was seen in nearly all patients with successful LOT-CRT.

Another study by Wu et al. in 2021 demonstrated the utility of LBB pacing as an adjunct to CRT.

HBP and LBBP demonstrated a similar absolute increase (D) in LVEF (þ23.9% vs þ24%, P ¼ 0.977) and rate of normalized final LVEF (74.4% vs 70.0%, P ¼ 0.881) at 1-year followup. This was significantly higher than in the BVP group (D LVEF þ16.7% and 44.9% rate of normalized final LVEF, P < 0.005). HBP and LBBP also demonstrated greater improvements in NYHA class compared with BVP.

They concluded that These improvements were significantly greater than those seen in patients treated with BVP in this nonrandomized study.

The pacing parameters remained stable on follow up, suggesting that this technique can potentially overcome the limitations faced by His bundle pacing.

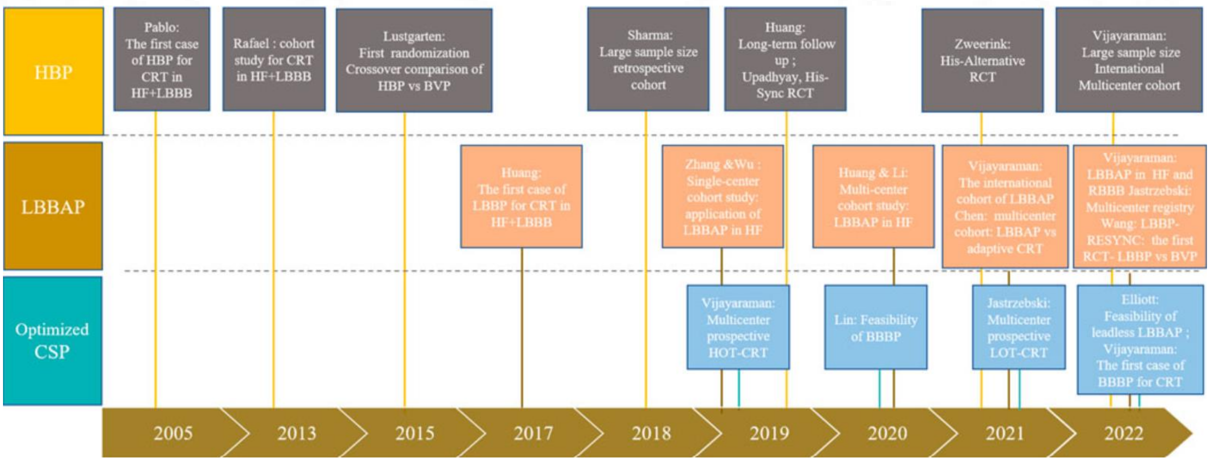


Figure 9. A timeline of the Studies for alternate conduction system pacing sites in CRT.

Left bundle branch block (LBBB)	For the purposes of this guideline, LBBB is defined by the 2009 AHA/ACCF/HRS Scientific Statement on recommendations for the standardization and interpretation of the electrocardiogram[11] as QRS duration $\geq$120 ms and a broad notched or slurred R-wave in leads I, aVL, V_5, and V_6.
Cardiac physiologic pacing (CPP)	CPP is defined as any form of cardiac pacing intended to restore or preserve ventricular synchrony. CPP can be achieved by engaging the intrinsic conduction system via CSP (eg, HBP or LBBAP) or CRT.
Conduction system pacing (CSP)	CSP involves recruitment of the intrinsic conduction system by either HBP or LBBAP.
His bundle pacing (HBP)	HBP involves the direct stimulation of the His bundle to engage the native conduction system. Based on location and pacing outputs, HBP may be selective (isolated recruitment of the His bundle) or nonselective (recruitment of both the local septal myocardium and the His bundle).[12]
Left bundle branch area pacing (LBBAP)	LBBAP is ventricular pacing that is intended to engage all or any part of the left bundle branch (LBB) fascicular system. Similar to HBP, various responses can be seen based on location and pacing outputs. These include selective LBBP (direct stimulation and isolated recruitment of the LBB fibers), nonselective LBBAP (direct stimulation and recruitment of both the local myocardium and the LBB fibers), or deep septal pacing (no direct recruitment of the LBB fibers).
Cardiac resynchronization therapy (CRT)	CRT aims to restore or preserve ventricular synchrony using left ventricular (LV) stimulation at appropriately timed right ventricular (RV) sensing or stimulation. CRT most commonly refers to BiV pacing, in which a pacing lead is implanted in the RV and another on the epicardial surface of the LV via an epicardial vein. Alternatively, the LV lead may be implanted endocardially or surgically on the epicardium. LV pacing alone in some situations may also deliver CRT. CSP for patients with dyssynchrony may also be considered a form of CRT, but for the purposes of this guideline, CRT refers to use of BiV or LV pacing. These pacing locations refer to standard anatomy but may differ in certain forms of congenital heart disease.

Figure 10. Latest APHRS guidelines outlining the definitions of the different modalities of pacing and CRT.

CURRENT RECOMMENDATIONS

ESC 2021 Guidelines on cardiac pacing and CRT, give a Class I recommendation for CRT for symptomatic patients with HF in SR with LVEF >150 ms, and LBBB QRS morphology despite OMT, and a class IIa recommendation for symptomatic patients with HF in SR with LVEF <-35%, QRS duration 130149 ms, and LBBB QRS morphology despite OMT.

MATERIALS AND METHODS

DESIGN: Prospective observational study- comparing 2 arms- CRT arm and LBB pacing arm

Sample size: 20 subjects in each arm.

Study period: September 2021 to May 2023

Patients were assigned to either arm based on physician discretion at the time of the procedure.

INCLUSION CRITERIA:

- Patients with Non ischemic dilated cardiomyopathy
- >18 years of age
- Baseline LBBB, QRSd > 130 ms
- HFrEF(LVEF </= 35%)

EXCLUSION CRITERIA

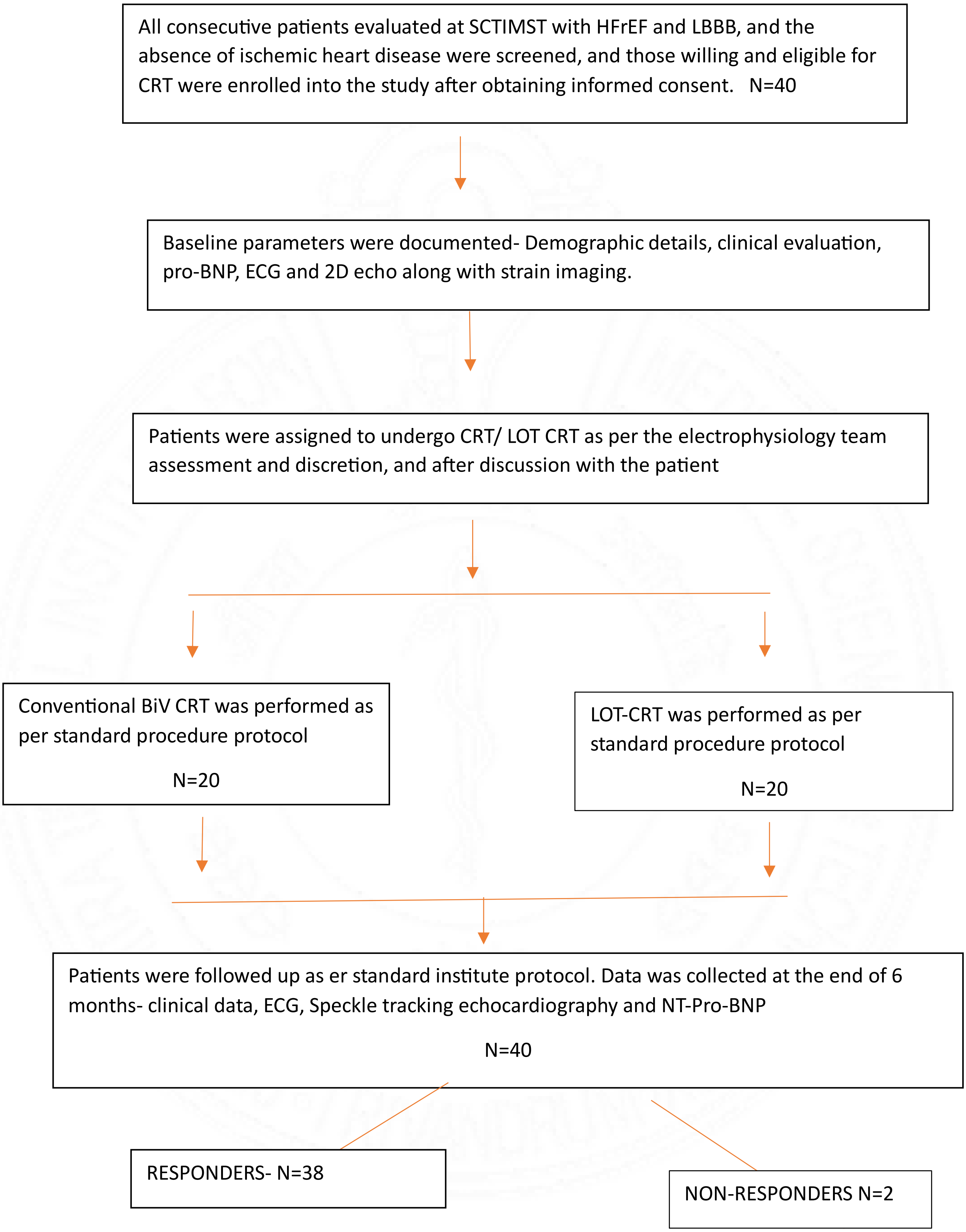
- Patients having Bradyarhythmia as indication for pacing
- Not willing/ not consented for participation in the study

STUDY PROTOCOL

- Consecutive patients with HFrEF and LBBB who fulfilled the inclusion criteria were enrolled after taking informed consent, and were assigned to either undergo CRT or LOT-CRT based on the physician discretion and after discussion with the patient and family.
- After collection of baseline data, patients then electively underwent the procedure, performed by the team of electrophysiologists at SCTIMST, Thiruvananthapuram.

- They received standard periprocedural and post procedural care as per institute protocols.
- 2D ECHO & STE was performed in both groups by using Philips Epiq 7 machine in detail and parameters were noted in a pre-designed format.
- They were followed up for 6 months, and at their routine visit at the comprehensive devices clinic at SCTIMST, they were evaluated and data was collected, which included clinical data, ECG, NT-Pro-BNP and 2D echo with STE
- LBBB was defined by Strauss Criteria- QRS duration 140 ms (men) or 130 ms (women), QS or rS in leads V1 and V2, and mid-QRS notching or slurring in 2 of leads V1, V2, V5, V6, I, and aVL.

STUDY PROTOCOL



2D ECHO parameters at the diagnosis and during follow-up was gathered from medical records of the institute.

LV Ejection Fraction was calculated on the basis of Teichholz formula, with LV end diastolic (LVEDd) and end systolic (LVESd) diameters measured in parasternal long axis view. Follow-up examination was performed as per existing guidelines (37).

Principal Investigator (PI) in supervision of other investigators performed all echocardiographs.

MR was graded based on vena contracta width and ratio of MR area/ left atrial area to none (0), trivial (1+), mild (2+), moderate (3+) and severe (4+), based on current guidelines (38–40)

SPECKLE TRACKING ECHOCARDIOGRAPHY:

Myocardial strain was measured in all segments of left ventricle.

The degree of deformation is reported as percentage of peak longitudinal strain (LS) in systole. Decreased myocardial shortening (impaired function) is represented by lower absolute values.

Depth-adjusted two-dimensional (2D) LV images was acquired from the apical 2-, 3- and 4-chamber views for off-line measurements of LV-GLS using STE.

Three consecutive cardiac cycles using a frame rate >60 fps were acquired.

It was verified, whether peak systolic strain from each LV segment was measured prior to aortic valve closure.

The LS was calculated in each segment separately.

LV-GLS was calculated as the average of peak strain values from 18 LV segments

Raw data was transferred to a workstation for off-line analysis using dedicated two-dimensional speckle tracking software (QLab, Philips).

If the automated tracking was not satisfactory at visual assessment, manual adjustment of the region of interest was performed.

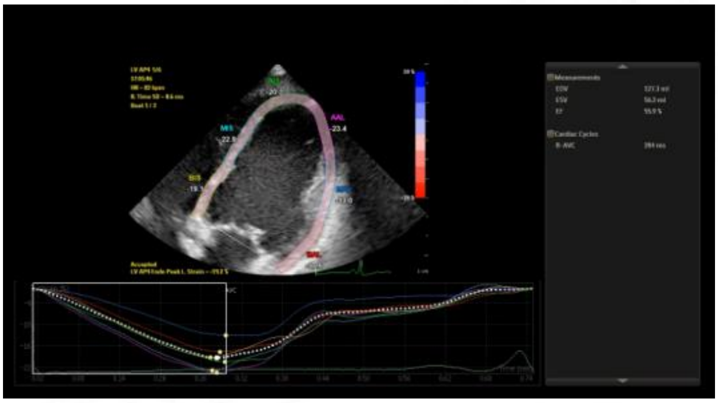


Figure 11. Speckle tracking using Philips EPIQ software- apical 3 chamber view.

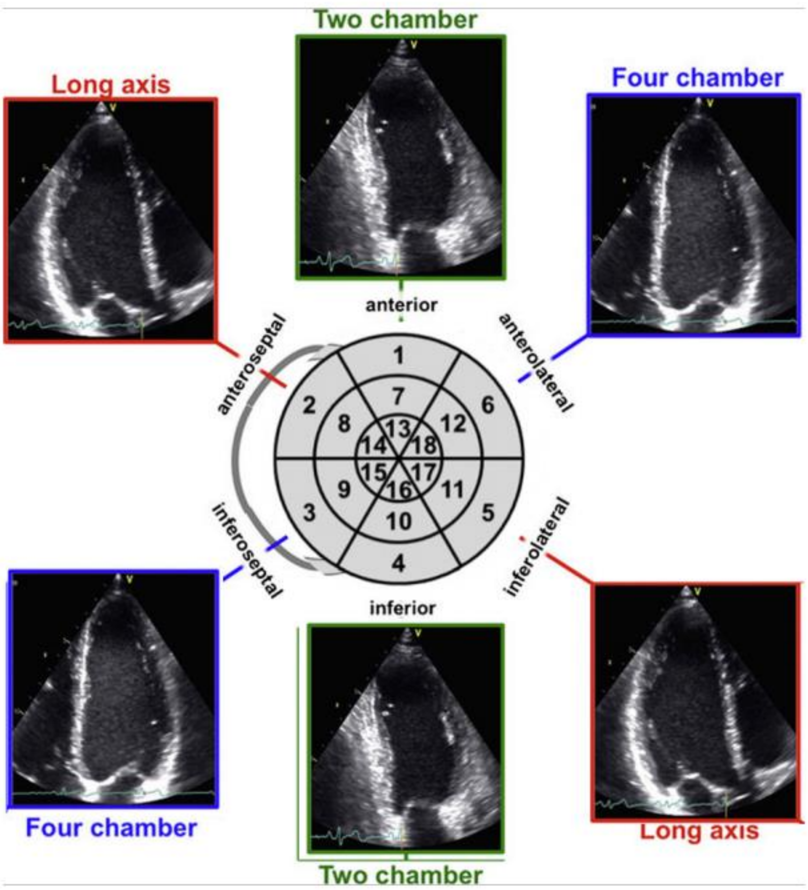


Figure 12. The different views used in strain imaging and the corresponding myocardial segments.

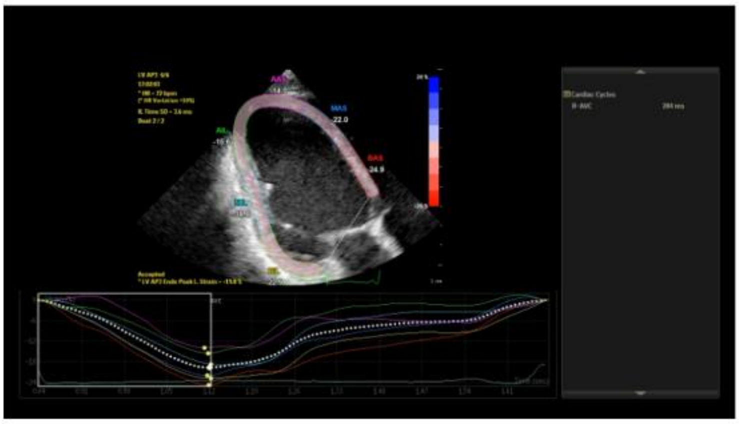


Figure 13. Apical 2 chamber view assessment in strain imaging.

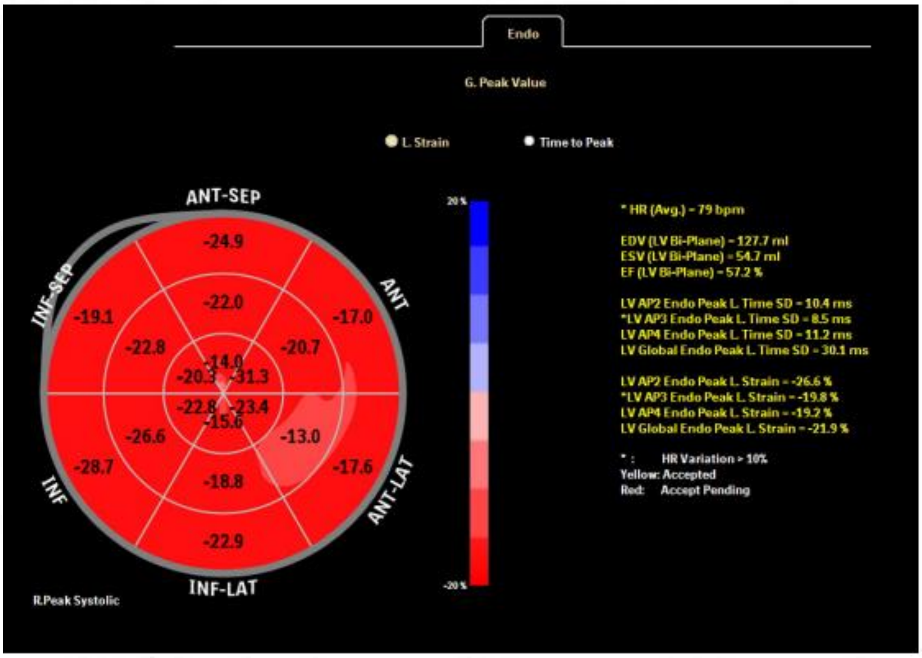


Figure 14. The Bull's eye plot , showing the Global and segmental myocardia strain values, in a normal patient.

DATA COLLECTION:

- At Enrollment:
  - Demographic details
  - Symptoms and NYHA Functional Class
  - Medication history
  - NT-Pro-BNP
  - ECG
  - Echocardiography:
    - LV dimensions and EF
    - LVEDV/ LVESV
    - MR/ TR
    - TAPSE
    - Longitudinal Strain assessment:- in AP2C, AP3C and AP4C views, and GLS.
    - SD of Time to peak Longitudinal strain- index of mechanical dispersion

AT FOLLOW UP

- NYHA Functional Class
- NT-Pro-BNP
- ECG
- Echocardiography:
    - LV dimensions and EF
    - LVEDV/ LVESV
    - MR/ TR
    - TAPSE
    - Longitudinal Strain assessment:- in AP2C, AP3C and AP4C views, and GLS.
    - SD of Time to peak Longitudinal strain- index of mechanical dispersion

AIMS AND OBJECTIVES:

- To compare the efficacy of LOT-CRT with conventional biventricular pacing in improvement of LV function in patients with HFrEF
- To assess the change in mechanical ventricular dyssynchrony as assessed by echocardiography after LOT-CRT and Biventricular CRT.
- To compare the clinical outcomes in patients undergoing LOT-CRT and BiV CRT

STATISTICAL ANALYSIS:

- Data were entered in MS-Excel and analyzed in SPSS V25.
- Descriptive statistics were represented with percentages for qualitative data, Mean with SD or Median with IQR for quantitative data.
- The Shapiro wilk test was applied to find normality.
- Chi-square test, Fisher Exact test were applied for comparison of proportions.
- Mann-whitney U test was applied for comparison between medians
- Wilcoxon test was calculated to compare paired samples. $P<0.05$ was considered as statistically significant.

RESULTS

A total of 40 patients were studied, of which 35% were in the age group of 50-60 years, with a mean age of 56 years. This was similar across both the groups: i.e Patients who underwent LOT-CRT and patients who underwent BiV CRT.

45% of patients in the LOT-CRT group were males, while 80% of patients In the BiV CRT group were males.

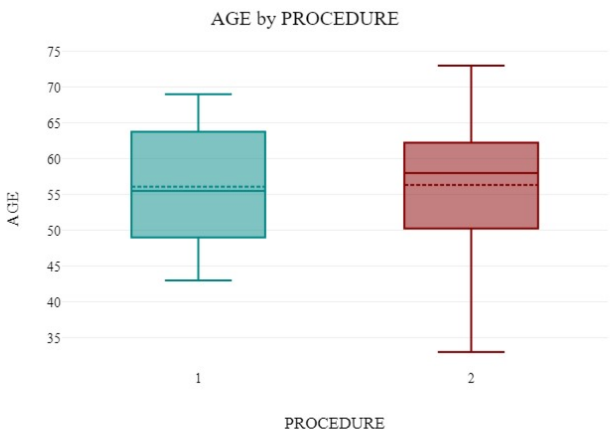


Figure 15. A box plot showing the age distribution of patients. 1- BiV CRT 2. LOT-CRT

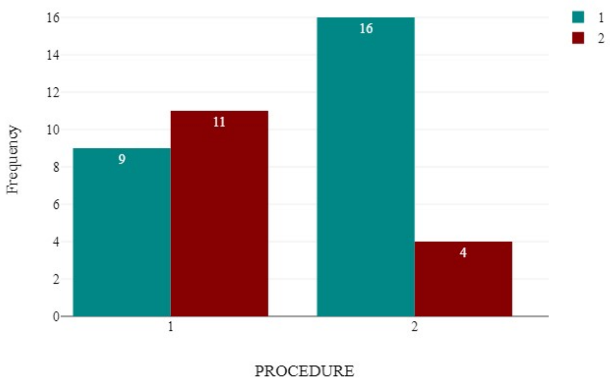


Figure 16. Bar Diagram showing the gender distribution. Geen= female and red= male, 1- BiV CRT and 2- LOT CRT

All of the patients had severe LV dysfunction with ejection fraction of </= 35% at baseline, and LBBB with QRSd > 120 ms at baseline.

SYMPTOMATOLOGY

SYMPTOMS	LOT-CRT		Biventricular CRT	
	Count	%	Count	%
exertional dyspnoea	18	90%	19	95%
recurrent heart failure	6	30%	8	40%
fatigue	5	25%	1	5%
syncope	0	0%	2	10%
paroxysmal nocturnal dyspnoea	2	10%	2	10%
palpitation	0	0%	1	5%

Table 2. The symptomatology of patients enrolled for the study.

Most patients had symptoms of exertional dyspnoea and fatigue. 40% of patients also had prior history of heart failure admissions, with symptoms of recurrent heart failure.

All of these patients were stabilised prior to being enrolled in the study. Guideline directed medical therapy for heart failure was initiated and optimised in all patients prior to the procedure.

6 patients enrolled had history of recurrent heart failure, and 4 among those were admitted with the index event of decompensated heart failure, who were stabilised with in hospital diuretics and supportive management prior to the procedure. The medications were prescribed as follows

MEDICATION	LOT-CRT	BIVENTRICULAR CRT
BETA BLOCKERS	19(95%)	19(95%)
SGLT2 INHIBITORS	15(75%)	16(80%)
ACEI/ARNI	17(85%)	16(80%)
ALDOSTERONE ANTAGONIST	14(70%)	15(75%)

Table 3. Preprocedure heart failure medication use in patients enrolled.

BASELINE CHARACTERISTICS

DEMOGRAPHICS

PARAMETER	LOT-CRT n=20	BiV CRT n=20	P VALUE
AGE IN YEARS	56	56	0.28
MALE	9	16	0.048
ATRIAL FIBRILLATION	2	1	
INTRINSIC QRS DURATION(msec)	165.1	165.85	0.83
LVEF(%)	30.45	29.65	0.52
NYHA FUNCTIONAL CLASS			0.16
II	13	08	
III	07	10	
IV	00	02	
NT PRO-BNP(pg/Ml)	3213	3589	0.14
Mean duration of follow up(days)	176.85	163.85	0.512

Table 4. Baseline demographic parameters of patients enrolled for the study.

Baseline parameters were comparable across patients enrolled in both groups. The mean QRS duration was comparable in both groups, and no statistically significant baseline differences noted.

Echo parameters were also analysed at baseline

VARIABLE	LOT-CRT			BiVCRT			
	MEAN	SD	IQR	MEAN	SD	IQR	P-VALUE
LVIDD(mm)	58.65	5.50	7.50	63.25	10.19	13.00	0.142
LVIDS(mm)	47.15	5.19	6.75	50.80	9.79	12.75	0.365
EF(%)	30.45	5.36	6.75	29.65	5.14	8.50	0.529
LVEDV(ml)	153.90	17.28	24.50	165.85	21.51	24.00	0.109
LVESV(ml)	113.85	12.90	18.00	120.65	17.75	30	0.003

Table 5. Baseline echocardiographic parameters of patients enrolled for the study.

The baseline echo parameters were also comparable across both groups with no statistically significant differences noted.

Strain parameters:

PARAMETERS	LOT-CRT	BiVCRT
SEPTAL TO PW DELAY(ms)	199.85+-17.48	189.45+/-32.35
AP4C PEAK STRAIN(%) MEAN	-11.57	-10.86
AP3C PEAK STRAIN(%) MEAN	-11.97	-11.11
AP2C PEAK STRAIN(%) MEAN	-11.77	-12.155
GLS(%) MEAN	-11.64	-11.01
LV GLOBAL ENDO. PEAK L. TIME SD(ms)	87+/- 6.75	83.40+/-10.67

Table 6. Baseline strain echocardiography and dyssynchrony parameters

The Calculated baseline parameters of dyssynchrony and strain were also comparable.

The Mean septal to posterior wall delay as assessed by M-Mode and tissue doppler imaging in parasternal ling axis images were 199.85 ms in patients assigned to LOT-CRT and 189.45

in patients assigned to Biventricular CRT. The strain parameters in Apical 4 chamber, 3 chamber and 2 chamber views were comparable, and reduced overall. The mean Global Longitudinal strain(GLS) was -11.64% in the LOT-CRT arm and -11.01% in the Biventricular CRT arm, which was statistically comparable.

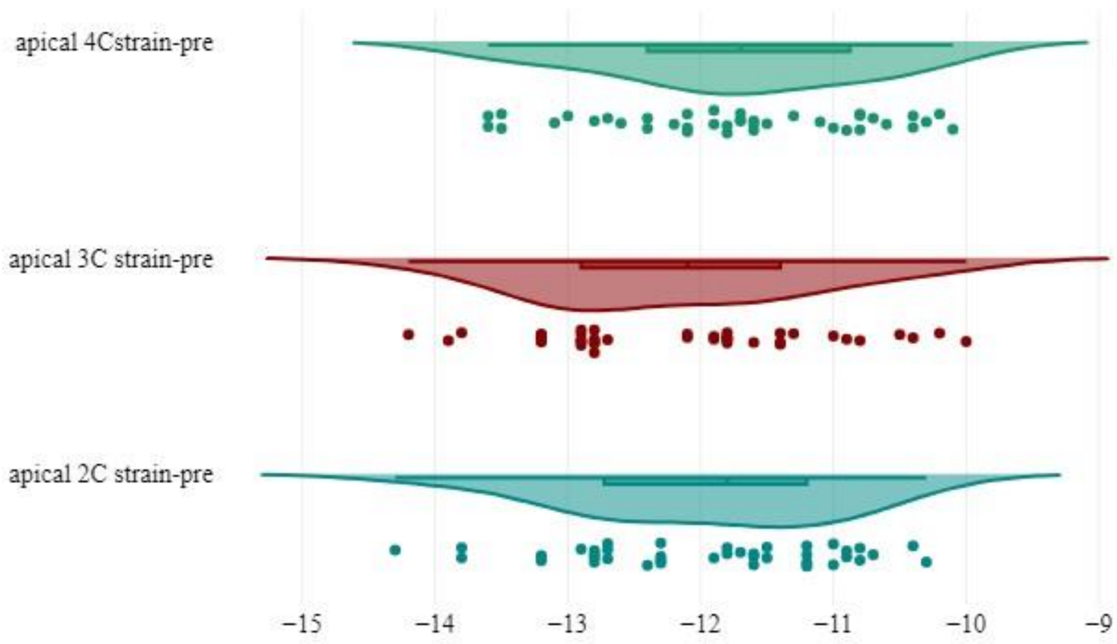


Figure 17. Scatter drop chart showing the distribution of Longitudinal strain.

These patients then underwent the procedure and were followed up as per institute protocols.

Post procedure clinical outcomes:

PARAMETER	LOT-CRT n=20	BiV CRT n=20	P VALUE
INTRINSIC QRS DURATION(msec)	117.53	134.28	0.001
LVEF(%)	43.55	41.55	0.134
NYHA FUNCTIONAL CLASS			0.16
I	06	05	
II	14	15	
NT PRO-BNP(pg/Ml)	1034.45	1017.25	0.529

Table 7. Post procedure clinical parameters and Pro-BNP

POST PROCEDURE ECHO PARAMETERS

VARIABLE	LOT-CRT		BiVCRT		
	MEAN	SD	MEAN	SD	P-VALUE
EF(%)	43.55	2.44	41.55	4.71	0.134
LVEDV(ml)	112.8	15.50	128.7	18.30	**0.003**
LVESV(ml)	66.70	10.76	84.70	19.68	**<0.001**

Table 8. Post procedure echocardiography parameters

Strain parameters

PARAMETERS	LOT-CRT	BiVCRT	P VALUE
SEPTAL TO PW DELAY(ms)	83.65+/-7.03	94.85+/-19.43	**0.046**
AP4C PEAK STRAIN(%) MEAN	-13.89	-13.15	0.16
AP3C PEAK STRAIN(%) MEAN	-12.76	-12.79	**0.04**
AP2C PEAK STRAIN(%) MEAN	-13.39	-12.87	0.20
GLS(%) MEAN	-13.43	-12.98	0.09
LV GLOBAL ENDO. PEAK L. TIME SD(ms)	60.20+/-4.75	64.7+/-9.39	**0.007**

Table 9. Post procedure strain and dyssynchrony parameters.

	PROCEDURE		P-value
	LOT-CRT	Biventricular CRT	
	Mean	Mean	
GLS Pre	11.61	11.01	0.12
GLS Post	13.43	12.98	0.09
P-value	<0.001	<0.001	

Table 10. Post procedure values of Global Longitudinal Strain.

Variable	**LBB**				**Biventricular**				**P-value**
	Mean	SD	Median	IQR	Mean	SD	Median	IQR	
SEPTAL TO PW DELAY Pre	199.85	17.48	207.00	23.00	189.45	32.35	182.00	31.50	0.046
SEPTAL TO PW DELAY-Post	83.65	7.03	82.50	9.50	94.85	19.43	88.00	26.00	0.086
Difference (Post-Pre)	-116.20	21.67	-124.50	31.50	-94.60	40.73	-85.00	50.00	**0.01**
P-value	<0.001				<0.001				

Table 11. A comparison of the pre and post values of Septal to Posterior wall delay, and the quantified improvement post procedure

Post procedure, both modalities of treatment showed improved clinical parameters. 5 patients in the biventricular arm and 4 patients in the LOT-CRT arm were completely asymptomatic (NYHA Functional class I) at the end of the follow up period.

Pro BNP showed a significant reduction post procedure, although the difference between the 2 groups was not statistically significant.

Echocardiographic parameters showed that the ejection fraction significantly improved in both arms, although the difference between the two groups was not statistically significant.

The dyssynchrony parameters and parameters of strain imaging were analysed.

The septal to posterior wall delay in patients who underwent LOT-CRT improved to a mean of 83.65 ms, , while those who underwent Biventricular CRT had a mean septal to posterior wall delay of 94.85 msec. The improvement in the septal to posterior wall delay from the baseline was also analysed, which showed a better improvement in patients who underwent LOT-CRT, and this difference was statistically significant.

The Global Longitudinal strain compared between the 2 groups was not statistically significant, however, the eman values showed better improvement in GLS in patients who underwent LOT CRT.

The Standard deviation of time to peak longitudinal strain, was 60.20 in the LOT-CRT groul and 64.27 in the Biventricular CRT group, and difference across the groups was statistically significant.

Overall, most parameters including ejection fraction, and the Strain parameters including Global longitudinal strain, were comparable across both the groups at the end of the follow up period, with patients who underwent LOT CRT having better improvement in GLS and Reduction in The standard deviation of time to peak Global strain.

Among the Biventricular CRT group, two patients had less that 15% reduction in LVEDV and The ejection fraction remained less than 40%. These patients were deemed non-responders, and evaluation showed that both of these patients had Dilated cardiomyopathy secondary to Sarcoidosis as confirmed by PET imaging, and subsequently were initiated on Antiinflammatory therapy.

The Left bundle lead parameters in patients who underwent LOT CRT were also assessed at the end of the follow up period, and all patients had stable parameters and stable lead thresholds.

Lead impedance declined significantly after the acute phase and remained stable throughout the whole observation period in all patients

Phrenic nerve stimulation (PNS) was documented in two patients in the BiV-CRT group and was ameliorated by downgrading the outputs

DISCUSSION

Our study is one of the few studies done to compare the efficacy of LOT-CRT versus conventional biventricular pacing in patients with heart failure with reduced ejection fraction, and one of the first from the Indian Subcontinent to study the outcomes on follow up in these patients.

Most available studies compare the clinical and electrocardiographic parameters, ours is the first dtudy to compare the echocardiographic parameters, particularly strain imaging parameters in these patients, to demonstrate the mechanical effects of LOT-CRT versus biventricular pacing in these patients.

In our study, we have included only patients with non ischemic cardiomyopathy. This ensures better homgenisation of the study population across both the groups, and eliminated other factors including the presence of ischemic scar and non viable myocardial regions to be a biasing factor.

The mean ages across both the groups was fairly similar, and this correlayed well with most studies in this population for BiV CRT.

The preponderance of female patients in the biventricular CRT arm as compared to the LOT-CRT arm- may be due to Patient related factors- i.e ventricular dimensions and septal thickness, whick may have precluded the implantation of the left bundle lead.

All of the patients Had LBBB with wide QRS complexes. Other abnormalities like RBBB were excluded from the study- to allow better homogenization of the study population. The QRS duration in our study was a mean of 165, which compares with other Studies by Jastrebski et al. (182+/-25).

The LBBA lead was placed instead of the RV lead in the LOT-CRT group to obtain greater electrical synchrony due to

(1) direct depolarization of the LV conduction system

(2) bypass the slow cell-to-cell conduction from the right to the left side of the interventricular septum

This was assessed by the change in QRS duration following the procedure, which was found to be 42.25 ms(42.1 in BiV CRT and 45.75 in LOT-CRT group). Prior studies mention the degree of narrowing post Procedure of QRS complex by 27.3 ms, across most studies. A higher degree of improvement may be seen in this study due to the exclusion of patients with ischemic and scarred myocardial segments. The Degree of QRS narrowing is comparable across both groups.

In a study by Sweeney et al,22 QRS narrowing of 25 ms was associated with both response and super-response to CRT. This QRS narrowing can be appreciated immediately following the procedure, and is usually taken as a surrogate for the efficacy of CRT and to predict the long term improvement in clinical parameters. On comparison of echocardiographic parameters, we found that there was a trend towards better outcome at 6 months favouring the LOT-CRT study group.

The clinical response and improvement in NYHA class was seen In 90% of our patients across both the groups, with 95% of patients undergoing LOT-CRT and 90% of patients who underwent BiV CRT at 6 months. This was comparable to prior studies, which showed A clinical response of 87%, in patients undergoing LOT CRT, as per the LBBAP collaborative Study group.

LVEF increased by ~9% in the above mentioned Study by International LBBAP group, as compared to 12.75% in our study group(13.35% in LOT CRT group versus 12.15% in BiV

CRT group). This showed a trend towards better outcomes at same level of QRS duration reduction in the LOT-CRT group, suggesting an additional beneficial effect on cardiac remodelling that occurs during the period after the procedure, where direct conduction system pacing was more beneficial. This is also reflected in the study group with a higher number of responders and super responders in the LOT-CRT group.

Cardiac remodelling following CRT has been previously studied. the assessment of left ventricular remodeling after CRT is determined with the reduction of LVESV ≥ 15% or the increase in the absolute value of LVEF ≥ 5% at 6-12 months. It is well established that the LV remodeling induced by CRT has been related to the improvement of the quality of life, functional class, reduction of mortality, and HF hospitalizations.

Studies documenting the effect of negative cardiac remodelling in patients with Biventricular CRT have shown benefit at 6-12 months post procedure.

However, there are no large trials demonstrating the long term benefits and reverse remodelling following LOT-CRT.

Our study has shown comparable Longitudinal strain parameters at 6 month follow up in patients with BiV CRT and LOT-CRT, with a trend towards better improvement in GLS in LOT CRT. The Standard deviation od time to peak strain reduced significantly in patients with LOT CRT compared to BiV CRT, however, the clinical significance of this and the value of the parameter to predict response to CRT needs to be evaluated in larger studies.

The percentage of non responders in our study was low(2 patients), as compared to other studies(17% in LBBAP Collaborative study). This may again m\be attributed to patient selection and the exclusion of ischemic Cardiomyopathy. The number of non responders In our study was too small to make any statistical conclusions regarding the predictors of response/ improvement following procedure.

Both the patients who did not respond in our study, were diagnosed with cardiac sarcoidosis and this could imply that the myocardial involvement in sarcoidosis has a bearing on the outcomes. Underlying myocardial dysfunction, and Intraventricular conduction disturbances or distal conduction system disease may not be addressed by CRT. The effects and significance of the above needs to be studied in larger patient groups.

Overall findings suggest comparable outcomes of conventional Biventricular CRT and LOT CRT. This technique of physiological / conduction system pacing also shows a trend towards better clinical outcomes and echocardiographic parameters including global longitudinal strain at the end of the follow up period of ~ 6 months.

The findings are promising, and in this select subset of patients with non ishchemic dilated cardiomyopathy with severe LV dysfunction and LBBB, the use of LOT-CRT is beneficial and should be offered, with the benefit of more physiological pacing, and stable lead parameters on follow up.

Further studies, and long term studies are required to explore the potential long term benefits on mechanical synchrony and reverse cardiac remodelling over a longer follow up period.

The benefits of this technique of LOT-CRT in a wider patient population of patients with conventional CRT indications also warrant further study, in terms of procedural success and long term outcomes.

CLINICAL IMPLICATIONS:

In patients eligible for CRT, empirical CRT based on BiV pacing without regard to the mechanism underlying electrical dyssynchrony may not fully achieve optimal clinical outcomes.

LOT-CRT may provide an alternate, individualized, more tailored approach to CRT in patients with advanced peripheral conduction disease. This approach needs to be further studied in a randomized fashion.

Further, newer research interest in this also focuses on the use of isolated Left bundle pacing without the placement of LV lead, which has also proven to have comparable immediate and long term effects, as compared by the study by LBBAP international Collaborative group.

This aspect also requires further randomization and long term studies

RESULTS:

Conduction system pacing, particularly Left bundle branch area pacing Cardiac resynchronisation Therapy(LOT CRT) has comparable outcomes to conventional Biventricular CRT in patients with Non ischemic dilated cardiomyopathy and severe LV dysfunction with underlying Left budle branch block, with the potential additional advantage of achieving near physiological pacing, and a trend towards better mechanical synchrony and beneficial effect on reverse cardiac remodelling at 6 months, and may be considered in this select subset of patients.

LIMITATIONS

1. Lack of uniform criteria for the selection of patients to undergo LOT-CRT or BiV CRT, leading to potential selection and operator bias.
2. Lack of randomisation
3. A small number of patients were non responders- and the number was not enough to perform statistically relevant analysis to assess the predictors of outcome.

Thus, Further larger studies are necessary to assess the value and explore the potential benefits of this novel approach of LOT CRT.

SUMMARY AND IMPLICATIONS

1. The outcomes of LOT CRT and convention Biventricular CRT in patients with HFrEF and LBBB, are comparable with respect to the clinical and electrocardiographic parameters, with narrowing of QRS duration to about 125 ms, and a Significant improvement in NYHA Functional Class and Pro-BNP.
2. The long term effects and follow up data at 6 months show a trend towards better outcomes with LOT CRT, with respect to the improvement in LVEF and Global Longitudinal Strain.
3. The other parameters of mechanical dysynchrony including the Septal to posterior wall delay were comparable across patients who underwent LOT CRT and Biventricular CRT.
4. The index of dispersion on strain imaging i.e the standard deviation of time to peak longitudinal strain, showed a significant improvement in patients who underwent LOT CRT.
5. Although the difference in overall GLS is not statistically significant, this may imply a more favourable outcome on reverse cardiac remodelling, seen as a delayed benefit of CRT after 3-12 months.
6. LOT CRT is a safe, and effective procedure comparable to conventional biventricular CRT, and all patients had stable lead parameters and capture thresholds on follow up.
7. These findings suggest that LOT CRT may be a considered as a first choice thetapeuric intervention in this select subset of patients with HFrEF of non ischemic etiology and LBBB with QRS duration more that 150 ms, with a potentially better long term benefit and better outcomes.

CONCLUSION:

This study shows that LOT CRT has comparable clinical benefit and improvement in electrical synchrony as Biventricular CRT, and a potential benefit of better outcomes on follow up due to reverse cardiac remodelling, and may be considered as a therapeutic intervention of choice in patients with Heart failure with reduced ejection fraction and Left bundle branch block.

ANNEXURE

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pooja prasad- comparision of BiV CRT and LOT CRT

General metrics

51,007	7,738	539	30 min 57 sec	59 min 31 sec
characters	words	sentences	reading time	speaking time

Score

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Writing Issues

572	295	277
Issues left	Critical	Advanced

Plagiarism

8 %

37 sources

8% of your text matches 37 sources on the web or in archives of academic publications

ANNEXURE-B IEC APPROVAL LETTER

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया

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Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/1884/MAY/2022 15.11.2022

Dr. Pooja Prasad
Senior Resident
Department of Cardiology
SCTIMST, Thiruvananthapuram

Dear Dr. Pooja Prasad,

The Institutional Ethics Committee held on 13th May, 2022, reviewed and discussed your application to conduct the study titled "**COMPARISION OF CLINICAL AND ECHOCARDIOGRAPHIC MARKERS IN PATIENTS UNDERGOING CARDIAC RESYNCHRONIZATION THERAPY AND LEFT BUNDLE BRANCH PACING IN HEART FAILURE WITH REDUCED EJECTION FRACTION**" (IEC/1884).

The following members of the Ethics Sub-committee were present at the meeting held on 13th May, 2022.

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
2.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
3.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
4.	Dr. P. Manickam	BSMS, MSc (Epid)., PhD	Male	Health Science Expert/ Social Scientist	No
5.	Adv. Priya Kaimal	LLM, MBL	Female	Legal Expert	No
6.	Dr. Manikandan.S	MBBS,MD,PDCC	Male	Clinician	Yes
7.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

Page 1 of 2

The following documents were reviewed:

Original submission

1. *Checklist Form*
2. *Covering letter addressed to the Chairperson, IEC, SCTIMST*
3. *Declaration Form*
4. *IEC Application Form*
5. *Thesis Protocol*
6. *CV of PI and Co-PIs*
7. *Data Collection Form*
8. *Patient Information Sheet and Consent Form in English and Malayalam*
9. List of abbreviations
10. SRC Recommendation Letter

Revised submission

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST*
2. *Checklist Form*
3. *Covering letter addressed to the Chairperson, IEC, SCTIMST*
4. *Declaration Form*
5. *IEC Application Form*
6. *Thesis Protocol*
7. *List of abbreviations*
8. *CV of PI and Co-PIs*
9. *Patient Information Sheet and Consent Form in English and Malayalam*
10. *Data Collection Form*

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Dr. G. Srinivas
Member Secretary, IEC

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
INSTITUTIONAL ETHICS COMMITTEE (IEC) SCTIMST THIRUVANANTHAPURAM

Page 2 of 2

ANNEXURE C – PATIENT INFORMATION

Patient Information Sheet TITLE OF THE STUDY: COMPARISION OF CLINICAL AND ECHOCARDIOGRAPHIC MARKERS IN PATIENTS UNDERGOING CRT AND LEFT BUNDLE BRANCH PACING IN HEART FAILURE WITH REDUCED EJECTION FRACTION You are being requested to participate in this study where we will assess the symptoms before and after the different pacemaker procedures for heart failure. 2d echocardiography will also be performed before and after the procedure. Your participation in this study would contribute immensely to improving future care of patients with heart failure.we will be able to compare the outcomes of the different types of procedures, which will help us tailor the therapy for patients in future If you take part what will you have to do? The study will require your consent after clarifying all related queries.All treatment that you have and will be receiving shall be as per routine protocols of the institution and it will not be changed during this study. The participation in the study is purely voluntary and there will be no difference in your treatment or follow up if you decide not to cooperate for the study. Will you have to pay for the investigations? No additional investigations will be needed apart from routine protocols. What happens if you are detected to have any fresh problems during the study? No additional risks are anticipated due to the study Will your personal details be kept confidential? The results of this study may be published in a medical journal for advancement of medical sciences and surgical standards of care.You will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission. If you have any further questions, please ask Dr.Pooja Prasad(Tel 9945713382,pooja90prasad@gmail.com) For any clarifications regarding the study's ethics clearance you may contact the Member Secretary of the SCTIMST-IEC. The phone number is: 234(O) 0471-2524234 and the email id is iec.mem.sec@sctimst.ac.in

CONSENT FORM

Title of the study: COMPARISION OF CLINICAL AND ECHOCARDIOGRAPHIC MARKERS IN PATIENTS UNDERGOING CARDIAC RESYNCHRONIZATION THERAPY AND LEFT BUNDLE BRANCH PACING IN HEART FAILURE WITH REDUCED EJECTION FRACTION

Participant's name: Age (in years): I_________________________, son/ daughter/husband/wife/ —————————————————of ____ declare that (Please tick boxes)

• I have read the above information provided to me regarding the study:[ ]

• I have clarified any doubts that I had. [ ]

• I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]

• I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the study. I agree to this access [ ]

• I understand that my identity will not be revealed in any information released to third parties or published [ ]

• I voluntarily agree to take part in this study [ ]

• I have been provided with the contact numbers of the principle investigator, in case I want to know more about the study and participants rights [ ].

• I received a copy of this signed consent form [ ]

Name:

Signature:

Name of witness:

Date:

Signature:

Relation to participant:

Obtaining Consent: I attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

Name :

Signature :

Date :

Place : SCTIMST, Thiruvananthapuram

ANNEXURE-D – Curriculum Vitae

POOJA PRASAD

Prasad	Pooja	
Last Name	First Name	Middle Name
Date of Birth (dd/mm/yy) 25/09/90		Sex Female
Study Site Affiliation (e.g. Principal Investigator, Co-Investigator, Coordinator): Principal Investigator		
Professional Mailing Address (Include Institution name)	Study Site Address (Include Institution name)	
pooja90prasad@gmail.com	Senior Resident, Department of Cardiology, SCTIMST	
Telephone (Office):	Mobile Number:9945713382	
Telephone (Residence):	Email pooja90prasad@gmail.com	

Academic Qualifications (Most recent qualification first)

Degree/Certificate	Year	Institution, Country
MD internal Medicine	2018	RGUHS, India
MBBS	2014	RGUHS, India

Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration Karnataka State Council registration; 104325

Current and previous positions (most recent position first)

Month and Year	Title	Institution/Company, Country
2020 march-dec	Registrar, Cardiology	KIMS, TVM
February 2019- Feb 2020	Senior Resident, Department of Medicine	Bowring Hospital, Bangalore
July 2019- Feb2020	Senior Resident, Department of Medicine	Vydehi Institute of Medical Sciences, blr

Brief summary of relevant research experience:
Dessertation undertaken as a part of postgraduate course, titled "Comparision Of Accuracy Of Light's Criteria, Adenosine Deaminase And Pseudocholinesterase Levels In The Etiological Diagnosis Of Pleural Effusion".

Current project/s at hand:

Signature: Pooja. Prasad.	Date: 08.01 .2022 Place: TVM