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'Optimized' LV only pacing using a dual chamber pacemaker as a cost effective alternative to CRT

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A B S T R A C T

Background: Cardiac Resynchronization therapy (CRT) remains largely under-used in developing countries owing to the high cost of therapy. In this pilot study, we explore 'optimized' Left Ventricle Only Pacing (LVOP) as a cost effective alternative to cardiac resynchronization therapy in selected patients with heart failure.
Hypothesis: In economically poorer patients with heart failure, left bundle branch block (LBBB) and intact AV node conduction, synchronization can be obtained using a dual chamber pacemaker (leads in right atrium and Left ventricle) with the help of 2D strain imaging.
Methods and results: 4 patients underwent LVOP for symptomatic heart failure. Post procedure 'optimization' was done using 12 lead electrocardiography and 2D- Strain imaging. Difference between Time to Peak longitudinal strain and Aortic valve Closure (**Diff $T_{PL\text{-}AC}$**) was calculated for each segment at different AV delays and the AV delay with the smallest **Diff $T_{PL\text{-}AC}$** was programmed. The mean AV delay that resulted in electrical and mechanical synchrony was 150 ms. After a mean follow up of 6 months, all patients had improved by at least 1 NYHA class. The mean reduction in QRS duration post procedure was −54.5 ± 22.82 ms and the mean improvement in EF was 7 ± 2.75%.
Conclusion: Optimized LVOP using 2D strain and ECG can be a cost-effective alternative to CRT in patients with LBBB, heart failure and normal AV node conduction.

1. Introduction

Cardiac Resynchronization Therapy (CRT) is a class I recommendation for patients with Heart failure, left bundle branch block (LBBB) and wide QRS [1–3]. While the benefits of synchronized left ventricular pacing in this group of patients remains unquestioned, the cost of therapy still remains a concern, especially in developing countries with poor coverage of health insurance among its citizens. In this pilot study we explore the possibility of Left ventricle only pacing (LVOP) using a dual chamber pacemaker as a cost effective alternative in patients who were not implanted a CRT citing financial constraints. We also describe a new strategy to optimize 'synchrony' in these patients and report the short term effectiveness of this strategy.

1.1. Hypothesis

In economically poorer patients with LBBB and heart failure, synchronization can be obtained by using a dual chamber pacemaker with leads placed in the RA and LV. 12 lead electrocardiogram (ECG) and 2-Dimensional Strain imaging can be used to optimize electrical and mechanical synchronization of left ventricle.

2. Methods

The study was conducted at Kasturba Medical College Hospital, Mangalore, which is a tertiary cardiac referral center in Southern India. Symptomatic patients with heart failure, LBBB and wide QRS

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who were not implanted a CRT for financial reasons were enrolled between June 2015 and June 2016. The study was approved by the institute's ethics committee and written informed consent was obtained from all patients.

2.1. Inclusion criteria

Patients with dilated Cardiomyopathy, NYHA class III-IV, LBBB and QRS >150 ms who were not willing for CRT (citing financial reasons) were included in the study. All patients required to have good AV Nodal conduction as evidenced by a normal PR interval and 1:1 AV conduction at rates >120/min on a 24-hr Holter.

2.2. Exclusion criteria

1. Patient's willingness for a CRT.
2. Renal dysfunction (serum Creatinine >1.5 mg/l).
3. First degree or any higher grade of AV block.
4. Patients with atrial fibrillation.
5. Patients with an indication for ICD for secondary prevention.

2.3. Implantation

All patients underwent routine blood investigations, standard 12 lead electrocardiogram (ECG) and a detailed 2-D echocardiogram prior to implantation. Right atrial (RA) and Left ventricular (LV) leads were implanted using standard technique described for conventional CRT implantation. After securing both leads, a suitable Pulse generator (VDD, DDD or DDDR) was used to complete the procedure. In patients with good sinus rates (as assessed by a pre-procedure Holter recording) only VDD pacemaker was used while in others a DDD or DDDR was used.

2.4. Programming

2.4.1. Targeting electrical synchrony

After implantation all patients underwent detailed programming to define the best AV delay that resulted in the narrowest QRS. For this, serial ECGs were recorded at 25 mm/s speed and 10 mm/mV calibration at different AV delays, starting at a sensed AV (SAV) delay of 180 ms (or paced AV delay (PAV) of 210 ms, in case of sinus node dysfunction), with serial decrement of 20 msec, up to SAV of 80 msec (or PAV of 110 msec). The AV delay that resulted in 'fused' QRS complexes with pre-excitation of the LV was programmed (Fig. 1). Fused QRS- was defined as the complex in which the initial deflection was preserved (as in intrinsic rhythm) but timed LV activation resulted in a narrower QRS duration.

2.5. SAV-sensed AV delay

2.5.1. 2-Dimensional strain imaging

All patients were subjected to strain imaging prior to discharge. Grey scale images at frame rate 55–90 frames per second from three standard apical views (4 chamber, 2 chamber and 3 chamber) were acquired on Vivid 9 using a 3.5-MHz ultrasound probe (GE-Vingmed Ultrasound, Horten, Norway). Off-line analysis of strain and speckle tracking was performed using EchoPac PC version BT09 (GE Vingmed Ultrasound, Horten, Norway).

The following parameters of interest were evaluated:

1. Aortic valve closure time ($\mathbf{T}_{AC}$).
2. **Time to peak longitudinal strain** ($\mathbf{T}_{PL}$)- T_{PL} was calculated for each segment and a bulls eye chart representing the same was recorded.
3. **Time to peak longitudinal Strain- Time to Aortic Valve closure** (**Diff** $\mathbf{T}_{PL\text{-}AC}$)- was calculated for each segment by referencing the $\mathbf{T}_{PL}$ for each segment to the aortic valve closure time. A Bulls eye chart representing the same was created.

Strain imaging was recorded at different AV delays (SAV-180 to 80 ms or PAV 210 to 110 ms) (for patients with sinus node dysfunction) and the $\mathbf{T}_{PL}$ and **Diff** $\mathbf{T}_{PL\text{-}AC}$ at each AV delay was analyzed for the basal and mid segments. The AV delay with the smallest **Diff** $\mathbf{T}_{PL\text{-}AC}$ was considered best indicator of '**Mechanical Synchrony**' (Fig. 2).

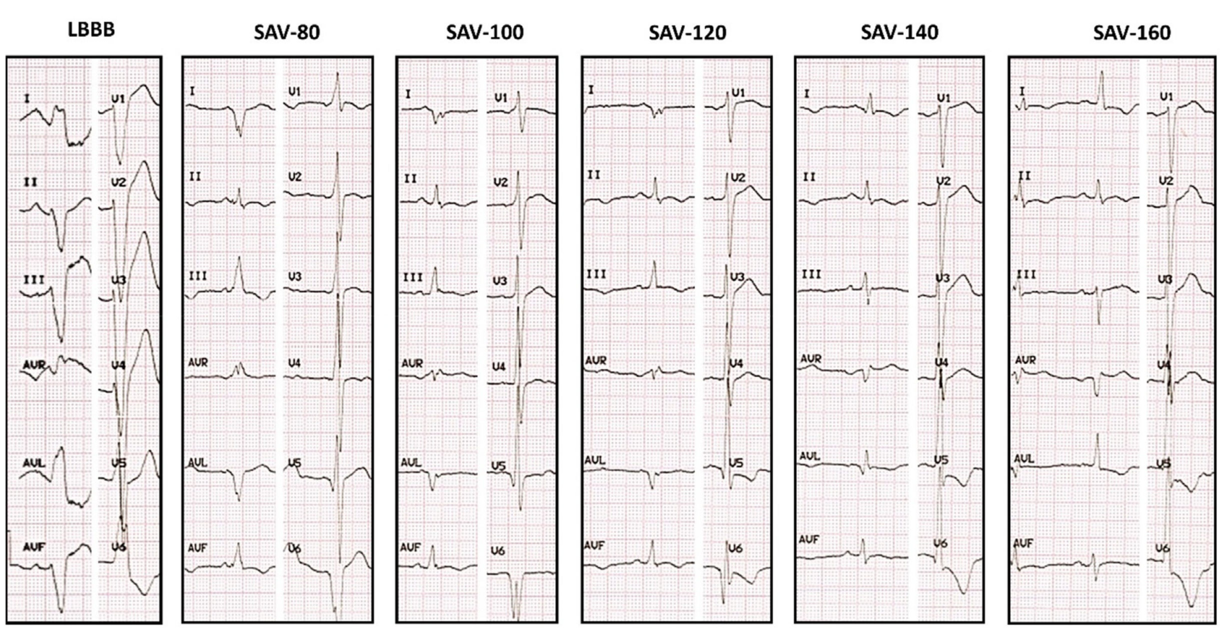


Fig. 1. Electrical fusion: Predominant LV pacing (q in I and AVL and R in V1) is evident at SAV of 80–120 ms with Fusion-QRS complexes noted at longer SAVs (140 and 160 ms). SAV of 140 ms results in the narrowest QRS.

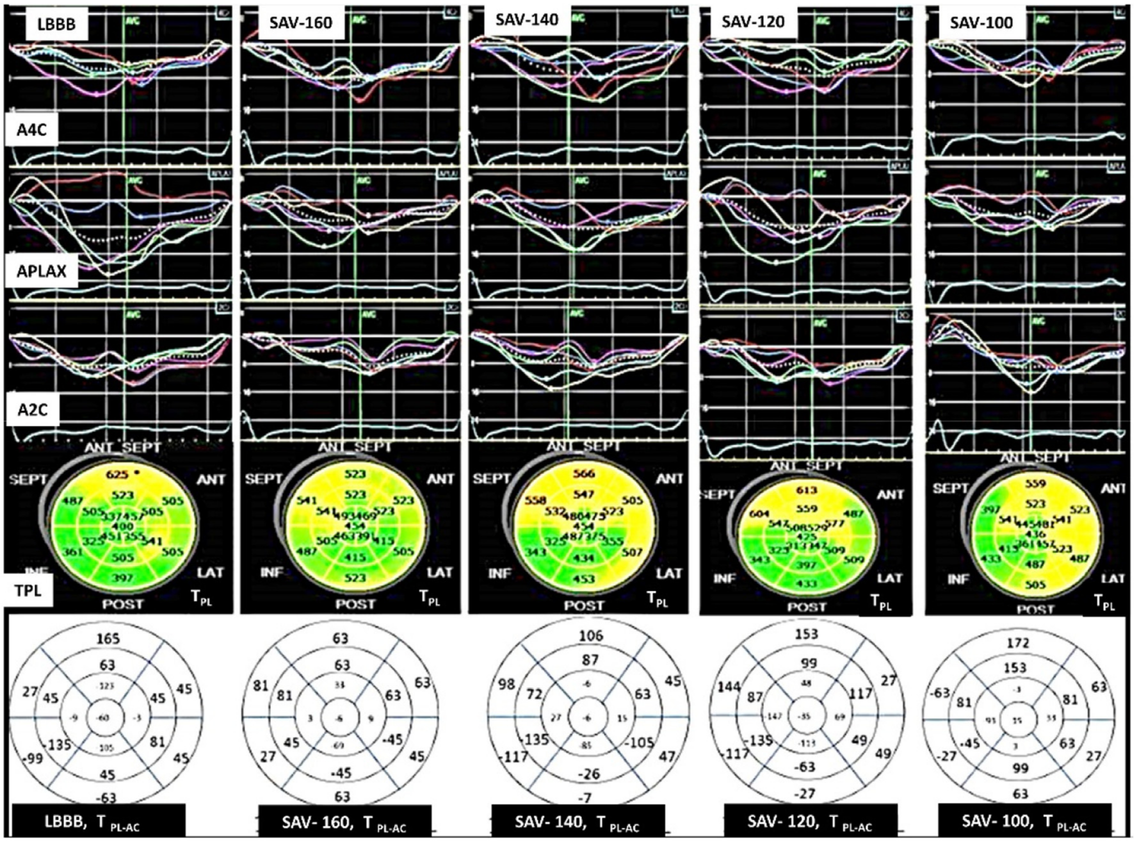


Fig. 2. Mechanical Fusion.
The vertical columns represent mechanical fusion at baseline (LBBB) and at different AV delays. The first three rows represent 2D strain images in A4C, APLAX and A2C views at different AV delays. The fourth row represents TPL and the fifth row represents T_{PL-AC} at these delays. The most homogenous contraction is seen to occur at SAV of 160 ms (The least **Diff** $\mathbf{T}_{PL-AC}$ between basal and mid segments).
A4C- Apical 4 Chamber, APLAX- Apical Parasternal long axis, A2C- Apical 2 Chamber.

The AV delay that resulted in the best electrical synchrony and the best mechanical synchrony was determined for each patient and in case of a difference, the AV delay that resulted in the best mechanical synchrony was programmed.

2.6. Follow up

Post discharge patients were followed up at 1 week, 1 month and then at 3 month intervals. A detailed 2D echo was performed at each visit and any change in functional class or any complication or hospitalization was noted.

3. Results

A total of 4 patients were enrolled in the study. The baseline characteristics of the patients along with pacemaker implant data is presented in Table 1. All patients underwent successful implantation without any peri-procedural complications. Table 2 represents the Programming data in the 4 patients. The mean SAV that resulted in electrical synchrony was 150 ms (range: 140–160 ms). Best mechanical synchrony was also obtained in the same range of SAV (140–160 ms). The short term outcome data of the 4 patients is presented in Table 3 and Fig. 3. The mean duration of follow up was 6 months. All patients improved by at least 1 NYHA class and the average improvement in EF was 7%.One patient had a narrower intrinsic QRS within 8 m of LVOP (Fig. 4).

Table 1
Clinical characteristics.

Mean Age (yrs)	62.3 (Range:54–68)
Sex	
Male	2 (50%)
Female	2 (50%)
NYHA class	
NYHA III	3 (75%)
NYHA III/IV	1 (25%)
Mean QRS duration (ms)	172.5 ± 13
EF (%)	26.75 ± 2.21
Implant Data	
Pulse Generator	
VDD	3 (75%)
DDD	1 (25%)
LV threshold (mV)	0.9 ± 0.3
Atrial threshold (mV)	0.5 ± 0.2
P waves (mV)	2.5 ± 0.5
R waves (mV)	11 ± 3

4. Discussion

Although several hemodynamics and short term outcomes studies have proven non-inferiority of LV only pacing (vs BiV pacing) [4–8], it's clinical implications are limited, owing to the widespread acceptance of BiV pacing world-over. The economic situation in developing nations provides a unique opportunity to explore the clinical impact of LV only pacing. For example, As India has an average per capita GDP of 1581$ (2015 World Bank statistics)

Table 2
Electrical and Mechanical Synchronization data.

	Patient 1	Patient 2	Patient 3	Patient 4
QRS duration (pre LVOP)	174	166	190	160
QRS duration (post LVOP)	100	126	116	130
QRS shortening post LVOP	74	40	64	30
SAV resulting in electrical Synchrony	140	160	140	160
SAV resulting in mechanical synchrony	140	140	160	160

All the values are in milliseconds (ms).
LVOP- LV only pacing, SAV-sensed AV delay.

[9] and the minimum cost of CRT-D in the country would be upwards of 10000 $, making CRT-D an unrealistic option to the greater majority of heart failure patients who would otherwise benefit from therapy. In this study we have shown that optimized LV only pacing enables good electrical and mechanical synchrony and improves short term outcomes in select patients with heart failure and LBBB. While the benefits of resynchronization are preserved, the cost of therapy is under $ 3000, making it an affordable and useful option for patients with LBBB and heart failure.

Several single center studies, randomized trials and one meta-analysis have conclusively proven that LV only stimulation is non-inferior to BiV stimulation in terms of acute hemodynamic response, clinical and echocardiographic improvement in patients with heart failure and LBBB [4–8,10–14]. This has led the European Society Cardiology 2013 guidelines to suggest that LV only pacing could be considered as low cost strategy in patients with heart failure and LBBB which could also increase the longevity of the device [3].

4.1. Optimizing LV only pacing

Programing the right AV delay is crucial for optimizing benefit from LV only Pacing. In comparison to prior studies on LV only pacing our study significantly differs in terms of the techniques used to optimize LV pacing. Most studies on LV only pacing have used either the mitral inflow E and A patterns or have used a short AV delay (similar to BiV pacing) to optimize AV synchrony [4,14]. We ensured electrical synchrony by targeting a 'fused' QRS complex that was partially depolarized intrinsically and partially through timed LV pacing. We also used Strain imaging to ensure that most segments contracted in sync and that their peak contractions occurred around the closure of aortic valve (mechanical synchrony).

Auricchio et al. in a small but elegant study that used non-contact mapping in patients with heart failure and LBBB suggested that Left bundle (and hence septal) activation may be preserved in some patients with LBBB. The authors proposed that a zone of slow electrical conduction within the left ventricle could be responsible for the conduction delay [15]. In another study Varma et al. reported similar RV activation times between normal individuals and those with heart failure and LBBB [16]. These, and several other reports suggest that RV activation and sometimes septal activation may be preserved in patients with heart failure and LBBB, questioning the need for RV pacing in these patients, especially since the deleterious effects of RV pacing are well established [16–20]. It has been proposed that optimal LV pacing occurs when a timed LV depolarization 'fuses' with the native intrinsic depolarization occurring via the intact AV node. This concept of 'fused wave-front', although hypothesized, and also hemodynamically demonstrated in the Electrophysiology laboratory, has not be proven clinically [17,21]. In this study, we successfully attempted fusion by serially prolonging the AV delay until initial depolarization of QRS (initial q or r) occurred intrinsically through the AV node. Post implant, all 4 patients had the initial direction of ventricular depolarization similar to intrinsic rhythm (LBBB) but with a shorter QRS duration suggesting successful fusion. The average AV delay that resulted in fusion was 160 ms. Attaining fusion with LVOP using conventional CRT systems is difficult as longer AV delays cannot be programmed in CRT. Since ventricular 'Sensing' is a function of the RV lead in conventional CRT, longer AV delays would potentially inhibit CRT. Hence most prior studies have programmed short AV delays during LVOP which could explain the lack of fused complexes.

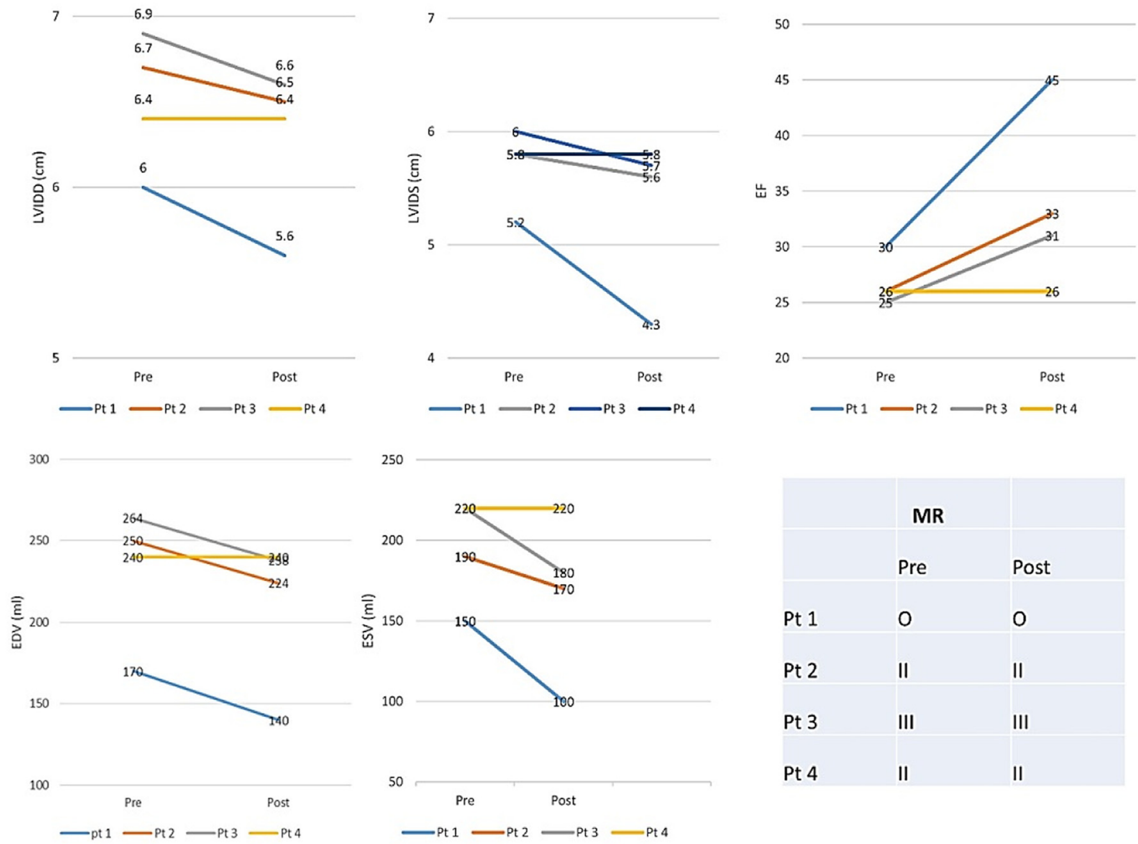
Table 3
Follow up data.

Follow up duration (months)	6 ± 2.16 (Range:3–8)
Improvement in NYHA Class	
By 1 class	3 (75%)
By 2 classes	1 (25%)
Hospitalization for recurrent heart failure	0 (0%)
Change in QRS duration (ms)	−54.5 ± 22.82
Change in Echocardiographic parameters	
LVIDD (mm)	- 0.25 ± 0.72
LVIDS (mm)	- 0.35 ± 0.81
EDV (ml)	- 31 ± 73.61
ESV (ml)	- 28 ± 68.43
EF (%)	+7 ± 2.75

EDV-End-diastolic volume, EF-Ejection fraction, ESV end-systolic volume, LVID- Left ventricular end-diastolic dimension, LVIS-Left ventricular end-systolic dimension, NYHA -New York Heart Association.

4.2. Mechanical synchrony

Electrical and mechanical synchrony do not always correlate [22,23]. Mechanical dyssynchrony as assessed by Tissue Doppler Imaging (TDI) and Strain have been proposed as useful tools for predicting response to CRT [24–28]. In patients with heart failure and LBBB Intra ventricular dyssynchrony is evidenced by the early time-to-peak contraction of the septal segments and delayed time-to-peak contraction of the lateral segments. A septo-lateral delay of >65 ms is a marker of mechanical dyssynchrony and predicts response to CRT [24]. In an attempt to ensure mechanical synchrony we evaluated a new and simple parameter: Time to peak longitudinal strain − Time to Aortic valve closure (**Time** $_{PL-AC}$). While T_{PL} represents time to peak contraction of an individual segment, **Time** $_{PL-AC}$ represents the time to peak contraction with respect to Aortic valve closure. Segments with peak contraction prior to aortic valve closure record a negative **Time** $_{PL-AC}$ while segments with peak contraction after Aortic valve closure register a positive **Time** $_{PL-AC}$ value. Evaluating the **Time** $_{PL-AC}$ for each segment at different AV delays (at 20 ms increments) enabled us to optimize mechanical synchrony. The AV interval that ensured most basal and mid segments had their peak contraction around aortic valve closure (least **Time** $_{PL-AC}$) and thereby contracted synchronously was considered most optimal AV delay.



	MR	
	Pre	Post
Pt 1	O	O
Pt 2	II	II
Pt 3	III	III
Pt 4	II	II

Fig. 3. Echocardiographic parameters before and after Optimized LV Pacing.
EDV-End-diastolic volume, EF-Ejection fraction, ESV end-systolic volume, LVID- Left ventricular end-diastolic dimension, LVIS-Left ventricular end-systolic dimension, MR- Mitral regurgitation.

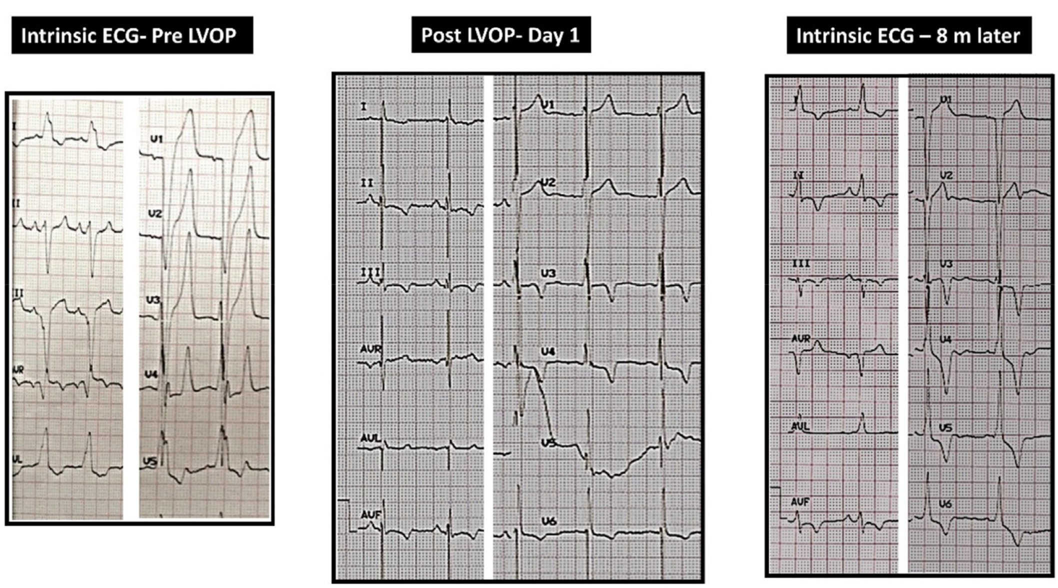


Fig. 4. Follow up.
The narrowing of the intrinsic QRS within 8 months of LVOP can be clearly noticed. LVOP- LV only pacing.

4.3. Follow up

Consistent with previous reports our study showed improvement in functional class and echocardiographic parameters with LVOP over a short follow up of 6 months. Interestingly, in one patient the intrinsic LBBB had narrowed by 40 ms within 8 months of LVOP, which is clear evidence of electrical remodeling. The follow up duration was too short to comment on mortality.

4.4. Limitations

Firstly, the obvious absence of a defibrillator lead is a major limitation in the study. Whether LVOP in the absence of defibrillation will have any effect on mortality is questionable. Future studies with larger cohort of patients and longer duration of follow up are warranted to evaluate its effect on mortality. Secondly, since most patients underwent VDD pacemaker implantation, any need for atrial pacing in the future would limit the usefulness of the device. Thirdly, the study included only heart failure patients with LBBB and intact AV conduction. Our proposed strategy of optimized LVOP is unlikely to benefit patients with impaired nodal conduction. Lastly, optimization was done at rest and hence the effect of dynamic changes in the AV nodal conduction at different heart rates on optimization remains uncertain.

5. Conclusion

Our pilot study suggests that optimized LVOP pacing (with a dual chamber pacemaker) may be used as a cost-effective alternative to CRT, for symptom improvement, in poorer patients with heart failure, LBBB and good AV conduction. Adequate electrical and mechanical Synchrony can be obtained even with a dual chamber pacemaker and LV only pacing by proper ‘optimization’ using 2D strain and ECG.

Conflict of interest

None.

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