ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Dual versus conventional cardiac resynchronization: A pilot study

Pradip Kumar Ghoshal[1], Subhraprakash Pramanik[2], Tanmoy Kanti Goswami[3], Rajarshi Mondal[4], Arunava Biswas[5], Asish Biswas[6]

[1]Associate Professor, [2]Resident, [4]Assistant Professor, Department of Cardiology, Institute of Post Graduate Medical Education and Research, Kolkata, [3,5]Associate Professor, Department of Pharmacology, Barasat Government Medical College and Hospital, Barasat, [6]Professor, Department of Pharmacology, Maharaja Jitendra Narayan Medical College and Hospital, Coochbehar, West Bengal, India

Submission: 30-04-2024 Revision: 22-05-2024 Publication: 01-07-2024

ABSTRACT

Background: Systolic heart failure treatment now includes cardiac resynchronization therapy (CRT) as a necessary element. CRT has been shown to have advantageous impacts on mortality, hospitalization rates, and quality of life. Approximately 30% of patients fail to respond to traditional CRT implantation. **Aims and Objectives:** This study aimed to compare the outcome of dual resynchronization by placing the right ventricular pacing lead at His bundle or left bundle branch area against conventional CRT. **Materials and Methods:** This longitudinal follow-up study of a total of 35 patients undergoing CRT device placement for assessment of safety, efficacy, and feasibility of the procedure and post-procedural complications and correlation with parameters obtained from electrocardiogram and echocardiography parameters in a tertiary care set up in India. **Results:** Among this matched population (mean age 64 years) there was a higher responder rate with the newer technique of dual resynchronization compared to conventional CRT (83% vs. 70%). **Conclusion:** Dual resynchronization therapy is feasible and safe and provides better electrical resynchronization compared to conventional CRT and could be a better alternative, especially when suboptimal electrical resynchronization is obtained.

Key words: Cardiac device; Implantation; Comparison

Access this article online

Website:

http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v15i7.65304

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Cardiac resynchronization therapy (CRT) has become an integral component of systolic heart failure therapy. The beneficial effect of CRT includes improved quality of life, fewer hospitalizations, and decreased mortality.[1] The anti-arrhythmic effects of CRT are well known.[2,3] In patients responding to CRT left-ventricular reverse remodeling leads to a reduction of myocardial stretch and favorable neuro-humoral changes.[5,6] Furthermore, it can invoke profound changes on the sub-cellular level.[7,8] Those effects might translate into a stabilizing effect on cardiac electrophysiology.[9,10]

Furthermore, despite careful patient selection and elaborate efforts in post-implantation management CRT is only successful in about 70% of patients.[4] Around 30% of patients are non-responders following conventional CRT implantation. Right ventricular (RV) apical lead may itself cause ventricular dys-synchrony. A search for an alternate way of pacing strategy for a more physiologic approach to overcome the adversities is developing over recent years. His bundle pacing (HBP) or left bundle branch (LBB) area pacing emerges as an alternative to conventional CRT.

Aims and objectives

The current study was undertaken with the primary objective to compare the outcome of a dual resynchronization by placing the RV pacing lead at his bundle or LBB area (along with left ventricular (LV) pacing lead in coronary sinus branches) against conventional CRT. Moreover, the secondary objective was the electrocardiographic and

Address for Correspondence:
Dr. Arunava Biswas, Associate Professor, Department of Pharmacology, Barasat Government Medical College and Hospital, Barasat, West Bengal, India. **Mobile:** +91-9674328329. **E-mail:** drabiswas@gmail.com

echocardiography (ECHO) assessment of the impact of cardiac resynchronization on ventricular function.

MATERIALS AND METHODS

After obtaining the Institutional Ethics Committee approval a hospital-based longitudinal observational study was carried out for a period of 21 months (September 2021–May 2023) on adult patients who received cardiac resynchronization devices and were admitted to the Department of Cardiology of Institute of Post Graduate Medical Education and Research, Kolkata. Patients who were duly informed about the study and those who consented to participate in the study and those who required CRT according to standard treatment protocol were included.

Patients aged below the age of 18 years; who were found to be critically ill on admission; who underwent atrial-based pacing (AAI pacing) were excluded from the study; an ejection fraction of below 20% and not fulfilling criteria for cardiac resynchronization device implantation; recently diagnosed heart failure (<1 month) or with a grossly evident cause of progressive heart failures such as coronary artery disease or valvular heart disease; who had been re-admitted for pulse generator replacement or undergone repeat implantation due to a complication for a primary implantation before study period were all excluded from this study. A purposive random sampling of subjects was done based on inclusion and exclusion criteria during the data collection period and a total of (n=35) patients were divided into two groups.

ECHO evaluation

This was done during admission, at 1st follow-up after 1 month, and 2nd follow-up after 6 months. ECHO was done using the Mindray DC-70 Ultrasound System (Shenzen, China) machine using the P4-2E transducer for adult cardiac ultrasound.

Implantation procedure

Coronary sinus pacing was performed according to the established standards for bi-ventricular CRT. The LBB area implantation procedure was performed using a thin (4.1-F), active helix, screw-in pacing lead (model 3830; 69 cm; Medtronic Inc., Minneapolis) and dedicated delivery sheaths (C315HIS, C304, Medtronic Inc.). His bundle's potential was recorded and/or the tricuspid annulus appraised electrophysiologically and fluoroscopically were used as anatomical landmarks.

The LBB area located 1.5–2 cm apically from the distal. His bundle or the superior aspect of the tricuspid annulus site was targeted. At this site, the paced QRS complex should be preferentially characterized by the normal axis in the frontal plane (R in lead I, R/Rs in lead II, and rS in lead III). "Lead deployment" was performed under fluoroscopic and electrocardiogram (ECG) guidance.

The current investigators aimed to obtain "paced QRS complex" with an r0 deflection in lead V1 and features of "LBB capture." Attempts were made to obtain LBB capture, but left ventricular septal (LVS) pacing was considered acceptable.

The following procedure-related data were recorded: Fluoroscopy time, LBB area pacing (LBBAP) capture threshold, LV capture threshold, sensing, acute complications, and V-V interval programming. The following ECG-based data were obtained: LBBAP QRS duration and V6 R-wave peak time (V6RWPT), paced biventricular (BiV) CRT QRS duration, and the presence of LBB capture.

Follow-up

"Post-implantation" follow-up was performed as per standards for each of the participants and data from the final "follow-up visit" were used for analysis. For clinical and "ECHO response," a minimum follow-up of 6 months was adopted for the purpose of this study.

Definitions and measurements

"LBB capture" was diagnosed as per currently used criteria/methods, which include "QRS morphology transition" during the "threshold test" (to either selective "LBB capture" or "LVS capture"), "paced V6RWPT," 90 ms, and diagnostic response during programmed stimulation.[11]

The "QRS duration," both for native and for "paced QRS complexes," was obtained using the "global QRS measurement method" (from the earliest onset or "pacing spike" to the "latest offset" with all 12-lead ECGs recorded simultaneously).

The "ejection fraction and LV volumes" were calculated using "Simpson's biplane method." ECHO response was "defined as _5% increase in LV ejection fraction" (LVEF). Super-responder status was "defined as an absolute improvement in LVEF by _20% or an increase of LVEF to a value of 50%."

Statistical analysis

Categorical variables were expressed as counts and percentages, and continuous variables were reported as mean 6 standard deviations. For continuous variables, differences in two groups were assessed using the unpaired Student t-test and the Mann–Whitney test. For categorical variables, the

Chi-squire and Fisher exact tests were used. Paired data were compared using the t-test if normally distributed.

The relevant data have been compiled in the form of multiple charts and diagrams and statistical analysis has been carried out using statistical software IBM Statistical Package for the Social Sciences 20.0 software (IBM, NY, USA) using relevant statistical methods. P<0.05 was taken as considered statistically significant.

RESULTS

A total of 35 patients underwent CRT procedures. The baseline characteristics of the study population with their post procedural parameters were depicted in [Table 1]. Out of those 12 patients of LBB block (LBBB) morphology underwent conduction system pacing. LBBB area pacing was confirmed by fluoroscopically and ECG changes were noted during intraoperative and post-operative programming. No cases of intraventricular septum perforation or lead dislodgement occurred. Coronary sinus lead and atrial leads are also positioned simultaneously.

Initially, two patients were attempted for HBP but due to non-suitable location and higher threshold, they were subjected to conventional bi-ventricular pacing with RV apical lead placement.

Among control groups RV apical lead along with coronary sinus leads and atrial leads were placed successfully in 23 patients. There were no cases of post-procedural infection or replacement of the device needed. Six patients were lost on follow-up so they were excluded from the study.

The study population was well-matched with respect to age, sex, co-morbidities, clinical, and laboratory profiles. There were also expected post-procedure improvements regarding ECG and ECHO parameters.

The bar diagram (Figure 1) shows only 17% of cases and 30% of controls were non-responders to device therapy. The difference was noticeable but not significant statistically (P=0.37) probably due to the small sample size.

There was no significant difference except pacing threshold which shows higher values in LBBB area pacing was quite expected [Table 2]. This study shows the feasibility of conduction system pacing as well as conventional BiV-CRT and the results are non-inferior.

DISCUSSION

This study presents a single-center experience with a mid-term 6 months follow-up of the LBB optimized-CRT technique, i.e., dual resynchronization, as conduction system pacing with LV pacing (coronary sinus lead) was done in contrast to conventional resynchronization with BiV pacing CRT, where RV apical pacing with LV pacing, was done, in non-consecutive patients with advanced chronic heart failure and wide QRS complex. It addresses those pertinent initial questions that are related to the rationale behind this new alternative pacing method and provides data on its safety, feasibility, and outcomes.

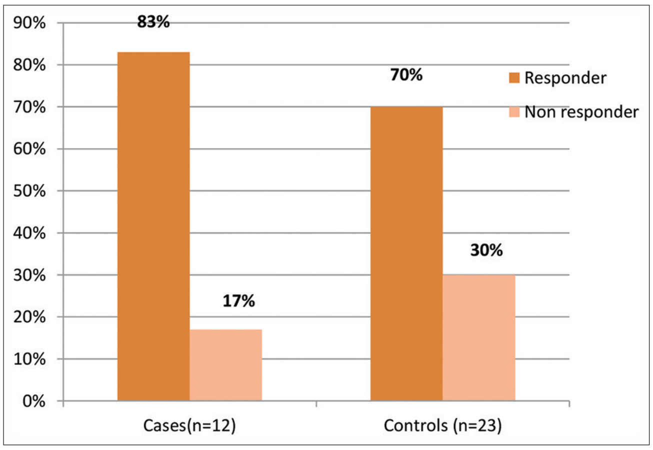

Figure 1: Distribution of the responders and non-responders among the study population

Electrical synchrony

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" and (2) bypass the slow "cell-to-cell conduction" from the "right to left" side of the interventricular septum. The impact of "LOT-CRT" on electrical synchrony might translate to favorable long-term clinical outcomes, as the degree of "QRS narrowing" in CRT was related to decreased long-term mortality while the degree of "QRS prolongation" was related to increased mortality.[12,13]

In a study by Sweeney et al.,[14] QRS narrowing 25 ms was associated with both "response" and "super response" to CRT with an odds ratio of 2.35 and 2.75, respectively.

Although "LBB Area Pacing" alone can achieve "electrical synchrony" of the LV, as documented in a few mid-sized non-randomized studies,[15,16] the following arguments support keeping the "CV pacing lead" in a CRT system in patients with advanced conduction system disease.

First, delayed activation of the lateral wall of the LV in patients with heart failure might result not only from discrete lesions in LBB that can be bypassed by "LBB pacing" but also from widespread and/or "distal delay" in the conduction system. The electrical uncoupling, myocardial scars, or "functional conduction block" can lead to delay in "LV lateral wall activation" as well.

Table 1: Baseline characteristics and post-procedural parameters of study populations

Variables	Cases (n=12)	Controls (n=23)	P-value
Age in years	64.2±6.9	64.9±7.7	0.79
Gender (M: F)	M75%: F25%	M65%: F35%	0.55
Body mass index in kg/m^2	23.1±2.9	23.1±2.6	0.95
Diabetes mellitus	16%	21%	0.72
Hypertension	50%	34%	0.38
ICMP	16%	13%	0.77
NYHA III/IV	16%	17%	0.95
Atrial fibrillation	16%	17%	0.95
NYHA class before implant	2.7±0.7	2.9±0.8	0.56
NYHA class after implant	2.08±0.51	2.3±0.5	0.21
NYHA level improvement	1.5±0.5	1.3±0.5	0.39
QRS before implant	162.7±6.3	159.2±8.8	0.23
QRS after implant	135.2±13.9	134.6±14.5	0.90
EF before implant	29.1±4.4	29.4±3.2	0.78
EF after implant	37.2±5.4	37.4±5.6	0.90
LVIDD before implant	66.8±4.1	65.3±4.4	0.33
LVIDD after implant	60.8±5.1	60.6±4.2	0.91
EDV before implant	170.2±7.4	167.6±8.4	0.37
EDV after implant	136.2±10.5	138.7±14.0	0.58
ESV before implant	110.5±8.9	107.2±8.8	0.29
ESV after implant	95.0±10.6	95.0±10.5	0.99
Procedure time	134.6±17.2	138.4±18.3	0.550
Fluoroscopic time	27.0±8.2	30.9±6.2	0.120
Pacing threshold	1.1±0.5	0.7±0.2	0.004
CRT-D	9 (75%)	16 (70%)	
CRT-P	3 (25%)	7 (30%)	
LBBB	12 (100%)	20 (87%)	
IVCD	0 (0%)	3 (13%)	
Responder	10 (83%)	16 (70%)	
Non-responder	2 (17%)	7 (30%)	

NYHA: New York heart association, LVIDD: Left ventricular internal dimension in diastole, EDV: End diastolic volume, CRT: Cardiac resynchronization therapy, ESV: End-systolic volume, EF: Ejection fraction, LBBB: Left bundle branch block, IVCD: Intraventricular conduction delays

Upadhyay et al.,[17] demonstrated that patients with "LBBB" on ECG, even diagnosed according to the "Strauss criteria" that are considered specific, might have "intact septal LBB activation".

Such conduction abnormality can be corrected or compensated for by "CV 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.

A further argument that "LBBAP" alone might not be able to fully restore "physiological activation" of the LV comes from studies that assessed the "ECG marker of the LV lateral wall activation time" – V6RWPT. During "LBBAP" in patients with "narrow QRS complex" and diseased "His-Purkinje conduction system," V6RWPT values differ.

In patients with "narrow QRS complexes," V6RWPT closely follows "intrinsic native activation times" and, as expected, remains within the norm for the V6 "intrinsicoid deflection time" (i.e, 50–60 ms; "LBB latency" of 20–30 ms). In contrast, in patients with "LBBB," "non-specific intraventricular conduction delay" or "asystole V6RWPT values," despite confirmed "LBB capture," is much longer and not infrequently greater than the normal physiological "LV lateral wall activation times."[18]

In the present study, "V6RWPT" during "LBBAP" was quite long which suggests that despite "proximal LBB capture," additional "LV conduction delay" remained, and "CV LV pacing" might have been needed to correct this.

The "HBP lead" should not be connected to the "RV port" because of the risk of atrial "over sensing" and ventricular "under sensing."

Table 2: Parameter changes on follow-up among responders group

Variables	Responder cases n=10	Responder controls (n=16)	P-value
Procedure time	133.8±13.3	133.3±16.5	0.94
Fluoroscopic time	25.6±8.3	29.2±6.1	0.21
Pacing threshold	1.0±0.7	0.7±0.2	0.04
QRS before implant	162.3±6.5	158.7±8.4	0.26
QRS after implant	130.2±8.2	126.9±7.5	0.31
EF before implant	28.8±4.8	29.5±3.4	0.66
EF after implant	38.1±5.6	40.4±3.7	0.21
LVIDD before implant	66.0±4.0	65.2±3.8	0.61
LVIDD after implant	59.3±4.1	59.5±3.2	0.89
EDV before implant	172.0±6.7	168.8±8.6	0.33
EDV after implant	132.8±7.5	131.2±6.9	0.59
ESV before implant	109.4±9.2	105.7±6.7	0.24
ESV after implant	91.6±7.7	90.4±4.5	0.61

LVIDD: Left ventricular internal dimension in diastole, EDV: End diastolic volume, ESV: End-systolic volume

The "quadripolar LV lead" can be used with the option of "multipoint pacing" if necessary and ventricular sensing or arrhythmia detection is normal. In addition, in patients with "intact atrioventricular conduction" and "non-specific intraventricular conduction delay," "HBP" without any correction of "LV conduction delay" does not provide any advantage over adaptive "LV-only pacing."

In contrast, "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 the potential risk of a late rise in "capture thresholds." "LBBAP" has consistently been shown to achieve "low and stable" capture thresholds with "high R-wave" amplitudes. ECHO and clinical outcomes significantly improved, compared to baseline, in the group of patients with advanced conduction disease and severe heart failure.

Clinical implications

There is a great diversity in both the extent and the location of the conduction disorders that cause the electromechanical delay. In patients eligible for the CRT, empirical CRT based on the BiV pacing without regard to the mechanism underlying electrical "dyssynchrony" may not fully achieve optimal clinical outcomes.

Conduction system or more preferably LBB optimized-CRT may provide an alternate, more individualized approach to CRT in patients having advanced peripheral conduction disease. This approach may need to be further studied in a randomized fashion. This study suggests that LBB capture might be related to feasible and non-inferior outcomes than LV septal capture when combined with coronary venous LV pacing and probably should be the preferred procedural goal among CRT candidates. Further studies are needed to clarify the clinical difference between LV septal pacing and LBB pacing, especially in patients with chronic heart failure.

Limitations of the study

The major limitation of this observational study was the non-consecutive patient design and lack of "uniform criteria" to select patients for "conduction system-CRT" rather than for "BiV-CRT," leading to potential selection and operator bias.

Lack of randomization and "ECG-only" comparison between "conduction system-CRT" and "conventional BiV-CRT" were other limitations. Our aim was to primarily demonstrate the "feasibility of the conduction system-CRT approach." Randomized studies with longer-term follow-up may be necessary to assess the value of this "novel CRT concept" in clinical practice.

One practical procedure-related limitation concerned the need to use an additional lead and "capping" of the "RV pace/sense lead" and loss of magnetic resonance imaging conditionality. In the future, it may be possible to use a "defibrillation coil alone" in the RV to eliminate the need for "RV pace/sense capping." However, in this study, we did not observe any "sensing issues" related to this approach during "follow-up," but this needs to be carefully considered during implantation.

CONCLUSION

Dual resynchronization therapy is feasible and safe and provides better electrical resynchronization compared to conventional CRT and could be a better alternative, especially when suboptimal electrical resynchronization is obtained. Randomized controlled trials comparing dual resynchronization, i.e., conduction system optimized with LV pacing CRT and conventional BiV-CRT are needed.

ACKNOWLEDGMENT

The authors sincerely acknowledges the effort and contribution of the paramedical and nursing staffs from the Department of Cardiology, Institute of Post Graduate Medical Education and Research, Kolkata.

REFERENCES

1. Di Biase L, Gasparini M, Lunati M, Santini M, Landolina M, Boriani G, et al. Antiarrhythmic effect of reverse ventricular remodeling induced by cardiac resynchronization therapy: The InSync ICD (Implantable Cardioverter-Defibrillator) Italian Registry. J Am Coll Cardiol. 2008;52(18):1442-1449.
https://doi.org/10.1016/j.jacc.2008.07.043
2. Barsheshet A, Wang PJ, Moss AJ, Solomon SD, Al-Ahmad A, McNitt S, et al. Reverse remodeling and the risk of ventricular tachyarrhythmias in the MADITCRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy). J Am Coll Cardiol. 2011;57(24):2416-2423.
https://doi.org/10.1016/j.jacc.2010.12.041
3. Arya A, Haghjoo M, Dehghani MR, Alasti M, Alizadeh H, Kazemi B, et al. Effect of cardiac resynchronization therapy on the incidence of ventricular arrhythmias in patients with an implantable cardioverter-defibrillator. Heart Rhythm. 2005;2(10):1094-1098.
https://doi.org/10.1016/j.hrthm.2005.07.007
4. Singh JP and Gras D. Biventricular pacing: Current trends and future strategies. Eur Heart J. 2012;33(3):305-313.
https://doi.org/10.1093/eurheartj/ehr366
5. St John Sutton M, Ghio S, Plappert T, Tavazzi L, Scelsi L, Daubert C, et al. Cardiac resynchronization induces major structural and functional reverse remodeling in patients with New York Heart Association class I/II heart failure. Circulation. 2009;120(19):1858-1865.
https://doi.org/10.1161/CIRCULATIONAHA.108.818724

6. Ukkonen H, Sundell J and Knuuti J. Effects of CRT on myocardial innervation, perfusion and metabolism. Europace. 2008;10(Suppl 3):iii114-117.

https://doi.org/10.1093/europace/eun228

7. Sachse FB, Torres NS, Savio-Galimberti E, Aiba T, Kass DA, Tomaselli GF, et al. Subcellular structures and function of myocytes impaired during heart failure are restored by cardiac resynchronization therapy. Circ Res. 2012;110(4):588-597.

https://doi.org/10.1161/CIRCRESAHA.111.257428

8. Kass DA. Pathobiology of cardiac dyssynchrony and resynchronization. Heart Rhythm. 2009;6(11):1660-1665.

https://doi.org/10.1016/j.hrthm.2009.08.017

9. Aiba T and Tomaselli G. Electrical remodeling in dyssynchrony and resynchronization. J Cardiovasc Transl Res. 2012;5(2):170-179.

https://doi.org/10.1007/s12265-012-9348-9

10. Chakir K, Daya SK, Aiba T, Tunin RS, Dimaano VL, Abraham TP, et al. Mechanisms of enhanced beta-adrenergic reserve from cardiac resynchronization therapy. Circulation. 2009;119(9):1231-1240.

https://doi.org/10.1161/CIRCULATIONAHA.108.774752

11. Briongos-Figuero S, Estévez-Paniagua Á, Sánchez-Hernández A, Muñoz-Aguilera R. Combination of current and new electrocardiographic-based criteria: A novel score for the discrimination of left bundle branch capture. Europace. 2023;25(3):1051-1059

https://doi.org/10.1093/europace/euac276

12. Jastrzebski M, Baranchuk A, Fijorek K, Kisiel R, Kukla P, Sondej T, et al. Cardiac resynchronization therapyinduced acute shortening of QRS duration predicts long-term mortality only in patients with left bundle branch block. Europace. 2021;21:281-289.

https://doi.org/10.1093/europace/euy254

13. Kronborg MB, Nielsen JC and Mortensen PT. Electrocardiographic patterns and long-term clinical outcome in cardiac resynchronization therapy. Europace. 2010;12:216-222.

https://doi.org/10.1093/europace/eup364

14. Sweeney MO, Hellkamp AS, van Bommel RJ, Schalij MJ, Borleffs CJ and Bax JJ. QRS fusion complex analysis using wave interference to predict reverse remodeling during cardiac resynchronization therapy. Heart Rhythm. 2014;11(5):806-813.

https://doi.org/10.1016/j.hrthm.2014.01.021

15. Vijayaraman P, Ponnusamy S, Cano O, Sharma PS, Naperkowski A, Subsposh FA, et al. Left bundle branch area pacing for cardiac resynchronization therapy: Results from the International LBBAP Collaborative Study Group. JACC Clin Electrophysiol. 2021;7(2):135-147.

https://doi.org/10.1016/j.jacep.2020.08.015

16. Huang W, Wu S, Vijayaraman P, Su L, Chen X, Cai B, et al. Cardiac resynchronization therapy in patients with nonischemic cardiomyopathy using left bundle branch pacing. JACC Clin Electrophysiol. 2020;6(7):849-858.

https://doi.org/10.1016/j.jacep.2020.04.011

17. Upadhyay GA, Cherian T, Shatz DY, Beaser AD, Aziz Z, Ozcan C, et al. Intracardiac delineation of septal conduction in left bundle branch block patterns: Mechanistic evidence of left intra-Hisian block circumvented by His pacing. Circulation. 2019;139(16):1876-1888.

https://doi.org/10.1161/CIRCULATIONAHA.118.038648

18. Jastrzebski M, Kielbasa G, Curila K, Moskal P, Bednarek A, Rajzer M, et al. Physiology-based electrocardiographic criteria for left bundle branch capture. Heart Rhythm. 2021;18(6):935-943.

https://doi.org/10.1016/j.hrthm.2021.02.021

Authors' Contributions:
PKG and SP- Concept, design of study and literature search, and experimental studies; **SP and TKG**- Data acquisition, data analysis, and statistical analysis; **AB and AsB**- Manuscript preparation; **AB and PKG**- Manuscript editing and manuscript review.

Work attributed to:
Department of Cardiology, Institute of Post Graduate Medical Education and Research, Kolkata, West Bengal, India.

Orcid ID:
Arunava Biswas - https://orcid.org/0000-0002-9676-3410

Source of Support: Nil, **Conflicts of Interest:** None declared.