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Conduction system pacing: What's missing for the paradigm shift?

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Published in
Frontiers in Cardiovascular Medicine

ISSN 1664-8714
ISBN 978-2-83252-120-5
DOI 10.3389/978-2-83252-120-5

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Conduction system pacing: What's missing for the paradigm shift?

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Citation

Marcantoni, L., Anselmino, M., eds. (2023). *Conduction system pacing: What's missing for the paradigm shift?* Lausanne: Frontiers Media SA.

doi: 10.3389/978-2-83252-120-5

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Editorial
PUBLISHED 24 March 2023
DOI 10.3389/fcvm.2023.1163370

OPEN ACCESS

EDITED AND REVIEWED BY
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SPECIALTY SECTION
This article was submitted to Cardiac Rhythmology, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 10 February 2023
ACCEPTED 14 March 2023
PUBLISHED 24 March 2023

CITATION
Marcantoni L, Zanon F and Anselmino M (2023) Editorial: Conduction system pacing: What's missing for the paradigm shift?
Front. Cardiovasc. Med. 10:1163370.
doi: 10.3389/fcvm.2023.1163370

Editorial: Conduction system pacing: What's missing for the paradigm shift?

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KEYWORDS

arrhythimas, heart failiure, pacing (left bundle branch block), pacing & electrophysiology, conduction system

Editorial on the Research Topic
Conduction system pacing: What's missing for the paradigm shift?

Since 1950 pacemaker technology has experienced tremendous improvements, however, despite the evident and well-known clinical benefits, right ventricle apical pacing, being non-physiologic, may secondarily induce, in a not neglectable percentage of patients, undesired detrimental effects (1). Conduction System Pacing (CSP), namely His Bundle Pacing (HBP) and Left Bundle Branch Pacing (LBBP), has therefore gained increasing attention, and presents today the potential to become the first pacing modality in many clinical scenarios. Through the direct capture of the His-Purkinje system CSP maintains electrical and mechanical physiology in patients with narrow QRS, whereas potentially restores ventricular synchrony in case of underlying bundle branch blocks (2, 3).

In the early 2000s, the restricted number of available tools confined HBP in the hands of pioneers that could only share small, single-center experiences. Further knowledge on cardiac pacing physiology and development of new dedicated tools by the industry has, instead, favored the definitive CSP spread up (4). Three-dimensional sheaths equipped with septal curves facilitate the perpendicular lead orientation towards the septum, favoring lead fixation even in complex anatomies as those of patients with dilated heart or underlying structural disease. The availability of different designs and sizes ease the path to successful CSP not only by lumenless fixed screw, but also for stylet driven leads, adapting to the characteristics of any candidate. Non less importantly, the integration with electroanatomical mapping systems further facilitates the procedure by reducing learning curves and radiation exposure to the patient and the staff (5).

Through contributions from leading experts in the field, the present Special Issue presents a contemporary perspective on CSP. The increasing body of evidence surely confirms the more than promising outcomes of this innovative approach, however, by highlighting indistinctively both positive and negative insights, places emphasis on what is already clear and what, instead, is still lacking for routine CSP in clinical practice. Based on the original research, reviews, brief reports, and opinion papers included in the Issue two main considerations emerge.

The first is that research on LBBP outnumbers by far that on HBP. The likely explanation relates to the less technically challenging procedure compared to HBP, with low pacing threshold and appropriate sensing values more easily achieved. The limited experience

with LBBB, compared to HBP, however requires further research and dedicated studies to fully uncover all underlying aspects and mechanisms. The reader of the Issue will find insights on the implant technique Pooter et al. and the in-depth electrophysiological features of the three different capture modes occurring during LBBP: selective, non-selective or left ventricular septal pacing Curila et al. Original aspects on LB trunk or LB fascicular capture are also described Liu et al.

The second consideration that emerges is that the general feeling of the Electrophysiology community is that CSP may represent a real alternative to standard biventricular pacing (BiV) for resynchronization purposes in heart failure patients that remain symptomatic despite optimal medical treatment Gui et al., Jiang et al., Hua et al., Fu et al. Heart failure CSP implants have been broadly performed, although they have yet to become a standard, guideline-recommended approach. Within clinical studies registered on ClinicalTrials.gov, about 30 in the recruitment phase relate to CSP, and, within these, the majority investigates this innovative pacing technique as an alternative to standard BiV by classical epicardial left ventricle lead placed through coronary sinus branching.

Overall, the present Issue supports the evidence that a true paradigm shift appears compelling. Before recommending CSP as first line treatment for both proximal and distal conduction disturbances and, even more, as an alternative to standard BiV, the Electrophysiology community, however, awaits larger experiences. Evidence from randomized trials is to date lacking, and urgently needed before recommending CSP as routine clinical practice. There is, however, no doubt that CSP will play (in fact, it already does) a central role in cardiac pacing strategies. Ongoing research and implementation of new dedicated devices and algorithms will permit to decide if CSP will become the default approach, enabling all Electrophysiologist to abandon right ventricle apical pacing, particularly in patients with expected high pacing burden. In the meantime, we hope the readers of Frontiers in Cardiovascular Medicine will find the current Special Issue helpful in broadening their understanding on CSP.

Author contributions

LM and MA conceived the editorial. FZ revised the text. All authors contributed to the article and approved the submitted version.

Conflict of interest

MA is consultant for Biosense Webster and Boston Scientific; clinical proctor for Medtronic; and has received educational grants from Abbott. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Sweeney MO, Prinzen FW. A new paradigm for physiologic ventricular pacing. *J Am Coll Cardiol.* (2006) 47(2):282–8. doi: 10.1016/j.jacc.2005.09.029

2. Vijayaraman P, Chung MK, Dandamudi G, Upadhyay GA, Krishnan K, Crossley G, et al. His bundle pacing. *J Am Coll Cardiol.* (2018) 72(8):927–47. doi: 10.1016/j.jacc.2018.06.017

3. Zhang S, Zhou X, Gold MR. Left bundle branch pacing: JACC review topic of the week. *J Am Coll Cardiol.* (2019) 74(24):3039–49. doi: 10.1016/j.jacc.2019.10.039

4. Kircanski B, Boveda S, Prinzen F, Sorgente A, Anic A, Conte G, et al. Conduction system pacing in everyday clinical practice: EHRA physician survey. *Europace*. (2022): euac201. doi: 10.1093/europace/euac201

5. Richter S, Ebert M, Bertagnolli L, Gebauer R, Lucas J, Scheller D, et al. Impact of electroanatomical mapping-guided lead implantation on procedural outcome of his bundle pacing. *Europace*. (2021) 23(3):409–20. doi: 10.1093/europace/euaa292

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 27 July 2021
doi: 10.3389/fcvm.2021.661885

Feasibility and Safety of Left Bundle Branch Pacing for Advance Aged Patients: A Multicenter Comparative Study

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OPEN ACCESS

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Specialty section:
This article was submitted to Cardiac Rhythmology, a section of the journal Frontiers in Cardiovascular Medicine

Received: 31 January 2021
Accepted: 23 June 2021
Published: 27 July 2021

Citation:
Ren Z, Cai B, Wang S, Jia P, Chen Y, Guo R, Li H, Zhang J, Xiong J, Zhang J, Yang H, Li X, Xu Y, Chen X and Zhao D (2021) Feasibility and Safety of Left Bundle Branch Pacing for Advance Aged Patients: A Multicenter Comparative Study. Front. Cardiovasc. Med. 8:661885. doi: 10.3389/fcvm.2021.661885

Background: Left bundle branch pacing (LBBP) has been shown to be a safe and effective means to achieve physiological pacing. However, elderly patients have increased risks from invasive procedures and the risk of LBBP in elderly patients is not known. We aimed to investigate the safety and efficacy of LBBP in elderly patients >80 years of age.

Methods: From December 2017 to June 2019, 346 consecutive patients with symptomatic bradycardia, 184 patients under 80 years of age and 162 over 80 years, were included and underwent LBBP. The safety and prognosis of LBBP were comparatively evaluated by measured pacing parameters, periprocedural complications, and follow-up clinical events.

Results: Compared with the younger, the elderly group had worse baseline cardiac and renal function. LBBP was achieved successfully in both groups with comparable fluoroscopic time and paced QRS duration (110.0 [102.0, 118.0] ms for the young vs. 110.0 [100.0, 120.0] ms for the elderly, $P = 0.874$). Through a follow-up of 20.0 ± 6.1 months, pacing parameters were stable while higher threshold and impedance were observed in the elderly group. In the evaluation of safety, overall procedure-related complication rates were comparable (4.4 vs. 3.8%, young vs. elderly). For prognosis, similar rates of major adverse cardiocerebrovascular events (7.1 vs. 11.9%, young vs. elderly) were observed.

Conclusions: Compared to younger patients, LBBP could achieve physiological pacing in patients over 80 with comparable midterm safety and prognosis. Long-term safety and benefits of LBBP, however, necessitate further evaluation.

Keywords: physiological pacing, left bundle branch pacing, elderly, symptomatic bradycardia, safety

INTRODUCTION

Physiological pacing—imitating the normal cardiac conduction pathway—has long been put forward as a means of restoring atrioventricular synchrony. This concept has been historically redefined since the first His-bundle pacing attempt to achieve ventricular synchrony in 2000 (1). Thereafter, a growing body of evidence shows the efficacy of His-bundle pacing (2, 3). However, most studies utilize advanced pacemakers for a limited population (4–6), which cannot be generalized to patients requiring a more cost-effective therapy. In addition, early battery depletion often occurred as a result of the elevated pacing threshold, impeding the application of His-bundle pacing (7). Su et al. optimized the technique by pacing at the distal His-bundle or even closer to the left bundle branch (LBB), presenting a narrow QRS with steady pacing parameters (8). Furthermore, in 2017 they reported the first case of LBB pacing (LBBP) that safely corrected the LBB block in a heart failure patient and showed steady pacing parameters during follow-up (9). Based on current evidence, LBBP seems to be a safe and effective alternative to conventional pacing (10–12).

As the conductive pathway degenerates, aged patients had a higher incidence of symptomatic bradycardia, which can only be corrected by implantation of a pacemaker. Nevertheless, elderly patients have distinctive features compared with the general population: more tortuous veins, lower BMI, and lower cardiac mass (13). These differences increase the potential risks of the implantation procedure. Additionally, comorbidities like hypertension, ischemic heart disease, and chronic renal disease (14) are pervasive in the elderly population, which could further worsen the prognosis for pacemaker implantation. Although, LBBP is a promising approach, inevitable transseptal lead fixation and mapping of His and LBB potential would presumably pose a higher risk for complications. To our knowledge, no current study has investigated the feasibility and safety of LBBP specifically in an advanced age population.

Therefore, our multicenter comparative study was designed to observe the feasibility and safety of LBBP in patients over age 80 compared to younger patients.

MATERIALS AND METHODS

Study Sample

From October 2018 to June 2019, 346 consecutive patients from Shanghai Tenth people's Hospital, Zhongshan Hospital of Fudan University, and Xiamen Cardiovascular Hospital admitted with symptomatic bradycardia were included. Symptomatic bradycardia was defined as ECG recorded sick sinus syndrome, atrial fibrillation with long R-R interval, high grade, 2nd and 3rd degree atrial ventricular (AV) block, which were in accordance with the 2013 ESC guidelines (15). Patients were excluded if they indicated and received cardiac resynchronization therapy (CRT) or implantation of implantable cardioverter-defibrillator (ICD). Written forms of consent were acquired from every patient before the procedure. Our study complied with the Declaration of Helsinki and was approved by the local ethical committee of Shanghai Tenth People's Hospital.

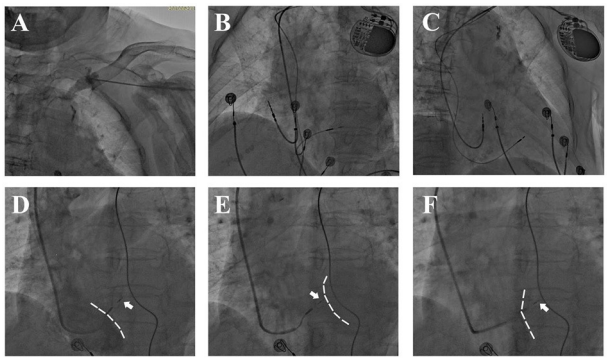

FIGURE 1 | Fluoroscopy during LBBP. **(A)** Venous angiography after puncture showed a tortuous left subclavian vein. **(B,C)** Postprocedural fluoroscopy showed a fixed 3,830 lead in the IVS and atrial lead in right atrial appendage. **(D–F)** Lead depth measured by the relative position of 3,830 electrode (*white arrow*) and IVS during screwing. **(D,E)** Angiography *via* 8.5 F puncture sheath delineated RV silhouette [**(D)**, *dashed white line*] while delayed contrast delineated LV silhouette [**(E)**, *dashed white line*]. **(F)** Angiography *via* C315 sheath showed RV side of IVS (*dashed white line*).

LBBP Procedure

Location and Fixation

Details of His-bundle pacing procedure was reported in a previous study (16). Through, the left subclavian vein or axillary vein (**Figure 1A**), an 8.5 F sheath was placed after a fixed curved sheath (C315 His, Medtronic) distally advanced beyond the tricuspid annulus (**Figures 1B,C**). A Select Secure™ lead (model 3830, 69 CM, Medtronic, Minneapolis, MN, USA) was then cannulated to locate the His-bundle by capturing the His-bundle potential displayed on electrocardiogram (ECG, Bard recorder, Bard Electrophysiology Laboratory System, MA). Afterwards, under a right anterior oblique (RAO) 30° view, activation mapping was conducted 1 cm anterior to His-bundle to locate the eligible site—the proximal LBB, where left and right activations fuse incompletely and show a negative "W" waveform on lead V1. Then, the electrode was manipulated perpendicularly to the interventricular septum (IVS) and screwed clockwise until it reached the left ventricular (LV) subendomyocardium. During the procedure, the duration from the pacing signal to the peak of R wave (on V4-V6 lead) is measured as pacing to left ventricular activation time (p-LVAT), It reflects the activation time of the lateral wall of the left ventricle. An eligible site of left bundle capture was confirmed if selective LBBP was demonstrated by ECG, if p-LVAT shortened abruptly >10 ms through increasing pacing output, or if p-LVAT stayed shortest and stable at the site (17, 18).

Procedural Safety

To ensure safe and stable pacing, pacing thresholds, sensing, and impedance were measured. The intrinsic and paced QRS duration and p-LVAT were measured and optimized to mimic physiological conduction (**Figure 2**).

In order to prevent perforation and optimize fixation, the lead depth in the IVS was approximated under digital

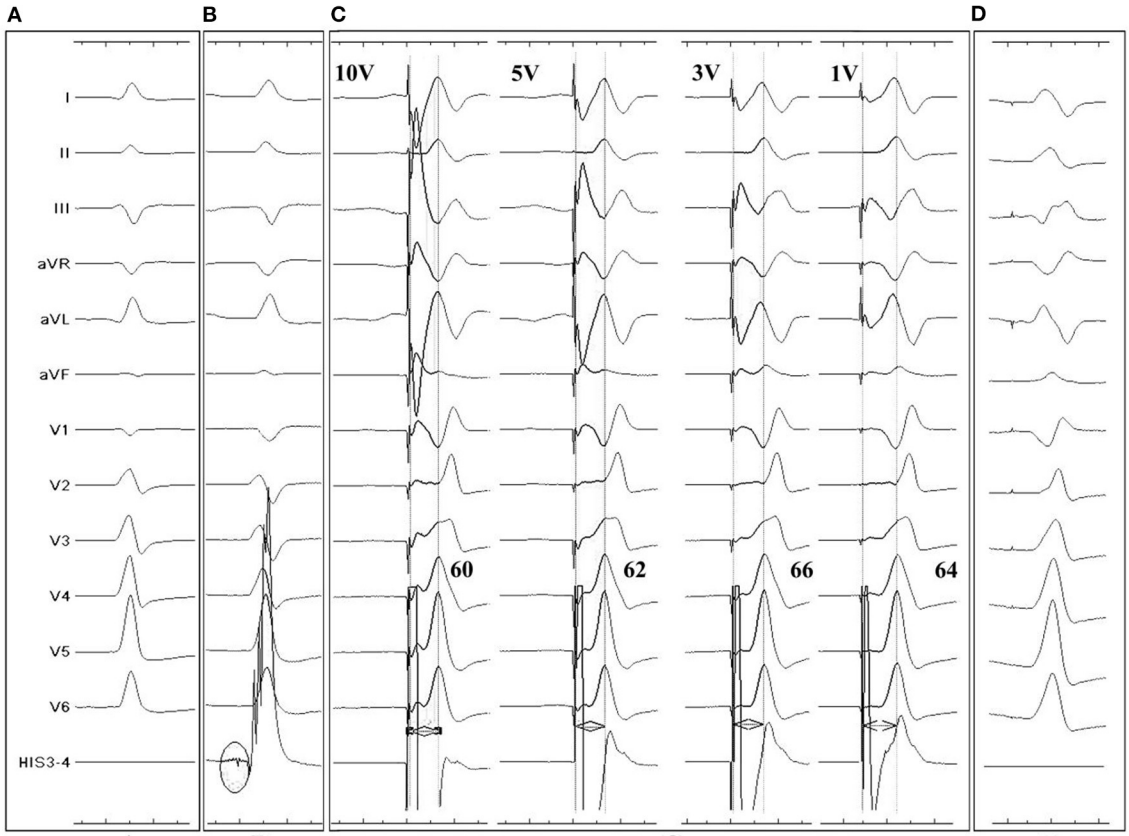

FIGURE 2 | Twelve-lead and intracardiac electrocardiograms (ECG) during LBBP for a 96-year-old III° AVB patient. **(A):** Intrinsic rhythm showed a QS morphology in V1 lead. **(B)** LBB potential recorded by pacing tip (*black circle*) when the lead reached LV endocardium. **(C)** p-LVAT measured by unipolar pacing after fixation. Under different pacing output, QRS showed similar RBB block pattern and p-LVAT stayed short, indicating capture of LBB. **(D)** Postprocedural ECG recording. A QR pattern was shown in V1 lead. Paced QRS duration was similar to intrinsic.

subtraction angiography (DSA) by injecting contrast media *via* the puncture sheath and C315 sheath (**Figures 1D–F**). Firstly, the angiography would delineate the silhouette of the right ventricle (RV) while delayed contrast delineated the LV silhouette. The contrast *via* C315 sheath would retain at the RV side of IVS, and the distance between the retention of contrast and the tip of pacing lead was measured as the lead depth in the IVS. For patients with AV block or complete LBB block, a temporary pacemaker was placed prior to LBBP in case of complete AV block resulting from injury of the His-bundle or proximal LBB.

Pacing Parameters and Device Programming

Paced QRS duration was routinely measured from the end of pacing signal to the end of QRS complex under bipolar pacing at acceptable pacing output, with a pulse width of 0.42 ms during the procedure. Pacing output and AV delay were adjusted individually to achieve optimal QRS morphology before discharge. During follow-up, pacing threshold, sense, impedance, and AV delay were routinely measured, with a pulse width of 0.40 ms.

Safety and Prognosis Evaluation

Safety was evaluated by periprocedural and follow-up safety events, including lead-related complications such as lead failure, fracture, and dislodgement, pocket-related complications such as pocket hematoma and infection, and procedure-related complications such as pneumothorax, pericardial effusion, and cardiac tamponade.

Prognosis was evaluated by all-cause mortality, rehospitalization due to cardiovascular disease (CVD), and major adverse cardiocerebrovascular events (MACE) during follow-up. MACE was defined as the onset of severe cardiocerebrovascular events including acute myocardial infarction, acute decompensated heart failure, cardiac tamponade, malignant arrhythmia, stroke (infarction and hemorrhage), pacemaker reimplantation, and death due to CVD.

In the 1st, 3rd, and 12th month following LBBP procedure, patients were required to have outpatient or inpatient follow-up (if they were immobilized). Comprehensive medical histories were taken and physical examinations were conducted by experienced cardiologists. Device programming was required at every follow-up, and 24-h Holter and transthoracic

echocardiography (TTE) were performed when physicians considered them necessary.

Statistical Analysis

Continuous parameters were described as a mean ± standard deviation (SD) if they conformed to normal distribution, while those without a normal distribution were presented as the median and interquartile ranges (IQR). The *p*-value was generated from two sample *t*-tests or a Mann-Whitney test according to the equality of variance, or singed-rank test if a normal distribution was not presented. Repeated measures analysis of variance was applied to analyze the repeated measurements of pacemaker, electrocardiographic, and echocardiographic parameters. Categorical variables were described as percentages (%) and *p*-values were analyzed with χ^2 tests or Fisher exact tests (when theoretical frequency was lower than 5). The incidence of procedure related complications, MACE, and CVD hospitalization were analyzed using Kaplan-Meier estimate, with *P*-value generated from Log-Rank test. A two-sided *P*-value of <0.05 was considered statistically significant. SAS 9.4 software (SAS Institute Inc., Cary, NC, USA) was used to conduct the analysis.

RESULTS

Sample Characteristics

The median age of the younger and the elderly groups were 73.0 [65.0, 77.0] years and 84.0 [82.0, 87.0] years, respectively. The proportion of male and female patients were similar. The indications were similar between groups. Compared with the younger group, the elderly had significantly deteriorated renal function (estimated glomerular filtration fraction (eGFR) 65.2 ± 26.6 vs. 89.1 ± 30.8 ml/min/1.73m^2, $P < 0.001$). Although, the cardiac function evaluated by left ventricular ejection fraction (LVEF) ($P = 0.275$) was similar, the level of N-terminal pro-brain natriuretic peptide (NT-proBNP) was higher (the elderly group vs. the younger group, 1076.0 [324.0, 2513.0] vs. 273.7 [100.6, 752.7] pg/ml, $P < 0.001$) and cardiac function evaluated by New York Heart Association (NYHA) grading was worse in the elderly group ($P < 0.001$). In addition, the prevalence of heart failure was higher in the elderly group (25.2 vs. 11.5%, $P = 0.001$). Of note, although, there was an unequal distribution of IVS thickness between the younger and the elderly group measured by TTE ($P = 0.010$ generated by Wilcoxon sign rank test), such a difference was too small in value to be clinically significant. Other comorbidities and medications were similar. Detailed information is listed in **Table 1**.

Periprocedural Measurements

LBBP was achieved in all 346 patients. The fluoroscopic time and dosage were similar between groups. Paced QRS duration (110.0 [102.0, 118.0] vs. 110.0 [100.0, 120.0] ms, $P = 0.874$) were shortened and comparable between groups. After lead fixation, lead sense was similar (13.3 ± 4.5 vs. 12.9 ± 4.5 mV), while higher pacing threshold (0.73 ± 0.31 vs. 0.87 ± 0.43 V, $P < 0.001$) and impedance (686.3 ± 175.0 vs. 732.1 ± 180.5 ohms, $P < 0.01$) were observed in the elderly group (**Figure 3**). Of note, a higher proportion of temporary pacemaker implantation prior to LBBP was observed in the elderly group (18.2 vs. 8.8%). Details are presented in **Table 2**.

Evaluation of Safety and Prognosis

Over a 20.0 ± 6.1 month period, five (1.5%) patients were lost to follow-up. During follow-up, there was a rise of pacing threshold in the elderly group ($P < 0.01$ in both groups), which was higher than that of the younger group in the 12th month (young vs. elderly 0.74 ± 0.22 vs. 0.87 vs. 0.39 V, $P < 0.01$). The sensing was risen in both groups, while the it was comparable between groups. And the impedance was decreased in both groups ($P < 0.01$ in both groups), although, it was higher in the elderly group (young vs. elderly, 479.2 ± 80.0 vs. 528.3 ± 66.7 ohms, $P < 0.001$). Such minor changes of pacing parameters indicates that the lead has a stable performance through a mid-term follow-up.

In terms of safety, the incidence of procedure-related complications was similar in both the young (4.4%) and elderly group (3.8%). The overall MACE incidence was comparable in the elderly group (young 7.1 vs. elderly 11.9%, $P = 0.157$). Notably, the incidence of cerebral infarction (0 vs. 3.1%, $P = 0.050$) and myocardial infarction (2.5 vs. 0%, $P = 0.099$) were non-significantly higher in the elderly group. In addition, a similar proportion of patients underwent rehospitalization due to CVD during follow-up (young 12.1 vs. elderly 13.8%, $P = 0.321$). Follow-up details are listed in **Table 3** and survival analysis of procedure related complications, MACE, and rehospitalization due to CVD are demonstrated in **Figure 4**.

Cardiac function measured by TTE were collected and compared in 73 younger and 50 elderly patients. Statistic significant improvement of LVEF was observed in both the young ($P < 0.001$) and elderly groups ($P < 0.001$). Only one younger patient had worsening cardiac function (LVEF dropped from 60 to 24%) resulting from pneumonia-induced acute heart failure (**Figure 5**).

DISCUSSION

Our multicenter comparative study compared the profiles of 159 elderly patients aged over 80 with 182 younger patients with symptomatic bradycardia who underwent LBBP. Our findings suggest that physiological pacing *via* LBBP can be performed in elderly patients without increasing the risk of complications and that midterm prognosis of elderly patients undergoing LBBP was comparable with the younger patient group.

Population aging is a major issue, with one report estimating over 150 million Chinese citizens will be over 80 by 2050 (19). Elderly patients should be considered as a special community, as they have more co-morbidities and worse prognosis. Especially in the consideration of pacemaker implantation, elderly patients had more tortuous veins, lower BMI, and lower cardiac mass, which accounts for the higher risk of complications such as pneumothorax, lead dislodgement, perforation, and loss of capture (20). Therefore, investigating the safety and prognosis of pacemaker implantation in the advanced aged population is of great importance.

TABLE 1 | Baseline characteristics of both young and elderly patients.

Variables	Overall *N* = 341	Young (<80) *N* = 182	Elderly (≥80) *N* = 159	*P*-value
Age, yrs	80.0 [71.0, 84.0]	72.0 [65.0, 77.0]	84.0 [82.0, 87.0]	**<0.001**
Gender (male), *n* (%)	173 (50.7)	94 (51.7)	79 (49.7)	0.717
IVS thickness, mm	10.0 [10.0, 11.0]	10.0 [10.0, 11.0]	10.0 [10.0, 11.0]	**0.010**
LVEF, %	60.0 [55.0, 62.0]	60.0 [57.0, 62.0]	60.0 [55.0, 62.0]	0.275
NT-proBNP, pg/ml	539.4 [181.3, 1576.0]	273.7 [100.6, 752.7]	1076.0 [324.0, 2513.0]	**<0.001**
eGFR, ml/min/1.73m^{2*}	79.2 ± 31.4	89.1 ± 30.8	65.2 ± 26.6	**<0.001**
NYHA, *n* (%)				**0.003**
IV	23 (6.7)	9 (5.0)	14 (8.8)	
III	49 (14.4)	20 (11.0)	29 (18.2)	
II	95 (27.7)	42 (23.1)	53 (33.3)	
I	174 (50.7)	111 (61.0)	63 (39.6)	
Indications, *n* (%)				0.887
SSS	127 (37.2)	72 (39.6)	55 (34.6)	
AF with long R-R interval	53 (15.5)	27 (14.8)	26 (16.4)	
AVB^{+}	147 (43.1)	75 (41.2)	72 (45.3)	
Lead revision	2 (0.6)	1 (0.6)	1 (0.6)	
Battery depletion	12 (3.5)	7 (3.9)	5 (3.1)	
Medical history, *n* (%)				
Heart failure	61 (17.9)	21 (11.5)	40 (25.2)	**0.001**
AF/AFL	101 (29.1)	51 (28.0)	49 (31.0)	0.788
DCM	5 (1.5)	3 (1.7)	2 (1.3)	1.000
HCM	12 (3.5)	5 (2.8)	7 (4.4)	0.408
Coronary artery disease	93 (27.3)	44 (24.2)	49 (30.8)	0.170
Hypertension	253 (74.2)	130 (71.4)	123 (77.4)	0.212
Diabetes mellitus	85 (24.9)	47 (25.8)	38 (23.9)	0.682
Medications, *n* (%)				
Antiplatelet agents	87 (25.5)	41 (22.5)	46 (29.0)	0.389
Oral anticoagulants	31 (9.1)	16 (8.8)	15 (9.4)	0.837

Continuous variables are described as mean ± SD or median with IQR, while categorical variables are presented as percentages (%). AF, denotes atrial fibrillation; AFL, atrial flutter; AVB, atrial ventricular block; BMI, body mass index; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration fraction; HCM, hypertrophic cardiomyopathy; IVS, interventricular septum; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association grading of cardiac function; SSS, sick sinus syndrome.

**eGFR was calculated by MDRD formula.*

$^{+}$AVB includes high grade AVB, II° AVB Mobitz type 2 and III° AVB. The bold value indicates significant P-value ($P < 0.05$).

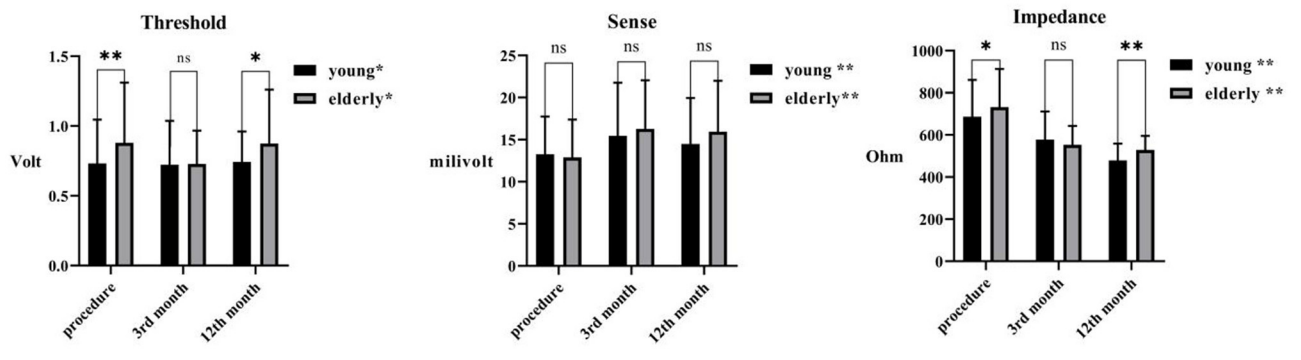

FIGURE 3 | Pacing parameters during LBBP in the 3rd and 12th month after implantation between young and elderly groups. * and ** indicates statistical significance, $p < 0.05$ and 0.01, respectively, and ns denotes non-significance.

TABLE 2 | Procedural details of LBBP.

Parameters	Overall *N* = 341	Young (<80) *N* = 182	Elderly (≥80) *N* = 159	*P*-value
Fluoroscopic time, min	10.3 [7.4, 16.2]	11.2 [7.7, 16.6]	9.65 [7.4, 15.3]	0.311
Fluoroscopic dosage, mGy	135.9 [85.9, 246.8]	138.5 [96.2, 255.8]	130.0 [76.5, 226.0]	0.227
Preprocedural measurements				
QRS duration, ms	104.0 [94.0, 136.5]	102.0 [93.0, 137.0]	106.0 [94.0, 136.0]	0.600
LBB block, *n* (%)	25 (7.4)	11 (6.1)	14 (8.8)	0.329
RBB block, *n* (%)	38 (11.2)	21 (11.6)	17 (10.7)	0.804
Temporary pacemaker, *n* (%)	45 (13.2)	16 (8.8)	29 (18.2)	**0.010**
Intraprocedural measurements				
Paced QRS duration, ms	110.0 [102.0, 118.0]	110.0 [102.0, 118.0]	110.0 [100.0, 120.0]	0.874
LBB potential recorded, *n* (%)	164 (54.3)	86 (58.9)	78 (50.0)	0.121
p-LVAT, ms	72.0 [66.0, 80.0]	72.0 [66.0, 80.0]	70.0 [64.0, 78.0]	0.299

LBB, denotes left bundle branch; p-LVAT, pacing to left ventricle activation time; RBB, right bundle branch. The bold value indicates significant P-value (P < 0.05).

TABLE 3 | Safety and prognosis between younger and elderly patients.

Events	Overall *N* = 341	Young (<80) *N* = 182	Elderly (≥80) *N* = 159	*P*-value
Procedure related complications	14 (4.1)	8 (4.4)	6 (3.8)	0.140
Lead fracture, *n* (%)	0	0	0	1.000
Lead dislodgement, *n* (%)	1 (0.3)	0	1 (0.6)	0.946
Atrial perforation, *n* (%)	1 (0.3)	0	1 (0.6)	0.946
Ventricular perforation, *n* (%)	0	0	0	1.000
Pocket hematoma, *n* (%)	3 (0.9)	2 (1.1)	1 (0.6)	0.565
Pocket infection, *n* (%)	4 (1.2)	4 (2.2)	0	0.169
Incision algesia, *n* (%)	1 (0.3)	1 (0.5)	0	0.946
Pericardial effusion, *n* (%)	5 (1.5)	1 (0.5)	4 (2.5)	0.291
MACE	32 (9.4)	13 (7.1)	19 (11.9)	0.157
Acute myocardial infarction, *n* (%)	4 (1.2)	0	4 (2.5)	0.099
Acute heart failure, *n* (%)	15 (4.4)	9 (4.9)	6 (3.8)	0.794
Ventricular fibrillation, *n* (%)	1 (0.3)	1 (0.5)	0	0.946
Cerebral infarction, *n* (%)	5 (1.5)	0	5 (3.1)	0.050
Subdural hemorrhage, *n* (%)	1 (0.3)	1 (0.5)	0	0.946
Pacemaker reimplantation, *n* (%)	1 (0.3)	1 (0.5)	0	0.946
Cardiac tamponade, *n* (%)	1 (0.3)	0	1 (0.6)	0.946
Death due to CVD, *n* (%)	4 (1.2)	1 (0.5)	3 (1.9)	0.522
Rehospitalization due to CVD, *n* (%)	44 (12.9)	22 (12.1)	22 (13.8)	0.321
All-cause mortality, *n* (%)	9 (2.6)	3 (1.6)	6 (3.8)	0.377

CVD, denotes cardiovascular disease; MACE, major adverse cardiocerebrovascular events.

LBBP is a novel and feasible pacing maneuver to achieve physiological pacing. LBBP requires the capture of left bundle branch potential to mimic the normal electric conduction. In our multicenter study, LBB potential is recorded in 54.3% of the population, and 58.9% of the younger group and 50.0% of the elderly group, respectively. The capture of left conduction system could be hard, as most studies on LBBP reported that the ratio of LBB potential capture ranged between 50 and 80% (3, 12, 21, 22). An animal study has confirmed that positioning the lead deep enough to the left septal subendomyocardium could easily capture the left conduction system (23). Therefore, based on our findings, we believe that in most situations the capture of the left conduction system is mostly dependent on lead manipulation rather than age and condition of patients. Besides, several clinical evidences validated that LBBP could be achieved safely (3, 10, 12, 24). However, most studies have failed to evaluate

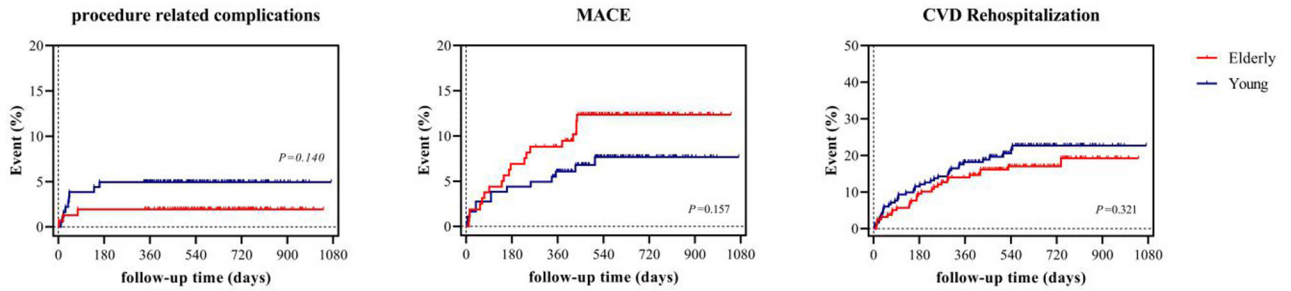

FIGURE 4 | Survival analysis of procedure related complications, MACE, and rehospitalization due to CVD. MACE denotes major adverse cardiovascular event, CVD cardiovascular disease.

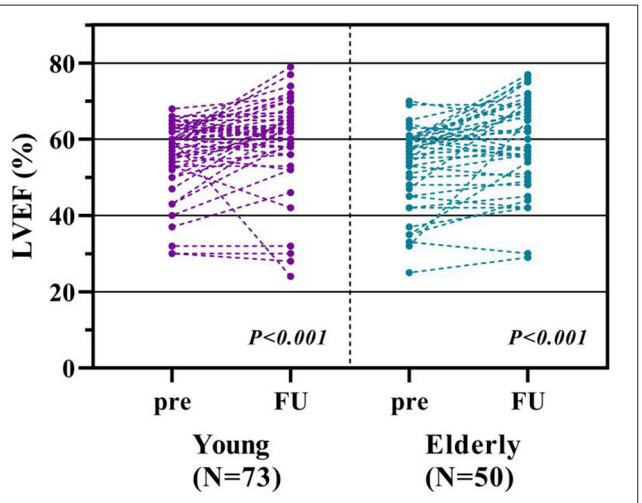

FIGURE 5 | Comparison of echocardiographic measurements. Figure from the left to the right showed the comparison of preprocedural and the 12th month measurements of left ventricular ejection fraction (LVEF) between young and elderly groups.

the efficacy in the advanced elderly population. In our evaluation of safety, through a follow-up of 20.0 ± 6.1 months, the incidence of overall safety events was low in both groups and similar to that of previous studies (21). Among complications related to LBBP, lead-related complications rarely occur. Chen et al. reported two complications in 612 patients (24) and Su et al. reported two cases of lead dislodgement in 632 patients (10), which are similar to the incidence in our study. Since Huang et al. (16) published and standardized the LBBP maneuver and criteria (18), complications like lead dislodgement have been rarely reported in an experienced center.

Specifically, elderly patients undergoing LBBP were at a higher risk of perforation and should be independently considered. One previous study has shown that ventricular perforation is correlated with several factors during conventional pacing, including the use of temporary pacemakers, use of steroids, use of helical screw leads, BMI of <20, and old age (13). Most importantly, their study indicates that a thinning of the cardiac wall in the elderly population and excessive leads in the RV were the major risk factors contributing to perforation. In the consideration of LBBP, multiple leads were routinely used including one or two active fixation 3,830 leads and sometimes temporary pacing lead, which could presumably pose a higher risk of complication, especially when LBBP was performed in the elderly population. In the present study, four out of five cases of periprocedural pericardial effusion occurred in the elderly group and one case of cardiac tamponade occurred requiring pericardiocentesis, which failed to reach a statistical significance. Compared with previous studies on LBB and His-bundle pacing, the incidence of perforation ranged from 0 to 3%, (10, 12, 24) which was relatively low and comparable with ours.

Collectively, we believe the overall safety of LBBP in the elderly is acceptable in an experienced center. However, we acknowledge that the incidence of complications was still too low to detect the significance; larger scaled studies are warranted to provide stronger evidence on safety in the elderly population. Based on our experience, LBBP should be performed with extra caution in patients with advanced age, while assessment of lead depth by angiography could help prevent perforation. We recommend assessment of lead depth with the following criteria: (1) Unipolar pacing impedance at the distal tip should be > 500 ohms (sharp decrement indicates perforation into LV); (2) Once LBB potential has been recorded and pacing parameters are acceptable, screwing should be immediately stopped; and (3) Under DSA, we judged lead depth by continuously injecting contrast (**Figures 1D–F**). In addition, when retracting the delivery sheath, a rebound of the distal portion of the lead should be monitored to confirm stable fixation (16).

Last but not least, the benefits of LBBP in patients over the age of 80 was also comparable with the younger population. LBBP could achieve physiological conduction, mechanical synchrony, and correct LBB block (3, 6, 25, 26), and presumably could improve the outcomes of patients with bradycardia. Our multicenter study showed that LBBP in elderly patients could indeed achieve comparable shortening of QRS duration and improvement of cardiac function with the younger group, and such results were in accord with the previous published studies (3, 12, 26). However, although,

not statistically significant, there was a tendency of higher incidence of MACE in the elderly group including acute myocardial infarction and cerebral infarction. We believe such a tendency resulted from the high rate of comorbidities in the elderly population. Therefore, we believe that LBBP could correct bradycardia with better electrical and mechanical synchrony in elderly patients, but the benefits should not be overestimated.

LIMITATION

Our results should be interpreted with caution. First, our results cannot be extrapolated to patients who undergo pacemaker implant for reasons other than symptomatic bradycardia. Second, we aimed to compare the performance of LBBP between two age groups, while a comparison of LBBP with conventional RV pacing in the elderly population could better validate the benefits and risks of LBBP. Well-designed, large-scaled, comparative studies are required to further illustrate the safety and efficacy of LBBP in the elderly population. In addition, although, the sample size was considerable and the follow-up period was over 1 year, it was still too short to detect a late difference between groups. Studies of a larger scale and with longer follow-up periods are necessary to validate the long-term safety and benefits of LBBP.

CONCLUSIONS

Compared to the younger group, LBBP could be achieved in patients over 80 years old with symptomatic bradycardia, and comparable mid-term safety and prognosis can be observed. Long-term safety and benefits of LBBP still require further evaluation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by ethics committee of Shanghai Tenth People's Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

DZ, XC, and SW contributed to the interpretation of data for the work. ZR and BC contributed to drafting the work. PJ, YC, JuZ, JiZ, HY, and XL contributed to the acquisition of data. RG, HL, and JX contributed to the analysis and revision of the work. DZ, XC, and YX contributed to the conception of the work. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the National Nature Science Foundation of China [Grant No. JX 81900292 and SW 81900456], Fundamental Research Funds for the Central Universities [Grant No. SW 2042018kf0102], Renmin Hospital of Wuhan University [Grant No. SW RMYD2018M37], Clinical Research Plan of SHDC, YX, [Grant No. SHDC2020CR1040B], and XC, [Grant No. SHDC2020CR4003].

ACKNOWLEDGMENTS

The authors would like to offer their sincere thanks to Prof. Weijian Huang from the Heart Center of the First Affiliated Hospital of Wenzhou Medical University and Prof. Kenneth A. Ellenbogen from VCU Pauley Heart Center of Medical college of Virginia for their support and precious advice.

REFERENCES

1. Deshmukh P, Casavant DA, Romanyshyn M, Anderson K. Permanent, direct His-bundle pacing: a novel approach to cardiac pacing in patients with normal His-Purkinje activation. *Circulation.* (2000) 101:869–77. doi: 10.1161/01.CIR.101.8.869
2. Huang W, Zhou X, Ellenbogen KA. Pursue physiological pacing therapy: A better understanding of left bundle branch pacing and left ventricular septal myocardial pacing *Heart Rhythm.* (2021). doi: 10.1016/j.hrthm.2021.05.013. [Epub ahead of print].
3. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, et al. Long-term outcomes of His bundle pacing in patients with heart failure with left bundle branch block. *Heart.* (2019) 105:137–43. doi: 10.1136/heartjnl-2018-313415
4. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, et al. Benefits of permanent His bundle pacing combined with atrioventricular node ablation in atrial fibrillation patients with heart failure with both preserved and reduced left ventricular ejection fraction. *J Am Heart Assoc.* (2017) 6:e005309. doi: 10.1161/JAHA.116.005309
5. Sharma PS, Naperkowski A, Bauch TD, Chan JYS, Arnold AD, Whinnett ZI, et al. Permanent His bundle pacing for cardiac resynchronization therapy in patients with heart failure and right bundle branch block. *Circ Arrhythm Electrophysiol.* (2018) 11:e006613. doi: 10.1161/CIRCEP.118.006613
6. Wu S, Su L, Vijayaraman P, Zheng R, Cai M, Xu L, et al. Left bundle branch pacing for cardiac resynchronization therapy: non-randomized on-treatment comparison with his bundle pacing and biventricular pacing. *Can J Cardiol.* (2021) 37:319–28. doi: 10.1016/j.cjca.2020.04.037
7. Sharma PS, Dandamudi G, Naperkowski A, Oren JW, Storm RH, Ellenbogen KA, et al. Permanent His-bundle pacing is feasible, safe, and superior to right ventricular pacing in routine clinical practice. *Heart Rhythm.* (2015) 12:305–12. doi: 10.1016/j.hrthm.2014.10.021
8. Su L, Wu S, Wang S, Wang Z, Xiao F, Shan P, et al. Pacing parameters and success rates of permanent His-bundle pacing in patients with narrow QRS: a single-centre experience. *Europace.* (2019) 21:763–70. doi: 10.1093/europace/euy281
9. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, et al. A novel pacing strategy with low and stable output: pacing the left bundle branch immediately

beyond the conduction block. *Can J Cardiol.* (2017) 33:1736.e1731–3. doi: 10.1016/j.cjca.2017.09.013
10. Su L, Wang S, Wu S, Xu L, Huang Z, Chen X, et al. Long-term safety and feasibility of left bundle branch pacing in a large single center study. *Circ Arrhythm Electrophysiol.* (2021) 14:e009261. doi: 10.1161/CIRCEP.120.009261
11. Huang W, Wu S, Vijayaraman P, Su L, Chen X, Cai B, et al. Cardiac resynchronization therapy in patients with non-ischemic cardiomyopathy using left bundle branch pacing. *JACC Clin Electrophysiol.* (2020) 6:849–58. doi: 10.1016/j.jacep.2020.04.011
12. Chen X, Jin Q, Bai J, Wang W, Qin S, Wang J, et al. The feasibility and safety of left bundle branch pacing vs. right ventricular pacing after mid-long-term follow-up: a single-centre experience. *Europace.* (2020) 22:ii36–44. doi: 10.1093/europace/euaa294
13. Mahapatra S, Bybee KA, Bunch TJ, Espinosa RE, Sinak LJ, McGoon MD, et al. Incidence and predictors of cardiac perforation after permanent pacemaker placement. *Heart Rhythm.* (2005) 2:907–11. doi: 10.1016/j.hrthm.2005.06.011
14. Antonelli D, Freedberg NA, Bushari LI, Feldman A, Turgeman Y. Permanent pacing in non-agenarians over 20-year period. *Pacing Clin Electrophysiol.* (2015) 38:48–53. doi: 10.1111/pace.12499
15. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J.* (2013) 34:2281–329. doi: 10.1093/eurheartj/eht150
16. Huang W, Chen X, Su L, Wu S, Xia X, Vijayaraman P. A beginner's guide to permanent left bundle branch pacing. *Heart Rhythm.* (2019) 16:1791–6. doi: 10.1016/j.hrthm.2019.06.016
17. Chen X, Wu S, Su L, Su Y, Huang W. The characteristics of the electrocardiogram and the intracardiac electrogram in left bundle branch pacing. *J Cardiovasc Electrophysiol.* (2019) 30:1096–101. doi: 10.1111/jce.13956
18. Wu S, Chen X, Wang S, Xu L, Xiao F, Huang Z, et al. Evaluation of the criteria to distinguish left bundle branch pacing from left ventricular septal pacing. *JACC Clin Electrophysiol.* (2021). doi: 10.1016/j.jacep.2021.02.018. [Epub ahead of print].
19. Fang EF, Scheibye-Knudsen M, Jahn HJ, Li J, Ling L, Guo H, et al. A research agenda for aging in China in the 21st century. *Ageing Res Rev.* (2015) 24:197–205. doi: 10.1016/j.arr.2015.08.003
20. Armaganijan LV, Toff WD, Nielsen JC, Andersen HR, Connolly SJ, Ellenbogen KA, et al. Are elderly patients at increased risk of complications following pacemaker implantation? A meta-analysis of randomized trials. *Pacing Clin Electrophysiol.* (2012) 35:131–4. doi: 10.1111/j.1540-8159.2011.03240.x
21. Li Y, Chen K, Dai Y, Li C, Sun Q, Chen R, et al. Left bundle branch pacing for symptomatic bradycardia: implant success rate, safety, and pacing characteristics. *Heart Rhythm.* (2019) 16:1758–65. doi: 10.1016/j.hrthm.2019.05.014
22. Sharma PS, Dandamudi G, Herweg B, Wilson D, Singh R, Naperkowski A, et al. Permanent His-bundle pacing as an alternative to biventricular pacing for cardiac resynchronization therapy: a multicenter experience. *Heart Rhythm.* (2018) 15:413–20. doi: 10.1016/j.hrthm.2017.10.014
23. Chen X, Jin Q, Li B, Jia J, Sharma PS, Huang W, et al. Electrophysiological parameters and anatomical evaluation of left bundle branch pacing in an in vivo canine model. *J Cardiovasc Electrophysiol.* (2020) 31:214–9. doi: 10.1111/jce.14300
24. Chen X, Wei L, Bai J, Wang W, Qin S, Wang J, et al. Procedure-related complications of left bundle branch pacing: a single-center experience. *Front Cardiovasc Med.* (2021) 8:645947. doi: 10.3389/fcvm.2021.645947
25. Ye Y, Wu S, Su L, Sheng X, Zhang J, Wang B, et al. Feasibility and Outcomes of Upgrading to Left Bundle Branch Pacing in Patients With Pacing-Induced Cardiomyopathy and Infranodal Atrioventricular Block. *Front Cardiovasc Med.* (2021) 8:674452. doi: 10.3389/fcvm.2021.674452
26. Cai B, Huang X, Li L, Guo J, Chen S, Meng F, et al. Evaluation of cardiac synchrony in left bundle branch pacing: insights from echocardiographic research. *J Cardiovasc Electrophysiol.* (2020) 31:560–9. doi: 10.1111/jce.14342

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frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 03 September 2021
doi: 10.3389/fcvm.2021.712051

Novel Wide-Band Dielectric Imaging System Guided Lead Deployment for His Bundle Pacing: A Feasibility Study

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Introduction: His bundle pacing (HBP) is the most widely used physiological pacing modality, but difficulties in locating the His bundle lead to high fluoroscopic exposure. An electroanatomical mapping (EAM) system can be an efficient tool to achieve HBP implantation with near-zero fluoroscopic visualization.

Methods: In the study, 20 patients who had indications for pacemaker implantation were prospectively enrolled and underwent HBP implantation either with the conventional fluoroscopy approach (the standard group) or guided by a novel KODEX-EPD mapping system (the EAM-guided group). The success rate, procedural details, pacing parameters, and procedure-related complications were compared between the two groups.

Results: In the study, 20 consecutive patients were randomized with 10 patients in each group. HBP was successfully achieved in nine patients in the standard group and nine patients in the EAM-guided group. The procedural time was similar between the EAM-guided group vs. the standard group (85.40 ± 22.34 vs. 86.50 ± 15.05 min, $p = 0.90$). In comparison with the standard group, the EAM-guided group had a significant shorter total fluoroscopic time (FT) (1.45 ± 0.58 vs. 12.36 ± 5.46 min, $p < 0.01$) and His lead fluoroscopic time (HL-FT) (0.84 ± 0.56 vs. 9.27 ± 5.44 min, $p < 0.01$), while lower total fluoroscopic dose (3.13 ± 1.24 vs. 25.38 ± 11.15 mGy, $p < 0.01$) and His lead fluoroscopic dose (1.85 ± 1.17 vs. 19.06 ± 11.03 mGy, $p < 0.01$). No significant differences were observed in paced QRS duration and pacing parameters between the two groups. During a 3-month follow-up, one patient had a capture threshold increased >1 V/1.0 ms in the standard group, while no other complications were recorded in either group.

Conclusion: The KODEX-EPD system could facilitate HBP implantation with significantly reduced FT and dose without compromising the procedural time.

Keywords: His bundle pacing, radiation exposure, electroanatomical mapping, fluoroscopy, implantation technique

OPEN ACCESS

Edited by:
Richard Gary Trohman, Rush University, United States

Reviewed by:
Gaurav Upadhyay, University of Chicago Medicine, United States
Kumar Narayanan, Medicover Hospitals, India

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Specialty section:
This article was submitted to Cardiac Rhythmology, a section of the journal Frontiers in Cardiovascular Medicine

Received: *19 May 2021*
Accepted: *26 July 2021*
Published: *03 September 2021*

Citation:
Hua W, Liu X, Gu M, Niu H-x, Chen X, Tang M and Zhang S (2021) Novel Wide-Band Dielectric Imaging System Guided Lead Deployment for His Bundle Pacing: A Feasibility Study. Front. Cardiovasc. Med. 8:712051. doi: 10.3389/fcvm.2021.712051

INTRODUCTION

The traditional right ventricular pacing (RVP) is associated with a higher risk of atrial fibrillation and heart failure and is regarded as a non-physiological pacing modality (1). His bundle pacing (HBP) maintains synchronous ventricular activation by direct stimulation of the His-Purkinje conduction system, which avoids the deleterious effects in RVP, and is considered as an alternative choice in patients who need frequent ventricular pacing (2). However, locating the His bundle (HB) region can be challenging and time-consuming, resulting in significantly higher fluoroscopic exposure compared to traditional RVP (3). In our previous studies, we found that the procedural and fluoroscopic time (FT) could be shortened by a contrast injection visualization technique, however, the overall FT was still relatively longer (4, 5). The higher fluoroscopic exposure can cause damage to both the patients and operators (6). A three-dimensional (3D) electroanatomical mapping (EAM) system has been applied as an efficient way to achieve zero fluoroscopic visualization of the HB region (7). A 3D anatomical image obtained by the EAM system can provide a reliable anatomical reference for searching the HB region with significantly reduced fluoroscopic exposure. Recent studies showed the feasibility of EAM-guided HBP implantation by using the Ensite NavX (St. Jude Medical, St. Paul, MN, USA) or CARTO (Biosense Webster Inc, Irvine, CA, USA) mapping system (8–10).

A KODEX-EPD cardiac imaging and navigation system (EPD Solutions, Philips, Best, The Netherlands) is a novel imaging system that uses dielectric imaging to acquire and display high-resolution anatomical images (11, 12). This system distinguishes materials and generates images based on their different dielectric properties, which is determined by their conductivity and permittivity with respect to the frequency of the electrical field. Compared to the traditional impedance-based systems that use single frequency electrical potential measurements, this dielectric-based system measures conductivity and permittivity at multiple frequencies to determine the dielectric dispersion pattern, which is subsequently used to generate a function that relates the dielectric dispersion to the spatial position in the thorax (**Supplementary Table 1** and **Supplementary Figure 1**). This method is theoretically less susceptible to the inhomogeneities in the body structures and movement of the organs such as heart beat and respiration, which allows for a high spatial resolution. Previous studies showed that this system could provide a computed tomography-like image, and the image quality generated by this system was noninferior to CARTO (13, 14).

In our center, we previously reported a case of HBP implantation facilitated by this novel KODEX-EPD system (15). Since then, we have applied it in a series of patients. In this study, we aimed to assess the feasibility of the KODEX-EPD system-guided HBP implantation in a cohort of patients and compare the procedural outcomes with those who achieved HBP using the conventional fluoroscopy approach.

MATERIALS AND METHODS

This is a prospective, randomized study that enrolled 20 patients with bradycardia with an indication for pacing therapy in Fuwai Hospital, Beijing, China from September to December 2020. All patients were grouped by the random number table method and underwent HBP implantation either with the conventional fluoroscopy approach (the standard group) or guided by a novel KODEX-EPD mapping system (the EAM-guided group). The patients were excluded if they: (1) needed implantable cardioverter defibrillator or cardiac resynchronization therapy; (2) were <18-years-old. This study was approved by the Ethics Committee of Fuwai Hospital and written informed consent was obtained from all the patients.

Implantation Tools

All HBP implantations in this study were performed by using the Select Secure 3830 pacing lead (Medtronic Inc, Minneapolis, MN, USA) and the fixed-curve C315 HIS sheath (Medtronic Inc, Minneapolis, MN, USA).

Implantation Procedure in the Standard Group

The procedure of HBP implantation in the standard group was the same as previously described (3). In brief, under the right anterior oblique 30° (RAO 30°) fluoroscopic view, the 3830 pacing lead was placed at the junction of the atrioventricular ring to search the ideal lead deployment site for HBP where the His potential could be recorded or the HB could be captured by unipolar pace mapping (**Figure 1**). The lead was fixed where the pacing parameters were satisfactory. The unsuccessful HBP were defined as: (1) the HB capture threshold or the correction threshold for bundle branch block (BBB) > 2.5 V/1 ms in three attempts; (2) the total FT was more than 20 min.

Implantation Procedure in the EAM-Guided Group

In the EAM-guided group, the procedure of the HBP implantation was similar to the previously reported, and was mainly divided into two steps (**Figure 2**) (15):

1. Locate the HB Region
   Before the procedure, multiple anisotropic fields were induced by the external dielectric sensors attached to the body surface of the patient. After local anesthesia and the puncture of the left subclavian vein, the quadripolar catheter (Abbott Inc, St Paul, MN, USA) was advanced into the right atrium (RA). Then the KODEX-EPD system was connected to the catheter, which received the sophisticated electrical field information transmitted from the catheter. Based on the electrical field information, the 3D cardiac anatomical image was calculated, and the images of superior vena cava (SVC), inferior vena cava (IVC), RA, tricuspid valve annulus (TVA), right atrial appendage (RAA), and right ventricle (RV) were visualized by roving the catheter within the cardiac chamber without fluoroscopy (**Figures 3**, **4**). Among them, the TVA was highlighted, and the HB region where the HB potential

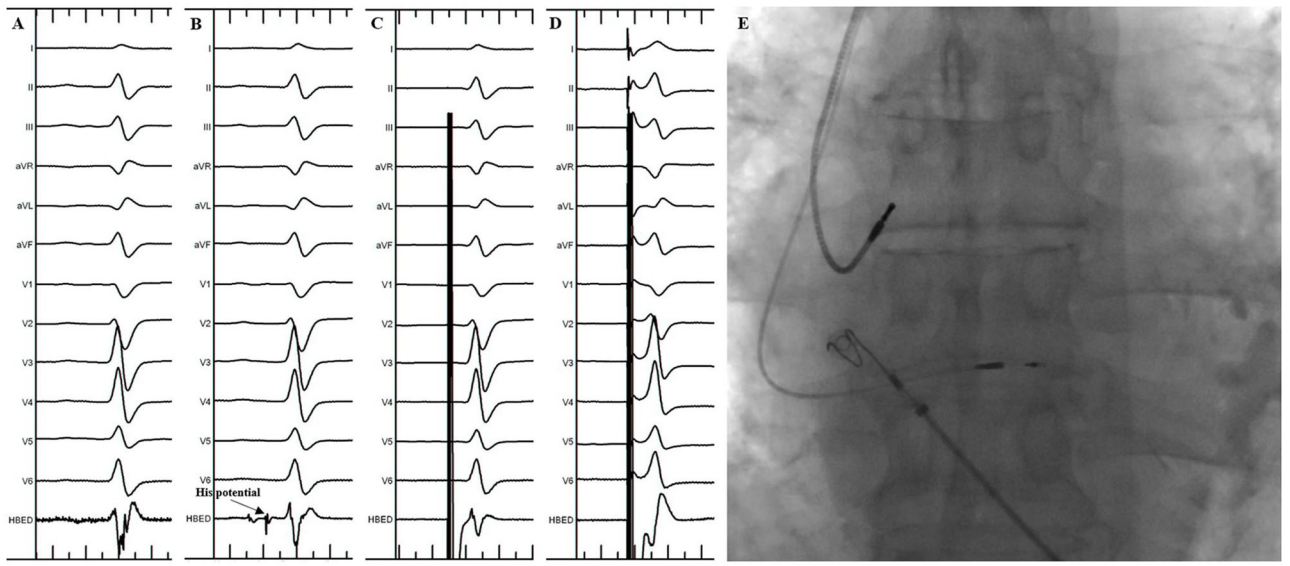

FIGURE 1 | His Bundle Pacing implantation in the standard group. **(A)** Sinus rhythm before the procedure. **(B)** His potential was recorded during the procedure. **(C)** Selective His bundle pacing was confirmed at a lower pacing output. **(D)** Nonselective His bundle pacing was achieved at a higher pacing output. **(E)** Final lead location in the fluoroscopic image.

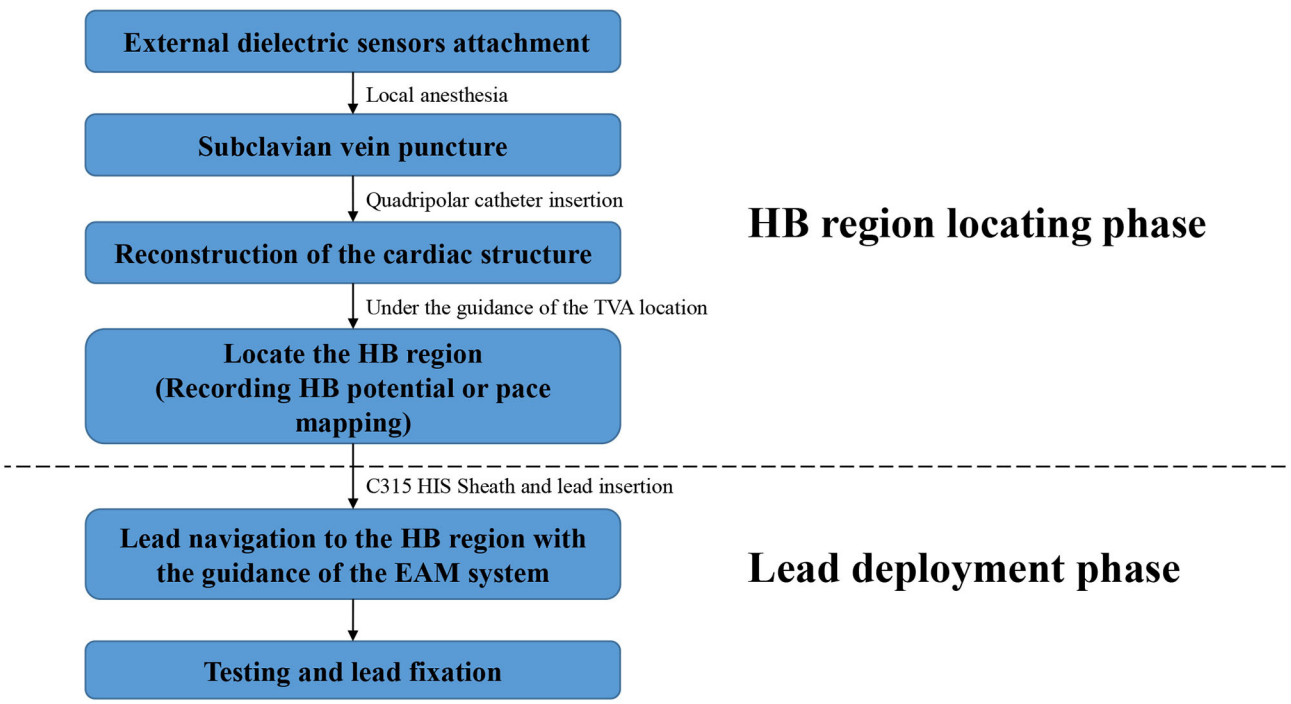

FIGURE 2 | Flowchart of the procedure details in the EAM-guided group. EAM, electroanatomical mapping; HB, His bundle.

could be recorded was marked under the guidance of the TVA location. The pace mapping (usually 10 mA at 2 ms) was sometimes used to assist in locating the HB region, and the region where the paced QRS morphology showed a selective HBP (S-HBP) or nonselective HBP (NS-HBP) pattern was also marked as the HB region.

2. HB Lead Deployment Guided by the KODEX-EPD System
Once the HB region was successfully marked, the quadripolar catheter was removed and the C315 HIS sheath was advanced into the RA. Then the 3830 pacing lead was advanced through the sheath with the distal tip exposed. The bipolar sites at the proximal end of the pacing lead were connected to the

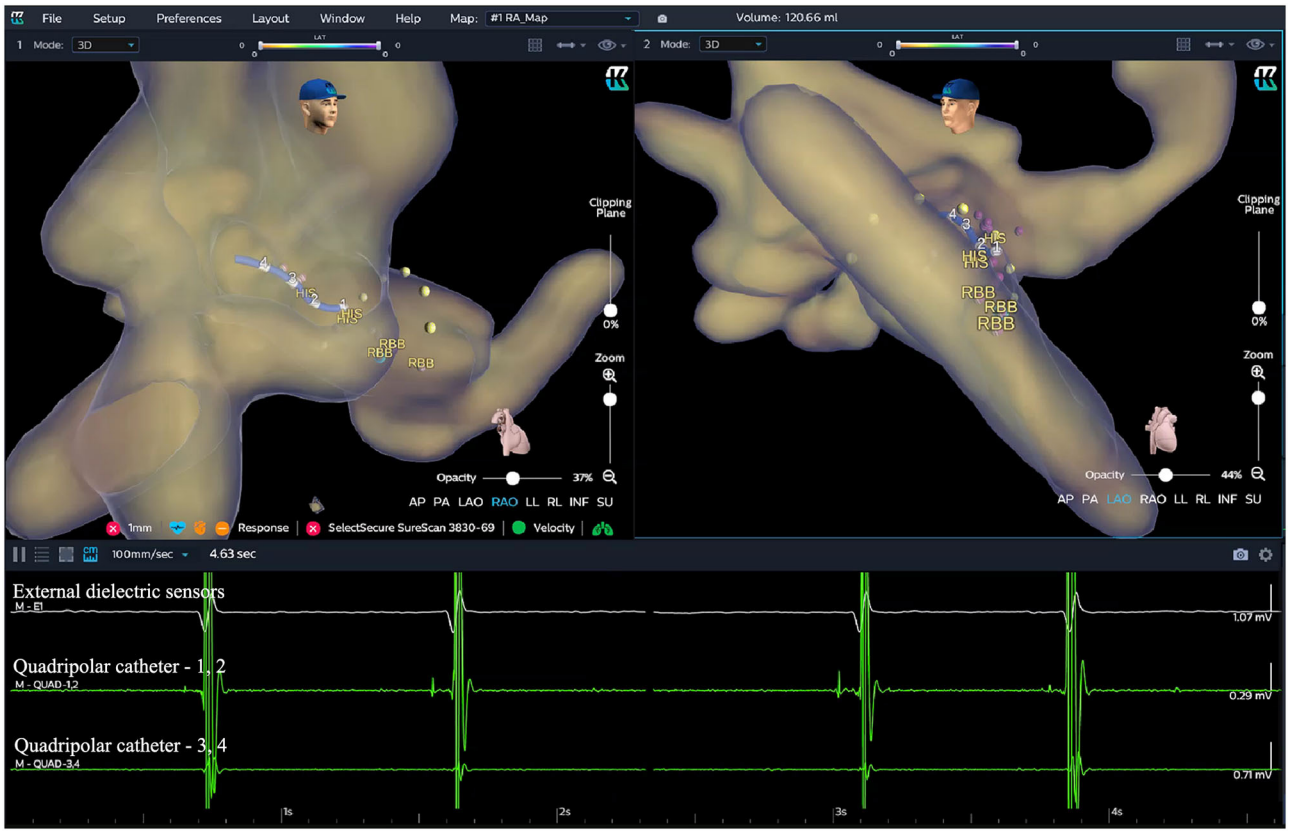

FIGURE 3 | Locating the HB region in the EAM-guided group. Based on the electrical field information, the three-dimensional (3D) cardiac anatomical image was calculated and visualized by moving the catheter without fluoroscopy. The TVA was highlighted (yellow dots in the figure), and the HB region (purple dots in the figure) where the HB potential could be recorded was marked under the guidance of the TVA location. EGMs from top to bottom showed the cardiac signal recorded from the external dielectric sensors, quadripolar catheter 1–2, and quadripolar catheter 3–4, respectively. EAM, electroanatomical mapping; EGM, electrogram; HB, His bundle; RBB, right bundle branch; TVA, tricuspid valve annulus.

KODEX-EPD system, and the lead was navigated to the HB region under the guidance of this system (**Figure 5**). The glass view provided by this system could give an enhanced perception of the lead location and orientation within the heart (**Figure 5**). The lead was finally fixed in the HB region where the pacing parameters were satisfactory (**Figure 5**). Similarly, the atrial lead could be placed in the RAA according to the anatomical image shown in this system without fluoroscopy. The criteria of unsuccessful HBP were similar to those in the standard group.

Data Collection and Follow-Up

Baseline data, such as demographic characteristics, implantation indications, and electrocardiographic measurements were collected at the enrollment. The total FT was the primary endpoint of this study, which was defined as the fluoroscopic duration from delivering the guidewire to the final lead fixation. The His lead fluoroscopic time (HL-FT) was defined as the fluoroscopic duration from advancing the 3830 pacing lead to the His lead fixation. In addition, the procedural time (PT), total fluoroscopic dose (FD), and His lead fluoroscopic dose (HL-FD) were also recorded. The S-HBP was defined as capturing only the HB without adjacent myocardium, which demonstrated an isoelectric interval between the pacing stimulus and the QRS onset. The NS-HBP was defined as capturing both the HB and the adjacent myocardium, in which no isoelectric interval could be observed. The pacing parameters that include capture threshold, R-wave amplitude, and impedance were recorded during the procedure and at 3-month follow-up, and the capture thresholds in patients with BBB recorded in this study were all correction thresholds. Echocardiographic measurements, such as left ventricular ejection fraction (LVEF) and left ventricular end-diastolic dimension (LVEDD) were performed at baseline and 3-month follow-up. The procedure-related complications such as capture threshold increased >1 V/1.0 ms, loss of capture, and lead dislodgement were also tracked during the follow-up.

Statistical Analysis

Based on the experience at the center, the mean total FT for conventional HBP implantation was estimated at 12 min with a SD of 5 min. By assuming a 75% reduction in total FT by using the EAM system, at least 14 patients required 90% power to

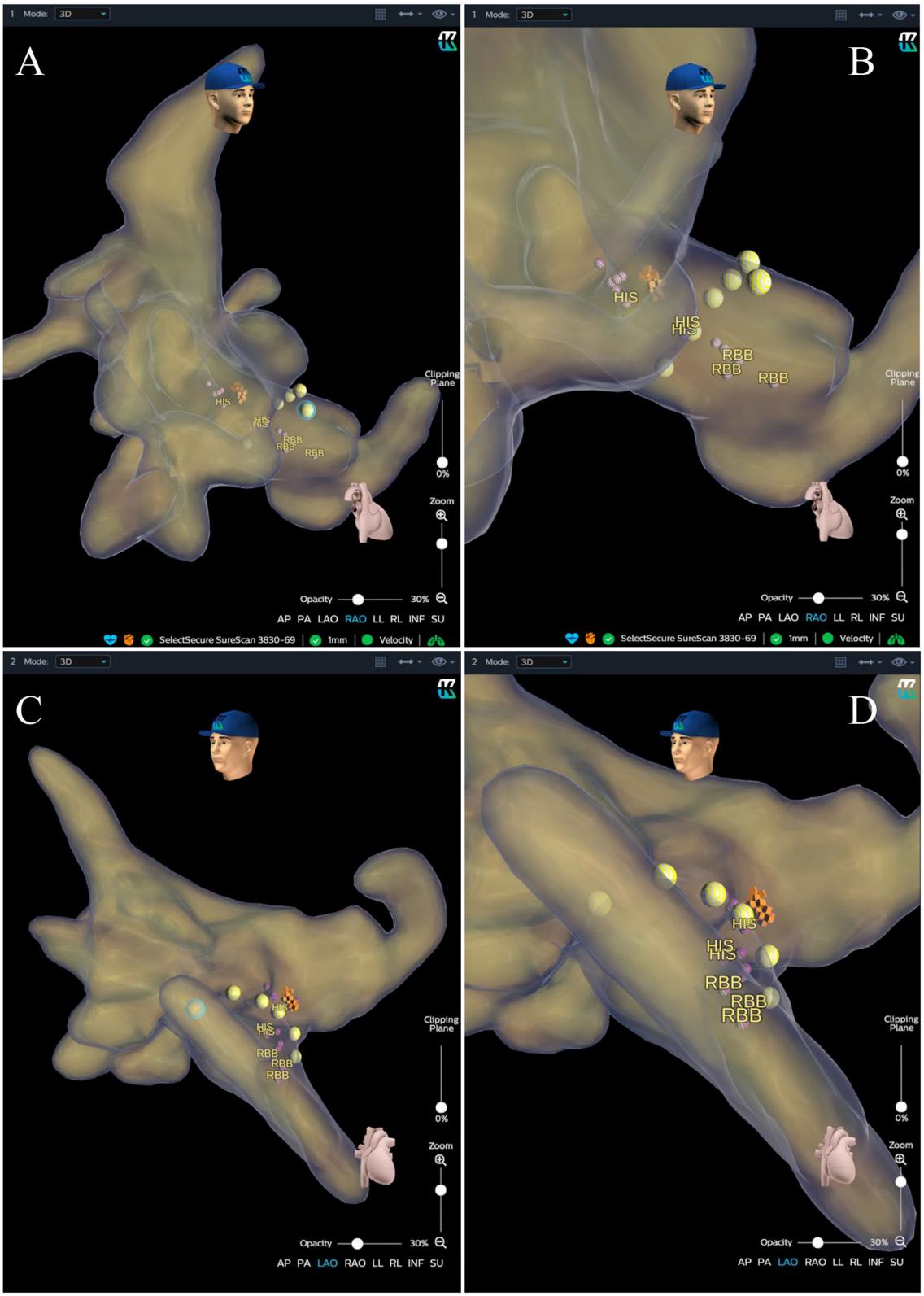

FIGURE 4 | Anatomical image calculated by the KODEX-EPD system. **(A)** Anatomical image in RAO view. **(B)** Enlarged image in RAO view. **(C)** Image in LAO view. **(D)** Enlarged image in LAO view. The purple and orange dots represent the sites where the His bundle potential can be recorded. The yellow dots represent the path of the tricuspid valve annulus. LAO, left anterior oblique; RAO, right anterior oblique; RBB, right bundle branch.

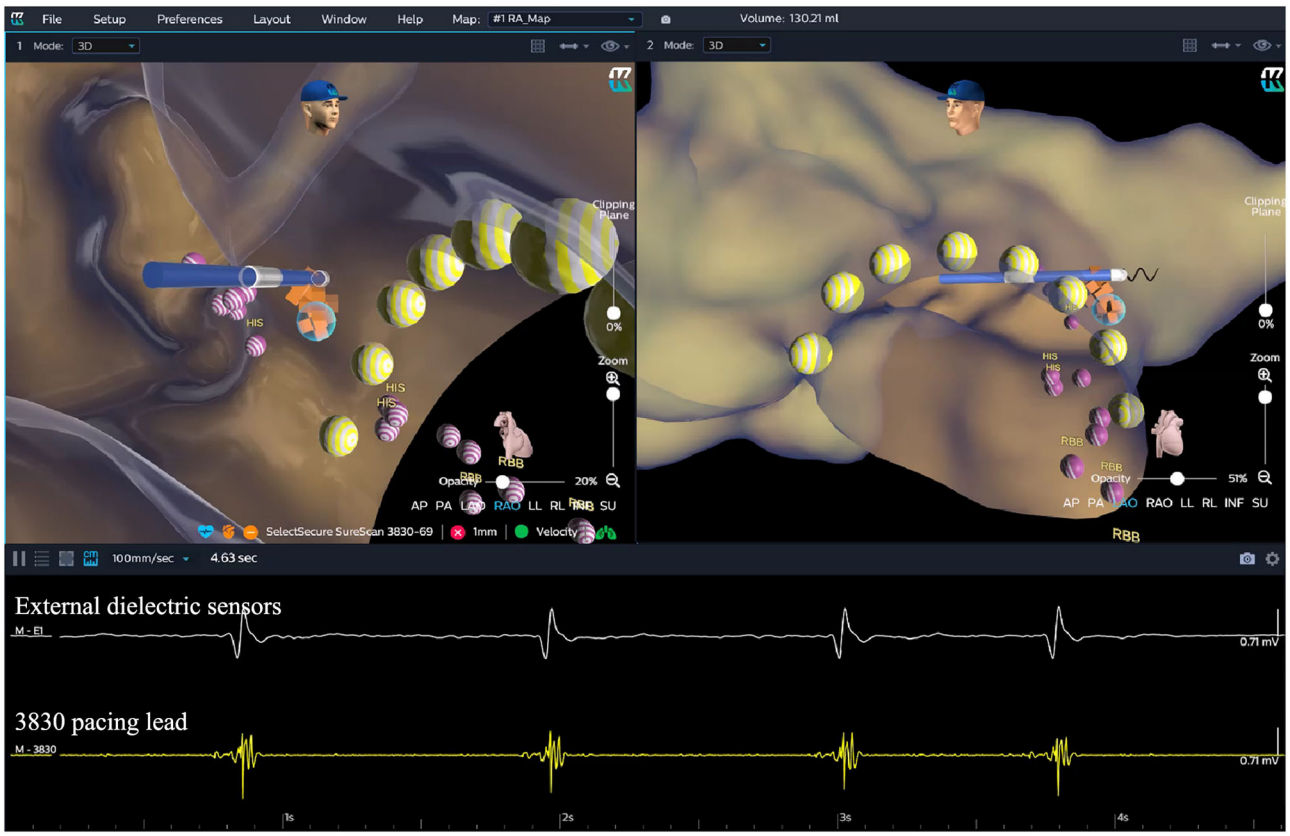

FIGURE 5 | HB lead deployment in the EAM-guided group. After the HB region was successfully marked, the lead was navigated to the HB region under the guidance of the KODEX-EPD system without fluoroscopy. The glass view provided by this system (setting of "opacity") could give an enhanced perception of the lead location and orientation within the heart. The lead was finally fixed in the target HB region. The yellow dots represent the path of the tricuspid valve annulus. The purple dots represent the sites where the HB potential can be recorded. The orange dots represent the target HB region. EGMs from top to bottom showed the cardiac signal recorded from the external dielectric sensors and the 3830 pacing lead, respectively. EAM, electroanatomical mapping; EGM, electrogram; HB, His bundle; RBB, right bundle branch.

detect this mean time reduction with a significance level of $\alpha = 0.05$. Assuming a 10% withdrawal or implant failure rate, at least 16 patients were needed to be randomized. The continuous data were described as mean ± SD and categorical data were performed as frequencies or percentages. An independent two-sample *t*-test was used to compare the differences between two groups if the data were normally distributed, while Wilcoxon signed-rank test was performed for data that were not normally distributed. Fisher's exact probabilities test was used for categorical variables to determine the differences between groups. A two-sided $P < 0.05$ was considered statistically significant. All the statistical analyses were performed using SPSS Statistics version 22.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Baseline Characteristics

In the study, from September to December 2020, 20 consecutive patients were randomized with 10 patients in each group. As summarized in **Table 1**, there were no significant differences in baseline characteristics between the two groups. More patients had atrioventricular block (AVB) than sinus node dysfunction (SND) as an indication for pacing therapy in both the groups. The baseline QRS duration in the standard group was similar to that in the EAM-guided group (115.7 ± 20.2 ms vs. 111.2 ± 18.5 ms, $P = 0.38$). Overall, the baseline LVEF and LVEDD were normal in both the groups.

Procedural Outcomes

The HBP implantation was successfully achieved in nine patients in the standard group and nine patients in the EAM-guided group. One case in the standard group was considered as unsuccessful as it failed to confirm HB capture within 20 min of total FT. In this case, the lead was finally placed at the left bundle branch (LBB) area. One unsuccessful case in the EAM-guided group had advanced His-ventricular conduction disease (HV interval of 80 ms) and left bundle branch block (LBBB), and the pacing output for correcting the conduction block was >2.5 V/1 ms after three lead screw-in attempts at the HB region. Then the lead was further advanced toward the cardiac apex by approximately 2 cm and was placed at the right side of the ventricular septum where the paced morphology showed a "W"

TABLE 1 | Baseline characteristics between the two groups.

	Standard group ($n = 10$)	EAM guided group ($n = 10$)	*P*-value
Demographics			
Age (years)	57.6 ± 16.2	55.4 ± 15.3	0.76
Male	6 (60.0%)	7 (70.0%)	1.00
Comorbidities			
Hypertension	5 (50.0%)	4 (40.0%)	1.00
Diabetes mellitus	2 (20.0%)	2 (20.0%)	1.00
Coronary disease	3 (30.0%)	2 (20.0%)	1.00
Indications			1.00
SND	3 (30.0%)	4 (40.0%)	
AVB	7 (70.0%)	6 (60.0%)	
Baseline ECG			
QRS duration (ms)	115.7 ± 20.2	111.2 ± 18.5	0.38
LBBB	2 (20.0%)	1 (10.0%)	1.00
RBBB	0 (0.0%)	1 (10.0%)	1.00
Echocardiography			
LVEF (%)	60.5 ± 6.1	59.4 ± 5.5	0.68
LVEDD (mm)	51.4 ± 6.4	49.9 ± 3.8	0.53

AVB, atrioventricular block; ECG, electrocardiogram; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; RBBB, right bundle branch block; SND, sinus node dysfunction.

pattern in lead V1. After a transient fluoroscopy to confirm the lead perpendicular to the septum, the lead was screwed deep into the left side of the interventricular septum and the paced morphology was carefully monitored to confirm LBB capture (16). Finally, left bundle branch pacing (LBBP) was achieved with a paced QRS duration of 120 ms and a peak left ventricular activation time of 70 ms.

Procedural Details in the EAM-Guided Group

The procedural details for individual patients in the EAM-guided group are listed in **Table 2**. As listed in **Table 2**, nine (90.0%) patients successfully underwent HBP implantation with the guidance of the KODEX-EPD system. Among them, S-HBP was achieved in four (44.4%) patients. The total FT was <2 min in each of the successful patients, and the HL-FT was <1 min in eight of nine patients. In addition, the total FD was <3 mGy in five of nine successful patients, and the HL-FD was <2 mGy in most of the patients (seven of nine).

Procedural Details and Outcomes Between Two Groups

As shown in **Table 3**, there were no significant differences in PT between the EAM-guided group vs. the standard group (85.40 ± 22.34 vs. 86.50 ± 15.05 min, $p = 0.90$). Compared to the standard group, the EAM-guided group had a significant shorter total FT (1.45 ± 0.58 vs. 12.36 ± 5.46 min, $p < 0.01$) and HL-FT (0.84 ± 0.56 vs. 9.27 ± 5.44 min, $p < 0.01$). In addition, the total FD (3.13 ± 1.24 vs. 25.38 ± 11.15 mGy, $p < 0.01$) and the HL-FD (1.85 ± 1.17 vs. 19.06 ± 11.03 mGy, $p < 0.01$) in the EAM-guided group were significantly lower as compared to those in the standard group.

For patients who had successfully achieved HBP implantation, no significant differences were observed in paced QRS duration between the two groups (the EAM-guided group vs. the standard group: 120.89 ± 17.18 vs. 123.33 ± 20.10 ms, $p = 0.79$). The pacing parameters such as capture threshold (1.10 ± 0.42 vs. 1.19 ± 0.35 V/1 ms, $p = 0.63$), R-wave amplitude (5.23 ± 1.99 vs. 5.27 ± 2.30 mV, $p = 0.97$), and impedance (556.11 ± 98.67 vs. 576.67 ± 98.08 Ω, $p = 0.66$) were similar between the EAM-guided group vs. the standard group.

Three-Month Follow-Up

During the 3-month follow-up, no significant differences were observed in the pacing parameters (capture threshold, R-wave amplitude, and impedance) and echocardiographic measurements between the two groups (**Table 3**). One patient in the standard group had a capture threshold increased >1 V/1.0 ms (from 1.1 V/1 ms to 2.3 V/1 ms), and no additional intervention was undertaken. No other procedure-related complications were recorded in both the groups.

DISCUSSION

In this study, we evaluated a novel KODEX-EPD mapping system that could develop a 3D anatomical image to help in locating the target HB region. The main findings of this study were: (1) the KODEX-EPD system could facilitate HBP implantation with a similar success rate compared to the standard approach; (2) the fluoroscopic time and dose in the EAM-guided group were significantly lower than those in the standard group, while the procedural time was not prolonged; (3) the pacing parameters were similar between the two groups.

His bundle pacing is considered as a physiological pacing modality in patients who need frequent ventricular pacing (17). However, locating the HB region can be challenging and time-consuming due to the small volume of the HB, which results in a significantly increased fluoroscopic exposure compared to the traditional RVP implantation (3). Those effects might increase the risk of genetic transformation or cancer to both the patients and operators (6). The EAM system, which is mainly used in the ablation procedure, is a common tool for zero fluoroscopic visualization of the cardiac structure, and can significantly reduce the radiation exposure of the interventional therapy (7). In addition, compared with the two-dimensional (2D) image obtained by the fluoroscopic image, the 3D anatomical image provided by the EAM system is more efficient in guiding the lead deployment in the pacemaker implantation. The previous studies showed the feasibility of the EAM-guided lead deployment for HBP implantation (8–10). In those studies, they evaluated two conventional EAM systems that include the Ensite NavX and CARTO mapping system.

KODEX-EPD cardiac imaging and navigation system is a novel wide-band dielectric imaging system, which is designed to acquire and analyze the dielectric energy and use this information to display a high-resolution, real-time 3D

TABLE 2 | EAM-guided group case list.

Case No.	Pacemaker indication	Baseline QRSd (ms)/Morphology	Capture type	Paced QRSd (ms)	PT (min)	Total FT (min)	HL-FT (min)	Total FD (mGy)	HL-FD (mGy)
1	AVB	110	S-HBP	110	113	1.8	1.2	3.7	2.5
2	SND	104	S-HBP	104	92	1.1	0.6	2.3	1.3
3	AVB	96	S-HBP	96	78	1.2	0.5	2.4	1.0
4	AVB	106	NS-HBP	132	89	1.5	0.9	3.2	2.0
5	AVB	148/LBBB	Failed, LBBP	120	94	2.9	2.3	6.3	4.9
6	SND	102	NS-HBP	142	63	1.5	0.6	3.2	1.3
7	SND	104	S-HBP	104	77	1.2	0.7	2.7	1.6
8	SND	88	NS-HBP	130	104	1.4	0.7	3.2	1.7
9	AVB	138/RBBB	NS-HBP	134	83	0.9	0.4	2.0	1.0
10	AVB	116	NS-HBP	136	72	1.0	0.5	2.3	1.2

AVB, atrioventricular block; EAM, electroanatomical mapping; FD, fluoroscopic dose; FT, fluoroscopic time; HL-FD, His lead fluoroscopic dose; HL-FT, His lead fluoroscopic time; LBBB, left bundle branch block; LBBP, left bundle branch pacing; NS-HBP, nonselective His bundle pacing; PT, procedural time; QRSd, QRS duration; RBBB, right bundle branch block; S-HBP, selective His bundle pacing; SND, sinus node dysfunction.

TABLE 3 | Implantation and follow-up results.

	Standard group ($n = 10$)	EAM guided group ($n = 10$)	*P*-value
Successful HBP	9 (90.0%)	9 (90.0%)	1.00
Dual chamber pacemaker	10 (100.00%)	10 (100.00%)	*N/A*
Procedural details*			
PT (min)	85.40 ± 22.34	86.50 ± 15.05	0.90
Total FT (min)	12.36 ± 5.46	1.45 ± 0.58	<0.01
HL-FT (min)	9.27 ± 5.44	0.84 ± 0.56	<0.01
Total FD (mGy)	25.38 ± 11.15	3.13 ± 1.24	<0.01
HL-FD (mGy)	19.06 ± 11.03	1.85 ± 1.17	<0.01
Paced QRSd (ms)	123.33 ± 20.10	120.89 ± 17.18	0.79
Pacing parameters			
Capture threshold (V/1 ms)	1.19 ± 0.35	1.10 ± 0.42	0.63
R-wave amplitude (mV)	5.27 ± 2.30	5.23 ± 1.99	0.97
Impedance (Ω)	576.67 ± 98.08	556.11 ± 98.67	0.66
Parameters at follow-up			
Capture threshold (V/1 ms)	1.29 ± 0.32	1.10 ± 0.29	0.21
R-wave amplitude (mV)	5.51 ± 2.84	5.53 ± 2.03	0.93
Impedance (Ω)	489.44 ± 67.77	479.22 ± 72.91	0.76
Echocardiography at follow-up			
LVEF (%)	62.00 ± 4.85	60.22 ± 4.41	0.30
LVEDD (mm)	51.11 ± 6.35	49.67 ± 3.12	0.55

EAM, electroanatomical mapping; FD, fluoroscopic dose; FT, fluoroscopic time; HBP, His bundle pacing; HL-FD, His lead fluoroscopic dose; HL-FT, His lead fluoroscopic time; PT, procedural time; QRSd, QRS duration; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

**Including patients who failed to achieve HBP.*

image of the cardiac structure (**Supplementary Table 1** and **Supplementary Figure 1**) (11, 12). The anatomical information needed to create the cardiac image is based on the dielectric signals acquired by the external dielectric sensors and the electrophysiological catheter. Even without physical contact with the cardiac wall, the dielectric sensing could show the detailed anatomical information inside of the heart and other structures such as the coronary sinus ostium, pulmonary veins, and atrioventricular valve. The image quality acquired by the KODEX-EPD system is noninferior to the CARTO mapping system as evaluated by the previous studies (13, 14). In addition, during the procedure, the anatomical image can be displayed as a novel panoramic (PANO) view, which transforms the 3D cardiac structure into a virtual 2D panoramic picture (**Figure 6**). This view allows all the anatomically relevant structures to be seen in one view, which could simplify the catheter or the lead navigation with minimal image maneuvering and make the operator free from the assistance of adjusting the map. Those features can improve the procedural efficiency. The previous studies showed the feasibility of using the KODEX-EPD system in radiofrequency or cryoballoon ablation in clinical practice (14, 18–20).

In this study, we evaluated the feasibility of using this novel mapping system to perform HBP implantation in a cohort of patients. The results showed that the fluoroscopic time and dose were significantly decreased under the guidance of the KODEX-EPD system without compromising the procedural time. To the best of our knowledge, this is the first study that evaluates the feasibility of using this system to guide the HB lead deployment in a cohort of patients with pacing indications. In addition, the KODEX-EPD system can not only facilitate the HBP implantation but also help to guide LBB lead deployment as shown in a patient with failed HBP implantation in the EAM-guided group.

The KODEX-EPD system is compatible with most of the catheters and the leads which are currently used in clinical practice, such as the 3830 pacing lead which is commonly used in His-Purkinje conduction system pacing. In our previous case study, in order to avoid the additional expenses, we did not choose the quadripolar catheter for EAM but directly used the 3830 pacing lead for the whole procedure. In this study, we used the quadripolar catheter instead of the pacing lead for EAM.

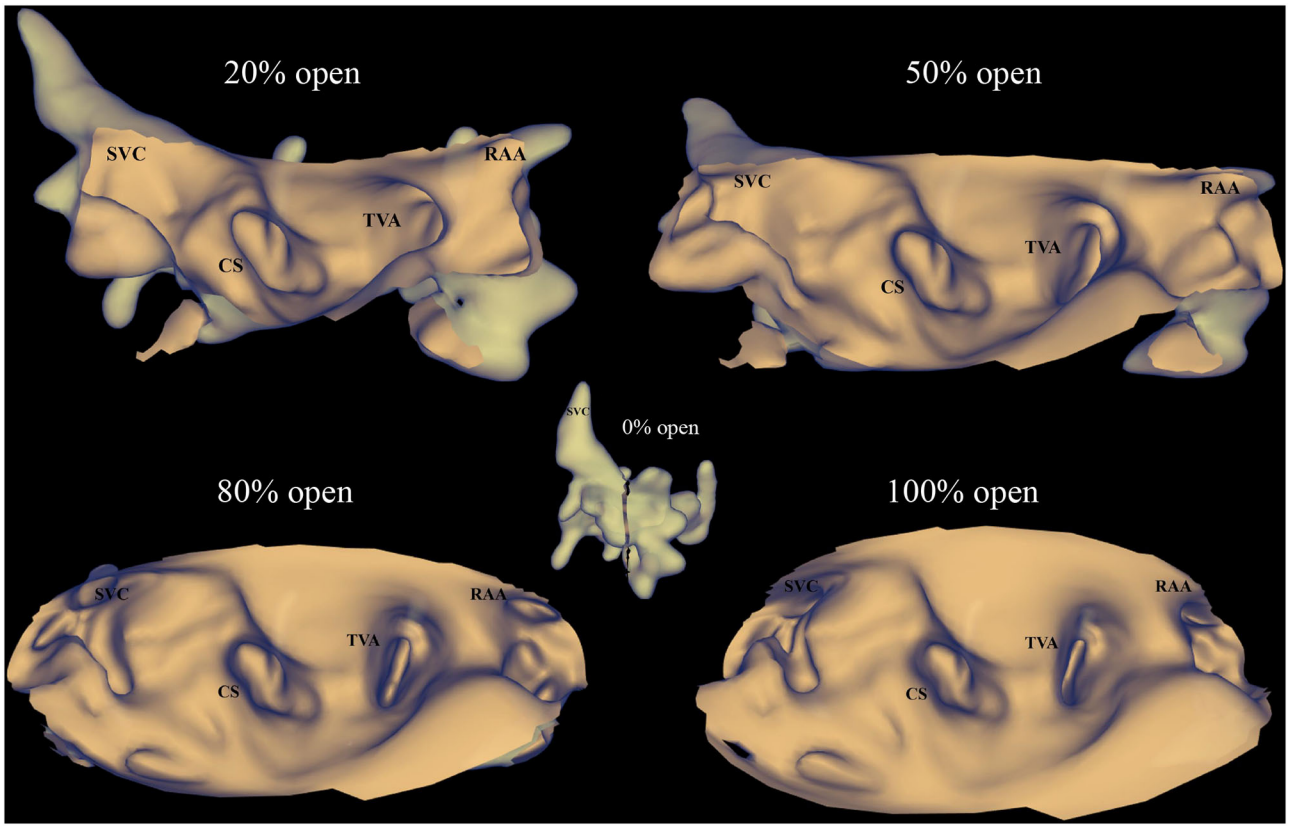

FIGURE 6 | PANO view of the KODEX-EPD system. The anatomical image in the KODEX system can be displayed as a novel panoramic (PANO) view, which transforms the 3D cardiac structure into a virtual two-dimensional (2D) panoramic picture. This view allows all the anatomically relevant structures to be seen in one view. The percentage of open (0% open to 100% open) represents the degree of transformation from a 3D image to a flattened image, 0% open means the image is still shown as a 3D cardiac structure, while 100% open means the full unfolding of the 3D cardiac structure. CS, coronary sinus; RAA, right atrial appendage; SVC, superior vena cava; TVA, tricuspid valve annulus.

After the anatomical image was obtained, the HB region could be immediately located according to the anatomical relationship between the HB region and the TVA, and the lead was directly deployed at the HB region. All of the above steps could be achieved with near-zero fluoroscopic visualization, which significantly reduced the fluoroscopic exposure as shown in this study. In order to ensure the safety of the patients, the following steps should be performed under fluoroscopy: (1) delivering the guidewire; (2) removing the sheath; and (3) confirming a proper slack at the lead location (21). These steps added only minimal radiation exposure while the total fluoroscopic time and dose in the EAM-guided group were significantly decreased compared to the standard group. This EAM-guided technique is particularly suitable for specific patients, such as pregnant women.

Limitations

Several limitations should be emphasized in this study. First, it was a single center study with a small sample size. However, this pilot study showed a significant reduction in the fluoroscopic time and dose, suggesting that this novel EAM system could be a novel zero fluoroscopic guidance tool for HBP implantation. Multicenter studies with a larger population are needed to further evaluate other potential merits with this EAM system. In addition, the mapping system and the catheter need additional costs, which could be offset by a significant reduction in fluoroscopic exposure and a potential improvement in procedural efficiency.

CONCLUSIONS

The KODEX-EPD system can facilitate HBP implantation with significant reduced fluoroscopic time and dose. Further studies with larger sample size are needed to evaluate other potential merits with this EAM system.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by this study was approved by the Ethics Committee of

Fuwai Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WH, MT, and SZ contributed to the conception and design of the study. MG, H-xN, and XC performed pacemaker implantation. XL and MG performed data collection and analysis. The first draft of the manuscript was written by WH and XL and all authors commented on the previous versions of the manuscript. All authors read and approved the final manuscript.

FUNDING

This study was supported by the National Natural Science Foundation of China, Beijing, China (Grant Number: 82070349), the Fundamental Research Funds for Central Universities (Grant Number: 3332019047), and the Innovation Funds for Graduate Students of Peking Union Medical College (Grant Number: 2019-1002-33).

ACKNOWLEDGMENTS

We thank Dr. Shlomo Ben-Haim (Hobart Group, London, UK) for his diligent review of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.712051/full#supplementary-material

REFERENCES

1. Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation.* (2003) 107:2932–7. doi: 10.1161/01.CIR.0000072769.17295.B1
2. Vijayaraman P, Chung MK, Dandamudi G, Upadhyay GA, Krishnan K, Crossley G, et al. His bundle pacing. *J Am Coll Cardiol.* (2018) 72:927–47. doi: 10.1016/j.jacc.2018.06.017
3. Vijayaraman P, Dandamudi G, Zanon F, Sharma PS, Tung R, Huang W, et al. Permanent His bundle pacing: Recommendations from a multicenter his bundle pacing Collaborative Working Group for standardization of definitions, implant measurements, and follow-up. *Hear Rhythm.* (2018) 15:460–8. doi: 10.1016/j.hrthm.2017.10.039
4. Liu X, Niu H-X, Gu M, Chen X, Hu Y, Cai M, et al. Contrast-enhanced image-guided lead deployment for left bundle branch pacing. *Hear Rhythm.* (2021) 18:1318–25. doi: 10.1016/j.hrthm.2021.04.015
5. Gu M, Niu H, Hu Y, Liu X, Zhang N, Cai M, et al. Permanent his bundle pacing implantation facilitated by visualization of the tricuspid valve annulus. *Circ Arrhythm Electrophysiol.* (2020) 13:e008370. doi: 10.1161/CIRCEP.120.008370
6. Miller DL, Balter S, Schueler BA, Wagner LK, Strauss KJ, Vañó E. Clinical radiation management for fluoroscopically guided interventional procedures. *Radiology.* (2010) 257:321–32. doi: 10.1148/radiol.10091269
7. Lemery R. Interventional electrophysiology at the crossroads: cardiac mapping, ablation and pacing without fluoroscopy. *J Cardiovasc Electrophysiol.* (2012) 23:1087–91. doi: 10.1111/j.1540-8167.2012.02373.x
8. Orlov M V, Koulouridis I, Monin AJ, Casavant D, Maslov M, Erez A, et al. Direct Visualization of the his bundle pacing lead placement by 3-dimensional electroanatomic mapping: technique, anatomy, and practical considerations. *Circ Arrhythm Electrophysiol.* (2019) 12:e006801. doi: 10.1161/CIRCEP.118.006801
9. Hu Y, Ding L, Hua W, Gu M, Cai M, Chen X, et al. Comparison between His-bundle pacing guided by Ensite NavX system and conventional fluoroscopy. *J Interv Card Electrophysiol Int J Arrhythm Pacing.* (2020) 57:107–14. doi: 10.1007/s10840-019-00660-6
10. Sharma PS, Huang HD, Trohman RG, Naperkowski A, Ellenbogen KA, Vijayaraman P. Low fluoroscopy permanent his bundle pacing using electroanatomic mapping: a feasibility study. *Circ Arrhythm Electrophysiol.* (2019) 12:e006967. doi: 10.1161/CIRCEP.118.006967
11. Nicholls M, Kodex-EPD. mapping for AF ablation. *Eur Heart J.* (2019) 40:3003–5. doi: 10.1093/eurheartj/ehz647
12. Abeln BGS, van den Broek JLPM, van Dijk VF, Balt JC, Wijffels MCEF, Dekker LRC, et al. Dielectric imaging for electrophysiology procedures: The technology, current state, and future potential. *J Cardiovasc Electrophysiol.* (2021) 32:1140–6. doi: 10.1111/jce.14971
13. Romanov A, Dichterman E, Schwartz Y, Ibragimov Z, Ben-David Y, Rodriguez H, et al. High-resolution, real-time, and nonfluoroscopic 3-dimensional cardiac imaging and catheter navigation in humans using a novel dielectric-based system. *Hear Rhythm.* (2019) 16:1883–9. doi: 10.1016/j.hrthm.2019.06.020
14. Maurer T, Mathew S, Schlüter M, Lemes C, Riedl J, Inaba O, et al. High-resolution imaging of LA anatomy using a novel wide-band dielectric mapping system: first clinical experience. *JACC Clin Electrophysiol.* (2019) 5:1344–54. doi: 10.1016/j.jacep.2019.06.020
15. Hua W, Hu Y-R, Gu M, Cai C, Chen X-H, Niu H-X, et al. Feasible approach for His bundle pacing using a novel mapping system in patients receiving pacemaker therapy. *Hear case reports.* (2019) 5:433–5. doi: 10.1016/j.hrcr.2019.06.003
16. Huang W, Chen X, Su L, Wu S, Xia X, Vijayaraman P, et al. Beginner's guide to permanent left bundle branch pacing. *Hear Rhythm.* (2019) 16:1791–6. doi: 10.1016/j.hrthm.2019.06.016
17. Kusumoto FM, Schoenfeld MH, Barrett C, Edgerton JR, Ellenbogen KA, Gold MR, et al. 2018 ACC/AHA/HRS Guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the heart rhyt. *J Am Coll Cardiol.* (2019) 74:e51–e156. doi: 10.1161/CIR.0000000000000628
18. Cauti FM, Solimene F, Stabile G, Polselli M, Schillaci V, Arestia A, et al. Occlusion tool software for pulmonary vein occlusion verification in atrial fibrillation cryoballoon ablation. *Pacing Clin Electrophysiol.* (2021) 44:63–70. doi: 10.1111/pace.14130
19. Cauti FM, Rossi P, Polselli M, Iaia L, Giannitti CM, Bianchi S. Occlusion tool software for pulmonary vein occlusion verification in atrial fibrillation cryoballoon ablation to avoid the use of contrast injection. *Hear case reports.* (2020) 6:516–9. doi: 10.1016/j.hrcr.2020.05.011

20. Rillig A, Rottner L, Nodorp M, Lin T, Weimann J, Münkler P, et al. Novel Wide-Band Dielectric imaging system and occlusion tool to guide cryoballoon-based pulmonary vein isolation: feasibility and first insights. *Circ Arrhythm Electrophysiol.* (2020) 13:e009219. doi: 10.1161/CIRCEP.120.009219
21. Beer D, Subzposh FA, Colburn S, Naperkowski A, Vijayaraman P. His bundle pacing capture threshold stability during long-term follow-up and correlation with lead slack. *Europace.* (2020) 23:757–66doi: 10.1093/europace/euaa350

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 11 November 2021
doi: 10.3389/fcvm.2021.758500

Comparison of the Acute Effects of Different Pacing Sites on Cardiac Synchrony and Contraction Using Speckle-Tracking Echocardiography

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Specialty section:
This article was submitted to Cardiovascular Imaging, a section of the journal Frontiers in Cardiovascular Medicine

Received: *14 August 2021*
Accepted: *20 October 2021*
Published: *11 November 2021*

Citation:
Xie H, Chen X, Wang Y, Cheng Y, Zhao Y, Liu Y, Liu Y, Ge Z, Chen H and Shu X (2021) Comparison of the Acute Effects of Different Pacing Sites on Cardiac Synchrony and Contraction Using Speckle-Tracking Echocardiography. Front. Cardiovasc. Med. 8:758500. doi: 10.3389/fcvm.2021.758500

Background: Cardiac pacing in patients with bradyarrhythmia may employ variable pacing sites, which may have different effects on cardiac function. Left bundle branch pacing (LBBP) is a new physiological pacing modality, and the acute outcomes on cardiac mechanical synchrony during LBBP remain uncertain. We evaluated the acute effects of four pacing sites on cardiac synchrony and contraction using speckle-tracking echocardiography, and comparisons among four different pacing sites were rare.

Methods: We enrolled 21 patients with atrioventricular block or sick sinus syndrome who each sequentially underwent acute pacing protocols, including right ventricular apical pacing (RVAP), right ventricular outflow tract pacing (RVOP), His bundle pacing (HBP), and left bundle branch pacing (LBBP). Electrocardiograms and echocardiograms were recorded at baseline and during pacing. The interventricular mechanical delay (IVMD), the standard deviation of the times to longitudinal peak strain during 17 segments (PSD), and the Yu index were used to evaluate ventricular mechanical synchrony. Layer-specific strain was computed using two-dimensional speckle tracking technique to provide in-depth details about ventricular synchrony and function.

Results: Left ventricular ejection fraction (LVEF) and tricuspid annulus plane systolic excursion (TAPSE) were significantly decreased during RVAP and RVOP but were not significantly different during HBP and LBBP compared with baseline. RVAP and RVOP significantly prolonged QRS duration, whereas HBP and LBBP showed non-significant effects. IVMD and PSD were significantly increased during RVAP but were not significantly different during RVOP, HBP, or LBBP. LBBP resulted in a significant improvement in the IVMD and Yu index compared with RVAP. No significant differences in mechanical synchrony were found between HBP and LBBP.

Conclusion: Among these pacing modalities, RVAP has a negative acute impact on cardiac synchrony and contraction. HBP and LBBP best preserve physiological cardiac synchrony and function.

Keywords: cardiac synchrony, physiological pacing, echocardiography, His bundle pacing, left bundle branch pacing

INTRODUCTION

Cardiac pacing, an effective therapy for patients with bradyarrhythmia, has multiple modalities, including right ventricular apical pacing (RVAP) (1), right ventricular outflow tract pacing (RVOP) (2), His bundle pacing (HBP) (3), and left bundle branch pacing (LBBP) (4). RVAP is the traditional mode and has the advantage of long-term lead stability and ease of access, but it impairs left ventricular (LV) function due to asynchronous electrical activation (5). As an alternative, RVOP allows more physiological stimulation; however, a previous study indicated that the long-term clinical outcomes of RVOP were not superior to those of RVAP (6). HBP activates the intrinsic His-Purkinje conducting system, thus preserving synchronized ventricular contraction (7); it is limited by high and unstable pacing thresholds, long implantation times, and high dislodgement rates (8). LBBP, a recent form of His-Purkinje system pacing introduced by Huang et al. in 2017 (4), is considered to provide physiological activation. In this modality, the block position is circumvented and the left bundle branch (LBB) area is directly activated to synchronize LV contraction with a low and stable threshold. However, the right bundle branch is ignored and right bundle branch block (RBBB) has occurred; whether LBBP contributes to ventricular mechanical dyssynchrony remains uncertain. Long-term cardiac systolic asynchrony leads to remodeling of the cardiac contraction and electrophysiological characteristics and further aggravates the electrical and mechanical dyssynchrony, increasing the risk of atrial fibrillation and heart failure (9).

This study evaluated the acute effects of different pacing sites on cardiac synchrony and contraction in patients with atrioventricular block (AVB) or sick sinus syndrome (SSS) using echocardiography.

METHODS

Study Population

Between March and June 2018, we prospectively enrolled consecutive patients with AVB or SSS who were scheduled for pacemaker implantation. The inclusion criteria were: (1) no history of pacemaker implantation, (2) no pregnancy, (3) at least 18 years of age, (4) New York Heart Association (NYHA) classification I or II. Patients were excluded for the following conditions: (1) severe valvular regurgitation, (2) recent acute myocardial infarction, (3) a history of cardiac surgery or atrioventricular node ablation, (4) poor acoustic window condition, (5) confirmed infra-His bundle block, or (6) the presence of severe chronic diseases. The study conformed with the 1975 Declaration of Helsinki, and the protocol was approved by the Zhongshan Hospital Ethics Committee. All patients provided their written informed consent to participate in the study.

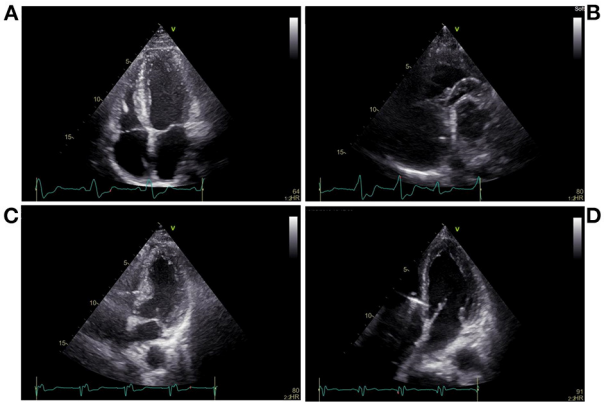

FIGURE 1 | Echocardiography during pacing at different sites. **(A)** Right ventricular apical pacing, **(B)** Right ventricular outflow tract pacing, **(C)** His bundle pacing, **(D)** Left bundle branch pacing.

Pacing Procedure

The pacing procedures were performed in a cardiac catheterization laboratory. Twelve-lead electrocardiogram (ECG) and intracardiac electrograms were simultaneously displayed and continuously recorded during all pacing interventions on a multichannel Bard Electrophysiology Lab System recorder (Bard, Haverhill, MA, USA). A catheter with a 6-Fr quadripolar electrode was inserted *via* the right external jugular vein; the electrodes were positioned within the right ventricular (RV) apex (RVA) and RV outflow tract (RVOT) (**Figures 1A,B**). For HBP, a preformed sheath (C315 HIS, Medtronic, Minneapolis, MN USA) was inserted *via* the right external jugular vein and placed in the region near the tricuspid valve septal leaflet. A Select Secure pacing lead (Model 3830, 69 cm, Medtronic) was delivered along the sheath with its distal part beyond the tip of the sheath for HBP recording (**Figure 1C**). For LBBP, the lead was twisted deeply through the ventricular septum from the RV septum to the endocardium of the LV septum to activate the LBB region (**Figure 1D**). According to the intracardiac electrograms, the LBB potential gradually appeared and increased as the electrode was screwed in, and the QRS morphology was gradually transformed from LBBB to RBBB. The interval between the LBB potential and ventricular activation was shorter than between the His bundle potential

Abbreviations: RVAP, Right ventricular apical pacing; RVOP, Right ventricular outflow tract pacing; HBP, His bundle pacing; LBBP, Left bundle branch pacing; RBBB, Right bundle branch block; AVB, Atrioventricular block; SSS, Sick sinus syndrome; ECG, Electrocardiogram; LVEDD, Left ventricular end-diastolic dimension; LVESD, Left ventricular end-systolic dimension; TAPSE, Tricuspid annulus plane systolic excursion; LVEF, Left ventricular ejection fraction; IVMD, Interventricular mechanical delay; GLPS, Global longitudinal peak strain; PSD, Standard deviation of time to longitudinal peak strain of 17 segments; Ts, Time to longitudinal peak strain; LVendo, Left ventricular endocardium; LVmid, Left ventricular mid-myocardium; LVepi, Left ventricular epicardium; RVendo, Right ventricular endocardium; RVmid, Right ventricular mid-myocardium; RVepi, Right ventricular epicardium; Lat_ap, the Ts of apical segment of lateral wall of left ventricular; Lat_mid, the Ts of middle segment of lateral wall of left ventricular; Lat_bas, the Ts of basal segment of lateral wall of left ventricular; RV_ap, the Ts of apical segment of lateral wall of right ventricular; RV_mid, the Ts of middle segment of lateral wall of right ventricular; RV_bas, the Ts of basal segment of lateral wall of right ventricular; LV-RV_bas, the difference of the Ts between basal segments of left ventricular and right ventricular lateral wall; LV-RV_mid, the difference of the Ts between middle segments of left ventricular and right ventricular lateral wall; LV-RV_ap, the difference of the Ts between apical segments of left ventricular and right ventricular lateral wall; RVP, Right ventricular pacing; LVP, Left ventricular pacing; CRT, cardiac resynchronization therapy.

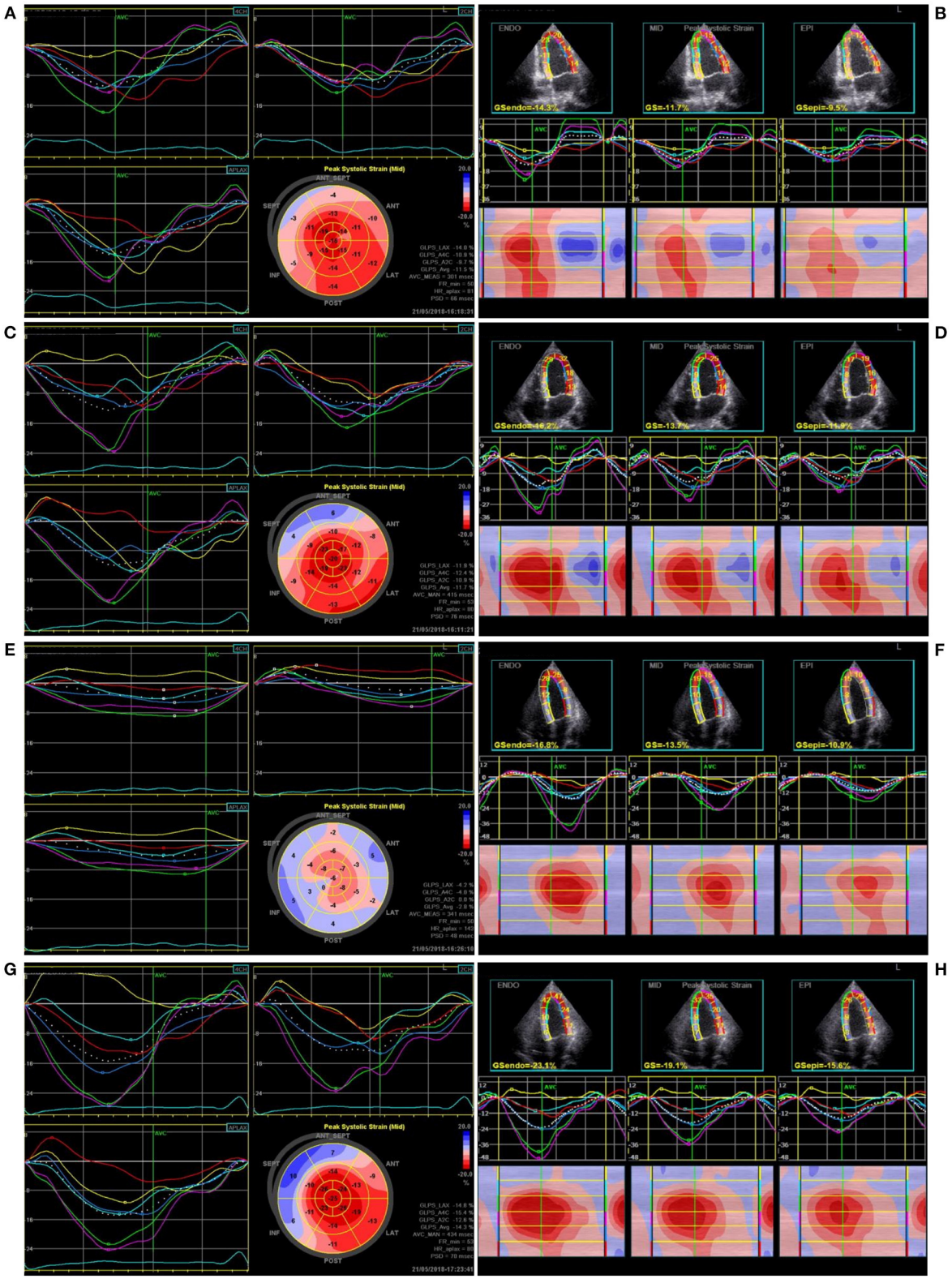

FIGURE 2 | The ventricular global longitudinal peak strain and longitudinal layer-special strain observed in one patient during pacing at different sites. **(A,B)** Right ventricular apical pacing, **(C,D)** Right ventricular outflow tract pacing, **(E,F)** His bundle pacing, **(G,H)** Left bundle branch pacing.

and ventricular activation. The imaging characteristics of LBBP showed that the pacing site was in the ventricular septum. The left or right anterior oblique projection was used to assist in identifying catheter positions; endocardial ECG was utilized to confirm these positions.

Each pacing mode was separated by a 10-min washing-out interval. In all patients, the pacing sequence ended with LBBP, and the lead was left in place after LBBP. During each procedure, the atrial lead was implanted in the right atrium appendage. Both the atrial and ventricular leads at the four pacing sites were connected to the programmer (Medtronic 2290) in DDD mode, with an AV delay of 150 ms and a pacing output of 3.5 V/0.5 ms during unipolar configuration.

ECG and Echocardiography

ECGs and echocardiography were performed at baseline and during each pacing modality. During each session, patients were kept in the left lateral decubitus position with the ECG connected. Two-dimensional echocardiography was performed, according to current guidelines, using a Vivid E95 scanner (GE Vingmed Ultrasound, Horten, Norway) equipped with an M5S probe (4.0-MHz transducer) having frame rates higher than 40 fps (10). LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and tricuspid annulus plane systolic excursion (TAPSE) were derived from M-mode images. The LV ejection fraction (LVEF) was measured using the biplane Simpson's method, per guideline recommendations (11). To evaluate interventricular dyssynchrony, we measured the interventricular mechanical delay (IVMD) as the time interval between the beginning of QRS and the beginning of the systolic waves of aortic and pulmonary ejections, using conventional Doppler (12). Intraventricular dyssynchrony was assessed using the Yu index, defined as the standard deviation of the time between the onset of QRS and the peak systolic velocity of tissue Doppler for 12 LV segments (six basal and six middle) in apical triplane-mode (4-V probe) (13, 14).

The apical triplane-mode data were analyzed offline using an EchoPAC 203 workstation (GE Vingmed Ultrasound). The best cardiac cycle with good quality or clear endocardial boundaries was chosen, and the endocardial borders were automatically identified and tracked throughout the cardiac cycle. If the images were not optimal, manual adjustments were made. The LV wall of each apical view was divided into six segments. The global longitudinal peak strain (GLPS) (**Figures 2A,C,E,G**) and the standard deviation of the time to longitudinal peak strain of 17 segments (PSD) were automatically calculated. The longitudinal strain of the ventricular endocardium, mid-myocardium, and epicardium (**Figures 2B,D,F,H**) and the time to longitudinal peak strain (Ts) of the basal, middle, and apical segments of the lateral ventricular wall were simultaneously obtained. All echocardiograms were analyzed by an independent echocardiologist, blinded to the pacing modalities.

TABLE 1 | Baseline characteristics of patients.

	Patients ($n = 21$)
Age (years)	66.1 ± 13.0
Gender (male, *n*)	15 (71%)
Heart rate (beats/min)	53.8 ± 16.2
QRS duration (ms)	118.8 ± 24.6
First-degree AVB with AF (*n*, %)	1 (5%)
Second-degree AVB (*n*, %)	10 (47%)
Third-degree AVB (*n*, %)	8 (38%)
SSS (*n*, %)	2 (10%)

Data are presented as mean ± standard (SD) for continuous variables, and number of subjects (n) and percentage (%) for categorical variables. AF, Atrial flutter; AVB, Atrioventricular block; SSS, Sick sinus syndrome.

TABLE 2 | Comparison of the acute change of different pacing sites on cardiac contraction.

	Baseline	**RVA**	**RVOT**	**HIS**	**LBB**
LVEDV (mL)	79.0 ± 20.7	68.6 ± 22.9	69.1 ± 24.5	66.0 ± 20.9	64.6 ± 19.5*
LVESV (mL)	27.0 ± 9.7	28.8 ± 14.0	29.4 ± 15.8	25.7 ± 12.9	24.6 ± 10.8
LVEF (%)	65.6 ± 7.0	59.5 ± 8.8*	58.8 ± 9.4*	62.7 ± 6.9	62.8 ± 5.3
TAPSE (mm)	21.2 ± 3.4	17.4 ± 2.8*	17.6 ± 3.0*	19.4 ± 2.6#	19.1 ± 2.7#
GLPS (%)	−20.1 ± 4.7	−13.1 ± 4.1*	−14.1 ± 4.0*	−14.2 ± 3.9*	−14.9 ± 3.2*
LVendo (%)	−21.5 ± 3.3	−16.7 ± 4.9*	−16.6 ± 5.1*	−16.3 ± 4.3*	−19.4 ± 4.1
LVmid (%)	−18.7 ± 2.8	−14.3 ± 4.3*	−14.2 ± 4.3*	−14.3 ± 3.8*	−16.5 ± 3.6
LVepi (%)	−16.3 ± 2.5	−12.4 ± 3.8*	−12.0 ± 3.6*	−12.4 ± 3.4*	−14.3 ± 3.1
RVendo (%)	−21.2 ± 5.0	−16.0 ± 5.6*	−16.7 ± 4.4*	−16.3 ± 5.7*	−17.0 ± 3.8*
RVmid (%)	−18.8 ± 4.6	−14.1 ± 5.6*	−14.4 ± 4.1*	−14.0 ± 5.4*	−14.5 ± 3.5*
RVepi (%)	−16.8 ± 4.4	−12.7 ± 5.9*	−12.7 ± 3.8*	−12.3 ± 5.3*	−12.7 ± 3.2*

*Values are mean ± (SD). RVA, right ventricular apex; RVOT, right ventricular outflow tract; HIS, His bundle; LBB, left bundle branch; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; GLPS, global longitudinal peak strain; The longitudinal strain of left ventricular endocardium (LVendo), mid-myocardium (LVmid) and epicardium (LVepi) were measured in apical four chamber view; The longitudinal strain of right ventricular endocardium (RVendo), mid-myocardium (RVmid) and epicardium (RVepi) were measured in apical four chamber view. *$P < 0.05$ vs. baseline, #$P < 0.05$ vs. RVA.*

Statistical Analyses

Continuous variables are described as means ± standard deviations; categorical variables are described as counts or percentages. When the data were or approximated normal distributions, comparisons among three or more conditions were evaluated using repeated measures one-way analysis of variance tests followed by the Tukey *post-hoc* analysis. Otherwise, the Friedman test was performed, and Dunn's *post-hoc* test was used to adjust the *P*-value. Statistical significance was defined as a two-sided $P < 0.05$. All statistical analyses were performed using GraphPad Prism 7.0 (GraphPad Software, San Diego, CA, USA).

RESULTS

Baseline Characteristics

A total of 21 patients (15 men and 6 women) were enrolled in the study, with a mean age of 66.1 ± 13.0 years. All procedures were successfully performed in these patients. Of these, 19 patients were diagnosed with AVB, including one with first-degree AVB, 10 with second-degree AVB, and eight with third-degree AVB, and two with SSS. The mean heart rate was 53.8 ± 16.2 beats/min and the mean QRS duration was 118.8 ± 24.6 ms at the baseline ECG (**Table 1**).

Cardiac Systolic Function

To compare the acute changes in cardiac contraction between the different pacing sites, we measured the LVEDV, LVESV, LVEF, and TAPSE. We also evaluated the GLPS and the longitudinal layer-specific myocardial strains of the LV and RV [endocardium (endo), mid-myocardium (mid), and epicardium (epi): LVendo, LVmid, LVepi, RVendo, RVmid, and RVepi] in the apical four-chamber view using EchoPAC 203 (**Table 2**). LVEDV, LVESV, LVEF, GLPS, and LV strains were used to evaluate left ventricle systolic function, whereas TAPSE and RV strains for right ventricle systolic function.

Echocardiography Parameters

The LVEDV during LBBP was significantly smaller than at baseline ($p < 0.01$, **Figure 3A**), whereas the LVESV was not significantly different across the various pacing sites. The mean LVEF was significantly lower during RVAP [59.5 ± 8.8% ($p < 0.05$)] and RVOP [58.8 ± 9.4% ($p < 0.01$)] than at baseline (65.6 ± 7.0%) (**Figure 3B**). Compared with baseline, the TAPSE during RVAP ($p < 0.001$) and RVOP ($p < 0.01$) were significantly reduced (**Figure 3D**); however, the TAPSE during HBP and LBBP had no significant difference. In addition, the TAPSE during HBP and LBBP were significantly higher than during RVAP ($p < 0.001$ and $p < 0.05$, respectively; **Figure 3D**).

Strain

At all pacing sites, the absolute values of GLPS ($p < 0.001$, **Figure 3C**), RVendo, RVmid, and RVepi were significantly lower than at baseline (**Figure 3F**). Except for LBBP, the absolute values of LVendo, LVmid, and LVepi at the other three pacing sites were also significantly lower than at baseline (**Figure 3E**).

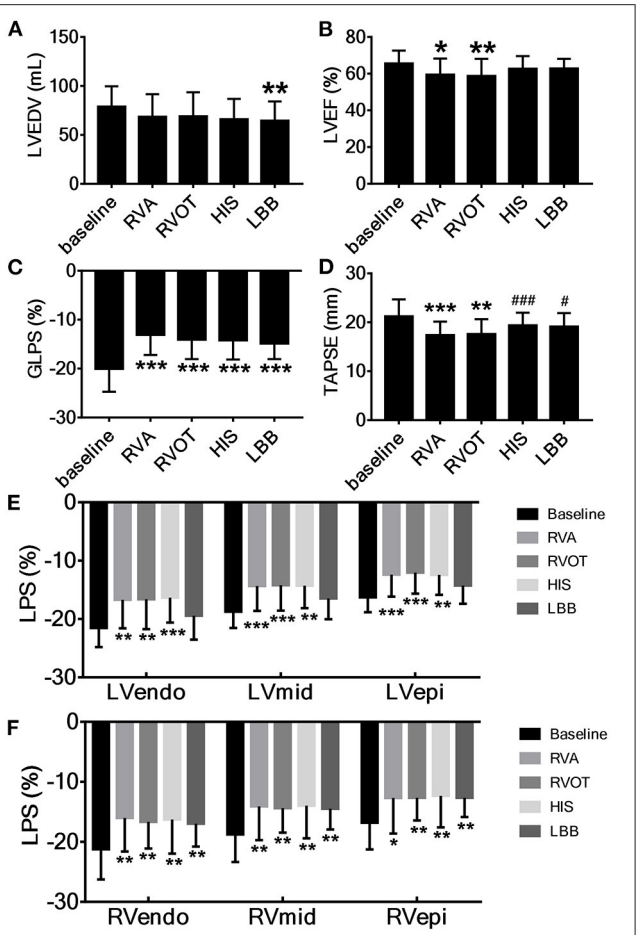

FIGURE 3 | Acute change in cardiac contraction associated with pacing at the different sites. **(A)** LVEDV, left ventricular end-diastolic volume, **(B)** LVEF, left ventricular ejection fraction, **(C)** GLPS, global longitudinal peak strain, **(D)** TAPSE, tricuspid annular plane systolic excursion. **(E)** The longitudinal strain of left ventricular endocardium (LVendo), mid-myocardium (LVmid) and epicardium (LVepi). **(F)** The longitudinal strain of right ventricular endocardium (RVendo), mid-myocardium (RVmid) and epicardium (RVepi). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs. baseline, $^{\#}P < 0.05$, $^{\#\#\#}P < 0.001$ vs. right ventricular apex (RVA).

Cardiac Synchrony

We analyzed heart rate (HR) and QRS duration using ECG; IVMD, PSD, and the Yu index were analyzed by echocardiography. Moreover, we also measured the Ts of the apical, middle, and basal segments of the lateral wall of left ventricle (Lat_ap, Lat_mid, Lat_bas, respectively) or right ventricle (RV_ap, RV_mid, RV_bas, respectively) in the four-chamber view, as well as the difference in Ts between the basal, middle, and apical segments of left and right ventricle lateral walls (LV-RV_bas, LV-RV_mid, LV-RV_ap, respectively; **Table 3**).

Electrical Synchrony

The mean HR at baseline was 53.8 ± 16.2 beats/min. The HR at four pacing sites was significantly increased ($p < 0.001$, **Figure 4A**). The mean QRS duration at baseline was

TABLE 3 | Comparison of the acute effect of different pacing sites on cardiac synchrony.

	Baseline	RVA	RVOT	HIS	LBB
HR (beats/min)	53.8 ± 16.2	78.8 ± 13.4*	79.0 ± 13.2*	78.6 ± 9.7*	77.8 ± 9.1*
QRS duration (ms)	118.8 ± 24.6	160.7 ± 24.7*	140.9 ± 13.9*,#	114.8 ± 18.2#,Δ	116.2 ± 11.6#,Δ
IVMD (ms)	3.1 ± 23.1	32.0 ± 30.5*	22.6 ± 21.4	1.0 ± 21.1#,Δ	−14.9 ± 28.3#,Δ
PSD (ms)	52.6 ± 17.4	70.3 ± 17.7*	62.2 ± 18.9	62.0 ± 19.7	58.6 ± 16.8
Yu index (ms)	57.6 ± 28.7	66.9 ± 33.2	63 ± 33.9	51.6 ± 25.0	44.5 ± 21.9#
Lat_ap (ms)	387.3 ± 46.9	357.2 ± 58.9	358.8 ± 50.9	403.9 ± 58.8	353.3 ± 63.3
Lat_mid (ms)	411.5 ± 53.1	382.9 ± 59.4	396.7 ± 62.8	404.0 ± 90.0	377.2 ± 68.4
Lat_bas (ms)	431.2 ± 71.3	411.3 ± 53.1	419.7 ± 68.9	408.8 ± 95.5	396.6 ± 74.1
RV_bas (ms)	369.8 ± 49.6	307.4 ± 97.3	307.0 ± 77.9	373.9 ± 97.5	330.7 ± 76.8
RV_mid (ms)	366.4 ± 49.8	302.0 ± 92.4	314.1 ± 83.0	379.8 ± 66.3	334.1 ± 55.1
RV_ap (ms)	380.5 ± 45.1	356.1 ± 56.7	349.4 ± 77.5	409.6 ± 87.4	374.1 ± 84.5
LV-RV_bas (ms)	61.4 ± 83.0	93.3 ± 130.8	112.0 ± 73.8	34.8 ± 117.7	67.5 ± 94.3
LV-RV_mid (ms)	45.1 ± 75.7	71.3 ± 118.3	63.6 ± 69.0	24.2 ± 85.8	33.6 ± 67.0
LV-RV_ap (ms)	6.8 ± 55.0	−6.6 ± 90.3	16.6 ± 65.4	−5.9 ± 85.2	−23.4 ± 89.6

Values are mean ± (SD). RVA, right ventricular apex; RVOT, right ventricular outflow tract; HIS, His bundle; LBB, left bundle branch; IVMD, interventricular mechanical delay; PSD, the standard deviation of time to longitudinal peak strain of 17 segments; Yu index, the standard deviation of time from QRS to peak systolic velocity in ejection phase for 12 LV segments; Lat_ap, Lat_mid, Lat_bas, the time to peak longitudinal strain of apical (ap), middle (mid) and basal (bas) segment of lateral (Lat) wall of left ventricle in four chamber view; RV_bas, RV_mid, RV_ap, the time to peak longitudinal strain of apical (ap), middle (mid) and basal (bas) segment of lateral wall of right ventricle (RV) in four chamber view; LV-RV_bas, LV-RV_mid, LV-RV_ap, The difference of the time to peak longitudinal strain between basal (or middle or apical) segment of left ventricular and right ventricular lateral wall; HR, heart rate. $^{*}P < 0.05$ *vs. baseline,* $^{\#}P < 0.05$ *vs. RVA,* $^{\Delta}P < 0.05$ *vs. RVOT.*

118.8 ± 24.6 ms but was significantly longer during RVAP and RVOP ($p < 0.001$, $p < 0.01$, respectively; **Figure 4B**); the mean QRS durations during HBP and LBBP had no significant difference (**Figure 4B**). Compared with RVAP, RVOP had a smaller effect on QRS duration ($p < 0.05$, **Figure 4B**). HBP and LBBP had significantly narrower QRS durations ($p < 0.001$ and $p < 0.001$, respectively; **Figure 4B**) compared with RVAP or RVOP.

Interventricular Mechanical Dyssynchrony

The mean IVMD during RVAP was 32.0 ± 30.5 ms and was significantly longer than at baseline (3.1 ± 23.1 ms, $p < 0.01$; **Figure 4C**). There was no significant difference in IVMD between baseline and either HBP or LBBP (**Figure 4C**). Meanwhile, the IVMD during HBP and LBBP were significantly shorter than during RVAP ($p < 0.01$ and $p < 0.001$, respectively; **Figure 4C**) or RVOP ($p < 0.001$, $p < 0.01$ respectively, **Figure 4C**). The PSD was significantly larger during RVAP than at baseline ($p < 0.001$; **Figure 4D**) but was not significantly different from baseline during RVOP, HBP, or LBBP (**Figure 4D**). To explore the local synchrony of the ventricles, we compared the Ts of three segments (LV-RV_bas, LV-RV_mid, LV-RV_ap) and failed to find significant differences.

Intraventricular Mechanical Dyssynchrony

The mean Yu index was 57.6 ± 28.7 ms at baseline, 66.9 ± 33.2 ms during RVAP, 63 ± 33.9 ms during RVOP, 51.6 ± 25.0 ms during HBP and 44.5 ± 21.9 ms during LBBP. The Yu index during LBBP was significantly shorter than during RVAP ($p < 0.05$; **Figure 4E**).

DISCUSSION

Pacemaker implantation is necessary for patients with a high degree AVB, where various pacing modalities can be chosen according to their respective advantages. The RVA and RVOT are conventional pacing sites because of their stability and ease of pacemaker implantation. However, previous studies have reported that RVAP increases the mortality and hospitalization rates of patients with heart failure (15) and does not alleviate cardiac valvular regurgitation or improve long-term clinical outcomes (16). The stimulus for RV pacing (RVP) must pass through the myocardial tissue first and then reach the conduction system, extending the activation time of the left ventricle. The conduction sequence during RVAP is contrary to that of the normal sequence. These limitations lead to cardiac electrical dyssynchrony and regional cardiac contraction discordance, ultimately causing ventricular mechanical dyssynchrony. Thus, physiological pacing is urgently required to maintain normal electrical conduction and achieve cardiac electrical and mechanical synchrony. HBP is considered an ideal physiological pacing mode duo to the relatively normal sequence of ventricular electrical activation and ventricular contraction synchrony, leading to better hemodynamics. In 2018, the American College of Cardiology, American Heart Association, and American Heart Rhythm Society jointly published guidelines for the evaluation and management of patients with bradycardia and cardiac conduction delay, and included HBP for the first time (17). Recently, LBBP has attracted broad interest as a new physiological pacing modality. In the present study, RVAP, RVOP, HBP, and LBBP were performed in the same patients and the acute effects on cardiac synchrony and contraction of pacing at these sites were compared. To a

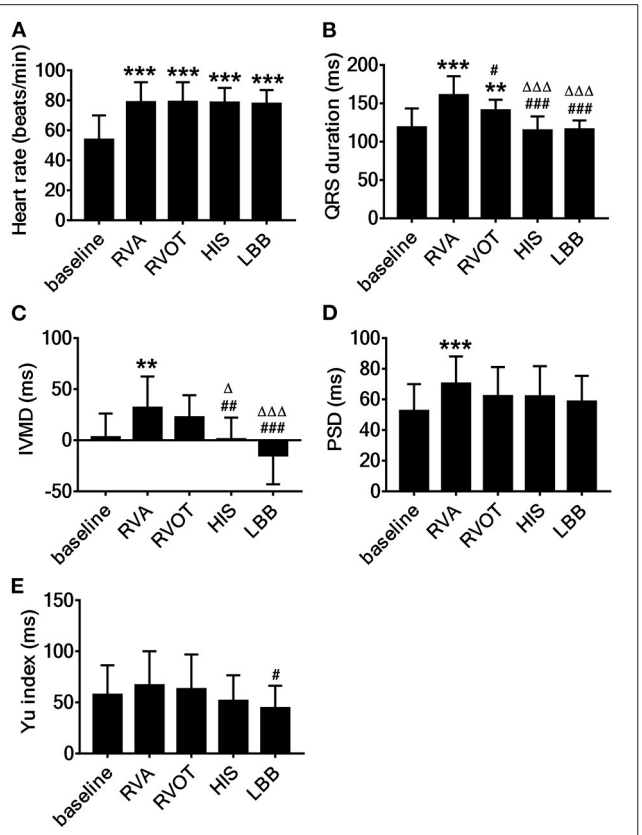

FIGURE 4 | Acute effect on cardiac synchrony associated with pacing at the different sites. **(A)** Heart rates, **(B)** QRS duration, **(C)** IVMD, interventricular mechanical delay, **(D)** PSD, the standard deviation of time to longitudinal peak strain of 17 segments, **(E)** Yu index, the standard deviation of time from QRS to peak systolic velocity in ejection phase for 12 left ventricular segments. $^{**}P < 0.01$, $^{***}P < 0.001$ vs. baseline, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ vs. right ventricular apex (RVA), $^{\Delta}P < 0.05$, $^{\Delta\Delta\Delta}P < 0.001$ vs. right ventricular outflow tract (RVOT).

certain extent, the acute effects on cardiac synchrony can help predict long-term outcomes. Patients who had acute deteriorated LV synchrony after cardiac resynchronization therapy (CRT) demonstrated worse outcomes than those who had improved LV synchrony (18).

Cardiac Systolic Function

Many studies have investigated the feasibility, safety, and clinical outcomes of HBP. Sharma et al. (8) attempted HBP in 94 patients, and succeeded in 75(80%). They found that the HBP group required longer implantation times and a higher pacing threshold than the RVP group (98 patients). Heart failure hospitalization was significantly reduced in patients with >40% ventricular pacing in the HBP group than in the RVP group. For patients with no response to CRT or failure of LV electrode implantation, HBP corrected basal conduction disturbances and improved echocardiographic measurements as an alternative treatment for CRT (19). HBP was also employed to control atrial fibrillation in patients with heart failure who underwent atrioventricular node ablation, significantly improving their LVEF and NYHA classification (20). Our results provide complementary information with previous findings that showed that LVEF and TAPSE deteriorated during RVAP and RVOP, but had little influence on HBP and LBBP; LBBP evidently improved LVEDV. We measured GLPS and longitudinal layer-specific myocardial strains to accurately evaluate the regional mechanical motion of the ventricular myocardium. Although the longitudinal layer-specific strains of LV and RV and GLPS were significantly decreased at all pacing sites as the HR was corrected to within the normal range, LBBP showed the least impact. These results indicate that HBP and LBBP best maintained cardiac contraction. However, HBP has several limitations (21), including the requirement for skilled operation due to the difficulty in locating the His bundle and having a high pacing threshold and low sense. It is also not applicable to blocks below His bundle or to diffuse ventricular blocks caused by myocardial disease. Moreover, HBP cannot provide protection when cardiac conduction system lesions deteriorate. Hence, the investigation of new LV pacing (LVP) sites is required. In 2003, Peschar et al. (22) first conducted LVP in anesthetized, open-chest dogs with normal ventricular conduction. The immediate results demonstrated better maintained LV pump functioning associated with the LVP sites than with RVP sites. Mills et al. (23) carried out LVP in dogs after atrioventricular nodal ablation and further verified that LVP was superior to RVP in chronically maintaining LV contractile coordination and pump function. LV septal pacing was first clinically applied in 2016 and showed better hemodynamic effects than RVP (24). In 2017, Huang et al. (4) successfully implemented the first LBBP in a heart failure patient with LBBB, and the cardiac function of the patient improved during 1 year of follow-up. Previous studies have reported that RBBB can be corrected during LBBP. Li et al. observed a narrowing of the complete RBBB morphology using unipolar LBBP at a high output (25). Sometimes bipolar pacing (26) or adjusting atrioventricular delay (4) can also correct incomplete RBBB. In this study, LBBP did not induce RBBB and did not influence cardiac hemodynamics. However, further studies with long-term follow-up are necessary.

Cardiac Synchrony

Cardiac synchrony is essential for cardiac structure and function, and cardiac resynchronization can reverse LV remodeling and reduce the risk of heart failure events (27, 28). Pastore et al. (29) performed permanent HBP in 37 patients with normal cardiac function and added an RVA backup lead in each patient. Compared with HBP, RVAP resulted in a wider QRS duration, significantly longer LV isovolumetric contraction and relaxation times, and higher pulmonary arterial systolic pressure. In this study, we evaluated electrical and mechanical synchrony at four pacing sites. The QRS duration is the main index used to evaluate electrical synchrony; its normal value is <120 ms. RVAP and RVOP significantly prolonged the QRS duration, which did not change and remained within the normal range during HBP and LBBP. Therefore, RVAP and RVOP caused electrical dyssynchrony; HBP and LBBP preserved physiological electrical synchrony.

Currently, multiple methods are utilized to evaluate mechanical synchrony. For example, Zhang et al. (30) adopted gated, single-photon emission computed tomography (SPECT) myocardial perfusion imaging to study the LV mechanical synchrony associated with HBP and found that HBP resulted in better LV mechanical synchrony parameters. However, SPECT is a procedure that involves radiation and cannot be performed in the catheterization laboratory or at the bedside. Echocardiography is accurate and convenient for measuring cardiac contraction and hemodynamics in real-time without radiation exposure. So far, little is known about the acute outcomes on cardiac mechanical synchrony during LBBP, and comparisons among four different pacing sites are rare. In this study, the IVMD, PSD, and Yu index were used to evaluate inter- and intraventricular synchrony. We found that RVAP distinctly extended IVMD and PSD, and the Yu index tended to deteriorate during RVAP, suggesting that RVAP causes inter- and intraventricular dyssynchrony. LBBP significantly improved the IVMD and Yu index compared with RVAP. Among the four pacing modalities, RVAP resulted in the most unfavorable acute impact on mechanical synchrony, whereas HBP and LBBP had little influence on mechanical synchrony. LBBP represented the best physiological pacing mode and maintained ventricular synchrony.

This study was limited by its small sample size. Further, we only measured the immediate changes in myocardial mechanics after implantation of pacemaker electrodes. The long-term effects of pacing at each site require further investigation.

CONCLUSION

Our study compared acute changes in cardiac synchrony and contraction among four pacing modalities (RVAP, RVOP, HBP, and LBBP) in the same patients (each with AVB or SSS), to evaluate the effect of the His-Purkinje system pacing on ventricular electrical and mechanical synchrony. Echocardiographic parameters including LVEF, GLPS, TAPSE, IVMD, PSD, and Yu index, provided more detailed evaluations of ventricular synchrony and contraction at different pacing sites than QRS duration. HBP and LBBP demonstrated similar added value in preserving physiological hemodynamics and cardiac function, implying their interchangeability under some conditions. Our results showed that LBBP could maintain cardiac hemodynamics similar to or better than HBP, providing more evidence for this alternative of physiological pacing modality. In conclusion, our study suggests that LBBP is an effective physiological pacing mode as HBP, which preserved normal cardiac contraction and synchrony.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Zhongshan Hospital Affiliated to Fudan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XS and HC contributed to the research design, analyzed the data, and critically revised the manuscript. XC contributed to the research design. HX contributed to the data collection, analyzed the data, and drafted the paper. YW contributed to the collection and analyzed the data. YC, YZ, and YaL contributed to the data interpretation. YuL and ZG contributed to critically revised the manuscript. All authors read and approved the final manuscript.

FUNDING

This study was funded by National Natural Science Foundation of China (No. 82071933) and Shanghai Science, Technology Commission Science and technology innovation plan (No. 20JC1418400), 2018 Clinical Trial Funding of Zhongshan Hospital, Fudan University (No. 2018ZSLC14), and Youth Foundation of Shanghai Municipal Health Commission (No. 20194Y0272).

ACKNOWLEDGMENTS

We thank all patients who participated in this study.

REFERENCES

1. Charles RG, Clarke LM, Drysdale M, Sequeira RF. Endocardial pacing electrode design and rate of displacement. *Br Heart J*. (1977) 39:515–6. doi: 10.1136/hrt.39.5.515
2. Akerström F, Pachón M, Puchol A, Jiménez-López J, Segovia D, Rodríguez-Padial L, et al. Chronic right ventricular apical pacing: adverse effects and current therapeutic strategies to minimize them. *Int J Cardiol*. (2014) 173:351–60. doi: 10.1016/j.ijcard.2014.03.079
3. Deshmukh P, Casavant DA, Romanyshyn M, Anderson K. Permanent, direct His-bundle pacing: a novel approach to cardiac pacing in patients with normal His-Purkinje activation. *Circulation*. (2000) 101:869–77. doi: 10.1161/01.CIR.101.8.869
4. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, et al. A novel pacing strategy with low and stable output: pacing the left bundle branch immediately beyond the conduction block. *Can J Cardiol*. (2017) 33:1736.e1–3. doi: 10.1016/j.cjca.2017.09.013
5. Prinzen FW, Hunter WC, Wyman BT, McVeigh ER. Mapping of regional myocardial strain and work during ventricular pacing: experimental study using magnetic resonance imaging tagging. *J Am Coll Cardiol*. (1999) 33:1735–42. doi: 10.1016/S0735-1097(99)00068-6
6. Gong X, Su Y, Pan W, Cui J, Liu S, Shu X. Is right ventricular outflow tract pacing superior to right ventricular apex pacing in patients with normal cardiac function? *Clin Cardiol*. (2009) 32:695–9. doi: 10.1002/clc.20677
7. Moriña Vázquez P, Barba Pichardo R, Venegas Gamero J, Alvarez Saiz A, Moreno Lozano V, Fernández Gómez JM, et al. Permanent pacing of the

bundle of His after radiofrequency atrioventricular node ablation in patients with suprahisian conduction disturbances. *Rev Esp Cardiol*. (2001) 54:1385–93. doi: 10.1016/S0300-8932(01)76521-9
8. Sharma PS, Dandamudi G, Naperkowski A, Oren JW, Storm RH, Ellenbogen KA, et al. Permanent his-bundle pacing is feasible, safe, and superior to right ventricular pacing in routine clinical practice. *Heart Rhythm*. (2015) 12:305–12. doi: 10.1016/j.hrthm.2014.10.021
9. Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation*. (2003) 107:2932–7. doi: 10.1161/01.CIR.0000072769.17295.B1
10. Douglas PS, Carabello BA, Lang RM, Lopez L, Pellikka PA, Picard MH, et al. 2019 ACC/AHA/ASE key data elements and definitions for transthoracic echocardiography: a report of the American College of Cardiology/American Heart Association Task Force on clinical data standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards) and the American Society of Echocardiography. *J Am Coll Cardiol*. (2019) 74:403–69. doi: 10.1016/j.jacc.2019.02.027
11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. (2015) 28:1–39.e14. doi: 10.1016/j.echo.2014.10.003
12. Bax JJ, Bleeker GB, Marwick TH, Molhoek SG, Boersma E, Steendijk P, et al. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol*. (2004) 44:1834–40. doi: 10.1016/j.jacc.2004.08.016
13. Gabriel RS, Bakshi TK, Scott AG, Christiansen JP, Patel H, Wong SP, et al. Reliability of echocardiographic indices of dyssynchrony. *Echocardiography*. (2007) 24:40–6. doi: 10.1111/j.1540-8175.2006.00348.x
14. Silva CE, Barretto AC. Echocardiographic assessment of cardiac resynchronization therapy. *Arq Bras Cardiol*. (2005) 84:503–7. doi: 10.1590/S0066-782X2005000600016
15. De Sisti A, Márquez MF, Tonet J, Bonny A, Frank R, Hidden-Lucet F. Adverse effects of long-term right ventricular apical pacing and identification of patients at risk of atrial fibrillation and heart failure. *Pacing Clin Electrophysiol*. (2012) 35:1035–43. doi: 10.1111/j.1540-8159.2012.03371.x
16. Shimony A, Eisenberg MJ, Filion KB, Amit G. Beneficial effects of right ventricular non-apical vs. apical pacing: a systematic review and meta-analysis of randomized-controlled trials. *Europace*. (2012) 14:81–91. doi: 10.1093/europace/eur240
17. Kusumoto FM, Schoenfeld MH, Barrett C, Edgerton JR, Ellenbogen KA, Gold MR, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: executive summary: a report of the american college of cardiology/american heart association task force on clinical practice guidelines, and the heart rhythm society. *Heart Rhythm*. (2019) 16:e227–79. doi: 10.1016/j.hrthm.2018.10.036
18. Friehling M, Chen J, Saba S, Bazaz R, Schwartzman D, Adelstein EC, et al. A prospective pilot study to evaluate the relationship between acute change in left ventricular synchrony after cardiac resynchronization therapy and patient outcome using a single-injection gated SPECT protocol. *Circ Cardiovasc Imaging*. (2011) 4:532–9. doi: 10.1161/CIRCIMAGING.111.965459
19. Barba-Pichardo R, Manovel Sánchez A, Fernández-Gómez JM, Moriña-Vázquez P, Venegas-Gamero J, Herrera-Carranza M. Ventricular resynchronization therapy by direct His-bundle pacing using an internal cardioverter defibrillator. *Europace*. (2013) 15:83–8. doi: 10.1093/europace/eus228
20. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, et al. Benefits of permanent his bundle pacing combined with atrioventricular node ablation in atrial fibrillation patients with heart failure with both preserved and reduced left ventricular ejection fraction. *J Am Heart Assoc*. (2017) 6:e005309. doi: 10.1161/JAHA.116.005309
21. Vijayaraman P, Naperkowski A, Subzposh FA, Abdelrahman M, Sharma PS, Oren JW, et al. Permanent His-bundle pacing: long-term lead performance and clinical outcomes. *Heart Rhythm*. (2018) 15:696–702. doi: 10.1016/j.hrthm.2017.12.022
22. Peschar M, de Swart H, Michels KJ, Reneman RS, Prinzen FW. Left ventricular septal and apex pacing for optimal pump function in canine hearts. *J Am Coll Cardiol*. (2003) 41:1218–26. doi: 10.1016/S0735-1097(03)00091-3
23. Mills RW, Cornelussen RN, Mulligan LJ, Strik M, Rademakers LM, Skadsberg ND, et al. Left ventricular septal and left ventricular apical pacing chronically maintain cardiac contractile coordination, pump function and efficiency. *Circ Arrhythm Electrophysiol*. (2009) 2:571–9. doi: 10.1161/CIRCEP.109.882910
24. Mafi-Rad M, Luermans JG, Blaauw Y, Janssen M, Crijns HJ, Prinzen FW, et al. Feasibility and acute hemodynamic effect of left ventricular septal pacing by transvenous approach through the interventricular septum. *Circ Arrhythm Electrophysiol*. (2016) 9:e003344. doi: 10.1161/CIRCEP.115.003344
25. Li X, Li H, Ma W, Ning X, Liang E, Pang K, et al. Permanent left bundle branch area pacing for atrioventricular block: feasibility, safety, and acute effect. *Heart Rhythm*. (2019) 16:1766–73. doi: 10.1016/j.hrthm.2019.04.043
26. Kadish AH, Schmaltz S, Morady F. A comparison of QRS complexes resulting from unipolar and bipolar pacing: implications for pace-mapping. *Pacing Clin Electrophysiol*. (1991) 14(5 Pt 1):823–32. doi: 10.1111/j.1540-8159.1991.tb04113.x
27. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol*. (2008) 52:1834–43. doi: 10.1016/j.jacc.2008.08.027
28. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. (2005) 352:1539–49. doi: 10.1056/NEJMoa050496
29. Pastore G, Aggio S, Baracca E, Fraccaro C, Picariello C, Roncon L, et al. Hisian area and right ventricular apical pacing differently affect left atrial function: an intra-patients evaluation. *Europace*. (2014) 16:1033–9. doi: 10.1093/europace/eut436
30. Zhang J, Guo J, Hou X, Wang Y, Qian Z, Li K, et al. Comparison of the effects of selective and non-selective His bundle pacing on cardiac electrical and mechanical synchrony. *Europace*. (2018) 20:1010–7. doi: 10.1093/europace/eux120

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frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 30 November 2021
doi: 10.3389/fcvm.2021.772548

Conduction System Pacing for Post Transcatheter Aortic Valve Replacement Patients: Comparison With Right Ventricular Pacing

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OPEN ACCESS

Edited by:
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Reviewed by:
Hussam Ali, Center for Clinical Arrhythmology and Electrophysiology, MultiMedica (IRCCS), Italy
Paul Schoenhagen, Case Western Reserve University, United States
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Specialty section:
This article was submitted to Cardiac Rhythmology, a section of the journal Frontiers in Cardiovascular Medicine

Received: *08 September 2021*
Accepted: *04 November 2021*
Published: *30 November 2021*

Citation:
Niu H-X, Liu X, Gu M, Chen X, Cai C, Cai M, Zhang S and Hua W (2021) Conduction System Pacing for Post Transcatheter Aortic Valve Replacement Patients: Comparison With Right Ventricular Pacing. Front. Cardiovasc. Med. 8:772548. doi: 10.3389/fcvm.2021.772548

Introduction: For patients who develop atrioventricular block (AVB) following transcatheter aortic valve replacement (TAVR), right ventricular pacing (RVP) may be associated with adverse outcomes. We assessed the feasibility of conduction system pacing (CSP) in patients who developed AVB following TAVR and compared the procedural and clinical outcomes with RVP.

Methods: Consecutive patients who developed AVB following TAVR were prospectively enrolled, and were implanted with RVP or CSP. Procedural and clinical outcomes were compared among different pacing modalities.

Results: A total of 60 patients were enrolled, including 10 who were implanted with His bundle pacing (HBP), 20 with left bundle branch pacing (LBBP), and 30 with RVP. The HBP group had significantly lower implant success rate, higher capture threshold, and lower R-wave amplitude than the LBBP and RVP groups ($p < 0.01$, respectively). The RVP group had a significantly longer paced QRS duration (153.5 ± 6.8 ms, $p < 0.01$) than the other two groups (HBP: 121.8 ± 8.6 ms; LBBP: 120.2 ± 10.6 ms). During a mean follow-up of 15.0 ± 9.1 months, the LBBP group had significantly higher left ventricular ejection fraction (LVEF) (54.9 ± 6.7% vs. 48.9 ± 9.1%, $p < 0.05$) and shorter left ventricular end-diastolic diameter (LVEDD) (49.7 ± 5.6 mm vs. 55.0 ± 7.7 mm, $p < 0.05$) than the RVP group. While the HBP group showed trends of higher LVEF ($p = 0.016$) and shorter LVEDD ($p = 0.017$) than the RVP group. Four patients in the RVP group died—three deaths were due to progressive heart failure and one was due to non-cardiac reasons. One death in the LBBP group was due to the non-cardiac reasons.

Conclusions: CSP achieved shorter paced QRS duration and better cardiac structure and function in post-TAVR patients than RVP. LBBP had a higher implant success rate and better pacing parameters than HBP.

Keywords: conduction system pacing, transcatheter aortic valve replacement, his bundle pacing, left bundle branch pacing, right ventricular pacing, outcomes

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is an effective treatment option for patients with severe aortic stenosis at moderate-to-high surgical risk. However, a high-degree or complete atrioventricular block (AVB) is a well-recognized complication of TAVR, which requires permanent pacemaker implantation. Patients undergoing TAVR usually have left ventricular systolic dysfunction, and right ventricular pacing (RVP) in these patients may increase the risk of heart failure (HF) and is associated with adverse clinical outcomes (1). His bundle pacing (HBP), which is regarded as a physiological pacing modality, is associated with reduced risk of HF hospitalization and pacing-induced cardiomyopathy compared with RVP (2). However, the implant success rate of HBP in post-TAVR patients is only about 50–63% (3, 4). More recently, left bundle branch pacing (LBBP) has been shown to be a safe and effective alternative to HBP, and is considered an alternative approach for conduction system pacing (CSP) (5). Unlike HBP, LBBP is more likely to cross the block site and achieve ideal pacing parameters. Several small-sample studies have evaluated the feasibility of CSP in post-TAVR patients. However, comparisons between CSP and RVP in post-TAVR patients have not been well-described (3, 6, 7). In this study, we assessed the feasibility of CSP in a cohort of post-TAVR patients and compared the procedural and clinical outcomes of TAVR with RVP.

MATERIALS AND METHODS

In this prospective, non-randomized, single-center study, 60 consecutive patients who developed AVB following TAVR and required pacemaker implantation were enrolled. Patients were excluded if they previously implanted with any cardiac implantable electronic devices. The patients were randomized to receive RVP or CSP. Those randomized to receive CSP were alternately allocated to attempt HBP or LBBP (first attempt HBP, second attempt LBBP, third attempt HBP, fourth attempt LBBP, etc…). However, if HBP was unsuccessful, LBBP was attempted and vice versa. If both types of the CSP (HBP and LBBP) were unsuccessful, RVP was finally performed (**Figure 1**). This study was approved by the Ethics Committee of Fuwai Hospital, and written informed consent was obtained from all patients.

Implantation Procedure

In this study, TAVR was performed using the self-expandable Venus A-Valve (Venus MedTech, Hangzhou, China) in patients with symptomatic severe aortic stenosis at moderate-to-high surgical risk. The RVP implantation was performed using the conventional transvenous approach, and the ventricular lead was placed at the right ventricle. The implantation procedures of HBP and LBBP were performed using the conventional method or with the guidance of the visualization technique previously described by our team (8–10). All CSP implantations were performed using the fixed-curve C315 HIS sheath (Medtronic Inc, Minneapolis, MN) and the Select Secure 3830, pacing lead (Medtronic Inc, Minneapolis, MN).

Target His Bundle Region

The His bundle (HB) region was defined as the region where the HB potential could be recorded or the HB could be captured by unipolar pacing. The HB region could also be located under the guidance of our visualization technique (8), which showed the

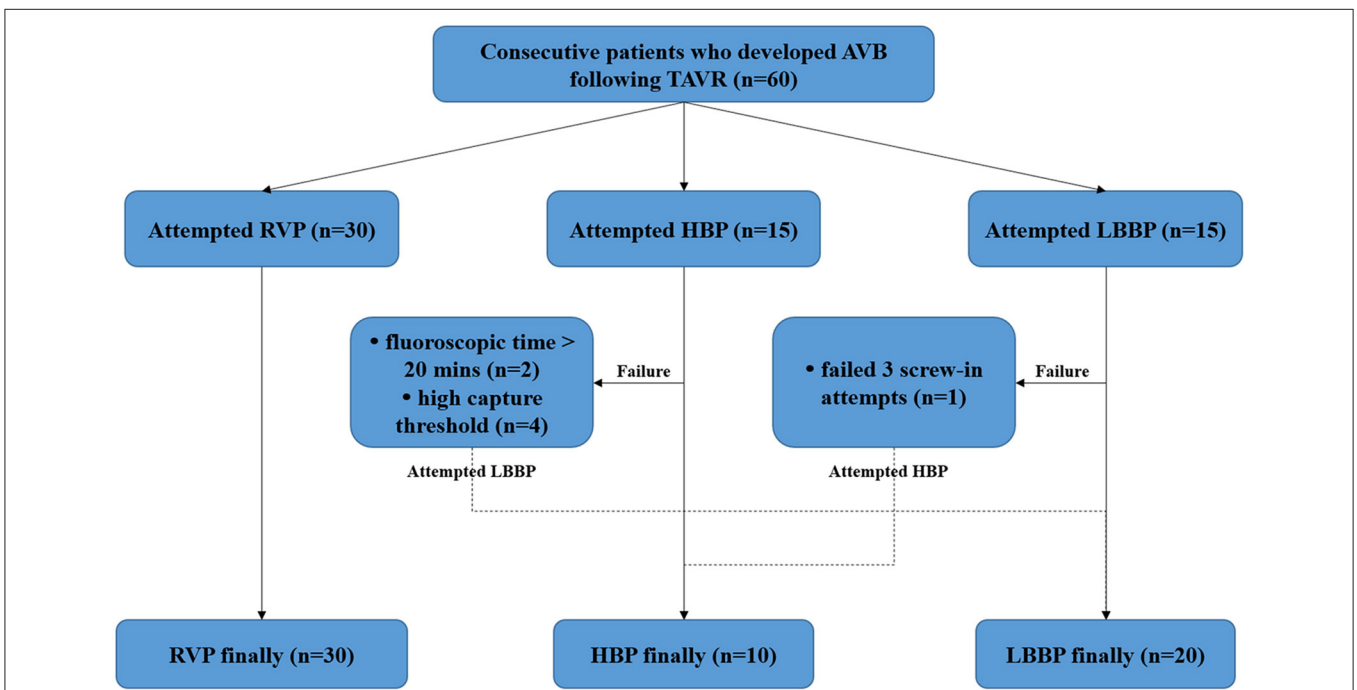

FIGURE 1 | Study flow diagram. AVB, atrioventricular block; HBP, His bundle pacing; LBBP, left bundle branch pacing; RVP, right ventricular pacing; TAVR, transcatheter aortic valve replacement.

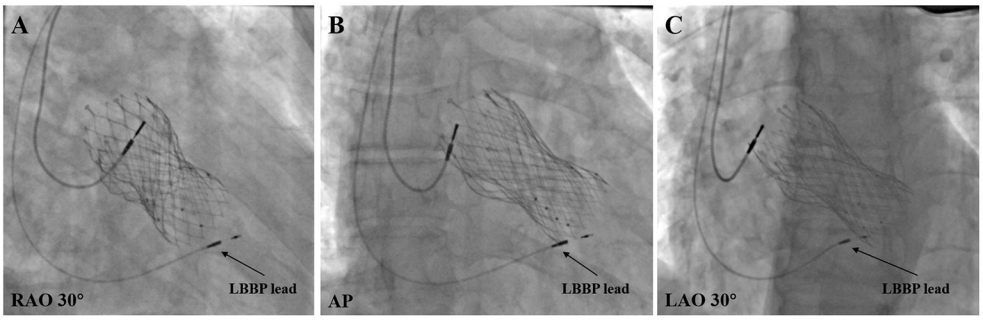

FIGURE 2 | Final LBBP lead location in post-TAVR patients. **(A)** LBBP lead location under RAO 30° fluoroscopic view. **(B)** LBBP lead location under anteroposterior (AP) fluoroscopic view. **(C)** LBBP Lead location under LAO 30° fluoroscopic view. LBBP, left bundle branch pacing; LAO, left anterior oblique; RAO, right anterior oblique.

location of the tricuspid value annulus (TVA) by injecting 10–20 mL contrast medium through the C315 HIS sheath below the root of the tricuspid septal leaflet. The fluoroscopic image of the TVA location was saved as an anatomic reference, which was then used to locate the HB region based on the positional relationship between the HB region and TVA as previously described (8).

Target Left Bundle Branch Region

After the HB region was identified, the lead was moved toward the right ventricular apex by ∼1–2 cm. The initial screw-in site was defined as right-side site of the ventricular septum where the paced QRS morphology in lead V1 showed a "W" pattern. Then, the lead was screwed deep into the myocardium by carefully monitoring the pacing morphology to confirm left bundle branch (LBB) capture. Successful LBB capture was assumed in patients with a paced QRS morphology in lead V1 showing a right bundle branch block (RBBB) pattern and met at least one of the three criteria including: (1) recording of an LBB potential; (2) short and constant left ventricular activation time (LVAT) at different pacing outputs or abruptly shortened LVAT at high output; and (3) demonstration of selective LBB capture. In addition, the target LBB region could also be located based on the positional relationship between the LBB region and TVA provided by the visualization technique (9).

Lead Fixation and Testing

The lead was fixed at the ideal location where the pacing parameters were satisfactory (**Figure 2**). The CSP was considered unsuccessful if the capture threshold was >2.5 V/0.4 ms in three attempts, or the total fluoroscopic time was >20 min.

Data Collection and Follow-Up

Data on baseline characteristics, valve types, and indications for pacemaker implantation were collected at enrollment. Post-implantation follow-up was performed at 3, 6, 12, and then routinely every 12 months. Data from the last follow-up with a minimal of 6 months were used for analysis. Echocardiographic measurements including left ventricular end-diastolic diameter (LVEDD) and left ventricular ejection fraction (LVEF) were recorded at baseline and during each follow-up visit. Pacing parameters including capture threshold, R-wave amplitude, and impedance were recorded during the procedure and during each follow-up visit. Procedure-related complications including capture threshold increase by >1 V/0.4 ms, loss of capture, lead septal perforation, and lead dislodgement were recorded during follow-up. Clinical endpoints including death or hospitalization for HF after pacemaker implantation were also evaluated during follow-up.

TABLE 1 | Baseline characteristics.

	Value
Number of patients	60 (100%)
Demographics	
Age (years)	78.2 ± 5.4
Male	39 (65.0%)
Comorbidities	
Hypertension	31 (51.7%)
Diabetes mellitus	19 (31.7%)
Coronary artery disease	13 (21.7%)
Baseline electrocardiogram	
QRS duration (ms)	134.1 ± 30.8
LBBB	13 (21.7%)
RBBB	23 (38.3%)
Baseline echocardiography	
LVEF (%)	52.1 ± 8.4
LVEDD (mm)	52.4 ± 7.8
Valve type	
Venus A-Valve	60 (100%)
Indications for pacing	
High-degree AVB	20 (33.3%)
Complete AVB	40 (66.7%)
Dual chamber pacemaker	56 (93.3%)
Conduction system pacing	30 (50%)
Follow-up duration (month)	15.0 ± 9.1

AVB, atrioventricular block; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; RBBB, right bundle branch block.

TABLE 2 | Baseline characteristics among groups.

	HBP group ($n = 10$)	LBBP group ($n = 20$)	RVP group ($n = 30$)	*P*-value
Baseline electrocardiogram				
QRS duration (ms)	132.2 ± 30.5	133.8 ± 32.9	134.9 ± 30.6	0.98
LBBB	2 (20.0%)	4 (20.0%)	7 (23.3%)	0.95
RBBB	4 (40.0%)	7 (35.0%)	12 (40.0%)	0.93
NYHA functional class				
II	1 (10.0%)	3 (15.0%)	4 (13.3%)	0.93
III	4 (40.0%)	8 (40.0%)	10 (33.3%)	0.87
IV	5 (50.0%)	9 (45.0%)	16 (53.3%)	0.85
Baseline echocardiography				
LVEF (%)	52.1 ± 5.3	51.9 ± 8.5	52.3 ± 9.3	0.98
LVEDD (mm)	53.3 ± 5.9	52.7 ± 8.1	51.8 ± 8.4	0.77
Medications				
ACEI/ARB	2 (20.0%)	4 (20.0%)	5 (16.7%)	0.95
Beta-blocker	2 (20.0%)	5 (25.0%)	5 (16.7%)	0.77
Diuretics	7 (70.0%)	12 (60.0%)	19 (63.3%)	0.86
Aldosterone antagonist	1 (10.0%)	2 (10.0%)	4 (13.3%)	0.92

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HBP, His bundle pacing; LBBB, left bundle branch block; LBBP, left bundle branch pacing; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RBBB, right bundle branch block; RVP, right ventricular pacing.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation, and categorical variables were expressed as frequencies or percentages. Analysis of variance (ANOVA) was used for multiple comparisons in normally distributed data among groups, and *post-hoc* tests were performed for variables that showed a statistically significant difference. Kruskal–Wallis test was performed for data that were not normally distributed. The chi-squared or Fisher' s exact tests were used for categorical variables to determine differences among groups. A two-sided *P*-value < 0.05 was considered to indicate statistically significant differences. All statistical analyses were performed using the SPSS Statistics version 22.0 (IBM Corporation, Armonk, NY).

RESULTS

Baseline Characteristics

From April 2018 to December 2020, a total of 60 patients who developed AVB following TAVR and eventually had a pacemaker implanted in our center were prospectively enrolled. Baseline characteristics are summarized in **Table 1**. Briefly, patients' mean age was 78.2 ± 5.4 years, and 39 of 60 (65.0%) patients were male. Thirty-one (51.7%) patients had hypertension, 19 (31.7%) had diabetes mellitus, and 13 (21.7%) had coronary artery disease. For the baseline electrocardiogram, the mean native QRS duration was 134.1 ± 30.8 ms. Thirty-six (60%) patients had pre-existing conduction system block including LBBB in 13 (21.7%) and RBBB in 23 (38.3%). The mean LVEF was 52.1 ± 8.4 %, and the mean LVEDD was 52.4 ± 7.8 mm. All enrolled patients underwent TAVR using the self-expandable Venus A-Valve. The pacing indications included high-degree AVB and complete AVB, which accounted for 20 (33.3%) and 40 (66.7%) of the total patients, respectively.

Procedural Outcomes

The procedural outcomes are shown in **Figure 1**. RVP was attempted in 30 patients, and all were successfully implanted. Of the 30 patients who underwent CSP, 15 patients first tried HBP, and nine patients had a successful outcome. In two patients, the fluoroscopic time was >20 min and in four patients, the capture threshold was high. Subsequently, LBBP was attempted and successfully performed on these six patients. LBBP was first tried in 15 patients and was successfully achieved in 14 patients. The procedure in the remaining one patient was considered unsuccessful because of the failure to screw the lead into the myocardium after three screw-in attempts; HBP was then performed in this patient. Finally, a total of 10 patients were assigned to the HBP group, 20 to the LBBP group, and 30 to the RVP group. As shown in **Table 2**, no significant differences were observed in baseline characteristics including electrocardiographic measurements, echocardiogram, New York Heart Association (NYHA) functional class and medical therapy among the three groups.

As shown in **Table 3**, the implant success rate in the HBP group was significantly lower than that in the LBBP and RVP groups (62.5 vs. 95.2% vs. 100.0%, $p < 0.01$). No significant differences were observed in the paced QRS duration between the HBP and LBBP groups (121.8 ± 8.6 ms and 120.2 ± 10.6 ms), while in the RVP group, the paced QRS duration was significantly longer (153.5 ± 6.8 ms, $p < 0.01$). During the procedure, the capture threshold was significantly different among the three groups. Patients in the HBP group had the highest capture threshold (1.5 ± 0.4 V/0.4 ms), patients in the RVP group had the lowest (0.6 ± 0.2 V/0.4 ms), and those in the LBBP group had moderate capture threshold (0.8 ± 0.2 V/0.4 ms). The R-wave amplitude in the HBP group (5.7 ± 2.6 mV, $p < 0.01$) was significantly lower than those in the LBBP and RVP groups (11.2

TABLE 3 | Procedural and clinical outcomes among groups.

	HBP group ($n = 10$)	LBBP group ($n = 20$)	RVP group ($n = 30$)	*P*-value
Implant success rate (%)	10/16 (62.5%)	20/21 (95.2%)	30/30 (100.0%)	<0.01*
Paced QRS duration (ms)	121.8 ± 8.6	120.2 ± 10.6	153.5 ± 6.8	<0.01†
Pacing burden (%)	90.6 ± 8.1	91.6 ± 7.1	91.3 ± 10.0	0.72
Pacing parameters at implantation				
Capture threshold (V/0.4 ms)	1.5 ± 0.4	0.8 ± 0.2	0.6 ± 0.2	<0.01#
R-wave amplitude (mV)	5.7 ± 2.6	11.2 ± 3.0	11.5 ± 3.4	<0.01*
Impedance (Ω)	664.1 ± 76.6	696.2 ± 124.7	686.3 ± 110.8	0.76
Parameters at follow-up				
Capture threshold (V/0.4 ms)	1.7 ± 0.8	0.8 ± 0.1	0.6 ± 0.2	<0.01#
R-wave amplitude (mV)	5.6 ± 2.0	11.0 ± 2.2	11.8 ± 3.9	<0.01*
Impedance (Ω)	472.8 ± 49.8	507.6 ± 72.3	521.0 ± 78.2	0.20
Echocardiography at follow-up				
LVEF (%)	55.8 ± 3.9	54.9 ± 6.7	48.9 ± 9.1	0.02&
LVEDD (mm)	49.2 ± 3.3	49.7 ± 5.6	55.0 ± 7.7	0.03&
NYHA functional class at follow-up				
I	3 (30.0%)	5 (25.0%)	5 (16.7%)	0.61
II	6 (60.0%)	12 (60.0%)	16 (53.3%)	0.87
III	1 (10.0%)	2 (10.0%)	6 (20.0%)	0.55
IV	0 (0.0%)	1 (5.0%)	3 (10.0%)	0.65

HBP, His bundle pacing; LBBP, left bundle branch pacing; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RVP, right ventricular pacing.

**P < 0.05 between HBP group vs. LBBP group and RVP group.*

†P < 0.05 between RVP group vs. HBP group and LBBP group.

#P < 0.05 between each group.

&P < 0.05 between RVP group vs. LBBP group. Corrected P-value for RVP group vs. HBP group in follow-up LVEF was 0.16; Corrected P-value for RVP group vs. HBP group in follow-up LVEDD was 0.17.

± 3.0 mV and 11.5 ± 3.4 mV). No significant differences were observed in the impedance among the three groups during the procedure ($p = 0.76$).

Follow-Up Outcomes

The mean follow-up duration after pacemaker implantation was 15.0 ± 9.1 months. The pacing percentages were similar among the three groups (HBP group vs. LBBP group vs. RVP group: 90.6 ± 8.1% vs. 91.6 ± 7.1% vs. 91.3 ± 10.0%, $p = 0.72$). As shown in **Table 3**, the HBP group still had the highest capture threshold and the lowest R-wave amplitude among groups. For echocardiographic measurements, the LBBP group had significantly higher LVEF (54.9 ± 6.7% vs. 48.9 ± 9.1%, $p < 0.05$) and significantly shorter LVEDD (49.7 ± 5.6 mm vs. 55.0 ± 7.7 mm, $p < 0.05$) than the RVP group. The HBP group had trends of higher LVEF ($p = 0.16$) and lower LVEDD ($p = 0.17$) than the RVP group. The NYHA functional class was improved in all groups during follow-up, and was similar among the three groups.

Further analysis between CSP (combining HBP and LBBP) and RVP showed that CSP and RVP had similar baseline echocardiographic parameters, while CSP achieved higher LVEF (55.2 ± 5.8% vs. 48.9 ± 9.1%, $p < 0.01$) and shorter LVEDD (49.5 ± 4.9 mm vs. 55.0 ± 7.7 mm, $p < 0.01$) compared with RVP during follow-up (**Figure 3**). The NYHA functional class were improved in both types of the pacing modalities during follow-up (**Figure 4**).

One patient in the HBP group had a capture threshold increase of >1 V/0.4 ms (from 1.6 V/0.4 ms to 3.0 V/0.4 ms) during the 6-month follow-up, while no other procedure-related complications were observed in the other two groups during follow-up. In the RVP group, four patients died: three deaths were due to progressive HF and one death was due to non-cardiac reasons. In the LBBP group, one patient died because of non-cardiac reasons. No death was observed in the HBP group. Three patients in the RVP group required hospitalization for HF; no patients in the other two groups needed hospitalization.

DISCUSSION

In this study, we evaluated the feasibility of CSP in patients who developed AVB following TAVR, and compared its outcomes with traditional RVP. The main findings were shown as follows: (1) CSP was feasible in post-TAVR patients; (2) CSP obtained a narrower paced QRS duration during the procedure and achieved better cardiac structure and function during follow-up than RVP; and (3) LBBP had higher implant success rate and better pacing parameters than HBP. To the best of our knowledge, this is the first study to directly compare the CSP with RVP in patients who developed AVB following TAVR.

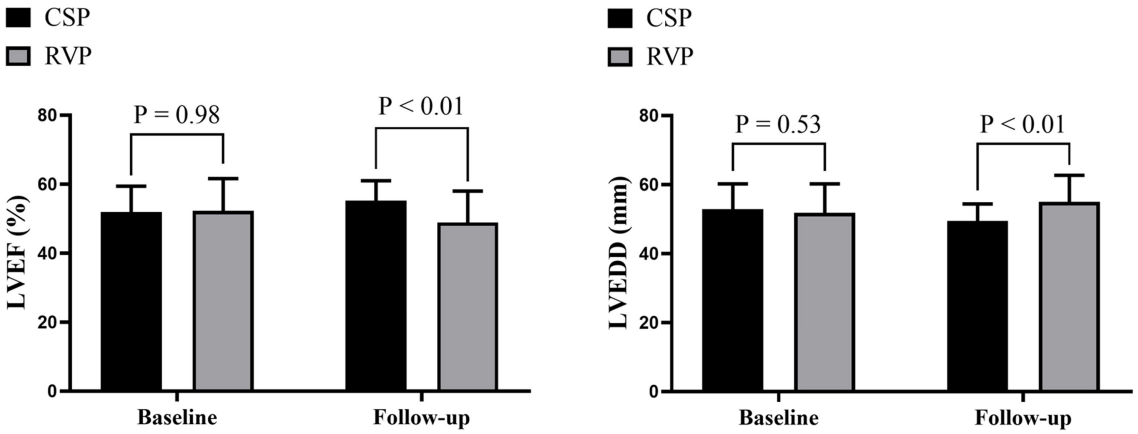

FIGURE 3 | Echocardiographic evaluation between CSP and RVP. CSP, conduction system pacing; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; RVP, right ventricular pacing.

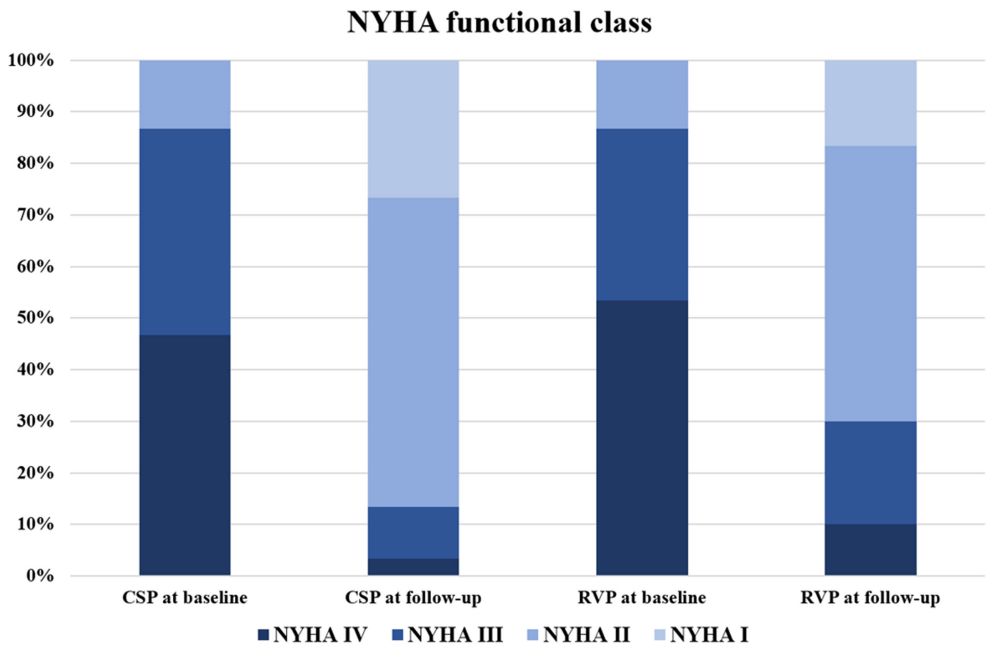

FIGURE 4 | NYHA functional class evaluation between CSP and RVP. CSP at baseline vs. RVP at baseline: $p = 0.94$; CSP at follow-up vs. RVP at follow-up: $p = 0.47$; CSP at baseline vs. CSP at follow-up: $p < 0.01$; RVP at baseline vs. RVP at follow-up: $p < 0.01$. CSP, conduction system pacing; NYHA, New York Heart Association; RVP, right ventricular pacing.

Conduction Disorders Following TAVR

TAVR is an effective treatment for patients with severe aortic stenosis at moderate-to-high surgical risk. However, the incidence of high-degree AVB or complete AVB is still relatively high because of direct mechanical compression of the artificial valve or perivalvular inflammation or edema caused by the TAVR procedure (11). The incidence of postoperative conduction system block requiring pacemaker implantation was reported in the range of 4.2–17.2% in previous studies (12–14). A long-term follow-up study showed that more than half of the post-TAVR patients with pacemaker implantation had a high percentage of ventricular pacing (15). In these patients, non-physiological pacing modality may offset the therapeutic effect after TAVR and impair the cardiac function. In addition, patients with severe aortic stenosis usually have left ventricular dysfunction; RVP in these patients may aggravate the cardiac dysfunction and lead to poor clinical outcomes. Previous studies have shown that patients with RVP implantation following TAVR had a significantly increased overall mortality compared with patients without pacemaker implantation (16).

CSP Implantation in Post-TAVR Patients

HBP directly actives the native cardiac conduction system, and is considered as a physiological pacing modality. However, several limitations restrict its wide application including high and unstable capture threshold, low R-wave amplitude, and high lead dislodgement rate (17, 18). In addition, since the lesion site of the conduction system caused by the TAVR procedure is usually located at the distal part of the His–Purkinje system, pacing the HB is difficult to cross the lesion site, resulting in a low implant success rate (19). Previous studies have shown that the implant success rate of HBP in post-TAVR patients is ∼50–63% (3, 4).

LBBP can achieve better pacing parameters and similar therapeutic effects by pacing the LBB conduction system, and is considered as an alternative CSP modality (20). In addition, LBBP captures the distal part of the conduction system and can more easily cross the block site, overcoming some limitations in application of HBP in post-TAVR patients (3). As shown in this study, LBBP achieved higher implant success rate, similar paced QRS duration, and more satisfactory pacing parameters than HBP. All these suggest that LBBP is more suitable than HBP as the primary treatment option for patients who need pacing therapy after TAVR.

Therapeutic Effects of Different Pacing Modalities

In this study, in addition to evaluating the feasibility of CSP implantation in post-TAVR populations, we also compared the echocardiographic measurements of CSP with traditional RVP. The results showed that for patients with pacemaker implantation after TAVR, CSP achieved better LVEF and LVEDD compared with RVP. To the best of our knowledge, this is the first study to compare the echocardiographic measurements of different pacing modalities in post-TAVR patients. However, due to the low incidence of the clinical endpoints in this study, we were unable to further evaluate whether this echocardiographic benefit could be translated into better long-term clinical outcomes.

Limitations

Our study has some limitations. First, this is a non-randomized, single-center study with a relatively small sample size. The sample size in the HBP group was small, resulting in insufficient statistical power to compare the difference in echocardiographic measurements compared to the other two groups. In addition, due to the small sample size, we were unable to identify the specific subgroup in the RVP group that was responsible for the worse echocardiographic measurements, nor to evaluate the risk factors of lead septal perforation in the elderly LBBP population (21). Multicenter randomized studies with larger sample size are needed to further confirm these conclusions. Second, the enrolled patients were all implanted with the same valve type, other valve types, especially balloon-expandable valves, may cause different types of injury to the conduction system, which may lead to different physiological characteristics and clinical outcomes. Finally, the low incidence of clinical endpoints made it difficult to compare the differences of clinical endpoints between groups. Further studies with larger sample size and longer follow-up duration are needed to evaluate the long-term clinical outcomes.

CONCLUSIONS

CSP achieved shorter paced QRS duration and better cardiac structure and function than RVP in patients who developed AVB following TAVR. Furthermore, LBBP had higher implant success rate and better pacing parameters than HBP.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by this study was approved by the Ethics Committee of Fuwai Hospital, and all patients provided written consent for participation. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WH and SZ contributed to the study conception and design. H-XN, MG, XC, and CC performed pacemaker implantation. H-XN, XL, MG, and MC performed data collection and analysis. The first draft of the manuscript was written by H-XN and XL, and all authors commented on previous versions of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the National Natural Science Foundation of China (Grant Number: 82070349), the Peking Union Medical College Youth Fund and Fundamental Research Funds for the Central Universities (Grant Numbers: 3332019047 and 2017320006), CAMS Innovation Fund for Medical Sciences (CIFMS, Grant Number: 2021-I2M-C&T-B-028), and the Innovation Funds for Graduate Students of Peking Union Medical College (Grant Number: 2019-1002-33).

REFERENCES

1. Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline qrs duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation.* (2003) 107:2932–7. doi: 10.1161/01.CIR.0000072769.17295.B1
2. Abdelrahman M, Subzposh FA, Beer D, Durr B, Naperkowski A, Sun H, et al. Clinical outcomes of his bundle pacing compared to right ventricular pacing. *J Am Coll Cardiol.* (2018) 71:2319–30. doi: 10.1016/j.jacc.2018.02.048

3. Vijayaraman P, Cano Ó, Koruth JS, Subzposh FA, Nanda S, Pugliese J, et al. His-purkinje conduction system pacing following transcatheter aortic valve replacement: feasibility and safety. *JACC Clin Electrophysiol.* (2020) 6:649–57. doi: 10.1016/j.jacep.2020.02.010
4. Sharma PS, Subzposh FA, Ellenbogen KA, Vijayaraman P. Permanent his-bundle pacing in patients with prosthetic cardiac valves. *Hear Rhythm.* (2017) 14:59–64. doi: 10.1016/j.hrthm.2016.09.016
5. Zhang S, Zhou X, Gold MR. Left bundle branch pacing: JACC review topic of the week. *J Am Coll Cardiol.* (2019) 74:3039–49. doi: 10.1016/j.jacc.2019.10.039
6. Zhang J, Yu F, Wang B, Fu G. Rapid reversal of heart failure by correcting left bundle branch block induced by transcatheter aortic valve replacement. *Pacing Clin Electrophysiol.* (2021) 44:203–7. doi: 10.1111/pace.14132
7. Guo J, Li L, Xiao G, Huang X, Li Q, Wang Y, et al. Feasibility and stability of left bundle branch pacing in patients after prosthetic valve implantation. *Clin Cardiol.* (2020) 43:1110–8. doi: 10.1002/clc.23413
8. Gu M, Niu H, Hu Y, Liu X, Zhang N, Cai M, et al. Permanent his bundle pacing implantation facilitated by visualization of the tricuspid valve annulus. *Circ Arrhythm Electrophysiol.* (2020) 13:e008370. doi: 10.1161/CIRCEP.120.008370
9. Liu X, Niu H-X, Gu M, Chen X, Hu Y, Cai M, Q16 et al. Contrast-enhanced image-guided lead deployment for left bundle branch pacing. *Hear Rhythm.* (2021) 18:1318–25. doi: 10.1016/j.hrthm.2021.04.015
10. Gu M, Hu Y, Hua W, Niu H, Chen X, Cai M, et al. Visualization of tricuspid valve annulus for implantation of his bundle pacing in patients with symptomatic bradycardia. *J Cardiovasc Electrophysiol.* (2019) 30:2164–9. doi: 10.1111/jce.14140
11. Judson GL, Agrawal H, Mahadevan VS. Conduction system abnormalities after transcatheter aortic valve replacement: mechanism, prediction, and management. *Interv Cardiol Clin.* (2019) 8:403–9. doi: 10.1016/j.iccl.2019.06.003
12. Moskowitz G, Hong KN, Giustino G, Gillinov AM, Ailawadi G, DeRose JJJ, et al. Incidence and risk factors for permanent pacemaker implantation following mitral or aortic valve surgery. *J Am Coll Cardiol.* (2019) 74:2607–20. doi: 10.1016/j.jacc.2019.08.1064
13. Leyva F, Qiu T, McNulty D, Evison F, Marshall H, Gasparini M. Long-term requirement for pacemaker implantation after cardiac valve replacement surgery. *Hear Rhythm.* (2017) 14:529–34. doi: 10.1016/j.hrthm.2016.11.029
14. Gaede L, Kim W-K, Liebetrau C, Dörr O, Sperzel J, Blumenstein J, et al. Pacemaker implantation after TAVI: predictors of AV block persistence. *Clin Res Cardiol.* (2018) 107:60–9. doi: 10.1007/s00392-017-1158-2
15. Hochstadt A, Merdler I, Meridor Y, Schwartz AL, Ingbir M, Ghantous E, et al. Effect of pacemaker implantation after transcatheter aortic valve replacement on long- and mid-term mortality. *Hear Rhythm.* (2021) 18:199–206. doi: 10.1016/j.hrthm.2020.10.013
16. Clementy N, Bisson A, Bodin A, Herbert J, Lacour T, Etienne C, et al. Outcomes associated with pacemaker implantation following transcatheter aortic valve replacement: a nationwide cohort study. *Hear Rhythm.* (2021). doi: 10.1016/j.hrthm.2021.06.1175. [Epub ahead of print].
17. Vijayaraman P, Dandamudi G, Zanon F, Sharma PS, Tung R, Huang W, et al. Permanent his bundle pacing: recommendations from a multicenter his bundle pacing collaborative working group for standardization of definitions, implant measurements, and follow-up. *Hear Rhythm.* (2018) 15:460–8. doi: 10.1016/j.hrthm.2017.10.039
18. Vijayaraman P, Chung MK, Dandamudi G, Upadhyay GA, Krishnan K, Crossley G, et al. His bundle pacing. *J Am Coll Cardiol.* (2018) 72:927–47. doi: 10.1016/j.jacc.2018.06.017
19. Su L, Wu S, Wang S, Wang Z, Xiao F, Shan P, et al. Pacing parameters and success rates of permanent his-bundle pacing in patients with narrow QRS: a single-centre experience. *Eurpace.* (2019) 21:763–70. doi: 10.1093/europace/euy281
20. Hua W, Fan X, Li X, Niu H, Gu M, Ning X, et al. Comparison of left bundle branch and his bundle pacing in bradycardia patients. *JACC Clin Electrophysiol.* (2020) 6:1291–9. doi: 10.1016/j.jacep.2020.05.008
21. Marazzato J, Caravati F, Blasi FBM, Refugjati T, Vilotta M, Torchio F, et al. Ventricular pacemaker lead in the left hemithorax: mechanisms and evidence-based management of a late-onset hazardous complication. *Clin Case Rep.* (2021) 9:e04617. doi: 10.1002/ccr3.4617

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 07 December 2021
doi: 10.3389/fcvm.2021.787414

Left Ventricular Myocardial Septal Pacing in Close Proximity to LBB Does Not Prolong the Duration of the Left Ventricular Lateral Wall Depolarization Compared to LBB Pacing

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Background: Three different ventricular capture types are observed during left bundle branch pacing (LBBp). They are selective LBB pacing (sLBBp), non-selective LBB pacing (nsLBBp), and myocardial left septal pacing transiting from nsLBBp while decreasing the pacing output (LVSP). Study aimed to compare differences in ventricular depolarization between these captures using ultra-high-frequency electrocardiography (UHF-ECG).

Methods: Using decremental pacing voltage output, we identified and studied nsLBBp, sLBBp, and LVSP in patients with bradycardia. Timing of ventricular activations in precordial leads was displayed using UHF-ECGs, and electrical dyssynchrony (e-DYS) was calculated as the difference between the first and last activation. The durations of local depolarizations (Vd) were determined as the width of the UHF-QRS complex at 50% of its amplitude.

Results: In 57 consecutive patients, data were collected during nsLBBp ($n = 57$), LVSP ($n = 34$), and sLBBp ($n = 23$). Interventricular dyssynchrony (e-DYS) was significantly lower during LVSP −16 ms (−21; −11), than nsLBBp −24 ms (−28; −20) and sLBBp −31 ms (−36; −25). LVSP had the same V1d-V8d as nsLBBp and sLBBp except for V3d, which during LVSP was shorter than sLBBp; the mean difference −9 ms (−16; −1), $p = 0.01$. LVSP caused less interventricular dyssynchrony and the same or better local depolarization durations than nsLBBp and sLBBp irrespective of QRS morphology during spontaneous rhythm or paced QRS axis.

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Edited by:
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Specialty section:
This article was submitted to Cardiac Rhythmology, a section of the journal Frontiers in Cardiovascular Medicine

Received: 30 September 2021
Accepted: 15 November 2021
Published: 07 December 2021

Citation:
Curila K, Jurak P, Vernooy K, Jastrzebski M, Waldauf P, Prinzen F, Halamek J, Susankova M, Znojilova L, Smisek R, Karch J, Plesinger F, Moskal P, Heckman L, Mizner J, Viscor I, Vondra V, Leinveber P and Osmancik P (2021) Left Ventricular Myocardial Septal Pacing in Close Proximity to LBB Does Not Prolong the Duration of the Left Ventricular Lateral Wall Depolarization Compared to LBB Pacing. Front. Cardiovasc. Med. 8:787414. doi: 10.3389/fcvm.2021.787414

Conclusions: In patients with bradycardia, LVSP in close proximity to LBB resulted in better interventricular synchrony than nsLBBp and sLBBp and did not significantly prolong depolarization of the left ventricular lateral wall.

Keywords: left bundle branch pacing, left septal myocardial pacing, UHF-ECG, dyssynchrony, depolarization duration

BACKGROUND

Left bundle branch (LBB) pacing is defined as the pacing of the trunk of the LBB or its proximal fascicles, usually with septal myocardial capture at low output (1). When pacing the LBB, three types of ventricular capture were identified during pacing maneuvers, i.e., decreasing the pacing output. The first is selective LBB capture (sLBBp), during which exclusively the LBB is captured. The second is non-selective LBB capture (nsLBBp), which is defined as concomitant LBB and adjacent left septal myocardial capture. The third is pure myocardial left septal capture (LVSP) which transits from nsLBBp during pacing maneuvers (1).

During nsLBBp, sLBBp, and LVSP, a QRS morphology with a right bundle branch block-like pattern is usually present in lead V1. However, this paced QRS pattern is also present in left septal positions that are shallower than positions where LBB capture could be observed during pacing maneuvers (2, 3). Our previous study used the ultra-high-frequency ECG (UHF-ECG) to show that myocardial capture of the left septum (in positions where nsLBBp was not obtainable with pacing outputs up to 5 V at 0.5 ms) produced less interventricular dyssynchrony but prolonged LV lateral wall depolarization durations compared to nsLBBp (4). The impact of pure myocardial left septal pacing using pacing positions, which are closer to the LBB, i.e., locations where left septal myocardial capture appears from nsLBBp while decreasing pacing outputs, is not known. Also, the impact of sLBBp on ventricular depolarization has not been described.

This study aimed to compare ventricular depolarization using UHF-ECG during LVSP, sLBBp, and nsLBBp in patients with bradycardia and an indication for pacing.

METHODS

Study Design and Study Population

In this prospective study, consecutive patients with an indication for pacemaker implantation due to bradycardia were included. The project was approved by the Ethics Committee of the Faculty Hospital Kralovske Vinohrady, Prague, CZ; all subjects signed informed consent before enrollment.

Pacemaker Implantation

The left subclavian approach was preferred per study protocol. The His bundle region was mapped using a SelectSecure™ lead (model 3830, 69 cm, Medtronic Inc., Minneapolis, MN), delivered through a fixed-curve sheath (C315 HIS, Medtronic, Minneapolis, MN), and the His bundle signal was identified. If mapping of the His bundle was not successful, the tricuspid valve annulus was visualized by injection of a contrast agent through the C315 His sheath. The lead was then moved toward the right ventricle, along a line between the HB region or the vertex of the tricuspid annulus and the RV apex. We aimed

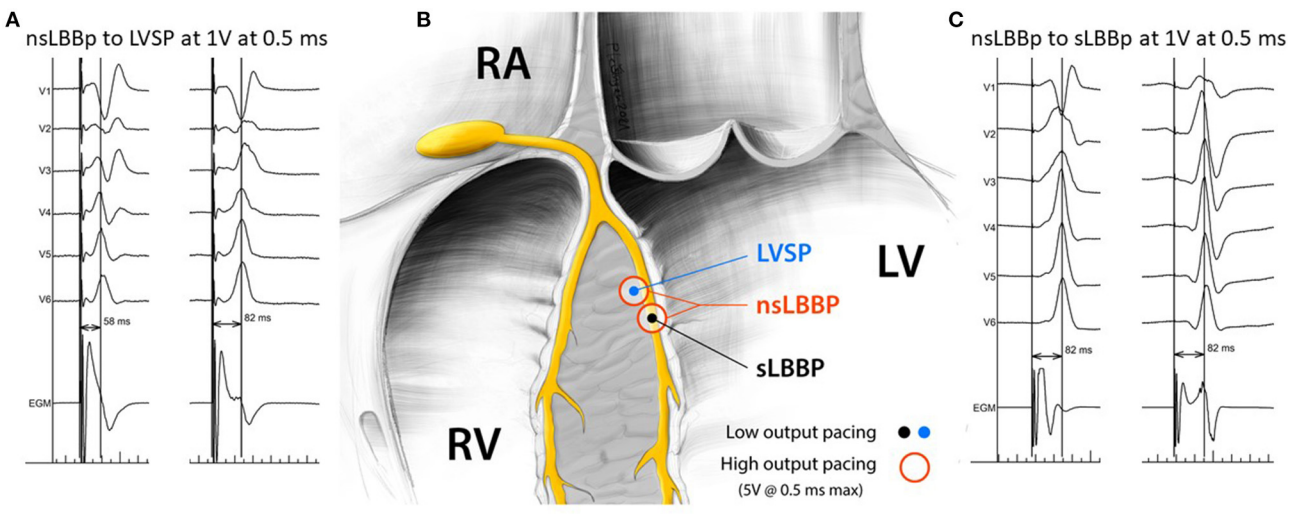

FIGURE 1 | Visualization of nsLBB to LVSP and nsLBBp to sLBBp transitions during pacing maneuvers **(A,C)** and representation of the position of the pacing lead tip in relation to the left Tawara branch for specified types of ventricular capture **(B)**.

for RV location where either the "W" morphology was seen in lead V1 or QRS complexes, with a preferably normal heart axis was observed during right septal pacing. Then, the lead was screwed deep into the septum to obtain a position on the left side of the interventricular septum producing nsLBBp during unipolar pacing with outputs up to a maximum of 5 V at 0.5 ms. nsLBBp was confirmed based on a change from nsLBBp-to-sLBBp or nsLBBp-to-LVSP using pacing maneuvers. Three types of ventricular capture were included in the study and are shown in **Figure 1** and described as follows:

(1) nsLBBp; i.e., concomitant LBB and myocardial capture was defined by a pseudo-RBBB morphology with the terminal r/R in V1 during pacing with an output of 5 V at 0.5 ms, which changed to sLBBp or LVSP while decreasing the pacing outputs.
(2) sLBBp; i.e., selective capture of the LBB, was observed after decreasing the pacing output from nsLBBp with unchanged V5 R wave peak time (RWPT); however, the QRS complex in V1 changed from qR to rsR or rSR (usually the R during sLBBp was wider than nsLBBp) and the EGM signal became "discrete" (5).
(3) LVSP; i.e., pure myocardial capture of the left septum without LBB capture, that was observed after decreasing the pacing output from nsLBBp, and when after the transition the V5 RWPT was prolonged > 10 ms, usually the R amplitude in V1 also decreased or changed from a terminal r/R morphology during nsLBBp to a terminal rs/Rs morphology (6).

If nsLBBp with a transition to sLBBp or LVSP, was not observed during pacing maneuvers, the implant procedure was marked as the procedure without proved LBB capture.

UHF-ECG Data Acquisition and Analysis of Other Measured Parameters

A VDI monitor (Ventricular Dyssynchrony Imaging monitor, ISI Brno, Cardion, FNUSA, CZ, 2018) was used to record and analyze the 5 kHz 14-lead ECG signals with a three

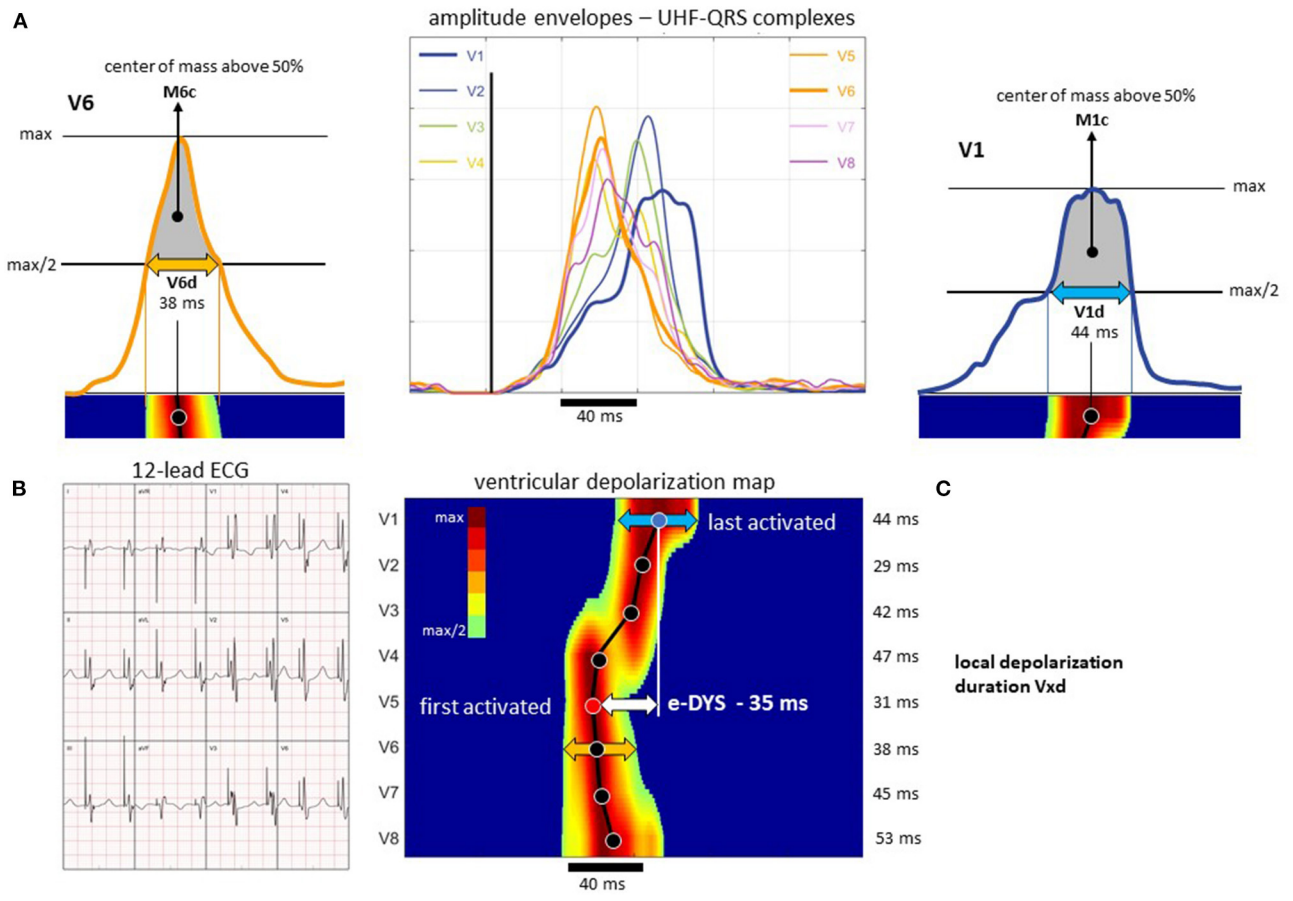

FIGURE 2 | Presentation of the UHF-QRS complexes, Mxc activation times, and Vxd local depolarization duration calculation; patient with sLBBp. **(A)** ultra-high-frequency amplitude envelopes of QRS complexes (UHF-QRS), Mxc computed as the center of mass above 50 percent threshold of the baseline to peak amplitude, Vxd determined as the depolarization duration at the 50 percent threshold of the baseline to peak amplitude. **(B)** 12-lead ECG. **(C)** Ventricular depolarization map with visualization of the M1-8c, electrical interventricular dyssynchrony e-DYS, and the V1-8d values. For details, see Jurak et al. (7). **(C)** The dark line connects the center of masses (solid points) under the specific lead (displayed on the y-axis). Time (ms) is displayed on the x-axis. In this case, the first activation occurred under V5 (M5c), and the last was under V1 (e-DYS = −35 ms). The width of depolarization under V1 is indicated by the blue arrow (V1d), under V6 by the orange arrow (V6d). The numerical parameters of the local depolarization duration (under each lead) are shown on the right side of **(C)**.

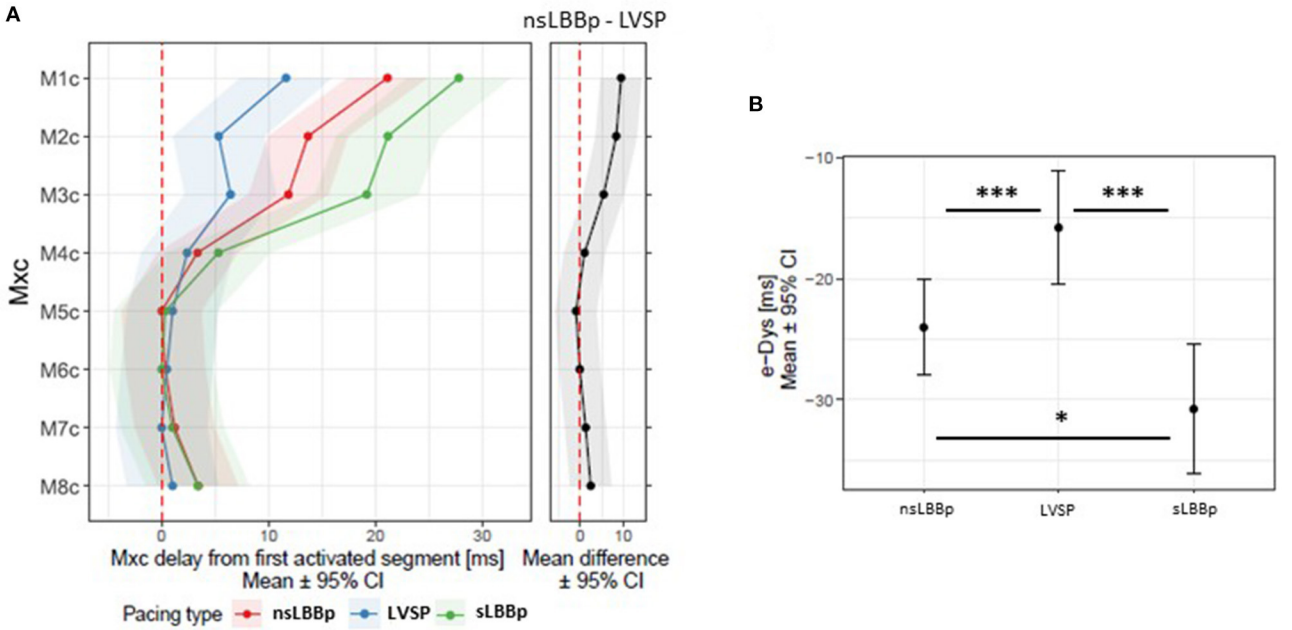

FIGURE 3 | (A) Local activation times M1c–8c (first activated segment was placed at 0 ms) and a comparison of e-DYS between nsLBBp, LVSP, and sLBBp **(B)**. $^{*}p < 0.05$; $^{***}p < 0.001$.

nV resolution and a frequency range of 1.5 kHz. Standard V1–V8 chest lead positions were used, except for lead V1, which was moved from the fourth to the 5th right parasternal intercostal space to obtain better signals from the lateral RV wall. UHF-ECG data for all captures were collected during 2–3 min of VVI pacing at 110 beats/min. Signal processing and UHF-ECG map construction are described in detail elsewhere (7). Median amplitude envelopes were computed in 16 frequency bands (150–1,000 Hz) for each chest lead. The broad-band QRS complex (UHF-QRS) was constructed as the average of the 16 normalized median amplitude envelopes and displayed as a colored map for V1–V8 leads. The local activation times were calculated as the center of mass (Mxc) of the UHF-QRS above the 50% threshold of the baseline-to-peak amplitude for each chest lead. The local depolarization durations under leads V1–V8 were computed as the UHF-QRS duration at 50% of its amplitude (the Vxd parameter). Interventricular electrical dyssynchrony, i.e., e-DYS (the maximum difference between M1-8c) and Vd_{mean} (mean value of V1-8d), were calculated—**Figure 2**. A positive e-DYS indicates delayed LV activation, and a negative e-DYS indicates delayed RV activation.

Global QRS durations (QRSd) were measured using an electrophysiology system (Labsystem Pro, Boston Scientific, USA) from the earliest to the last deflection in any of the 12 leads during spontaneous rhythms. During nsLBBp and LVSP, the beginning of the QRS was measured from the pacing artifact (QRSd) and during sLBBp it was measured from the earliest deflection identified after the pacing artifact. The paced V5 RWPT was measured from the pacing artifact to the maximum positive QRS amplitude in lead V5. All measurements were done at 200 mm/s using two consecutive beats, and their average values were taken.

During the procedure, 2–3 ml of contrast agent was injected through a C315 HIS sheath in the LAO projection; lead depth inside the septum was measured using an xViewer (Vidis, Prague, Czech Republic) and the distance between the tip and the anode ring of a 3,830 lead (10.8 mm) in LAO was used as a reference. The QRS axis in the frontal plane was calculated and considered left-deviated if it was −30° to −90°, normal (−29° to 105°), right-deviated (105° to 180°), or extreme deviated (−90° to −180°).

Statistics

An exploratory data analysis was performed for all parameters. Unpaired comparisons of continuous and categorical variables were made using the unpaired *t*-test and Chi-square test. Repeated measurement comparisons were made using a linear mixed effect model (LMEM) and the Tukey multiple comparison test. The results of these models are presented as means with 95% confidence intervals and comparisons as mean differences with 95% confidence intervals and *p*-values (**Figures 3–6**; **Supplementary Figures 1**, **2**). A *p*-value < 0.05 was considered statistically significant. RStudio version 1.2.1335 with R version 3.6.1 was used to perform statistical analyses. The LMEM was calculated using lme4 version 1.1–21. If not specified, values are shown as means (95% CI).

RESULTS

Lead placement in the left septal position resulting in nsLBBp that was confirmed using pacing maneuvers was successful in

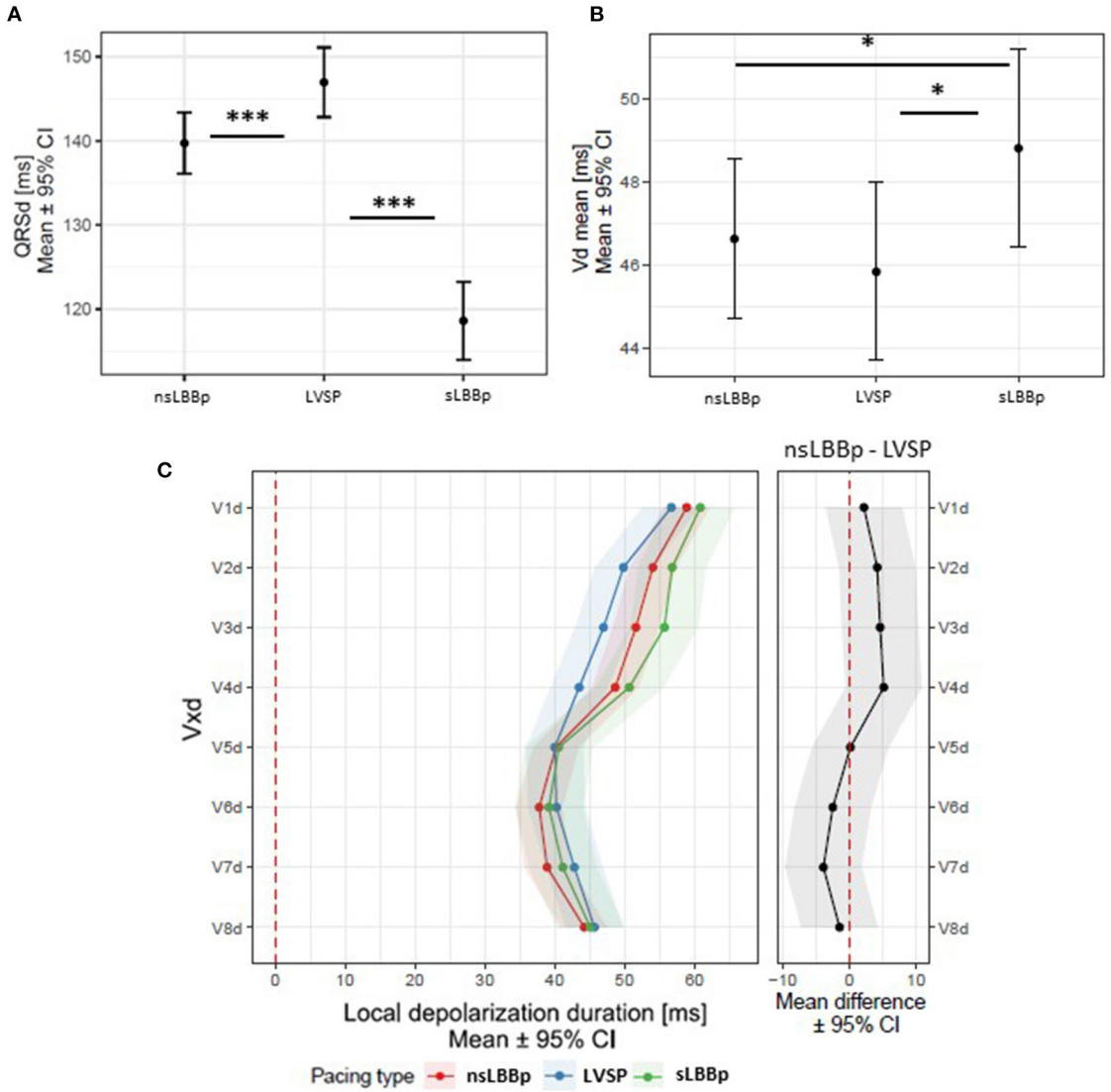

FIGURE 4 | (A) QRSd, Vd_{mean} **(B)**, and local depolarization durations (Vd in V1–V8) **(C)** between nsLBBp, LVSP, and sLBBp. *$p < 0.05$; ***$p < 0.001$.

57 of 96 (59%) patients, and these patients were included in the analyses. Patients without proved LBBp capture were more likely to suffer from heart failure, coronary artery disease, and type 2 diabetes mellitus compared to patients with proved nsLBBp capture (**Table 1**). Additionally, their septum's were thicker, and the indication for pacing was more often an AV block. In two patients, nsLBBp recordings were inadvertently omitted, and two other patients had two nsLBBp recordings (from different pacing locations). In total, we analyzed 57 nsLBBp, 23 sLBBp, and 34 LVSP in 57 patients with successful nsLBBp implants.

The LBB potential was not present in 7/23 (26%) patients with nsLBBp-to-sLBBp transition (4 of them with LBBB during spontaneous rhythm), and in 6/34 (18%) patients with nsLBBp-to-LVSP transition (2 with LBBB), $p = 0.26$. Lead tips in patients with LVSP transition were shallower [14.8 mm (13.9; 15.7)] than in patients with sLBBp transition [15.4 (14.5; 16.4], $p = 0.003$). The LV ejection fraction of patients with transition from nsLBBp-to-LVSP was lower [55% (53; 58)] and their septum's tended to be thinner [10.6 mm (10.1; 11.0)] compared to patients with nsLBBp-to-sLBBp transition [59% (58; 61) and 11.2 (10.7; 11.8), $p = 0.006$ and $p = 0.06$ respectively]. The groups did not differ in other clinical characteristics. LVSP had the longest V5 RWPT [86 ms (83; 89)], $p < 0.001$ compared to both nsLBBp [68 ms (65; 71)] and sLBBp [70 ms (67; 73)].

The sequence of ventricular activation under V4–V8 was the same during all three types of ventricular capture. More delayed activation of ventricular segments under V1–V3 led to significant e-DYS prolongation during both nsLBBp and sLBBp (**Figure 3**).

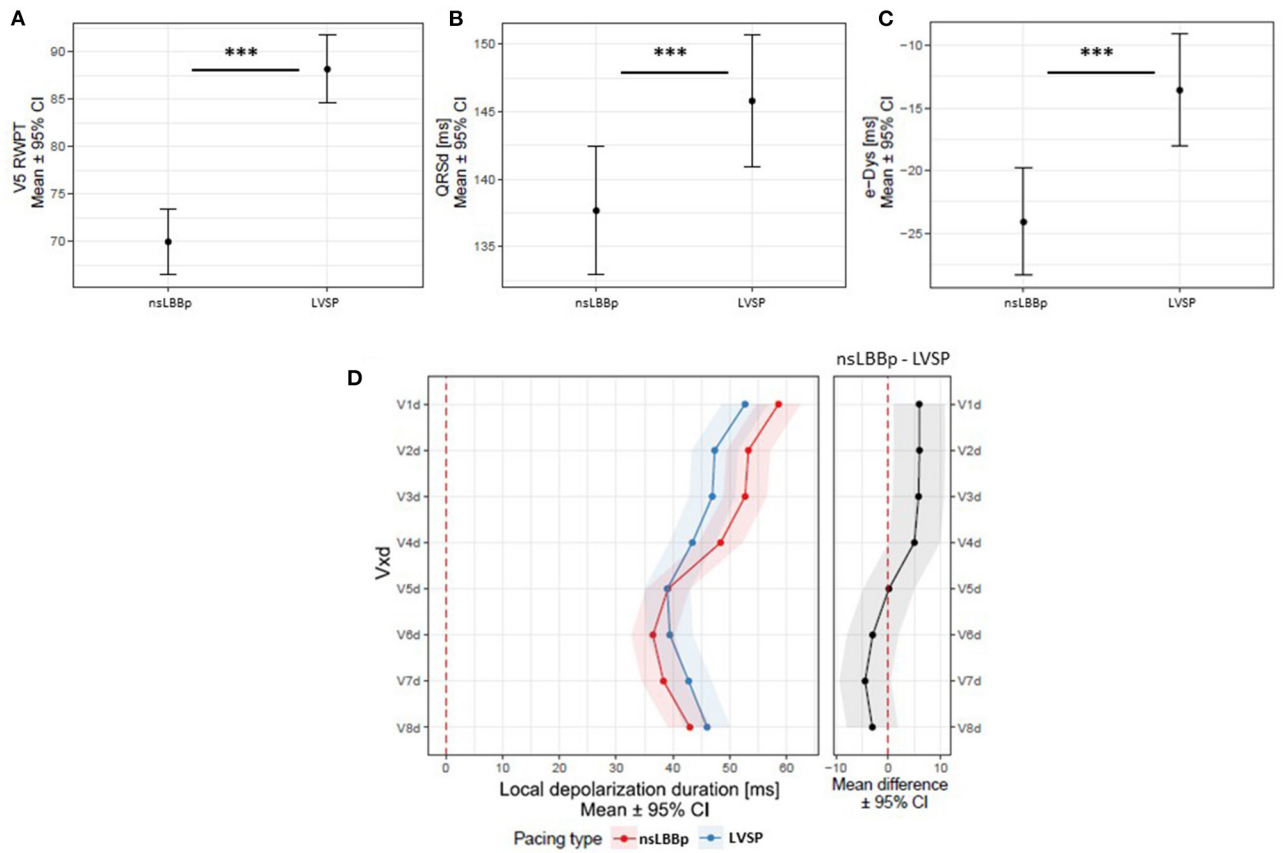

FIGURE 5 | (A) V5 RWPT, QRSd **(B)**, e-DYS **(C)**, and local depolarization durations (Vd in V1–V8) **(D)** between nsLBBp and LVSP with normal heart axes. ***$p < 0.001$.

A negative e-DYS, indicating delayed RV depolarization was present in all 23 sLBBp, 57 of 58 nsLBBp, and 29 of 34 LVSP.

sLBBp had the shortest QRSd, but its Vd_{mean} was longer than during both LVSP and nsLBBp. However, local depolarization durations associated with the depolarization of the LV lateral wall (V5–V8d) were the same during all three capture types. Local depolarization durations under V1–V4 were slightly prolonged during sLBBp, although a statistical difference was only reached in V3d for sLBBp vs. LVSP ($p = 0.01$). No differences in V1d−8d were observed between LVSP and nsLBBp (**Figure 4**).

Similar results with respect to the ventricular depolarization pattern were observed when comparing nsLBBp, LVSP, and sLBBp in patients without LBBB (non-LBBB group) and nsLBBp vs. LVSP in patients with QRSd below 120 ms (narrow QRS group); sLBBp were not included in this analysis because there were only six sLBBp in patients with narrow QRSs (**Supplementary Figures 1**, **2**).

Significant differences in the proportion of patients with a deviated heart axis were observed in studied capture types. Left or extreme axis deviations were the most common during sLBBp (16 of 23 captures (70%), one of them had an extreme axis deviation); a left axis deviation was present in 27 of 58 nsLBBp (47%). For LVSP, most of the paced QRS axes were normal (27 of 34; 79%).

To exclude the possible influence of lead placement in LBB fascicles (which results in heart axis deviation), we compared nsLBBp ($n = 31$) vs. LVSP ($n = 27$) with normal axes. The V5 RWPT and QRSd during LVSP were longer compared to nsLBBp, but both capture types showed the same local depolarization duration in leads V5–V8. However, LVSP resulted in shorter depolarization durations in V1 to V4 (V1d–V4d) than nsLBBp. Moreover, LVSP with a normal axis resulted in less interventricular dyssynchrony than nsLBBp with a normal heart axis (**Figure 5C**).

As a result of precise lead placement, two different nsLBBp capture types were present. The first with a transition from nsLBBp-to-LVSP, and the second was a transition from nsLBBp-to-sLBBp while decreasing the pacing output. To investigate if they were the same or represented two capture types with different impacts on ventricular depolarization, we compared them to each other. We found no difference in the V5 RWPT [68 ms (65; 71) vs. 69 ms (65; 72), $p = 0.9$], QRSd, or local depolarization duration between them. However, nsLBBp with

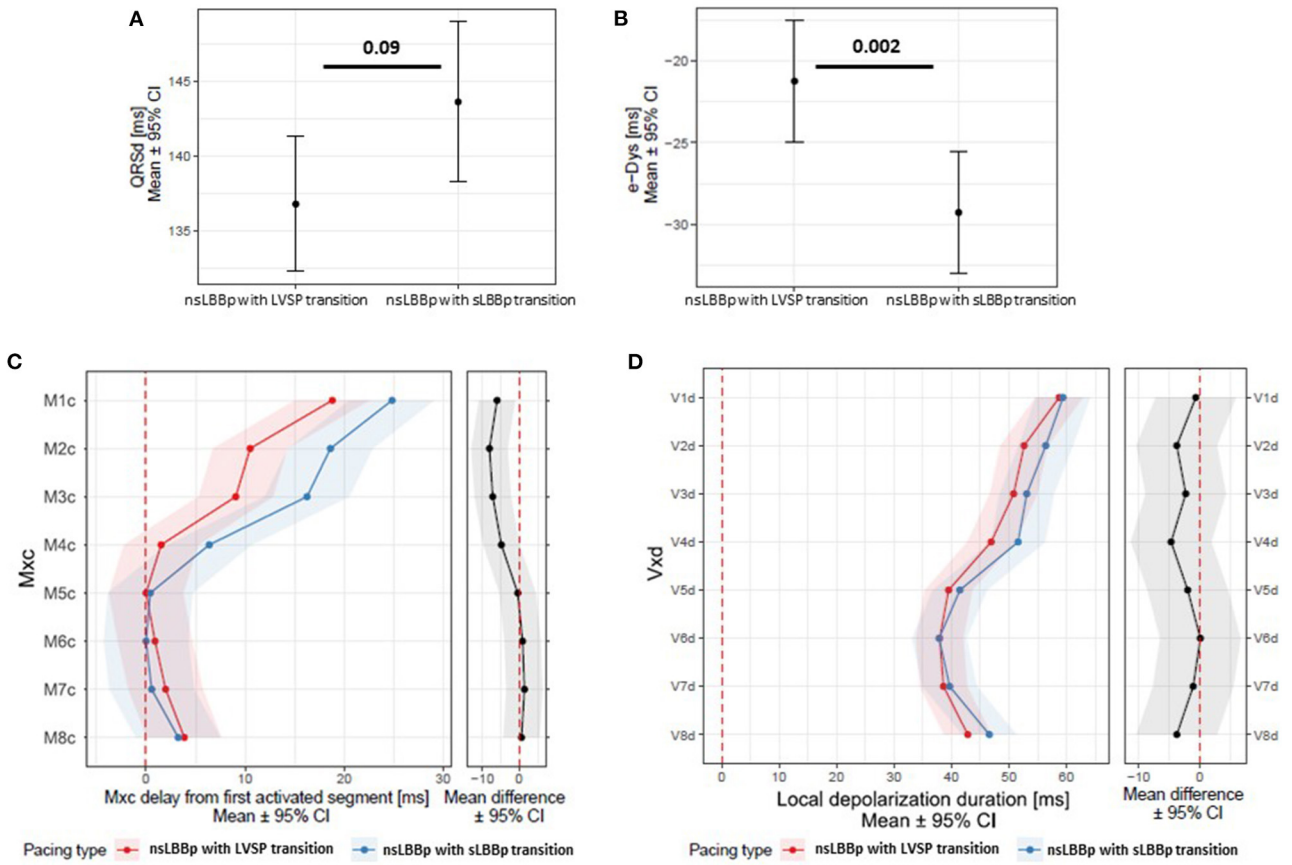

FIGURE 6 | (A) QRSd, e-DYS **(B)**, local activation times M1c-8c (first activated segment was placed at 0 ms) **(C)** and in **(D)** local depolarization durations (Vd in V1–V8) between nsLBBp with a transition to LVSP and nsLBBp with a transition to sLBBp while decreasing the pacing output.

a transition to LVSP had less delayed activation of myocardial segments under V1–V3 and shorter e-DYS than nsLBBp with a transition to sLBBp (**Figure 6**).

DISCUSSION

This study showed that significant differences exist between ventricular captures when pacing the LBB or left septal myocardium in the immediate vicinity of the LBB. They are:

(1) sLBBp and nsLBBp are equivalent with respect to LV depolarization, but sLBBp leads to greater interventricular dyssynchrony than nsLBBp.
(2) Left septal myocardial pacing from the location where nsLBBp could be achieved during increasing the pacing output up to 5 V at 0.5 ms (LVSP) not only preserves interventricular dyssynchrony better than sLBBp and nsLBBp, but it also does not significantly prolong LV lateral wall depolarization times in patients with bradycardia.
(3) Small differences in ventricular activation are present between the two types of nsLBBp based on the transition pattern seen during pacing maneuvers, i.e., nsLBBp with a transition to LVSP leads to less delayed activation in the leads placed above the septum and the right ventricle compared to nsLBBp with a transition to sLBBp.

Selective and Non-selective Left Bundle Branch Pacing

Pacing of the left bundle branch is a relatively new pacing approach that preserves left ventricular synchrony at the costs of creating left to right interventricular dyssynchrony (8). Two types of LBB pacing have been described. The first one was sLBBp, during which the tissue of the left bundle is exclusively captured. During the nsLBBp, both LBB and adjacent myocardial tissue are captured at the same time. This results in changes in the QRS morphology and EGM signal characteristics (1), and the resultant left ventricular depolarization is a mix of conductive tissue and myocardial activation. As our results showed, there were no differences between these two LBB capture types regarding the sequence of ventricular activation or local depolarization durations under the lead associated with the LV lateral wall depolarization. This suggests that the contribution of myocardial wave-front propagation on LV activation during nsLBBp is minimal, and both capture types should be considered equivalent

TABLE 1 | Clinical characteristics of all patients and patients with successful and unsuccessful nsLBBp implants.

	All $n = 96$	Patients with proved nsLLBp $n = 57$	Patients without proved nsLBBp $n = 39$	*p* value
Age (years), mean ± SD	77 ± 8	77 ± 8	77 ± 8	0.66
Male gender, *n* (%)	59 (61)	31 (54)	28 (72)	0.09
Comorbidities				
• Heart failure, *n* (%)	17 (18)	6 (11)	11 (28)	**0.02**
• Coronary heart disease, *n* (%)	37 (39)	16 (28)	21 (54)	**0.01**
• Diabetes mellitus, *n* (%)	41 (43)	18 (32)	23 (59)	**0.007**
• Hypertension, *n* (%)	79 (82)	46 (81)	33 (85)	0.62
LV ejection fraction (%), mean ± SD	56 ± 6	57 ± 6	56 ± 6	0.98
Septal thickness, mean ± SD	11.1 ± 2	10.9 ± 1	11.4 ± 2	**0.03**
Pacing indications				
• AV block, *n* (%)	57 (59)	28 (49)	29 (74)	**0.01**
• SSSy, *n* (%)	28 (29)	23 (40)	5 (13)	**0.004**
• Bi-, trifascicular block, *n* (%)	8 (8)	4 (7)	5 (13)	0.33
• Atrial fibrillation with planned AV junctional ablation, *n* (%)	3 (3)	2 (4)	0 (0)	ns
QRS morphology				
• LBBB, *n* (%)	13 (14)	6 (11)	7 (18)	0.29
• RBBB, *n* (%)	23 (24)	11 (19)	12 (31)	0.20
• IVCD, *n* (%)	11 (11)	7 (12)	4 (10)	0.23
• Narrow QRS, *n* (%)	49 (51)	33 (58)	16 (41)	0.10

SSSy, sick sinus syndrome; AV, atrioventricular; LBBB, left bundle branch block; RBBB, right bundle branch block; IVCD, non-specific intraventricular conduction delay; narrow QRS, QRSd < 120 ms. Bold values are used to highlite a significant difference. ns, nonsignificant.

with respect to LV depolarization. However, the increased delay in RV activation resulted in greater interventricular dyssynchrony during sLBBp. This is very likely the result of concomitant myocardial capture during nsLBBp, which enables earlier trans-septal electrical wave-front propagation and further RV depolarization.

Left Ventricular Septal Myocardial Pacing

The exact criteria for pacing the left ventricular septum were not established yet. Some studies described the differences in EGM signals, QRS morphology, duration, and paced V6 RWPT between LVSP that emerge from the nsLBBp while decreasing pacing output (1, 9). However, a pseudo-right bundle branch block pattern, usually considered the main marker of left septal pacing, is also present at shallower pacing positions than in location where LVSP transits from nsLBBp (2, 3). As we showed in our previous work on a similar group of patients with bradycardia using the same methodology for lead depth measurement, terminal rs/Rs morphology in V1 during left septal myocardial pacing appeared ∼2/3 (10 mm, i.e., 67%) of the distance between the right septum and pacing positions with nsLBBp. Terminal r/R morphology in V1 during left septal myocardial pacing was present on average 4/5 (12 mm, i.e., 81%) of the distance between the right septum and nsLBBp pacing positions (4). These two capture types resulted in less interventricular dyssynchrony but prolonged LV lateral wall depolarization duration compared to nsLBBp. Nonetheless, pacing from these positions did not lead to LBB capture when pacing with outputs up to 5 V at 0.5 ms, and LBBpotential was seen in a minority (7%) of cases. These are the main differences between pacing positions studied previously and left septal pacing with myocardial capture (LVSP) studied in this manuscript. LVSP was observed to be 98% of the distance between the right septum and nsLBBp pacing positions (14.8 mm vs. 15.1 mm), and LBBpotential was observed in a majority of cases (82%). LVSP caused the same interventricular dyssynchrony as left septal myocardial captures with terminal r/R morphology studied previously (4) (on average −16 ms). However, the LV lateral wall depolarization durations using LVSP in close proximity to LBB were shorter and similar to those seen during both sLBBp and nsLBBp. These findings demonstrate differences in ventricular depolarization during various types of left septal myocardial capture. They differ in the degree of interventricular dyssynchrony and the pattern of LV lateral wall activation. The deeper the lead is inserted into the septum during left septal myocardial pacing, the faster the LV lateral wall depolarization is obtained. The main difference in the LV activation pattern seen during LVSP compared to shallower left septal positions with myocardial capture is very likely related to the distance between the pacing lead tip and the left ventricular subendocardial His-Purkinje conductive tissue. With the LVSP in close proximity to LBB, the distance is so small that the contribution of the electrical wave-front originating from activated myocardial cells to LV depolarization is minimal. So, the ventricular depolarization is very similar to that seen during LBBp.

Non-selective LBBp With LVSP and sLBBp Transition During Pacing Maneuvers

Similar to His bundle pacing (HBp), the lead tip dedicated for LBB pacing can be placed inside the conductive tissue (sLBBp and nsLBBp present during pacing maneuvers) or adjacent to the LBB (LVSP and nsLBBp are seen during pacing maneuvers). In both situations, nsLBB captures are present at higher pacing outputs, and they are not considered different. As we showed, nsLBBp with a transition to LVSP was responsible for smaller interventricular dyssynchrony in our study. This was possibly due to shallow pacing positions with decreased left to right transseptal conduction times. Compared to HBp, in which the para-Hisian pacing position was well-described and is used in clinical practice (10, 11), reports on LBB pacing suggested preferential lead tip placement in the LBB to obtain sLBBp and nsLBBp at different pacing outputs (12, 13). However, as we have shown in our work, the pacing of the left septum in close proximity to LBB can be an alternative for patients with bradycardia. Both types of captures seen in this location (LVSP and nsLBBp) preserve interventricular synchrony better than captures seen when the lead tip is located inside the LBB (sLBBp and nsLBBp) and does not worsen LV depolarization pattern significantly. It is also worth mentioning that this pacing position is potentially safer for patients due to shallower lead placement, which decreases the risk of lead perforation into the LV.

Limitations

The results of the study cannot be generalized to patients with heart failure and cardiac resynchronization therapy indication since this study included only patients with an indication for pacemaker implantation due to bradycardia. This study was performed during actual implant procedures. UHF-ECG measurements were taken immediately after the lead was placed in the predefined positions and after confirmation of the type of ventricular capture. We cannot rule out that the resultant damage to conductive and myocardial tissue could have influenced the paced ventricular depolarization patterns. Data were not compared to any other invasive or non-invasive electrocardiographic methods, and no hemodynamic or echocardiographic measurements of mechanical dyssynchrony were performed during the procedure. In the case of three patients with complete persistent AV block of 3rd degree during the procedure, we used the morphology of the escape rhythm to classify them into one of QRS complex morphologies (narrow, LBBB, RBBB, and IVCD). This may have led to incorrect results in some of the analyses presented in the manuscript. In two patients, poor QRS signal quality did not allow for the construction of UHF-ECG maps; therefore, these patients were excluded from the study.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Faculty Hospital Kralovske Vinohrady, Prague. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

This paper was supported by the Charles University Research Program Q38, Research Centre program Nos. UNCE/MED/002 and 260530/SVV/2020, Ministry of Health of the Czech Republic, grant number NU21-02-00584, by the CAS project RVO:68081731, and the European Regional Development Fund - Project ENOCH No. CZ.02.1.01/0.0/0.0/16_019/0000868.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.787414/full#supplementary-material

Supplementary Figure 1 | (A) QRSd, e-DYS **(B)**, local activation times M1c−8c (first activated segment was placed at 0 ms) **(C)** and local depolarization durations (Vd in V1–V8) in **(D)** between nsLBBp, LVSP, and sLBBp in patients with non-LBB QRS morphology.

Supplementary Figure 2 | (A) QRSd, e-DYS **(B)**, local activation times M1c−8c (first activated segment was placed at 0 ms) **(C)** and local depolarization durations (Vd in V1–V8) in **(D)** between nsLBBp and LVSP in patients with narrow QRS morphology (QRSd < 120 ms).

REFERENCES

1. Huang W, Chen X, Su L, Wu S, Xia X, Vijayaraman P, et al. A beginner's guide to permanent left bundle branch pacing. *Heart Rhythm.* (2019) 16:1791–6. doi: 10.1016/j.hrthm.2019.06.016
2. Heckman LIB, Luermans JGLM, Curila K, Van Stipdonk AMW, Westra S, Smisek R, et al. Comparing ventricular synchrony in left bundle branch and left ventricular septal pacing in pacemaker patients. *J Clin Med.* (2021) 10:822. doi: 10.3390/jcm10040822
3. Jastrzebski, M, Moskal P. Reaching the left bundle branch pacing area within 36 heartbeats. *Kardiol Pol.* (2021) 79:587–8. doi: 10.33963/KP.15914
4. Curila K, Jurak P, Jastrzebski M, Prinzen F, Waldauf P, Halamek J, et al. The left bundle branch pacing compared to left ventricular septal myocardial pacing increases interventricular dyssynchrony but accelerates left ventricular lateral wall depolarization. *Heart Rhythm.* (2021) 18:1281–9. doi: 10.1016/j.hrthm.2021.04.025
5. Wu S, Sharma PS, Huang W. Novel left ventricular cardiac synchronization: left ventricular septal pacing or left bundle branch pacing? *Europace.* (2020) 22(Suppl. 2):ii10–8. doi: 10.1093/europace/euaa297
6. Su L, Wang S, Wu S, Xu L, Huang Z, Chen X, et al. Long-term safety and feasibility of left bundle branch pacing in a large single-center study. *Circ Arrhythm Electrophysiol.* (2021) 14:e009261. doi: 10.1161/CIRCEP.120.009261

7. Jurak P, Curila K, Leinveber P, Prinzen FW, Viscor I, Plesinger F, et al. Novel ultra-high-frequency electrocardiogram tool for the description of the ventricular depolarization pattern before and during cardiac resynchronization. *J Cardiovasc Electrophysiol.* (2020) 31:300–7. doi: 10.1111/jce.14299
8. Huang W, Su L, Wu S, Xu L, Xioa F, Zhou X, et al. A novel pacing strategy with low and stable output: pacing the left bundle branch immediately beyond the conduction block. *Can J Cardiol.* (2017) 33:1736.e1–e3. doi: 10.1016/j.cjca.2017.09.013
9. Jastrzebski M, Keilbasa G, Curila K, Moskal P, Bednarek A, Rajzer M, et al. Physiology-based electrocardiographic criteria for left bundle branch capture. *Heart Rhythm.* (2021) 18:935–43. doi: 10.1101/2020.12.24.20248827
10. Curila K, Jurak P, Halamek J, Prinzen F, Waldauf P, Karch J, et al. Ventricular activation pattern assessment during right ventricular pacing: Ultra-high-frequency ECG study. *J Cardiovasc Electrophysiol.* (2021) 32:1385–94. doi: 10.1111/jce.14985
11. Beer D, Sharma PS, Subzposh FA, Naperkowski A, Pietrasik GM, Durrm B, et al. Clinical outcomes of selective versus nonselective his bundle pacing. *JACC Clin Electrophysiol.* (2019) 5:766–74. doi: 10.1016/j.jacep.2019.04.008
12. Su L, Xu T, Cai M, Xu L, Vijayaraman P, Sharma PS, et al. Electrophysiological characteristics and clinical values of left bundle branch current of injury in left bundle branch pacing. *J Cardiovasc Electrophysiol.* (2020) 31:834–42. doi: 10.1111/jce.14377
13. Wu S, Chen X, Wang S, Xu L, Xiao F, Huang Z, et al., Evaluation of the criteria to distinguish left bundle branch pacing from left ventricular septal pacing. *JACC Clin Electrophysiol.* (2021) 7:1166–77. doi: 10.1016/j.jacep.2021.02.018

Conflict of Interest: Some of the participating research institutions have filed a European patent application EP 19212534.2: Method of electrocardiographic signal processing and apparatus for performing the method.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 05 January 2022
doi: 10.3389/fcvm.2021.781845

A Comparison of the Electrophysiological and Anatomic Characteristics of Pacing Different Branches of the Left Bundle Conduction System

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Introduction: Left bundle branch pacing (LBBP) is a rapidly growing conduction system pacing technique. However, little is known regarding the electrophysiological characteristics of different types of LBBP. We aimed to evaluate the electrophysiological characteristics and anatomic lead location with pacing different branches of the left bundle branch.

Methods: Consecutive bradycardia patients with successful LBBP were enrolled and classified into groups according to the paced electrocardiogram and the lead location. Electrocardiogram, pacing properties, vectorcardiogram, and lead tip location were analyzed.

Results: Ninety-one patients were enrolled, including 48 with the left bundle trunk pacing (LBTP) and 43 with the left bundle fascicular pacing (LBFP). The paced QRS duration in the LBTP group was significantly shorter than that in the LBFP group (108.1 ± 9.9 vs. 112.9 ± 11.2 ms, $p = 0.03$), with a more rightward QRS transition zone ($p = 0.01$). The paced QRS area in the LBTP group was similar to that during intrinsic rhythm (35.1 ± 15.8 vs. 34.7 ± 16.6 μVs, $p = 0.98$), whereas in the LBFP group, the paced QRS area was significantly larger compared to intrinsic rhythm (43.4 ± 15.8 vs. 35.7 ± 18.0 μVs, $p = 0.01$). The lead tip site for LBTP was located in a small fan-shaped area with the tricuspid valve annulus summit as the origin, whereas fascicular pacing sites were more likely in a larger and more distal area.

Conclusions: Pacing the proximal left bundle main trunk produced better electrical synchrony compared with pacing the distal left bundle fascicles. A visualization technique can facilitate achieving LBTP.

Keywords: left bundle branch pacing, left bundle trunk pacing, left bundle fascicular pacing, vectorcardiogram, visualization technique

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Specialty section:
This article was submitted to Cardiac Rhythmology, a section of the journal Frontiers in Cardiovascular Medicine

Received: *23 September 2021*
Accepted: *15 December 2021*
Published: *05 January 2022*

Citation:
Liu X, Gu M, Niu H-X, Chen X, Cai C, Zhao J, Cai M, Zhou X, Gold MR, Zhang S and Hua W (2022) A Comparison of the Electrophysiological and Anatomic Characteristics of Pacing Different Branches of the Left Bundle Conduction System. Front. Cardiovasc. Med. 8:781845. doi: 10.3389/fcvm.2021.781845

INTRODUCTION

Left bundle branch pacing (LBBP) is a conduction system pacing (CSP) technique, which overcomes some of the limitations with His bundle pacing (HBP) (1). Unlike the relatively small distribution of the His bundle (HB) region, the left bundle branch (LBB) is a major extension of the HB with a larger anatomical distribution. It is composed of a short and thick left bundle main trunk and two main fascicles, the left anterior fascicle (LAF) and left posterior fascicle (LPF) (2). Theoretically, pacing any parts of the LBB can capture the left sided conduction system. However, the impact of pacing site of the LBB on electrophysiological characteristics and ventricular synchrony is not well-studied.

Recently, the QRS area obtained by the 3-dimensional (3D) vectorcardiography (VCG) has emerged as a reliable index to evaluate ventricular synchrony (3). Compared with the traditional electrocardiogram (ECG), the VCG contains 3D information of the electrical forces, which provides additional valuable information to the ECG. Previous studies showed that the QRS area predicted cardiac resynchronization therapy (CRT) response better than the QRS duration, and was strongly associated with clinical outcomes (4, 5).

The aim of the present study was to compare electrophysiological characteristics and ventricular synchrony of different pacing sites of the LBB. In addition, a novel visualization technique was used to correlate anatomic location with paced LBB morphology to help guide pacing different components of the LBB (6).

MATERIALS AND METHODS

Consecutive patients who underwent LBBP with bradycardia indications including sinus node dysfunction (SND) or atrioventricular block (AVB) from Fuwai Hospital (Beijing, China) were analyzed. Patients were classified into two groups including the left bundle trunk pacing (LBTP) and the left bundle fascicular pacing (LBFP) group. The latter group included those with either a paced LAF or LPF morphology (**Figures 1**, **2**). Patients were excluded if they had a native QRS duration longer than 120 ms, including left bundle branch block (LBBB), right bundle branch block (RBBB), and non-specific intraventricular conduction disturbance (NIVCD). This study was approved by the Ethics Committee of Fuwai Hospital and all patients submitted the written informed consent.

Implantation Procedure

LBBP implantation was performed using the Select Secure 3830 pacing lead (Medtronic Inc., Minneapolis, MN) and the fixed-curve C315 HIS sheath (Medtronic Inc., Minneapolis, MN). The implantation procedure was performed as previously described (6). Successful LBBP was assumed in patients whose paced ECG morphology in lead V1 showing a RBBB pattern and also met at least one of the following three criteria: (1) recording of an LBB potential; (2) left ventricular activation time (LVAT) remained short and constant (<80 ms) at different pacing outputs or was abruptly shortened (≥10 ms) at high output; (3) demonstration of selective LBB capture.

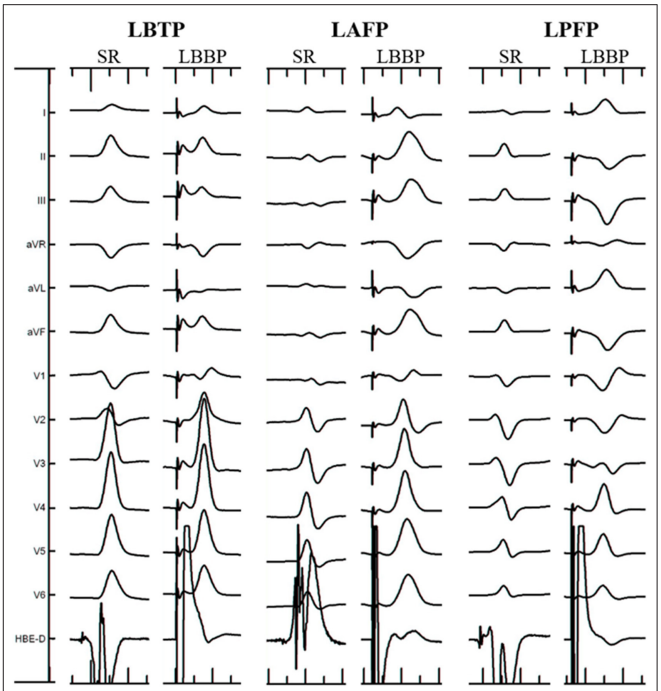

FIGURE 1 | Electrocardiographic characteristics of different ECG types. LAFP, left anterior fascicular pacing; LBBP, left bundle branch pacing; LBTP, left bundle trunk pacing; LPFP, left posterior fascicular pacing; SR, sinus rhythm.

LBB Lead Tip Location Evaluation

During the procedure, right ventriculography was performed with an injection below the root of the tricuspid septal leaflet with 10–15 ml contrast medium through C315 HIS sheath imaged in the right anterior oblique 30° (RAO 30°) fluoroscopic view. Then the fluoroscopic image of the tricuspid value annulus (TVA) was saved and served as a marker to help locate the target LBB region according to the positional relationship between the TVA and the LBB as revealed by our previous study. The target LBB area included area 1 and area 2. Area 1 was defined as a fan-shaped area drawn from the TVA summit with a radius of 15–35 mm and angle ranging from + 10 to −30°, area 2 was defined as a more distal fan-shaped area with a radius of 35–50 mm and angle ranging from + 10 to −60°. After the LBB lead was deployed, visualization of the TVA was performed again through another C315 HIS sheath to finally confirm the lead tip location (6). The horizontal and vertical distances between the LBB lead tip and the TVA summit were measured offline in each of the patients (**Figure 3**).

ECG Criteria for Determining the LBB Lead Tip Location

The criteria for determining the electrophysiological classification of LBB lead tip location was based on previous studies of the ECG morphology of left bundle fascicular block and fascicular ventricular arrhythmia (**Figure 1**) (7–10). The types of ECG criteria include: (1) LBTP: RBBB pattern; paced QRS morphology similar to sinus rhythm; (2) left anterior

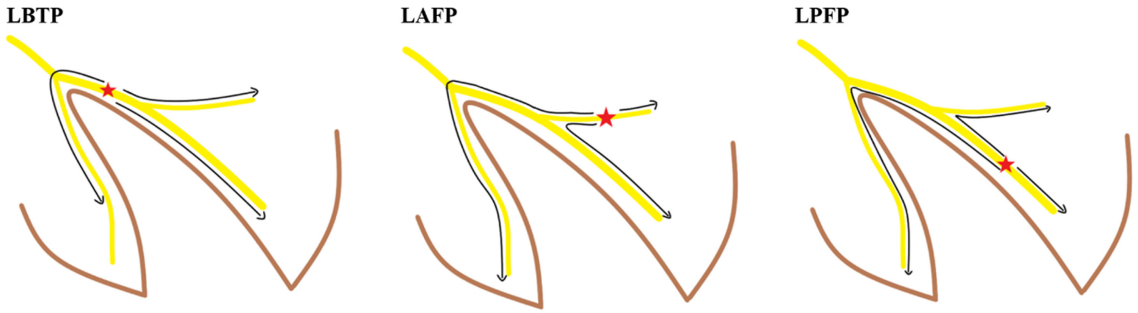

FIGURE 2 | Activation sequence of the conduction system in different ECG types. LAFP, left anterior fascicular pacing; LBTP, left bundle trunk pacing; LPFP, left posterior fascicular pacing.

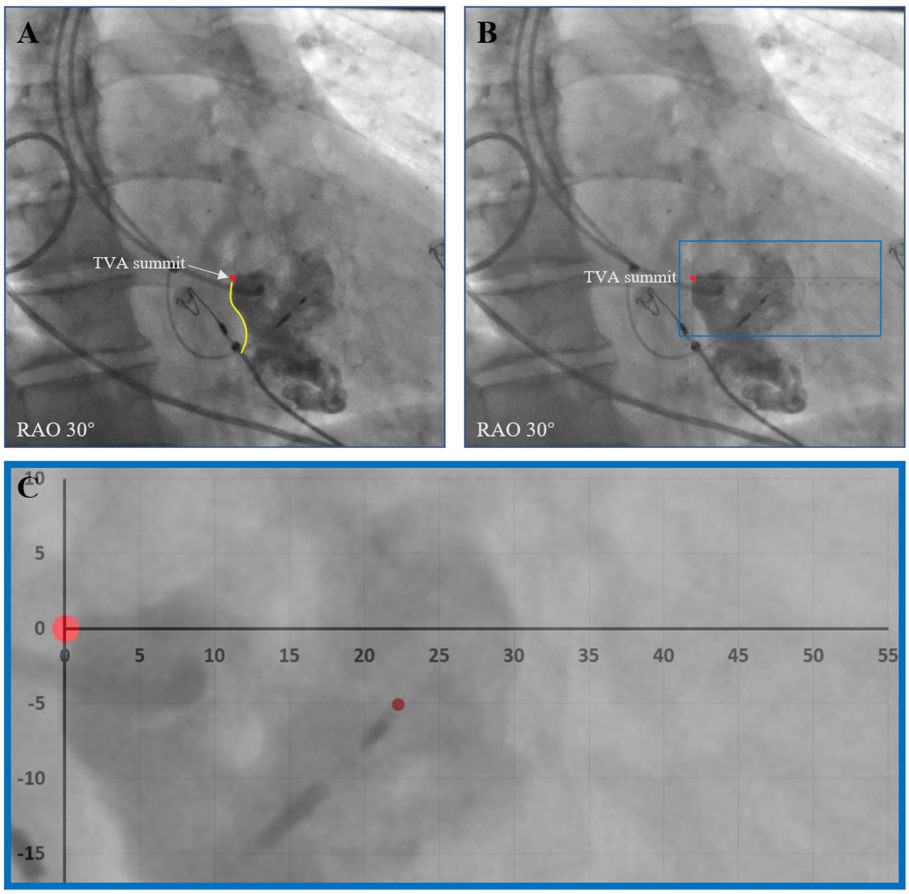

FIGURE 3 | Evaluation of the positional relationship between the LBB lead tip and the TVA. **(A)** After the LBB lead was deployed, visualization of the TVA was performed to show the TVA summit. **(B)** The horizontal and vertical distances between the LBB lead tip and the TVA summit were measured offline. **(C)** An enlarged view of the measurement. LBB, left bundle branch; RAO, right anterior oblique; TVA, tricuspid value annulus.

fascicular pacing (LAFP): RBBB pattern; dominant S wave in leads I and aVL; dominant R wave in leads II, III, and aVF; right-axis deviation; (3) left posterior fascicular pacing (LPFP): RBBB pattern; dominant R wave in leads I and aVL; dominant S wave in leads II, III, and aVF; left-axis deviation. Patients who met the ECG criteria of LBTP were classified into the LBTP group, whereas patients who meet the ECG criteria of LAFP or LPFP were classified into the LBFP group. All ECGs were evaluated by two independent experienced electrophysiologists blinded to the anatomic location. In cases of discrepancy between reviewers, a third electrophysiologist provided adjudication.

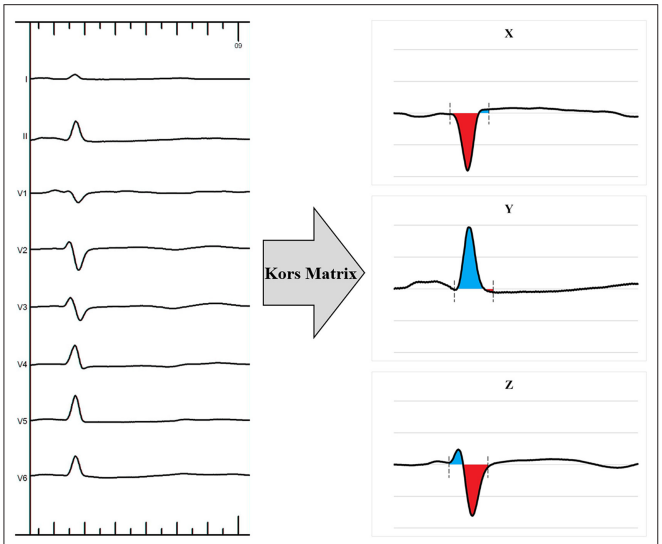

FIGURE 4 | Example of a 12-lead electrocardiogram transformed into a 3-dimensional vectorcardiogram using the Kors matrix.

ECG and VCG Analysis

For ECG analysis, the 12-lead ECG were recorded using an electrophysiology workstation (Bard, Boston Scientific, Lowell, MA). The QRS duration and QRS transition zone were recorded before and after the procedure. The LVAT was defined as the interval from the pacing stimulus to the R-wave peak of the QRS complex in leads V5-V6.

For VCG analysis, the customized MATLAB software (MathWorks Inc., Natick, MA) was used to convert the 12-lead ECG into the 3 orthogonal VCG leads (X, Y, and Z) using the Kors conversion matrix as described previously (**Figure 4**) (3, 11, 12). This matrix was based on a learning set from the Common Standards for Electrocardiography multilead library, including both patients and healthy individuals, and was generated by multiple linear regression. The VCG was synthesized by analyzing eight independent ECG leads (two limb leads and all six precordial leads) retrieved from the 12-lead ECG by the Kors conversion matrix. QRS area, which represents the extent of the unopposed electrical forces during ventricular activation, was calculated as the combined area under the QRS complex in the calculated vectorcardiographic X, Y, and Z leads [QRS area = (QRS area, x^2 + QRS area, y^2 + QRS area, z^2)$^{1/2}$].

Data Collection and Follow-Up

Baseline data including the demographic characteristics, indications for pacemaker implantation and echocardiographic measurements were collected at enrollment. Pacing parameters including capture threshold, R-wave amplitude, and impedance were recorded during the procedure and at 12-month follow-up. Procedural related complications including loss of capture, lead septal perforation, and lead dislodgement were tracked during follow-up.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation or as median (interquartile range), and categorical variables are expressed as frequencies or percentages. Independent two sample *t*-test or analysis of variance (ANOVA) test are used to compare the differences between groups if the data are normally distributed. Wilcoxon signed rank test or Kruskal-Wallis test are performed for data that are not normally distributed. Chi square or Fisher's exact test are used to compare categorical variables. For within patients' comparisons of continuous variables, paired *t*-test are used for normally distributed data and Wilcoxon signed rank test for non-normally distributed data. A two-sided $P < 0.05$ is considered statistically significant. All statistical analyses are performed using the SPSS Statistics version 22.0 (IBM Corporation, Armonk, NY).

RESULTS

Baseline Characteristics Among Groups

From April 2018 to January 2020, 127 patients successfully underwent LBBP implantation for bradycardia indications. Among this group, 36 patients were excluded for having underlying QRS prolongation, including 17 for LBBB, 11 for RBBB, and 8 for NIVCD. Accordingly, a total of 91 patients were included in the analysis. There were 48 patients classified into the LBTP group and 43 to the LBFP group. The LBFP group included 14 patients with LAFP and 29 with LPFP. There were no significant differences in baseline demographics, pacing indications, ECG, VCG, and echocardiographic measurements between patients with LAFP and LPFP (**Table 1**). These subgroups were pooled because these were relatively small cohorts that paced fascicles of the LBB. Similarly, there were no differences in baseline characteristics between the LBTP and LBFP groups (**Table 1**).

Electrophysiological Characteristics Among Groups

As shown in **Table 2**, the paced QRS duration in the LBTP group was significantly narrower than that in the LBFP group (108.1 ± 9.9 vs. 112.9 ± 11.2 ms, $p = 0.03$). In addition, the QRS transition zone in the LBTP group was more rightward than that in the LBFP group ($p = 0.01$). No significant differences were observed in LVAT between two groups (68.9 ± 6.4 vs. 67.7 ± 5.6 ms, $p = 0.35$).

VCG analysis showed that the paced QRS area in the LBTP group was similar to that during intrinsic rhythm (35.1 ± 15.8 vs. 34.7 ± 16.6 μVs, $p = 0.98$), whereas in the LBFP group, the paced QRS area was significantly larger compared to intrinsic ventricular activation (43.4 ± 15.8 vs. 35.7 ± 18.0 μVs, $p = 0.01$) (**Figure 5**). Paced QRS area was larger for the LBFP group compared with the LBTP group (43.4 ± 15.8 vs. 35.1 ± 15.8 μVs, $p = 0.01$) (**Table 2**; **Figure 5**).

Lead Tip Distribution Among Groups

As shown in **Table 2**, the proportion of patients in the LBTP group with the lead tip in Area 1 was significantly higher than that in the LBFP group (75.0 vs. 16.3%, $p < 0.01$). Conversely,

TABLE 1 | Baseline characteristics between groups.

	LBTP group ($n = 48$)	LBFP group ($n = 43$)			*P*-values	
		Total ($n = 43$)	LAFP ($n = 14$)	LPFP ($n = 29$)	LAFP vs. LPFP	LBTP vs. LBFP
Demographics						
Age (years)	58.2 ± 19.6	58.1 ± 16.6	59.1 ± 12.0	57.6 ± 18.6	0.78	0.75
Male	24 (50.0%)	22 (51.2%)	7 (50.0%)	15 (51.7%)	0.92	0.91
Comorbidities						
Hypertension	27 (56.3%)	22 (51.2%)	6 (42.9%)	16 (55.2%)	0.45	0.63
Diabetes mellitus	6 (12.5%)	6 (14.0%)	3 (21.4%)	3 (10.3%)	0.37	0.84
Coronary artery disease	10 (20.8%)	8 (18.6%)	2 (14.3%)	6 (20.7%)	0.93	0.79
Indications					0.45	0.67
SND	18 (37.5%)	18 (41.9%)	7 (50.0%)	11 (37.9%)		
AVB	30 (62.5.0%)	25 (58.1%)	7 (50.0%)	18 (62.1%)		
Baseline ECG						
QRS duration (ms)	94.8 ± 9.6	94.3 ± 9.3	92.9 ± 9.0	95.0 ± 9.5	0.49	0.83
QRS transition zone	4.0 (3.5, 4.5)	4.0 (3.5, 4.5)	4.0 (3.5, 5.0)	4.0 (3.5, 4.0)	0.07	0.90
Baseline VCG						
QRS area (μVs)	34.7 ± 16.6	35.7 ± 18.0	35.4 ± 20.6	35.8 ± 17.0	0.67	0.95
Echocardiography						
LVEF (%)	61.1 ± 6.2	60.4 ± 6.2	59.3 ± 6.7	61.0 ± 6.0	0.46	0.69
LVEDD (mm)	49.8 ± 6.3	48.7 ± 4.8	48.9 ± 4.2	48.6 ± 5.1	0.85	0.56

AVB, atrioventricular block; ECG, electrocardiogram; LAFP, left anterior fascicular pacing; LBFP, left bundle fascicular pacing; LBTP, left bundle trunk pacing; LPFP, left posterior fascicular pacing; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; SND, sinus node dysfunction; VCG, vectorcardiogram.

while the proportion of patients with the lead tip within area 2 was significantly lower (20.8 vs. 81.4%, $p < 0.01$). The positional relationship between the LBB lead tip and the TVA summit in each ECG type is shown in **Figure 6**, and the lead tip distribution of different ECG type in different areas is presented in **Table 3**. Overall, 97% (88 of 91) of patients had the lead tip within a fan-shaped area drawn from the TVA summit with the radius from 15 to 50 mm and the angle range from + 10 to −60 degrees (area 1 or area 2). Nearly half of the patients (43 of 91, 47%) had the lead tip within area 1. Among these patients, 84% (36 of 43) were classified into the LBTP group. The majority of patients (35 of 45, 78%) with lead tips in area 2 were classified into the LBFP group. Among the subgroup of LBFP, both LAFP and LPFP most commonly had the lead tip within area 2 (71 and 86%, respectively, $p = 0.45$). However, the overlapping distribution of the lead tip in different ECG types in area 2 makes it difficult to distinguish them by specific positioning method. In general, LAFP was more likely located in the upper part of the area 2, whereas LPFP was located in the lower part of the area 2 (**Figure 6**).

Further analysis between area 1 and area 2 showed that the patients having the lead tip within area 1 had a similar paced QRS area compared with their intrinsic rhythm (36.4 ± 16.1 vs. 35.9 ± 16.8 μVs, $p = 0.75$), whereas patients with the lead tip in area 2 had a significantly increased QRS area (42.6 ± 15.9 vs. 34.2 ± 17.7 μVs, $p < 0.01$) (**Figure 5**).

Twelve-Month Follow-Up

No significant differences were observed between implantation and 12-month follow-up for electrical parameters of the lead as shown in **Table 2**. Similarly, echocardiographic measurements including LVEDD and LVEF were similar at follow-up (**Table 2**). One patient in both the LBTP and LBFP groups had a lead septal perforation during the procedure. The lead was immediately repositioned with no post-implant adverse effects. One patient in the LBFP group had lead dislodgement during follow-up, so a right ventricular pacing (RVP) lead was placed.

DISCUSSION

LBBP is a rapidly increasing conduction system pacing modality. In the present study, we evaluated the electrophysiological characteristics of pacing different parts of the LBB by comparing the paced ECG and VCG parameters. The primary findings of our study were that pacing the left bundle main trunk achieved narrower paced QRS duration than pacing the left bundle fascicles, and that the QRS transition zone was more rightward. Moreover, LBTP had a QRS area similar to intrinsic rhythm, whereas in the LBFP group, the QRS area was significantly larger than during intrinsic rhythm. These observations indicate worse ventricular synchrony. Furthermore, imaging showed that most patients with the lead tip within area 1 had LBTP. Fascicular pacing was noted more commonly in a broad and more distal area (area 2), which was associated with an increased paced QRS area. Since the paced QRS morphology cannot be assessed until the lead is deployed deep in the septum, the imaging technique helps to minimize repeat lead repositioning which are associated with high risk of perforation or other complications, as well as to achieve LBTP.

Physiological Pacing in Bradycardia Patients

HBP is the most physiological pacing modality, as it activates the most proximal part of the native conduction system to achieve normal ventricular activation sequence (13). However, locating the HB can be challenging due to the small region of the HB. Moreover, the pacing parameters of HBP are less stable compared to traditional RVP with frequent high pacing thresholds (14). LBBP can overcome some of the limitations exists in HBP, and is considered as an alternative CSP technique (1). Anatomically, the LBB is divided into several parts. The main trunk of the LBB is usually short and thick, after a short path, it gives rise to its two main fascicles including a thin LAF and a wider LPF (2). However, little is known regarding the pacing characteristics at different LBB sites.

TABLE 2 | Procedural outcomes between groups.

	LBTP group ($n = 48$)	LBFP group ($n = 43$)	*P*-value
Lead tip distribution			
Within area 1	36 (75.0%)	7 (16.3%)	< 0.01
Within area 2	10 (20.8%)	35 (81.4%)	< 0.01
ECG parameters			
Paced QRS duration (ms)	108.1 ± 9.9	112.9 ± 11.2	0.03
LVAT (ms)	68.9 ± 6.4	67.7 ± 5.6	0.35
QRS transition zone	1.3 (1.0, 1.5)	1.5 (1.5, 2.0)	0.01
VCG parameters			
QRS area (μVs)	35.1 ± 15.8	43.4 ± 15.8	0.01
Pacing parameters			
Capture threshold (V/0.4 ms)	0.8 ± 0.2	0.8 ± 0.3	0.97
R-wave amplitude (mV)	11.1 ± 4.4	10.0 ± 3.9	0.21
Impedance (Ω)	674.1 ± 130.9	677.5 ± 133.6	0.83
Parameters at follow-up			
Capture threshold (V/0.4 ms)	0.7 ± 0.2	0.7 ± 0.2	0.83
R-wave amplitude (mV)	11.8 ± 4.2	11.0 ± 3.9	0.49
Impedance (Ω)	478.9 ± 80.0	489.3 ± 73.4	0.39
Echocardiography at follow-up			
LVEF (%)	61.2 ± 5.1	60.8 ± 5.08	0.65
LVEDD (mm)	49.6 ± 5.6	48.7 ± 6.0	0.38

ECG, electrocardiogram; LBFP, left bundle fascicular pacing; LBTP, left bundle trunk pacing; LVAT, left ventricular activation time; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; VCG, vectorcardiogram.

Evaluation of Ventricular Synchrony

The paced ECG QRS duration is a commonly used index to evaluate ventricular depolarization. In general, a longer paced QRS duration is considered to represent worse ventricular synchrony. However, the paced QRS complex is a reflection of total ventricular activation. In patients who achieve CSP, pacing at any part of the conduction system can achieve relatively rapid ventricular activation, thus generate a similar paced QRS duration. This makes it difficult to compare the subtle differences between pacing sites. In a previous study of pacing different branches of the left bundle conduction system in a different cohort of patients, it was shown that the paced QRS duration were similar for different locations (9). In the present study with a larger sample size and different grouping method, the results shows that the paced QRS duration in the LBFP group was longer than that in the LBTP group, suggesting worse ventricular synchrony. Both studies showed that LPFP was more common than LAFP, likely reflecting the size of these fascicles. It should be noticed that, though pacing different parts of the LBB produced different ventricular synchrony, the overall conduction velocity is relatively fast due to the capture of the conduction system, so the absolute differences in paced QRS duration were relatively small.

The paced QRS area calculated by the VCG has emerged as a more sensitive measure of dyssynchronous electrical activation. The VCG contains more complete information on electrical forces, as the QRS area calculated by the VCG is the combined

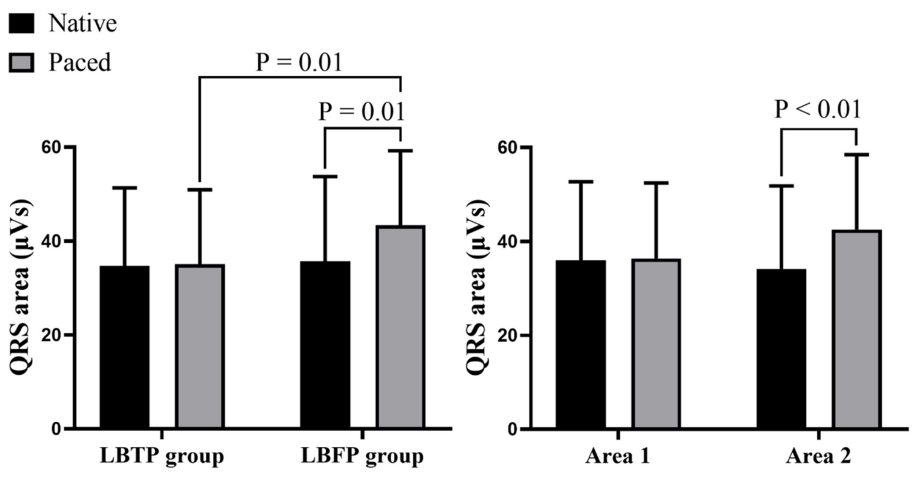

FIGURE 5 | Comparison of the QRS area between different groups and different areas. LBFP, left bundle fascicular pacing; LBTP, left bundle trunk pacing.

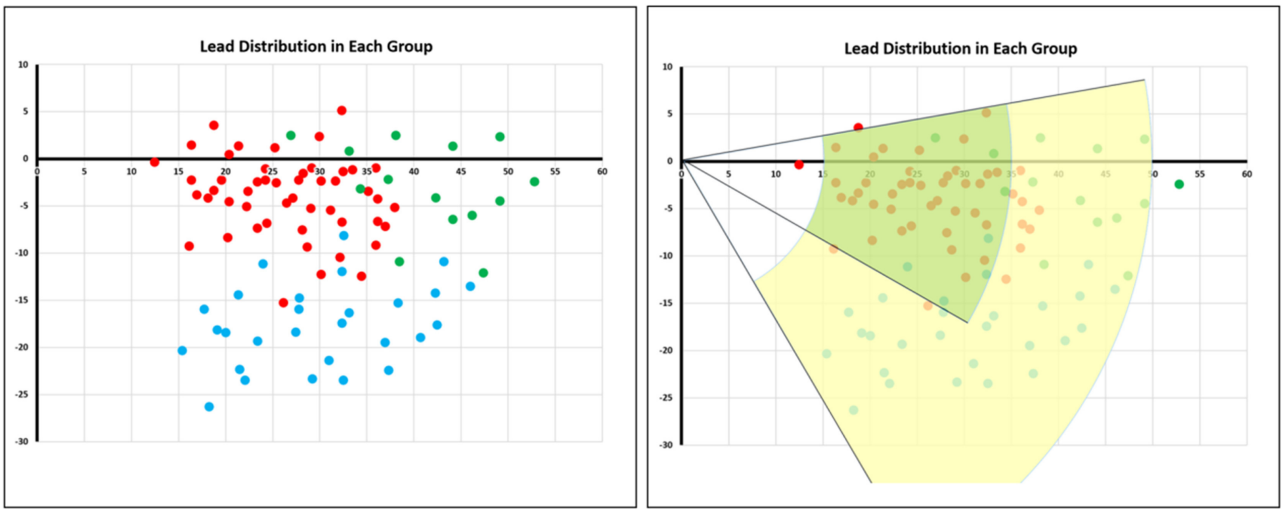

FIGURE 6 | Lead tip distribution in different electrocardiogram types. The red dots represented patients with LBTP, the green dots represented patients with LAFP, and the blue dots represented patients with LPFP. The green area termed area 1 was a fan-shaped area drawn from the TVA summit with the radius from 15 to 35 mm and the angle range from + 10 to −30 degrees. The yellow area termed area 2 was a fan-shaped area with the radius from 35 to 50 mm and the angle range from + 10 to −60 degrees. LAFP, left anterior fascicular pacing; LBTP, left bundle trunk pacing; LPFP, left posterior fascicular pacing; TVA, tricuspid value annulus.

TABLE 3 | Lead tip distribution in each ECG type.

	LBTP	LAFP	LPFP	Total
Area 1	36	3	4	43
Area 2	10	10	25	45
Other area	2	1	0	3
Total	48	14	29	91

LAFP, left anterior fascicular pacing; LBTP, left bundle trunk pacing; LPFP, left posterior fascicular pacing.

area under the QRS complex and represents the extent of unopposed electrical forces during ventricular activation (15). Previous studies showed the better predictive value of the QRS area than traditional QRS duration for echocardiographic response and clinical outcomes in CRT eligible patients (4, 5). In the present study, the paced QRS area in the LBFP group was significantly larger than during intrinsic rhythm or compared with LBTP, which further supports that ventricular synchrony is impaired with LBFP.

Ideal LBBP Location

Theoretically, pacing the proximal main trunk of the LBB should result in better cardiac synchrony compared with pacing the left bundle fascicles. LBTP preserves left ventricular synchrony by sequentially activating each segment of the left ventricle. Moreover, among patients without heart block, retrograde activation of the RBB can rapidly activate the right ventricle with less time delay, thus maintaining interventricular synchrony and potentially achieve more normal right ventricular synchrony (**Figure 2**). In contrast, pacing distal LBB fascicles leads to different ventricular activation sequences, thus resulting in impaired left ventricular synchrony, reflected in part by changes in paced QRS axis (2). Moreover, the longer distance of retrograde activation of RBB by LBBP may exacerbate delayed right ventricular activation, leading to significantly decreased interventricular synchrony (**Figure 2**) (16).

The present study shows that ventricular synchrony evaluated by both QRS duration and VCG is optimized and more physiologic by pacing the main trunk of the LBB conduction system. In addition, the superiority of pacing the proximal LBB was verified by the significantly different QRS area between pacing in proximal area 1 and distal area 2 defined by our visualization technique. All of these findings support pacing the proximal left bundle main trunk instead the distal LBB fascicles when possible. The visualization technique used in this study can facilitate activating this area, which occurred more commonly in the present study (53%) compared previously using the traditional fluoroscopic approach (25%) (9).

Clinical Perspectives

The findings of this study show the superiority of pacing the proximal left conduction system, as defined by either the ECG (left bundle main trunk) or the fluoroscopic lead tip location (area 1). While the present study was performed in a bradycardia population with a normal left ventricular function, providing the optimal LBBP would be crucial in heart failure patients who have left ventricular dyssynchrony and may benefit even more from LBTP. The visualization technique used in this study for LBBP lead deployment shortens procedural and fluoroscopic durations (6). Moreover, it facilitates achieving LBTP and reduces the need for repositioning to achieve LBBP. Finally, while LBTP achieves more physiologic activation compared with LBFP, CSP is superior to right ventricular pacing, with regard to paced QRS duration

and ventricular synchrony, regardless of whether it is HBP, LBTP or LBFP.

LIMITATIONS

The present study should be interpreted in light of certain methodological limitations. First, this was a single center study with a relatively small sample size. Second, only patients with a normal conduction system were evaluated. In other patient populations, the ventricular activation pattern may be different, and hence the results in this study may not be generalized to patients with conduction block. Third, the only acute measures of activation and electrical synchrony were assessed, and the absolute differences were relatively small. Whether these small differences are clinically significant will have to be shown in randomized clinical trials.

CONCLUSIONS

When performing LBBP, pacing the proximal left bundle main trunk produced optimal ventricular synchrony than pacing the distal LBB fascicles. With the guidance of a visualization technique, LBTP is facilitated to help maintained ventricular synchrony.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Fuwai Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WH, SZ, MGo, XZ, and XL contributed to the study conception and design. XL, MGu, H-XN, and XC performed pacemaker implantation. XL, CC, JZ, and MC performed data collection and analysis. XL and MGu wrote the first draft of the manuscript. All authors commented on previous versions of the manuscript and read and approved the final manuscript.

FUNDING

This work was supported by National Natural Science Foundation of China (Grant number: 82070349), Peking Union Medical College Youth Fund and Fundamental Research Funds for the Central Universities (Grant number: 3332019047, and 2017320006) and Innovation Funds for Graduate Students of Peking Union Medical College (Grant number: 2019-1002-33).

ACKNOWLEDGMENTS

We thank Hongyang Lu (Ph.D., Scientist in Medtronic Shanghai Ltd.) for providing help in vectorcardiography analysis.

REFERENCES

1. Zhang S, Zhou X, Gold MR. Left bundle branch pacing: JACC review topic of the week. *J Am Coll Cardiol.* (2019) 74:3039–49. doi: 10.1016/j.jacc.2019.10.039
2. Elizari MV. The normal variants in the left bundle branch system. *J Electrocardiol.* (2017) 50:389–99. doi: 10.1016/j.jelectrocard.2017.03.004
3. Salden FCWM, Luermans JGLM, Westra SW, Weijs B, Engels EB, Heckman LIB, et al. Short-term hemodynamic and electrophysiological effects of cardiac resynchronization by left ventricular septal pacing. *J Am Coll Cardiol.* (2020) 75:347–59. doi: 10.1016/j.jacc.2019.11.040
4. Okafor O, Zegard A, van Dam P, Stegemann B, Qiu T, Marshall H, et al. Changes in QRS area and QRS duration after cardiac resynchronization therapy predict cardiac mortality, heart failure hospitalizations, and ventricular arrhythmias. *J Am Heart Assoc.* (2019) 8:e013539. doi: 10.1161/JAHA.119.013539
5. van Deursen CJM, Vernooy K, Dudink E, Bergfeldt L, Crijns HJGM, Prinzen FW, et al. Vectorcardiographic QRS area as a novel predictor of response to cardiac resynchronization therapy. *J Electrocardiol.* (2015) 48:45–52. doi: 10.1016/j.jelectrocard.2014.10.003
6. Liu X, Niu H-X, Gu M, Chen X, Hu Y, Cai M, et al. Contrast-enhanced image-guided lead deployment for left bundle branch pacing. *Hear Rhythm.* (2021) 18:1318–25. doi: 10.1016/j.hrthm.2021.04.015
7. Surawicz B, Childers R, Deal BJ, Gettes LS, Bailey JJ, Gorgels A, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee. *J Am Coll Cardiol.* (2009) 53:976–81. doi: 10.1161/CIRCULATIONAHA.108.191095
8. Elizari M V, Acunzo RS, Ferreiro M. Hemiblocks revisited. *Circulation.* (2007) 115:1154–63. doi: 10.1161/CIRCULATIONAHA.106.637389
9. Lin J, Hu Q, Chen K, Dai Y, Chen R, Sun Q, et al. Relationship of paced left bundle branch pacing morphology with anatomic location and physiological outcomes. *Hear Rhythm.* (2021) 18:946–53. doi: 10.1016/j.hrthm.2021.03.034
10. Zhang J, Tang C, Zhang Y, Su X. Catheter ablation of premature ventricular complexes arising from the left fascicular system. *Hear Rhythm.* (2019) 16:527–35. doi: 10.1016/j.hrthm.2018.10.009
11. Kors JA, van Herpen G, Sittig AC, van Bemmel JH. Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. *Eur Heart J.* (1990) 11:1083–92. doi: 10.1093/oxfordjournals.eurheartj.a059647
12. Heckman LIB, Luermans JGLM, Curila K, Van Stipdonk AMW, Westra S, Smisek R, et al. Comparing ventricular synchrony in left bundle branch and left ventricular septal pacing in pacemaker patients. *J Clin Med.* (2021) 10:822. doi: 10.3390/jcm10040822
13. Vijayaraman P, Chung MK, Dandamudi G, Upadhyay GA, Krishnan K, Crossley G, et al. His bundle pacing. *J Am Coll Cardiol.* (2018) 72:927–47. doi: 10.1016/j.jacc.2018.06.017
14. Abdelrahman M, Subzposh FA, Beer D, Durr B, Naperkowski A, Sun H, et al. Clinical outcomes of his bundle pacing compared to right ventricular pacing. *J Am Coll Cardiol.* (2018) 71:2319–30. doi: 10.1016/j.jacc.2018.02.048
15. Engels EB, Mafi-Rad M, van Stipdonk AMW, Vernooy K, Prinzen FW. Why QRS duration should be replaced by better measures of electrical activation to improve patient selection for cardiac resynchronization therapy. *J Cardiovasc Transl Res.* (2016) 9:257–65. doi: 10.1007/s12265-016-9693-1
16. Curila K, Jurak P, Jastrzebski M, Prinzen F, Waldauf P, Halamek J, et al. Left bundle branch pacing compared to left ventricular septal myocardial pacing increases interventricular dyssynchrony but accelerates

left ventricular lateral wall depolarization. *Hear Rhythm.* (2021) 18:1281–9. doi: 10.1093/europace/euab116.396

Conflict of Interest: XZ is an employee of Medtronic. MGo receives consulting fees from Medtronic and Boston Scientific.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Cardiovascular Medicine

SYSTEMATIC REVIEW
published: 11 February 2022
doi: 10.3389/fcvm.2022.707148

Clinical Outcomes Associated With His-Purkinje System Pacing vs. Biventricular Pacing, in Cardiac Resynchronization Therapy: A Meta-Analysis

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Aims: His-Purkinje system pacing has recently emerged as an alternative to biventricular pacing (BIVP) in cardiac resynchronization therapy (CRT). The aim of this study was to conduct a meta-analysis comparing the clinical outcomes associated with His-Purkinje system pacing (HPSP) vs. BIVP in patients with heart failure. There is also a comparison of clinical outcomes of His-bundle pacing (HBP) and left bundle branch pacing (LBBP) in the His-Purkinje system.

Methods: We searched the Cochrane Library, Embase, and PubMed, for studies published between January 2010 and October 2021 that compared the clinical outcomes associated with HPSP vs. BIVP and HBP vs. LBBP in HPSP in patients who underwent CRT. The pacing threshold, R-wave amplitudes, QRS duration, New York Heart Association functional (NYHA), left ventricular ejection fraction (LVEF), and LV end-diastolic diameter (LVEDD) of heart failure, at follow-up, were extracted and summarized for meta-analysis.

Results: A total of 18 studies and 1517 patients were included in our analysis. After a follow-up period of 9.3 ± 5.4 months, the HPSP was found to be associated with shorter QRS duration in the CRT population compared to that in the BIVP (SMD, −1.17; 95% CI, −1.56 to −0.78; $P < 0.00001$; $I^2 = 74\%$). No statistical difference was verified between HBP and LBBP on QRS duration (SMD, 0.04; 95% CI, −0.32 to 0.40; $P = 0.82$; $I^2 = 84\%$). In the comparison of HPSP and BIVP, the LBBP subgroup showed improved LVEF (SMD, 0.67; 95% CI, 0.42–0.91; $P < 0.00001$; $I^2 = 0\%$), shorter LVEDD (SMD, 0.59; 95% CI, 0.93–0.26; $P = 0.0005$; $I^2 = 0\%$), and higher New York Heart Association functional class (SMD, −0.65; 95% CI, −0.86 to −0.43; $P < 0.00001$; $I^2 = 45\%$). In terms of pacing threshold and R-wave amplitude clinical outcomes, LBBP has a lower pacing threshold (SMD, 1.25; 95% CI, 1.12–1.39; $P < 0.00001$; $I^2 = 47\%$) and higher R-wave amplitude (MD, −7.88; 95% CI, −8.46 to −7.31; $P < 0.00001$; $I^2 = 8\%$) performance compared to HBP.

OPEN ACCESS

Edited by:
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Reviewed by:
Jiangang Zou, Nanjing Medical University, China
Yongquan Wu, Capital Medical University, China

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Specialty section:
This article was submitted to Cardiac Rhythmology, a section of the journal Frontiers in Cardiovascular Medicine

Received: *09 May 2021*
Accepted: *13 January 2022*
Published: *11 February 2022*

Citation:
Gui Y, Ye L, Wu L, Mai H, Yan Q and Wang L (2022) Clinical Outcomes Associated With His-Purkinje System Pacing vs. Biventricular Pacing, in Cardiac Resynchronization Therapy: A Meta-Analysis. Front. Cardiovasc. Med. 9:707148. doi: 10.3389/fcvm.2022.707148

Conclusion: Our meta-analysis showed that the HPSP produced higher LVEF, shorter QRS duration, and higher NYHA functional class in the CRT population than the BIVP as observed on follow-up. LBBP has a lower pacing threshold and higher R-wave amplitude. HPSP may be a new and promising alternative to BIVP in the future.

Keywords: cardiac resynchronization therapy, His-Purkinje system pacing, biventricular pacing, meta-analysis, biventricular pacing, meta-analysis (as topic)

HIGHLIGHTS

- QRS duration was shorter in His-Purkinje system pacing than in biventricular pacing.
- The left bundle branch pacing group in His-Purkinje system pacing is associated with improved LVEF, increased LVEDD, and higher NYHA functional class.
- In patients with heart failure who underwent cardiac resynchronization therapy, the His-Purkinje system pacing showed better results than biventricular pacing.
- LBBP has a lower pacing threshold and higher R-wave amplitude.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is used to treat patients with heart failure (HF), and ventricular systolic dyssynchrony. By electrically activating the heart in a coordinated manner, CRT can successfully restore mechanical synchrony. Traditionally, this therapy has been implemented using biventricular pacing. Studies have shown that biventricular pacing (BIVP) can improve symptoms, reduce hospitalization times, and prolong the survival of patients (1–4). However, multiple clinical trials have demonstrated that 30-40% of patients showed no changes after BIVP-based CRT (5–10).

In 2015, a crossover study by Lustgarten et al. showed that His-bundle pacing (HBP) can achieve clinical outcomes comparable to BIVP (11). Similarly, several other studies have suggested that HBP may be a suitable alternative for CRT non-responders and patients with failed left ventricle (LV) lead placement (12–14); some of these studies have even recommended HBP as frontline therapy for heart failure and left ventricle dyssynchrony (12–14). In addition, recent guidelines by the American College of Cardiology/American Heart Association have assigned HBP a grade II in terms of recommendation for replacing right ventricular pacing in patients who need chronic ventricular pacing with reduced LV ejection fraction (LVEF; 36–50%) (11, 15). More recently, however, studies compared HPSP with BIVP pacing and evaluated the potential advantages in CRT. The HPSP is characterized by a generation of strategies that can mimic pacing or fully restore normal atrioventricular (AV) activation, ensuring optimal clinical outcomes; it involves left bundle branch pacing (LBBP) and HBP. LBBP can correct left bundle branch blocks (LBBB) and, thus, lead to improvement of cardiac electrical dyssynchrony compared with conventional right ventricular apical pacing (16). LBBP produces a lower pacing capture threshold and higher R-wave amplitude than HBP and stimulates the conduction system of the heart as well as the deep septal myocardium (17, 18). The role of His-Purkinje conduction system is usually to produce true cardiac resynchronization. In contrast, some studies have concluded that ventricular mechanical synchronization parameters are significantly better in patients with HBP than in patients with right ventricular septal pacing (RVSP) (19, 20).

HBP is the most physiological pacing strategy for restoring normal ventricular excitation patterns (21). In the case of His bundle pacing (HBP), HBP corrects complete left bundle branch block (CLBBB) by activating the heart's intrinsic conduction system and thus providing natural ventricular excitation propagation (22, 23). There are currently no publications that comprehensively analyze and summarize the data generated from clinical trials that have evaluated the influence of HPSP therapy. Currently for the His-Purkinje conduction system, both the comparison with conventional BIVP pacing and the advantages and disadvantages of HBP vs. LBBP pacing in the His-Purkinje conduction system have a great role for CRT. Therefore, this study aimed to compare HPSP and BIVP in clinical outcomes in patients with HF and to conduct a meta-analysis.

METHODS

This study protocol has been published previously in PROSPERO (CRD42021235736).

Search Strategy

The meta-analysis was conducted according to the meta-analysis statement and the preferred reporting items for systematic reviews (24). We selected relevant studies published between January 2010 and October 2021 by searching PubMed, EMBASE, and Cochrane Library. Our search did not have any language restrictions. The search terms were "His bundle pacing" OR "Left branch bundle pacing" OR "biventricular pacing" AND "Cardiac Resynchronization Therapy." In addition, we also searched the list of references in the studies retrieved by our search criteria.

Study Eligibility Criteria

We included randomized clinical trials (RCTs) and observational studies which examined patients with HF requiring CRT. Specifically, studies were included if they (i) were RCTs, (ii) were observational studies, or (iii) reported empirical data regarding clinical outcomes, including Pacing threshold, R-wave amplitudes, QRS duration, LVEF, LV end-diastolic diameter (LVEDD), and New York Heart Association (NYHA) class of HF. Studies were excluded if they (i) were missing text, (ii) reported

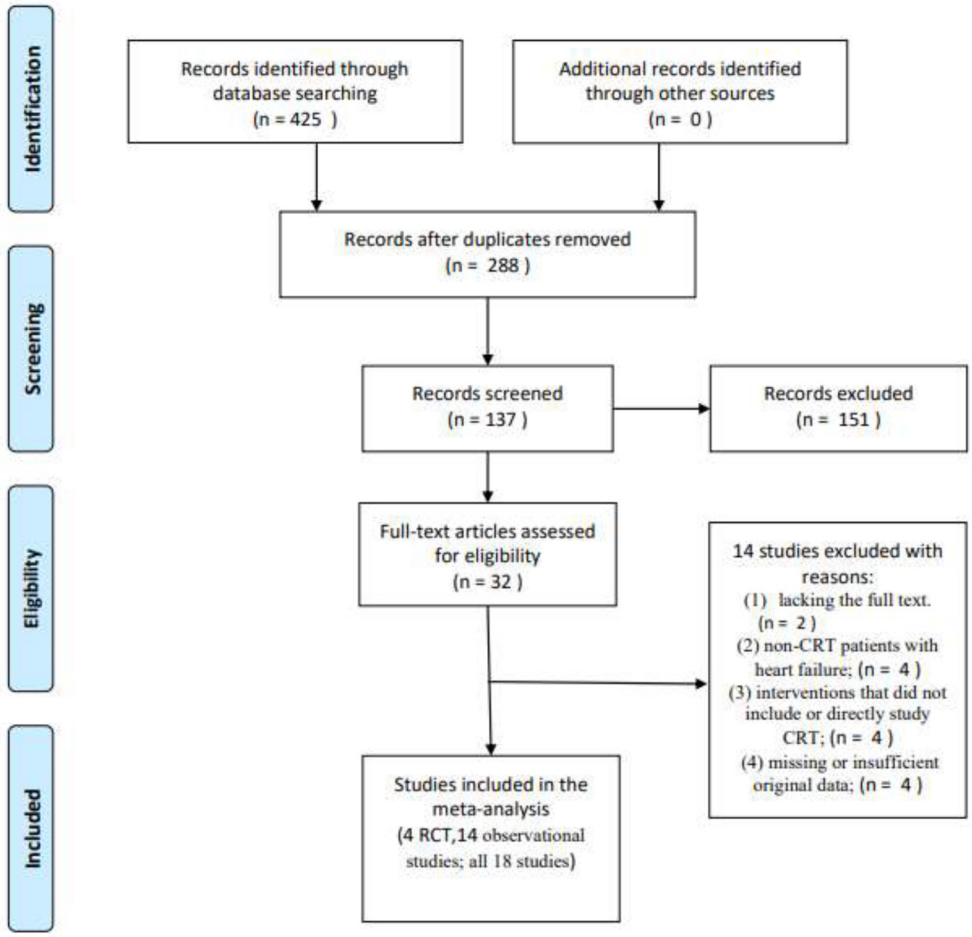

FIGURE 1 | A flow diagram showing how articles were selected for analysis, Moher et al. (28).

results from a previously included study, (iii) did not include or directly study CRT, or (iv) had missing data or insufficient original data.

Data Extraction

Two reviewers independently extracted data from the included RCTs and observational studies; disagreements were resolved by consensus through discussion. We recorded the following information from the included RCTs and observational studies: duration of follow-up, number of participants, and year of publication, and study design. We also extracted information on pacing threshold, R-wave amplitudes QRS duration, LVEF, LVEDD, and NYHA HF class.

Quality Assessment

Two reviewers independently assessed the RCTs included in this study using the Jadad scoring system (25), which assesses the methodological quality of RCTs. Investigations that received Jadad scores below 4 (out of a possible 5) were classified as low-quality, while those that scored $\geq$4 were deemed high-quality. Among the included observational studies, for the retrospective studies and cohort studies, assessment of using the Newcastle Ottawa scale (NOS) (26) to performed the quality of nonrandomized studies. Investigations that received NOS scores below 6 (out of a possible 9) were classified as low-quality, while those that scored $\geq$6 were deemed high-quality. When the format of the required data for inclusion was not suitable for the meta-analysis, the primary authors and publishing journals were contacted by email to access unpublished data.

Statistical Analyses

For all statistical analyses, RevMan 5.3 software (27) was used. A comprehensive analysis of individual studies was done to compare the different effects of His-Purkinje system pacing and BIVP in patients with HF. We assessed statistical heterogeneity with the Q statistic from the chi-square test and $P < 0.05$ represented a significant result. We dequantified the proportion of variation using the I^2 statistics between studies due to heterogeneity. It was considered that there was little heterogeneity between studies if $P \geq 0.1$, or $I^2 \leq 50\%$; $P < 0.1$, or $I^2 > 50\%$ indicated moderate heterogeneity, and $I^2 > 75\%$

indicated considerable heterogeneity, $I^2 \leq 50\%$ used fixed-effects model and $I^2 > 50\%$ used-random effects model. A subgroup analysis was attempted to find the source of heterogeneity. To analyze the literature for the presence or absence of publication bias, we used funnel plots. The mean and standard deviation were reported for continuous variables. Review Manager V5.3 (27) was used for all data processing analyses.

RESULTS

Study and Patient Characteristics

Initially, a total of 425 articles were retrieved. Out of which, 32 articles were retained for full article evaluation by reviewing the study titles with the abstracts. Duplicate reviews and duplicate case reports with non-relevant studies were excluded. These 32 studies underwent a thorough screening process as shown in **Figure 1**. Following the screening, 18 studies were included in our analysis; four of these were RCT studies, while 14 were observational studies. Ten of them are the comparison of HPSP with BIVP and eight are the comparison of HBP with LBBP in HPSP. Further details regarding the studies analyzed are shown in **Table 1**. The 18 included studies (11, 29–45), which were RCTs and observational studies, were scored using the Jadad scoring system and the NOS quality assessment system, as shown in **Figures 2A,B**.

QRS Duration

The heterogeneity between individual studies was tested by analyzing differences in the QRS duration in 482 patients from 10 studies ($I^2 = 74\%$). The random-effect model was used. As shown in **Figure 3A**, patients treated with the His-Purkinje system pacing had shorter QRS duration than those treated with BIVP (SMD, −1.17; 95% CI, −1.56 to −0.78; $P < 0.00001$; $I^2 = 74\%$; **Figure 3A**). Although the heterogeneity test between the 10 studies indicated that there was moderate heterogeneity, sensitivity analysis showed that the results did not change significantly among all the studies included.

The eight included papers on HBP and LBBP directly compared clinical outcomes. There was no significant difference between LBP and LBBP in the QRS duration index (SMD, 0.04; 95% CI, −0.32 to 0.40; $P = 0.82$; $I^2 = 84\%$; **Figure 3B**). HPSP produced a reduction in QRS duration compared to the BIVP group, but no differences were found when comparing within groups.

LV Function Assessment

LVEF was analyzed by fixed models in 436 patients from nine studies. The LVEF fraction was higher in the HPSP group, compared with that in the BIVP group (SMD, 0.47; 95% CI, 0.29–0.65; $P < 0.00001$; $I^2 = 42\%$; **Figure 4A**).There was little heterogeneity among the study results ($P < 0.00001$; $I^2 = 42\%$). Three studies were included in the evaluation of LVEDD differences. We used the fixed-effects model because of the heterogeneity between the studies ($I^2 = 0\%$). When compared with BIVP, the His-Purkinje system pacing indicated better performance (SMD, 0.59; 95% CI, 0.93–0.26; $P = 0.0005$; $I^2 = 0\%$; **Figure 4B**).

NYHA Functional Class

Of the eight included studies, seven of them reported a functionally relevant improvement analysis. We used the random-effect model because of the heterogeneity between the studies ($I^2 = 45\%$). Compared with BIVP, His-Purkinje system pacing indicated better performance (SMD, −0.65; 95% CI, −0.86 to −0.43; $P < 0.00001$; $I^2 = 45\%$, **Figure 5**). No evidence of publication bias was found, after passing the inspection of the corresponding funnel plots.

Pacing Threshold

In the eight papers we adopted on the direct comparison between LBBP and HBP, the pacing threshold indexes all showed a great advantage of LBBP (SMD, 1.25; 95% CI, 1.12–1.39; $P < 0.00001$; $I^2 = 47\%$, **Figure 6**).

R-wave Amplitudes

Seven of the eight included papers reported R-wave amplitudes, with LBBP reflecting considerable R-wave amplitudes compared to HBP (MD, −7.88; 95% CI, −8.46 to −7.31; $P < 0.00001$; $I^2 = 8\%$, **Figure 7**).

DISCUSSION

This systematic review and meta-analysis identified 18 trials with a total of 1,517 participants and compared cardiac electrophysiology and cardiac function in HPSP and BIVP and in HBP and LBBP. Ultimately, we concluded that HPSP resulted in a favorable improvement in QRS duration in patients with HF, while LBBP improved LV function and improved NYHA functional class in CRT candidates. When HBP and LBBP were directly compared in terms of the His-Purkinje system, LBBP demonstrated a lower pacing threshold and higher R-wave amplitude than HBP.

Several randomized controlled trials and observational studies have shown that long-term differences in LVEF have the potential to lead to interventricular dyssynchrony. One of the parameters of interventricular dyssynchrony is QRS duration (29–33, 35, 46). In the present study, the HPSP group performed better than the BIVP group in terms of QRS duration. It can also be argued that LBBP or HBP may produce better electromechanical synchronization and thus induce more synchronized LV contractions. In our study, HPSP improved the QRS duration by 22.23 ms relative to BIVP. Moreover, no difference in QRSd was found between LBBP and HBP ($P = 0.82$).

Sheng et al. (41) also confirmed that HBP and LBBP produce similar QRSd. During atrial fibrillation, LBBP is equally as viable as HBP. A unique finding of Sheng's (41) study was the difference in interventricular synchrony between HBP and LBBP. In contrast, the unipolar configuration of LBBP produced a slightly later contraction of the right ventricular myocardium compared to that produced by HBP. In bradycardic patients requiring CRT, HBP and LBBP led to similar QRSd and implantation success rates and shorter procedure and fluoroscopy times. However, the study (41) also noted a significantly lower pacing threshold for LBBP and a higher R-wave amplitude at implantation and

TABLE 1 | Basic characteristics of included studies analyzed during this study.

References	Type of study	Age (year)	QRSd	LVEF	Male (%)	Region	Period	Number of patients (physiologic/ BiVP)	Indication of pacing	Pacing sites	Follow-up months	Evaluated parameters
Li et al. (29)	Observational	56.8 ± 10.1	177.9 ± 18.8	29.3 ± 5.9	59.5	China	2020	27/54	LBBB (LVEF) ≤ 35%	LBBP BiVP	6 month	QRSd LVEF NYHA LVEDD
Wang et al. (30)	Observational case-control	63.4 ± 9.6	176.9 ± 19.6	26.5 ± 4.9	0.8	China	2020	10/30	HF LVEF ≤ 35% NYHA2-4	LBBP BiVP	6 month	QRSd LVEF NYHA LVEDD LVESV LVESD
Guo et al. (31)	Prospective observational	65.6 ± 8.6	165.7 ± 14.3	29.9 ± 4.5	0.428	China	2020	21/21	HF LBBB	LBBP BiVP	14.3 ± 7.2 month	QRSd LVEF NYHA LVEDD
Wu et al. (32)	Non-randomized observational	67.9 ± 11.1	163 ± 11.5	30.7 ± 6.6	0.5	China	2020	32/54	LVEF ≤ 40% LBBB	LBBP BiVP	12 month	QRSd LVEF NYHA LVESV LVESD
Lustgarten et al. (11)	Randomized controlled trial	71.33	169 ± 16	26 ± 55.6	0.66	Burlington	2015	29 (12/12)	QRSd > 130 ms	HBP BiVP	6 month	QRSd LVEF NYHA LVESV LVESD 6-min walk
Upadhyay et al. (33)	Randomized controlled trial	64 6 13	168.6 ± 18	28	0.62	Chicago	2019	21/20	HF	HBP BiVP	12 month	QRSd LVEF
Arnold et al. (34)	Observational	67 ± 10	158 ± 21	26 ± 7	0.53	British	2018	23/23	QRSd > 130 ms LVEF ≤ 35% NYHA2-4	HBP BiVP	12 month	QRSd
Vijayaraman et al. (35)	Observational	72 ± 15	183 ± 27	24 ± 7	0.85	Florida	2019	10/16	LVEF ≤ 40% LBBB	HBP BiVP	14 ± 10 month	QRSd LVEF NYHA LVEDD
Upadhyay et al. (36)	Randomized controlled trial	64 ± 13	168 ± 18	28	0.62	Chicago	2019	21/20	HF	HBP BiVP	12 month	QRSd LVEF
Vinther et al. (37)	Randomized controlled trial	65.8 ± 9.3	166 ± 15	30 ± 7	0.64	Denmark	2021	25/25	LVEF < 35, HF, LBBB	HBP BiVP	6 month	LVEF PT LVESV NYHA
Hua et al. (38)	Observational study	63.8 ± 13.4	108.6 ± 23.8	58 ± 7.7	0.51	China	2020	109/115	Symptomatic bradycardia	HBP LBBP	3 month	QRSd PT R-wave
Hou et al. (39)	Single-centre prospective	68.6 ± 11.3	105.8 ± 26.4	63.6 ± 4.2	0.647	China	2019	29/56	SND AVB (atrioventricular block)	HBP LBBP	4.5 ± 2.4 month	QRSd LVEF R-wave PT
Hu et al. (40)	Prospective, observational, nonrandomized	61.4 ± 18.1	119 ± 16.2	57.5 ± 9.5	0.64	China	2020	25/25	AVB	HBP LBBP	3 month	QRSd LVEF LVEDD R-wave PT
Sheng et al. (41)	Single-center prospective patient control	72.9 ± 9.0	96.5 ± 16.2	62 ± 12	0.654	China	2021	10/10	AF with slow ventricular rate	HBP LBBP	3 month	QRSd PT R-wave
Vijayaraman et al. (42)	Prospective, single-center observational study	75.7 ± 22	121 ± 30	53.5 ± 22.7	0.63	Florida	2021	143/182	AVB	HBP LBBP	24 month	QRSd PT R-wave
Vijayaraman et al. (43)	Observational retrospective	79 ± 8	138.7 ± 28.8	58 ± 12	0.57	Florida	2020	29/26	AVCD after TAVR	HBP LBBP	12 ± 13.7	QRSd PT R-wave LVEF
Qian et al. (44)	Single-centre observational	68.3 ± 12.1	142.3 ± 30.7	63 ± 53.8	0.562	China	2020	64/185	HF	HBP LBBP	12 month	QRSd PT R-wave LVEF
Ye et al. (45)	Non-controlled non-randomized prospective	78 ± 5	91 ± 10	35.1 ± 11.7	0.75	China	2020	14/13	AF	HBP LBBP	6 month	QRSd PT R-wave LVEF

AF, atrial fibrillation; AVB, atrioventricular block; AVCD, AV conduction disease; HF, heart failure; QRSd, QRS duration;#LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; PT, pacing thresholds; R-wave, R-wave amplitudes; NYHA, New York Heart Association; HBP, His-bundle pacing; LBBP, left bundle branch pacing, BIVP, biventricular pacing.

A

B

study	selection				Comparability	Exposure		
	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of Cases and Controls on the Basis of the Design or Analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate
Xiaofei Li	★	★	★	.	★★	★	★	★
Yao Wang	★	★	★	★	★★	★	★	★
Jincun Guo	★	★	★	★	★★	★	★	★
Shengjie Wu	★	★	★	★	★★	.	★	★
Ahran D Arnold	★	★	★	★	★★	★	★	★
Pugazhendhi Vijayaraman	★	★	★	★	★★	★	★	★
Wei Hua	★	★	★	.	.	★	★	★
Xiaofeng Hou	★	★	★	★	★★	★	.	
Yiran Hu	★	★	★	.	★★	★	★	★
XIA SHENG	★	★	★	.	★	.	★	★
Pugazhendhi Vijayaraman	★	★	★	★	★★	★	.	
Pugazhendhi Vijayaraman	★	★	★	★	★★	★	★	★
Zhiyong Qian	★	★	★	★	★★	★	★	★
Yang Ye	★	★	★	.	★★	★	★	★

FIGURE 2 | (A) Four of the included RCT studies were using scoring system at risk of bias. **(B)** Fourteen of the included studies using the Newcastle Ottawa scale (NOS).

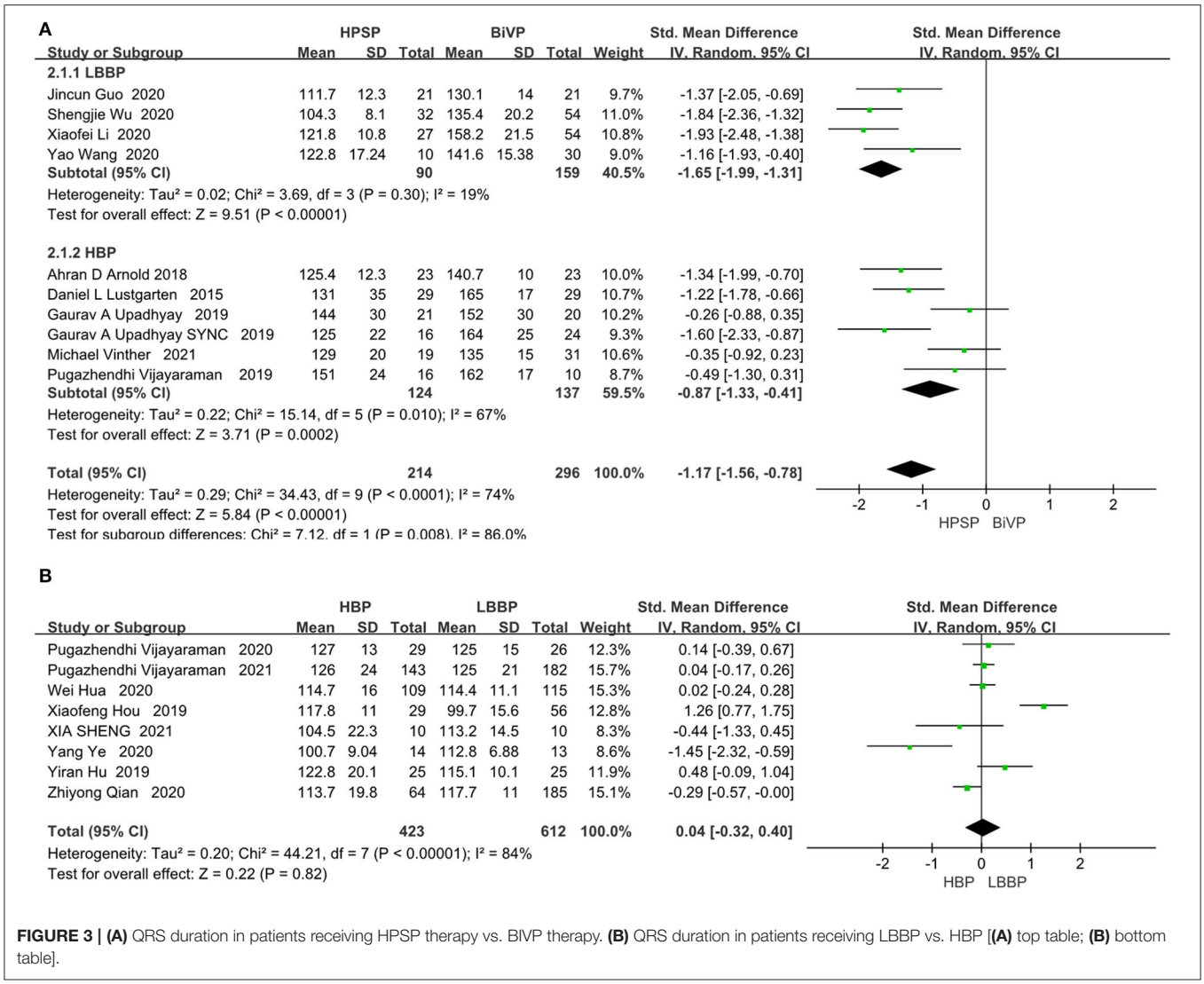

FIGURE 3 | (A) QRS duration in patients receiving HPSP therapy vs. BIVP therapy. **(B)** QRS duration in patients receiving LBBP vs. HBP [**(A)** top table; **(B)** bottom table].

at the 3-month follow-up. Moreover, LBBP has better clinical feasibility compared to the HBP. This is consistent with our findings comparing HBP with LBBP, in which LBBP improved pacing thresholds by an average of 0.62 ms over HBP and by 7.88 mv in R-wave amplitude. Chen et al. (47) demonstrated the clinical feasibility of LBBP by using a transventricular septal approach. Massing et al. (48) suggested that LBBP could directly branch out from the branch point of the His bundle in the cardiac structure under the endocardium on the left side of the septum, thus forming a reticular structure, so that the left bundle branch can be paced faster than by HBP through the septal approach. This may explain the better pacing threshold and R-wave amplitude of LBBP compared with HBP. Zhang et al. (49) attributed the narrow QRS pattern during LBBP to the activation of the right bundle branch of the ventricle by electrophysiological retrograde conduction, which forms a connection with intrinsic conduction fusion. Huang et al. (50) had a higher success rate and a stable lower pacing threshold with LBBP than HBP and a better perception of ventricular excitation (R-wave amplitude).

LBBP is now the preferred conduction system pacing modality for patients with pacing indications (20, 21). Li et al. (21) reported on LBBP in 33 patients with AVB and found that it has a success rate of more than 90%, produces low and stable thresholds, maintains LV synchronization, and has few complications. The current potential hypothesis is that LBBP further enriches physiological pacing and may even be more applicable to patients with AVB. Furthermore, Vinther et al. (37) found that His bundle improved ventricular function and quality of life, but this was at the cost of a higher pacing threshold. Hou et al. (39) found that left bundle branch pacing produced higher R-wave amplitude than HBP and lower capture threshold stability parameters than HBP. Qian et al. (44) concluded that His-Purkinje system pacing produces good electrical synchronization and narrow QRS time frames and that it has beneficial effects in maintaining cardiac function. In

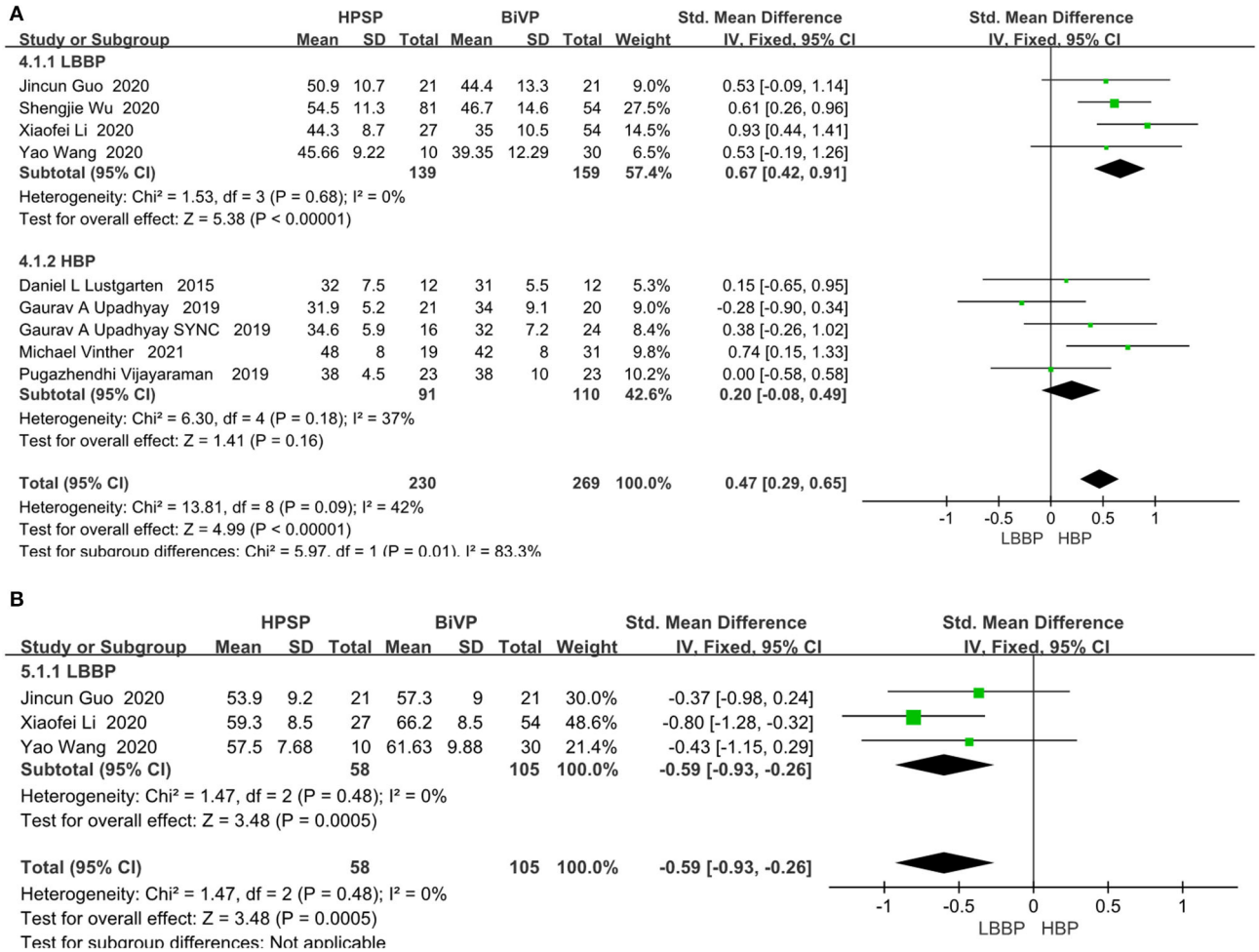

FIGURE 4 | (A) LVEF. **(B)** LVEDD. Left ventricular function pacing of the His-Purkinje system is required in patients with HF therapy vs. biventricular pacing therapy. Both LVEF and LVEDD were measured by echocardiography.

contrast, left bundle branch pacing showed superior lead stability in terms of pacing parameters. Ye et al. (45) found that both HBP and LBBP can be successfully implemented in the same patient with atrial fibrillation and that LBBP produces better and more stable parameters compared to HBP. Patients with AF with HF and arrhythmias benefit more from HPSP in terms of physical performance and echocardiographic parameters.

Overall, we concluded that HPSP produced better electromechanical synchronization than BIVP; further, when comparing HPSP within groups, LBBP had higher success rates, lower pacing thresholds, and higher R-wave amplitudes compared to HBP.

HPSP, a physiological pacing modality that directly stimulates the conduction system of the heart and maintains synchronization of ventricular electrical activation has produced better results compared to BIVP in clinical practice (41, 45). Lustgarten et al. (11) summarized the clinical outcome data from a 2015 study of 12 patients with a mean baseline LVEF of 26%; at the 6-month follow-up, HBP was shown to improve by 32% and BIVP by 31% ($P = 0.043$ and $P = 0.02$, respectively); the baseline NYHA grades for HBP and BIVP improved from 2.9 to 1.9 ($P < 0.01$ and $P < 0.01$, respectively). The multicenter 2019 RCT His-SYNC study by Upadhyay et al. (33) included 41 patients from 7 centers who met the criteria indications for CRT; 20 and 21 of these patients were randomized to the BIVP CRT and His CRT groups, respectively. Patients in both groups showed a significant improvement in LVEF after 6.2 months of follow-up, when compared with the baseline values. The median LVEF increased from 28.0 to 34.6% ($P < 0.001$) in patients treated with HBP CRT, whereas it increased from 27.7 to 32.0% ($P < 0.001$) in those treated with BIVP CRT. To determine the difference in LV function by pacing modality, we also compared LVEF, LVEDD, and NYHA. In our meta-analysis, LVEF was significantly improved in both groups compared with the baseline values at the 6-month follow-up. HPSP showed a 3.91% improvement in LVEF, a 5.36 mm reduction in LVEDD, and a 0.44 grade reduction in NYHA compared with BIVP. Clinical outcomes were similar for BIVP

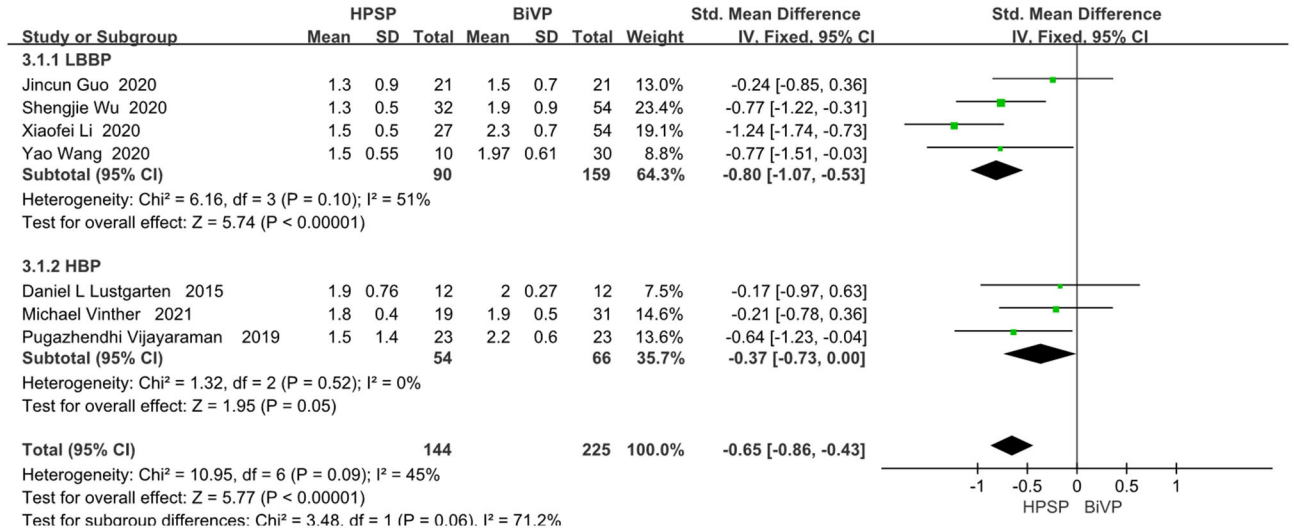

FIGURE 5 | New York Heart Association functional class in patients receiving His-Purkinje system pacing therapy vs. biventricular pacing therapy.

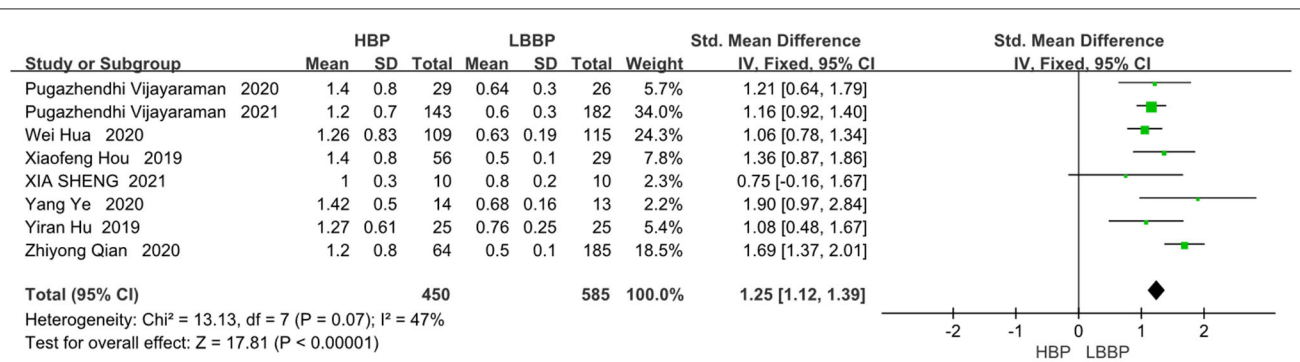

FIGURE 6 | Pacing thresholds in patients receiving comparison between HBP and LBBP in His-Purkinje system.

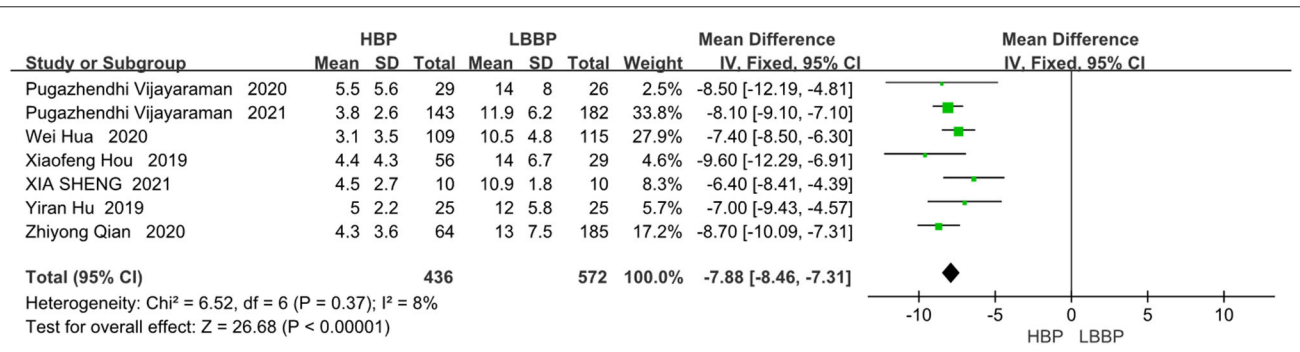

FIGURE 7 | R-wave amplitudes in patients receiving comparison between HBP and LBBP in His-Purkinje system.

and HBP. In patients with HF, cardiac resynchronization can be achieved by pacing the His-Purkinje system to correct LBBB. Theoretically, HPSP may be more physiologically consistent than BIVP because the latter still relies on stimuli that do not propagate through the normal conduction system but through the myocardium. The relatively small number of 18 studies analyzed may have influenced the results. Larger RCTs are needed to validate the relationship between His-Purkinje system pacing and BIVP.

In summary, we conclude that the His-Purkinje system produces higher LVEF, shorter QRS duration, and higher NYHA functional class in the CRT group compared to BIVP in pacing therapy overall. When comparing HPSP systems within groups, LBBP had a higher success rate, a lower pacing threshold, and higher R-wave amplitude compared to HBP. HPSP may be a new and promising alternative to BIVP in the future.

Study Limitations

This meta-analysis has several limitations. First, is a bias due to the small number of included relevant RCTs and the fact that most studies (29–32, 34, 35, 38–45) were *post-hoc* analyses. This bias may have influenced the conclusions of the present study. Second, the length of follow-up in the included literature takes longer to justify the results. Third, this study did not include data on mortality or cardiovascular hospitalization. Fourth, the complications after different pacing procedures are not discussed.

CONCLUSION

In conclusion, the HPSP can produce shorter QRS duration, higher LVEF, and higher NYHA functional class in the CRT population compared with BIVP as observed by follow-up. HPSP may be a new and promising alternative to BIVP in the future. LBBP has a lower pacing threshold and higher R-wave amplitude. Considering the clinical significance of pacing therapies, RCTs are required to further evaluate the efficacy of HPSP compared with BIVP in achieving CRT.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

This study was supported by the National Natural Science Foundation of China under Grant No. 81670447; the National Natural Science Foundation of Zhejiang Province under Grant No. LY15H020006; Zhejiang Province Key Subject of Medicine (Neurological Rehabilitation) and the Traditional Chinese Medicine Program of Zhejiang Provincial under Grant No. 2017ZZ001; the Zhejiang Provincial Health Commission Project under Grant No. 2017KY559; the National Natural Science Foundation of Zhejiang Province under Grant No. LY19H070003. LW is sponsored by Zhejiang Provincial Program for the Cultivation of High-Level Innovative Health Talents.

ACKNOWLEDGMENTS

The author wishes to thank all those who have helped.

REFERENCES

1. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. (2002) 346:1845–53. doi: 10.1056/NEJMoa013168
2. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. (2005) 352:1539–49. doi: 10.1056/NEJMoa050496
3. Daubert C, Gold MR, Abraham WT, Ghio S, Hassager C, Goode G, et al. Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction: insights from the European cohort of the REVERSE (resynchronization reverses remodeling in systolic left ventricular dysfunction) trial. *J Am Coll Cardiol*. (2009) 54:1837–46. doi: 10.1016/j.jacc.2009.08.011
4. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al. Cardiacresynchronization therapy for the prevention of heart-failure events. *N Engl J Med*. (2009) 361:1329–38. doi: 10.1056/NEJMoa0906431
5. Carluccio E, Biagioli P, Alunni G, Murrone A, Zingarini G, Coiro S, et al. Noncardiac factors for prediction of response to cardiac resynchronization therapy: the value of baseline, and of serial changes, in red cell distribution width. *Int J Cardiol*. (2017) 243:347–53. doi: 10.1016/j.ijcard.2017.05.123
6. Kydd AC, Khan FZ, Ring L, Pugh PJ, Virdee MS, Dutka DP. Development of a multiparametric score to predict left ventricular remodelling and prognosis after cardiac resynchronization therapy. *Eur J Heart Fail*. (2014) 16:1206–13. doi: 10.1002/ejhf.167
7. Martin CA, Gajendragadkar PR, Pugh PJ. Unusual cause of poor response to cardiac resynchronisation therapy. *Heart*. (2014) 100:514. doi: 10.1136/heartjnl-2013-305340
8. Thompson N, Derval N. Left ventricular endocardial stimulation in patients with a poor response to cardiac resynchronization therapy: what is next? *JACC Clin Electrophysiol*. (2016) 2:810–1. doi: 10.1016/j.jacep.2016.06.003
9. Wang J, Su Y, Bai J, Wang W, Qin S, Ge J. Elevated pulmonary artery pressure predicts poor outcome after cardiac resynchronization therapy. *J Interv Card Electrophysiol*. (2014) 40:171–8. doi: 10.1007/s10840-014-9890-2
10. Werys K, Petryka-Mazurkiewicz J, Blaszczyk L, Misko J, Spiewak M, Malek LA, et al. Cine dyscontractility index: a novel marker of mechanical dyssynchrony that predicts response to cardiac resynchronization therapy. *J Magn Reson Imaging*. (2016) 44:1483–92. doi: 10.1002/jmri.25295
11. Lustgarten DL, Crespo EM, Arkhipova-Jenkins I, Lobel R, Winget J, Koehler J, et al. His-bundle pacing versus biventricular pacing in cardiac resynchronization therapy patients: a crossover design comparison. *Heart Rhythm*. (2015) 12:1548–57. doi: 10.1016/j.hrthm.2015.03.048
12. Sharma PS, Dandamudi G, Herweg B, Wilson D, Singh R, Naperkowski A, et al. Permanent His-bundle pacing as an alternative to biventricular pacing for

cardiac resynchronization therapy: a multicenter experience. *Heart Rhythm.* (2018) 15:413–20. doi: 10.1016/j.hrthm.2017.10.014
13. Ajijola OA, Upadhyay GA, Macias C, Shivkumar K, Tung R. Permanent His-bundle pacing for cardiac resynchronization therapy: initial feasibility study in lieu of left ventricular lead. *Heart Rhythm.* (2017) 14:1353–61. doi: 10.1016/j.hrthm.2017.04.003
14. Shan P, Su L, Zhou X, Wu S, Xu L, Xiao F, et al. Beneficial effects of upgrading to His bundle pacing in chronically paced patients with left ventricular ejection fraction <50%. *Heart Rhythm.* (2018) 15:405–12. doi: 10.1016/j.hrthm.2017.10.031
15. Kusumoto FM, Schoenfeld MH, Barrett C, Edgerton JR, Ellenbogen KA, Gold MR, et al. ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: Executive summary—a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society. *J Am Coll Cardiol.* (2018) 74:932–87. doi: 10.1016/j.jacc.2018.10.043
16. Zhang J, Wang Z, Cheng L, Zu L, Liang Z, Hang F, et al. Immediate clinical outcomes of left bundle branch area pacing vs conventional right ventricular pacing. *Clin Cardiol.* (2019) 42:1–6. doi: 10.1002/clc.23215
17. Vigmond EJ, Stuyvers BD. Modeling our understanding of the His-Purkinje system. *Prog Biophys Mol Biol.* (2016) 120:179–88. doi: 10.1016/j.pbiomolbio.2015.12.013
18. Zhang J, Guo J, Hou X, Wang Y, Qian Z, Li K, et al. Comparison of the effects of selective and non-selective his bundle pacing on cardiac electrical and mechanical synchrony. *Europace.* (2018) 20:1010–7. doi: 10.1093/europace/eux120
19. Thosani AJ, Liu E, Shaw G, Belden W, Chenarides J. Rapid reversal of right ventricular pacing-induced cardiomyopathy by His bundle pacing. *Heart Rhythm Case Rep.* (2017) 3:189–91. doi: 10.1016/j.hrcr.2017.01.004
20. Vijayaraman P, Subzposh FA, Naperkowski A, Panikkath R, John K, Mascarenhas V, et al. Prospective evaluation of feasibility, electrophysiologic and echocardiographic characteristics of left bundle branch area pacing. *Heart Rhythm.* (2019) 16:1774–82. doi: 10.1016/j.hrthm.2019.05.011
21. Li X, Li H, Ma W, Ning X, Liang E, Pang K, et al. Permanent left bundle branch area pacing for atrioventricular block: feasibility, safety, and acute effect. *Heart Rhythm.* (2019) 16:1766–73. doi: 10.1016/j.hrthm.2019.04.043
22. Sharma PS, Vijayaraman P, Ellenbogen KA. Permanent his bundle pacing: shaping the future of physiological ventricular pacing. *Nat Rev Cardiol.* (2020) 17:22–36. doi: 10.1038/s41569-019-0224-z
23. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, et al. Benefits of permanent his bundle pacing combined with atrioventricular node ablation in atrial fibrillation patients with heart failure with both preserved and reduced left ventricular ejection fraction. *J Am Heart Assoc.* (2017) 6:e005309. doi: 10.1161/JAHA.116.005309
24. Liberati A, Altman DG, Tetzlaff J, Mulrow G, Gøtzsche PC, Ioannidis JPA et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* (2009) 6:e1000100. doi: 10.1371/journal.pmed.1000100
25. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials.* (1996) 17:1e12. doi: 10.1016/0197-2456(95)00134-4
26. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in metaanalyses. *Eur J Epidemiol.* (2010) 25:603–5. doi: 10.1007/s10654-010-9491-z
27. Review Manager (RevMan) [Computer program]. *Version 5.3*. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration (2014).
28. Moher D, Liberati A, Tetziaff J, Altman DG, The PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 6(7): e1000097. doi: 10.1371/journal.pmed1000097
29. Li X, Qiu C, Xie R, Ma W, Wang Z, Li H, et al. Left bundle branch area pacing delivery of cardiac resynchronization therapy and comparison with biventricular pacing. *ESC Heart Fail.* (2020) 7:1711–22. doi: 10.1002/ehf2.12731
30. Wang Y, Gu K, Qian Z, Hou X, Chen X, Qiu Y, et al. The efficacy of left bundle branch area pacing compared with biventricular pacing in patients with heart failure: a matched case-control study. *J Cardiovasc Electrophysiol.* (2020) 31:2068–77. doi: 10.1111/jce.14628
31. Guo J, Li L, Xiao G, Ye T, Huang X, Meng F, et al. Remarkable response to cardiac resynchronization therapy *via* left bundle branch pacing in patients with true left bundle branch block. *Clin Cardiol.* (2020) 43:1460–8. doi: 10.1002/clc.23462
32. Wu S, Su L, Vijayaraman P, Zheng R, Cai M, Xu L, et al. Left bundle branch pacing for cardiac resynchronization therapy: nonrandomized on-treatment comparison with his bundle pacing and biventricular pacing. *Can J Cardiol.* (2021) 37:319–28. doi: 10.1016/j.cjca.2020.04.037
33. Upadhyay GA, Vijayaraman P, Nayak HM, Verma N, Dandamudi G, Sharma PS, et al. On-treatment comparison between corrective His bundle pacing and biventricular pacing for cardiac resynchronization: a secondary analysis of the His-SYNC pilot trial. *Heart Rhythm.* (2019) 16:1797–807. doi: 10.1016/j.hrthm.2019.05.009
34. Arnold AD, Shun-Shin MJ, Keene D, Howard JP, Sohaib SMA, Wright IJ, et al. His resynchronization versus biventricular pacing in patients with heart failure and left bundle branch block. *J Am Coll Cardiol.* (2018) 72:3112–22. doi: 10.1016/j.jacc.2018.09.073
35. Vijayaraman P, Herweg B, Ellenbogen KA, Gajek J. His-optimized cardiac resynchronization therapy to maximize electrical resynchronization: a feasibility study. *Circ Arrhythm Electrophysiol.* (2019) 12:e006934. doi: 10.1161/CIRCEP.118.006934
36. Upadhyay GA, Vijayaraman P, Nayak HM, Verma N, Dandamudi G, Sharma PS, et al. His corrective pacing or biventricular pacing for cardiac resynchronization in heart failure. *J Am Coll Cardiol.* (2019) 74:157–9. doi: 10.1016/j.jacc.2019.04.026
37. Vinther M, Risum N, Svendsen JH, Møgelvang R, Philbert BT. A randomized trial of his pacing versus biventricular pacing in symptomatic HF patients with left bundle branch block (His-Alternative). *JACC Clin Electrophysiol.* (2021) 7:1422–32. doi: 10.1016/j.jacep.2021.04.003
38. Hua W, Fan X, Li X, Niu H, Gu M, Ning X, et al. Comparison of left bundle branch and His bundle pacing in bradycardia patients. *JACC Clin Electrophysiol.* (2020) 6:1291–9. doi: 10.1016/j.jacep.2020.05.008
39. Hou X, Qian Z, Wang Y, Qiu Y, Chen X, Jiang H, et al. Feasibility and cardiac synchrony of permanent left bundle branch pacing through the interventricular septum. *Europace.* (2019) 21:1694–702. doi: 10.1093/europace/euz188
40. Hu Y, Li H, Gu M, Hua W, Niu H, Zhang N, et al. Comparison between his-bundle pacing and left bundle branch pacing in patients with atrioventricular block. *J Interv Card Electrophysiol.* (2021) 62:63–73. doi: 10.1007/s10840-020-00869-w
41. Sheng X, Pan YW Yu C, Wang B, Zhang P, Li J, et al. Comparison of synchronization between left bundle branch and his bundle pacing in atrial fibrillation patients: an intra-patient-controlled study. *Pacing Clin Electrophysiol.* (2021) 44:1523–31. doi: 10.1111/pace.14331
42. Vijayaraman P, Patel N, Colburn S, Beer D, Naperkowski A, Subzposh FA. His-Purkinje conduction system pacing in atrioventricular block: new insights into site of conduction block. *JACC Clin Electrophysiol.* (2021) 8:73–85. doi: 10.1016/j.jacep.2021.07.007
43. Vijayaraman P, Cano Ó, Koruth JS, Subzposh FA, Nanda S, Pugliese J, et al. His-Purkinje conduction system pacing following transcatheter aortic valve replacement: feasibility and safety. *JACC Clin Electrophysiol.* (2020) 6:649–57. doi: 10.1016/j.jacep.2020.02.010
44. Qian Z, Qiu Y, Wang Y, Jiang Z, Wu H, Hou X, Zou J. Lead performance and clinical outcomes of patients with permanent His-Purkinje system pacing: a single-centre experience. *Europace.* (2020) 22(Suppl_2):ii45–ii53. doi: 10.1093/europace/euaa295
45. Ye Y, Zhang K, Yang Y, Jiang D, Pan Y, Sheng X, et al. Feasibility and safety of both His bundle pacing and left bundle branch area pacing in atrial fibrillation patients: intermediate term follow-up. *J Interv Card Electrophysiol.* (2021) 2021:1–10. doi: 10.1007/s10840-021-00964-6
46. Slotwiner DJ, Raitt MH, Del-Carpio MF, Mulpuru SK, Nasser N, Peterson PN. Impact of physiologic pacing versus right ventricular pacing among patients with left ventricular ejection fraction greater than 35%: a systematic review for the 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay.

J Am Coll Cardiol. (2018) 140:e483–503. doi: 10.1161/CIR.0000000000000629
47. Chen K, Li Y, Dai Y, Sun Q, Luo B, Li C, et al. Comparison of electrocardiogram characteristics and pacing parameters between left bundle branch pacing and right ventricular pacing in patients receiving pacemaker therapy. *Europace.* (2019) 21:673–80. doi: 10.1093/europace/euy252
48. Massing GK, James TN. Anatomical configuration of the his bundle and bundle branches in the human heart. *Circulation.* (1976) 53:609–21. doi: 10.1161/01.CIR.53.4.609
49. Zhang S, Zhou X, Gold MR. Left bundle branch pacing. *J Am Coll Cardiol.* (2019) 7:3039–49. doi: 10.1016/j.jacc.2019.10.039
50. Huang W, Chen X, Su L, Wu S, Xia X, Vijayaraman P, et al. beginner's guide to permanent left bundle branch pacing. *Heart Rhythm.* (2019) 16:1791–6. doi: 10.1016/j.hrthm.2019.06.016

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frontiers in Cardiovascular Medicine

PERSPECTIVE
published: 21 February 2022
doi: 10.3389/fcvm.2022.844152

A Guide to Left Bundle Branch Area Pacing Using Stylet-Driven Pacing Leads

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Left bundle branch area pacing (LBBAP) has emerged as a novel pacing modality which aims to capture the left bundle branch area and avoids the detrimental effects of right ventricular pacing. Current approaches for LBBAP have been developed using lumen-less pacing leads (LLL). Expanding the tools and leads for LBBAP might contribute to a wider adoption of this technique. Standard stylet-driven pacing leads (SDL) differ from current LLL as they are characterized by a wider lead body diameter, are stylet-supported and often have a non-isodiametric extendable helix design. Although LBBAP can be performed safely with SDL, the implant technique of LBBAP differs compared to LLL. In the current overview we describe in detail how different types of SDL can be used to target a deep septal position and provide a practical guide on how to achieve LBBAP using SDL.

Keywords: left bundle branch area pacing, stylet-driven pacing leads, lumen-less pacing lead, conduction system pacing, stylet-driven extendable screw lead

OPEN ACCESS

Edited by:
Lina Marcantoni, Hospital Santa Maria della Misericordia of Rovigo, Italy

Reviewed by:
Kevin Vernooy, Maastricht University Medical Centre, Netherlands
Haran Burri, Université de Genève, Switzerland

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Specialty section:
This article was submitted to Cardiac Rhythmology, a section of the journal Frontiers in Cardiovascular Medicine

Received: *27 December 2021*
Accepted: *25 January 2022*
Published: *21 February 2022*

Citation:
De Pooter J, Wauters A, Van Heuverswyn F and Le polain de Waroux J-B (2022) A Guide to Left Bundle Branch Area Pacing Using Stylet-Driven Pacing Leads. Front. Cardiovasc. Med. 9:844152. doi: 10.3389/fcvm.2022.844152

INTRODUCTION

Conduction system pacing (CSP) aims to pace the ventricles by capturing the conduction system at either the level of the His bundle (His bundle pacing, HBP) or the left bundle branch (left bundle branch area pacing, LBBAP). These new pacing techniques were developed to avoid the detrimental effects of pacing induced dyssynchrony with right ventricular pacing by offering more physiologic activation of the heart (1–3). Of the two techniques, HBP is deemed the most physiological as it captures the ventricular conduction system at its proximal origin, but its clinical applicability is limited by high pacing thresholds, low sensing amplitudes, oversensing issues, and a greater number of lead revisions (4, 5). Left bundle branch area pacing has subsequently emerged as an attractive alternative as it provides comparable physiological pacing to HBP but with lower pacing thresholds, higher sensing amplitudes, and more stable lead positions (3, 6–9). To obtain LBBAP, the pacing lead is positioned deep into the ventricular septum, along the course of the left bundle branch. Until now, LBBAP has been performed almost exclusively with a lumen-less pacing lead (LLL) with a fixed helix design (7–9). Detailed operator guides on how to perform LBBAP using LLL (LLL-LBBAP) have been previously published (10). Recently, LBBAP using standard stylet-driven pacing leads (SDL) has been reported to be safe and feasible (11, 12). However, due to the differences in lead and helix design, LBBAP with SDL (SDL-LBBAP) requires different handling and lead preparation. In the current overview, we describe in detail how LBBAP can be safely performed with different types of SDL and highlight the relevant differences with respect to LLL-LBBAP.

STYLET- AND SHEATH-GUIDED CONDUCTION SYSTEM PACING

Early in the evolution of CSP, HBP was attempted with SDL and custom-curved stylets (13). Although HBP was feasible with this approach, implant success was low and pacing thresholds remained often high and unstable. In 2006, Zanon et al. described a new approach for HBP using a long preshaped delivery sheath to guide the pacing lead toward the His bundle area (14). The use of such delivery sheaths allowed for a more stable position and better contact of the pacing lead with the His bundle area. It also allowed the use of a narrow-caliber LLL, which rapidly appeared associated with better long-term results and lead stability. With this sheath-guided approach, implant success of HBP increased to 90%. Since then, sheath-guided HBP has become the standard approach and is now also used to achieve LBBAP (9, 10). The widespread adoption of the sheath-guided method for LBBAP has also been driven by the use of LLL which requires, due to absence of stylet support, a dedicated delivery sheath to be directed toward the septum.

Current guiding sheaths for LBBAP are similar to those used for HBP. Several delivery sheaths are commercially available for CSP (both HBP and LBBAP) with the majority having a double curved design (**Supplementary Figure 1A**). The wide primary curve allows to cross the tricuspid valve toward the interventricular septum while the smaller secondary curve ensures lead positioning perpendicular to the septum. Currently available guiding sheaths differ with respect to size and angulation of the curves and have been developed to address differences in cardiac size or to target different sites of the conduction system. Deflectable-single curve-sheaths are also proposed for CSP but appears less appropriate for LBBAP as they have a tendency to bring the pacing lead in a potentially dangerous anterior position. Details regarding different delivery sheaths have been previously published (15).

LUMEN-LESS VS. STYLET-DRIVEN PACING LEADS: DIFFERENCES IN LEAD DESIGN

Different pacing leads used for LBBAP, are shown in **Supplementary Figure 1B** with details on lead and helix design summarized in **Table 1**. Largest experience with LBBAP has been obtained with a single type of LLL (SelectSecure, 3830 pacing lead, Medtronic Inc., Minneapolis, USA). Due to the absence of an inner lumen, the lead body measures only 4.1 Fr and the fixed helix (1.8 mm length) design results in an isodiametric lead. The electrically active helix of the SelectSecure pacing lead facilitates conduction system capture in both unipolar and bipolar pacing mode.

Standard stylet-driven pacing leads differ from LLL with respect to several important features. Standard stylet-driven pacing leads have an inner lumen which allows for stylet insertion. As a result, the lead body of SDL is wider than LLL and usually measures >5.5 Fr. Standard stylet-driven pacing leads are also stiffer than LLL when the stylet is inserted. The SDL helix has an extendable-retractable design. Fully extended the SDL helix

TABLE 1 | Lead specifications of different stylet-driven and lumen-less pacing leads used for left bundle branch area pacing.

Lead name	SelectSecure 3830	Solia S	Ingevity	Tendril 2088TC
Manufacturer	Medtronic	Biotronik	Boston Scientific	Abbott
Lead design	Lumen-less	Stylet-driven	Stylet-driven	Stylet-driven
Lead length (cm)	59/69/74	45/53/60	45/52/59	46/52/58/65/85/100
Lead body diameter (mm/Fr)	1.4 (4.1)	1.8 (5.6)	1.9 (5.7)	1.9 (5.8)
Helix design	Fixed, non-retractable	Retractable	Retractable	Retractable
Cathode design (Lead tip electrode)	Electrical active helix	Electrical active helix	Electrical active helix	Electrical active helix
Tip electrode length (mm)	1.8	1.8	1.8	2.0
Tip electrode surface area (mm^2)	3.6	4.5	4.5	6.9
Tip to ring electrode spacing (mm)	9	10	10.7	10
Anode ring electrode surface area (mm^2)	16.9	17.4	20	16
Anode ring electrode width (mm)	Not specified	1.9 (5.9)	2.0 (6.0)	Not specified
Outer isolation	Polyurethane	Polyurethane/Silicone	Polyurethane (55D)	Optim™
Inner isolation	Silicone/ETE	Silicone	Silicone	Silicone
Rotations to extend helix				
With straight stylet	NA	5–10	7	6–11
With J- stylet	NA	5–10	8	9–14
Maximal number of rotations	NA	17 (45 cm length) 21 (53 cm length) 23 (60 cm length)	30	No maximum specified
Steroid eluting	Yes	Yes	Yes	Yes
Steroid eluting	Beclomethasone Diproprionate	Dexamethasone Acetate	Dexacomethasone Acetate	Dexamethasone Sodium Phosphate

measures 1.8–2.0 mm in length, similar as the SelectSecure lead, but due to a wider diameter, the electrically active helix surface of SDL is larger compared to LLL. The lead body of SDL consists of an inner and outer coil which are separated by silicon insulation and rotate independently from each other. The inner coil is connected distally to the helix and proximally to the rotating pin of the pacing lead. Clockwise rotation of the connector pin allows extending the helix. However, when rotating the outer lead body of SDL, care must be taken to ensure that rotations of the outer lead body are adequately transferred to the inner coil. If the inner and outer coils do not rotate simultaneously, retraction of extended helices might occur and will hamper lead advancement in the septum.

LBBAP IMPLANT TECHNIQUE USING LUMEN-LESS PACING LEADS

Lumen-less pacing leads–left bundle branch area pacing has been described in detail by Huang et al. and most implantation techniques represent small variations on Huangs approach (10). With this approach, a single type of LLL (SelectSecure, model 3830, Medtronic Inc., Minneapolis, USA) is used and dedicated delivery sheaths are mandatory with this type of lead as it lacks the support of a stylet. Two sheaths, with a fixed double curve (C315 His, Medtronic Inc., Minneapolis, USA) or a deflectable curve (C304 and C304 His, Medtronic Inc., Minneapolis, USA) are available for use. The delivery sheath is advanced to the right ventricle over a J-tip guidewire. Using a right anterior oblique (RAO 20–30°) view on fluoroscopy can help to avoid unwanted CS cannulation, which tends to happen frequently due to the double curvature of the sheaths. Once in the right ventricle, the pacing lead is advanced through the delivery sheath and both sheath and lead are retracted to target the upper part of the septum. The implant height on the septum is determined by localizing the His bundle region and targeting a septal position >1 cm from the His region toward the apex in a RAO view. Slight counter clockwise rotation of the sheath and lead combination allows for perpendicular positioning on the septum which is best confirmed, in our experience, in a 25–30° left anterior oblique fluoroscopic (LAO) view. A small amount of contrast may also be injected to delineate the right septal border and confirm the appropriate septal position. In this position, unipolar pace mapping at the lead tip typically reveals a wide "W" shaped QRS morphology in lead V1 of the 12-lead surface electrocardiogram (ECG). The SelectSecure pacing lead is screwed into the septum by clockwise rotation of the outer lead body with the delivery sheath in close contact with the right septum in order to maintain a stable lead position on the septum. Lead advancement into the septum is further guided by unipolar pacing impedance, contrast injection, assessment of paced QRS morphology, observation of fixation beats, or presence of a left bundle branch potential on the unipolar lead tip electrogram (10, 16, 17). As the pacing lead reaches the course of the left bundle branch, the paced "W" shaped QRS morphology in lead V1 gradually changes to a narrow QRS morphology with a terminal r-wave in lead V1 (so-called incomplete right bundle branch block morphology). As such 12-lead ECG monitoring is mandatory for successful LBBAP. Different criteria to confirm capture of the left bundle branch and differentiate left bundle branch pacing from left sided myocardial capture have been proposed, although currently no consensus exists (10, 16, 18, 19).

LBBAP IMPLANT TECHNIQUE USING SDL

With SDL-LBBAP, delivery sheath manipulation and septal positioning is similar to that of LLL-LBBAP. Given the length of SDL helix, extending the helix alone will not penetrate the septum deep enough to achieve LBBAP. Therefore, similar to LLL-LBBAP, rotating the outer lead body of SDL is mandatory to access deep septal position (11, 12). However, when rotating the outer lead body of SDL, retraction of the helix may occur due to fixation in the tissue causing the outer coil to turn over the inner coil. Below we provide details on our approach to achieve LBBAP with different types of SDL.

Solia S Pacing Lead, Biotronik

The Solia S pacing lead (Biotronik, SE & Co., KG, Germany) is a 5.6 Fr SDL with an extendable helix design. The lead body consists of an outer and inner coil, with the latter connected to the electrical active helix. When used for LBBAP, our approach is to extend the helix in advance, generally before septal positioning is attempted (**Figure 1.1A**). Alternately, one can map the His area and perform pace mapping with the helix withdrawn, which give less chance to snag the tricuspid valvular apparatus. However, when performing pace mapping on the right side of the septum, unipolar impedances might be more accurate with extended helix and might allow a better reference impedance when screwing into the septum. To avoid helix retraction when clockwise rotating the outer lead body, the inner coil of Solia S lead needs to be pretensioned before insertion. Therefore, the green stylet-guide is connected to the lead pin and pressed against the silicone coating at the proximal portion of the lead (**Figure 1.1B**). To build up the torque on the inner coil, this green stylet-guide tool is rotated 8–10 times clockwise (**Figure 1.1C**). As such, the inner coil builds up tension and rotations of the outer lead body are better transferred in a one-to-one relation to the inner coil and helix. This preparation step avoids unwanted helix retraction during screwing. To maintain the tension, the green stylet-guide is kept on the pin of the pacing lead while screwing the Solia S lead toward a deep septal position. Advancement of the Solia S lead into the septum is further facilitated by fast rotation (to overcome resistance at the right septal subendocardial layer) and by keeping the stylet advanced to the tip of the pacing lead. The stylet and stylet guide are kept in position until the final position is reached (**Figure 1.1D**).

Ingevity Lead, Boston Scientific

The Ingevity pacing lead (Boston Scientific Inc., Marlborough, MA, USA) is a 5.7 Fr diameter SDL with an extendable helix design. The electrically active helix is extended in advance using the standard clip-on-tool. To screw the Ingevity lead in a deep septal position two approaches are used. With the first approach, clockwise rotations on the outer lead body are applied. This

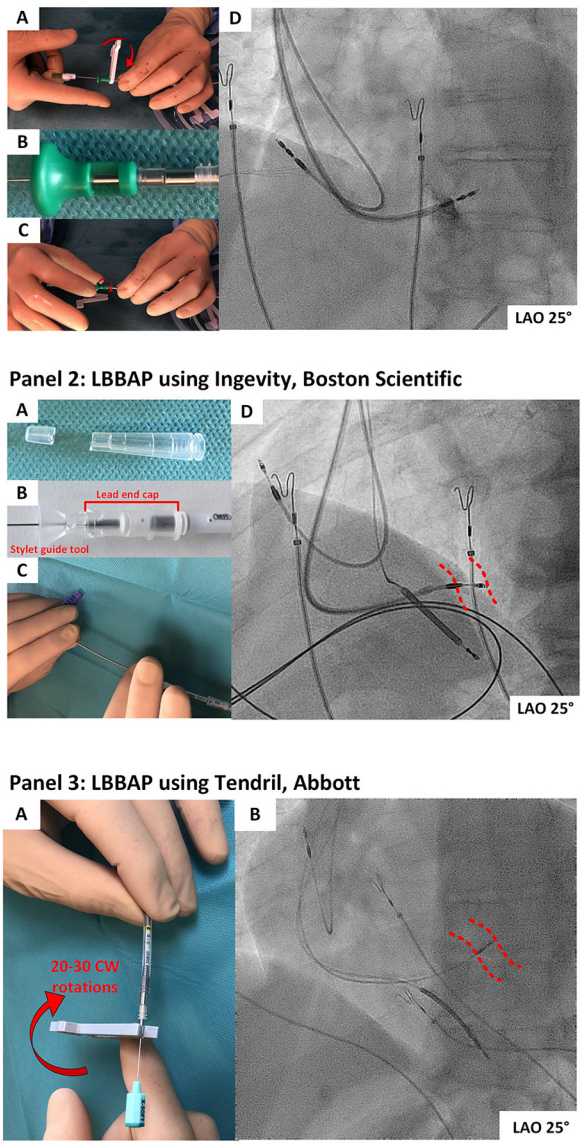

FIGURE 1 | (1.1) LBBAP using the Solia S lead (Biotronik). **(1A)** The helix is extended using the standard clip-on-tool with 10–15 clockwise rotations. **(1B)** The green stylet insertion tool is connected to the pin of the pacing lead and the silicon rubber separating the inner and outer coil. **(1C)** Tension to the lead is applied with 10 additional clockwise rotations on the green stylet insertion tool. **(1D)** Deep septal position of the Solia-S lead on fluoroscopy. **(1.2)** LBBAP using the Ingevity pacing lead (Boston Scientific). **(2A)** The closed end of a regular lead cap is cut. **(2B)** The lead cap is advanced over the lead pin toward the silicone rubber at the proximal part of the lead. The stylet insertion tool is forced between the lead end cap and the pin of the pacing lead and pushed toward the proximal lead part. **(2C)** The Ingevity lead is screwed in a deep septal position by applying clockwise rotations on the outer lead body. **(2D)** Deep septal position of the Ingevity lead on fluoroscopy. The red dotted lines indicate the septal borders. **(1.3)** LBBAP using the Tendril 2088TC pacing lead (Abbott). **(3A)** The tendril pacing lead can be screwed toward a deep septal position by continuous rotations with the clip-on tool on the pin of the pacing lead. As the helix grips into the tissue, it will further advance into the septum and pull the lead body toward a deep septal position. Often 20–30 clockwise (CW) rotations are needed. **(3B)** Deep septal position of a Tendril pacing lead. The red dotted lines indicate the septal borders.

generally leads to helix retraction, as described before, and further advancement in the septum becomes hampered, as the helix is no longer exposed. Helix retraction is often suggested by a sudden increase in pacing impedance (sometimes up to >2,000 Ohms). The helix needs to be extended once again using the clip-on-tool. Afterwards, new clockwise rotations on the outer lead body can be applied to further advance the lead. These maneuvers are repeated until a deep septal position is reached. A second method consists in extending the helix in advance and fixating the helix and inner coil to the outer lead coil. As the stylet-guide tool of this lead does not get over the proximal silicone seal of the lead, the tension created on the inner coil is not maintained. However, a custom-made fixation tool can be made from an IS-1 lead-end cap (20). First, the tip of an IS-1 lead end-cap is cut-off and the opened lead end-cap is slided over the proximal end of the pacing lead (beyond the proximal electrode). Secondly, with the stylet fully inserted in the lead, the stylet-guide tool is advanced onto the connector pin and around 15 rotations of the stylet-guide tool are applied to expose the helix and pretension the inner coil. Finally, without releasing the built-up tension, the lead-end cap is pulled back until the insertion tool is forced between the lead pin and the lead end cap. This technique allows to maintain the pretension on the inner coil and avoid helix retraction when clockwise rotations of the outer lead body of the Ingevity are applied (**Figure 1.2A–D**). With both approaches the stylet remains advanced to the tip of the pacing lead while screwing as this facilitates lead advancement into the septum.

Tendril 2088TC, Abbott

The Tendril 2088TC lead (Abbott, Inc., USA) is a 5.8 Fr SDL with an extended helix measuring 2 mm in length. The outer isolation of this lead consists of a polymer (Optim^{TM}) made of silicone and polyurethane. This particular insulation has the potential to become damaged when subject to rotations applied on the outer lead body. Therefore, rotating the outer lead body of the Tendril is not recommended to obtain a deep septal position. However, the helix extension mechanism of this lead is protected from overturning and helix fracture has not been described, even with numerous rotations. With the helix extended, the Tendril pacing lead is positioned at the right side of the septum and unipolar pace mapping is performed. The Tendril pacing lead is advanced into the septal tissue by continuous clockwise rotation of the connector pin using the standard clip-on-tool delivered with the lead (**Figure 1.3A,B**). As the helix grips the septal tissue, continuous rotation of the lead pin will advance the helix and lead body further into the septum. The tapered transition between the helix and lead body facilitates the advancement of the Tendril lead in the septum. Often, 20–30 rotations on the lead pin are needed before the lead reaches the left side of the septum.

PRECAUTIONS AND POTENTIAL PITFALLS WHEN USING SDL FOR LBBAP

With the stylet inserted, SDL are stiffer than LLL and care must be taken not to perforate through the septum when implanting LBBAP leads. It is recommended to screw SDL in

deep septal positions under fluoroscopic guidance and with continuous monitoring of the unipolar impedance and paced QRS. The lead implant depth can be assessed with contrast injection and based on the fluoroscopic landmarks of the pacing electrodes and interelectrode distance (**Table 1**). As the lead advances into the septum, the unipolar pacing impedance tends to rise initially but decrease by 50–100 ohms as it approaches the left sided septal border. If the impedance drops by more than 200 ohms during screwing, further lead advancement is not recommended as this indicates that the helix is at the edge of the left sided septum. Absolute values of unipolar pacing impedance depend on the type, length, and design of the SDL. As the Boston Scientific Ingevity lead is developed as a high impedance pacing lead, it demonstrates higher unipolar impedances than the Tendril or the Solia S leads. Therefore, we recommend using unipolar pacing impedance at the right side of the septum as an individual reference for impedance monitoring during screwing. Furthermore, unipolar pacing impedances measured from the stylet are reported to be comparable to unipolar pacing impedances measured from the lead pin (21).

A further potential pitfall of SDL is the risk of entanglement of the exposed helix in the right-sided subendocardial tissue. This so-called entanglement effect has previously been described in a cadaver model with LLL targeted to a deep septal position but can occur with any type of pacing lead (22). Entanglement of the helix occurs when the helix does not get grip on the septal tissue but instead becomes trapped in the septal subendocardial tissue. Prolonged rotation of the lead body without lead advancement into the septum, may eventually result in complete helix entrapment and difficulty in repositioning the lead (23). If entanglement is suspected, counter clockwise rotation and slight traction on the lead body while maintaining tension on the lead, usually untangles the lead.

DISCUSSION: THE USE OF SDL IN LBBAP AND FUTURE PERSPECTIVES

Reported experience with LBBAP using SDL is limited (11, 12). In a recent study, SDL- and LLL-LBBAP yielded similar implant success rates, procedural safety and pacing characteristics (11). Although larger studies are needed to confirm these results, SDL may offer advantages for LBBAP for several reasons. The thicker lead body of SDL together with the support of the stylet results in excellent torquability and stiffness when targeting deep septal positions with rotations applied on the outer lead body effectively transferred to the distal part of the lead and helix. Compared to LLL, unwanted twisting of the lead at the entry of the delivery sheath during implant is rarely observed. Furthermore, the larger lead body diameter of SDL also allows for an improved tissue grip when rotating the lead body. As such, and despite the larger lead body diameter, SDL are characterized by an easy penetration into the septum. Additionally, unipolar lead impedances can be monitored directly on the stylet of SDL, rather than through connection of the crocodile clamps on the lead pin (21). This approach avoids repetitive connection and disconnection of the clamps, limits less lead body rotations, and offers continuous unipolar pacing and reliable impedance monitoring during screwing. Another advantage with stylet-driven leads is that in the unfortunate event of post-operative lead dislodgment, the lead may be repositioned in a "conventional" right ventricular position without having to regain venous access. Disadvantages include the requirement for lead preparation and particular precautions to avoid unwinding of the helix during deep septal lead positioning for SDL leads with extendable helices. An additional drawback is that His bundle pacing is generally easier with lumen-less leads, and in case LBBAP with SDL does not give satisfactory results, HBP as backup might not be as easy with SDL. Although, the optimal lead design for LBBAP (and CSP in general) has not yet been determined, several of the features of current SDL may merit incorporation into future dedicated LBBAP lead designs.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

JD: article concept, drafting, writing, figures, and review. AW: concept and drafting. FV: critical review. J-BL: article concept, writing, and review. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.844152/full#supplementary-material

Supplementary Figure 1 | (A) Currently available delivery sheaths for left bundle branch area pacing. Note that steerable/single curve sheaths are not represented here as the secondary curve appears critical to correctly position the sheath before lead implantation. **(B)** Different types of pacing leads used for left bundle branch area pacing.

Supplementary Movie 1 | Preparation of the Solia S lead when used for LBBAP. The helix might be extended in advance. The green stylet-guide is connected to the lead pin and pressed against the silicone coating at the proximal portion of the lead. To pretension the lead, build up the torque on the inner coil is achieved by rotating the green stylet-guide tool 8–10 times clockwise.

Supplementary Movie 2 | Screwing of the Solia S lead during LBBAP. The stylet is advanced to the pin of the pacing lead and fast rotations on the outer lead body are applied to achieve a deep septal position.

Supplementary Movie 3 | Preparation of the Ingevity pacing lead when used for LBBAP. The helix is extended using the clip-on-tool. A lead end cap is cut and connected to the proximal pin of the pacing lead to avoid helix retraction. The stylet is inserted and kept advanced when screwing.

REFERENCES

1. Abdelrahman M, Subzposh FA, Beer D, Durr B, Naperkowski A, Sun H, et al. Clinical outcomes of his bundle pacing compared to right ventricular pacing. *J Am Coll Cardiol.* (2018) 71:2319–30. doi: 10.1016/j.jacc.2018.02.048
2. Mafi-Rad M, Luermans JG, Blaauw Y, Janssen M, Crijns HJ, Prinzen FW, et al. Feasibility and acute hemodynamic effect of left ventricular septal pacing by transvenous approach through the interventricular septum. *Circ Arrhythm Electrophysiol.* (2016) 9:e003344. doi: 10.1161/CIRCEP.115.003344
3. Salden FCWM, Luermans JGLM, Westra SW, Weijs B, Engels EB, Heckman LIB, et al. Short-term hemodynamic and electrophysiological effects of cardiac resynchronization by left ventricular septal pacing. *J Am Coll Cardiol.* (2020) 75:347–59. doi: 10.1016/j.jacc.2019.11.040
4. Teigeler T, Kolominsky J, Vo C, Shepard RK, Kalahasty G, Kron J, et al. Intermediate-term performance and safety of his-bundle pacing leads: a single-center experience. *Heart Rhythm.* (2021) 18:743–9. doi: 10.1016/j.hrthm.2020.12.031
5. Zanon F, Abdelrahman M, Marcantoni L, Naperkowski A, Subzposh FA, Pastore G, et al. Long term performance and safety of His bundle pacing: a multicenter experience. *J Cardiovasc Electrophysiol.* (2019) 30:1594–601. doi: 10.1111/jce.14063
6. Hou X, Qian Z, Wang Y, Qiu Y, Chen X, Jiang H, et al. Feasibility and cardiac synchrony of permanent left bundle branch pacing through the interventricular septum. *Europace.* (2019) 21:1694–702. doi: 10.1093/europace/euz188
7. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, et al. A novel pacing strategy with low and stable output: pacing the left bundle branch immediately beyond the conduction block. *Can J Cardiol.* (2017) 33:1736:e1–3. doi: 10.1016/j.cjca.2017.09.013
8. Su L, Wang S, Wu S, Xu L, Huang Z, Chen X, et al. Long-term safety and feasibility of left bundle branch pacing in a large single-center study. *Circ Arrhythm Electrophysiol.* (2021) 14:e009261. doi: 10.1161/CIRCEP.120.009261
9. Vijayaraman P, Subzposh FA, Naperkowski A, Panikkath R, John K, Mascarenhas V, et al. Prospective evaluation of feasibility, electrophysiologic and echocardiographic characteristics of left bundle branch area pacing. *Heart Rhythm.* (2019) 16:1774–82. doi: 10.1016/j.hrthm.2019.05.011
10. Huang W, Chen X, Su L, Wu S, Xia X, Vijayaraman P. A beginner's guide to permanent left bundle branch pacing. *Heart Rhythm.* (2019) 16:1791–6. doi: 10.1016/j.hrthm.2019.06.016
11. De Pooter J, Calle S, Timmermans F, Van Heuverswyn F. Left bundle branch area pacing using stylet-driven pacing leads with a new delivery sheath: a comparison with lumen-less leads. *J Cardiovasc Electrophysiol.* (2021) 32:439–48. doi: 10.1111/jce.14851
12. Zanon F, Marcantoni L, Pastore G, Baracca E. Left bundle branch pacing by standard stylet-driven lead: preliminary experience of two case reports. *HeartRhythm case reports.* (2020) 6:614–7. doi: 10.1016/j.hrcr.2020.06.005
13. Deshmukh P, Casavant DA, Romanyshyn M, Anderson K. Permanent, direct His-bundle pacing: a novel approach to cardiac pacing in patients with normal His-Purkinje activation. *Circulation.* (2000) 101:869–77. doi: 10.1161/01.CIR.101.8.869
14. Zanon F, Baracca E, Aggio S, Pastore G, Boaretto G, Cardano P, et al. A feasible approach for direct his-bundle pacing using a new steerable catheter to facilitate precise lead placement. *J Cardiovasc Electrophysiol.* (2006) 17:29–33. doi: 10.1111/j.1540-8167.2005.00285.x
15. Ravi V, El Baba M, Sharma PS. His bundle pacing: tips and tricks. *Pacing Clin Electrophysiol.* (2021) 44:26–34. doi: 10.1111/pace.14108
16. Jastrzebski M, Kiełbasa G, Curila K, et al. Physiology-based electrocardiographic criteria for left bundle branch capture. *Heart Rhythm.* (2021) 18:935–43. doi: 10.1101/2020.12.24.20248827
17. Jastrzebski M, Kiełbasa G, Curila K, Moskal P, Bednarek A, Rajzer M, et al. Programmed deep septal stimulation: a novel maneuver for the diagnosis of left bundle branch capture during permanent pacing. *J Cardiovasc Electrophysiol.* (2020) 31:485–93. doi: 10.1111/jce.14352
18. Wu S, Chen X, Wang S, Xu L, Xiao F, Huang Z, et al. Evaluation of the criteria to distinguish left bundle branch pacing from left ventricular septal pacing. *JACC Clin Electrophysiol.* (2021) 7:1166–77. doi: 10.1016/j.jacep.2021.02.018
19. Jastrzębski M. ECG and pacing criteria for differentiating conduction system pacing from myocardial pacing. *Arrhyth Electrophysiol Rev.* (2021) 10:172–80. doi: 10.15420/aer.2021.26
20. Gillis K, O'Neill L, Hilfiker G, Wielandts J-Y, Duytschaever M, Knecht S, et al. Left bundle branch area pacing using the Boston Scientific Ingevity stylet-driven active fixation lead: a technical report. *Acta Cardiol.* (2021).
21. Gillis K, O'Neill L, Wielandts JY, Hilfiker G, Vlase A, Knecht S, et al. Left bundle branch area pacing guided by continuous uninterrupted monitoring of unipolar pacing characteristics. *J Cardiovasc Electrophysiol.* (2022) 33:299–307. doi: 10.1111/jce.15302
22. Jastrzebski M, Moskal P, Hołda MK, Strona M, Bednarek A, Kiełbasa G, et al. Deep septal deployment of a thin, lumenless pacing lead: a translational cadaver simulation study. *Europace.* (2020) 22:156–61. doi: 10.1093/europace/euz270
23. le Polain de Waroux JB, Wielandts JY, Gillis K, Hilfiker G, Sorgente A, Capulzini L, et al. Repositioning and extraction of stylet-driven pacing leads with extendable helix used for left bundle branch area pacing. *J Cardiovasc Electrophysiol.* (2021). 32:1464–6. doi: 10.1111/jce.15030

Conflict of Interest: JD reports speaker fees and honoraria from Medtronic and Biotronik. AW reports speaker and consultancy fees from Biotronik and Boston Scientific. J-BL reports non-significant speaker fees and honoraria for proctoring and teaching activities from Medtronic, Boston Scientific, Abbott, and Biotronik.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 24 February 2022
doi: 10.3389/fcvm.2022.829733

Therapeutic Effect of His-Purkinje System Pacing Proportion on Persistent Atrial Fibrillation Patients With Heart Failure

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Background: His-Purkinje system pacing (HPSP) combined with atrioventricular node ablation is an effective therapy for atrial fibrillation (AF) patients with heart failure (HF). However, atrioventricular node ablation has some limitations and disadvantages. HPSP combined with β -blockers reduces intrinsic heart rate and increases pacing proportion, which may be an alternative to HPSP combined with atrioventricular node ablation. This study was to assess the therapeutic effect of different HPSP proportion on AF patients with HF.

Methods: The study enrolled 30 consecutive persistent AF patients with HF who underwent HPSP. Heart rate was controlled by medical therapy. NYHA class, NT-proBNP, echocardiographic parameters were assessed at follow-up. MACE was defined as the composite endpoint of readmission for HF and cardiac mortality.

Results: The AUC of pacing proportion for predicting MACE was 0.830 (SE = 0.140, 95%CI:0.649–0.941, $p = 0.018$), the optimal cut-off point of pacing proportion to predict MACE by ROC analysis was 71% (sensitivity:83.3%, specificity: 91.7%). In high pacing proportion group (>71%), there were significant improvements of NYHA class, NT-proBNP, LVEF and LVEDD from the baseline in wide QRS complex (QRSd>120 ms) patients and HFrEF patients at half year follow-up, and there were significant improvements in NYHA class, NT-proBNP from baseline in narrow QRS complex (QRSd≤120 ms) patients and HFpEF patients at half year follow-up, moderate but no significant improvements of LVEF and LVEDD were observed in these patients. In low pacing proportion group (≤71%), there were no significant improvements of NT-proBNP, LVEDD or LVEF regardless of baseline QRS duration or LVEF ($p > 0.05$).

Conclusion: High pacing proportion (>71%) of HPSP can improve clinical outcomes and echocardiographic parameters in persistent AF patients with wide QRS complex or HFrEF, and clinical outcomes in persistent AF patients with narrow QRS complex or HFpEF. High pacing proportion of HPSP has a beneficial effect on the prognosis of persistent AF patients with HF.

Keywords: persistent atrial fibrillation, heart failure, His-Purkinje system pacing, pacing proportion, prognosis

OPEN ACCESS

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Specialty section:
This article was submitted to Cardiovascular Therapeutics, a section of the journal Frontiers in Cardiovascular Medicine

Received: *06 December 2021*
Accepted: *31 January 2022*
Published: *24 February 2022*

Citation:
Tong F and Sun Z (2022) Therapeutic Effect of His-Purkinje System Pacing Proportion on Persistent Atrial Fibrillation Patients With Heart Failure. Front. Cardiovasc. Med. 9:829733. doi: 10.3389/fcvm.2022.829733

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in patients with heart failure (HF) (1, 2). AF and HF have similar risks and mechanisms (3) related to physiological processes that initiate and sustain each other (4). Current methods to control heart rate and rhythm in patients with AF include drug therapy, radiofrequency ablation (RFA) and cryoablation, but drug therapy is sometimes ineffective and may be accompanied by adverse reactions. Catheter ablation has a high recurrence rate of AF (5), especially the recurrence rate of persistent AF can reach up to 50% (6, 7). AF duration for more than 2 years and HF are identified as predictor for AF recurrence (6, 8). Therefore, the clinical treatment of AF with long duration and HF is still challenging.

2021 European Society of Cardiology (ESC) Guidelines on cardiac pacing and cardiac resynchronization therapy (CRT) proposed that CRT should be considered as a strategy for permanent AF patients with HF with left ventricular ejection fraction (LVEF)≤35% and QRS≥130 ms (9), as for patients with LVEF>35% or QRS<130 ms not regarded as candidates for CRT. His-Purkinje system pacing (HPSP) including His bundle pacing (HBP) and left bundle branch pacing (LBBP) can restore physiologic activation of the ventricles and maintain ventricular synchrony *via* intrinsic conduction pathway (10). Arnold et al. indicated slowly conducted AF, CRT in patients with HF and bundle branch block (BBB) as potential indication for HPSP through assessing recent evidence and current practice (10). In 2000, Deshmukh et al. first performed HBP and atrioventricular node (AVN) ablation in patients with AF, dilated cardiomyopathy and HF with reduced ejection fraction (HFrEF), and improvement of left ventricle dimensions and cardiac function were observed (11). In 2017, Huang et al. implemented HBP and AVN ablation in AF patients complicated with HFrEF or HF with preserved ejection fraction (HFpEF), and observed improvement in symptoms and echocardiographic parameters (12). However, after AVN ablation, HBP threshold increased by 0.5–1.5V (13). AVN ablation artificially causes complete atrioventricular block and pacer-dependence, and physiology of HPSP is also different from intrinsic conduction system. Therefore, clinically physicians can prescribe β-blockers for patients with persistent AF and HF to inhibit AVN conduction function and reduce intrinsic heart rate, so as to achieve a high proportion of HPSP and the purpose of rate and rhythm control. However, there are few studies on this therapy. This study aimed to assess the therapeutic effect of different HPSP proportion on persistent AF patients with HF.

METHODS

Study Patients

Consecutive patients who met the inclusion criteria were enrolled between October 2017 and July 2020. The inclusion criteria were the following: (1) Persistent AF with bradycardia or long RR interval, or AF recurrence after RFA, or unsuitable for RFA; (2) HF in New York Heart Association (NYHA) class was referred to II-IV class; (3) Patients were at least 18 years old and not pregnant.

Patients with any of the following conditions were excluded: (1) Severe mitral or aortic valve stenosis or regurgitation; (2) Congenital heart disease requiring cardiac surgery; (3) Severe chronic obstructive pulmonary disease; (4) Chronic kidney disease requiring long-term dialysis. The study was approved by ethics committees of Shengjing Hospital of China Medical University, and written informed consent has been obtained from all patients.

Implantation Procedure

HBP: C315 fixed curve delivery sheath (Medtronic) was sent to the right atrium or right ventricle through guide wire *via* subclavian vein or axillary vein. The SelectSecure 3830 lead (Medtronic) was navigated into the vicinity of His bundle (HB) through delivery sheath. During the lead placement procedure, the 12-lead electrocardiogram (ECG) and electrogram (EGM) *via* pacing lead were monitored and recorded. After HB potential was identified, ECG were recorded continuously by high pressure pacing method with higher than native heart rate. Through synchronous ECG, we could determine whether HB was captured. After the ideal position was determined, the pacemaker lead was vertically screwed into interventricular septum (IVS) to maintain the stability of the sheath, and to penetrates the fibrous capsule of the His bundle. Pacing thresholds, sensed R-wave amplitudes and lead impedances were measured. The morphology of ECG at different output voltages was recorded. Thresholds of selective and non-selective HB capture were recorded. Non-selective His bundle pacing (NS-HBP) was the first choice in our center, and the acceptable threshold was ≤2 V/0.5 ms. If parameters of HBP were not acceptable, LBBP or ventricular backup pacing would be attempted. The lower rate for HBP was initially set at 70 bpm.

Selective His bundle pacing (S-HBP) criteria: (1) The paced QRS duration (QRSd) and morphology are both identical to intrinsic QRS complex; (2) The pacing stimulus to QRS complex onset interval (PV interval) is identical to His-QRS onset interval (HV interval); (3) The potential of HB can be determined by a narrow QRS at low output pacing and the presence of QRS broadening at high output pacing; (4) Pacing signal can be seen from the beginning of QRS complex.

NS-HBP criteria: (1) PV interval is less than or equal to HV interval; (2) The potential of HB can be identified, with QRS widening at low output pacing and narrowing at capture of HB; (3) A pseudo pre-excitation wave can be immediately after HBP stimulus (**Figure 1**).

LBBP: SelectSecure 3,830 lead (Medtronic) was delivered through C315 fixed curve delivery sheath (Medtronic). During the lead placement procedure, the 12-lead ECG and EGM were monitored and recorded. Under fluoroscopic imaging in the right anterior oblique view, HB potential was first identified and HB region was used as an anatomical landmark. Then the sheath and the pacing lead were moved by 1–2 cm more distally along the RV septal surface toward the RV apex, and the pacing lead was perpendicularly screwed into IVS until the pacing lead helix to the left side of IVS. LBBP presented an QRS

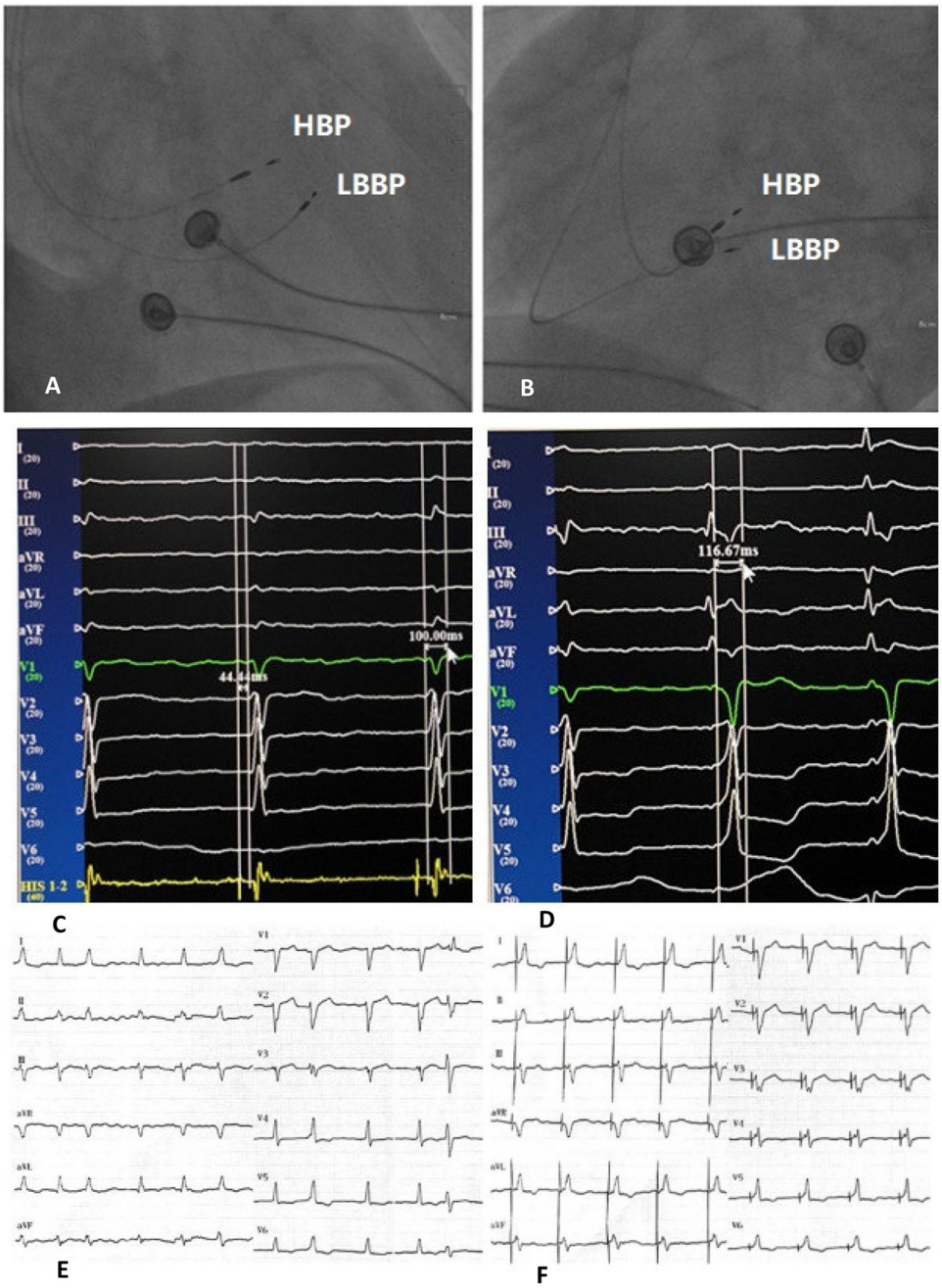

FIGURE 1 | Right anterior oblique fluoroscopic projections showing location of HBP lead and LBBP lead **(A)**. Left anterior oblique fluoroscopic projections showing location of HBP lead and LBBP lead **(B)**. Twelve-lead ECG and EGM from HBP leads of intrinsic rhythm and HV interval **(C)**. Twelve-lead ECG and EGM from HBP leads of NS-HBP **(D)**. Bedside twelve-lead ECG of intrinsic rhythm **(E)**. Bedside twelve-lead ECG of NS-HBP **(F)**. HBP, His bundle pacing; LBBP, left bundle branch pacing; ECG, electrocardiogram; EGM, electrogram; HV interval, His-QRS onset interval; NS-HBP, non-selective His bundle pacing.

pattern of right bundle branch block (RBBB), with reduced time interval between stimulation and peak left ventricular activation time (LVAT) in leads V5 and V6. The lower rate for HBP was initially set at 70 bpm.

LBBP criteria: (1) The morphology of pacing QRS complex are RBBB; (2) Left bundle branch (LBB) potential can be identified, but LBB potential prior to V wave can not be identified during left bundle branch block (LBBB); (3) LVAT is shortened, usually <80 ms (lead V5 or V6) (**Figure 2**).

Follow Up

Patients were followed in clinic at 1, 3, and 6 months. Pacing thresholds, sensed R-wave amplitudes, lead impedances and percentages of ventricular pacing were recorded at

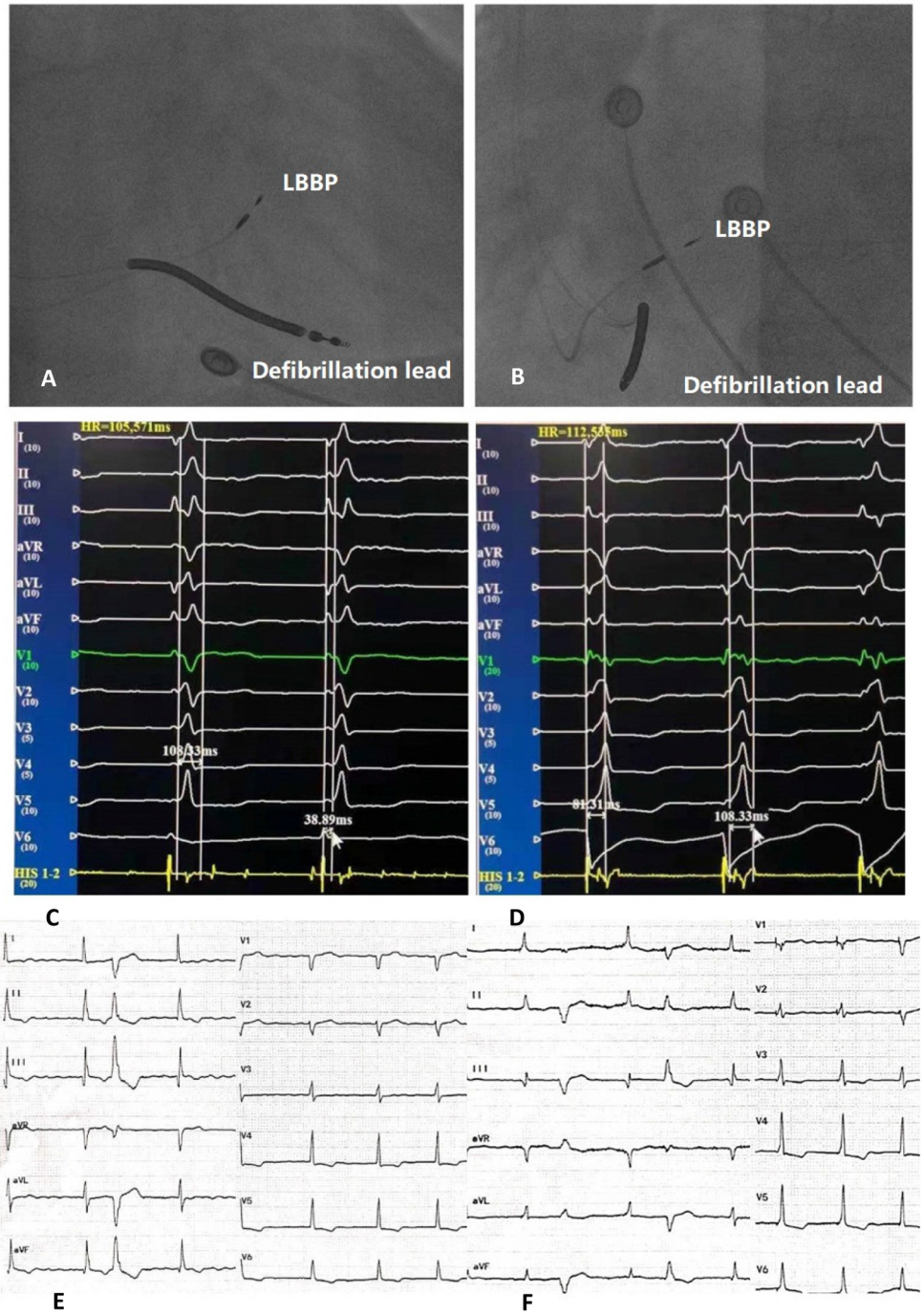

FIGURE 2 | Right anterior oblique fluoroscopic projections showing location of LBBP lead and defibrillation lead **(A)**. Left anterior oblique fluoroscopic projections showing location of LBBP lead and defibrillation lead **(B)**. Twelve-lead ECG and EGM from LBBP leads of intrinsic rhythm **(C).** Twelve-lead ECG and EGM from LBBP leads of LBBP and LVAT **(D)**. Bedside twelve-lead ECG of intrinsic rhythm **(E)**. Bedside twelve-lead ECG of LBBP **(F)**. LBBP, left bundle branch pacing; ECG, electrocardiogram; EGM, electrogram; LVAT, peak left ventricular activation time.

each visit. Routine ECG examination, N-terminal pro-brain natriuretic peptide (NT-proBNP) test were performed, and echocardiographic indices including left ventricular end diastolic dimension (LVEDD) and LVEF were measured during follow-up. At each follow-up visit, the dosage of β-blockers was adjusted according to pacing ratio, and the ventricular rate was controlled <60–80 beats/min as far as possible. The pacing rate was programmed to 60–80 beats/min. If necessary, the pacing rate set

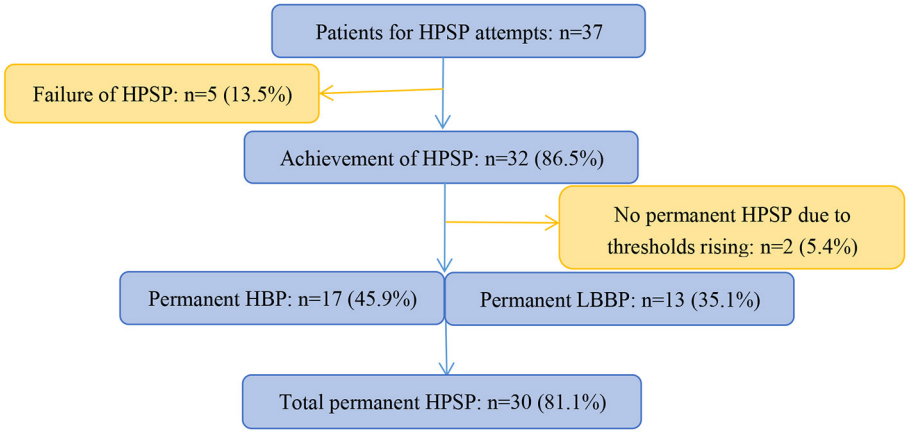

FIGURE 3 | Schematic summary of study and patient flow. HPSP, His-Purkinje system pacing; HBP, His bundle pacing; LBBP, left bundle branch pacing.

by the program could be increased to fulfill higher pacing ratio. After pacemaker was implanted, patients who were readmitted for HF or cardiac mortality would be recorded by phone, and the date of event would be recorded. Major adverse cardiovascular events (MACE) were defined as the composite endpoint of readmission for HF and cardiac mortality.

Statistical Analyses

Continuous variables were expressed as mean ± standard deviation (SD) in normal distribution and median ± interquartile in non-normal distribution. Categorical variables were presented as number of patients (%). Receiver operating characteristic (ROC) analysis was performed to determine the optimal cut-off point of pacing proportion to predict MACE, and area under curve (AUC) was calculated as a measure of test accuracy. The independent sample *T* test was used for normal distribution continuous variables to compare the baseline characteristics between high pacing proportion (HPP) and low pacing proportion (LPP), Mann Whitney U test was used for non-normal distribution continuous variables, and Pearson Chi-square test was used for category variables. Paired *T* tests were performed to compare the differences between the baseline time and half year follow-up time. MACE rate curves were constructed using the Kaplan-Meier method stratified by HPP and LPP, and were compared by log rank tests. All data management and statistical analyses were carried out using the SPSS version 24.0. All statistical tests were two-tailed, and $P < 0.05$ was considered to be statistically significant.

RESULTS

Implantation Results, Device Electrical Parameters and Patient Characteristics

In all 37 enrolled patients, HPSP were attempted (**Figure 3**). Failure of HPSP occurred in 5 of these patients (13.5%). HPSP was achieved in the remaining 32 patients (86.5%). Two patients did not achieve permanent HPSP due to thresholds rising (5.4%). Of the 30 patients with HPSP, 17 patients attempted permanent HBP (6 with S-HBP and 11 with NS-HBP), and 13 patients attempted LBBP. HPSP was performed in 13 patients with single-chamber pacemakers, 11 patients with dual-chamber pacemakers, 5 patients with dual-chamber implanted defibrillators, and 1 patient with CRT pacemakers.

HBP threshold, sensed R-wave amplitude, lead impedance at time of implant was 1.29 ± 0.47 V, 7.14 ± 4.13 mV, 357.5 ± 25.6 Ω, respectively. HBP threshold, sensed R-wave amplitude, lead impedance at time of half year follow-up was 1.52 ± 0.82 V, 7.29 ± 4.21 mV, 362.1 ± 45.7 Ω, respectively. LBBP threshold, sensed R-wave amplitude, lead impedance at time of implant was 0.88 ± 0.227 V, 16.19 ± 4.00 mV, 608.3 ± 69.9 Ω, respectively. LBBP threshold, sensed R-wave amplitude, lead impedance at time of half year follow-up was 0.78 ± 0.28 V, 17.25 ± 3.78 mV, 574.3 ± 77.2 Ω, respectively.

LBBB was present in 10 patients. RBBB was present in 5 patients. The native QRSd of 30 patients was 121.4 ± 29.5 ms, and the pacing QRSd was shortened to 111.8 ± 15.9 ms.

The follow-up period was 15.1 ± 9.4 months. The median follow-up period was 12.0 months. During the follow-up period, 2 patients were readmitted to hospital due to HF and 4 patients died of cardiac origin. **Figure 4** shows the predictive ability of pacing proportion for MACE by ROC analysis. The AUC of pacing proportion for predicting MACE was 0.830 (SE = 0.140, 95% confidence interval (CI):0.649–0.941, $p = 0.018$), indicating that pacing proportion had a significant predictive value for the prognosis of AF patients with HF. ROC analysis showed that the optimal threshold for pacing proportion to predict MACE was 71% (sensitivity:83.3%, specificity: 91.7%).

Baseline Characteristics of Patients Under High and Low Pacing Proportion

HPP was defined as pacing proportion>71% ($n = 23$), LPP was defined as pacing proportion≤71% ($n = 7$). Detailed baseline characteristics of patients were summarized in **Table 1**. Characteristics of patients such as gender, age, systolic blood pressure, heart rate, hypertension, diabetes, coronary heart

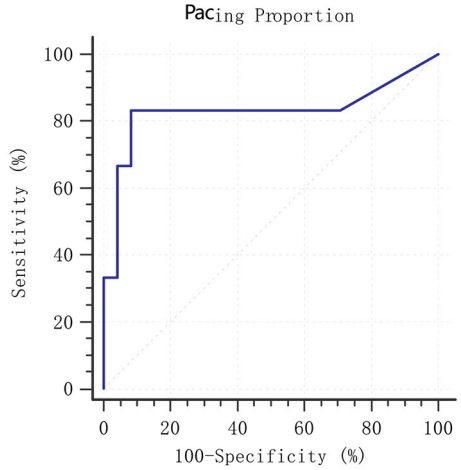

FIGURE 4 | ROC analysis of pacing proportion for prediction of MACE. MACE: composite endpoint of readmission for HF and cardiac mortality; ROC, receiver operating characteristic; MACE, major adverse cardiovascular events. HF, heart failure.

disease, percutaneous coronary intervention (PCI) history, smoking, hemoglobin, albumin, creatinine, NT-proBNP, native QRSd, LVEF, HBP were comparable between HPP group and LPP group (all $p > 0.05$). The dosages of β-blockers in HPP group were significantly lower than those in LPP group ($p = 0.018$).

Clinical Outcomes and Echocardiographic Changes of Patients Under High and Low Pacing Proportion

After half year of HPSP, there were significant overall improvements in NYHA class, NT-proBNP and LVEF in HPP group at half-year follow-up from the baseline. There were no significant changes of NT-proBNP, LVEF and LVEDD in LPP group at half-year follow-up from the baseline (**Table 2**).

Subgroup Analysis of Different QRSd and LVEF Patients for Clinical Outcomes and Echocardiographic Changes

All patients were divided into two subgroups based on QRSd: wide QRS complex group with QRS>120 ms ($n = 15$) and narrow QRS complex group with QRS≤120 ms ($n = 15$); and they were also divided into two subgroups based on LVEF: the HFpEF group with LVEF ≥40% ($n = 18$) and HFrEF group with LVEF<40% ($n = 12$).

In condition of HPP (>71%), NT-proBNP was reduced to 1,085 ± 2,074 ng/L after half year of HPSP from the baseline 2,757 ± 2,835 ng/L in patients of QRS>120 ms ($p = 0.010$), and to 1,219 ± 1,032 ng/L from baseline 2,930 ± 2,897 ng/L in the patients of QRS≤120 ms ($p = 0.032$). NYHA class was improved to 1.6 ± 0.9 after half year of HPSP from the baseline 3.2 ± 0.8 in patients of QRS>120 ms ($p < 0.001$), and to 1.6 ± 0.5 after HPSP from the baseline 3.0 ± 0.7 in patients of QRS≤120 ms ($p < 0.001$). NT-proBNP was reduced to 1,744 ± 2,472 ng/L after half year of HPSP from the baseline 4,205 ± 4,044 ng/L in HFrEF patients ($p = 0.032$), and to 840 ± 747 ng/L from baseline 2,123 ± 1,598 ng/L in the HFpEF patients ($p = 0.010$). NYHA class was improved to 1.9 ± 1.0 after half year of HPSP from the baseline 3.5 ± 0.8 in HFrEF patients ($p = 0.003$) and to 1.4 ± 0.5 after HPSP from the baseline 2.8 ± 0.6 in HFpEF patients ($p < 0.001$).

In condition of LPP (≤71%), after half year of HPSP, there were no significant changes of NT-proBNP and NYHA class in patients of QRS>120 ms (2.259 ± 2,107 ng/L, vs. baseline 2,760 ± 1634 ng/L, $p = 0.529$; 2.8 ± 1.1, vs. baseline 3.6 ± 0.5, $p = 0.099$), and QRS≤120 ms (2,709 ± 2,331 ng/L, vs. baseline 5,320 ± 4,267 ng/L, $p = 0.359$; 2.0 ± 0.0, vs. baseline 3.0 ± 0.0, $p = 0.225$). After half year of HPSP, there were no significant changes of NT-proBNP and NYHA class in HFrEF patients (2,870 ± 2,107 ng/L, vs. baseline 5,111 ± 3,399 ng/L, $p = 0.306$; 3.0 ± 0.8, vs. baseline 3.8 ± 0.5, $p = 0.058$)and HFpEF patients (1,985 ± 2,174 ng/L, vs. baseline 2,329 ± 1,756 ng/L, $p = 0.363$; 2.0 ± 1.2, vs. baseline 3.0 ± 0.0, $p = 0.182$).

Echocardiographic changes of HPP and LPP patients with different QRSd and LVEF were summarized in **Figure 5**.

TABLE 1 | Baseline clinical characteristics of patients under high and low pacing proportion.

Variables	High pacing proportion	Low pacing proportion	*P*-value
N	23	7	
Gender male	15 (65.2%)	5 (71.4%)	0.760
Age (years)	74.0 ± 10.8	69.0 ± 6.6	0.157
Systolic blood pressure (mmHg)	141.7 ± 26.5	131.3 ± 26.9	0.373
Heart rate (bpm)	84.5 ± 25.2	89.4 ± 36.3	0.685
Hypertension	14 (60.9%)	5 (71.4%)	0.612
Diabetes mellitus	9 (39.1%)	3 (42.9%)	0.860
Coronary heart disease	11 (47.8%)	3 (42.9%)	0.818
PCI history	2 (8.7%)	1 (14.3%)	0.666
Smoking	9 (39.1%)	4 (57.1%)	0.400
Hemoglobin (g/L)	134.3 ± 22.6	146.7 ± 24.8	0.222
Albumin (g/L)	36.9 ± 4.4	35.7 ± 3.6	0.531
Creatinine (umol/L)	91.4 ± 22.1	92.6 ± 20.1	0.897
NT-proBNP (ng/L)	1740 (1108–4123)	3013 (1406–4908)	0.207
Native QRSd (ms)	120.0 ± 30.2	125.7 ± 29.1	0.664
LVEF (%)	46.4 ± 14.6	42.3 ± 16.3	0.525
HBP	13 (56.5%)	4 (57.1%)	0.977
Pacing proportion (%)	93.7 ± 8.6	54.1 ± 16.8	<0.001
β-blockers (mg daily)	59.9 ± 52.1	120.6 ± 68.5	0.018
Angiotensin II receptor blockers	15 (65.2%)	7 (100.0%)	0.068
Diuretics	7 (30.4%)	4 (57.1%)	0.199

PCI, percutaneous coronary intervention; NT-proBNP, N-terminal pro-brain natriuretic peptide; QRSd, QRS duration; LVEF, left ventricular ejection fraction; HBP, His bundle pacing.

Data are presented as numbers (%), mean ± standard deviation, or median and interquartile range as appropriate and groups were compared using the Student's T test, Mann–Whitney U test or chi-square test as appropriate.

TABLE 2 | Clinical outcomes and echocardiographic changes of patients under high and low pacing proportion.

		NYHA class	NT-proBNP (ng/L)	LVEDD (mm)	LVEF (%)
High pacing proportion	Baseline	3.1 ± 0.8	2,916 ± 2,849	55.1 ± 8.3	46.0 ± 14.7
	Half year follow-up	1.6 ± 0.7	1,187 ± 1,609	52.4 ± 7.1	53.4 ± 10.5
	P-value	<0.001	0.014	0.009	0.001
Low pacing proportion	Baseline	3.4 ± 0.5	3,720 ± 2,913	63.0 ± 13.7	44.1 ± 16.0
	Half year follow-up	2.5 ± 1.1	2,428 ± 2,035	62.1 ± 12.9	44.9 ± 13.7
	P-value	0.021	0.206	0.429	0.700

NYHA class, New York Heart Association class; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction. Data are presented as mean ± standard deviation and groups were compared using the paired T tests.

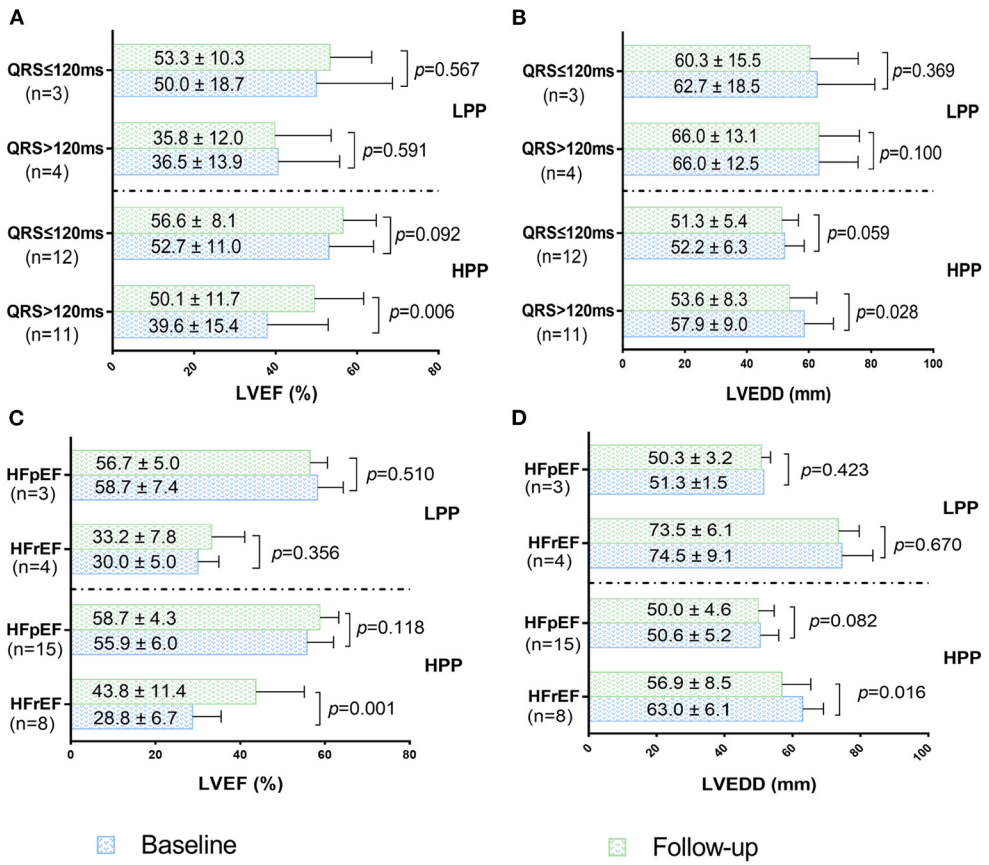

FIGURE 5 | LVEF changes of patients with wide QRS complex and narrow QRS complex under HPP and LPP **(A)**. LVEDD changes of patients with wide QRS complex and narrow QRS complex under HPP and LPP **(B)**. LVEF changes of patients with HFpEF and HFrEF under HPP and LPP **(C)**. LVEDD changes of patients with HFpEF and HFrEF under HPP and LPP **(D)**. HPP, high pacing proportion; LPP, low pacing proportion; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic dimension; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Compared with baseline echocardiographic parameters, LVEF significantly increased while LVEDD decreased in HFrEF and wide QRS complex (QRS>120 ms) patients when pacing proportion>71%. However, moderate but no significant improvements of LVEF and LVEDD were observed in HFpEF and narrow QRS complex (QRS≤120 ms) patients. In condition of pacing proportion≤71%, HFrEF and HFpEF patients showed no significant change in LVEF and LVEDD after half year of HPSP treatment regardless of QRSd (**Figure 5**).

Kaplan-Meier Curves Analysis for MACE Under High and Low Proportion

Kaplan-Meier survival curves analysis were performed for MACE in all patients under different pacing proportion. It showed that

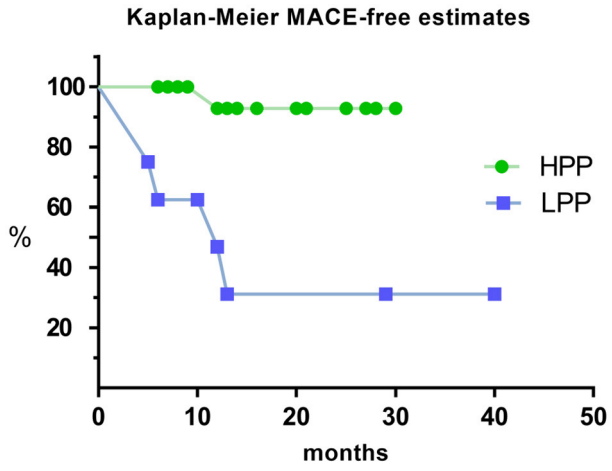

FIGURE 6 | Kaplan–Meier estimate for MACE of HPP and LPP. MACE: composite endpoint of readmission for HF and cardiac mortality. MACE, major adverse cardiovascular events; HPP, high pacing proportion; LPP, low pacing proportion.

patients in LPP had significantly higher MACE rate than patients in HPP (Log Rank test, $p < 0.001$; **Figure 6**).

DISCUSSION

Ventricular rhythm is irregular in AF with or without rapid ventricular rate. Fast ventricular rate has an acknowledged deleterious impact upon left ventricular systolic function (14, 15), and ventricular irregular rhythm itself also has adverse effects on left ventricular systolic function (4). Therefore, the treatment of AF should focus on rate control and rhythm control. HPSP combined with AVN ablation can not only achieve rate control and rhythm control, but also utilize the complete His-Purkinje pathway, which is beneficial to synchronous ventricular activation (16). If AF is complicated with BBB and wide QRS complex, whether LBBB or RBBB pattern, HPSP can overcome ventricular systolic asynchrony and improve cardiac function by correcting conduction block (17, 18). In patients with AF without AVN ablation,β-blockers can inhibit AVN conduction function and reduce intrinsic heart rate to achieve high proportion of HPSP and fulfill the purpose of rate control and rhythm control.

In this study, we found that higher pacing proportion of HPSP could significantly improve the clinical outcomes and echocardiographic results of AF patients complicated with HF. The clinical characteristics such as age, gender, co-morbidities, hepatic and renal function, cardiac function in HPP patients were similar to those in LPP. Therefore, the discrepancy of therapeutic effect between HPP and LPP could be attributed to pacing proportion itself. Nabeta et al. demonstrated that increasing the dose of β-blockers was an independent factor to improve the prognosis of HF patients treated with CRT (19). In our study, β-blockers dosage (59.9 ± 52.1 mg daily) (medication duration 5.04 ± 1.19 months) in HPP was significantly lower than that (120.6 ± 68.5 mg daily) (medication duration 4.71 ± 1.25 months) in LPP ($p = 0.018$), indicating that the clinical benefits of patients in HPP were further ascribed to the higher pacing proportion.

Boczar et al. showed that improvements in HF symptoms using NYHA classification based on severity, reduction of LVEDD, improvement of LVEF, were observed CRT in wide QRS complex (159.2 ± 28.6 ms) patients with AF and HF by implanting HB lead (17). In this study, HBP achieved an average pacing percentage of 97% through the optimization of medical therapy and appropriate device programming (17). Hayes et al. observed the proportion of biventricular pacing (BVP) > 98% could significantly reduce mortality rate (20). Jacobsson et al. also demonstrated that AF was associated with poor prognosis in patients with CRT, due to AF resulting in a decrease in the proportion of BVP. The proportion of BVP≤98% was an independent risk factor for poor prognosis in patients with CRT (21). Our study found that the effect could be observed when the proportion of HPSP was more than 71% in wide QRS complex AF patients with HF. The relatively low pacing ratio of HPSP to achieve therapeutic effect seemly presented its potential advantages over BVP. Furthermore, Arnold et al. demonstrated BVP still produced a non-physiological activation pattern (22), indicating the physiology of BVP inferior to that of HPSP, and Arnold et al. also found that HBP could provide better ventricular resynchronization and hemodynamic feedback than BVP (22). The study above gave us the plausibility of HPSP superior to BVP for HF complicated with AF. However, in 2019, a pilot head-to-head study comparing HBP with BVP demonstrated that HBP produced greater QRSd reduction than BVP, but no significant improvements in echocardiographic parameters as compared with BVP (23). In this first randomized controlled trials (RCT), high rate of crossover from HBP to BVP compromised the assessment of HBP efficacy, and half crossover exhibited non-specific intraventricular conduction delay which cannot be corrected by HBP, thus efficacy of HBP was offset. The discrepancy of pacing proportion in our study might be caused by not only pacing modes, but also the difference of native QRSd in study population. QRSd of the wide QRS complex patients in our study was 146.1 ± 18.9 ms, thus the degree of ventricular activation asynchrony was lower than that of the patients with CRT implantation (17, 21). The detrimental impact of native activation on ventricular remodeling was relatively low, suggesting a relatively low pacing proportion needed to achieve clinical benefits. On the basis of the above reasons, it is preliminarily explained the relatively low pacing proportion sufficient to improve the clinical condition compared with previous studies. Previous studies on paroxysmal AF complicated with HF revealed that the longer the sinus rhythm (SR) time (≥61%) was maintained, the more significant the improvement of life quality, 6-min walk test and NYHA classification were observed (24). For persistent AF patients with HPSP, ventricular activation sequence and rhythm are similar to those of SR. However, considering AF has not been corrected, the atrium loses contraction function and impairs 20% of cardiac output compared with SR in patients with paroxysmal AF (25). Therefore, SR time >61% was enough to achieve the purpose of treatment. Furthermore, QRSd of the patients included in this study was 114 ± 30 ms (24), ventricular synchronization was

even better than that of our study (QRSd = 121.4 ± 29.5 ms). As for HPSP application for persistent AF patients with HF, the analysis above gives a tendency that when the native QRSd is greater than pacing QRSd, the longer the native QRSd is, the higher pacing proportion of resynchronization therapy is needed to achieve clinical benefits. There could be a lower limit for the pacing proportion required for the effective treatment, but the establishment of the lower limit still needs further exploration.

In narrow QRS complex (< 120 ms) persistent AF patients with HF, regular paced ventricular rhythm by HPSP was a primary hemodynamic benefit due to the absence of BBB (26). Our study found that there were significant improvement of NYHA class and NT-proBNP when HPP was applied, but no significant improvements were observed in echocardiographic measurements. Deshmukh et al. performed AVN ablation and HBP in patients with narrow QRS complex (< 120 ms) AF and dilated cardiomyopathy, which showed the improvement of LVEDD and LVEF (11). Huang et al. implemented AVN ablation and HBP for patients with narrow QRS complex (107.1 ± 25.8 ms) AF and HF, and the echocardiographic parameters were also improved (12). Compared with the results of previous studies, the difference in the improvement of echocardiography in our study was related to the fact that our subjects did not undergo AVN ablation, and the pacing proportion was <100%. Therefore, AVN ablation was recommended for these patients to increase the pacing proportion to 100%, in order to further improve the therapeutic effect.

Our study found that HPSP proportion had a good predictive ability for MACE in persistent AF patients with HF (AUC = 0.830). The optimal cut-off point of pacing proportion related to prognosis was 71% during the follow-up period of 15.1 ± 9.4 months. Patients with QRSd > 120 ms or HFrEF in HPP group could showed significant improvement in clinical outcomes and echocardiographic results within 6 months after HPSP, which were similar to the results of Huang et al. (12). However, unlike previous studies (12), patients with QRSd ≤ 120 ms or HFpEF in HPP group showed modest, but no significant improvement in echocardiographic results. The discrepancy perhaps resulted from not only the absence of AVN ablation and pacing proportion being <100%, but also follow-up time of 6 months significantly shorter than follow-up time of 21.1 ± 9.3 months of Huang et al. (12). Although there is no clinical evidence of HPSP superior to BVP for patients with HF, 23 patients (76.7%) with LVEF>35% or QRS<130 ms in our study are not candidates for BVP according to 2021 ESC guidelines (9), and results of our study indicate the potential of HPSP in patients with HF who are not eligible for BVP, the potential as an alternative strategy to CRT (27), and the promising future for AF patients with HF.

Our study has some limitations that should be mentioned. This was a retrospective, observational single center study with a small patient population. We expected to perform a large-scale multicenter prospective clinical trial in the future. Furthermore, this study belonged to the self-control study and lacked a control group, so the differences in therapeutic effects of the HPSP group, internal medicine treatment group and catheter ablation group could not be obtained. Randomized controlled trials are expected to be conducted in the future to compare the differences in therapeutic effects of each treatment method. In this study, patients with pacing proportion >71% achieved significant clinical benefits. However, given the limited size of the study population and unevenly distributed pacing proportion, the pacing proportion amounting to 71% could only indicate that the higher the pacing proportion, the greater the clinical benefit. And it could not be interpreted as the lower limit of pacing proportion to achieve effective therapeutic effect. Large-scale observations are necessary to establish a lower limit for pacing proportion.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

REFERENCES

1. Anter E, Jessup M, Callans DJ. Atrial fibrillation and heart failure: treatment considerations for a dual epidemic. *Circulation.* (2009) 119:2516–25. doi: 10.1161/CIRCULATIONAHA.108.821306
2. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Rev Esp Cardiol.* (2017) 70:50. doi: 10.1016/j.rec.2016.11.033
3. Rosenberg MA, Manning WJ. Diastolic dysfunction and risk of atrial fibrillation: a mechanistic appraisal. *Circulation.* (2012) 126:2353–62. doi: 10.1161/CIRCULATIONAHA.112.113233
4. Prabhu S, Voskoboinik A, Kaye DM, Kistler PM. Atrial fibrillation and heart failure - cause or effect? *Heart Lung Circ.* (2017) 26:967–74. doi: 10.1016/j.hlc.2017.05.117
5. Wang S, Wu S, Xu L, Xiao F, Whinnett ZI, Vijayaraman P, et al. Feasibility and efficacy of His bundle pacing or left bundle pacing combined with atrioventricular node ablation in patients with persistent atrial fibrillation and implantable cardioverter-defibrillator therapy. *J Am Heart Assoc.* (2019) 8:e014253. doi: 10.1161/JAHA.119.014253
6. Sultan A, Lüker J, Andresen D, Kuch KH, Hoffmann E, Brachmann J, et al. Predictors of atrial fibrillation recurrence after catheter ablation: data from the german ablation registry. *Sci Rep.* (2017) 7:16678. doi: 10.1038/s41598-017-16938-6

7. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, et al. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med.* (2015) 372:1812–22. doi: 10.1056/NEJMoa1408288
8. Pallisgaard JL, Gislason GH, Hansen J, Johannessen A, Torp-Pedersen C, Rasmussen PV, et al. Temporal trends in atrial fibrillation recurrence rates after ablation between 2005 and 2014: a nationwide Danish cohort study. *Eur Heart J*. (2018) 39:442–9. doi: 10.1093/eurheartj/ehx466
9. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, et al. 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. *Europace*. (2022) 24:71–164. doi: 10.1093/europace/euab232
10. Arnold AD, Whinnett ZI, Vijayaraman P. His–Purkinje conduction system pacing: state of the art in 2020. *Arrhythm Electrophysiol Rev.* (2020) 9:136–45. doi: 10.15420/aer.2020.14
11. Deshmukh P, Casavant DA, Romanyshyn M, Anderson K. Direct His-bundle pacing: a novel approach to cardiac pacing in patients with normal His-Purkinje activation. *Circulation.* (2000) 101:869–77. doi: 10.1161/01.CIR.101.8.869
12. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, et al. Benefits of permanent his bundle pacing combined with atrioventricular node ablation in atrial fibrillation patients with heart failure with both preserved and reduced left ventricular ejection fraction. *J Am Heart Assoc.* (2017) 6:e005309. doi: 10.1161/JAHA.116.005309
13. Vijayaraman P, Subzposh FA, Naperkowski A. Atrioventricular node ablation and his bundle pacing. *Europace.* (2017) 19:iv10–16. doi: 10.1093/europace/eux263
14. Patel HJ, Pilla JJ, Polidori DJ, Pusca SV, Plappert TA, Sutton MS, et al. Ten weeks of rapid ventricular pacing creates a long-term model of left ventricular dysfunction. *J Thorac Cardiovasc Surg.* (2017) 119:834–41. doi: 10.1016/S0022-5223(00)70021-3
15. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol.* (2014) 7:31–8. doi: 10.1161/CIRCEP.113.000806
16. Lustgarten DL, Calame S, Crespo EM, Calame J, Lobel R, Spector PS. Electrical resynchronization induced by direct His-bundle pacing. *Heart Rhythm.* (2010) 7:15–21. doi: 10.1016/j.hrthm.2009.09.066
17. Boczar K, Sławuta A, Zabek A, Debski M, Vijayaraman P, Gajek J, et al. Cardiac resynchronization therapy with His bundle pacing. *Pacing Clin Electrophysiol.* (2019) 42:374–80. doi: 10.1111/pace.13611
18. Sharma PS, Naperkowski A, Bauch TD, Chan JYS, Arnold AD, Whinnett ZI, et al. Permanent His bundle pacing for cardiac resynchronization therapy in patients with heart failure and right bundle branch block. *Circ Arrhythm Electrophysiol.* (2018) 11:e006613. doi: 10.1161/CIRCEP.118.006613
19. Nabeta T, Inomata T, Iida Y, Ikeda Y, Iwamoto-Ishida, Ishii S, et al. Prognostic significance of beta-blocker up-titration in conjunction with cardiac resynchronization therapy in heart failure management. *Heart Vessels.* (2016) 31:1109–16. doi: 10.1007/s00380-015-0711-z
20. Hayes DL, Boehmer JP, Day JD, Gilliam FR 3rd, Heidenreich PA, Seth M, et al. Cardiac resynchronization therapy and the relationship of percent biventricular pacing to symptoms and survival. *Heart Rhythm.* (2011) 8:1469–75. doi: 10.1016/j.hrthm.2011.04.015
21. Jacobsson J, Reitan C, Carlson J, Borgquist R, Platonov PG. Atrial fibrillation incidence and impact of biventricular pacing on long-term outcome in patients with heart failure treated with cardiac resynchronization therapy. *BMC Cardiovasc Disord.* (2019) 19:195. doi: 10.1186/s12872-019-1169-1
22. Arnold AD, Shun-Shin MJ, Keene D, Howard JP, Sohaib SMA, Wright IJ, et al. His resynchronization versus biventricular pacing in patients with heart failure and left bundle branch block. *J Am Coll Cardiol.* (2018) 72:3112–22. doi: 10.1016/j.jacc.2018.09.073
23. Upadhyay GA, Vijayaraman P, Nayak HM, Verma N, Dandamudi G, Sharma PS, et al. His corrective pacing or biventricular pacing for cardiac resynchronization in heart failure. *J Am Coll Cardiol.* (2019) 74:157–9. doi: 10.1016/j.jacc.2019.04.026
24. Suman-Horduna I, Roy D, Frasure-Smith N, Talajic M, Lespérance F, Blondeau L, et al. Quality of life and functional capacity in patients with atrial fibrillation and congestive heart failure. *J Am Coll Cardiol.* (2013) 61:455–60. doi: 10.1016/j.jacc.2012.10.031
25. Mukharji J, Rehr RB, Hastillo A, Thompson JA, Hess ML, Paulsen WJ, et al. Comparison of atrial contribution to cardiac hemodynamics in patients with normal and severely compromised cardiac function. *Clin Cardio.* (1990) 13:639–43. doi: 10.1002/clc.4960130910
26. Padeletti L, Fantini F, Michelucci A, Pieragnoli P, Colella A, Musilli N, et al. Rate stabilization by right ventricular apex or His bundle pacing in patients with atrial fibrillation. *Europace.* (2005) 7:454–9. doi: 10.1016/j.eupc.2005.05.007
27. Lewis AJM, Foley P, Whinnett Z, Keene D, Chandrasekaran B. His bundle pacing: a new strategy for physiological ventricular activation. *J Am Heart Assoc.* (2019) 8:e010972. doi: 10.1161/JAHA.118.010972

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

MINI REVIEW
published: 09 March 2022
doi: 10.3389/fcvm.2022.835493

The Physiologic Mechanisms of Paced QRS Narrowing During Left Bundle Branch Pacing in Right Bundle Branch Block Patients

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Left bundle branch pacing (LBBP) is a physiological pacing technique that captures the left bundle branch (LBB) directly, causing the left ventricle (LV) to be excited earlier than the right ventricle (RV), resulting in a "iatrogenic" right bundle branch block (RBBB) pacing pattern. Several studies have recently shown that permanent LBBP can completely or partially narrow the wide QRS duration of the intrinsic RBBB in most patients with bradycardia, although the mechanisms by which this occurs has not been thoroughly investigated. This article presents a review of the LBBP in patients with intrinsic RBBB mentioned in current case reports and clinical studies, discussing the technique, possible mechanisms, future clinical explorations, and the feasibility of eliminating the interventricular dyssynchronization accompanied with LBBP.

Keywords: left bundle branch pacing, right bundle branch block, QRS complex, longitudinal dissociation, anodal stimulation

OPEN ACCESS

Edited by:
Matteo Anselmino, University of Turin, Italy

Reviewed by:
Hussam Ali, Center for Clinical Arrhythmology and Electrophysiology, MultiMedica Holding SpA, Scientific Institute for Research, Hospitalization and Healthcare (IRCCS), Italy

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Specialty section:
This article was submitted to Cardiac Rhythmology, a section of the journal Frontiers in Cardiovascular Medicine

Received: *14 December 2021*
Accepted: *16 February 2022*
Published: *09 March 2022*

Citation:
Zhu K, Sun Y, Lin M, Deng Y, Li L, Li G, Liu J, Wan X, Chang D and Li Q (2022) The Physiologic Mechanisms of Paced QRS Narrowing During Left Bundle Branch Pacing in Right Bundle Branch Block Patients. Front. Cardiovasc. Med. 9:835493. doi: 10.3389/fcvm.2022.835493

INTRODUCTION

For decades, right ventricular pacing (RVP) has been the standard treatment for patients with symptomatic bradyarrhythmia caused by sinus node dysfunction or atrioventricular conduction disease. RVP, however, has been established to cause electrical and mechanical dyssynchronization, which increases the risk of cardiac dysfunction, heart failure hospitalization, atrial fibrillation, and a higher mortality rate (1–3). Therefore, His bundle pacing (HBP), a physiologic pacing strategy, has been developed. Multiple observational studies have demonstrated the feasibility and therapeutic advantages of HBP in maintaining cardiac synchrony (4–9). However, the clinical applicability of HBP is restricted due to its high pacing threshold, low sensing amplitude, and technically challenging of implantation (6, 10, 11).

Left bundle branch pacing (LBBP) is a novel physiological pacing technique in which a Select Secure lead (Model 3830 69 cm, Medtronic Inc., Minneapolis, MN, United States) delivered through the Select Site preshaped sheath (C315HIS, Medtronic Inc., Minneapolis, MN, United States) is deeply rotated via a transventricular septal approach to capture the left bundle branch (LBB), including the trunk and its proximal branches. When compared to HBP, LBBP has been shown to be effective, feasible, and safe for correcting LBB block and maintaining physiological left ventricle (LV) activation, with a greater success rate and more stable lead parameters (12–16). But little is known about LBBP in patients with intrinsic right bundle branch block (RBBB) who have pacemaker indications.

LEFT BUNDLE BRANCH PACING TECHNIQUE AND ECG FEATURES

The presence of a paced RBBB pattern is a required but insufficient criterion for confirmation of LBB capture with a sensitivity of 100% (17). When the lead is advancing from the right ventricular septum to the left, the morphology of paced QRS complex changes dynamically, as seen by the W-shaped notch at the nadir of the QRS complex in lead V1 gradually moving to the end of that and eventually presenting a pseudo-RBBB pattern (13, 14). This is because LBBP can directly capture the LBB, causing the excitation of the left ventricular lateral wall to be to accelerated while the excitation of the right ventricle (RV) to be delayed (17–20). LBBP can be divided into two types: selective LBBP (SLBBP), which involves only LBB capture, and non-selective LBBP (NSLBBP), which involves LBB and surrounding myocardium capture. At a low output, SLBBP is achieved, with a typical paced RBBB morphology (QRS duration $>$ 0.12 s, rSR' pattern in leads V1 and V2, wide and slurred S wave in leads V6 and I). At a high pacing output, NSLBBP is achieved, with an atypical paced RBBB morphology (QR pattern and narrow R without a distinct notch in lead V1, narrow and small S wave without a notch in leads V6 and I) (17, 21).

LEFT BUNDLE BRANCH PACING IN RIGHT BUNDLE BRANCH BLOCK PATIENTS

Although the excitation sequence of LBBP in RBBB patients is comparable to that of the original, the morphology of paced RBBB differs dramatically from that of intrinsic RBBB. Gao et al. (19) compared the ECG characteristics of LBBP to those of intrinsic RBBB, and discovered that the majority of the QRS morphology in lead V1 of LBBP showed a Qr pattern, whereas the majority of intrinsic RBBB showed a rsR' pattern. Furthermore, they described an RBBB patient who completed SLBBP with the same terminal R' wave duration of 76 ms as the intrinsic, but which reduced to 58 ms as output increased, suggesting that NSLBBP could compensate for RV delay by capturing a portion of cardiomyocytes, which is consistent with the findings of the other studies (22, 23). According to Li et al. (15), 8 atrioventricular block (AVB) patients with RBBB completed LBBP, with five RBBB corrected successfully by bipolar LBBP at a low output or unipolar pacing at relatively high output. Several other studies have also suggested that LBBP might be a viable choice to correct the RBBB (24, 25). Lin et al. (26) employed unipolar LBBP to shorten the RBBB duration from 137.7 $\pm$ 19.2 ms to 118.7 $\pm$ 6.7 ms, and bipolar LBBP to shorten the RBBB duration even further to 105.0 $\pm$ 5.0 ms, eliminating interventricular conduction delay. Previous studies have also shown that LBBP can shorten the QRS duration of intrinsic RBBB by about 30ms (27), as summarized in **Table 1**. In the following article, we present two cases of LBBP shortening RBBB and not shortening RBBB (**Figures 1A,D**), and the sheath angiography of the first case (**Figure 1B**). We will focus on the potential mechanisms underlying paced QRS narrowing during LBBP in RBBB patients (**Figure 1C**), including the anatomy and electrophysiology of the His-Purkinje system, classical and possible alternative understandings of longitudinal dissociation and transverse interconnection, output dependence of transition from SLBBP to NSLBBP, components captured of unipolar tip pacing configuration (UTP) and bipolar tip pacing configuration (BTP).

ANATOMY AND ELECTROPHYSIOLOGY OF HIS-PURKINJE SYSTEM

The His-Purkinje system is composed predominantly of longitudinally oriented Purkinje cells, which have a conduction velocity of 2.3 m/s and are specialized for rapid conduction, whereas the ventricular muscle is composed of working myocardial cells with typical intercalated discs and has a conduction velocity is only 0.75 m/s (28, 29). His bundle travels within the inferior margin of the membranous septum before dividing into the LBB and right bundle branch (RBB) at the subjacent left side of the crest of the muscular interventricular septum (30).

The LBB is a broad ribbon-like structure that emerges beneath the endocardium of the non-coronary cusp of the aortic valve and divides into a thin left anterior fascicle (LAF) and a broad left posterior fascicle (LPF) (29, 31, 32). The ribbon-like structure and rich interfascicular connections of LBB provide an anatomical foundation for the LBBP. The RBB is a cord-like structure that most commonly originates at an obtuse angle from the His bundle (HB) or merges as a continuation of a rightward HB (29, 30, 33). Because of its slender anatomical structure and blood supply only from the right coronary artery, the RBB is prone to injury.

Longitudinal dissociation theory, that is, LBB and RBB were predominantly separated longitudinally inside the HB by collagen sheaths (29, 34), but only at a distance of less than 2-3 mm (35). The existence of transverse interconnection in the HB and the proximal bundle branches was proven by Lazzara et al. (36), and the existence of transverse interconnection in RBB was undisputed. RBBB narrowing by LBBP may be transversally propagated from LBB to RBB by stimulation bypassing the blocking site. However, the transverse velocity of the bundle branches is significantly lower than longitudinal velocity (36), it is not clear whether the lateral capture of RBB can compensate for the excitation delay of RV caused by intrinsic RBBB. Besides, if transverse interconnection coexists alongside longitudinal dissociation, LBBP should not take an RBBB pattern when the right conduction system is normal, yet this is not the case.

OUTPUT DEPENDENCE OF TRANSITION FROM SLBBP TO NSLBBP

SLBBP is characterized by the isoelectric interval between the pacing artifact and the V wave in the intracardiac

TABLE 1 | Summary of studies demonstrating paced QRS narrowing during LBBP in RBBB.

Study	RBBB QRS duration (ms)	Paced QRS duration (ms)	Stim-LVAT (ms)	Number of RBBB patients	Success narrowing rate
Li et al. (15)	120	106	None	8	62.5%
Zhu et al. (22)	169	114 (low output UTP)/ 104 (high output UTP)	80	1	None
Li et al. (23)	143.1 ± 16.6	122.9 ± 10.3	77.4 ± 8.0 (low output UTP)/ 75.8 ± 7.5 (high output UTP)	27	88.8%
Jiang et al. (24)	150 ± 13	121 ± 15	86 ± 15	33	75.7%
Chu et al. (25)	141	109 (low output UTP)/ 106 (high output UTP)	None	1	None
Lin et al. (26)	137.7 ± 19.2	118.7 ± 6.7 (UTP)/105.0 ± 5.0 (BTP)	82.0 ± 5.2 (UTP)/ 78.3 ± 3.9 (BTP)	6	75% (BTP)
Zhu et al. (27)	144.31 ± 4.83	114.26 ± 5.09 (UTP)/ 116.7 ± 46.29 (BTP)	None	32	None

LBBP, left bundle branch pacing; RBBB, right bundle branch block; Stim-LVAT, stimulus to left ventricular peak activation time; UTP, unipolar tip pacing configuration; BTP, bipolar tip pacing configuration.

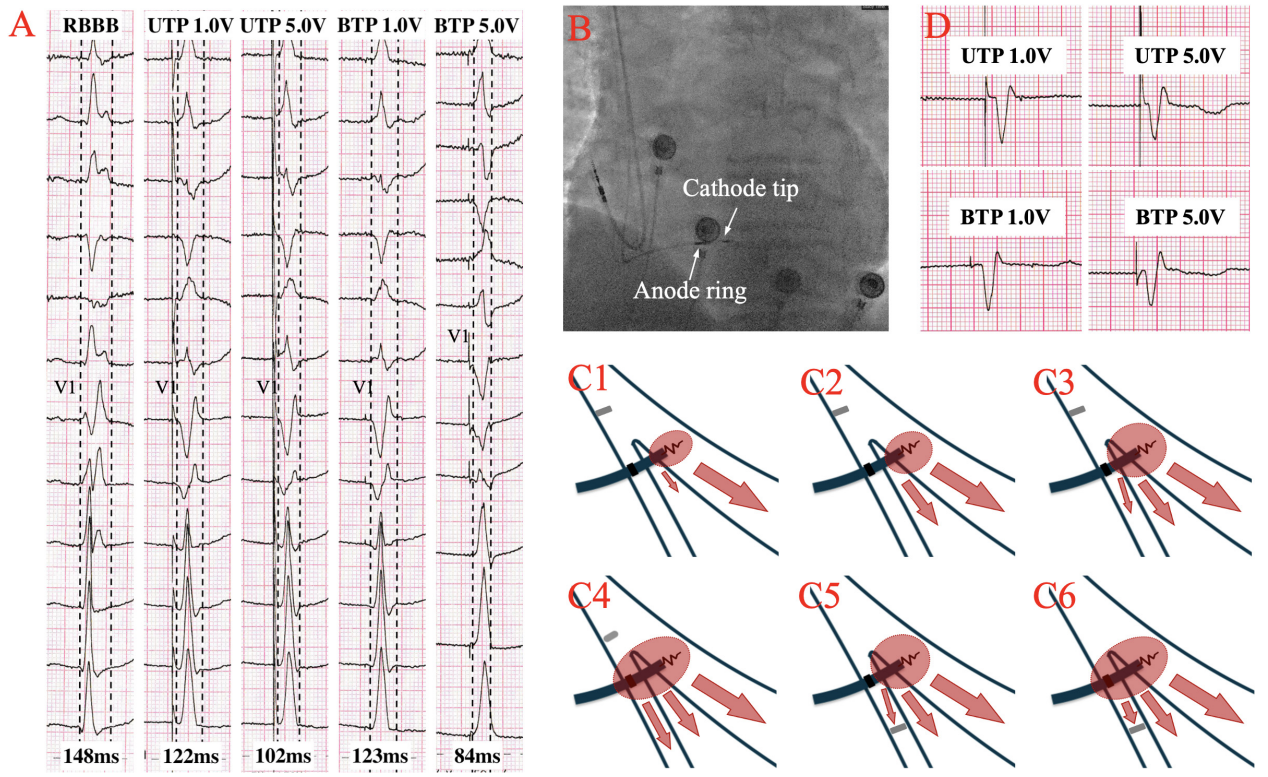

FIGURE 1 | (A) The QRS morphologies of intrinsic right bundle branch block (RBBB) under different pacing configurations of left bundle branch pacing (LBBP) at speed of 50 mm/s. QRS duration is shortened from intrinsic 148–122 ms at low output unipolar LBBP, and is further shortened to 102 ms at high output. The paced QRS morphology does not change significantly in unipolar pacing with low or high outputs, both presented a Qr pattern in lead V1. At low output bipolar LBBP, the paced QRS duration is 123 ms, which was similar to the performance at low output unipolar LBBP. However, at high output bipolar LBBP, the paced QRS duration is shortened to 84ms, and the paced QRS morphology changes significantly, showing that the r' wave at the end of the QRS in lead V1 disappeared, suggesting the RV delay was compensated. **(B)** Sheath angiography of 3830 lead after LBBP completion. **(C1–C6)** Schematic diagram of different pacing modes of LBBP performed on RBBB. **(C1–C3)** Low output unipolar LBBP only captures the left bundle branch (LBB) and a small portion of the surrounding myocardium to partially shorten the RBBB. High-output unipolar LBBP captures LBB and more surrounding myocardium, further shortening RBBB, and may even overcome the resistivity of fibrous sheaths of longitudinal dissociation to completely correct RBBB. **(C4)** High output bipolar LBBP captures both LBB and RBB to completely correct RBBB. **(C5,C6)** When conduction delay occurs at the terminal branch of the RBB, neither the unipolar nor bipolar LBBP can bypass the blockage. **(D)** A case with no significant changes in QRS morphology and duration of RBBB under different LBBP modes, suggesting that RBB distal block might be involved.

electrocardiogram, which indicates that only left conduction system is captured, resulting a typical RBBB pattern (17, 21). In patients with complete RBBB, the terminal R' duration in lead V1 after SLBBP was consistent with the original, indicating that SLBBP could only accelerate LV excitation (19). SLBBP transforms into NSLBBP as output increases, capturing LBB and surrounding myocardium, presenting an atypical RBBB pattern, and shortening QRS duration (17). The terminal R' duration of intrinsic RBBB in lead V1 similarly decreased as the output increased (19). However, the stimulus to left ventricular peak activation time (Stim-LVAT) remains constant and short in both SLBBP and NSLBBP regardless of output.

Li et al. (23) believed that low-output LBBP might capture LBB and surrounding myocardium, resulting in an incomplete RBBB pattern due to the delayed conduction of excitation to the distal RBB. High-output stimulation, on the other hand, was able to capture LBB, surrounding myocardium and RBB, shortening the RBBB QRS duration even further (15) (**Figures 1A,C1–C3**). While the emphasis remained on longitudinal dissociation theory and the necessity for high pacing output to overcome the resistivity of the fibrous sheath encasing the RBB within the HB. Finally, it is possible that, when the output increases, LBBP can capture more myocardium around LBB and partially compensate for the RV excitation delay caused by RBBB, thereby shortening the paced QRS duration, and even capturing RBB beyond the conduction block to completely correct RBBB.

UNIPOLAR TIP PACING AND BIPOLAR TIP PACING CONFIGURATION

The paced QRS complex with BTP is differs from that with UTP, probably due to anodal capture during bipolar pacing (37). RV anodal capture is observed during cardiac resynchronization therapy treatment using an LV tip-RV ring pacing mode. The high output RV ring anodal capture necessary to stimulate the myocardium might induce depolarization and hyperpolarization regions around the RV ring, that is, virtual electrode polarization effect (38), which can improve cardiac contractility and accelerate conduction velocity (39).

Shimeno et al. (18) observed that the mean threshold of anodal capture in NSLBBP was 4.9 ± 1.2V @ 0.4ms, and that the paced QRS duration was significantly shorter than that without anodal capture (121 ± 9 ms vs. 135 ± 8 ms). Similarly, the average threshold for simultaneous capture of LBB and RBB in cathode tip and anode ring bipolar pacing mode in Lin et al. 's study was 2.7 V @ 0.5 ms (26). LBBP with BTP configuration might also narrow the intrinsic RBBB duration (15, 23). This could be due to anodal capture, in which the anode ring penetrated the right side of the septum in a BTP configuration, allowing LBBP to stimulate the left and right septal myocardium as well as left conduction system simultaneously, partially compensating for the RV excitation delay caused by intrinsic RBBB (**Figures 1A,C4**). However, the output required to correct RBBB by anodal capture has not been reported, necessitating further study.

THE BLOCKAGE SITE OF THE RBB AND THE LEAD TIP SITE OF THE LBBP

The location of RBBB is quite crucial. The existence of two types of RBBB has been confirmed: proximal RBBB, in which conduction interruption occurs at the main right branch of HB, and distal RBBB, in which conduction delay occurs at the terminal part of the RBB (40). According to the longitudinal dissociation theory, a high percentage of RBBB may be in the main right branch of HB (29, 34). However, pacing at the LBB trunk, LAF, and LPF resulted in similar intraventricular and interventricular electrical synchrony, suggesting that the lead tip site of LBBP may not be so important (41). The blockade point in proximal RBBB is above the pacing site of LBBP. Stimulation of LBBP can bypass the blockage to capture RBB by the transverse interconnection between LBB and RBB or anodal capture of anode ring. However, it may be difficult for LBBP to capture RBB in the case of distal RBBB (**Figures 1C5,C6,D**), since it has been observed that RBB was injured at anatomic bifurcation could not be corrected by LBBP regardless of the pacing output (23, 42).

DISCUSSION

The precise mechanisms underlying the paced QRS narrowing during LBBP in RBBB patients remain unclear and are likely multifactorial. The possible mechanism is that high output unipolar pacing overcomes the resistivity of fibrous sheaths of longitudinal dissociation and captures RBB by bypassing the blockage through transverse interconnection, or excites a part of the right septal myocardium by anodal capture of bipolar pacing to compensate for RV delay under the prerequisite that pacing lead of LBBP is placed beyond the block site of RBBB.

RBBB is the electrocardiographic reflection of RV excitation delay caused by RBB sclerosis, fibrosis, or necrosis, and it is associated with an elevated risk of all-cause mortality in patients with cardiac and pulmonary disease. The intrinsic RBBB may be corrected with traditional RVP by adjusting the atrioventricular interval to achieve optimal fusion with the intact LBB, maintaining the physiological LV excitation while correcting the delayed RV excitation. However, many RBBB patients who require a pacemaker may develop complete AVB that is unable to achieve fusion and necessitates 100% RVP. Furthermore, during exercise, atrioventricular conduction may shorten, reducing optimal fusion to some extent. HBP has been reported as a viable alternative for cardiac resynchronization therapy in RBBB patients with advanced heart failure, reduced LV ejection fraction and wide QRS duration (7–9). However, its development has been limited by unsatisfactory electrical parameters and a low success rate. LBBP directly captures LBB to accelerate left ventricular lateral wall excitation to achieve LV synchronization similar to HBP, but to increase interventricular dyssynchronization to result in "iatrogenic" RBBB (16, 20), the long-term outcome of this accompanying effect is unclear. In some pacing configurations, such as high output UTP or BTP, LBBP can partially or even

completely correct intrinsic RBBB. In addition, the combination of LBBP and RVP can to achieve interventricular synchronization with proper biventricular pacing interval. In RBBB patients with high pacing percentage is expected, such as high-degree AVB, more physiological LBBP should be considered. This has sparked interest in whether LBBP can eliminate accompanying RBBB, and even whether LBBP can be an effective pacing therapy for RBBB patients with pacing indications to achieve more homogenous and physiologic interventricular synchronization rather than only intraventricular synchronization. It also makes sense to optimize the structure of pacing leads, such as adjusting the interelectrode distance so that the anode ring may be implanted more readily into the RBB region.

AUTHOR CONTRIBUTIONS

KZ: conceptualization and writing—original draft preparation. YS: writing—original draft preparation. ML, YD, LL, GL, JL, and XW: contribute to our revised draft and provide useful comments. DC and QL: supervision and writing—reviewing and editing. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by research grant no. 3502Z20214ZD1165 from Xiamen Municipal Bureau of Science and Technology.

REFERENCES

1. Thambo JB, Bordachar P, Garrigue S, Lafitte S, Sanders P, Reuter S, et al. Detrimental ventricular remodeling in patients with congenital complete heart block and chronic right ventricular apical pacing. *Circulation.* (2004) 110:3766–72. doi: 10.1161/01.Cir.0000150336.86033.8d
2. Leong DP, Mitchell AM, Salna I, Brooks AG, Sharma G, Lim HS, et al. Long-term mechanical consequences of permanent right ventricular pacing: effect of pacing site. *J Cardiovasc Electrophysiol.* (2010) 21:1120–6. doi: 10.1111/j.1540-8167.2010.01804.x
3. Tops LF, Schalij MJ, Bax JJ. The effects of right ventricular apical pacing on ventricular function and dyssynchrony implications for therapy. *J Am Coll Cardiol.* (2009) 54:764–76. doi: 10.1016/j.jacc.2009.06.006
4. Sharma PS, Dandamudi G, Naperkowski A, Oren JW, Storm RH, Ellenbogen KA, et al. Permanent His-bundle pacing is feasible, safe, and superior to right ventricular pacing in routine clinical practice. *Heart Rhythm.* (2015) 12:305–12. doi: 10.1016/j.hrthm.2014.10.021
5. Abdelrahman M, Subzposh FA, Beer D, Durr B, Naperkowski A, Sun H, et al. Clinical outcomes of his bundle pacing compared to right ventricular pacing. *J Am Coll Cardiol.* (2018) 71:2319–30. doi: 10.1016/j.jacc.2018.02.048
6. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, et al. Long-term outcomes of His bundle pacing in patients with heart failure with left bundle branch block. *Heart.* (2019) 105:137–43. doi: 10.1136/heartjnl-2018-313415
7. Sharma PS, Dandamudi G, Herweg B, Wilson D, Singh R, Naperkowski A, et al. Permanent his-bundle pacing as an alternative to biventricular pacing for cardiac resynchronization therapy: a multicenter experience. *Heart Rhythm.* (2018) 15:413–20. doi: 10.1016/j.hrthm.2017.10.014
8. Lustgarten DL, Crespo EM, Arkhipova-Jenkins I, Lobel R, Winget J, Koehler J, et al. His-bundle pacing versus biventricular pacing in cardiac resynchronization therapy patients: a crossover design comparison. *Heart Rhythm.* (2015) 12:1548–57. doi: 10.1016/j.hrthm.2015.03.048
9. Sharma PS, Naperkowski A, Bauch TD, Chan JYS, Arnold AD, Whinnett ZI, et al. Permanent his bundle pacing for cardiac resynchronization therapy in patients with heart failure and right bundle branch block. *Circ Arrhythm Electrophysiol.* (2018) 11:e006613. doi: 10.1161/circep.118.006613
10. Zanon F, Abdelrahman M, Marcantoni L, Naperkowski A, Subzposh FA, Pastore G, et al. Long term performance and safety of His bundle pacing: a multicenter experience. *J Cardiovasc Electrophysiol.* (2019) 30:1594–601. doi: 10.1111/jce.14063
11. Vijayaraman P, Naperkowski A, Subzposh FA, Abdelrahman M, Sharma PS, Oren JW, et al. Permanent his-bundle pacing: long-term lead performance and clinical outcomes. *Heart Rhythm.* (2018) 15:696–702. doi: 10.1016/j.hrthm.2017.12.022
12. Guo J, Li L, Meng F, Su M, Huang X, Chen S, et al. Short-term and intermediate-term performance and safety of left bundle branch pacing. *J Cardiovasc Electrophysiol.* (2020) 31:1472–81. doi: 10.1111/jce.14463
13. Huang W, Chen X, Su L, Wu S, Xia X, Vijayaraman P. A beginner's guide to permanent left bundle branch pacing. *Heart Rhythm.* (2019) 16:1791–6. doi: 10.1016/j.hrthm.2019.06.016
14. Li Y, Chen K, Dai Y, Li C, Sun Q, Chen R, et al. Left bundle branch pacing for symptomatic bradycardia: implant success rate, safety, and pacing characteristics. *Heart Rhythm.* (2019) 16:1758–65. doi: 10.1016/j.hrthm.2019.05.014
15. Li X, Li H, Ma W, Ning X, Liang E, Pang K, et al. Permanent left bundle branch area pacing for atrioventricular block: feasibility, safety, and acute effect. *Heart Rhythm.* (2019) 16:1766–73. doi: 10.1016/j.hrthm.2019.04.043
16. Vijayaraman P, Patel N, Colburn S, Beer D, Naperkowski A, Subzposh FA. His-purkinje conduction system pacing in atrioventricular block: new insights into site of conduction block. *JACC Clin Electrophysiol.* (2021) 8:73–85. doi: 10.1016/j.jacep.2021.07.007
17. Wu S, Chen X, Wang S, Xu L, Xiao F, Huang Z, et al. Evaluation of the criteria to distinguish left bundle branch pacing from left ventricular septal pacing. *JACC Clin Electrophysiol.* (2021) 7:1166–77. doi: 10.1016/j.jacep.2021.02.018
18. Shimeno K, Tamura S, Nakatsuji K, Hayashi Y, Abe Y, Naruko T. Characteristics and proposed mechanisms of QRS morphology observed during the left bundle branch pacing procedure. *Pacing Clin Electrophysiol* (2021) 44:1987–94. doi: 10.1111/pace.14382
19. Gao MY, Tian Y, Shi L, Wang YJ, Xie BQ, Qi J, et al. Electrocardiographic morphology during left bundle branch area pacing: characteristics, underlying mechanisms, and clinical implications. *Pacing Clin Electrophysiol.* (2020) 43:297–307. doi: 10.1111/pace.13884
20. Curila K, Jurak P, Jastrzebski M, Prinzen F, Waldauf P, Halamek J, et al. Left bundle branch pacing compared to left ventricular septal myocardial pacing increases interventricular dyssynchrony but accelerates left ventricular lateral wall depolarization. *Heart Rhythm.* (2021) 18:1281–9. doi: 10.1016/j.hrthm.2021.04.025
21. Chen X, Wu S, Su L, Su Y, Huang W. The characteristics of the electrocardiogram and the intracardiac electrogram in left bundle branch pacing. *J Cardiovasc Electrophysiol.* (2019) 30:1096–101. doi: 10.1111/jce.13956
22. Zhu K, Lin M, Li L, Chang D, Li Q. Left bundle branch pacing shortened the QRS duration of a right bundle branch block. *J Electrocardiol.* (2021) 68:153–6. doi: 10.1016/j.jelectrocard.2021.08.018
23. Li X, Fan X, Li H, Ning X, Liang E, Ma W, et al. ECG patterns of successful permanent left bundle branch area pacing in bradycardia patients with typical bundle branch block. *Pacing Clin Electrophysiol.* (2020) 43:781–90. doi: 10.1111/pace.13982
24. Jiang Z, Chang Q, Wu Y, Ji L, Zhou X, Shan Q. Typical BBB morphology and implantation depth of 3830 electrode predict QRS correction by left bundle branch area pacing. *Pacing Clin Electrophysiol.* (2020) 43:110–7. doi: 10.1111/pace.13849
25. Chu SY, Sheng QH, Chen ED, Jin H, Jiang J, Wang YL, et al. Is the left bundle branch pacing a choice to conquer the right bundle branch block?-A case

report. *Ann Noninvasive Electrocardiol.* (2021) 26:e12797. doi: 10.1111/anec.12797
26. Lin J, Chen K, Dai Y, Sun Q, Li Y, Jiang Y, et al. Bilateral bundle branch area pacing to achieve physiological conduction system activation. *Circ Arrhythm Electrophysiol.* (2020) 13:e008267. doi: 10.1161/circep.119.008267
27. Zhu K, Sun Y, Cai B, Li L, Li G, Liu J, et al. Left bundle branch pacing in patients with right bundle branch block. *Kardiol Pol.* (2021) 79:1127–9. doi: 10.33963/KP.a2021.0091
28. Desplantez T, Dupont E, Severs NJ, Weingart R. Gap junction channels and cardiac impulse propagation. *J Membr Biol.* (2007) 218(1–3):13–28. doi: 10.1007/s00232-007-9046-8
29. James TN, Sherf L. Fine structure of the His bundle. *Circulation.* (1971) 44:9–28. doi: 10.1161/01.cir.44.1.9
30. Massing GK, James TN. Anatomical configuration of the His bundle and bundle branches in the human heart. *Circulation.* (1976) 53:609–21. doi: 10.1161/01.cir.53.4.609
31. Elizari MV. The normal variants in the left bundle branch system. *J Electrocardiol.* (2017) 50:389–99. doi: 10.1016/j.jelectrocard.2017.03.004
32. Demoulin JC, Kulbertus HE. Histopathological examination of concept of left hemiblock. *Br Heart J.* (1972) 34:807–14. doi: 10.1136/hrt.34.8.807
33. Syed FF, Hai JJ, Lachman N, DeSimone CV, Asirvatham SJ. The infrahisian conduction system and endocavitary cardiac structures: relevance for the invasive electrophysiologist. *J Interv Card Electrophysiol.* (2014) 39:45–56. doi: 10.1007/s10840-013-9858-7
34. El-Sherif N, Amay YLF, Schonfield C, Scherlag BJ, Rosen K, Lazzara R, et al. Normalization of bundle branch block patterns by distal His bundle pacing. Clinical and experimental evidence of longitudinal dissociation in the pathologic his bundle. *Circulation.* (1978) 57:473–83. doi: 10.1161/01.cir.57.3.473
35. Myerburg RJ, Nilsson K, Befeler B, Castellanos A Jr., Gelband H. Transverse spread and longitudinal dissociation in the distal A-V conducting system. *J Clin Invest.* (1973) 52:885–95. doi: 10.1172/jci107253
36. Lazzara R, Yeh BK, Samet P. Functional transverse interconnections within the His bundle and the bundle branches. *Circ Res.* (1973) 32:509–15. doi: 10.1161/01.res.32.4.509
37. Kadish AH, Schmaltz S, Morady F. A comparison of QRS complexes resulting from unipolar and bipolar pacing: implications for pace-mapping. *Pacing Clin Electrophysiol.* (1991) 14(5 Pt 1):823–32. doi: 10.1111/j.1540-8159.1991.tb04113.x
38. Wikswo JP Jr., Lin SF, Abbas RA. Virtual electrodes in cardiac tissue: a common mechanism for anodal and cathodal stimulation. *Biophys J.* (1995) 69:2195–210. doi: 10.1016/s0006-349580115-3
39. Thakral A, Stein LH, Shenai M, Gramatikov BI, Thakor NV. Effects of anodal vs. cathodal pacing on the mechanical performance of the isolated rabbit heart. *J Appl Physiol (1985).* (2000) 89:1159–64. doi: 10.1152/jappl.2000.89.3.1159
40. Dancy M, Leech G, Leatham A. Significance of complete right bundle-branch block when an isolated finding. An echocardiographic study. *Br Heart J.* (1982) 48:217–21. doi: 10.1136/hrt.48.3.217
41. Lin J, Hu Q, Chen K, Dai Y, Chen R, Sun Q, et al. Relationship of paced left bundle branch pacing morphology with anatomic location and physiological outcomes. *Heart Rhythm.* (2021) 18:946–53. doi: 10.1016/j.hrthm.2021.03.034
42. Wu S, Su L, Zheng R, Xu L, Huang W. New-onset intrinsic and paced QRS morphology of right bundle branch block pattern after atrioventricular nodal ablation: longitudinal dissociation or anatomical bifurcation? *J Cardiovasc Electrophysiol.* (2020) 31:1218–21. doi: 10.1111/jce.14469

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frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 17 March 2022
doi: 10.3389/fcvm.2022.838708

Clinical Outcomes of Permanent Left Bundle Branch Area Pacing in Patients With Left Bundle Branch Block and Left Ventricular Ejection Fraction >35 vs. ≤35%

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OPEN ACCESS

Edited by:
Carlo de Asmundis, University Hospital Brussels, Belgium

Reviewed by:
Alexandre Almorad, University Hospital Brussels, Belgium
Weijian Huang, First Affiliated Hospital of Wenzhou Medical University, China

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Specialty section:
This article was submitted to Cardiac Rhythmology, a section of the journal Frontiers in Cardiovascular Medicine

Received: *18 December 2021*
Accepted: *21 February 2022*
Published: *17 March 2022*

Citation:
Jiang Z, Wu T, Wu Y, Chen Z, Yang W, Chen C, Zhou X and Shan Q (2022) Clinical Outcomes of Permanent Left Bundle Branch Area Pacing in Patients With Left Bundle Branch Block and Left Ventricular Ejection Fraction >35 vs. ≤35%. Front. Cardiovasc. Med. 9:838708. doi: 10.3389/fcvm.2022.838708

Aims: The present study aimed to compare the effects of left bundle branch area pacing (LBBAP) on cardiac function and clinical outcomes in patients with left bundle branch block (LBBB) and left ventricular ejection fraction (LVEF) >35 vs. ≤35%.

Methods and Results: Thirty-six consecutive patients with LBBB and LVEF < 50% were enrolled. All patients were followed up for a mean of 6 months. The successful LBBAP was defined as a paced QRS complex presented as right bundle branch block (RBBB) morphology and QRSd < 130 ms. Echocardiography parameters, pacing parameters and clinical outcomes were collected. The successful LBBAP was achieved in 77.8% of all cases (28/36). In LVEF > 35% group (70 ± 8 years, 9 male), the success rate was 81.0% (17/21). QRSd significantly decreased from 174 ± 23 ms to 108 ± 13 ms ($P < 0.001$). The pacing threshold and R-wave amplitude were 0.6 ± 0.2 V @ 0.5 ms and 12 ± 7 mV, respectively. In LVEF ≤ 35% group (69 ± 5 years, 9 male), the success rate was 73.3% (11/15) with QRSd decreasing from 188 ± 25 ms to 107 ± 11 ms ($P < 0.001$). The hyperresponders to LBBAP (functional recovery and LVEF ≥ 50%) in LVEF > 35% group was 52.9%, which were almost twice of that in LVEF ≤ 35% group (33.3%). Whether patients had LBBAP or left ventricular septal pacing (LVSP), patients in the LVEF > 35% group showed significantly lower incidence of heart failure hospitalizations or death from any cause (hazard ratio in LVEF > 35% group, 0.22; 95%CI, 0.06 to 0.75, $P = 0.011$).

Conclusions: LBBAP can significantly shorten the QRSd and improve cardiac function in LBBB patients with either LVEF > 35 or ≤ 35%. LBBAP should be considered as an effective therapy for preventing the deterioration of cardiac function in early-stage heart failure patients with LBBB and LVEF > 35%.

Keywords: left bundle branch block, left bundle branch area pacing, cardiac resynchronization therapy, QRS duration, heart failure

INTRODUCTION

It is well established that left bundle branch block (LBBB) has bad effect on left ventricular (LV) function independent of coexisting heart disease. The electromechanical dyssynchrony of the ventricular contractions can contribute to adverse remodeling, reduction of left ventricular ejection fraction (LVEF), and mitral regurgitation in the long term. Cardiac resynchronization therapy (CRT), which involves simultaneous pacing of both right and left ventricles is beneficial and widely used around the world. Major US (ACC/AHA/HRS) (1) and European Society of Cardiology (ESC) guidelines (2, 3) were consistent in issuing Class I and IIA recommendations for CRT in patients who have LVEF $\leq$ 35% and LBBB with a QRS duration (QRSd) $\geq$ 150 ms, and New York Heart Association (NYHA) class II, III, or ambulatory IV symptoms. However, when LVEF is more than 35%, the recommendation level degrades, which seems to be arbitrary. The LVEF cut-off of $\leq$ 35% is adopted by heart failure (HF) major clinical trials of CRT, such as COMPANION (4), because people with LVEF $\leq$ 35% have higher incidence of adverse events, both in terms of sensitivity and specificity of incidence. However, LVEF or LV systolic dysfunction are continuous variables. And LVEF measured by echocardiography is not highly precise compared to magnetic resonance imaging (MRI). In addition, patients with LVEF $>$ 35% are being neglected and the proportion of them is increasing. And they have similar characteristics and treatment patterns to those with LVEF $<$ 35%. In eraly-stage HF patients, those with LBBB have significantly worse clinical outcomes than patients without conduction system disease. Although common practice indicates that we implant CRT outside of guideline recommendations, randomized, multicenter studies in this population have not been conducted yet.

What's more, up to 30% of patients do not respond to CRT and the published data may be underestimated (5). Significant scar burden related to lead position (6), QRSd $<$150 ms (7), right ventricular failure (8), right bundle branch block (RBBB) morphology (9) have been demonstrated to be associated with lack of response. And in combination with national conditions of China, the price of CRT may be too high to be accepted in many patients. In 2017, Huang et al. (10) first reported a novel pacing method to correct the LBBB in the site of the left bundle branch (LBB) area with low and stable output; clinical outcome significantly improved over one year of follow-up. A large single center study (11), which included 632 patients who underwent left bundle branch area pacing (LBBAP), demonstrated that LBBAP was feasible and safe with high success rate in bradycardia or HF patients during long-term follow-up. And several studies (12, 13) have proved that LBBAP could achieve narrowing of QRS duration and improvement of clinical and echocardiographic outcomes in HF patients with LBBB, which means that LBBAP could be a promising resynchronization therapy alternative to biventricular pacing (BVP) for patients with CRT-indications. Since LBBAP is more convenient and cheaper compared to CRT, it would be of clinical interest whether LBBAP could benefit for the HF patients with LBBB and LVEF $>$ 35%. Consequently, this study was undertaken to compare the clinical outcomes of LBBAP in patients with LBBB and LVEF $>$ 35 vs. $\leq$ 35%.

METHODS

Study Population

This was a single-center retrospective study. Consecutive patients underwent LBBAP were enrolled from the First Affiliated Hospital of Nanjing Medical University between May 2017 and December 2020. Patients who met the following criteria were included: (1) complete LBBB morphology that met Strauss criteria (14); (2)echocardiographic evidence of LVEF $<$ 50%; (3) follow-up period over 6 months. All the patients included were provided written informed consent to the study protocol, and were approved by the Institutional Review Board.

Implantation Procedure

The technique of LBBAP procedure has been described in previous reports (15–19). Briefly, a ventricular pacing electrode (Medtronic 3830 electrode) with a 7-Fr guiding catheter (Model C315-S10; Medtronic Inc) was introduced into right ventricle via left subclavian or axillary vein, from His bundle area advanced 1–2 cm toward the right ventricle apex against the ventricular septum, then screwed through the interventricular septum (IVS) to the LBB area. When unipolar paced QRS complex presented as right bundle branch block morphology (qR or rSR' morphology in V1), and pacing parameters were satisfied, lead position and no perforation were assessed by angiogram through C315 sheath under left anterior oblique (LAO) 40°, the sheath was removed and lead was fixed. Successful LBBAP was defined as unipolar paced QRS morphology present as RBBB pattern and QRSd $<$ 130 ms (15). If successful LBBAP could not be achieved after 5 attempts of lead positioning or fluoroscopy duration exceeded 30 min, the left ventricular septum pacing (LVSP) was also accepted, placing the 3,830 lead in the LV mid-septum to achieve a relatively narrow QRSd (17).

Data Collection

The baseline characteristics and medical history of participants were collected at enrollment. The LBBAP paced electrocardiogram (ECG) were interpreted by two cardiologists. The stimulus to peak LV activation time (SPLVAT), defined as the duration between the ventricular stimulation signal and R peak in lead V5, was measured, which meant LBBAP indirectly captured either the main LBB or its branches as previously described (15, 17, 18). Other electrocardiographic parameters such as the intrinsic QRSd, paced QRSd (pQRSd) were also measured. Pacing parameters like pacing thresholds, pacing impedance, R-wave amplitude were recorded. Echocardiographic parameters including left atrial dimension (LAD), left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD) and LVEF were also recorded.

Follow Up

Patients were followed up in the clinic or in hospital at baseline, 3, 6 and 12 months. Clinical characteristics, echocardiographic parameters and lead-related complications were recorded.

LBBAP responder was defined as a patient who had an LVEF improvement of at least 5% at the 6-month follow-up. Patients were considered to be "hyperresponders" (20), if they met two following criteria: functional recovery and LVEF $\geq$ 50%. The primary composite endpoint included death from any cause or hospitalizations for HF. The diagnosis of HF hospitalization was made by professional physicians, if patients were developing symptoms that current treatments could not control and have to be hospitalized again due to the congestive HF.

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation (SD). Categorical variables were expressed as numbers and percentage values and compared using chi-square or Fisher's exact test. Comparisons between continuous variables were tested using Student's *t*-test. Kaplan–Meier survival curves were used to estimate for the combined endpoint of time to death or first HF hospitalization. The log rank test compared survival curves between two groups. Statistical analysis was performed using SPSS version 20.0 software. All *P*-values were two-tailed and *P*-values < 0.05 were considered significant.

RESULTS

Baseline Characteristics

From May 2017 to December 2020, 496 patients underwent LBBAP. Of the 69 patients who had complete LBBB morphology, 33 patients with normal LVEF were excluded. Finally, 36 LBBB patients (age: 70 $\pm$ 7 years, male = 18) underwent an attempted LBBAP. There were 15 LBBB patients with LVEF $\leq$ 35% (27.9 $\pm$ 4.7), 21 LBBB patients with LVEF $>$ 35% (40.2 $\pm$ 4.5). Successful LBBAP was achieved in 77.8% (28/36) of cases. The baseline characteristics were summarized in **Table 1**. There was no difference in age, sex, QRSd, drug utilization and complications including hypertension, diabetes mellitus, renal insufficiency, syncope, coronary artery disease and atrial fibrillation (AF) between the two groups. The LAD, LVEDD and LVESD were significantly higher in LVEF $\leq$ 35% group (46 $\pm$ 8 vs. 41 $\pm$ 7, $P < 0.05$; 72 $\pm$ 9 vs. 58 $\pm$ 6, $P < 0.001$; 63 $\pm$ 8 vs. 46 $\pm$ 5, $P < 0.001$).

TABLE 1 | Baseline characteristics.

	All patients (*n* = 36)	LVEF ≤35% (*n* = 15)	LVEF >35% (*n* = 21)	*P*–value
LBBAP success rate (%)	28 (77.8)	11 (73.3)	17 (81.0)	0.69
Age (years)	70 ± 7	69 ± 5	70 ± 8	0.55
Male (%)	18 (50)	9 (60.0)	9 (42.9)	0.50
QRS duration (ms)	180 ± 25	188 ± 25	174 ± 23	0.10
Hypertension (%)	23 (63.9)	7 (46.7)	16 (76.2)	0.09
Diabetes mellitus (%)	8 (22.2)	2 (13.3)	6 (28.6)	0.42
Renal insufficiency (%)	8 (22.2)	5 (33.3)	3 (14.3)	0.24
Syncope (%)	3 (8.3)	2 (13.3)	1 (4.8)	0.56
Coronary artery disease (%)	10 (27.8)	4 (26.7)	6 (28.6)	1.00
Paroxysmal AF (%)	4 (11.1)	2 (13.3)	2 (9.5)	1.00
Persistent AF (%)	6 (16.7)	2 (13.3)	4 (19.0)	1.00
Beta-blocker (%)	35 (97.2)	15 (100.0)	20 (95.2)	1.00
ACE inhibitor/ARB (%)	16 (44.4)	7 (46.7)	9 (42.9)	1.00
Diuretics (%)	29 (80.6)	13 (86.7)	16 (76.2)	0.67
Digitalis (%)	10 (27.8)	6 (40.0)	4 (19.0)	0.26
Sacubitril valsartan (%)	26 (72.2)	11 (73.3)	15 (71.4)	1.00
dapagliflozin (%)	6 (16.7)	2 (13.3)	4 (19.0)	1.00
LAD (mm)	43 ± 8	46 ± 8	41 ± 7	0.04
LVEDD (mm)	64 ± 10	72 ± 9	58 ± 6	<0.001
LVESD (mm)	53 ± 10	63 ± 8	46 ± 5	<0.001
LVEF (%)	35.1 ± 7.6	27.9 ± 4.7	40.2 ± 4.5	<0.001

AF, atrial fibrillation; ACE, angiotensin converti enzyme; ARB, angiotensin receptor blocker; LAD, left atrial dimension; LVEDD, left ventricular end–diastolic dimension; LVESD, left ventricular end–systolic dimension; LVEF, left ventricular ejection fraction.

Pacing Parameters

In LVEF $\leq$ 35% group, the QRSd significantly decreased from 188 $\pm$ 25 ms to 107 $\pm$ 11 ms ($P < 0.001$) and the SPLVAT was 88 $\pm$ 13 ms. In LVEF $>$ 35% group, the QRSd also decreased from 174 $\pm$ 23 ms to 108 $\pm$ 13 ms ($P < 0.001$), and the SPLVAT was 88 $\pm$ 15 ms. In **Table 2**, during the LBBAP procedure, R-wave amplitude of LVEF $>$ 35% group was significantly higher than LVEF $\leq$ 35% group (12 $\pm$ 7 mV vs. 7 $\pm$ 3 mV, $P < 0.01$). The pacing threshold, pacing impedance, paced QRSd and SPLVAT between the two groups were of no significance.

TABLE 2 | Pacing parameters in successful LBBAP patients.

	LVEF ≤35% (*n* = 11)	LVEF >35% (*n* = 17)	*P*-value
Pacing threshold (V/0.5ms)	0.9 ± 0.4	0.6 ± 0.2	0.08
R–wave amplitude (mV)	7 ± 3	12 ± 7	0.008
Pacing impedance (Ω)	661 ± 112	709 ± 127	0.32
Paced QRS duration (ms)	107 ± 11	108 ± 13	0.73
SPLVAT (ms)	88 ± 13	88 ± 15	1.00

SPLVAT, stimulus peak to left ventricular activation time.

Clinical Outcomes

During the follow-up of a mean of 6 months, no complications associated with LBBAP such as lead perforation and dislodgement, pericardial effusion, pneumothorax, and thromboembolism were observed. There was one person in each group who had pocket infection and underwent incision and drainage of pocket. Clinical endpoint in successful LBBAP patients at the 12-month follow-up was shown in **Table 3**. The primary outcome occurred in 3 of 17 patients (17.6%) in LVEF $>$ 35% group and 5 of 11 patients (45.5%) in LVEF $\leq$ 35% group. In addition, as shown in **Figure 1**, in all 36 patients recruited, the Kaplan-Meier survival curve of the primary endpoint of LVEF $>$ 35% group including hospitalization for HF or death from any cause was significantly higher than of LVEF $\leq$ 35% group (hazard ratio in LVEF $>$ 35% group, 0.22; 95%CI, 0.06 to 0.74, $P = 0.011$). And so did the Kaplan-Meier survival curve of death from any cause with *P*-value < 0.05.

As it was shown in **Table 4** and **Figure 2**, LAD, LVEDD, LVESD had shortened and LVEF had improved in both groups,

TABLE 3 | Clinical endpoints in successful LBBAP patients at the 12-month follow-up.

	LVEF ≤35% (*n* = 11)	LVEF >35% (*n* = 17)	*P*-value
Death (%)	2 (18.2)	0 (0)	0.07
Heart failure hospitalization (%)	3 (27.3)	3 (17.6)	0.32
The primary composite endpoint (%)	5 (45.5)	3 (17.6)	0.10

but there was no difference in ΔLAD, ΔLVEDD, ΔLVESD and ΔLVEF between the two groups. However, the number of LBBAP hyperresponders in LVEF > 35% group was 9 (52.9%), which was almost twice of that in LVEF ≤ 35% group (33.3%).

In our study, a total of 3 patients died (one at 8 month, two at 1 month) after LBBAP due to progressive HF. The baseline LVEF of these patients were below 35%. Of them, 2 accepted LBBAP and 1 accepted LVSP. They were over 70 years old and had HF for many years with N-terminal pro-B-type natriuretic peptide (NT-proBNP) over 7000 pg/ml before LBBAP. Two of them had chronic kidney disease (21), which is a major contributor to mortality and HF exacerbations. One patient with LVEF below 25% died soon after LVSP due to ventricular fibrillation.

DISCUSSION

In this study, we found that LBBAP could significantly shorten the QRSd and improve the cardiac function in LBBB patients with LVEF > 35%. Compared with LVEF ≤ 35%, patients with LVEF > 35% showed lower risk of combined endpoint of death from any cause or hospitalizations for HF and better echocardiographic response to LBBAP.

Active measures have been taken on those patients with LVEF ≤ 35% and the mortality and hospitalization have been decreasing in recent years. However, patients with higher LVEF are not being treated positively and promptly at the same time. The data from the American Heart Association's Get With The Guidelines (GWTG)(22) which included 110,621 patients showed that preserved and borderline LVEF (>40%) accounted for about half of all HF hospitalizations and the number was on increase. And LVEF is recognized to be an independent predictor of mortality and morbility in HF patients (23). Patients with LVEF ranging from 36 to 45% still have higher risk of adverse outcomes. Further, Witt et al. (24) proved that in patients with LVEF between 35 and 50%, those with LBBB had poorer clinical outcomes than those without conduction disease in the long-term follow-up.

Recently, there have been some studies which aim to prove the effect of CRT in patients with LVEF > 35%. Fung et al. (25) and Foley et al. (26) both reported that CRT could improve cardiac function and reverse LV remodeling in small groups of HF patients with LVEF > 35%. And in PROSPECT trial (27), CRT improved the clinical composite score (CCS) and decreased left ventricular end-systolic volume (LVESV) similarly in patients with LVEF ≤ 35 and >35%. However, In REVERSE (28), the study discovered that in patients with LVEF > 30%, CCS was improving by CRT but of no significance. Besides, a statistically

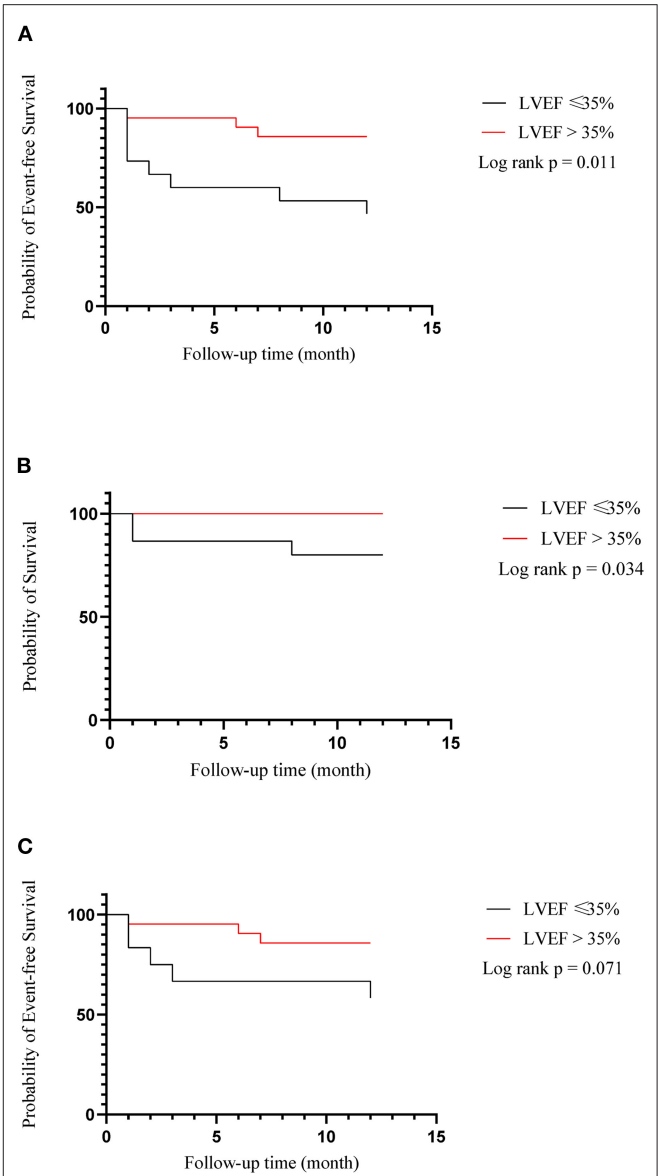

FIGURE 1 | Kaplan–meier estimates of death or hospitalization for heart failure (composite primary outcome), death from any cause and hospitalization for heart failure among all of 36 patients recruited. **(A)** Heart failure hospitalization or death from any cause; **(B)** Death from any cause; **(C)** Heart failure hospitalization.

significant decrease of LV end diastolic volume index (LVEDVi) was only seen in patients with LVEF < 30%. Reasons why REVERSE showed lower LV reverse remodeling than the other studies are unclear. Interestingly, a prospective, randomized, controlled, double-blinded study called MIRACLE EF study (29) which aimed to prove that CRT could achieve clinical benefit in patients combined with moderately reduced LVEF (36–50%) and LBBB with the minimum 24-month follow-up. However the study was stopped after 13 months due to poor recruitment and enrolling only 44 patients. Reasons are complicated but one reason may be in short of understanding the feasibility and

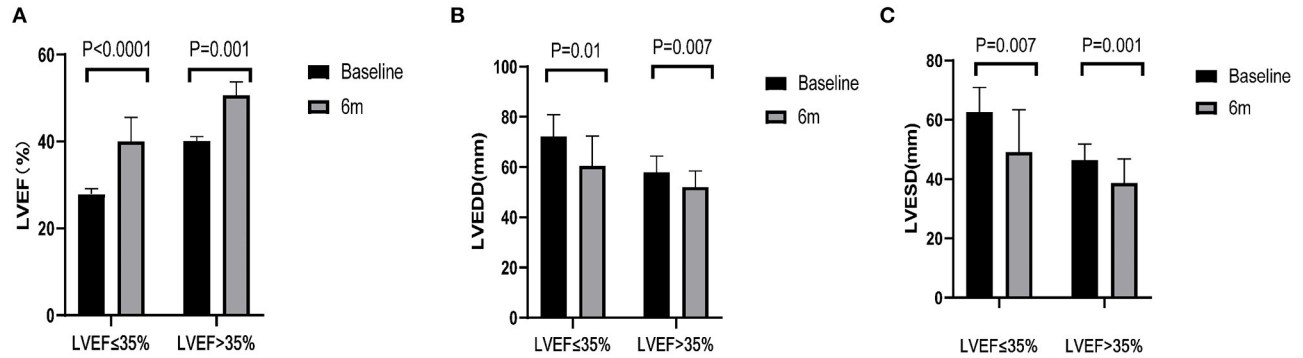

FIGURE 2 | Echocardiographic parameters. **(A–C)** Left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD) and left ventricular end-systolic dimension (LVESD) of patients pre-left bundle branch area pacing (LBBAP) and 6 months after LBBAP.

TABLE 4 | LBBAP response and clinical outcomes at 6-month follow-up.

	LVEF ≤35% (*n* = 9)	**LVEF >35% (*n* = 17)**	***P*-value**
LVEF decrease	1 (11.1)	3 (17.6)	1.00
LVEF improve <5%	3 (33.3)	3 (17.6)	0.63
LVEF improve ≥5%	2 (22.2)	2 (11.8)	0.59
LVEF ≥50% (hyperresponders)	3 (33.3)	9 (52.9)	0.43
Change in LAD	−1.8 ± 5.6	−2.5 ± 3.8	0.75
Change in LVEDD	−9.3 ± 8.6	−5.8 ± 6.2	0.24
Change in LVESD	−11.7 ± 11.0	−7.6 ± 8.5	0.30
Change in LVEF	12.6 ± 14.9	10.2 ± 13.4	0.68

LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction. Two patients in LVEF ≤ 35% group died in the follow-up with no echocardiography recorded.

necessity of preventive treatment in this population. Current studies show contradictory results and the sample size is too small to be convincing. Besides, there is a lack of non-CRT group comparison and multicenter, randomized study to reflect the clinical effect of CRT in HF patients with LVEF > 35%, especially in the presence of LBBB.

Since the population of patients with LBBB and LVEF from 36 to 50% has been on the increase and the prognosis of them is quite poor if any proper measure is taken, there exists the need to take effective interventions ahead of time. Except for CRT, LBBAP is another appropriate choice as a new strategy for physiological pacing to achieve electrical synchrony of LV with high success rate.

In recent years, there has been many articles to prove the safety and feasibility of LBBAP in LBBB patients. Zhang et al. (30) used to demonstrate that QRSd was significantly shortened with shorter interventricular mechanical delay by LBBAP. And in 2020, Guo et al. (12) made a comparison between LBBAP and biventricular pacing (BIV) and the study showed that LBBAP could restore electrical synchrony better and achieve greater improvement in echocardiographic and clinical outcomes. We can take LBBAP to be a feasible treatment as a rescue pacing method or as the primary pacing strategy for HF patients with CRT indications (13, 31).

Our research and previous studies have yielded similar results. Furthermore, in LVEF >35% group, the number of hyperresponders is more than that in LVEF ≤ 35% group. Meanwhile, in this group, more than half of the patients had LV restored [defined as return to NYHA I and LVEF > 50% (32)]. And LVEF > 35% group has higher R-wave amplitude, possibly because fewer people in this group have myocardial injury, fibrosis, or infarction, which contributes to better response to LBBAP. Besides, there may be a "sweet spot" (33) for LBBAP as well, just like CRT. If the ventricular function gets worse to a certain level, the myocardium is too "sick" to respond to any therapy. As a result of the decline in LVEF, adverse remodeling also progressed so that the cardiac function of patients is hard to return to normal.

In all the 36 patients recruited in our study, whether patients have LBBAP or LVSP, compared with LVEF ≤ 35% group, patients in LVEF > 35% group show significantly lower incidence of death from any cause or hospitalization for HF via LBBAP ($P = 0.011$). Besides, all-cause mortality is significantly lower in the LVEF > 35% group as well ($P = 0.034$). In our study, many of patients with primary endpoints had chronic kidney disease or persistent AF before procedure, both of which can accelerate the overall progression of HF independently. And in EAARN score (34), renal failure with GRF <60 mL/min/1.73 m^2 was predictive of poor outcomes in patients treated with CRT. Besides, AF was associated with poorer survival in CRT patients despite the benefits of the therapy.

Limitation

First, our study did not directly verify that LBBAP captured the cardiac conduction system by recording left bundle branch potential. Due to LBBB in most of patients, the potential could not be recorded in the conventional way; it could be achieved by double leads method, but this is not practical in regular clinical practice. In any event, our results of degree of narrowing QRSd and SPLVAT were comparable with other studies using direct left bundle branch potential recording (17–19). Thus the definition of LBBAP used in our study may include both left bundle branch pacing (LBBP) and LVSP. Nonetheless, LBBAP was supposed to have the same effect as LBBP. Second, the sample size was relatively small and follow-up was short-term. A large-scale

randomized study with longer follow-up is necessary to clarify the role of LBBAP in these patients.

CONCLUSION

LBBAP could significantly shorten QRS duration and improve cardiac function during medium-and-short term follow up in patients with LBBB and LVEF between 35 and 50%. The degree of echocardiographic and clinical improvement by LBBAP in these patients was better than those with LVEF $\leq$ 35%. Thus, LBBAP is a promising physiological ventricular pacing which could be an effective therapy for preventing the deterioration of cardiac function in early-stage HF patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the First Affiliated Hospital of Nanjing Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

This work was supported by the First Affiliated Hospital of Nanjing Medical University (JSPH-511C-2018-5).

ACKNOWLEDGMENTS

We are thankful for all the volunteers who participated in this study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.838708/full#supplementary-material

REFERENCES

1. Writing Committee M, Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation.* (2013) 128:e240–327. doi: 10.1161/CIR.0b013e31829e8776
2. European Society of C, European Heart Rhythm A, Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). *Developed in collaboration with the European Heart Rhythm Association (EHRA). Europace.* (2013) 15:1070–118. doi: 10.1093/europace/eut206
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* (2016) 37:2129–200. doi: 10.1093/eurheartj/ehw128
4. Bristow MR, Feldman AM, Saxon LA. Heart failure management using implantable devices for ventricular resynchronization: Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial. COMPANION Steering Committee and COMPANION Clinical Investigators. *J Card Fail.* (2000) 6:276–85. doi: 10.1054/jcaf.2000.9501
5. Birnie DH, Tang AS. The problem of non-response to cardiac resynchronization therapy. *Curr Opin Cardiol.* (2006) 21:20–6. doi: 10.1097/01.hco.0000198983.93755.99
6. Adelstein EC, Saba S. Scar burden by myocardial perfusion imaging predicts echocardiographic response to cardiac resynchronization therapy in ischemic cardiomyopathy. *Am Heart J.* (2007) 153:105–12. doi: 10.1016/j.ahj.2006.10.015
7. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med.* (2009) 361:1329–38. doi: 10.1056/NEJMoa0906431
8. Haddad F, Doyle R, Murphy DJ, Hunt SA. Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure. *Circulation.* (2008) 117:1717–31. doi: 10.1161/CIRCULATIONAHA.107.653584
9. Bilchick KC, Kamath S, DiMarco JP, Stukenborg GJ. Bundle-branch block morphology and other predictors of outcome after cardiac resynchronization therapy in Medicare patients. *Circulation.* (2010) 122:2022–30. doi: 10.1161/CIRCULATIONAHA.110.956011
10. Huang W, Chen X, Su L, Wu S, Xia X, Vijayaraman P. A beginner's guide to permanent left bundle branch pacing. *Heart Rhythm.* (2019) 16:1791–6. doi: 10.1016/j.hrthm.2019.06.016
11. Su L, Wang S, Wu S, Xu L, Huang Z, Chen X, et al. Long-term safety and feasibility of left bundle branch pacing in a large single-center study. *Circ Arrhythm Electrophysiol.* (2021) 14:e009261. doi: 10.1161/CIRCEP.120.009261
12. Guo J, Li L, Xiao G, Ye T, Huang X, Meng F, et al. Remarkable response to cardiac resynchronization therapy via left bundle branch pacing in patients with true left bundle branch block. *Clin Cardiol.* (2020) 43:1460–8. doi: 10.1002/clc.23462
13. 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) 7:135–47. doi: 10.1016/j.jacep.2020.08.015
14. Strauss DG, Selvester RH, Wagner GS. Defining left bundle branch block in the era of cardiac resynchronization therapy. *Am J Cardiol.* (2011) 107:927–34. doi: 10.1016/j.amjcard.2010.11.010
15. Chen K, Li Y, Dai Y, Sun Q, Luo B, Li C, et al. Comparison of electrocardiogram characteristics and pacing parameters between left bundle branch pacing and right ventricular pacing in patients receiving pacemaker therapy. *Europace.* (2019) 21:673–80. doi: 10.1093/europace/euy252
16. Chen X, Wu S, Su L, Su Y, Huang W. The characteristics of the electrocardiogram and the intracardiac electrogram in left bundle branch pacing. *J Cardiovasc Electrophysiol.* (2019) 30:1096–101. doi: 10.1111/jce.13956

17. Li X, Li H, Ma W, Ning X, Liang E, Pang K, et al. Permanent left bundle branch area pacing for atrioventricular block: Feasibility, safety, and acute effect. *Heart Rhythm.* (2019) 16:1766–73. doi: 10.1016/j.hrthm.2019.04.043
18. Li Y, Chen K, Dai Y, Li C, Sun Q, Chen R, et al. Left bundle branch pacing for symptomatic bradycardia: Implant success rate, safety, and pacing characteristics. *Heart Rhythm.* (2019) 16:1758–65. doi: 10.1016/j.hrthm.2019.05.014
19. Vijayaraman P, Subzposh FA, Naperkowski A, Panikkath R, John K, Mascarenhas V, et al. Prospective evaluation of feasibility and electrophysiologic and echocardiographic characteristics of left bundle branch area pacing. *Heart Rhythm.* (2019) 16:1774–82. doi: 10.1016/j.hrthm.2019.05.011
20. Castellant P, Fatemi M, Bertault-Valls V, Etienne Y, Blanc JJ. Cardiac resynchronization therapy: "nonresponders" and "hyperresponders". *Heart Rhythm.* (2008) 5:193–7. doi: 10.1016/j.hrthm.2007.09.023
21. Schefold JC, Filippatos G, Hasenfuss G, Anker SD, von Haehling S. Heart failure and kidney dysfunction: epidemiology, mechanisms and management. *Nat Rev Nephrol.* (2016) 12:610–23. doi: 10.1038/nrneph.2016.113
22. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. *Circulation.* (2012) 126:65–75. doi: 10.1161/CIRCULATIONAHA.111.080770
23. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J.* (2016) 37:455–62. doi: 10.1093/eurheartj/ehv464
24. Witt CM, Wu G, Yang D, Hodge DO, Roger VL, Cha YM. Outcomes with left bundle branch block and mildly to moderately reduced left ventricular function. *JACC Heart Fail.* (2016) 4:897–903. doi: 10.1016/j.jchf.2016.07.002
25. Fung JW, Zhang Q, Yip GW, Chan JY, Chan HC, Yu CM. Effect of cardiac resynchronization therapy in patients with moderate left ventricular systolic dysfunction and wide QRS complex: a prospective study. *J Cardiovasc Electrophysiol.* (2006) 17:1288–92. doi: 10.1111/j.1540-8167.2006.00612.x
26. Foley PW, Stegemann B, Smith RE, Sanderson JE, Leyva F. Cardiac resynchronization therapy in patients with mildly impaired left ventricular function. *Pacing Clin Electrophysiol.* (2009) 32:S186–189. doi: 10.1111/j.1540-8159.2008.02280.x
27. Chung ES, Katra RP, Ghio S, Bax J, Gerritse B, Hilpisch K, et al. Cardiac resynchronization therapy may benefit patients with left ventricular ejection fraction >35%: a PROSPECT trial substudy. *Eur J Heart Fail.* (2010) 12:581–7. doi: 10.1093/eurjhf/hfq009
28. Linde C, Daubert C, Abraham WT, St John Sutton M, Ghio S, Hassager C, et al. Impact of ejection fraction on the clinical response to cardiac resynchronization therapy in mild heart failure. *Circ Heart Fail.* (2013) 6:1180–9. doi: 10.1161/CIRCHEARTFAILURE.113.000326
29. Linde C, Curtis AB, Fonarow GC, Lee K, Little W, Tang A, et al. Cardiac resynchronization therapy in chronic heart failure with moderately reduced left ventricular ejection fraction: Lessons from the Multicenter InSync Randomized Clinical Evaluation MIRACLE EF study. *Int J Cardiol.* (2016) 202:349–55. doi: 10.1016/j.ijcard.2015.09.023
30. Zhang W, Huang J, Qi Y, Wang F, Guo L, Shi X, et al. Cardiac resynchronization therapy by left bundle branch area pacing in patients with heart failure and left bundle branch block. *Heart Rhythm.* (2019) 16:1783–90. doi: 10.1016/j.hrthm.2019.09.006
31. Jastrzebski M, Moskal P, Huybrechts W, Curila K, Sreekumar P, Rademakers LM, et al. Left bundle branch-optimized cardiac resynchronization therapy (LOT-CRT): results from an international LBBAP collaborative study group. *Heart Rhythm.* (2022) 19:13–21. doi: 10.1016/j.hrthm.2021.07.057
32. Kutyifa V, Kloppe A, Zareba W, Solomon SD, McNitt S, Polonsky S, et al. The influence of left ventricular ejection fraction on the effectiveness of cardiac resynchronization therapy: MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy). *J Am Coll Cardiol.* (2013) 61:936–44.
33. Gasparini M, Galimberti P. Device therapy in heart failure: has CRT changed "the sickest benefit the most" to "the healthiest benefit the most?" *J Am Coll Cardiol.* (2013) 61:945–7. doi: 10.1016/j.jacc.2012.11.048
34. Khatib M, Tolosana JM, Trucco E, Borras R, Castel A, Berruezo A, et al. EAARN score, a predictive score for mortality in patients receiving cardiac resynchronization therapy based on pre-implantation risk factors. *Eur J Heart Fail.* (2014) 16:802–9. doi: 10.1002/ejhf.102

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

SYSTEMATIC REVIEW
published: 22 March 2022
doi: 10.3389/fcvm.2022.849143

Pacing Characteristics of His Bundle Pacing vs. Left Bundle Branch Pacing: A Systematic Review and Meta-Analysis

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Edited by:
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Specialty section:
This article was submitted to Cardiac Rhythmology, a section of the journal Frontiers in Cardiovascular Medicine

Received: *05 January 2022*
Accepted: *21 February 2022*
Published: *22 March 2022*

Citation:
Zhuo W, Zhong X, Liu H, Yu J, Chen Q, Hu J, Xiong Q and Hong K (2022) Pacing Characteristics of His Bundle Pacing vs. Left Bundle Branch Pacing: A Systematic Review and Meta-Analysis. Front. Cardiovasc. Med. 9:849143. doi: 10.3389/fcvm.2022.849143

Background: His bundle pacing (HBP) is a physiological pacing strategy, which aims to capture the His bundle-Purkinje system and synchronously activate the ventricles. Left bundle branch pacing (LBBP) is a newly discovered physiological pacing technique similar to HBP. We conducted this meta-analysis to compare the pacing parameters and clinical results between HBP and LBBP.

Methods: We systematically retrieved studies using the PubMed, Embase database, and Cochrane Library. Mean difference (MD) and relative risk (RR) with their 95% confidence intervals [CIs] were used to measure the outcomes. A random-effect model was used when studies were of high heterogeneity.

Results: A total of seven studies containing 867 individuals were included. Compared with HBP, LBBP was associated with higher implant success rates (RR: 1.12, 95% CI: 1.05–1.18; $I^2 = 60\%$, $P = 0.0003$), lower capture threshold at implantation (V/0.5 ms) (MD: 0.63, 95% CI: 0.35–0.90, $I^2 = 89\%$, $P < 0.0001$) and capture threshold at follow-up (V/0.5 ms) (MD: 0.76, 95% CI: 0.34–1.18, $I^2 = 93\%$, $P = 0.0004$), and larger sensed R wave amplitude (mV) at implantation (MD: 7.23, 95% CI: 5.29–9.16, $P < 0.0001$) and sensed R wave amplitude (mV) at follow-up (MD: 7.53, 95% CI: 6.85–8.22, $P < 0.0001$). In LBBP recipients, greater QRS wave complex reduction was found in the paced QRS duration at follow-up compared with HBP recipients at follow-up (MD: 6.12, 95% CI: 1.23–11.01, $I^2 = 0\%$, $P = 0.01$). No statistical differences were found in procedure duration, fluoroscopy time, native left ventricular ejection fractions (LVEF), LVEF improvement, native QRS duration, and QRS reduction from the native QRS duration vs. paced QRS duration at implantation.

Conclusion: Current evidence suggests that pacing characteristics are better in LBBP compared with HBP. Further prospective studies are needed to validate the clinical advantages of LBBP.

Keywords: his bundle pacing, left bundle branch pacing, prognosis, physiologic pacing, pacing parameters

INTRODUCTION

Traditional right ventricular pacing (RVP), including right ventricular apical, septal, or outflow tract pacing, does not result in synchronous ventricular activation and contraction. It is associated with an increased risk of ventricular remodeling and atrial fibrillation (AF) and can lead to left ventricular dysfunction (1–4).

The development of biventricular pacing (BVP) may have a beneficial hemodynamic effect on patients with left bundle branch block and can improve the prognosis of patients with symptomatic heart failure (5, 6). Despite BVP significantly improving prognosis compared with RVP (7), 1/3 of patients with BVP indications do not gain significant clinical benefit after treatment (8, 9).

His bundle pacing (HBP), by capturing and conducting *via* His bundle-Purkinje fibers and then by activating the ventricle from the normal physiological sequence, is considered to be the most physiological pacing strategy (10). It is effective in the treatment of bradycardia arrhythmias and chronic AF with heart failure. However, there are still some limitations with HBP, such as long fluoroscopy times, high pacing thresholds, and high incidences of early battery depletion and lead dislodgement (11). Recently, Huang et al. reported left bundle branch pacing (LBBP) as an alternative to HBP (12). LBBP has a physiological pacing effect similar to HBP, and some studies have evaluated its safety and effectiveness (13–15).

Currently, few clinical studies are comparing HBP with LBBP. The purpose of this meta-analysis is to further analyze the current clinical studies, comparing pacing parameters, clinical safety, and efficacy of HBP vs. LBBP.

METHODS

The study was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (16).

Search Strategy

We systematically searched relevant studies in PubMed, Embase database, and Cochrane Library up until October 15, 2021. No language or publication restrictions were placed. The MeSH terms and free text words were used to retrieve studies. The first group of keywords was linked to HBP ("His bundle pacing" or "Hisian pacing" or "para-His bundle pacing" or "para-Hisian pacing"). The second group of keywords was linked to LBBP ("left bundle branch pacing" or "left bundle branch area pacing"). The two groups of keywords were combined using the Boolean operator "AND." The studies were selected independently by two reviewers (Wen Zhuo and Xiaojie Zhong). Endnote X8 was used to manage the studies. These two authors independently reviewed the title and abstract and excluded the irrelevant studies. Full texts were further scrutinized to assess whether the studies could be included in the meta-analysis. The controversy was resolved by discussion or consultation with additional coauthors (Qinmei Xiong and Jinzhu Hu).

Selection Criteria

Eligible studies that focused on a direct comparison between HBP and LBBP were included in line with the following criteria: (1) published in English with an available full text; (2) measurable parameters have been reported, such as implantation success rates, procedure duration, fluoroscopy time, QRS duration, left ventricular ejection fractions (LVEF), sensed R wave amplitude, or capture threshold; and (3) the follow-up duration was at least 3 months.

Studies were excluded if (1) they were certain publication types, such as reviews, meta-analyses, notes, case reports, or conference abstracts; (2) they had overlapping study populations; or (3) the full text was unavailable.

Data Extraction and Quality Assessment

The data were extracted independently by two authors (Wen Zhuo and Hualong Liu) on a standard data extraction form. The following information was extracted from the studies: author's name, publication year, study design, country, sample size, follow-up duration, age, sex ratio, number of participants, primary diseases, procedure duration, fluoroscopy time, native LVEF, LVEF at follow-up, native QRS duration, QRS duration at implantation and follow-up, sensed R wave amplitude at implantation and follow-up, and capture threshold at implantation and follow-up. The quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS). Each study was scored based on selection, comparability, and outcome by two reviewers independently. One star would be given to a positive response to one question on the scale. The maximum number of stars each article could get was 9. We considered a study with a NOS score >6 stars to be of high quality.

Outcomes

The procedural outcomes included the implant success rates, procedure duration, and fluoroscopy time. The efficacy outcomes included QRS duration reduction (native QRS duration minus paced QRS duration at implantation and native QRS duration minus paced QRS duration at follow-up), sensed R wave amplitude at implantation, sensed R wave amplitude at follow-up, paced capture threshold at implantation, paced capture threshold at follow-up, native LVEF, and LVEF improvement (LVEF at follow-up minus native LVEF).

Statistical Analysis

We used Review Manager 5.3 (Cochrane Collaboration, Copenhagen, Denmark) to perform our meta-analysis. Mean difference (MD) was used for the outcomes of continuous variables, whereas relative risk (RR) was used for the categorized variables. The 95% confidence intervals (CIs) for MD and RR were also calculated. Heterogeneity among studies was assessed using chi-squared and I-squared tests. A $P < 0.10$ was considered

Abbreviations: HBP, His bundle pacing; LBBP, Left bundle branch pacing; MD, Mean difference; CIs, Confidence intervals; RR, Relative risk; AF, Atrial fibrillation; RVP, Right ventricular pacing; BVP, Biventricular pacing; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; LVEF, Left ventricular ejection fractions; NOS, Newcastle-Ottawa Scale; MeSH, Medical Subject Headings; RevMan, Review Manager.

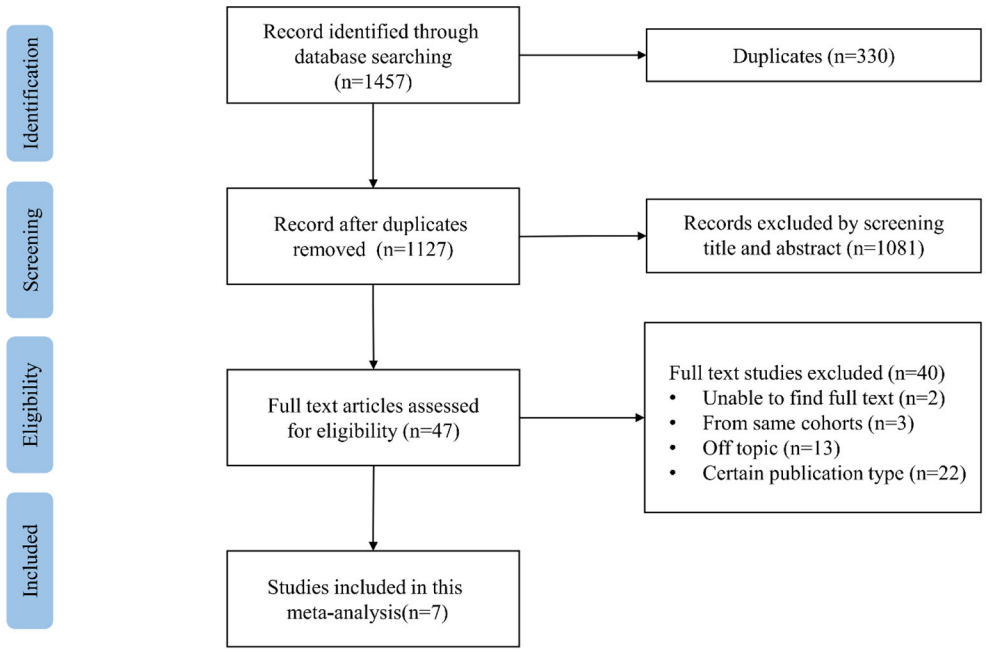

FIGURE 1 | Flowchart of study selection.

to indicate the existence of heterogeneity among the studies. We considered substantial heterogeneity to exist when $I^2 > 50\%$ and a random-effect model was used. Otherwise, a fixed-effect model was used.

RESULTS

Literature Search

Our search results are summarized in the PRISMA flowchart (**Supplementary Table**). The process of literature searching is shown in **Figure 1**. We initially identified 1,457 potential data sources through electronic retrieval strategies with 330 duplicates. After reviewing the titles and abstracts, 47 studies were qualified for a full review. Then intensive reading was done, and 40 studies were excluded, among which 13 articles were off-topic, two studies were without full text, and 3 studies had overlapping study populations. Among the studies describing the same cohort, we selected the studies including the largest number of participants. A total of 22 articles were excluded by publication type, including eight case-report studies, four review studies, and 10 conference abstracts. Finally, seven studies were found to be eligible for the meta-analysis (15, 17–22).

Study Characteristics

A total number of 867 individuals were included for analysis. Among them, 476 were men, and the estimated mean age of all individuals was 68.8 ± 12.9 years. **Table 1** provides the main characteristics and the relevant parameters of the included studies. Basic parameters of clinical studies were extracted, such as author's name, year of publication, regions, study design, age, sex, follow-up duration, number of participants, and primary diseases. The quality of the included studies was high, with NOS scores varying from 8 to 9, and the results are shown in **Table 2**.

Procedure Assessment

Data from the four included studies (17–19, 21) were extracted to analyze the implant success rates. As shown in **Figure 2A**, LBBP was associated with a statistically significant higher success rate compared with HBP (RR: 1.12, 95%CI: 1.05–1.18; $I^2 = 60\%$, $P = 0.0003$). In total, three included studies (17, 21, 22) measured the mean procedure duration, and two studies (21, 22) reported the fluoroscopy time. No statistical difference was observed in the procedure duration between patients who received HBP or LBBP (MD: 14.00, 95% CI: −0.96–28.95, $I^2 = 65\%$, $P = 0.07$; **Figure 2B**). There was no significant difference in fluoroscopy time between HBP or LBBP recipients (MD: 2.56, 95% CI: −7.43–12.56, $I^2 = 97\%$, $P = 0.62$; **Figure 2C**). Due to the existence of heterogeneity, a random model was used.

In total, four studies (18, 19, 21, 22) reported surgical complications on at least one of the following: lead dislodgement, loss of capture, macro displacement, increase in pacing threshold, and pocket infection. Kaplan–Meier estimates for overall complication rate were not analyzed due to lack of data.

Efficacy Assessment

R-Wave Amplitude

In total, four studies (17, 18, 20, 22) reported R wave amplitudes. As shown in **Figure 3A**, our study found that the sensed R wave amplitude at implantation of LBBP recipients was larger than HBP recipients (MD: 7.23, 95% CI: 5.29–9.16, $P < 0.0001$). Due to the existence of significant heterogeneity ($I^2 = 79\%$), a random model was used. The sensed R wave amplitude at follow-up was

TABLE 1 | Basic characteristics of studies included in the meta-analysis.

References	Study design	Region	Number of participants (*N*)	Follow-Up duration	Age (year)	Male (%)	Disease	Date of included patients	Implant success (%)
Hou et al. (15)	Prospective study	China	HBP: 29; LBBP:56	1/6 M	HBP:69.1 ± 10.4; LBBP: 68.3±11.8	HBP:65.5; LBBP: 64.3	SND/AVB/AF	2018.1–2018.9	Not mentioned
Hua et al. (17)	Retrospective study	China	HBP:125; LBBP:126	3 M	HBP:62.2 ± 15.2; LBBP: 65.3 ± 11.1	HBP:56.8; LBBP:46	Bradycardia	2018.1–2019.4	HBP:87.2%; LBBP:91.3%
Molina-Lerma et al. (18)	Retrospective study	Spain	HBP:45; LBBP:42	3 M	HBP:75.5; LBBP:76	HBP:62.2; LBBP:59.5	Not mentioned	HBP:2018.1–2018.12; LBBP:2019.1–2019.12	Not mentioned
Qian et al. (19)	Retrospective study	China	HBP:64; LBBP:185	3/6 M/1 Y	HBP:66.7 ± 10.8; LBBP:68.9 ± 12.5	HBP:59.4; LBBP:55.1	Bradycardia/HF	2014.9–2019.8	HBP:87.6%; LBBP:95.9%
Sheng et al. (20)	Retrospective study	China	26	3 M	72.9 ± 9.0	65.4	Bradycardia/AF	2019.1–2019.6	Not mentioned
Vijayaraman (21)	Retrospective study	Multiple centers	HBP:46; LBBP:28	12.0 ± 13.7 M	79 ± 8	57	Not mentioned	Not mentioned	HBP:63%; LBBP:93%
Wu (22)	Prospective, non-randomized study	China	HBP:49; LBBP:32	1 Y	HBP:68.3 ± 10; LBBP:67.2 ± 13	HBP:63.3; LBBP:43.8	LBBB/HF/CRT recipients	2012.12–2018.12	HBP:99.2%; LBBP:98.9%

HBP, his-bundle pacing; LBBP, left bundle branch pacing; AF, atrial fibrillation; AVB, atrioventricular block; SND, sinus node dysfunction; HF, heart failure; LBBB, left bundle branch blocked.

TABLE 2 | Quality assessment based on the Newcastle–Ottawa scale.

Study	Representativeness of the patient	Selection of the controls	Ascertainment Of intervention	Demonstration that outcome of interest was not present at the start of the study	Comparability-age and gender	Comparability-Other factors	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total
1. Hua et al. (17)	1	1	1	1	1	1	1	0	1	8
2. Molina-Lerma et al. (18)	1	1	1	1	1	1	1	0	1	8
3. Qian et al. (19)	1	1	1	1	1	1	1	1	1	9
4. Sheng et al. (20)	1	1	1	1	1	1	1	0	1	8
5. Vijayaraman (21)	1	1	1	1	1	1	1	1	1	9
6. Wu (22)	1	1	1	1	1	1	1	1	1	9
7. Hou et al. (15)	1	1	1	1	1	1	1	1	1	9

Average score: 8.57.

also assessed in HBP and LBBP recipients; the results also showed that R wave amplitude was larger in LBBP recipients than HBP recipients (MD: 7.53, 95% CI: 6.85–8.22, $P < 0.0001$; **Figure 3B**). The heterogeneity among these studies was low ($I^2 = 41\%$), and a fixed model was used.

Capture Threshold

In total, four studies (17, 20–22) reported the paced capture threshold at implantation and follow-up. A statistically significant difference was observed at implantation and follow-up in capture threshold. Pooled results showed that capture threshold was lower in patients with LBBP at implantation (MD: 0.63, 95% CI: 0.35–0.90, $I^2 = 89\%$; $P < 0.0001$, **Figure 3C**) and follow-up (MD: 0.76, 95% CI: 0.34–1.18, $I^2 = 93\%$, $P = 0.0004$; **Figure 3D**).

Reduction of QRS Duration

QRS duration was evaluated in six studies, including five studies (15, 17, 20–22) that reported the native QRS duration and the paced QRS duration at implantation and two studies (17, 18) that reported the native QRS duration and the paced QRS duration at follow-up.

We compared QRS duration reduction in our meta-analysis by subtracting paced QRS duration at implantation from the native QRS duration and subtracting paced QRS duration from the native QRS duration at follow-up. As shown in **Figures 3E,F**, no statistical difference was observed in native QRS duration and the reduction of QRS duration between paced QRS duration at implantation (MD: 3.02, 95% CI: −0.81–6.84, $I^2 = 33\%$, $P = 0.12$) and native QRS duration (MD: −3.29, 95% CI: −13.29–6.71, $I^2 = 85\%$, $P = 0.52$). In LBBP recipients, greater QRS reduction was found in the paced QRS duration at follow-up compared with HBP recipients (MD: 6.12, 95% CI: 1.23–11.01, $I^2 = 0\%$, $P = 0.01$; **Figure 3G**).

Left Ventricular Ejection Fractions

In total, two studies (21, 22) reported the LVEF values at baseline and after follow-up to assess the cardiac function of HBP and LBBP recipients. **Figure 3H** shows no statistical difference in native LVEF between HBP and LBBP recipients (MD: −0.82, 95% CI: −3.45–1.80, $P = 0.45$). As shown in **Figure 3I**, no statistical difference in LVEF improvement was found between HBP and LBBP recipients (MD: −1.43, 95% CI: −5.11–2.25, $P = 0.45$). There was no heterogeneity among these studies ($I^2 = 0\%$).

DISCUSSION

In this meta-analysis, it can be observed that LBBP is associated with a higher implant success rate than HBP, and the QRS duration was shorter after follow-up compared with native QRS duration. Second, data show that LBBP recipients have larger R wave amplitudes and lower capture thresholds than HBP recipients postoperatively and after follow-up, while no statistically significant difference in reduction of QRS duration was found between these pacing modalities at baseline. Other pacing parameters and clinical characteristics did not differ significantly between LBBP and HBP.

Since no randomized controlled trials (RCTs) have been published comparing the assessment of the safety and effectiveness of HBP and LBBP, our findings provide some evidence that compared with HBP, LBBP may be easier to implant and has better pacing parameters including capture threshold and R wave amplitude.

Although HBP provides physiological pacing and benefits many patients, it still has some limitations in practice. In addition to electrogram recordings, defining the anatomical region of the HB requires fluoroscopy. When patients have anatomical variations or enlarged right atria, locating the area of the HB can be challenging, which complicates implantation. In some instances, it is difficult to determine where to screw in the lead as well as whether the depth and direction of the lead are appropriate. Optimal lead placement may depend on the use of three-dimensional electroanatomic mapping and/or intracavitary ultrasound (23). The LBB is widely distributed below the left septal endocardium, making it easier to place the lead and capture the left ventricular conduction system (24). These aspects might explain the higher success rate of LBBP.

Previous studies have shown that the HBP capture threshold is significantly higher than the traditional RVP capture threshold (11, 25), which will lead to faster battery depletion and more frequent lead revisions. The exact mechanism is not clear, which may be related to the lead relaxation caused by tricuspid valve movement, inadequate lead fixation, and local fibrosis of the tissue around the lead. However, LBBP can maintain a low pacing threshold during the follow-up period and show higher R wave amplitude (11, 14, 26). This can be explained by noting that the LBBP lead is positioned deep within the left ventricular septum and close to the myocardial tissue, stimulating not only the specialized conduction system but also the deep myocardium of the interventricular septum. Of note, Kawashima et al. found three variations in His bundle anatomy (27), showing that 79% of His bundle are insulated by myocardial fibers, suggesting that the low amplitude of R wave in HBP may be related to the myocardial limitations around the HB region. His bundle encapsulation by myocardial fibrous sheaths may be linked to high capture thresholds during HBP. Our findings show that LBBP has a higher R wave amplitude and a lower capture threshold than HBP, which is consistent with the above studies.

QRS duration is an important indicator of ventricular systolic synchronization in ECG parameters. HBP keeps the electromechanical activity of left and right ventricles synchronized, showing a narrow QRS duration on ECG. The typical pacing QRS morphology of LBBP is characterized by an incomplete right bundle branch block pattern, resulting in longer pacing QRS duration than intrinsic QRS duration (28). However, LBBP may also lead to a narrow QRS duration due to the activation of the right bundle branch by retrograde conduction, intrinsic conduction fusion, and the communications between the bundle branches (29).

In this study, we first analyzed the QRS duration reduction by subtracting paced QRS at implantation from the native QRS duration. In total, three studies reported prolonged QRS duration by LBBP (15, 17, 20), and two studies reported shortened QRS duration by LBBP (21, 22). The final combined results show that

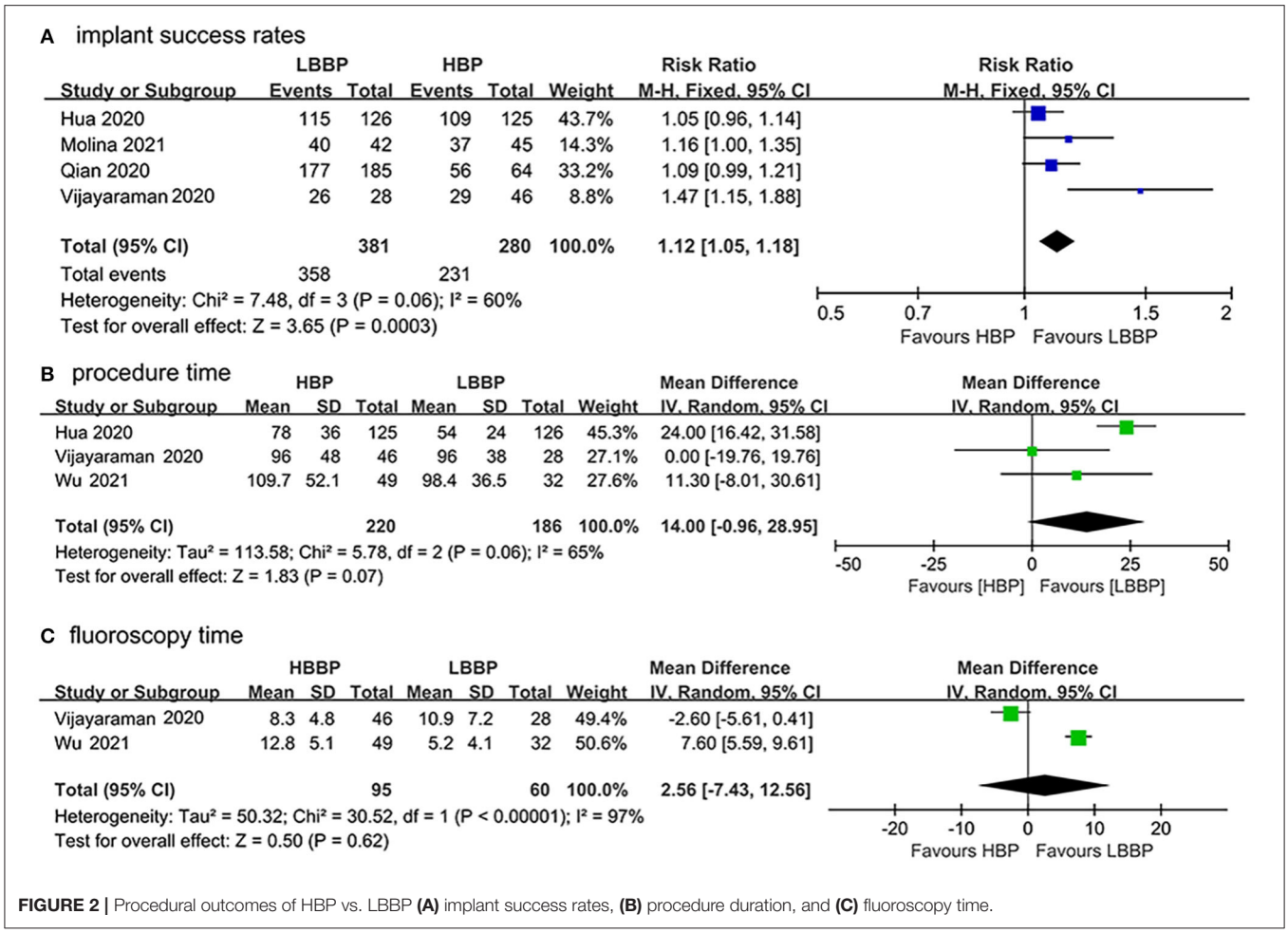

FIGURE 2 | Procedural outcomes of HBP vs. LBBP **(A)** implant success rates, **(B)** procedure duration, and **(C)** fluoroscopy time.

there is no statistical difference in the changes in QRS duration between HBP and LBBP at implantation. Then we analyzed QRS duration reduction by subtracting paced QRS duration at follow-up from the native QRS duration, and our results demonstrated that QRS duration reduction from LBBP is greater than that of HBP at follow-up. It can also be interpreted that LBBP recipients have a lower rate of lead dislodgement, suggesting that the long-term stability of LBBP is better than that of HBP. However, the limited data make it hard to confirm the better performance of LBBP than HBP, and more studies are needed for further verification.

Several studies have shown that HBP and LBBP can improve the LVEF of patients (12, 14, 30, 31). Our results showed no statistical difference in the improvement of LVEF between HBP and LBBP, and both pacing modes had a positive effect on patients with left ventricular dysfunction, indicating that despite LBBP demonstrating better pacing parameters, HBP is not inferior to LBBP in improving cardiac function.

Other pacing parameters, including the mean procedure time and fluoroscopy time, were not statistically different between LBBP and HBP due to the small number of included studies. As for the fluoroscopy time, Vijayaraman et al. (21) had a longer fluoroscopy time in LBBP than in HBP, contrary to Wu et al. (22). The learning curve of HBP has shown that procedure time and fluoroscopy time were shorter with increasing operator experience (32). The differences in procedure time and fluoroscopy time in different studies may be related to the skills and experience of different operators.

LIMITATIONS

Our meta-analysis has several limitations, and the results should be interpreted with caution. First, the included studies are observational cohort studies with small sample sizes rather than randomized controlled trials. Second, owing to only two studies reporting the QRS duration at baseline and follow-up, the real relationship of QRS duration reduction at baseline and follow-up among HBP or LBBP recipients needs to be further investigated. Third, QRS morphology could not be analyzed because of limited reporting in the included studies. Fourth, the primary disease of LBBP or HBP recipients could not be distinguished due to a lack of data. Fifth, as LBBP is a newly discovered pacing technique, the included studies had a short follow-up duration, no longer than 1 year, and long-term outcomes are unavailable. Consequently, multicenter, double-blinded RCTs are still needed to validate the clinical advantages of LBBP.

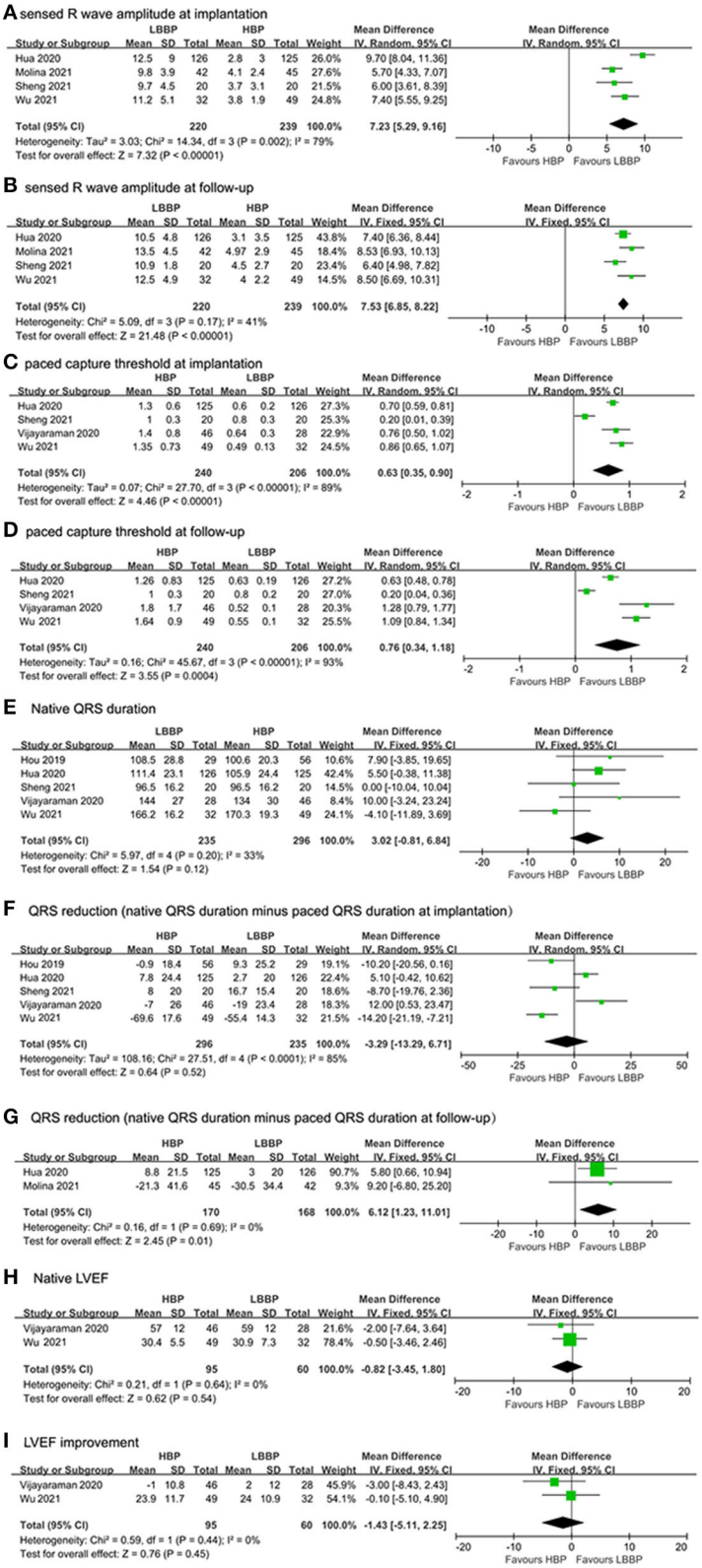

FIGURE 3 | Efficacy characteristics of implantation outcomes and surgical complications: **(A)** capture threshold at implantation, **(B)** capture threshold at follow-up, **(C)** sensed R wave amplitude at implantation, **(D)** sensed R wave amplitude at follow-up, **(E)** native QRS duration, **(F)** QRS duration reduction (native QRS duration minus paced QRS duration at implantation), **(G)** QRS duration reduction (native QRS duration minus paced QRS duration at follow-up), **(H)** native LVEF, and **(I)** LVEF improvement.

CONCLUSION

This meta-analysis has shown that compared with HBP, LBBP is associated with a higher implant success rate, larger R wave amplitude, and lower capture threshold. Pacing characteristics are better with LBBP compared with HBP. LBBP appears to be a promising, possibly superior, and alternative to HBP.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

HL, JY, QC, JH, QX, and KH: supervision. QX and KH: conceptualisation and formal analysis. HL, JY, QC, JH, QX, XZ, and KH: validation, writing—review, and editing. WZ and XZ: investigation. XZ: data curation. WZ: formal analysis, writing—original draft, visualization, and project administration. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by the Science and Technology Research Project of the Education Department of Jiangxi Province (200192) and Science and Technology Plan of Jiangxi Provincial Health Commission (202130420).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.849143/full#supplementary-material

REFERENCES

1. Spath NB, Wang K, Venkatasumbramanian S, Fersia O, Newby DE, Lang CC, et al. Complications and prognosis of patients undergoing apical or septal right ventricular pacing. *Open Heart.* (2019) 6:e000962. doi: 10.1136/openhrt-2018-000962
2. Tayal B, Fruelund P, Sogaard P, Riahi S, Polcwiartek C, Atwater BD, et al. Incidence of heart failure after pacemaker implantation: a nationwide Danish Registry-based follow-up study. *Eur Heart J.* (2019) 40:3641–3648. doi: 10.1093/eurheartj/ehz584
3. Goessens G. High resolution autoradiographic studies of Ehrlich tumour cell nucleoli. Nucleolar labelling after [3H]actinomycin D binding to DNA or after [3H]TdR or [3H]uridine incorporation in nucleic acids. *Exp Cell Res.* (1976) 100:88–94. doi: 10.1016/0014-4827(76)90330-X
4. Khurshid S, Epstein AE, Verdino RJ, Lin D, Goldberg LR, Marchlinski FE, et al. Incidence and predictors of right ventricular pacing-induced cardiomyopathy. *Heart Rhythm.* (2014) 11:1619–25. doi: 10.1016/j.hrthm.2014.05.040
5. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med.* (2005) 352:1539–49. doi: 10.1056/NEJMoa050496
6. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med.* (2009) 361:1329–38. doi: 10.1056/NEJMoa0906431
7. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med.* (2001) 344:873–80. doi: 10.1056/NEJM200103223441202
8. Doshi RN, Gupta N. Cardiac resynchronization therapy: past, present, and future. *Rev Cardiovasc Med.* (2007) 8:69–77.
9. Vijayaraman P, Bordachar P, Ellenbogen KA. The continued search for physiological pacing: where are we now? *J Am Coll Cardiol.* (2017) 69:3099–114. doi: 10.1016/j.jacc.2017.05.005
10. Zhang J, Guo J, Hou X, Wang Y, Qian Z, Li K, et al. Comparison of the effects of selective and non-selective his bundle pacing on cardiac electrical and mechanical synchrony. *Europace.* (2018) 20:1010–7. doi: 10.1093/europace/eux120
11. Vijayaraman P, Naperkowski A, Subzposh FA, Abdelrahman M, Sharma PS, Oren JW, et al. Permanent his-bundle pacing: long-term lead performance and clinical outcomes. *Heart Rhythm.* (2018) 15:696–702. doi: 10.1016/j.hrthm.2017.12.022
12. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, et al. A novel pacing strategy with low and stable output: pacing the left bundle branch immediately beyond the conduction block. *Can J Cardiol.* (2017) 33:1736.e1–3. doi: 10.1016/j.cjca.2017.09.013
13. Wu S, Su L, Wang S, Vijayaraman P, Ellenbogen KA, Huang W. Peri-left bundle branch pacing in a patient with right ventricular pacing-induced cardiomyopathy and atrioventricular infra-Hisian block. *Europace.* (2019) 21:1038. doi: 10.1093/europace/euz031
14. Vijayaraman P, Subzposh FA, Naperkowski A, Panikkath R, John K, Mascarenhas V, et al. Prospective evaluation of feasibility and electrophysiologic and echocardiographic characteristics of left bundle branch area pacing. *Heart Rhythm.* (2019) 16:1774–82. doi: 10.1016/j.hrthm.2019.05.011
15. Hou X, Qian Z, Wang Y, Qiu Y, Chen X, Jiang H, et al. Feasibility and cardiac synchrony of permanent left bundle branch pacing through the interventricular septum. *Europace.* (2019) 21:1694–702. doi: 10.1093/europace/euz188
16. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* (2009) 6:e1000097. doi: 10.1371/journal.pmed.1000097
17. Hua W, Fan X, Li X, Niu H, Gu M, Ning X, et al. Comparison of left bundle branch and his bundle pacing in bradycardia patients. *JACC Clin Electrophysiol.* (2020) 6:1291–9. doi: 10.1016/j.jacep.2020.05.008
18. Molina-Lerma M, Macias-Ruiz R, Sanchez-Millan P, Jimenez-Jaimez J, Tercedor-Sanchez L, Alvarez M. Comparative analysis of his-bundle pacing and left bundle branch area pacing: acute and short-term results. *Rev Espanola Cardiol.* (2021) 74:628–30. doi: 10.1016/j.rec.2020.12.006
19. Qian Z, Qiu Y, Wang Y, Jiang Z, Wu H, Hou X, et al. Lead performance and clinical outcomes of patients with permanent his-purkinje system pacing: a single-centre experience. *Europace.* (2020) 22:ii45–53. doi: 10.1093/europace/euaa295
20. Sheng X, Pan YW, Yu C, Wang B, Zhang P, Li J, et al. Comparison of synchronization between left bundle branch and his bundle pacing in atrial fibrillation patients: an intra-patient-controlled study. *Pacing Clin Electrophysiol.* (2021) 44:1523–31. doi: 10.1111/pace.14331
21. Vijayaraman P, Cano O, Koruth JS, Subzposh FA, Nanda S, Pugliese J, et al. His-Purkinje conduction system pacing following transcatheter aortic valve replacement: feasibility and safety. *JACC Clin Electrophysiol.* (2020) 6:649–57. doi: 10.1016/j.jacep.2020.02.010
22. Wu S, Su L, Vijayaraman P, Zheng R, Cai M, Xu L, et al. Left bundle branch pacing for cardiac resynchronization therapy: nonrandomized on-treatment comparison with his bundle pacing and biventricular pacing. *Can J Cardiol.* (2021) 37:319–28. doi: 10.1016/j.cjca.2020.04.037

23. Vijayaraman P, Ellenbogen KA. Approach to permanent his bundle pacing in challenging implants. *Heart Rhythm.* (2018) 15:1428–31. doi: 10.1016/j.hrthm.2018.03.006
24. Chen X, Jin Q, Li B, Jia J, Sharma PS, Huang W, et al. Electrophysiological parameters and anatomical evaluation of left bundle branch pacing in an in vivo canine model. *J Cardiovasc Electrophysiol.* (2020) 31:214–9. doi: 10.1111/jce.14300
25. Abdelrahman M, Subzposh FA, Beer D, Durr B, Naperkowski A, Sun H, et al. Clinical outcomes of his bundle pacing compared to right ventricular pacing. *J Am Coll Cardiol.* (2018) 71:2319–30. doi: 10.1016/j.jacc.2018.02.048
26. Li X, Li H, Ma W, Ning X, Liang E, Pang K, et al. Permanent left bundle branch area pacing for atrioventricular block: feasibility, safety, and acute effect. *Heart Rhythm.* (2019) 16:1766–73. doi: 10.1016/j.hrthm.2019.04.043
27. Sharma PS, Trohman R. An electro-anatomic atlas of his bundle pacing: combining fluoroscopic imaging and recorded electrograms. *Card Electrophysiol Clin.* (2018) 10:483–90. doi: 10.1016/j.ccep.2018.05.009
28. Vijayaraman P, Dandamudi G, Zanon F, Sharma PS, Tung R, Huang W, et al. Permanent his bundle pacing: recommendations from a multicenter his bundle pacing collaborative working group for standardization of definitions, implant measurements, and follow-up. *Heart Rhythm.* (2018) 15:460–8. doi: 10.1016/j.hrthm.2017.10.039
29. Zhang S, Zhou X, Gold MR. Left bundle branch pacing: JACC review topic of the week. *J Am Coll Cardiol.* (2019) 74:3039–49. doi: 10.1016/j.jacc.2019.10.039
30. Lustgarten DL, Crespo EM, Arkhipova-Jenkins I, Lobel R, Winget J, Koehler J, et al. His-bundle pacing versus biventricular pacing in cardiac resynchronization therapy patients: a crossover design comparison. *Heart Rhythm.* (2015) 12:1548–57. doi: 10.1016/j.hrthm.2015.03.048
31. Ajijola OA, Upadhyay GA, Macias C, Shivkumar K, Tung R. Permanent his-bundle pacing for cardiac resynchronization therapy: initial feasibility study in lieu of left ventricular lead. *Heart Rhythm.* (2017) 14:1353–61. doi: 10.1016/j.hrthm.2017.04.003
32. De Leon J, Seow SC, Boey E, Soh R, Tan E, Gan HH, et al. Adopting permanent his bundle pacing: learning curves and medium-term outcomes. *Europace.* (2021) 25:euab278. doi: 10.1093/europace/euab278

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frontiers in Cardiovascular Medicine

OPINION
published: 28 March 2022
doi: 10.3389/fcvm.2022.845312

Which Is More Likely to Achieve Cardiac Synchronization: Left Bundle Branch Pacing or Left Ventricular Septal Pacing?

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Keywords: left bundle branch pacing, left ventricular septal pacing, cardiac resynchronization therapy, right ventricular pacing, physiological pacing

INTRODUCTION

In advanced heart failure patients with low left ventricular ejection fraction and left bundle branch block (LBBB), cardiac resynchronization therapy (CRT) *via* stimulation of both the right ventricle (RV) and the left ventricular lateral wall is a recommended therapeutic strategy (1–3). However, conventional biventricular pacing causes a dyssynchronous cardiac contraction due to non-physiological fusion of paced propagation, with a non-response rate of up to 30% (4, 5). In 2016, Mafi-Rad et al. (6) established the viability of the left ventricular septal pacing (LVSP) *via* a trans-interventricular septal approach in 10 patients with sinus node dysfunction, which shortened QRS duration and preserved acute left ventricular contractility compared to RV pacing. Huang et al. refined LVSP and introduced first left bundle branch pacing (LBBP) in 2017 (7), which could restore physiological left ventricular contractility in a patient with LBBB by pacing left bundle branch (LBB) immediately beyond the conduction blockage with satisfactory pacing parameters. Many studies have demonstrated the feasibility and stability of LBBP in patients with pacemaker indications, and it has been proposed that LBBP is a novel physiological pacing method for delivering CRT for achieving electric resynchronization in patients with LBBB (8–10).

BRIEF PACING MECHANISMS OF LBBP AND LVSP

Selective LBBP (SLBBP) and non-selective LBBP (NSLBBP) are two subgroups of LBBP. SLBBP, that is, only the LBB trunk or its proximal fascicles is captured (**Figure 1A**). NSLBBP, that is, concomitant LBB and adjacent myocardium are captured (**Figures 1B,E**). It is LVSP if just the left ventricular septal myocardium is captured (**Figure 1D**). Both LVSP and LBBP usually present a paced pseudo right bundle branch block (RBBB) pattern in lead V1 (11), with the percentage of direct evidence that LBBP captured LBB ranging between 60 and 90% (12–14). Therefore, LBBP described in some previous studies was actually LVSP. A method to measure the time from stimulus to left ventricular activation at high and low outputs in lead V5 or V6 (Stim-LVAT) to distinguish LBBP from LVSP with a specificity of 100% has recently been presented (11). If the Stim-LVAT remains shortest and constant (prolonged $\leq$ 10 ms) as the pacing output decreases, it must be LBBP, because LBBP directly captures the LBB resulting in physiologically LV excitation; otherwise LVSP can be considered, because LVSP excites left ventricular septum first, rather than LBB. SLBBP and NSLBBP can be distinguished by the discrete component and isoelectric interval between the pacing artifact and V wave on intracardiac electrogram with unchanged Stim-LVAT (11).

OPEN ACCESS

Edited by:
Matteo Anselmino, University of Turin, Italy

Reviewed by:
Jacqueline Joza, McGill University Health Centre, Canada

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Specialty section:
This article was submitted to Cardiac Rhythmology, a section of the journal Frontiers in Cardiovascular Medicine

Received: *29 December 2021*
Accepted: *07 March 2022*
Published: *28 March 2022*

Citation:
Zhu K, Chang D and Li Q (2022) Which Is More Likely to Achieve Cardiac Synchronization: Left Bundle Branch Pacing or Left Ventricular Septal Pacing? Front. Cardiovasc. Med. 9:845312. doi: 10.3389/fcvm.2022.845312

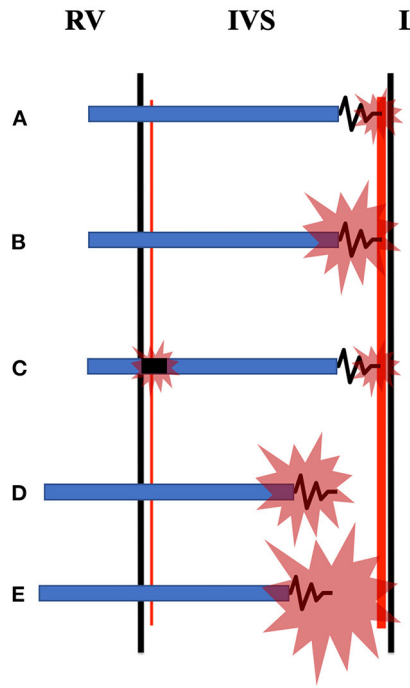

FIGURE 1 | Diagrammatic sketch of left bundle branch pacing (LBBP) and left ventricular septal pacing (LVSP) with different pacing modes. **(A)** Selective LBBP (SLBBP) captures only the left bundle branch (LBB) trunk or its proximal bundle, resulting in physiologically left ventricle (LV) excitation but delayed right ventricle (RV) excitation. Non-selective LBBP (NSLBBP) is divided into two types: **(B)**, which excites the LBB and surrounding myocardium, and **(E)**, which excites the LBB and the left ventricular septal myocardium. **(C)** In bipolar pacing configuration, the cathode tip of LBBP captures the LBB and the anode ring captures the right bundle branch at the same time, probably due to the anodal capture. **(D)** LVSP captures only the left ventricular septal myocardium. RV, right ventricle; IVS, interventricular septum; LV, left ventricle.

COMPARISON OF LBBP AND LVSP IN INTERVENTRICULAR SYNCHRONY

In the paper published in *Frontiers in Cardiovascular Medicine*, Curila et al. (15) used ultra-high-frequency electrocardiography to compare ventricular depolarization in SLBBP, NSLBBP, and LVSP in 57 bradycardia patients, which were rigorously distinguished by Stim-LVAT. They concluded that LVSP preserved interventricular synchrony and had the same or better local depolarization durations than NSLBBP and SLBBP. Furthermore, they investigated two different types of NSLBBP capture, namely, NSLBBP with LBB and adjacent myocardium captured (**Figure 1B**), and NSLBBP with LBB and left septal myocardium captured (**Figure 1E**). NSLBBP with LBB and adjacent myocardium captured, that is, NSLBBP is converted to SLBBP with a shortest and constant Stim-LVAT while decreasing the pacing outputs. NSLBBP with LBB and left septal myocardium captured, that is, NSLBBP is converted to LVSP with prolonged Stim-LVAT while decreasing the pacing outputs. They evaluated the two types of NSLBBP capture and found no statistical difference in Stim-LVAT between the two types, but NSLBBP with LBB and left septal myocardium captured showed greater interventricular synchronization.

Then, which pacing strategy is more physiological, LBBP or LVSP? SLBBP and NSLBBP, unlike LVSP, capture the intrinsic conduction system and rapidly excite LV to maintain left ventricular synchrony at levels comparable to intrinsic left ventricular activation (16). At the same time, activation propagates slowly from left to right in the interventricular septum to excite RV, resulting in interventricular dyssynchrony. LVSP, on the other hand, captures left ventricular septal myocardium, resulting in direct left-to-right septal activation, preserving interventricular dyssynchrony. The terminal R′/r′ wave duration in lead V1, which indicates delayed right ventricular excitation, was significantly longer in LBBP than in LVSP (17), also indicating that LBBP caused more pronounced interventricular dyssynchrony than LVSP. However, this interventricular synchrony of LVSP may not be physiological. Instead of using the same stimulation marker, such as the pacing artifact, Curila et al. calculated interventricular dyssynchrony in SLBBP, NSLBBP, and LVSP as the difference between the first and last activation (15). There is no doubt that Stim-LVAT of LVSP is significantly longer than that of LBBP, implying that the LV excitation in LVSP occurs later than in LBBP. As a result, the improved interventricular synchronization of LVSP is attributable to greater overlap of LV and RV activation produced by delayed activation of both the LV and the RV (18).

Curila et al. only evaluated the LBBP with unipolar pacing configuration, not bipolar pacing configuration (15). Lin et al. developed a bilateral bundle branch area pacing strategy that involves stimulating the cathode and anode in various pacing configurations to capture both LBB and right bundle branch (RBB) area, which can diminish delayed right ventricular activation caused by LBBP and result in more physiological ventricular activation (19). It is essentially LBBP with bipolar pacing configuration (**Figure 1C**), with the cathode tip capturing LBB and the anode ring capturing RBB area. Shimeno et al. also revealed that the terminal R′/r′ wave duration of LBBP with bipolar pacing configuration is shorter than that of LVSP, presumably due to the contribution of the anodal capture during bipolar pacing (17). In addition, some previous studies and case reports have shown that LBBP can shorten the QRS duration of intrinsic RBBB or even completely correct RBBB (19–23), while LVSP cannot, but the underlying mechanism remains unclear and needs further study.

CONCLUSION

Compared with LVSP, LBBP is a more ideal pacing strategy for CRT, and many studies have confirmed its safety, stability and efficacy. Future study will focus on how to diminish RBBB associated with LBBP in order to obtain better physiological interventricular synchrony. For example, adjusting the atrioventricular delay to combined LV stimulation by LBBP with intrinsic RV excitation in patients with normal RBB conduction, or modifying the interelectrode distance of pacing lead to better complete bilateral bundle branch area pacing in patients with RBBB. Although LVSP in close proximity to

LBB can be an alternative choice, clinically, this is essentially NSLBBP. The pacing output necessary to convert LVSP to NSLBBP, on the other hand, had not been investigated, and it was unknown if this output would have an adverse effect on pacemaker battery longevity. The long-term clinical effects of LVSP and LBBP remains unclear. Current studies solely examine the differences in electrophysiologic characteristics between LVSP and LBBP, such as Stim-LVAT, QRS duration, terminal R' wave duration, QRS area, etc. In the future, it will be necessary to evaluate the echocardiographic activation of LVSP and LBBP, encompassing not only intraventricular synchronization, but also interventricular synchronization.

AUTHOR CONTRIBUTIONS

KZ wrote the original manuscript and conceptualized the idea. DC and QL supervised and wrote and edited the manuscript for publication. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by Research Grant No. 3502Z20214ZD1165 from Xiamen Municipal Bureau of Science and Technology.

REFERENCES

1. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med.* (2005) 352:1539–49. doi: 10.1056/NEJMoa050496
2. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med.* (2002) 346:1845–53. doi: 10.1056/NEJMoa013168
3. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med.* (2001) 344:873–80. doi: 10.1056/NEJM200103223441202
4. Ploux S, Eschalier R, Whinnett ZI, Lumens J, Derval N, Sacher F, et al. Electrical dyssynchrony induced by biventricular pacing: implications for patient selection and therapy improvement. *Heart Rhythm.* (2015) 12:782–91. doi: 10.1016/j.hrthm.2014.12.031
5. Birnie DH, Tang AS. The problem of non-response to cardiac resynchronization therapy. *Curr Opin Cardiol.* (2006) 21:20–6. doi: 10.1097/01.hco.0000198983.93755.99
6. Mafi-Rad M, Luermans JG, Blaauw Y, Janssen M, Crijns HJ, Prinzen FW, et al. Feasibility and acute hemodynamic effect of left ventricular septal pacing by transvenous approach through the interventricular septum. *Circ Arrhythm Electrophysiol.* (2016) 9:e003344. doi: 10.1161/CIRCEP.115.003344
7. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, et al. A novel pacing strategy with low and stable output: pacing the left bundle branch immediately beyond the conduction block. *Can J Cardiol.* (2017) 33:1736.e1731–e1733. doi: 10.1016/j.cjca.2017.09.013
8. 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) 6:849–58. doi: 10.1016/j.jacep.2020.04.011
9. Wu S, Su L, Vijayaraman P, Zheng R, Cai M, Xu L, et al. Left bundle branch pacing for cardiac resynchronization therapy: nonrandomized on-treatment comparison with his bundle pacing and biventricular pacing. *Can J Cardiol.* (2021) 37:319–28. doi: 10.1016/j.cjca.2020.04.037
10. Guo J, Li L, Xiao G, Ye T, Huang X, Meng F, et al. Remarkable response to cardiac resynchronization therapy via left bundle branch pacing in patients with true left bundle branch block. *Clin Cardiol.* (2020) 43:1460–8. doi: 10.1002/clc.23462
11. Wu S, Chen X, Wang S, Xu L, Xiao F, Huang Z, et al. Evaluation of the criteria to distinguish left bundle branch pacing from left ventricular septal pacing. *JACC Clin Electrophysiol.* (2021) 7:1166–77. doi: 10.1016/j.jacep.2021.02.018
12. Heckman LIB, Luermans J, Curila K, Van Stipdonk AMW, Westra S, Smisek R, et al. Comparing ventricular synchrony in left bundle branch and left ventricular septal pacing in pacemaker patients. *J Clin Med.* (2021) 10:822. doi: 10.3390/jcm10040822
13. Jastrzebski M, Kiełbasa G, Curila K, Moskal P, Bednarek A, Rajzer M, et al. Physiology-based electrocardiographic criteria for left bundle branch capture. *Heart Rhythm.* (2021) 18:935–43. doi: 10.1016/j.hrthm.2021.02.021
14. Jastrzebski M, Kiełbasa G, Moskal P, Bednarek A, Kusiak A, Sondej T, et al. Fixation beats: a novel marker for reaching the left bundle branch area during deep septal lead implantation. *Heart Rhythm.* (2021) 18:562–9. doi: 10.1016/j.hrthm.2020.12.019
15. Curila K, Jurak P, Vernooy K, Jastrzebski M, Waldauf P, Prinzen F, et al. Left ventricular myocardial septal pacing in close proximity to LBB does not prolong the duration of the left ventricular lateral wall depolarization compared to LBB pacing. *Front Cardiovasc Med.* (2021) 8:787414. doi: 10.3389/fcvm.2021.787414
16. Vijayaraman P, Patel N, Colburn S, Beer D, Naperkowski A, Subzposh FA. His-Purkinje conduction system pacing in atrioventricular block: new insights into site of conduction block. *JACC Clin Electrophysiol.* (2022) 8:73–85. doi: 10.1016/j.jacep.2021.07.007
17. Shimeno K, Tamura S, Nakatsuji K, Hayashi Y, Abe Y, Naruko T. Characteristics and proposed mechanisms of QRS morphology observed during the left bundle branch pacing procedure. *Pacing Clin Electrophysiol.* (2021) 44:1987–94. doi: 10.1111/pace.14382
18. Huang W, Zhou X, Ellenbogen KA. Pursue physiological pacing therapy: a better understanding of left bundle branch pacing and left ventricular septal myocardial pacing. *Heart Rhythm.* (2021) 18:1290–1. doi: 10.1016/j.hrthm.2021.05.013
19. Lin J, Chen K, Dai Y, Sun Q, Li Y, Jiang Y, et al. Bilateral bundle branch area pacing to achieve physiological conduction system activation. *Circ Arrhythm Electrophysiol.* (2020) 13:e008267. doi: 10.1161/CIRCEP.119.008267
20. Li X, Li H, Ma W, Ning X, Liang E, Pang K, et al. Permanent left bundle branch area pacing for atrioventricular block: feasibility, safety, and acute effect. *Heart Rhythm.* (2019) 16:1766–73. doi: 10.1016/j.hrthm.2019.04.043
21. Li X, Fan X, Li H, Ning X, Liang E, Ma W, et al. ECG patterns of successful permanent left bundle branch area pacing in bradycardia patients with typical bundle branch block. *Pacing Clin Electrophysiol.* (2020) 43:781–90. doi: 10.1111/pace.13982
22. Zhu K, Sun Y, Cai B, Li L, Li G, Liu J, et al. Left bundle branch pacing in patients with right bundle branch block. *Kardiol Pol.* (2021) 79:1127–9. doi: 10.33963/KP.a2021.0091

23. Zhu K, Lin M, Li L, Chang D, Li Q. Left bundle branch pacing shortened the QRS duration of a right bundle branch block. *J Electrocardiol.* (2021) 68:153–6. doi: 10.1016/j.jelectrocard.2021.08.018

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BRIEF RESEARCH REPORT
published: 09 June 2022
doi: 10.3389/fcvm.2022.885201

An Electrocardiographic Characterization of Left Bundle Branch Area Pacing-Induced Right Ventricular Activation Delay: A Comparison With Native Right Bundle Branch Block

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OPEN ACCESS

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Specialty section:
This article was submitted to Cardiac Rhythmology, a section of the journal Frontiers in Cardiovascular Medicine

Received: *27 February 2022*
Accepted: *17 May 2022*
Published: *09 June 2022*

Citation:
Ozpak E, Demolder A, Kizilkilic S, Calle S, Timmermans F and De Pooter J (2022) An Electrocardiographic Characterization of Left Bundle Branch Area Pacing-Induced Right Ventricular Activation Delay: A Comparison With Native Right Bundle Branch Block. Front. Cardiovasc. Med. 9:885201. doi: 10.3389/fcvm.2022.885201

Background: Left bundle branch area pacing (LBBAP) induces delayed RV activation and is thought to be harmless, since the electrocardiographic signature is reminiscent to native RBBB. However, to what extent the delayed RV activation during LBBAP truly resembles that of native RBBB remains unexplored.

Methods: This study included patients with incomplete RBBB (iRBBB), complete RBBB (cRBBB) and patients who underwent LBBAP. Global and right ventricular activation times were estimated by QRS duration and R wave peak time in lead V1 (V1RWPT) respectively. Delayed RV activation was further characterized by duration, amplitude and area of the terminal R wave in V1.

Results: In patients with LBBAP ($n = 86$), QRS duration [120 ms (116, 132)] was longer compared to iRBBB patients ($n = 422$): 104 ms (98, 110), $p < 0.001$, but shorter compared to cRBBB ($n = 223$): 138 ms (130, 152), $p < 0.001$. V1RWPT during LBBAP [84 ms (72, 92)] was longer compared to iRBBB [74 ms (68, 80), $p < 0.001$], but shorter than cRBBB [96 ms (86, 108), $p < 0.001$]. LBBAP resulted in V1 R′ durations [42 ms (28, 55)] comparable to iRBBB [42 ms (35, 49), $p = 0.49$] but shorter than in cRBBB [81 ms (68, 91), $p < 0.001$]. During LBBAP, the amplitude and area of the V1 R′ wave were more comparable with iRBBB than cRBBB. V1RWPT during LBBAP was determined by baseline conduction disease, but not by LBBAP capture type.

Conclusion: LBBAP-induced delayed RV activation electrocardiographically most closely mirrors the delayed RV activation as seen with incomplete rather than complete RBBB.

Keywords: left bundle branch area pacing, conduction system pacing, cardiac pacing, right ventricular activation, ventricular activation time

INTRODUCTION

Right ventricular (RV) apex pacing has been considered the standard pacing approach since its first attempt in 1958 (1). Although this pacing strategy meets its primary objective (pacing the heart), it can induce a dyssynchronous ventricular activation which can lead to pacing-induced cardiomyopathy, adverse cardiac remodeling and increased mortality (2–8). Conduction system pacing (CSP) recently emerged as an alternative pacing approach to achieve physiological pacing and it may avoid the detrimental effects of RV pacing. Among the CSP modalities, His bundle pacing (HBP) is considered the most physiological since it optimally mimics the normal cardiac conduction, but it is limited by high capture thresholds, low sensing amplitudes and low implant success in patients with infranodal conduction disease (9, 10). On the other hand, left bundle branch area pacing (LBBAP) is a novel approach to achieve physiological pacing and has more favorable pacing characteristics (i.e., lower pacing thresholds and higher sensing amplitudes) compared to HBP (11–15). LBBAP aims to capture the left bundle branch (LBB) and results in a fast and homogenous activation of the left ventricle (LV) comparable to HBP (16). In contrast, activation of the RV is delayed, which is not the case in HBP. This delayed RV activation is electrocardiographically characterized by a right bundle branch block (RBBB) pattern on the electrocardiogram (ECG), and is considered one of the hallmarks of successful LBBAP (17). In patients without structural heart disease, delayed RV activation due to native RBBB is generally considered benign as it does not result in adverse outcome (18–23), and therefore it can be postulated that LBBAP-induced delayed RV activation is probably benign. However, to what extent LBBAP-induced delayed RV activation truly resembles native RBBB activation in healthy individuals is currently unknown. This study aims to compare the electrocardiographic characteristics of delayed RV activation in patients with native RBBB vs. patients with LBBAP-induced RBBB-like ECG pattern.

METHODS

Study Design

The study enrolled consecutive adult in- and outpatients diagnosed with either incomplete RBBB (iRBBB) or complete RBBB (cRBBB) on standard twelve-lead ECG between January 2015 and September 2018. LBBAP patients implanted between March 2020 and October 2021 were included in the LBBAP group.

All patients were recruited at the Ghent University Hospital. The study was approved by the Ethics Committee of the Ghent University Hospital.

Selection of iRBBB and cRBBB Patients

Contemporary definitions of iRBBB and cRBBB were used to select RBBB patients. QRS duration cut-offs used for iRBBB and cRBBB were 110–119 and ≥120 ms respectively (22). Patients with iRBBB and cRBBB were identified by the Marquette 12SL algorithm (GE Healthcare, Chicago, IL, United States) in the Muse ECG database (GE Healthcare).

LBBAP Implant and Definition of Capture Type

LBBAP implant was performed as previously described and both lumen-less and conventional stylet-driven pacing leads were used (17, 24). Successful LBBAP was defined as either conduction system capture (left bundle branch pacing, LBBP) or myocardial capture (left ventricular septal pacing, LVSP). Following criteria were used to define the type of capture (15, 17, 25, 26): (1) appearance of a Qr, qR, rSr pattern in lead V1, (2) observed transition in pacing responses (non-selective, selective LBBP or myocardial capture) with changes in unipolar pacing output, (3) stimulus to R wave peak time in lead V6 <75 ms in patients with baseline narrow QRS or RBBB or ≤80 ms in patients with left bundle branch block (LBBB) or intraventricular conduction delay (IVCD) (26). Patients that fulfilled the first criterium and at least one additional criterium were considered LBBP; if only the first criterium was met, the pacing response was defined as LVSP (17).

Electrocardiographic Analysis

ECG's were recorded at a paper speed of 25 mm/s and a calibration of 10 mm/mV with MAC 5500 ECG recording devices (GE Healthcare). To avoid any fusion with intrinsic rhythm during LBBAP, paced QRS morphologies were obtained during VVI pacing with a lower rate 20–30 beats higher then intrinsic heart rate. Global ventricular activation was measured as global QRS duration, in which the QRS was measured from its onset to the latest QRS offset in any lead (22, 27). The right ventricular activation time (RVAT) was estimated by the R wave peak time in lead V1 (V1RWPT), measured from QRS onset to the peak of the R wave in lead V1 (i.e., the R wave in case of qR pattern and the r′ wave in rSr′ pattern). Left ventricular activation time (LVAT) was calculated from QRS onset to the R wave peak in lead V6 (V6RWPT) (26, 28). The interval between the R wave peak time in V6 and V1 was defined as the V6–V1 interpeak interval (V6V1 IPI) and used as an estimation of interventricular electrical dyssynchrony (29).

All electrocardiographic measurements were performed with digital calipers and adapted sweep speeds of 50 mm/s on the digitally stored ECG's. The delayed RV activation was further characterized by measuring the duration, amplitude and area of the delayed R wave in V1 using automated measurements provided by the 12SL algorithm (GE Healthcare) (30).

Statistical Analysis

Categorical variables are expressed as absolute number (percentage). Continuous variables are expressed as mean ± standard deviation in case of Gaussian distribution or median [1st; 3rd quartile] if data follow a non-Gaussian distribution. Normality was tested using the Shapiro–Wilk test. To compare means and medians of continuous variables among groups the one-way ANOVA and Kruskall Wallis test was used. The Wilcoxon signed rank test was used for paired comparison of non-Gaussian distributed continuous variables. Multivariate analysis was performed to assess determinants of delayed RV activation using multiple regression analysis. Statistical significance was set at a two-tailed probability level of <0.05. All

statistical analyses were performed using SPSS software (version 28.0, IBM, Armonk, NY, United States).

RESULTS

Patient Characteristics

Overall, the study included 731 patients with delayed RV activation: 422 patients with iRBBB, 223 patients with cRBBB and 86 patients with LBBAP. Baseline patient characteristics are summarized in **Table 1**.

In patients who underwent LBBAP, pacing indication was atrioventricular block in 62%, brady-tachy syndrome in 17%, sinus node disease in 16% and heart failure in 5%. In patients undergoing LBBAP, baseline QRS measured 112 ms (94, 147), with 55% having narrow QRS, 14.5% left bundle branch block (LBBB), 14.5% RBBB and 17% non-specified intraventricular conduction delay (NIVCD). LBBAP pacing response was labeled as LBBP (non-selective and selective) in 62 (72%) patients, whereas LVSP was achieved in 24 (28%) patients.

Ventricular Activation Times During LBBAP in Comparison to iRBBB and cRBBB Patients

Representative examples of ventricular activation time measurements with iRBBB, cRBBB and LBBAP are shown in **Figure 1**. Paced QRS duration during LBBAP was 120 ms (116, 132), whereas QRS duration of iRBBB and cRBBB patients was 104 ms (98, 110) and 138 ms (130, 152) respectively ($p < 0.001$). V1RWPT during LBBAP was 84 ms (72, 92) and longer compared to iRBBB patients [74 ms (68, 80), $p < 0.001$], but shorter in comparison to cRBBB patients [96 ms (86, 108), $p < 0.001$] (**Figure 2A**). V6RWPT during LBBAP [44 ms (36, 56)] was only slightly longer than V6RWPT measured during iRBBB [40 ms (36, 44), $p < 0.001$] and cRBBB [38 ms (36, 44), $p < 0.001$]. The V6V1 IPI for LBBAP patients was comparable to iRBBB patients [36 ms (24, 45) and 34 ms (28, 40), respectively; $p = 0.70$]. Compared to cRBBB, the V6V1 IPI was shorter for LBBAP patients [58 ms (48, 68) vs. 36 ms (24, 45), $p < 0.001$].

R′ duration in V1 with LBBAP-induced RBBB was 42 ms (28, 55) and was comparable to V1 R′ duration in iRBBB patients [42 ms (35, 49), $p = 0.49$], but shorter than in cRBBB patients [81 ms (68, 91), $p < 0.001$] (**Figure 2B**). Mean V1 R′ amplitude during LBBAP measured 297 uV (175, 645), which was also smaller compared to cRBBB patients, but larger than iRBBB patients [respectively 761 uV (551, 1,010) and 195 uV (126, 298), $p < 0.001$] (**Figure 2C**). R′ area in V1 during LBBAP [316 uVs (134, 831)] was smaller compared to cRBBB [1,782 uVs (1,182, 2,498), $p < 0.001$], but larger than in patients with iRBBB [236 uVs (140, 399), $p = 0.008$] (**Figure 2D**).

Ventricular Activation Times During LBBAP According to Baseline Conduction Disease

With LBBAP, QRS duration shortened from 153 ms (142, 160) to 116 ms (104, 136) ($p < 0.001$) in patients with LBBB, from 147 ms (137, 158) to 136 ms (122, 136) ($p = 0.009$) in RBBB patients and from 135 ms (128, 153) to 128 ms (118, 133) ($p = 0.33$) in patients with NIVCD. In patients with baseline narrow QRS (<120 ms), QRS duration increased from 94 ms (84, 106) to 120 ms (115, 128) ($p < 0.001$) with LBBAP. Ventricular activation times during LBBAP according to baseline conduction disease are summarized in **Table 2**. The longest V1RWPT were observed in LBBAP patients with pre-existing RBBB [84 ms (72, 92)] and NIVCD [90 ms (83, 100)], although the differences with narrow QRS [82 ms (72, 89)] and LBBB [72 ms (65, 79)] patients were small ($p = 0.014$). R′ duration in V1 was significantly shorter for patients with narrow QRS [39 ms (20, 52)] undergoing LBBAP, compared to LBBAP patients with underlying RBBB [46 ms (38, 74)], LBBB [48 ms (38, 55)] and NIVCD [49 ms (35, 66)], $p = 0.04$. Of interest, in LBBAP patients with presumed delay of the right bundle branch conduction (such as RBBB and NIVCD patients), the V1RWPT and V1 R′ duration were still shorter compared to cRBBB patients ($p = 0.03$ and $p < 0.001$, respectively).

Ventricular Activation Times During LBBAP According to LBBAP Capture Type

V1RWPT values were comparable for patients with LBBP ($n = 62$) and LVSP ($n = 24$): 84 ms (72, 88) vs. 80 ms (72, 91), respectively ($p = 0.43$); and V1RWPT of both LBBP and LVSP patients resembled more V1RWPT of iRBBB patients compared to cRBBB patients.

V6RWPT values were shorter in LBBP patients [42 ms (33, 54)] compared to patients with LVSP capture type [52 ms (45, 62), $p = 0.01$]. Due to the comparable V1RWPT but different V6RWPT, patients with LBBP presented with longer V6V1 IPI compared to LVSP [40 ms (32, 48) vs. 26 ms (24, 37), respectively, $p = 0.001$].

In patients with LBBP, V1 R′ duration, amplitude and area [respectively 42 ms (27, 58), 337 uV (193, 686), 332 uVs (231, 418)] were comparable to LVSP [45 ms (31, 54), $p = 0.45$; 254 uV (168, 523), $p = 0.76$; 285 uVs (129, 494), $p = 0.45$).

Determinants of Delayed Right Ventricular Activation in iRBBB, cRBBB and LBBAP Patients

Due to differences in baseline characteristics between iRBBB, cRBBB and LBBAP patients (**Table 1**), determinants of delayed RV activation were analyzed. In univariate analysis ischemic heart disease, history of atrial fibrillation and presence of heart failure were associated with longer V1RWPT and V1 R′ duration among the entire population of iRBBB, cRBBB and LBBAP patients. However, in a multiple regression analysis only the presence of heart failure and patient group (iRBBB, cRBBB and LBBAP) remained significant and independently associated with V1RWPT and V1 R′ duration.

DISCUSSION

Main Findings

This study is the first to compare the electrocardiographic pattern of LBBAP-induced delayed RV activation to the delayed RV activation observed in patients with conduction

TABLE 1 | Baseline patient characteristics.

	iRBBB ($n = 422$)	cRBBB ($n = 223$)	LBBAP ($n = 86$)	p-value
Baseline patient characteristics				
Age, years	51 ± 18	57 ± 21	69 ± 16	$p < 0.001$
Female gender, *n* (%)	282 (67)	164 (74)	61 (71)	$p = 0.20$
Weight, kg	75 ± 15	76 ± 19	80 ± 19	$p = 0.05$
Length, cm	174 ± 10	170 ± 10	169 ± 13	$p < 0.001$
Medical history				
Ischemic heart disease, *n* (%)	72 (17%)	46 (21%)	24 (28%)	$p < 0.001$
Acute coronary syndrome, *n* (%)	12 (3%)	46 (21%)	10 (12%)	$p < 0.001$
Heart failure, *n* (%)	24 (6%)	46 (21%)	7 (8%)	$p < 0.001$
Atrial fibrillation, *n* (%)	4 (2%)	4 (1%)	32 (37%)	$p < 0.001$
Echocardiographic characteristics				
Left atrial diameter, mm	36 ± 7	40 ± 9	40 ± 9	$p < 0.001$
Left ventricular end diastolic diameter, mm	46 ± 6	48 ± 7	49 ± 9	$p = 0.007$
Electrocardiographic characteristics				
QRS duration, ms	104 (98, 110)	138 (130, 152)	112 ms (94, 147)	$p < 0.001$

Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as number of patients (percentage).
iRBBB, incomplete right bundle branch block; cRBBB, complete right bundle branch block. LBBAP, left bundle branch area pacing.

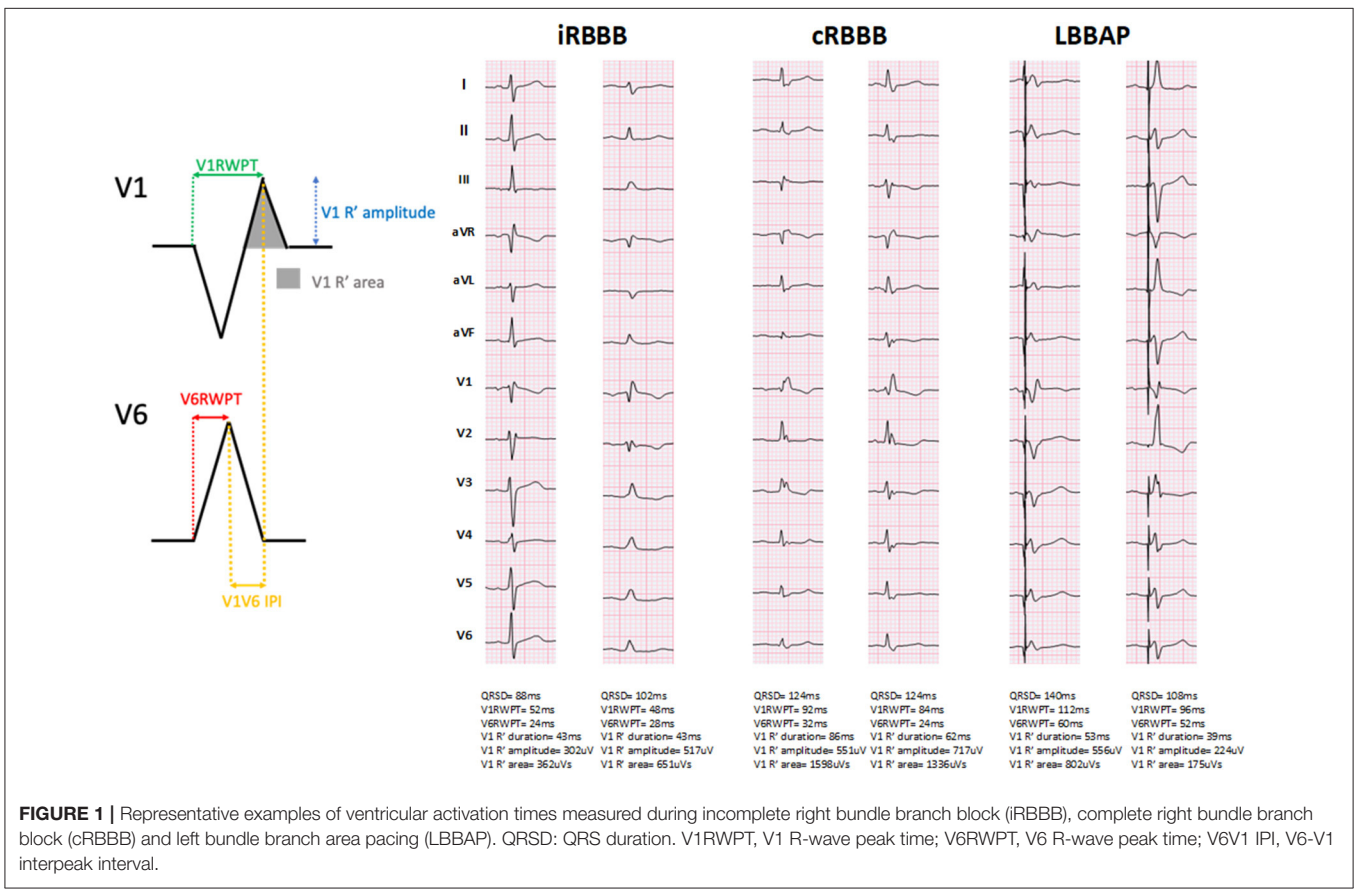

FIGURE 1 | Representative examples of ventricular activation times measured during incomplete right bundle branch block (iRBBB), complete right bundle branch block (cRBBB) and left bundle branch area pacing (LBBAP). QRSD: QRS duration. V1RWPT, V1 R-wave peak time; V6RWPT, V6 R-wave peak time; V6V1 IPI, V6-V1 interpeak interval.

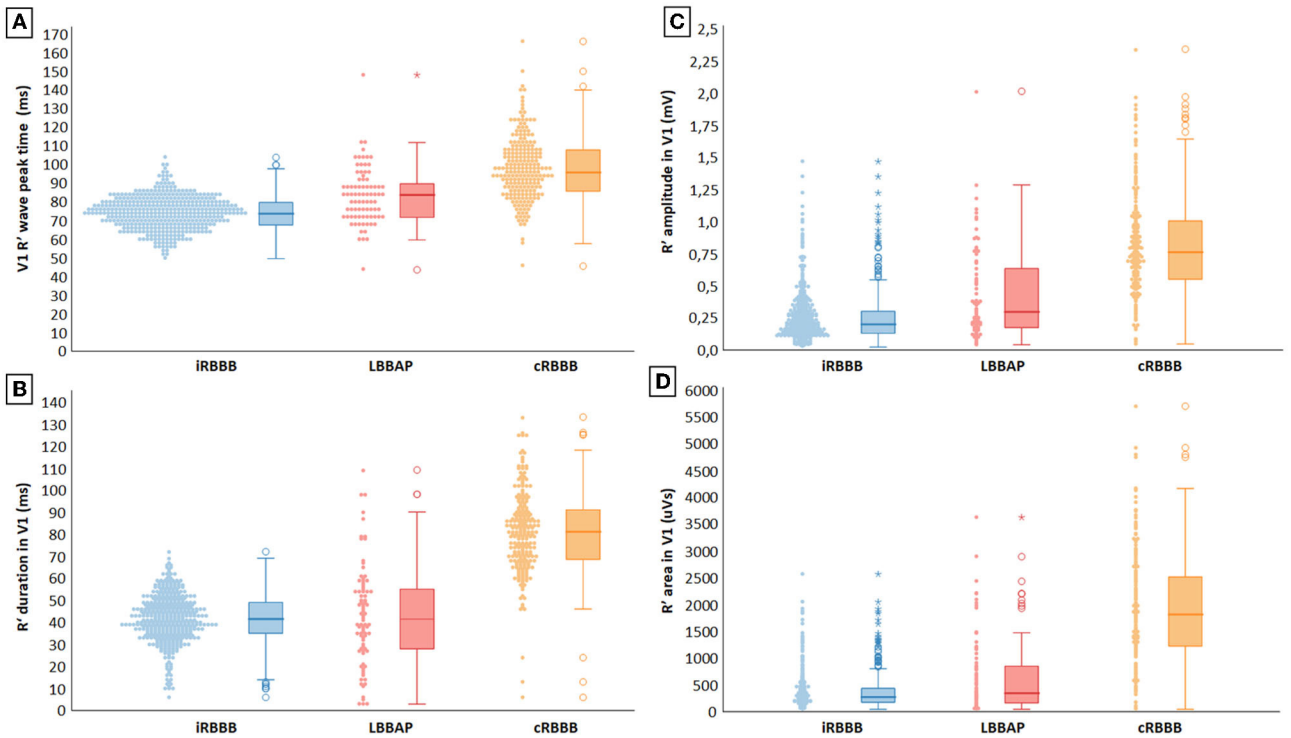

FIGURE 2 | (A–D) Electrocardiographic characterization of delayed RV activation during incomplete right bundle branch block (iRBBB), complete right bundle branch block (cRBBB) and left bundle branch area pacing (LBBAP).

TABLE 2 | Ventricular activation times during native conduction and LBBAP according to baseline conduction disease.

	V6RWPT (ms)	V1RWPT (ms)	V1 R′ duration (ms)	V1 R′ amplitude (uV)	V1 R′ area (uVs)	V6V1 IPI
iRBBB ($n = 422$)	40 (36, 44)	74 (68, 80)	42 (35, 49)	195 (126, 298)	236 (140, 399)	34 (28, 40)
cRBBB ($n = 223$)	38 (36, 44)	96 (86, 108)	81 (68, 91)	761 (551, 1010)	1782 (1182, 2498)	58 (48, 68)
LBBAP mean ($n = 86$)	44 (36, 56)	84 (72, 92)	42 (28, 55)	297 (175, 645)	316 (134, 831)	36 (24, 45)
LBBAP: narrow QRS ($n = 47$)	44 (36, 56)	82 (72, 89)	39 (20, 52)	246 (144, 504)	263 (213, 418)	32 (24, 45)
LBBAP: LBBB ($n = 12$)	40 (32, 44)	72 (65, 79)	48 (38, 55)	449 (217, 782)	509 (94, 428)	32 (24, 44)
LBBAP: RBBB ($n = 12$)	46 (29, 62)	84 (72, 92)	46 (28, 74)	251 (135, 652)	325 (205, 451)	40 (24, 56)
LBBAP: NIVCD ($n = 15$)	46 (40, 62)	90 (83, 100)	49 (35, 66)	530 (240, 871)	798 (241, 448)	38 (32, 58)

iRBBB, incomplete right bundle branch block; cRBBB, complete right bundle branch block; LBBAP: left bundle branch area pacing; RBBB, right bundle branch block; LBBB, left bundle branch block; NIVCD, non-specified intraventricular conduction delay; V6V1 IPI, V6-V1 interpeak interval.

delay of the right bundle branch. Our results show that the delayed RV activation during LBBAP electrocardiographically mirrors more closely to native iRBBB than cRBBB, with activation times in between those of iRBBB and cRBBB patients. With LBBAP, the delayed RV activation seems to be determined by the underlying conduction disease rather than the type of LBBAP capture (i.e., conduction system capture vs. myocardial capture).

Left Bundle Branch Area Pacing and Left and Right Ventricular Activation Times

LBBAP aims to capture the left bundle branch itself (LBBP) or the left-sided septal myocardium (LVSP) in the direct area of the left bundle branch. Several studies investigated the contraction and activation patterns of the left ventricle (LV) during LBBAP and revealed a fast and homogenous activation of the LV resulting in beneficial hemodynamic effects of LBBAP (12, 15). Although

LV activation during LBBP seems to occur earlier compared to LVSP, differences are small and may not be clinically relevant. This could be explained by the deep left-sided septal position of the pacing lead that quickly activates the adjacent left-sided conduction fibers. Indeed, at the left side of the septum, the LBB is a widely arborized structure and a pacing lead with a deep septal position is more likely to be embedded in close proximity to the conduction system, resulting in a homogenous LV activation (12, 15). With LBBAP, the fast LV activation is estimated by the so-called LVAT or either R wave peak time in lead V6 of the ECG and is often used to define successful LBBAP (26, 28). Both measurements are used interchangeably and assess the interval between the pacing stimulus or QRS onset and the R wave peak time in lead V4, V5 or V6. The shorter these intervals, the faster and probably more homogenous the LV is thought to be activated (26). Our findings show small differences in LVAT between native RBBB and LBBAP (38 vs. 44 ms), which are potentially not even clinically significant considering normal LVAT ranges between 35 and 40 ms (31).

In contrast to the LV activation patterns with LBBAP, data on delayed RV activation during LBBAP are scarce. As LBBAP aims to capture the LBB, the activation waveform needs to propagate from the left to the right ventricle. The exact mechanism of RV activation during LBBAP has not been elucidated, although retrograde invasion of the conduction system is suggested (32). Irrespective of the exact mechanism, RV activation during LBBAP is delayed compared to LV activation (33, 34). This delayed RV activation is characterized by an RBBB pattern on the ECG, which is considered one of the hallmarks of successful LBBAP (17). The delayed RV activation during LBBAP has gained little attention and only a few reports measured RVAT (measured as the interval from pacing stimulus or QRS onset to R wave peak time in lead V1) (26, 28). No previous study assessed the electrocardiographic pattern of delayed RV activation as such. Our results show that with LBBAP, the delayed RV activation encompasses ventricular activation times in between native iRBBB and cRBBB. Despite differences in baseline characteristics in patients with iRBBB, cRBBB and LBBAP, only presence of heart failure was independently associated with longer V1RWPT and V1 R′ duration, but could only partially account for the differences in right ventricular activation times between iRBBB, cRBBB and LBBAP patients.

Of interest, we observed that the delayed RV activation during LBBAP is determined by baseline conduction delay and blocks, but not by the type of LBBAP capture. Indeed, both LBBP and LVSP resulted in similar electrocardiographic characteristics of delayed RV activation. This raises the hypothesis that RV activation with both LBBP and LVSP almost always occurs by activation of the right-sided conduction system capture, as pure myocardial conduction toward the RV would result in ECG characteristics of delayed RV activation resembling more to those seen with cRBBB. Moreover, even in patients with baseline cRBBB, LBBAP further shortens QRS duration, V1RWPT and V1 R′ duration, suggesting that RV activation occurs through the right-sided conduction system. Whether the pacing impulse during LBBAP systematically invades the right-sided conduction system and whether activation of the RV occurs through transseptal activation, or invading connection fibers between the left and right bundle branch or exclusively by retrograde invasion of the left bundle branch needs to be further elucidated (35).

Long-Term Impact of LBBAP-Induced RV Activation Delay

LBBAP is emerging as a popular pacing modality with growing worldwide adoption. This is mainly explained as LBBAP is characterized by excellent pacing characteristics (low pacing thresholds and high sensing amplitudes), overcoming the main limitations of HBP while still offering a near physiological pacing strategy. The first experience with LBBAP was published in 2017 and several questions remain unanswered regarding the long-term safety, lead performance, feasibility of lead extraction and most important, the long-term clinical outcome. Reports have shown preservation of left ventricular ejection fraction (LVEF) in patients with normal cardiac function undergoing LBBAP and significant improvements in LVEF when LBBAP is implanted in heart failure patients with reduced LVEF (14, 36). However, the follow-up time of these studies was limited, and the impact on right ventricular function have not been considered to date.

During ventricular pacing the normal sequence of electrical activation and electro-mechanical coupling is disrupted. It has been well established that with standard RV apical pacing the delayed activation of the LV can lead to deterioration of the LVEF, pacing-induced cardiomyopathy and adverse outcome including increased mortality (10, 12–14, 17). The pathophysiology of pacing-induced dyssynchrony has been studied during RV apical pacing and can be explained by two observations. First, regions with the earliest activation (i.e., the ventricle which is paced) will contract first, leading to a discoordinated mechanical contraction, reduced ventricular efficiency and increased cavity pressure (37). Secondly, the late-activated segments show increased myocardial work, reduced myocardial blood flow and differences in oxygen consumption and glucose uptake between the first and last activated regions (38). This is a well-known principle in pacing physiology: the ventricle that is first activated exhibits the least myocardial workload, whereas the late-activated ventricle shows increased myocardial workload. Therefore, the delayed RV activation during LBBAP could theoretically result in a higher workload for the RV and might adversely affect the RV over time, but this remains to be explored.

Although both LBBAP and RBBB result in delayed RV activation, global ventricular activation patterns are unlikely to be identical. Indeed, with non-selective LBBP (the most frequently observed LBBAP pacing response during follow-up), direct myocardial capture of the basal septum occurs, which is different from septal activation during RBBB.

To estimate the long-term effects of delayed RV activation by LBBAP, the prognostic outcome of patients with RBBB is sometimes extrapolated to patients with LBBAP. Our results show that the LBBAP-induced delayed RV activation is situated in between incomplete and complete RBBB, and mirrors more closely to iRBBB than to cRBBB. We believe that this observation may be relevant with regard to long-term outcome of LBBAP.

First, it shows that with LBBAP the delayed RV activation still occurs by activation of the right-sided conduction system, resulting in only moderate conduction delay and probably a more physiological RV contraction than would be the case with purely myocardial conduction (as the LV experiences during RV apical pacing). Secondly, iRBBB has not been associated with adverse outcome in large population studies. As such, the delayed activation of the RV during LBBAP is unlikely to convey an adverse outcome.

Although it is traditionally accepted that in patients without evidence of cardiac disease, cRBBB is not associated with increased risk of cardiac morbidity or mortality, conflicting data have emerged over the last years about the long-term prognostic significance of incidental cRBBB, especially when cRBBB is associated with heart failure (39). However, very few patients with LBBAP experience cRBBB characteristics with such wide QRS duration, as shown by our results. One group of particular interest in whom LBBAP could result in detrimental effects on the RV are patients with a depressed RV function at the time of LBBAP implant. In these patients, slight delay in RV activation during LBBAP could theoretically result in a further decline of the dysfunctional right ventricle.

The effects of pacing-induced delayed RV activation by LBBAP require careful follow-up and should be addressed in long-term follow-up studies. No assessments of mechanical contraction patterns or function of the RV were performed in this study, although we recognize that long-term follow-up studies with thorough evaluation of the myocardial contraction properties of the RV during LBBAP are needed. Non-invasive ECG imaging or ultra-high frequency ECG might better assess local activation times and depolarization characteristics of specific ventricular segments and could contribute to further insights into the exact mechanism of RV activation during LBBAP.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University Hospital Ghent. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

EO and JD contributed to the conception and design of the article. EO, AD, SC, and JD contributed to the statistical analysis of the article. SK contributed to the literature research. EO wrote the first draft of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

REFERENCES

1. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, et al. 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J.* (2021) 42:3427–520. doi: 10.1093/eurheartj/ehab364
2. Khurshid S, Epstein AE, Verdino RJ, Lin D, Goldberg LR, Marchlinski FE, et al. Incidence and predictors of right ventricular pacing-induced cardiomyopathy. *Heart Rhythm.* (2014) 11:1619–25. doi: 10.1016/j.hrthm.2014.05.040
3. Khurshid S, Liang JJ, Owens A, Lin D, Schaller R, Epstein AE, et al. Longer paced QRS duration is associated with increased prevalence of right ventricular pacing-induced cardiomyopathy. *J Cardiovasc Electrophysiol.* (2016) 27:1174–9. doi: 10.1111/jce.13045
4. Kiehl EL, Makki T, Kumar R, Gumber D, Kwon DH, Rickard JW, et al. Incidence and predictors of right ventricular pacing-induced cardiomyopathy in patients with complete atrioventricular block and preserved left ventricular systolic function. *Heart Rhythm.* (2016) 13:2272–8. doi: 10.1016/j.hrthm.2016.09.027
5. Lamas GA, Lee KL, Sweeney MO, Silverman R, Leon A, Yee R, et al. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. *N Engl J Med.* (2002) 346:1854–62. doi: 10.1056/NEJMoa013040
6. Sharma AD, Rizo-Patron C, Hallstrom AP, O'Neill GP, Rothbart S, Martins JB, et al. Percent right ventricular pacing predicts outcomes in the DAVID trial. *Heart Rhythm.* (2005) 2:830–4. doi: 10.1016/j.hrthm.2005.05.015
7. Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation.* (2003) 107:2932–7. doi: 10.1161/01.CIR.0000072769.17295.B1
8. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the dual chamber and VVI implantable defibrillator (DAVID) Trial. *JAMA.* (2002) 288:3115–23. doi: 10.1001/jama.288.24.3115
9. Teigeler T, Kolominsky J, Vo C, Shepard RK, Kalahasty G, Kron J, et al. Intermediate-term performance and safety of his-bundle pacing leads: a single-center experience. *Heart Rhythm.* (2021) 18:743–9. doi: 10.1016/j.hrthm.2020.12.031
10. Zanon F, Abdelrahman M, Marcantoni L, Naperkowski A, Subzposh FA, Pastore G, et al. Long term performance and safety of his bundle pacing: a multicenter experience. *J Cardiovasc Electrophysiol.* (2019) 30:1594–601. doi: 10.1111/jce.14063
11. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, et al. A novel pacing strategy with low and stable output: pacing the left bundle branch immediately beyond the conduction block. *Can J Cardiol.* (2017) 33:1736e1–3. doi: 10.1016/j.cjca.2017.09.013
12. Salden F, Luermans J, Westra SW, Weijs B, Engels EB, Heckman LIB, et al. Short-term hemodynamic and electrophysiological effects of cardiac resynchronization by left ventricular septal pacing. *J Am Coll Cardiol.* (2020) 75:347–59. doi: 10.1016/j.jacc.2019.11.040
13. Su L, Wang S, Wu S, Xu L, Huang Z, Chen X, et al. Long-term safety and feasibility of left bundle branch pacing in a large single-center study. *Circ Arrhythm Electrophysiol.* (2021) 14:e009261. doi: 10.1161/CIRCEP.120.009261
14. Vijayaraman P, Ponnusamy S, Cano Ó, 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) 7:135–47. doi: 10.1016/j.jacep.2020.08.015
15. Vijayaraman P, Subzposh FA, Naperkowski A, Panikkath R, John K, Mascarenhas V, et al. Prospective evaluation of feasibility, electrophysiologic and echocardiographic characteristics of left bundle branch area pacing. *Heart Rhythm.* (2019) 16:1774–82. doi: 10.1016/j.hrthm.2019.05.011

16. Heckman L, Vijayaraman P, Luermans J, Stipdonk AMW, Salden F, Maass AH, et al. Novel bradycardia pacing strategies. *Heart.* (2020) 106:1883–9. doi: 10.1136/heartjnl-2020-316849
17. Huang W, Chen X, Su L, Wu S, Xia X, Vijayaraman P, et al. Beginner's guide to permanent left bundle branch pacing. *Heart Rhythm.* (2019) 16:1791–6. doi: 10.1016/j.hrthm.2019.06.016
18. Alventosa-Zaidin M, Guix Font L, Benitez Camps M, Roca Saumell C, Pera G, Alzamora Sas MT, et al. Right bundle branch block: prevalence, incidence, and cardiovascular morbidity and mortality in the general population. *Eur J Gen Pract.* (2019) 25:109–15. doi: 10.1080/13814788.2019.1639667
19. Fahy GJ, Pinski SL, Miller DP, McCabe N, Pye C, Walsh MJ, et al. Natural history of isolated bundle branch block. *Am J Cardiol.* (1996) 77:1185–90. doi: 10.1016/S0002-9149(96)00160-9
20. Fleg JL, Das DN, Lakatta EG. Right bundle branch block: long-term prognosis in apparently healthy men. *J Am Coll Cardiol.* (1983) 1:887–92. doi: 10.1016/S0735-1097(83)80204-6
21. Liao YL, Emidy LA, Dyer A, Hewitt JS, Shekelle RB, Paul O, et al. Characteristics and prognosis of incomplete right bundle branch block: an epidemiologic study. *J Am Coll Cardiol.* (1986) 7:492–9. doi: 10.1016/S0735-1097(86)80458-2
22. Surawicz B, Childers R, Deal BJ, Gettes LS, Bailey JJ, Gorgels A, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol.* (2009) 53:976–81. doi: 10.1161/CIRCULATIONAHA.108.191095
23. Thrainsdottir IS, Hardarson T, Thorgeirsson G, Sigvaldason H, Sigfusson N. The epidemiology of right bundle branch block and its association with cardiovascular morbidity—the Reykjavik Study. *Eur Heart J.* (1993) 14:1590–6. doi: 10.1093/eurheartj/14.12.1590
24. De Pooter J, Calle S, Timmermans F, Van Heuverswyn F. Left bundle branch area pacing using stylet-driven pacing leads with a new delivery sheath: a comparison with lumen-less leads. *J Cardiovasc Electrophysiol.* (2021) 32:439–48. doi: 10.1111/jce.14851
25. Chen X, Wu S, Su L, Su Y, Huang W. The characteristics of the electrocardiogram and the intracardiac electrogram in left bundle branch pacing. *J Cardiovasc Electrophysiol.* (2019) 30:1096–101. doi: 10.1111/jce.13956
26. Jastrzebski M, Kiełbasa G, Curila K, Moskal P, Bednarek A, Rajzer M, et al. Physiology-based electrocardiographic criteria for left bundle branch capture. *Heart Rhythm.* (2021) 18:935–43. doi: 10.1016/j.hrthm.2021.02.021
27. De Pooter J, El Haddad M, Stroobandt R, De Buyzere M, Timmermans F. Accuracy of computer-calculated and manual QRS duration assessments: clinical implications to select candidates for cardiac resynchronization therapy. *Int J Cardiol.* (2017) 236:276–82. doi: 10.1016/j.ijcard.2017.01.129
28. Jastrzębski M. ECG and pacing criteria for differentiating conduction system pacing from myocardial pacing. *Arrhythm Electrophysiol Rev.* (2021) 10:172–80. doi: 10.15420/aer.2021.26
29. Jastrzebski M, Burri H, Kiełbasa G, Curila K, Moskal P, Bednarek A, et al. The V6-V1 interpeak interval: a novel criterion for the diagnosis of left bundle branch capture. *Europace.* (2021). doi: 10.1093/europace/euab164
30. Huang T, James CA, Tichnell C, Murray B, Xue J, Calkins H, et al. Statistical evaluation of reproducibility of automated ECG measurements: an example from arrhythmogenic right ventricular dysplasia/cardiomyopathy clinic. *Biomed Signal Process Control.* (2014) 13:23–30. doi: 10.1016/j.bspc.2014.03.009
31. Boles U, Almuntaser I, Brown A, Murphy RR, Mahmud A, Feely J. Ventricular activation time as a marker for diastolic dysfunction in early hypertension. *Am J Hypertens.* (2010) 23:781–5. doi: 10.1038/ajh.2010.58
32. Zhang S, Zhou X, Gold MR. Left bundle branch pacing: JACC review topic of the week. *J Am Coll Cardiol.* (2019) 74:3039–49. doi: 10.1016/j.jacc.2019.10.039
33. Curila K, Jurak P, Jastrzebski M, Prinzen F, Waldauf P, Halamek J, et al. Left bundle branch pacing compared to left ventricular septal myocardial pacing increases interventricular dyssynchrony but accelerates left ventricular lateral wall depolarization. *Heart Rhythm.* (2021) 18:1281–9. doi: 10.1016/j.hrthm.2021.04.025
34. Heckman L, Luermans J, Salden F, van Stipdonk AMW, Mafi-Rad M, Prinzen F, et al. Physiology and practicality of left ventricular septal pacing. *Arrhythm Electrophysiol Rev.* (2021) 10:165–71. doi: 10.15420/aer.2021.21
35. Lazzara R, Yeh BK, Samet P. Functional transverse interconnections within the his bundle and the bundle branches. *Circ Res.* (1973) 32:509–15. doi: 10.1161/01.RES.32.4.509
36. Ravi V, Hanifin JL, Larsen T, Huang HD, Trohman RG, Sharma PS. Pros and cons of left bundle branch pacing: a single-center experience. *Circ Arrhythm Electrophysiol.* (2020) 13:e008874. doi: 10.1161/CIRCEP.120.008874
37. Prinzen FW, Hunter WC, Wyman BT, McVeigh ER. Mapping of regional myocardial strain and work during ventricular pacing: experimental study using magnetic resonance imaging tagging. *J Am Coll Cardiol.* (1999) 33:1735–42. doi: 10.1016/S0735-1097(99)00068-6
38. Prinzen FW, Vernooy K, De Boeck BW, Delhaas T. Mechano-energetics of the asynchronous and resynchronized heart. *Heart Fail Rev.* (2011) 16:215–24. doi: 10.1007/s10741-010-9205-3
39. Adesanya CO, Yousuf KA, Co C, Gaur S, Ahmed S, Pothoulakis A, et al. Is wider worse? QRS duration predicts cardiac mortality in patients with right bundle branch block. *Ann Noninvasive Electrocardiol.* (2008) 13:165–70. doi: 10.1111/j.1542-474X.2008.00216.x

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Cardiovascular Medicine

TYPE Review
PUBLISHED 27 September 2022
DOI 10.3389/fcvm.2022.923394

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Cardiac Rhythmology, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 19 April 2022
ACCEPTED 06 September 2022
PUBLISHED 27 September 2022

CITATION
Hua J, Kong Q and Chen Q (2022) Alternative pacing strategies for optimal cardiac resynchronization therapy.
Front. Cardiovasc. Med. 9:923394.
doi: 10.3389/fcvm.2022.923394

Alternative pacing strategies for optimal cardiac resynchronization therapy

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Cardiac resynchronization therapy (CRT) *via* biventricular pacing (BVP) improves morbidity, mortality, and quality of life, especially in subsets of patients with impaired cardiac function and wide QRS. However, the rate of unsuccessful or complicated left ventricular (LV) lead placement through coronary sinus is 5–7%, and the rate of "CRT non-response" is approximately 30%. These reasons have pushed physicians and engineers to collaborate to overcome the challenges of LV lead implantation. Thus, various alternatives to BVP have been proposed to improve CRT effectiveness. His bundle pacing (HBP) has been increasingly used by activating the His–Purkinje system but is constrained by challenging implantation, low success rates, high and often unstable thresholds, and low perception. Therefore, the concept of pacing a specialized conduction system distal to the His bundle to bypass the block region was proposed. Multiple clinical studies have demonstrated that left bundle branch area pacing (LBBAP) has comparable electrical resynchronization with HBP but is superior in terms of simpler operation, higher success rates, lower and stable capture thresholds, and higher perception. Despite their well-demonstrated effectiveness, the transvenous lead-related complications remain major limitations. Recently, leadless LV pacing has been developed and demonstrated effective for these challenging patient cohorts. This article focuses on the current state and latest progress in HBP, LBBAP, and leadless LV pacing as alternatives for failed or non-responsive conventional CRT as well as their limits and prospects.

KEYWORDS

cardiac resynchronization therapy, biventricular pacing, His bundle pacing, left bundle branch area pacing, leadless LV pacing, review

Introduction

Heart failure (HF) is a cardiovascular epidemic, with high morbidity and mortality and poor quality of life, especially in patients with HF and reduced ejection fraction (HFrEF) (1). According to the 2021 European HF guidelines, sodium–glucose cotransporter 2 inhibitors (SGLT2i) are used as a first-line therapy

along with angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor–neprilysin inhibitors (ARNI), β-blockers, and mineralocorticoid receptor antagonists (MRA) (2). However, the HF symptoms of some patients cannot be resolved, despite optimized medical treatments (OMT).

Cardiac resynchronization therapy (CRT) is a well-established modality that offers remarkable clinical benefits for patients with medically refractory HF (3). It has a class IA indication for symptomatic HF patients with sinus rhythm (SR), a QRS ≥ 150 ms, left bundle branch block (LBBB) QRS morphology, and a left ventricular ejection fraction (LVEF) ≤ 35%, despite OMT according to the 2021 European Society of Cardiology (ESC) guidelines on CRT (4). Conventional CRT *via* biventricular pacing (BVP) is non-physiological with the fusion of the epicardial LV wavefront and the endocardial wavefront from the right ventricular (RV) apex, leaving some degree of dyssynchrony. However, conventional CRT is precluded in a proportion of eligible candidates due to anatomic or technical constraints such as occluded venous access, an inappropriate coronary sinus (CS) anatomy, or a high threshold in regions of fibrosis (5, 6). In addition, approximately 30% of recipients are non-responsive to CRT due to the inability to effectively stimulate diseased tissue, or suboptimal LV lead placement (7, 8).

For these reasons, physicians and engineers have been working together to overcome the challenges of LV lead implantation but have also shown increased interest in developing physiological pacing techniques to improve CRT effectiveness. His bundle pacing (HBP) has increased in use by activating the His bundle but is restricted by implant challenges, low success rates, and a high and often unstable pacing threshold (9–12). Therefore, the concept of pacing the specialized conduction system distal to the His bundle to bypass the block region has been introduced (13). Multiple clinical studies reported that left bundle branch area pacing (LBBAP) has electrical resynchronization that is comparable with that of HBP but superior due to its simpler operation, higher success rate, and low and stable pacing threshold (13–17). Despite their well-demonstrated effectiveness, the resulting complications of transvenous leads and typical pocket infections remain a non-negligible limitation (18, 19). Thus, leadless cardiac pacing has been engineered and demonstrated as having potential efficacy for treating those challenging patient cohorts (20, 21).

From CS epicardial pacing to leadless endocardial stimulation, various LV pacing alternatives reportedly improve CRT effectiveness (**Figure 1**). This review focuses on the current state and latest progress of HBP, LBBAP, and leadless LV pacing as alternatives for impossible or failed conventional CRT as well as their limits and future areas of improvement.

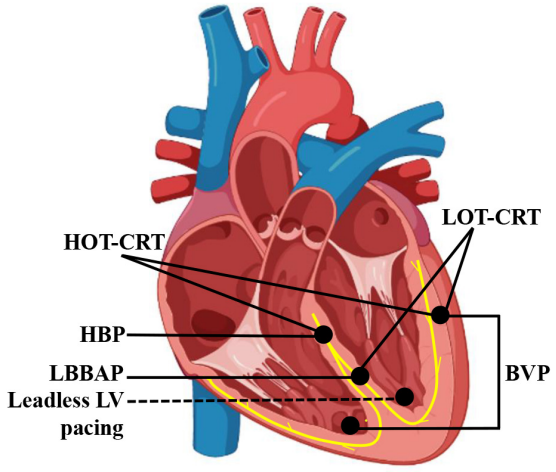

FIGURE 1
Schematic diagram of pacing electrode positions of different CRT modalities. BVP, biventricular pacing; CRT, cardiac resynchronization therapy; HBP, His bundle pacing; HOT-CRT, His-optimized CRT; LBBAP, left bundle branch area pacing; LOT-CRT, LBBAP-optimized CRT.

Benefits and limits of biventricular pacing-cardiac resynchronization therapy

The efficacy of CRT in patients with HF has been demonstrated in numerous trials. The Multisite Stimulation in Cardiomyopathies (MUSTIC) study was the first to assess the clinical outcomes of CRT in 67 patients with severe HF (22). Finally, 48 patients completed both phases of the study. The quality-of-life score improved by 32%, while hospitalizations decreased by 67.7%. Similarly, the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial was the first double-blind trial to assess the CRT outcomes in 453 patients with moderate to severe HF with an LVEF ≤ 35% and QRS ≥ 130 ms (23). CRT improved the New York Heart Association (NYHA) class, quality of life, and LVEF and reduced hospitalization and intravenous interventions. The Cardiac Resynchronization–Heart Failure (CARE-HF) trial was mainly conducted to assess the morbidity and mortality of CRT in 813 patients with HF (NYHA class III/IV) (24). The results indicated that CRT reduced mortality of any cause, increased the LVEF, and improved symptoms and quality of life. Subsequently, the REVERSE, MADIT-CRT, and RAFT trials assessed the efficacy of CRT in mildly symptomatic HF (25–27). These results showed that CRT significantly delayed the time to the first HF hospital stay or death, reduced the risk of HF events, and improved LV reverse remodeling.

However, approximately 30% of candidates respond unfavorably to CRT or even worsen (23, 24, 28). In fact, the optimal LV pacing site is not always consistent with the right branch of the CS. In addition, phrenic stimulation, occlusion of the CS anatomy, or other anatomical constraints would hamper the procedure. Thus, several approaches based on BVP-CRT, such as the adaptive CRT algorithm (29), the SyncAV algorithm (30), and multipoint pacing (MPP) (31), have improved the effectiveness of BVP-CRT. Notably, the optimal electrode position was not equal to that of the optimal treatment. In addition, little experience has been gained regarding the optimal programming of pacemakers after MPP. Furthermore, the higher battery use of MPP also prevents its recommendation.

Alternative pacing strategies for conventional cardiac resynchronization therapy

Despite great advances in multipolar LV electrodes and MPP, non-response due to suboptimal lead position remains a critical problem. To overcome the challenges of the CS approach, physicians have strived for alternative solutions, such as surgical LV epicardial lead placement, LV endocardial pacing, or HBP to most recently leadless LV pacing. However, surgical LV epicardial lead placement does not always deliver additional improvement in the LVEF versus conventional CRT, and it is inherently more invasive and challenging in patients with a previous history of heart surgery (32). Moreover, the greatest concern for LV endocardial pacing is the risk of thromboembolic complications and the need for lifelong anticoagulation (33). By contrast, physiological pacing modalities have advantages over conventional LV epicardial and endocardial pacing. Next, this review focuses on the progress, limits, and prospects of HBP, LBBAP, and leadless LV pacing used for CRT.

His bundle pacing for cardiac resynchronization therapy

His bundle pacing activates the His–Purkinje system (HPS) and restores physiological activation of the ventricles. HBP is defined as the presence or absence of His–Purkinje conduction disease (HPCD) according to four basic criteria (34): (1) relationship between the His-QRS (H-QRS) and stimulus-QRS (S-QRS) intervals; (2) the presence or absence of direct capture of the local ventricular electrogram (EGM) on the pacing lead; (3) QRS duration (QRSd) and morphology; and (4) capture thresholds. Broadly, there are two forms of HBP: selective HBP (S-HBP), in which the His bundle is exclusively captured; and non-selective HBP (NS-HBP), in which both the His bundle and its surrounding ventricular tissues are captured. The form of S-HBP or NS-HBP is usually dependent on the location of the pacing electrode in relation to the His bundle and the surrounding tissue (35). S-HBP can be differentiated from NS-HBP by review of the His bundle EGM on the pacing lead (34, 36): the local ventricular EGM is discrete and separate from the pacing stimulus on S-HBP, whereas it is fused with the pacing stimulus on NS-HBP. The specific criteria for S-HBP or NS-HBP are as follows (9, 34):

S-HBP: (1) S-QRS = H-QRS with an isoelectric interval. In patients with HPCD, S-QRS $\leq$ H-QRS with BBB correction and S-QRS $\leq$ or $>$ H-QRS without BBB correction; (2) discrete local ventricular EGM in HBP leads with the stimulus to the local ventricle (S-V) = His to the local ventricle (H-V); (3) paced QRS = native QRS. In patients with HPCD, paced QRS $<$ native QRS with BBB correction; paced QRS = native QRS without BBB correction; and 4) a single capture threshold (His capture) was observed. In patients with HPCD, two distinct His capture thresholds (with and without BBB correction) may be observed.

NS-HBP: (1) S-QRS $<$ H-QRS (usually 0, $S\text{-}QRS_{end}$ = $H\text{-}QRS_{end}$) with or without an isoelectric interval. In patients with HPCD, $S\text{-}QRS_{end}$ $<$ $H\text{-}QRS_{end}$ with BBB correction; (2) direct capture of local ventricular EGM in HBP lead by a stimulus artifact; (3) paced QRS $>$ native QRS. In patients with HPCD, paced QRS $\leq$ native QRS with BBB correction and paced QRS $>$ native QRS without BBB correction; (4) usually, two distinct capture thresholds (His bundle capture and RV capture) are observed. In patients with HPCD, three distinct capture thresholds (with or without correction for BBB and RV capture) may be observed.

Theoretically, S-HBP may be advantageous over NS-HBP in terms of clinical outcomes. Instead, few hemodynamic and clinical differences were observed between these two forms of capture, probably owing to the rapid conduction of the HPS relative to the ventricular myocardial conduction (37, 38).

Evidence for resynchronization using His bundle pacing

In 2000, HBP was first described in 12 HF patients with atrial fibrillation, cardiomyopathy, and improvements in LV function after HBP and atrioventricular node ablation (39). In 2012, a series of direct HBP (DHBP) was reported in 16 patients after CS approach failure (40). Of these, LBBB was corrected in 13 of 16 patients, and permanent HBP (pHBP) was performed successfully in nine of 13 patients. LBBB was corrected using pHBP, with a mean QRS reduction (166 $\pm$ 8 to 97 $\pm$ 9 ms; $P < 0.01$). Subsequently, a prospective study assessed the HBP outcomes of patients with HF and LBBB (18). A total of 74 patients were enrolled, and pHBP was successful in 56 of them (75.7%). Of them, 30 had completed a 3-year follow-up with an increased mean LVEF (32.4 $\pm$ 8.9% to 55.9 $\pm$ 10.7%, $P < 0.001$) and decreased LV end-systolic volume (LVESV; 137.9 $\pm$ 64.1 to

52.4 ± 32.6 mL, $P < 0.001$). Similarly, the outcomes of HBP were explored in 106 CRT-eligible or -failed patients (41). Among them, HBP was successful in 95 patients (89.6%). During an average follow-up of 14 months, it also delivered significant QRS narrowing, increased LVEF, and improved NYHA class. Lead-related complications were observed in seven patients. These studies demonstrated that HBP may be a promising treatment for failed BVP.

His bundle pacing versus biventricular pacing for cardiac resynchronization therapy

Multiple studies demonstrated that HBP may be an effective alternative to BVP; however, whether it is equal to or better than BVP requires further evaluation. The first crossover study to compare the outcomes of HBP and BVP enrolled 29 patients for HBP as an alternative to BVP (10). Finally, 21 of 29 patients achieved narrow-paced QRSd. The baseline LVEF was 26% with improvements at 6 months in the HBP (32%) and BVP (31%). A similar result of HBP delivering a greater reduction in QRSd, LV activation time (LVAT), and LV dyssynchrony index (LVDI) than BVP was reported (42). The His-SYNC trial was the first randomized comparison of HBP and BVP using treatment-received (TR) and per-protocol (PP) analyses (43). A total of 41 patients were enrolled and randomized into HBP ($n = 21$) and BVP ($n = 20$) groups. Compared with BVP, HBP achieved a narrower mean QRSd, regardless of TR or PP analyses (TR: 125 ± 22 vs. 164 ± 25 ms, $P < 0.001$; PP: 124 ± 19 vs. 162 ± 24 ms, $P < 0.001$). Furthermore, a non-significant trend toward a higher echocardiographic response was observed. There were also no significant intergroup differences in CV hospitalization and mortality. Another randomized trial of HBP versus BVP (His-Alternative) was performed in patients with symptomatic HF and LBBB (44). The pacing thresholds of HBP were higher than those of BVP, both at implantation and at the 6-month follow-up. Using PP analysis, the LVEF was significantly increased, and the 6-month LVESV was lower in patients with HBP than in those with BVP. These data revealed that HBP was equivalent to, or even better than, BVP in some cases; however, further investigations are required to confirm these findings.

His-optimized cardiac resynchronization therapy

The use of HBP alone may not always be optimal for obtaining QRS narrowing. Several studies have explored whether CRT could maximize electrical resynchronization by HBP fused with sequential LV pacing, termed His-optimized CRT (HOT-CRT) (45–48). HOT-CRT was attempted in 27 patients with LBBB/intraventricular conduction defect (IVCD) partially corrected by HBP alone (45). HOT-CRT produced a greater narrowing of the mean QRSd to 120 ± 16 ms (vs. baseline, BVP, or HBP; $P < 0.0001$). LVEF improved significantly (from 24 ± 7% to 38 ± 10%, $P = 0.001$) after a mean follow-up of 14 ± 10 months. Similar results with a narrower QRSd, increased LVEF, and improved NYHA were reported in other studies (46–48). In addition, HOT-CRT versus HBP resulted in significant QRS narrowing, thus achieving electrical resynchronization in four of five patients with IVCD (45). These data indicate that HOT-CRT produced more pronounced QRS narrowing and improved clinical outcomes than HBP alone. Particularly, HOT-CRT could further optimize electrical resynchronization in patients with advanced cardiomyopathy and conduction disease; however, this finding requires further verification.

Limits of His bundle pacing

These trials indicated that HBP generates a narrow paced QRS and improves clinical outcomes, which seem potential for CRT. However, HBP has some limitations. First, the major limit is the inability to map the precise location of the His bundle, which is approximately 1–2 mm in diameter (49). The mean success rate of HBP was approximately 79.8% (mostly were performed with the SelectSecure 3830 lead; Medtronic, Minneapolis, MN, United States), while the lead-related complication rate was 6% (50). Second, 30–40% of LBBB cannot be corrected by HBP because of the presence of lesions distal or more extensive to the conduction tract during implantation (51). Third, the HBP threshold increased over time. About 53.6% of patients had a significant increase in the His capture threshold after a mean follow-up of 3 years (18). A progressive increase in the pacing threshold implies a shortened battery longevity. HBP may also undersense the ventricle and oversense the atrium, thus resulting in crosstalk. Finally, most of the current research conclusions on the application of HBP in HF with LBBB were derived from the data of HBP with failed BVP, while large-scale randomized controlled clinical trials of HBP and BVP are lacking. Furthermore, the number of patients who responded to HBP and did not respond to BVP was small, and similarly, the number of patients who included HOT-CRT with IVCD HF and were refractory to BVP or HBP was small.

Left bundle branch area pacing for cardiac resynchronization therapy

In 2017, Huang et al. (13) first introduced left bundle branch pacing (LBBP) in a patient with HF and LBBB and confirmed its feasibility and safety. LBBP captures the proximal LBB or its branches with or without the LV septal myocardium. LV septal

pacing (LVSP) exclusively captures the LV septal myocardium. However, during the early stage of LBBP, the criteria for LBB capture are not well defined and uniform. With the increased use and further research on LBBP, the definition of LBB capture is gradually becoming definitive (52). Broadly, there are two forms of LBBP: selective LBBP (S-LBBP) exclusively captures the LBB, whereas non-selective LBBP (NS-LBBP) captures the LBB along with the surrounding local myocardium. The detailed characteristics of LBBP are defined as follows: (1) RBBB pattern, (2) LBB potential, (3) S-LBBP with specific ECG changes and a discrete component on EGM, and (4) a constant and shortest stimulus to the LVAT, regardless of high or low pacing outputs. LBBP is differentiated from LVSP based on the mentioned characteristics of the indirect criteria for LBB capture. Thus, LVSP is mistakenly considered LBBP in some cases. Wu et al. (53) proposed retrograde His bundle potential or anterograde left conduction system potentials to directly confirm LBB capture, which can more accurately distinguish between LBBP and LVSP. However, this method is complicated and unsuitable for routine clinical use. In this context, the concept of LBB area pacing (LBBAP) has been proposed, that is, LBBP or LVSP, without clear evidence for LBB capture (4). During LBBAP, the QRS morphologies in lead V1 are typically demonstrated as Qr (60.7%), qR (19.6%), rSR' (7.1%), or QS (12.5%) patterns, and the duration of the terminal R' wave was significantly shorter than that of native RBBB (54).

Evidence for resynchronization using left bundle branch area pacing

Several single-center studies with short follow-up periods have confirmed the potential of LBBAP in patients with HF and wide QRS (13, 55). A prospective multicenter medium-term study assessed LBBP in patients with LBBB and non-ischemic cardiomyopathy (56). LBBP was successful in 61 of 63 patients (97%). It produced a shortened mean QRSd (169 ± 16 to 118 ± 12 ms, $P < 0.001$), increased LVEF (33 ± 8% to 55 ± 10%, $P < 0.001$), decreased LVESV (123 ± 61 to 67 ± 39 mL, $P < 0.001$), and improved NYHA class (2.8 ± 0.6 to 1.4 ± 0.6, $P < 0.001$). A subsequent long-term trial with a larger sample size ($N = 632$) assessed LBBP feasibility and safety (57). LBBP was successful in 618 (97.8%) patients, and the mean follow-up was 18.6 ± 6.7 months. A significant decrease in QRSd was observed in patients with LBBB. LVEF after LBBP improved in patients with QRS ≥ 120 ms ($N = 88$). No serious complications occurred during the procedure or follow-up. A similar result was reported by another large study ($N = 325$) (19) in which LBBAP was successfully achieved in 277 (85%) patients. During a mean follow-up period of 6 ± 5 months, LBBAP also resulted in significant QRS narrowing and improved LVEF. In a current meta-analysis, LBBP for CRT resulted in a narrower QRSd and an increased LVEF than baseline (58). Nonetheless, relatively few studies have examined LVSP for CRT. To date, LVSP has been demonstrated to generate short-term hemodynamic improvement and electrical resynchronization equal to that of BVP and possibly HBP (59). These data demonstrated that LBBAP may be a promising rescue strategy for failed BVP; however, further investigations are needed.

Left bundle branch area pacing versus biventricular pacing for cardiac resynchronization therapy

Several clinical trials have explored whether LBBAP is equal or superior to conventional CRT (15–17, 60, 61). In these studies, LBBAP/LBBP produced a narrower paced QRSd than did BVP as expected. Accordingly, LBBAP/LBBP resulted in an increased LVEF and improved NYHA class. LBBAP improved the LVEF more than BVP in this study (16). By contrast, LBBAP/LBBP was equivalent to BVP in other studies (15, 17, 61). LBBP, HBP, and BVP were compared in 137 non-randomized patients with an LVEF ≤ 40% and typical LBBB (60). Finally, HBP and LBBP delivered similar improvement in the LVEF and NYHA class after the 1-year follow-up, which was significantly higher than that in BVP. Furthermore, some meta-analyses of LBBAP for CRT have been reported (62, 63). A meta-analysis compared LBBAP and BVP for CRT (62). Compared with BVP, LBBAP produced significantly narrower QRSd with a mean difference (MD) 29.18 ms, LVEF improvement of 6.93%, LVEDD reduction of 2.96 mm, and NYHA class improvement of 0.54. Similarly, a network meta-analysis compared LBBAP, HBP, and BVP for patients requiring CRT (63). Compared with BVP, LBBAP produced greater LVEF improvement with an MD of 7.17%, followed by an HBP of 4.06%. In addition, HBP produced a narrower QRSd with an MD of 31.58 ms, followed by an LBBAP of 27.40 ms. There were no differences in LVEF improvement and QRS narrowing for LBBAP versus HBP. These data indicated that LBBAP, comparable with HBP, may be superior to BVP, but further evaluations are needed.

Left bundle branch area pacing-optimized cardiac resynchronization therapy

To our knowledge, proximal LBB pacing is inherently limited by its inability to restore physiological activation of the lateral wall of the LV in patients with a distal conduction delay (19). Thus, it may not always be optimal for QRS narrowing by LBBAP alone. Whether LBBAP-optimized CRT (LOT-CRT), LBBAP combined with CS LV pacing, would be advantageous over LBBAP or BVP is unknown. Thus, the LOT-CRT was assessed in an international multicenter study of non-consecutive patients who were indicated for

CRT or non-responders (64). LOT-CRT was successful in 91 of 112 patients (81%). The average follow-up was 7.8 ± 2.3 months. LOT-CRT generated significantly greater narrowing of QRSd to 144 ± 22 ms (vs. baseline, BVP, and LBBAP, $P < 0.0001$), increased LVEF (28.5 ± 9.9% to 37.2 ± 12%, $P < 0.0001$), and decreased LVEDD (62.0 ± 8.9 to 59.1 ± 9.1 mm, $P < 0.0442$) and *N*-terminal pro-hormone B-type natriuretic peptide (5,668 ± 8,249 to 2,561 ± 3,555 pg/mL, $P < 0.0001$). These results indicated that LOT-CRT provided greater electrical resynchronization and clinical benefits than BVP or LBBAP alone, but further research is needed to confirm this finding.

Limits of left bundle branch area pacing

Multiple studies demonstrated the technical advantages and clinical potential of LBBAP. It has comparable LV synchrony with HBP but a high success rate of 81.1–97% (15, 16, 19, 56, 65) and a low lead-related complication rate of 1.5% (65) with the SelectSecure 3830 lead (Medtronic, Minneapolis, MN, United States). Currently, other stylet-driven conventional active fixation pacing leads can also effectively obtain LBBAP, such as the Solia S60 lead (Biotronik, SE & Co., KG, Germany) (66–68), the Ingevity pacing lead (Boston Scientific Inc., Marlborough, MA, United States) (68), and the Tendril 2088TC lead (Abbott, Inc., United States) (68, 69). In addition, LBBAP has a lower and stable threshold and high perception, and it is preferred for patients with a block far beyond the His bundle branch. Furthermore, the broad and expansive nature of LBB makes LBBAP implantation simpler and faster than that of HBP (70). However, some issues should still be noted, including its acute and long-term safety. Several complications may occur during the procedure, such as LV perforation as the lead advances into the deep interventricular septum (IVS) (71). Thus, a pre-procedural IVS thickness evaluation would be safer. Furthermore, the lead should be rapidly rotated until it penetrated deep into IVS, and fluoroscopic image and pacing parameters and morphologies should be monitored to avoid the perforation of IVS during the process (13, 19). In addition, the safety of postoperative lead extraction after a long duration has been the focus of much attention. Chen et al. (72) reported that three of 612 patients repositioned the lead during the follow-up (one postoperative septum perforation and one postoperative lead dislodgement at 1 month, and one postoperative lead dislodgement at 1 month after repositioned for 5 months). These leads were extracted and repositioned at different sites, and the parameters were stable at an additional 1-year follow-up. Similarly, Su et al. (57) reported a septal perforation during the follow-up in one patient, and the lead was removed and reimplanted without serious complications. Collectively, further research is needed to firmly establish the safety of LBBAP for CRT, particularly for lead extraction over a long duration after the procedure.

Leadless left ventricular pacing: New direction for patients after coronary sinus approach failure

Despite the well-demonstrated effects of HBP and LBBAP, transvenous leads and typical pocket infections remain a non-negligible limitation (18, 19). Leadless cardiac pacing has been proposed to address these complications. The WiSE-CRT system (EBR Systems Inc., Sunnyvale, CA, United States) is the only currently available leadless LV pacing system that comprises a subcutaneous pulse generator transmitter and LV endocardial receiver electrode (73). In this system, acoustic energy is converted from the pulse generator transmitter, located subcutaneously at the fourth, fifth, or sixth intercostal space, to electrical stimulation of a receiver electrode implanted into the LV cavity. The system works in conjunction with a co-implant of RV pacing, which could be a conventional device such as a pacemaker or implantable cardioverter defibrillator (ICD) or a leadless pacemaker such as Micra (Medtronic, Minneapolis, MN, United States). Biventricular pacing is accomplished by perceiving the RV pacing output of the co-implant, followed by the system immediately transducing acoustic energy to electrical stimulation of the LV electrode, thus achieving near-synchronous RV and LV pacing.

Evidence for leadless pacing

In 2014, the Wireless Stimulation Endocardially for CRT (WiSE-CRT) study (20) included 17 HF patients, two-thirds of whom showed ≥ 1 NYHA class improvement at the 6-month follow-up. The Safety and Performance of Electrodes implanted in the Left Ventricle (SELECT-LV), a prospective multicenter non-randomized trial, enrolled 35 CRT-indicated patients who "failed" conventional CRT and underwent implantation of leadless pacing (21). The procedure was successfully performed in 34 (97.1%) patients. Of them, 84.8% ($N = 28$) showed an improved clinical composite score and 66% ($N = 21$) gained a ≥ 5% absolute increase in the LVEF at 6 months. Of note, serious procedure/device-related complications were observed in 8.6% of patients ($N = 3$) within 24 h and 22.9% of patients ($N = 8$) between 24 h and 1 month. A real-world experience with the WiSE-CRT system was shared in an international trial (ClinicalTrials.gov identifier: NCT02610673) (74) in which procedural success and the delivery of biventricular endo-pacing occurred in 85 of 90 patients (94.4%). The acute (within 24 h), 1- to 30-day, and 1- to 6-month complication rates were 4.4% ($N = 4$), 18.8% ($N = 17$), and 6.7% ($N = 6$), respectively. A total of five deaths (5.6%) occurred within 6 months. HF

symptoms improved in 70% of patients. Subsequently, the Stimulation of the Left Ventricular Endocardium for Cardiac Resynchronization Therapy (SOLVE-CRT) trial assessed the short-term outcomes of the WiSE-CRT system in cases without prior implant experience (75). WiSE-CRT was successful in all 31 patients. Of them, 30 completed the 6-month follow-up. In total, 14 (46.7%) patients achieved ≥ 1 NYHA class improvements and an improved LVEF, decreased LVESV, and increased LV end-diastolic volume (LVEDV); three (9.7%) device-related complications occurred: insufficient LV pacing (N = 1), embolization of an unanchored LV electrode (N = 1), and skin infection (N = 1). These results indicated that biventricular endo-pacing from the WiSE-CRT system was effective in cases of failed conventional CRT or non-response, but complications must be noted.

Totally leadless cardiac resynchronization therapy

The aforementioned trials of leadless LV endocardial pacing were combined with a traditional pacemaker or ICD instead of a totally leadless CRT. The successful coexistence of Micra and the WISE-CRT system was first reported in 2019 (76). Also, two other cases were published in the same year or later (77, 78). The patients in these case reports have a common characteristic, that is, they have a complex history including old age, infection, valvular replacement surgery, or venous occlusion. These patients achieved a narrower QRSd and satisfactory clinical outcomes without serious complications after leadless CRT. These cases raised the possibility of completely leadless CRT. Subsequently, multiple European centers shared their experiences with totally leadless CRT (79). A total of eight patients from six centers underwent combination treatment with Micra and WiSE-CRT systems. The QRSd reduction immediately after WiSE-CRT implantation was significant (204.38 ± 30.26, 137.5 ± 24.75 ms, P = 0.012), and it was maintained at the 6-month follow-up. Only a significant improvement in the LVEF was achieved after WiSE-CRT implantation (28.43 ± 8.01% vs. 39.71 ± 11.89%, P = 0.018) without evidence of LV reverse remodeling and improved NYHA class. A current meta-analysis of leadless LV pacing for CRT (80) included five studies (four with RV leads of conventional devices and one with Micra) involving 181 total patients in the final analysis. The success rate of the procedure was 90.6%. It generated a mean increase in the LVEF with an MD of 6.3% and NYHA class improvement of 0.43. Notably, the procedure-related complications and mortality rates were 23.8% and 2.8%, respectively. However, this new pacing modality was used in only a small number of patients, and further studies are needed to confirm its feasibility and safety.

TABLE 1 Comparison of BVP, HBP, LBBAP, and leadless LV pacing.

	BVP	HBP	LBBAP	Leadless LV pacing
Since (year)	1990	2000	2017	2014
Lead	LV lead, RV lead, (RA lead)	His lead, (RA lead)	LBB lead, (RA lead)	RV lead/none
LV or His or LBB lead position	CS	Proximal to His-bundle or in the His-bundle	Distal to His-bundle	Into the LV cavity
LV or His or LBB lead threshold	Generally high (15–17, 60)	Generally high and unstable (43, 44, 60)	Generally lower and stable (13–17, 60)	Generally high (20, 78)
Stim-LVAT	Mildly shortened	Significantly shortened	LBBP: shortest and constant LVSP: longer than LBBP	Theoretically near normal
Implant success rate	92.4%∼97% (23–25)	79.8% (50)	81.1%∼97% (15, 16, 19, 56, 65)	90.6% (80)
ΔLVEF	+ 3.7%∼5.9% (23–25)	+10.87∼14.32% (50)	+ 14.31∼ 22.69% (58)	+4.35∼8.19% (80)
ΔQRSd	−20∼−12 ms (23)	−50.67∼−36.34 ms (50)	−61.64∼−53.72 ms (58)	−67∼−27.3 ms (21, 79)
Procedure-related complication rate	6.1∼12.6% (23–25)	6% (50)	1.5% (65)	23.8% (80)
Battery life	5–6.5 years	Comparable to BVP	Relative longer than HBP	Mean of 18 months (9–42 months)
Advantages	Conventional approach with high level of evidence, well managed technique	Physiological stimulation, narrower paced QRSd	Physiological stimulation, narrower paced QRSd, low and stable threshold	No transvenous lead, endocardial pacing, no need for long-term anticoagulation
Disadvantages	Electrical constraint, high threshold, limited location possibility, phrenic stimulation	Transvenous lead, high threshold, technical and challenging procedure	Risk of IVS perforation, long-term safety and lead extraction need further evaluated	Recent technique with little evidence, need for an acoustic window, complex procedure

BVP, biventricular pacing; CS, coronary sinus; HBP, His bundle pacing; LBBAP, left bundle branch area pacing; LBBP, left bundle branch pacing; LV, left ventricular; LVEF, left ventricular ejection fraction; LVSP, left ventricular septal pacing; QRSd, QRS duration; RA, right atrium; RV, right ventricle; stim-LVAT, stimulus to left ventricular activation time. Δ represents an absolute increase from baseline after pacing.

Limits of leadless left ventricular pacing

Taken together, these data support the efficacy of leadless LV pacing as an alternative in patients in whom CRT is impossible or ineffective. It significantly reduces diaphragm stimulation, avoids mitral regurgitation, and can be performed at multiple physiological pacing positions. In addition, the receiver electrode was completely endothelialized for approximately 4 weeks; therefore, long-term anticoagulation was not required (74). However, leadless LV pacing has several limitations. First, it is challenging to choose a suitable acoustic window (distance < 10 cm and angulation < 30°) to effectively transmit ultrasound. Second, some regions of the left lateral free wall of the enlarged LV may be difficult to reach owing to the current delivery sheath. Third, the battery life projections averaged 18 months (range, 9–42 months) (20), which is often overestimated and should be improved. Moreover, the procedure is complex and has a relatively high complication rate. However, security issues are a common problem in the early stages of any novel technique. Improvements in the safety profile, such as different delivery sheaths, increased operator experience, and practice modifications, would reduce its complication rates and increase its widespread use. Additionally, pre-procedural cardiac computed tomography can be used to identify the optimal positioning of the receiver electrode based on indicators such as scar burden, simulated latest activation (81), and hemodynamic assessment (82).

Conclusion

In summary, HBP, LBBAP, and leadless LV pacing have been demonstrated as potential alternatives for optimal CRT when conventional CRT fails. Each technique has its advantages and disadvantages (**Table 1**). HBP and LBBAP have shown more effective electrical resynchronization than conventional BVP. Accordingly, they provided equivalent or even superior clinical outcomes in some challenging cohorts. However, transvenous leads remain a major limitation of these pacing modalities. Thus, leadless LV pacing has been developed and demonstrated to provide more physiological LV endocardial activation coupled with clinical benefits. Furthermore, the advantage of leadless LV pacing would become more pronounced in cases of venous occlusion or lead infection. With a better understanding of HBP, LBBAP, leadless LV pacing, and their appropriate candidates, it is more likely that the most suitable alternative will be chosen when conventional CRT is impossible or ineffective.

Author contributions

JH conducted the reference analysis and wrote the manuscript. QK contributed to the reference collection and manuscript revision. QC contributed to the topic conception, manuscript revision, and decided to submit for publication. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the National Natural Science Foundation of China (grant no. 81360025).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Tomasoni D, Adamo M, Lombardi CM, Metra M. Highlights in heart failure. *ESC Heart Fail.* (2019) 6:1105–27. doi: 10.1002/ehf2.12555

2. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* (2021) 42:3599–726.

3. St John Sutton MG, Plappert T, Abraham WT, Smith AL, DeLurgio DB, Leon AR, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation.* (2003) 107:1985–90. doi: 10.1161/01.CIR.0000065226.24159.E9

4. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, et al. 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J.* (2021) 42:3427–520. doi: 10.1093/eurheartj/ehab699

5. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, et al. Results of the predictors of response to CRT (PROSPECT) trial. *Circulation.* (2008) 117:2608–16. doi: 10.1161/CIRCULATIONAHA.107.743120

6. Prinzen FW, Vernooy K, Auricchio A. Cardiac resynchronization therapy: state-of-the-art of current applications, guidelines, ongoing trials, and areas of

controversy. *Circulation.* (2013) 128:2407–18. doi: 10.1161/CIRCULATIONAHA.112.000112

7. Daubert C, Behar N, Martins RP, Mabo P, Leclercq C. Avoiding non-responders to cardiac resynchronization therapy: a practical guide. *Eur Heart J.* (2017) 38:1463–72.

8. Auricchio A, Prinzen FW. Non-responders to cardiac resynchronization therapy: the magnitude of the problem and the issues. *Circ J.* (2011) 75:521–7. doi: 10.1253/circj.CJ-10-1268

9. Vijayaraman P, Chung MK, Dandamudi G, Upadhyay GA, Krishnan K, Crossley G, et al. His bundle pacing. *J Am Coll Cardiol.* (2018) 72:927–47. doi: 10.1016/j.jacc.2018.06.017

10. Lustgarten DL, Crespo EM, Arkhipova-Jenkins I, Lobel R, Winget J, Koehler J, et al. His-bundle pacing versus biventricular pacing in cardiac resynchronization therapy patients: a crossover design comparison. *Heart Rhythm.* (2015) 12:1548–57. doi: 10.1016/j.hrthm.2015.03.048

11. Subzposh FA, Vijayaraman P. Long-term results of his bundle pacing. *Card Electrophysiol Clin.* (2018) 10:537–42.

12. Zanon F, Ellenbogen KA, Dandamudi G, Sharma PS, Huang W, Lustgarten DL, et al. Permanent his-bundle pacing: a systematic literature review and meta-analysis. *Europace.* (2018) 20:1819–26. doi: 10.1093/europace/euy058

13. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, et al. A novel pacing strategy with low and stable output: pacing the left bundle branch immediately beyond the conduction block. *Can J Cardiol.* (2017) 33:1736. doi: 10.1016/j.cjca.2017.09.013

14. Zhang W, Huang J, Qi Y, Wang F, Guo L, Shi X, et al. Cardiac resynchronization therapy by left bundle branch area pacing in patients with heart failure and left bundle branch block. *Heart Rhythm.* (2019) 16:1783–90. doi: 10.1016/j.hrthm.2019.09.006

15. Guo J, Li L, Xiao G, Ye T, Huang X, Meng F, et al. Remarkable response to cardiac resynchronization therapy via left bundle branch pacing in patients with true left bundle branch block. *Clin Cardiol.* (2020) 43:1460–8. doi: 10.1002/clc.23462

16. Li X, Qiu C, Xie R, Ma W, Wang Z, Li H, et al. Left bundle branch area pacing delivery of cardiac resynchronization therapy and comparison with biventricular pacing. *ESC Heart Fail.* (2020) 7:1711–22. doi: 10.1002/ehf2.12731

17. Wang Y, Gu K, Qian Z, Hou X, Chen X, Qiu Y, et al. The efficacy of left bundle branch area pacing compared with biventricular pacing in patients with heart failure: a matched case-control study. *J Cardiovasc Electrophysiol.* (2020) 31:2068–77. doi: 10.1111/jce.14628

18. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, et al. Long-term outcomes of his bundle pacing in patients with heart failure with left bundle branch block. *Heart.* (2019) 105:137–43. doi: 10.1136/heartjnl-2018-313415

19. Vijayaraman P, Ponnusamy S, Cano Ó, 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) 7:135–47. doi: 10.1016/j.jacep.2020.08.015

20. Auricchio A, Delnoy PP, Butter C, Brachmann J, Van Erven L, Spitzer S, et al. Feasibility, safety, and short-term outcome of leadless ultrasound-based endocardial left ventricular resynchronization in heart failure patients: results of the wireless stimulation endocardially for CRT (WiSE-CRT) study. *Europace.* (2014) 16:681–8. doi: 10.1093/europace/eut435

21. Reddy VY, Miller MA, Neuzil P, Søgaard P, Butter C, Seifert M, et al. Cardiac resynchronization therapy with wireless left ventricular endocardial pacing: the SELECT-LV study. *J Am Coll Cardiol.* (2017) 69:2119–29. doi: 10.1016/j.jacc.2017.02.059

22. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med.* (2001) 344:873–80. doi: 10.1056/NEJM200103223441202

23. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med.* (2002) 346:1845–53. doi: 10.1056/NEJMoa013168

24. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med.* (2005) 352:1539–49. doi: 10.1056/NEJMoa050496

25. Daubert C, Gold MR, Abraham WT, Ghio S, Hassager C, Goode G, et al. Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction: insights from the European cohort of the REVERSE (resynchronization reverses remodeling in systolic left ventricular dysfunction) trial. *J Am Coll Cardiol.* (2009) 54:1837–46.

26. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med.* (2009) 361:1329–38. doi: 10.1056/NEJMoa0906431

27. Birnie DH, Ha A, Higginson L, Sidhu K, Green M, Philippon F, et al. Impact of QRS morphology and duration on outcomes after cardiac resynchronization therapy: results from the resynchronization-defibrillation for ambulatory heart failure trial (RAFT). *Circ Heart Fail.* (2013) 6:1190–8. doi: 10.1161/CIRCHEARTFAILURE.113.000380

28. Singh JP, Klein HU, Huang DT, Reek S, Kuniss M, Quesada A, et al. Left ventricular lead position and clinical outcome in the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT) trial. *Circulation.* (2011) 123:1159–66. doi: 10.1161/CIRCULATIONAHA.110.000646

29. Martin DO, Lemke B, Birnie D, Krum H, Lee KL, Aonuma K, et al. Investigation of a novel algorithm for synchronized left-ventricular pacing and ambulatory optimization of cardiac resynchronization therapy: results of the adaptive CRT trial. *Heart Rhythm.* (2012) 9:1807–14. doi: 10.1016/j.hrthm.2012.07.009

30. Wang J, Liang Y, Chen H, Wang W, Bai J, Chen X, et al. Patient-tailored SyncAV algorithm: a novel strategy to improve synchrony and acute hemodynamic response in heart failure patients treated by cardiac resynchronization therapy. *J Cardiovasc Electrophysiol.* (2020) 31:512–20. doi: 10.1111/jce.14315

31. Forleo GB, Santini L, Giammaria M, Potenza D, Curnis A, Calabrese V, et al. Multipoint pacing via a quadripolar left-ventricular lead: preliminary results from the Italian registry on multipoint left-ventricular pacing in cardiac resynchronization therapy (IRON-MPP). *Europace.* (2017) 19:1170–7. doi: 10.1093/europace/euw094

32. van Dijk VF, Fanggiday J, Balt JC, Wijffels M, Daeter EJ, Kelder JC, et al. Effects of epicardial versus transvenous left ventricular lead placement on left ventricular function and cardiac perfusion in cardiac resynchronization therapy: a randomized clinical trial. *J Cardiovasc Electrophysiol.* (2017) 28:917–23. doi: 10.1111/jce.13242

33. Gamble JHP, Herring N, Ginks MR, Rajappan K, Bashir Y, Betts TR. Endocardial left ventricular pacing across the interventricular septum for cardiac resynchronization therapy: clinical results of a pilot study. *Heart Rhythm.* (2018) 15:1017–22. doi: 10.1016/j.hrthm.2018.02.032

34. Vijayaraman P, Dandamudi G, Zanon F, Sharma PS, Tung R, Huang W, et al. Permanent his bundle pacing: recommendations from a multicenter his bundle pacing collaborative working group for standardization of definitions, implant measurements, and follow-up. *Heart Rhythm.* (2018) 15:460–8.

35. Vijayaraman P, Dandamudi G, Bauch T, Ellenbogen KA. Imaging evaluation of implantation site of permanent direct his bundle pacing lead. *Heart Rhythm.* (2014) 11:529–30. doi: 10.1016/j.hrthm.2013.01.027

36. Keene D, Arnold A, Shun-Shin MJ, Howard JP, Sohaib SA, Moore P, et al. Rationale and design of the randomized multicentre his optimized pacing evaluated for heart failure (HOPE-HF) trial. *ESC Heart Fail.* (2018) 5:965–76. doi: 10.1002/ehf2.12315

37. Zhang J, Guo J, Hou X, Wang Y, Qian Z, Li K, et al. Comparison of the effects of selective and non-selective his bundle pacing on cardiac electrical and mechanical synchrony. *Europace.* (2018) 20:1010–7. doi: 10.1093/europace/eux120

38. Upadhyay GA, Tung R. Selective versus non-selective his bundle pacing for cardiac resynchronization therapy. *J Electrocardiol.* (2017) 50:191–4. doi: 10.1016/j.jelectrocard.2016.10.003

39. Deshmukh P, Casavant DA, Romanyshyn M, Anderson K. Permanent, direct his-bundle pacing: a novel approach to cardiac pacing in patients with normal his-purkinje activation. *Circulation.* (2000) 101:869–77. doi: 10.1161/01.CIR.101.8.869

40. Barba-Pichardo R, Manovel Sánchez A, Fernández-Gómez JM, Moriña-Vázquez P, Venegas-Gamero J, Herrera-Carranza M. Ventricular resynchronization therapy by direct his-bundle pacing using an internal cardioverter defibrillator. *Europace.* (2013) 15:83–8. doi: 10.1093/europace/eus228

41. Sharma PS, Dandamudi G, Herweg B, Wilson D, Singh R, Naperkowski A, et al. Permanent his-bundle pacing as an alternative to biventricular pacing for cardiac resynchronization therapy: a multicenter experience. *Heart Rhythm.* (2018) 15:413–20. doi: 10.1016/j.hrthm.2017.10.014

42. Arnold AD, Shun-Shin MJ, Keene D, Howard JP, Sohaib SMA, Wright IJ, et al. His resynchronization versus biventricular pacing in patients with heart failure and left bundle branch block. *J Am Coll Cardiol.* (2018) 72:3112–22. doi: 10.1016/j.jacc.2018.09.073

43. Upadhyay GA, Vijayaraman P, Nayak HM, Verma N, Dandamudi G, Sharma PS, et al. On-treatment comparison between corrective His bundle pacing and biventricular pacing for cardiac resynchronization: a secondary analysis of the His-SYNC Pilot Trial. *Heart Rhythm.* (2019) 16:1797–807. doi: 10.1016/j.hrthm.2019.05.009

44. Vinther M, Risum N, Svendsen JH, Møgelvang R, Philbert BTA. Randomized trial of his pacing versus biventricular pacing in symptomatic hf patients with left bundle branch block (his-alternative). *JACC Clin Electrophysiol.* (2021) 7:1422–32. doi: 10.1016/j.jacep.2021.04.003

45. Vijayaraman P, Herweg B, Ellenbogen KA, Gajek J. His-optimized cardiac resynchronization therapy to maximize electrical resynchronization: a feasibility study. *Circ Arrhythm Electrophysiol.* (2019) 12:e006934. doi: 10.1161/CIRCEP.118.006934

46. Deshmukh A, Sattur S, Bechtol T, Heckman LIB, Prinzen FW, Deshmukh P. Sequential his bundle and left ventricular pacing for cardiac resynchronization. *J Cardiovasc Electrophysiol.* (2020) 31:2448–54. doi: 10.1111/jce.14674

47. Padeletti L, Pieragnoli P, Ricciardi G, Innocenti L, Checchi L, Padeletti M, et al. Simultaneous his bundle and left ventricular pacing for optimal cardiac resynchronization therapy delivery: acute hemodynamic assessment by pressure-volume loops. *Circ Arrhythm Electrophysiol.* (2016) 9:5. doi: 10.1161/CIRCEP.115.003793

48. Senes J, Mascia G, Bottoni N, Oddone D, Donateo P, Grimaldi T, et al. Is his-optimized superior to conventional cardiac resynchronization therapy in improving heart failure? Results from a propensity-matched study. *Pacing Clin Electrophysiol.* (2021) 44:1532–9. doi: 10.1111/pace.14336

49. Padala SK, Cabrera JA, Ellenbogen KA. Anatomy of the cardiac conduction system. *Pacing Clin Electrophysiol.* (2021) 44:15–25. doi: 10.1111/pace.14107

50. Qi J, Jia X, Wang Z. His bundle pacing for cardiac resynchronization therapy: a systematic literature review and meta-analysis. *J Interv Card Electrophysiol.* (2020) 59:463–70. doi: 10.1007/s10840-020-00827-6

51. 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. *Circulation.* (2019) 139:1876–88. doi: 10.1161/CIRCULATIONAHA.118.038648

52. Chen X, Wu S, Su L, Su Y, Huang W. The characteristics of the electrocardiogram and the intracardiac electrogram in left bundle branch pacing. *J Cardiovasc Electrophysiol.* (2019) 30:1096–101. doi: 10.1111/jce.13956

53. Wu S, Chen X, Wang S, Xu L, Xiao F, Huang Z, et al. Evaluation of the criteria to distinguish left bundle branch pacing from left ventricular septal pacing. *JACC Clin Electrophysiol.* (2021) 7:1166–77. doi: 10.1016/j.jacep.2021.02.018

54. Gao MY, Tian Y, Shi L, Wang YJ, Xie BQ, Qi J, et al. Electrocardiographic morphology during left bundle branch area pacing: characteristics, underlying mechanisms, and clinical implications. *Pacing Clin Electrophysiol.* (2020) 43:297–307. doi: 10.1111/pace.13884

55. Hou X, Qian Z, Wang Y, Qiu Y, Chen X, Jiang H, et al. Feasibility and cardiac synchrony of permanent left bundle branch pacing through the interventricular septum. *Europace.* (2019) 21:1694–702. doi: 10.1093/europace/euz188

56. 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) 6:849–58. doi: 10.1016/j.jacep.2020.04.011

57. Su L, Wang S, Wu S, Xu L, Huang Z, Chen X, et al. Long-term safety and feasibility of left bundle branch pacing in a large single-center study. *Circ Arrhythm Electrophysiol.* (2021) 14:e009261. doi: 10.1161/CIRCEP.120.009261

58. Zhong C, Xu W, Shi S, Zhou X, Zhu Z. Left bundle branch pacing for cardiac resynchronization therapy: a systematic literature review and meta-analysis. *Pacing Clin Electrophysiol.* (2021) 44:497–505. doi: 10.1111/pace.14174

59. Salden F, Luermans J, Westra SW, Weijs B, Engels EB, Heckman LIB, et al. Short-term hemodynamic and electrophysiological effects of cardiac resynchronization by left ventricular septal pacing. *J Am Coll Cardiol.* (2020) 75:347–59.

60. Wu S, Su L, Vijayaraman P, Zheng R, Cai M, Xu L, et al. Left bundle branch pacing for cardiac resynchronization therapy: nonrandomized on-treatment comparison with his bundle pacing and biventricular pacing. *Can J Cardiol.* (2021) 37:319–28.

61. Hua J, Chen Y, Yu J, Xiong Q, Xia Z, Xia Z, et al. Long-term outcomes of left bundle branch area pacing versus biventricular pacing in patients with heart failure and complete left bundle branch block. *Heart Vessels.* (2022) 37:1162–74. doi: 10.1007/s00380-021-02016-5

62. Liu J, Sun F, Wang Z, Sun J, Jiang X, Zhao W, et al. Left bundle branch area pacing vs. biventricular pacing for cardiac resynchronization therapy: a meta-analysis. *Front Cardiovasc Med.* (2021) 8:669301. doi: 10.3389/fcvm.2021.669301

63. Hua J, Wang C, Kong Q, Zhang Y, Wang Q, Xiong Z, et al. Comparative effects of left bundle branch area pacing, his bundle pacing, biventricular pacing in patients requiring cardiac resynchronization therapy: a network meta-analysis. *Clin Cardiol.* (2022) 45:214–23. doi: 10.1002/clc.23784

64. Jastrzębski M, Moskal P, Huybrechts W, Curila K, Sreekumar P, Rademakers LM, et al. Left bundle branch-optimized cardiac resynchronization therapy (LOT-CRT): results from an international LBBAP collaborative study group. *Heart Rhythm.* (2022) 19:13–21. doi: 10.1016/j.hrthm.2021.07.057

65. Vijayaraman P, Herweg B, Verma A, Sharma PS, Batul SA, Ponnusamy SS, et al. Rescue left bundle branch area pacing in coronary venous lead failure or nonresponse to biventricular pacing: results from International LBBAP collaborative study group. *Heart Rhythm.* (2022) 19:1272–80. doi: 10.1016/j.hrthm.2022.04.024

66. De Pooter J, Calle S, Timmermans F, Van Heuverswyn F. Left bundle branch area pacing using stylet-driven pacing leads with a new delivery sheath: a comparison with lumen-less leads. *J Cardiovasc Electrophysiol.* (2021) 32:439–48. doi: 10.1111/jce.14851

67. Zanon F, Marcantoni L, Pastore G, Baracca E. Left bundle branch pacing by standard stylet-driven lead: preliminary experience of two case reports. *HeartRhythm Case Rep.* (2020) 6:614–7. doi: 10.1016/j.hrcr.2020.06.005

68. De Pooter J, Wauters A, Van Heuverswyn F, Le Polain de Waroux JB. A Guide to left bundle branch area pacing using stylet-driven pacing leads. *Front Cardiovasc Med.* (2022) 9:844152. doi: 10.3389/fcvm.2022.844152

69. Daniëls F, Adiyaman A, Aarnink KM, Oosterwerff FJ, Verbakel JRA, Ghani A, et al. The zwolle experience with left bundle branch area pacing using stylet-driven active fixation leads. *Clin Res Cardiol.* (2022) 2022:1–10. doi: 10.1007/s00392-022-02048-5

70. Anderson RH, Yanni J, Boyett MR, Chandler NJ, Dobrzynski H. The anatomy of the cardiac conduction system. *Clin Anat.* (2009) 22:99–113. doi: 10.1002/ca.20700

71. Li X, Li H, Ma W, Ning X, Liang E, Pang K, et al. Permanent left bundle branch area pacing for atrioventricular block: feasibility, safety, and acute effect. *Heart Rhythm.* (2019) 16:1766–73. doi: 10.1016/j.hrthm.2019.04.043

72. Chen X, Wei L, Bai J, Wang W, Qin S, Wang J, et al. Procedure-related complications of left bundle branch pacing: a single-center experience. *Front Cardiovasc Med.* (2021) 8:645947. doi: 10.3389/fcvm.2021.645947

73. Sieniewicz BJ, Gould JS, Rimington HM, Ioannou N, Rinaldi CA. transseptal delivery of a leadless left ventricular endocardial pacing electrode. *JACC Clin Electrophysiol.* (2017) 3:1333–5. doi: 10.1016/j.jacep.2017.04.020

74. Sieniewicz BJ, Betts TR, James S, Turley A, Butter C, Seifert M, et al. Real-world experience of leadless left ventricular endocardial cardiac resynchronization therapy: a multicenter international registry of the WiSE-CRT pacing system. *Heart Rhythm.* (2020) 17:1291–7. doi: 10.1016/j.hrthm.2020.03.002

75. Okabe T, Hummel JD, Bank AJ, Niazi IK, McGrew FA, Kindsvater S, et al. Leadless left ventricular stimulation with WiSE-CRT system - initial experience and results from phase I of SOLVE-CRT study (nonrandomized, roll-in phase). *Heart Rhythm.* (2022) 19:22–9. doi: 10.1016/j.hrthm.2021.06.1195

76. Montemerlo E, Pozzi M, De Ceglia S, Santini F, Piazzi E, Rovaris G. First-in-man fully leadless transvenous CRT-P with a transseptal implant of WISE-CRT(§) system and micra(§) PM. *Pacing Clin Electrophysiol.* (2019) 42:1489–92. doi: 10.1111/pace.13750

77. Funasako M, Neuzil P, Dujka L, Petru J, Sediva L, Simon J, et al. Successful implementation of a totally leadless biventricular pacing approach. *HeartRhythm Case Rep.* (2020) 6:153–7. doi: 10.1016/j.hrcr.2019.12.002

78. Galand V, Polin B, Martins RP, Leclercq C. An entirely leadless cardiac resynchronization therapy. *Eur Heart J.* (2019) 40:858–9. doi: 10.1093/eurheartj/ehy746

79. Carabelli A, Jabeur M, Jacon P, Rinaldi CA, Leclercq C, Rovaris G, et al. European experience with a first totally leadless cardiac resynchronization therapy pacemaker system. *Europace.* (2021) 23:740–7.

80. Wijesuriya N, Elliott MK, Mehta V, Sidhu BS, Behar JM, Niederer S, et al. Leadless left ventricular endocardial pacing for cardiac resynchronization therapy: a systematic review and meta-analysis. *Heart Rhythm.* (2022) 19:1176–83.

81. Sidhu BS, Lee AWC, Haberland U, Rajani R, Niederer S, Rinaldi CA. Combined computed tomographic perfusion and mechanics with predicted activation pattern can successfully guide implantation of a wireless endocardial pacing system. *Europace.* (2020) 22:298. doi: 10.1093/europace/euz227

82. Sohal M, Hamid S, Perego G, Della Bella P, Adhya S, Paisey J, et al. A multicenter prospective randomized controlled trial of cardiac resynchronization therapy guided by invasive dP/dt. *Heart Rhythm.* (2021) 2:19–27. doi: 10.1016/j.hroo.2021.01.005

frontiers | Frontiers in Cardiovascular Medicine

TYPE Systematic Review
PUBLISHED 25 October 2022
DOI 10.3389/fcvm.2022.939850

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Cardiac Rhythmology, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 09 May 2022
ACCEPTED 03 October 2022
PUBLISHED 25 October 2022

CITATION
Zhang Y, Jia Y, Liu J and Du R (2022) A systematic review and Bayesian network meta-analysis comparing left bundle branch pacing, his bundle branch pacing, and right ventricular pacing for atrioventricular block. *Front. Cardiovasc. Med.* 9:939850. doi: 10.3389/fcvm.2022.939850

A systematic review and Bayesian network meta-analysis comparing left bundle branch pacing, his bundle branch pacing, and right ventricular pacing for atrioventricular block

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Background: Although right ventricular pacing (RVP) is recommended by most of the guidelines for atrioventricular block, it can cause electrical and mechanical desynchrony, impair left ventricular function, and increase the risk of atrial fibrillation. Recently, the His–Purkinje system pacing, including His bundle pacing (HBP) and left bundle branch pacing (LBBP), has emerged as a physiological pacing modality. However, few studies have compared their efficacy and safety in atrioventricular block (AVB).

Methods and results: The PubMed, Web of Science, Cochrane Library, and ScienceDirect databases were searched for observational studies and randomized trials of patients with atrioventricular block requiring permanent pacing, from database inception until 10 January 2022. The primary outcomes were complications and heart failure hospitalization. The secondary outcomes included changes in left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter (LVEDD), pacing parameters, procedure duration, and success rate. After extracting the data at baseline and the longest follow-up duration available, a pairwise meta-analysis and a Bayesian random-effects network meta-analysis were performed. Odds ratios (ORs) with 95% confidence intervals (CIs) or 95% credible intervals (CrIs) were calculated for dichotomous outcomes, whereas mean differences (MDs) with 95% CIs or 95% CrIs were calculated for continuous outcomes. Seven studies and 1,069 patients were included. Overall, 43.4% underwent LBBP, 33.5% HBP, and 23.1% RVP. Compared with RVP, LBBP and HBP were associated with a shorter paced QRS duration and a more preserved LVEF. HBP significantly increased the pacing threshold and reduced the R-wave amplitude. There was no difference in the risk of complications or the implant success rate. The pacing threshold remained stable during follow-up for the three pacing

modalities. The pacing impedance was significantly reduced in HBP, while a numerical but non-significant pacing impedance decrease was observed in both LBBP and RVP. LBBP was associated with an increased R-wave amplitude during follow-up.

Conclusion: In this systematic review and network meta-analysis, HBP and LBBP were superior to RVP in paced QRS duration and preservation of LVEF for patients with atrioventricular block. LBBP was associated with a lower pacing threshold and a greater R-wave amplitude than HBP. However, the stability of the pacing output of LBBP may be a concern. Further investigation of the long-term efficacy in left ventricular function and the risk of heart failure hospitalization is needed.

Systematic review registration: [https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=315046], identifier [CRD42022315046].

KEYWORDS

network meta-analysis, left bundle branch pacing, left bundle branch area pacing, His–Purkinje system pacing, atrioventricular block

Introduction

Right ventricular pacing (RVP) is the traditional pacing modality recommended for patients with atrioventricular block by most of the guidelines (1, 2), with a shorter procedure time and an easier learning curve. However, RVP with a high ventricular pacing rate can increase the risk of atrial fibrillation, pacing-induced cardiomyopathy, heart failure hospitalization, and death (3, 4).

Recent scientific evidence has shown the efficacy and safety of the His–Purkinje system pacing, with significant improvements in exercise capacity, ventricular synchrony, left ventricular ejection fraction (LVEF), and so on (5). Few studies have compared the effectiveness of left bundle branch pacing (LBBP), His bundle pacing (HBP), and RVP in patients with atrioventricular block, especially LBBP vs. HBP. Thus, we aimed to comprehensively compare the clinical outcomes and pacing parameters of these three pacing modalities for atrioventricular block.

The evidence was assessed in a network meta-analysis. Network meta-analyses synthesize direct and indirect evidence in a network of trials that compare multiple interventions (6). This method allows for a comparison of the three pacing modalities for atrioventricular block despite the paucity of head-to-head comparisons.

Abbreviations: AVB, atrioventricular block; CI, confidence interval; CrI, credible interval; CRT, cardiac resynchronization therapy; HBP, His bundle pacing; HPSP, His–Purkinje system pacing; HFH, heart failure hospitalization; LBBP, left bundle branch pacing; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; MD, mean difference; NMA, network meta-analysis; PCM, pacemaker-induced cardiomyopathy; RVP, right ventricular pacing; SUCRA, surface under the cumulative ranking curve; UHF-ECG, ultra-high-frequency electrocardiography.

Methods

This is a systematic review and network meta-analysis of pacing modality intervention trials in atrioventricular block. The research question was developed with the PICOS framework as follows:

Participants: Patients with atrioventricular block.

Intervention and comparator: Left bundle branch pacing, His bundle pacing, and right ventricular pacing.

Outcomes: (1) Pacing parameters, including paced QRS duration (ms), pacing impedance (Ω), pacing threshold (V), and R-wave amplitudes (mV). (2) Clinical outcomes, including complications and heart failure hospitalization. (3) Left ventricular function, including LVEF (%) and left ventricular end-diastolic diameter (LVEDD) (mm). (4) Procedure duration (min) and success rate.

Studies: Observational studies and randomized trials.

Reporting was conducted according to the Preferred Reporting Items for Systematic Review and Network Meta-analysis (PRISMA-NMA) statement (7). This study was registered at the Prospective International Register of Systematic Reviews (PROSPERO). The registration number is CRD42022315046.

Data sources

The PubMed, Web of Science, Cochrane Library, and ScienceDirect databases were consulted to identify English-language studies on LBBP, HBP, and RVP for the treatment of atrioventricular block from database inception until 10 January 2022. Details of the electronic search strategies are summarized in the **Supplementary materials**.

Study selection criteria

Eligible studies included observational studies and randomized trials comparing the effects of LBBP or HBP vs. RVP for atrioventricular block in pacing parameters, clinical outcomes, left ventricular function, procedure duration, and success rate. Exclusion criteria were studies with population or outcome stratification not of interest, or with fewer than 10 patients per study group. No additional information was requested from the study authors.

Study identification

Two investigators (YZ and YJ) individually screened the articles by title, abstract, and full text. The inclusion of a study was decided by consensus between the two investigators. Disagreements were resolved by discussion, and if no agreement could be reached, a third senior investigator (JL) made the decision.

Outcomes and data extraction

The primary outcomes were complications and heart failure hospitalization. The secondary outcomes included changes in LVEF and LVEDD, pacing parameters, procedure duration, and success rate. The pacing threshold was the His lead for HBP and LBBP and RV lead for RVP at 0.4, 0.5, or 1.0 ms. The complications included those requiring treatment or reintervention during the perioperative period or at follow-up. **Supplementary Table 1** shows the detailed definitions of the complications reported by the included studies.

For each outcome, data at baseline and the longest available follow-up time point were extracted. Other extracted data included characteristics of the study design, baseline demographic characteristics (age, sex, number of patients), duration of treatment, and follow-up duration.

For the randomized crossover trials, data were included from the first period, before crossing over, to avoid the risk of any carryover effect (8).

Risk of bias and publication bias assessment

The quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS) for observational studies and the risk of bias 2 tool (ROB 2.0) for randomized trials. Publication bias was assessed with funnel plots and Egger's test for every outcome comparison.

Data analysis

The initial analysis consisted of a two-group outcome comparison between LBBP or HBP and RVP for all outcomes. Then, for each endpoint, a Bayesian random-effects NMA was conducted with the three pacing strategies. Odds ratios (ORs) with 95% confidence intervals (CIs) or 95% credible intervals (CrIs) were calculated for dichotomous outcomes, whereas mean differences (MDs) with 95% CIs or 95% CrIs were calculated for continuous outcomes. The I^2 index was calculated to assess heterogeneity. An I^2 of less than 25% was viewed as low heterogeneity, between 25% and 50% as moderate, and over 50% as high heterogeneity (9). Treatments for each outcome were ranked based on the surface under the cumulative ranking curve (SUCRA) method, which vary from 0 to 100% and represent the probability that the treatment evaluated is the best. All analyses were conducted using RevMan version 5.4.1, R version 4.1.2 with the "gemtc" and "netmeta" packages, and JAGS 4.3.0.

Results

In total, 1,428 studies were retrieved, of which 485 duplicates were excluded. A total of 813 irrelevant records were excluded by a screening of titles and abstracts. After a full-text assessment of the remaining 130 articles, 7 studies met the pre-defined inclusion criteria and were included in the meta-analysis (10–16). The flowchart of the literature selection process is shown in **Figure 1**.

Among the seven included studies, three compared LBBP with RVP (n = 339 vs. n = 216 patients), three compared LBBP with HBP (n = 228 vs. n = 260 patients), and 1 compared HBP with RVP (n = 19 vs. n = 19 patients) with follow-up durations between 3 and 24 months. Initial enrollment ranged from 2007 to 2020. Five were observational studies, one was a randomized controlled trial, and one was a randomized crossover trial. In total, 1,069 patients from 11 centers across five countries were included. The pacing indication was atrioventricular block, and 736 (68.8%) patients in six studies had a preserved left ventricular ejection fraction > 40%. The mean age of the patient population was 67.7 years. Of these, 464 (43.4%) underwent LBBP, 247 (23.1%) HBP, and 358 (33.5%)

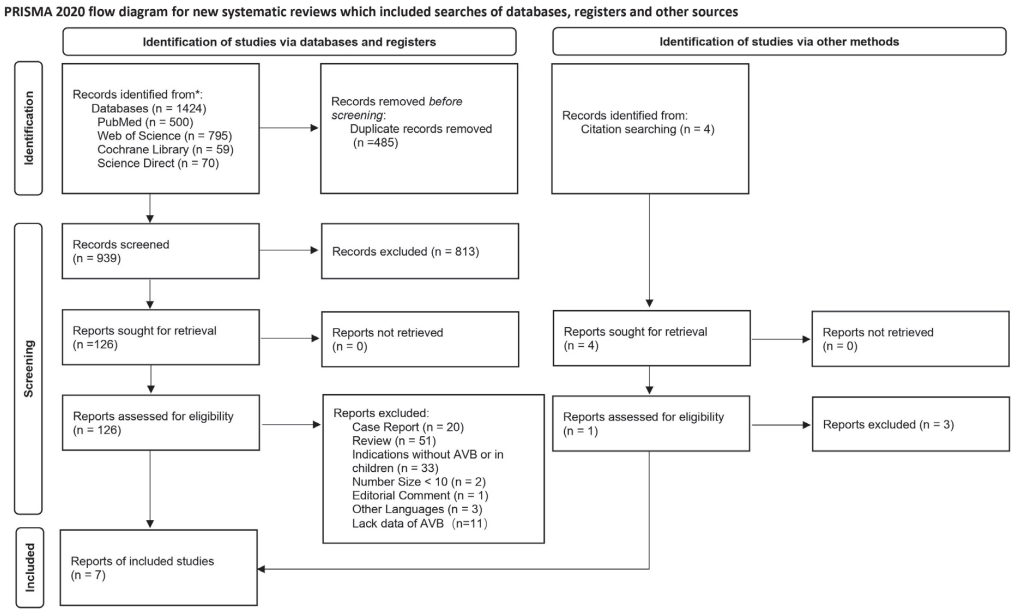

FIGURE 1
Flowchart of the literature selection process.

TABLE 1 Demographic data of all studies.

Author, year	Study design	Country	Indication	Follow up (months)	Male, *n*	Pacing mode	Number of patients, *n*	Success rate (%)	Baseline LVEF (%)	3830 used
Hu et al. (10)	Observational	China	AVB	3	32	HBP	25	76	59.3 ± 11.3	Yes
						LBBP	25	88	57.7 ± 7.8	Yes
Hasumi et al. (13)	Observational	Japan	AVB with preserved LVEF	6	NR	HBP	21	64	NR	Yes
						LBBP	71	81	NR	Yes
Vijayaraman et al. (15)	Observational	USA	Advanced AVB	12∼24	211	HBP	182	NR	NR	Yes
						LBBP	151	NR	NR	Yes
Li et al. (11)	Observational	China	AVB and LVEF > 50% at baseline	12	242	RVP	246	100	61.5 ± 6.4	–
						LBBP	120	95.5	61.7 ± 7.4	Yes
Zhang et al. (14)	Observational	China	AVB	12∼24	30	RVP	33	100	56.29 ± 5.40	–
						LBBP	37	87.9	55.08 ± 4.32	Yes
Riano Ondiviela et al. (12)	Randomized controlled trial	Spain	Third-degree AVB with preserved LVEF	3	37	RVP	60	95	NR	NR
						LBBP	60	95	NR	
Kronborg et al. (16)	Randomized crossover trial	Denmark	AVB with a preserved LVEF > 40%	12	30	RVP	19	97	NR	–
						HBP	19	84	NR	Yes

AVB, atrioventricular block; HBP, His bundle pacing; LBBP, left bundle branch pacing; LVEF, left ventricular ejection fraction; NR, not reported; RVP, right ventricular pacing.

RVP. The overall success rate of LBBP was 93.5% (360/385). The characteristics of the included trials are presented in Table 1.

Risk of bias for individual studies

The NOS for observational studies ranged from 3 to 8, the ROB 2.0 for the randomized crossover trial was low risk, and for the randomized controlled trial, there were some concerns (see Supplementary Table 2 and Supplementary Figure 1).

Pairwise meta-analysis

Among the seven included studies, three compared LBBP with RVP, three compared LBBP with HBP, and one compared HBP with RVP. The pairwise meta-analysis could only be conducted for LBBP vs. RVP and LBBP vs. HBP. Supplementary Figure 2 shows the outcomes and

studies included in the pairwise meta-analyses. The results of the pairwise meta-analysis are summarized in **Table 2**. Compared with HBP, LBBP was associated with a lower pacing threshold, greater R-wave amplitude, and higher pacing impedance at follow-up, while there was no significant difference in procedure duration, paced QRS duration, pacing impedance after implantation, or risks of complications. LBBP demonstrated significant improvements over RVP in terms of a shorter paced QRS duration, more preserved LVEF, smaller LVEDD, and reduced risk of heart failure hospitalization. LBBP was associated with lower pacing impedance after implantation than RVP, with no difference in pacing impedance at follow-up, implant success rate, pacing threshold, R-wave amplitudes, or complications. **Supplementary Figures 4–26** show the forest plots for the corresponding outcomes.

Pacing parameters

Paced QRS duration

Left bundle branch pacing was associated with a significantly shorter paced QRS duration than RVP (MD, −42.42; 95% CI, −44.68 to −40.17; $p < 0.00001$; $I^2 = 18\%$). LBBP did not shorten the paced QRS duration relative to HBP (MD, −3.32; 95% CI, −9.57 to 2.93; $p = 0.30$; $I^2 = 41\%$).

Pacing impedance

Compared with RVP, LBBP demonstrated a lower pacing impedance at the time of implantation (MD, −68.48; 95% CI, −136.40 to −0.55; $p = 0.05$; $I^2 = 52\%$), with no significant difference at follow-up (MD, −94.96; 95% CI, −211.65 to 21.73; $p = 0.11$; $I^2 = 87\%$). There was no significant difference in pacing impedance between LBBP and HBP after implantation (MD, 107.71; 95% CI, −101.90 to 317.32; $p = 0.31$; $I^2 = 96\%$), but LBBP resulted in a significantly higher pacing impedance compared with HBP at follow-up (MD, 36.69; 95% CI, 22.51 to 50.86; $p < 0.00001$; $I^2 = 0\%$).

Pacing threshold

The pacing threshold in the LBBP group was significantly lower than in the HBP group at the time of implantation (MD, −0.58; 95% CI, −0.69 to −0.47; $p < 0.00001$; $I^2 = 0\%$) and follow-up (MD, −0.59; 95% CI, −0.72 to −0.46; $p < 0.00001$; $I^2 = 0\%$). There was no significant difference between LBBP and RVP in the pacing threshold, whether at the time of implantation or follow-up.

R-wave amplitude

Left bundle branch pacing was associated with a higher R-wave amplitude than HBP at the time of implantation (MD, 7.95; 95% CI, 7.01 to 8.89; $p < 0.00001$; $I^2 = 0\%$) and follow-up (MD, 9.73; 95% CI, 4.64 to 14.82; $p = 0.0002$; $I^2 = 94\%$). There was no significant difference between LBBP and RVP at the time of implantation or follow-up.

Left ventricular function

There was only one included study (10) comparing LBBP and HBP reporting LVEF and LVEDD. Hu et al. (10) found that there was no statistical difference in LVEF ($p = 0.764$) or LVEDD ($p = 0.957$) at the 3-month follow-up between LBBP and HBP.

Left ventricular ejection fraction

No significant difference was found in baseline LVEF between LBBP and RVP. At follow-up, LBBP demonstrated a higher LVEF than RVP (MD, 4.32; 95% CI, 3.02 to 5.61; $p < 0.00001$; $I^2 = 0\%$).

Left ventricular end-diastolic diameter

No statistically significant difference was found in baseline LVEDD between LBBP and RVP. At follow-up, LBBP was associated with a smaller LVEDD than RVP (MD, −3.63; 95% CI, −6.46 to −0.80; $p = 0.01$; $I^2 = 88\%$).

Clinical outcomes

Complications

There was no significant difference in the risk of complications, whether between LBBP and RVP or between LBBP and HBP.

Heart failure hospitalization

Left bundle branch pacing reduced the risks of heart failure hospitalization in comparison with RVP (MD, 0.21; 95% CI, 0.08 to 0.53; $p = 0.001$; $I^2 = 0\%$). None of the included studies compared the risk of heart failure hospitalization between LBBP and HBP.

Chronic evolution of pacing parameters

To explore the stability of the pacing output for the three pacing modalities, a pairwise meta-analysis was conducted to compare the changes in pacing parameters during follow-up. **Supplementary Figures 27–35** show the corresponding forest plots.

For LBBP, the R-wave amplitude increased during follow-up (MD, −2.12; 95% CI, −4.05 to −0.20; $p = 0.03$; $I^2 = 86\%$), while the pacing threshold remained stable. A numerical but non-significant decrease in the pacing impedance was observed in both LBBP and RVP. The pacing threshold and R-wave amplitude remained stable during follow-up in the RVP group. HBP demonstrated a decreased pacin gimpedance at follow-up (MD, 71.04; 95% CI, 24.24–117.83; $p = 0.003$; $I^2 = 79\%$), while pacing threshold and R-wave amplitude remained stable.

Network meta-analysis

Supplementary Figure 3 shows the studies and selected outcomes included in the network meta-analyses. Both LBBP and HBP shortened the paced QRS duration and improved LVEF compared with RVP. HBP increased the pacing threshold

TABLE 2 Results of pairwise meta-analyses.

		Pairwise meta-analysis			
		Procedure duration (min)		Implant success rate	
		N, n	OR; 95%CI; *p*	*N, n*	OR; 95%CI; *p*
LBBP vs. HBP		2 (207 vs. 168)	−0.57; (−21.24, 20.11); 0.96		NA
LBBP vs. RVP			NA	3 (339 vs. 217)	0.27; (0.04,1.80); 0.18
HBP vs. RVP			NA		NA
		Pacing parameters			
		QRS duration (ms)		Pacing threshold (V)	
		N, n	MD; 95%CI; *p*	*N, n*	MD; 95%CI; *p*
LBBP vs. HBP	Baseline	2 (207 vs. 168)	11.74; (−5.76, 29.24); 0.19	2 (207 vs. 168)	**−0.58; (−0.69, −0.47); <0.00001**
	Follow-up	2 (207 vs. 168)	−3.32; (−9.57, 2.93); 0.3	2 (207 vs. 168)	**−0.59; (−0.72, −0.46); <0.00001**
LBBP vs. RVP	Baseline	3 (339 vs. 217)	2.20; (−3.11, 7.51); 0.42	3 (339 vs. 217)	0.02; (−0.05, 0.08); 0.61
	Follow-up	3 (339 vs. 217)	**−42.43; (−44.68, −40.18); <0.00001**	2 (279 vs. 157)	0.01; (−0.13, 0.14); 0.94
HBP vs. RVP	Baseline		NA		NA
	Follow-up				
		Pacing parameters			
		R wave amplitude (mV)		Pacing impedance (Ω)	
		N, n	MD; 95%CI; *p*	*N, n*	MD; 95%CI; *p*
LBBP vs. HBP	Baseline	2 (207 vs. 168)	**7.95; (7.01, 8.89); <0.00001**	2 (207 vs. 168)	107.71; (-101.90, 317.32); 0.31
	Follow-up	2 (207 vs. 168)	**9.73; (4.64, 14.82); 0.0002**	2 (207 vs. 168)	**36.69; (22.51, 50.86); <0.00001**
LBBP vs. RVP	Baseline	3 (339 vs. 217)	0.73; (−1.23, 2.70); 0.46	2 (279 vs. 157)	**−68.48; (−136.40, −0.55); 0.05**
	Follow-up	2 (279 vs. 157)	0.85; (−1.03, 2.72); 0.38	2 (279 vs. 157)	−94.96; (−211.65, 21.73); 0.11
HBP vs. RVP	Baseline		NA		NA
	Follow-up				
		Left ventricular function			
		LVEF (%)		LVEDD (mm)	
		N, n	MD; 95%CI; p	*N, n*	MD; 95%CI; *p*
LBBP vs. HBP	Baseline		NA		NA
	Follow-up				
LBBP vs. RVP	Baseline	2 (279 vs. 157)	−0.22; (−1.49, 1.04); 0.73	2 (279 vs. 157)	0.67; (−1.27, 2.60); 0.50
	Follow-up	2 (279 vs. 157)	**4.32; (3.02, 5.61); <0.00001**	2 (279 vs. 157)	**−3.63; (−6.46, −0.80); 0.01**
HBP vs. RVP	Baseline		NA		NA
	Follow-up				
		Clinical outcomes			
		Complications		Heart failure hospitalization	
		N, n	OR; 95%CI; *p*	*N, n*	OR; 95%CI; *p*
LBBP vs. HBP		2 (207 vs. 168)	1.30; (0.57, 2.97); 0.53		NA
LBBP vs. RVP		3 (339 vs. 217)	0.77; (0.24, 2.46); 0.66	2 (279 vs. 157)	**0.21; (0.08, 0.53); 0.001**
HBP vs. RVP			NA		NA

(Continued)

10.3389/fcvm.2022.939850

TABLE 2 (Continued)

	Chronic evolution of pacing parameters			
	Pacing threshold (V)		Pacing impedance (Ω)	
	N, n	MD; 95%CI; *p*	*N, n*	MD; 95%CI; *p*
LBBP	4 (486)	−0.04; (−0.13, 0.05); 0.37	4 (486)	103.38; (−21.01, 227.77); 0.1
HBP	3 (206)	−0.08; (−0.23, 0.08); 0.34	3 (206)	**71.04; (24.24, 117.83); 0.003**
RVP	3 (195)	−0.01; (−0.04, 0.02); 0.48	3 (195)	76.74; (−6.18, 159.67); 0.07
	R wave amplitude (mV)			
	N, n	MD; 95%CI; *p*		
LBBP	4 (486)	**−2.12; (−4.05, −0.20); 0.03**		
HBP	3 (206)	−0.10; (−0.66, 0.45); 0.71		
RVP	3 (195)	−0.89; (−3.36, 1.58); 0.48		

Bold values indicate statistical differences. CI, confidence interval; HBP, His bundle pacing; LBBP, left bundle branch pacing; LVEF, left ventricular ejection fraction; MD, mean difference; N, number of studies; n, number of participants; NA, not applicable; RVP, right ventricular pacing.

after implantation and at follow-up, and reduced the R-wave amplitude after implantation. Network meta-analysis showed that there was no difference in success rate, complications, or pacing impedance after implantation or at follow-up among the three pacing modalities. Indirect comparisons showed that there was no difference in procedure duration or LVEDD at follow-up. Table 3 shows the league tables for procedure duration, implant success, pacing parameters, left ventricular function, and clinical outcomes. The network plots for all the outcomes are shown in Supplementary Figures 36, 37.

Procedure duration

No significant difference was observed in procedure duration for any comparisons. The comparison between HBP and RVP was indirect.

Implant success

None of the comparisons showed significant differences in implant success.

Paced QRS duration

There was no significant difference in baseline QRS duration among the three groups. However, at follow-up, the paced QRS duration of RVP was significantly higher than that of LBBP (MD, 42.75; 95% CrI, 38.60 to 47.75) and HBP (MD, 40.33; 95% CrI, 33.74 to 46.67), while there was no significant difference between LBBP and HBP.

Pacing impedance

No significant difference was observed for any comparisons in pacing impedance, whether after implantation or during follow-up.

Pacing threshold

In the NMA, HBP increased the pacing threshold compared with LBBP (MD, 0.67; 95% CrI, 0.35 to 1.10) and RVP (MD, 0.73; 95% CrI, 0.41 to 1.27) after implantation. At follow-up, HBP increased the pacing threshold compared with LBBP (MD, 0.73; 95% CrI, 0.12 to 1.40) and RVP (MD, 0.88; 95% CrI, 0.19 to 1.70). No significant difference was observed for LBBP vs. RVP.

R-wave amplitude

His bundle pacing exerted a lower R-wave amplitude compared with LBBP (MD, −7.29; 95% CrI, −10.21 to −4.25) and RVP (MD, −6.36; 95% CrI, −9.56 to −2.89) after implantation. HBP decreased the R-wave amplitude relative to LBBP at follow-up (MD, −8.43; 95% CrI, −15.27 to −1.32). No significant difference was observed for LBBP vs. RVP.

Left ventricular function assessment

Left ventricular ejection fraction

There was no significant difference in LVEF at admission among the three groups. At follow-up, RVP decreased LVEF relative to HBP (MD, −4.91; 95% CrI, −9.44 to −0.53) and LBBP (MD, −4.33; 95% CrI, −7.32 to −1.43). There was no significant difference between LBBP and HBP.

Left ventricular end-diastolic diameter

Additionally, there was no significant difference in LVEDD at baseline or follow-up. The comparison between HBP and RVP was indirect.

Complications

No major differences among the three pacing modalities were observed.

TABLE 3 League tables of network meta-analysis.

*Procedure duration (min)			Success rate		
LBBP			LBBP		
−0.63 (−24.64, 23.54)	HBP		0.56 (−2.54, 3.36)	HBP	
24.26 (−10.48, 59.21)	24.86 (−17.93, 66.58)	RVP	−2.06 (−5.04, −0.04)	−2.65 (−5.90, 0.20)	RVP
Baseline QRS duration (ms)			**Paced QRS duration (ms)**		
LBBP			LBBP		
10.12 (−4.30, 21.92)	HBP		−2.45 (−8.84, 3.16)	HBP	
3.86 (−6.61, 14.38)	−6.19 (−19.15, 9.23)	RVP	**−42.75 (−47.75, −38.60)**	**−40.33 (−46.67, −33.74)**	RVP
Baseline pacing impedance (Ω)			**Pacing impedance at follow-up (Ω)**		
LBBP			LBBP		
95.56 (−68.86, 253.21)	HBP		2.89 (−112.49, 121.58)	HBP	
−139.22 (−323.81, 48.50)	−44.05 (−204.39, 118.86)	RVP	−67.35 (−183.21, 49.64)	−70.57 (−203.51, 62.04)	RVP
Baseline pacing threshold (V)			**Pacing threshold at follow-up (V)**		
LBBP			LBBP		
−0.67 (−1.10, −0.35)	HBP		**−0.73 (−1.40, −0.12)**	HBP	
0.06 (−0.18, 0.42)	**0.73 (0.41, 1.27)**	RVP	0.14 (−0.45, 0.82)	**0.88 (0.19, 1.70)**	RVP
Baseline R wave amplitude (mV)			**R wave amplitude at follow-up (mV)**		
LBBP			LBBP		
7.29 (4.25, 10.21)	HBP		**8.43 (1.32, 15.27)**	HBP	
0.92 (−1.55, 3.48)	**−6.36 (−9.56, −2.89)**	RVP	2.13 (−4.84, 9.15)	−6.28 (−14.21, 1.76)	RVP
*Baseline LVEF (%)			LVEF at follow-up (%)		
LBBP			LBBP		
−1.03 (−6.26, 4.75)	HBP		−0.57 (−5.16, 3.96)	HBP	
−0.31 (−2.22, 1.46)	0.66 (−5.32, 6.34)	RVP	**4.33 (1.43, 7.32)**	**4.91 (0.53, 9.44)**	RVP
*Baseline LVEDD (mm)			*LVEDD at follow-up (mm)		
LBBP			LBBP		
−0.55 (−5.58, 4.37)	HBP		−0.19 (−7.03, 6.87)	HBP	
0.57 (−1.30, 2.59)	1.13 (−4.17, 6.57)	RVP	−3.61 (−8.21, 0.88)	−3.45 (−11.72, 4.65)	RVP
Complications					
LBBP					
0.36 (−0.77, 1.64)	HBP				
−0.18 (−1.56, 1.30)	−0.55 (−2.35, 1.29)	RVP			

Bold values indicate statistical differences. *Comparisons between HBP and RVP were indirect. HBP, His bundle pacing; LBBP, left bundle branch pacing; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LV function, left ventricular function; RVP, right ventricular pacing.

TABLE 4 Relative rankings of HBP, LBBP, and RVP based on SUCRA values (*after implantation/at follow-up).

Outcomes	Procedure duration (min)	Implant success	Paced QRS duration (follow-up) (ms)	Pacing impedance* (Ω)	Pacing threshold* (V)	R-wave amplitude* (mV)	LVEF (follow-up) (%)	LVEDD (follow-up) (mm)	Complications
Pacing modality	SUCRA (%)	SUCRA (%)	SUCRA (%)	SUCRA (%)	SUCRA (%)	SUCRA (%)	SUCRA (%)	SUCRA (%)	SUCRA (%)
LBBP	29.9	34.5	**91.9**	57.9/31.5	61.2/60.5	**91.4/88.8**	69.5	**74.0**	43.3
HBP	28.8	18.4	58.1	8.1/30.1	0.4/1.3	0.2/3.1	**79.3**	64.7	**72.9**
RVP	**91.3**	**97.1**	0.0	**84.1/88.4**	**88.4/88.2**	58.4/58.1	1.13	11.4	33.9

HBP, His bundle pacing; LBBP, left bundle branch pacing; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; RVP, right ventricular pacing; SUCRA, surface under the cumulative ranking curve. Bold values are the top one value of SUCRA ranking.

Subgroup analysis

Subgroup analyses were performed by excluding the randomized trials. **Supplementary Table 3** shows that the subgroup analyses were consistent with the main analysis except for the results of implant success rate and LVEF at follow-up, which may be explained by the small number of studies and indirect comparisons between HBP and RVP after excluding the randomized trials.

Ranking results

The SUCRA ranking results (**Table 4**) showed that RVP had the highest probability of being the best intervention for a shorter procedure duration, higher implant success rate, greater pacing impedance, and lower pacing threshold based on the SUCRA value (91.3%, 97.1%, 84.1%/88.4%, and 88.4%/88.2%, respectively). HBP was ranked the top one for fewer complications (72.9%) and more preserved LVEF at follow-up (79.3%). LBBP was the top one in terms of a shorter paced QRS duration (91.9%), higher R-wave amplitude after implantation (91.4%) and at follow-up (88.8%), and smaller LVEDD at follow-up (74.0%). However, considering that the sample sizes of the different interventions varied greatly, the results might be highly biased and should be interpreted with caution.

Sensitivity analysis

Sensitivity analysis was performed by comparing the results of network meta-analysis between the Bayesian framework and the frequentist framework (**Supplementary Table 5**). Overall, the sensitivity analysis was consistent with the main analysis except for the procedure duration, implant success rate, R-wave amplitude, and LVEDD at follow-up, which may be restricted by the small sample size.

Publication of bias assessment

Supplementary Figures 38–40 show the funnel plots and results of Egger's test for every outcome comparison.

Discussion

After combining the direct and indirect evidence, we obtained several important findings: (a) Compared with RVP, LBBP and HBP were associated with a shorter paced QRS duration and more preserved LVEF. (b) HBP significantly increased the pacing threshold and reduced the R-wave amplitude. (c) There was no difference in the risk of complications and implant success rate. However, some debatable results need further discussion, (a) LBBP demonstrated a higher pacing impedance at follow-up than HBP and a lower pacing impedance after implantation than RVP in pairwise meta-analysis. Further analysis showed that during follow-up, there was a significant impedance decrease in the HBP group, while a numerical impedance decrease was observed in LBBP and RVP. Pacing impedance may decrease when a lead insulation breach or intracavity lead dislodgement occurs (17). For LBBP, lead dislocation was the most common complication (10 in 427, 2.3%) as shown in **Supplementary Table 1**. However, the lead dislodgement rate of HBP is relatively low. In the included 228 HBP cases, only one patient developed lead dislodgement. Besides, some pathophysiological changes, such as pneumothorax and pericardial or pleural effusion, can cause indefinite impedance changes. **Supplementary Table 1** shows that two patients developed pneumothorax, and two suffered from pericardial effusion in the HBP group. In addition, the possibility of local fibrosis cannot be excluded. However, whether these conditions are the determinants of the impedance change remains unknown. Besides, due to the small number of included studies, there was a high heterogeneity, so further investigation is needed. (b) Network meta-analysis showed that there was no difference in LVEDD among the three pacing modalities, while pairwise meta-analysis showed that LBBP could reduce LVEDD compared with RVP. SUCRA ranking results also showed that LBBP was the top one for a smaller LVEDD at follow-up. The possible reasons behind this inconsistency may be bias caused by the small number of included studies and indirect comparisons between HBP and RVP. (c) Only two included studies compared LBBP

versus RVP reported the rates of heart failure hospitalization (HFH). Comparisons of LBBP vs. HBP and HBP vs. RVP were missing, so the risk of HFH remains unknown for these procedures.

Permanent pacemaker implantation is a common approach to the management of bradycardia and conduction system disease. RVP has been the standard therapy with easy implantation and stable long-term pacing parameters. The current 2018 multi-society guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay lists RVP as the only recommended pacing strategy for patients with EF more than 50% (class IIa) (1). The 2021 ESC guideline on cardiac pacing and cardiac resynchronization therapy suggests that HBP may be considered as an alternative to RV pacing in patients with AVB and LVEF > 40%, who are anticipated to have > 20% ventricular pacing (class IIb) (2). Long-term RVP can promote fibrosis and disarrays of endocardial myocytes and myofibrils (18, 19), cause asynchronous ventricular contraction, and negatively affect the hemodynamic status, leading to pacemaker-induced cardiomyopathy (PCM) and a deterioration of heart function (20, 21). PCM is defined as a drop in the left ventricular ejection fraction (LVEF) of more than 10% from baseline after excluding other differential diagnoses (4, 20). It has been reported that the prolongation of paced QRS duration, as a surrogate marker of interventricular desynchrony, has a significant correlation with PCM (22). Our study supported that physiologic pacing, both HBP and LBBP, is associated with a narrower paced QRS duration compared to RVP, which may confer a lower risk of developing pacing-induced cardiomyopathy. Additional studies are required to determine whether LBBP or HBP could be the first-line approach for pacing.

For paced QRS duration and LVEF at follow-up, there was no significant difference between LBBP and HBP in the meta-analysis. Theoretically, HBP was more physiologic than LBBP, which may lead to a shorter paced QRS duration in the HBP group. However, SUCRA ranking results showed that LBBP was the top one for a shorter paced QRS duration. First, the non-selective HBP produces a longer paced QRS duration compared with selective HBP, which may affect the overall paced QRS duration in the HBP arm. Second, the rapid conduction velocity in the Purkinje fibers may result in fast retrograde activation of the right bundle, leading to a short paced QRS duration in LBBP. In our analysis, although LBBP (SUCRA 91.9%) is slightly more advantageous than HBP (SUCRA 58.1%) in a shorter paced QRS duration, SUCRA ranking results showed that HBP was ranked the top one for a more preserved LVEF at follow-up. There may be several possible reasons. While it has been shown that a narrower QRS in biventricular stimulation implies better clinical results, it has not been confirmed that this is also true regarding the conduction system pacing. Ultra-high-frequency electrocardiography (UHF-ECG) is another tool for ventricular dyssynchrony assessment. Studies by Curila et al. showed that there was no difference in the electrical ventricular synchrony measured by UHF-ECG between selective and non-selective HBP, although the paced QRS durations differ (23). In another study, Curila et al. reported that LBBP caused less physiological ventricular depolarization compared to HBP using UHF-ECG (24), which may affect further left ventricular function. Besides, there may be other factors related to left ventricular function. The paced QRS axis, which may be a predictor of pacing-induced left ventricular dysfunction (25), remained identical to the intrinsic one no matter in the selective or the non-selective HBP (26). However, Hu et al. (10) observed a 40.9% (9 in 22) left axis deviation of paced QRS in the LBBP group, higher than those in HBP. Moreover, HBP can also reduce T peak to T end (Tp-Te) duration, which is associated with arrhythmia and mortality (27). Whether LBBP may change the Tp-Te duration or not is unknown. We need more trials to evaluate the difference in these metrics between LBBP and HBP, and whether these will affect left ventricular function. A network meta-analysis in patients requiring cardiac resynchronization therapy (CRT) (28) reported that LBBP (SUCRA 97.2%) was the best treatment for improvements of LVEF, followed by HBP (SUCRA 52.5%). This may be explained by the difference in the pacing indications and baseline LVEF. Most of the CRT patients in the meta-analysis conducted by Juan Hua et al. (28) had a baseline LVEF < 35%, while in our meta-analysis, 68.8% of patients had a preserved LVEF > 40%. Thus, HBP may be advantageous over LBBP for AVB patients with preserved left ventricular function. However, due to the small number of included studies, further long-term, randomized trials are needed to explore the performance of HBP and LBBP in different pacing indications.

Compared with traditional leads with retractable screws, improvements in lead designs and delivery sheaths can increase the success rate. Barba-Pichardo et al. reported an HBP success rate of 35.4% using traditional leads (Tendril SDX electrodes, St Jude, MN, USA) in AVB patients in 2008 (29). The HBP success rate in AVB patients increased to 84% by using new tools (Select Secure, Model number 3830, Medtronic Inc., Minneapolis, MN, USA) as reported by Vijayaraman et al. (30). Moreover, with the same leads but increased experience, the success rate of HPCSP in the same center increased from 84% in 2015 (30) to 97% in 2020 (15). In our meta-analysis, six included studies used 3830 leads, and the success rate increased over time as shown in **Supplementary Table 6**. Due to the widespread network of left bundle branch Purkinje fibers, the capture of the left conduction system could be easily achieved and remained stable. Theoretically, LBBP may be superior to HBP in terms of a shorter procedure time and more stable pacing output (31). However, there was no difference in the procedure duration or success rate between HBP and LBBP in our study. The SUCRA results showed that HBP was similar to LBBP in procedure time (28.8% vs. 29.9%). This may be related to the learning curve of LBBP. In the future, designs of new tools and accumulating experience may increase the success rate and

shorten the procedure time. Regarding the chronic evolution of the pacing output at follow-up, our analysis showed that the pacing threshold of the three pacing strategies remained stable during follow-up. The pacing impedance was significantly reduced in HBP, and a numerical pacing impedance decrease was observed in both LBBP and RVP. In the LBBP group, the R-wave amplitude increased during follow-up, whether oversensing in the long-term would occur or not remains unknown. Overall, the long-term stability of the pacing output of LBBP needs further investigation.

The risk of complications did not differ for the three pacing modalities in the meta-analysis, while SUCRA results showed that complications were least likely to occur in HBP. **Supplementary Table 1** shows that for HBP, lead revision due to a progressive increase in the capture threshold accounted for 2.2% of cases (5 in 228). Other than lead revision, higher pacing thresholds with HBP may cause increased battery drainage (32), leading to a potential increase in healthcare costs, so cost-effectiveness may be another concern for HBP. New devices with longer battery life are necessary. **Supplementary Table 1** shows that lead dislocation was the most common complication of LBBP (10 in 427, 2.3%), followed by septal perforation (8 in 427, 1.9%). Monitoring pacing parameters closely and assessing ventricular septal thickness by echocardiography before implantation is very important (31). With the development of new tools for precise localization and lead fixation, the risks of lead complications are expected to decline. However, further investigation of the safety of LBBP is still needed. Moreover, the mortality rate and heart failure hospitalization rate remain unknown for both procedures. Hence, large, long-term randomized controlled trials are needed to verify the efficacy, safety, and outcome of LBBP in comparison to other pacing methods.

Study limitations

First, the sample size of the included studies was limited, which may lead to an underestimation of the actual effects, and most of the studies were observational studies, which reduced their validity compared with randomized controlled trials. Second, the difference in study design, pacing indication, follow-up time, and publication bias could cause intrinsic bias. Third, only one included study compared HBP vs. RVP, and some outcomes were indirect comparisons between HBP and RVP, leading to imbalanced network comparisons. In addition, the data from crossover design trials may influence the results. Fourth, we only included studies with AVB participants. Studies with non-selected populations or other bradycardia indications, such as sinus node disease and AV node ablation, were excluded. We also excluded the studies without the outcomes we need (33), which may cause bias. Moreover, most of the studies of physiologic pacing were performed in experienced centers, so the success rates and clinical outcomes might not apply to all clinical settings. Further multi-institutional data are needed.

Conclusion

Our results demonstrated that HBP and LBBP were superior to RVP in paced QRS duration and preservation of LVEF for patients with atrioventricular block. LBBP was associated with a lower pacing threshold and greater R-wave amplitude than HBP. However, the stability of the pacing output of LBBP may be a concern. Further investigation of the long-term efficacy in left ventricular function and the risk of heart failure hospitalization is needed.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

YZ and RD conceptualized and designed the research. YZ, YJ, and JL were responsible for the acquisition, analysis, and interpretation of data. YZ drafted the manuscript. YJ, JL, and RD critically revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.939850/full#supplementary-material

References

1. Kusumoto FM, Schoenfeld MH, Barrett C, Edgerton JR, Ellenbogen KA, Gold MR, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: executive summary: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol.* (2019) 74:932–87. doi: 10.1016/j.jacc.2018.10.043

2. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, et al. 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J.* (2021) 42:3427–520. doi: 10.1093/eurheartj/ehab364

3. Khurshid S, Liang JJ, Owens A, Lin D, Schaller R, Epstein AE, et al. Longer paced QRS duration is associated with increased prevalence of right ventricular pacing-induced cardiomyopathy. *J Cardiovasc Electrophysiol.* (2016) 27:1174–9. doi: 10.1111/jce.13045

4. Kiehl EL, Makki T, Kumar R, Gumber D, Kwon DH, Rickard JW, et al. Incidence and predictors of right ventricular pacing-induced cardiomyopathy in patients with complete atrioventricular block and preserved left ventricular systolic function. *Hear Rhythm.* (2016) 13:2272–8. doi: 10.1016/j.hrthm.2016.09.027

5. Zanon F, Ellenbogen KA, Dandamudi G, Sharma PS, Huang W, Lustgarten DL, et al. Permanent his-bundle pacing: a systematic literature review and meta-analysis. *Europace.* (2018) 20:1819–26. doi: 10.1093/europace/euy058

6. Mills EJ, Thorlund K, Ioannidis JPA. Demystifying trial networks and network meta-analysis. *BMJ.* (2013) 346:f2914. doi: 10.1136/bmj.f2914

7. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* (2009) 6:e1000097. doi: 10.1371/journal.pmed.1000097

8. Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol.* (2002) 31:140–9. doi: 10.1093/ije/31.1.140

9. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol Methods.* (2006) 11:193–206. doi: 10.1037/1082-989X.11.2.193

10. Hu Y, Li H, Gu M, Hua W, Niu H, Zhang N, et al. Comparison between his-bundle pacing and left bundle branch pacing in patients with atrioventricular block. *J Interv Card Electrophysiol.* (2021) 62:63–73. doi: 10.1007/s10840-020-00869-w

11. Li X, Zhang J, Qiu C, Wang Z, Li H, Pang K, et al. Clinical outcomes in patients with left bundle branch area pacing vs. right ventricular pacing for atrioventricular block. *Front Cardiovasc Med.* (2021) 8:685253. doi: 10.3389/fcvm.2021.685253

12. Riano Ondiviela A, Cabrera Ramos M, Ruiz Arroyo J, Ramos Maqueda J. Left bundle branch pacing: efficacy and safety compared to right ventricular outflow tract pacing. *EP Eur.* (2021) 23:388. doi: 10.1093/europace/euab116.388

13. Hasumi E, Fujiu K, Nakanishi K, Komuro I. Impacts of left bundle/peri-left bundle pacing on left ventricular contraction. *Circ J.* (2019) 83:1965–7. doi: 10.1253/circj.CJ-19-0399

14. Zhang S, Guo J, Tao A, Zhang B, Bao Z, Zhang G. Clinical outcomes of left bundle branch pacing compared to right ventricular apical pacing in patients with atrioventricular block. *Clin Cardiol.* (2021) 44:481–7. doi: 10.1002/clc.23513

15. Vijayaraman P, Patel N, Colburn S, Beer D, Naperkowski A, Subzposh FA. His-purkinje conduction system pacing in atrioventricular block: new insights into site of conduction block. *JACC Clin Electrophysiol.* (2022) 8:73–85. doi: 10.1016/j.jacep.2021.07.007

16. Kronborg MB, Mortensen PT, Poulsen SH, Gerdes JC, Jensen HK, Nielsen JC. His or para-his pacing preserves left ventricular function in atrioventricular block: a double-blind, randomized, crossover study. *Europace.* (2014) 16:1189–96. doi: 10.1093/europace/euu011

17. Swerdlow CD, Koneru JN, Gunderson B, Kroll MW, Ploux S, Ellenbogen KA. Impedance in the diagnosis of lead malfunction. *Circ Arrhythmia Electrophysiol.* (2020) 13:172–86. doi: 10.1161/CIRCEP.119.008092

18. Tse H-F, Lau C-P. Selection of permanent ventricular pacing site: how far should we go? *J Am Coll Cardiol.* (2006) 48:1649–51. doi: 10.1016/j.jacc.2006.07.027

19. Manolis AS. The deleterious consequences of right ventricular apical pacing: time to seek alternate site pacing. *Pacing Clin Electrophysiol.* (2006) 29:298–315. doi: 10.1111/j.1540-8159.2006.00338.x

20. Abdin A, Yalin K, Zink MD, Napp A, Gramlich M, Marx N, et al. Incidence and predictors of pacemaker induced cardiomyopathy: a single-center experience. *J Electrocardiol.* (2019) 57:31–4. doi: 10.1016/j.jelectrocard.2019.08.016

21. Dreger H, Maethner K, Bondke H, Baumann G, Melzer C. Pacing-induced cardiomyopathy in patients with right ventricular stimulation for >15 years. *Europace.* (2012) 14:238–42. doi: 10.1093/europace/eur258

22. Kim JH, Kang K-W, Chin JY, Kim T-S, Park J-H, Choi YJ. Major determinant of the occurrence of pacing-induced cardiomyopathy in complete atrioventricular block: a multicentre, retrospective analysis over a 15-year period in South Korea. *BMJ Open.* (2018) 8:e019048. doi: 10.1136/bmjopen-2017-019048

23. Curila K, Prochazkova R, Jurak P, Jastrzebski M, Halamek J, Moskal P, et al. Both selective and nonselective his bundle, but not myocardial, pacing preserve ventricular electrical synchrony assessed by ultra-high-frequency ECG. *Hear Rhythm.* (2020) 17:607–14. doi: 10.1016/j.hrthm.2019.11.016

24. Curila K, Jurak P, Jastrzebski M, Prinzen F, Waldauf P, Halamek J, et al. Left bundle branch pacing compared to left ventricular septal myocardial pacing increases interventricular dyssynchrony but accelerates left ventricular lateral wall depolarization. *Hear Rhythm.* (2021) 18:1281–9. doi: 10.1016/j.hrthm.2021.04.025

25. Kim S-H, Oh Y-S, Nam G-B, Choi K-J, Park JS, Park SW, et al. Paced QRS axis as a predictor of pacing-induced left ventricular dysfunction. *J Interv Card Electrophysiol.* (2014) 41:223–9. doi: 10.1007/s10840-014-9950-7

26. Archontakis S, Sideris K, Laina A, Arsenos P, Paraskevopoulou D, Tyrovola D, et al. His bundle pacing: a promising alternative strategy for anti-bradycardic pacing – report of a single-center experience. *Hell J Cardiol.* (2022) 64:77–86. doi: 10.1016/j.hjc.2021.10.005

27. Tse G, Gong M, Wong WT, Georgopoulos S, Letsas KP, Vassiliou VS, et al. The T peak - T end interval as an electrocardiographic risk marker of arrhythmic and mortality outcomes: a systematic review and meta-analysis. *Hear Rhythm.* (2017) 14:1131–7. doi: 10.1016/j.hrthm.2017.05.031

28. Hua J, Wang C, Kong Q, Zhang Y, Wang Q, Xiong Z, et al. Comparative effects of left bundle branch area pacing, his bundle pacing, biventricular pacing in patients requiring cardiac resynchronization therapy: a network meta-analysis. *Clin Cardiol.* (2022) 45:214–23. doi: 10.1002/clc.23784

29. Barba-Pichardo R, Moriña-Vázquez P, Venegas-Gamero J, Frutos-López M, Moreno-Lozano V, Herrera-Carranza M. The potential and reality of permanent his bundle pacing. *Rev Española Cardiol.* (2008) 61:1096–9. doi: 10.1016/S1885-5857(09)60014-1

30. Vijayaraman P, Naperkowski A, Ellenbogen KA, Dandamudi G. Electrophysiologic insights into site of atrioventricular block. *JACC Clin Electrophysiol.* (2015) 1:571–81. doi: 10.1016/j.jacep.2015.09.012

31. Huang W, Chen X, Su L, Wu S, Xia X, Vijayaraman P. A beginner's guide to permanent left bundle branch pacing. *Hear Rhythm.* (2019) 16:1791–6. doi: 10.1016/j.hrthm.2019.06.016

32. Sharma PS, Dandamudi G, Herweg B, Wilson D, Singh R, Naperkowski A, et al. Permanent his-bundle pacing as an alternative to biventricular pacing for cardiac resynchronization therapy: a multicenter experience. *Hear Rhythm.* (2018) 15:413–20. doi: 10.1016/j.hrthm.2017.10.014

33. Pastore G, Zanon F, Baracca E, Aggio S, Corbucci G, Boaretto G, et al. The risk of atrial fibrillation during right ventricular pacing. *Europace.* (2016) 18:353–8. doi: 10.1093/europace/euv268

frontiers | Frontiers in Cardiovascular Medicine

TYPE Review
PUBLISHED 18 November 2022
DOI 10.3389/fcvm.2022.901046

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Cardiac Rhythmology, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 21 March 2022
ACCEPTED 31 October 2022
PUBLISHED 18 November 2022

CITATION
Fu Y, Liu P, Jin L, Li Y, Zhang Y, Qin X and Zheng Q (2022) Left bundle branch area pacing: A promising modality for cardiac resynchronization therapy. *Front. Cardiovasc. Med.* 9:901046. doi: 10.3389/fcvm.2022.901046

Left bundle branch area pacing: A promising modality for cardiac resynchronization therapy

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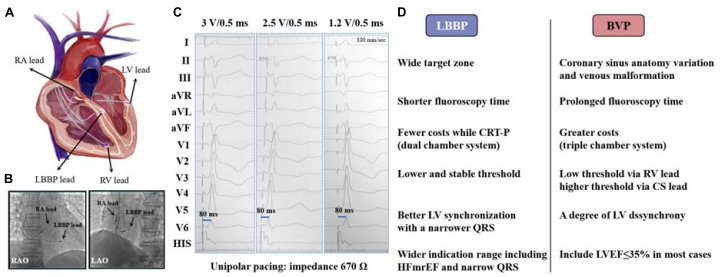
Cardiac resynchronization therapy (CRT) is recognized as the first-line management for patients with heart failure (HF) and conduction disorders. As a conventional mode for delivering CRT, biventricular pacing (BVP) improves cardiac function and reduces HF hospitalizations and mortality, but there are still limitations given the high incidence of a lack of response rates. Alternative pacing methods are needed either for primary or rescue therapy. In recent years, conduction system pacing (CSP) has emerged as a more physiological pacing modality for simultaneous stimulation of the ventricles, including His bundle pacing (HBP) and left bundle branch pacing (LBBP). CSP activates the His-Purkinje system, allowing normal ventricular stimulation. However, HBP is technically challenging with a relatively low success rate, high pacing threshold, and failure to correct distal conduction abnormalities. Therefore, LBBP stands out as a novel ideal physiological pacing modality for CRT. Several non-randomized studies compared the feasibility and safety of LBBP with BVP and concluded that LBBP is superior to BVP for delivering CRT with a narrower QRS and greater improvements in left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) functional class. Concurrently, some studies showed lower and stable pacing thresholds and greater improvement of B-type natriuretic peptide (BNP) levels, as well as better mechanical synchronization and efficiency. LBBP ensures better ventricular electromechanical resynchronization than BVP. In this review, we discuss current knowledge of LBBP, compare LBBP with BVP, and explore the potential of LBBP to serve as an alternative primary therapy to realize cardiac resynchronization.

KEYWORDS

cardiac resynchronization therapy, heart failure, biventricular pacing, conduction system pacing, left bundle branch pacing



GRAPHICAL ABSTRACT

(A) A photographic representation of LBBP and BVP; **(B)** location of LBBP lead in RAO and LAO 30° view; **(C)** paced ECG after LBBP: a paced RBBB QRS morphology (qR in lead V1) is presented, p-LVAT remains constant and short (80 ms) across different outputs (3, 2.5, and 1.2 V) at the impedance of 670 Ω, but retrograde HIS potential is not recorded; **(D)** advantages of LBBP over BVP. LBBP, left bundle branch pacing; BVP, biventricular pacing; RA, right atrium; LV, left ventricle; RV, right ventricle; CS, coronary sinus; CRT-P, cardiac synchronization therapy-pacemaker; RAO, right anterior oblique; LAO, left anterior oblique; pLVAT, stimulus-to-peak LV activation time; LVEF, left ventricular ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction.

Introduction

Heart failure (HF) is the terminal state of various cardiovascular diseases that are prone to conduction defects (1), especially the left bundle branch block (LBBB). LBBB can result in ventricular dyssynchrony, which subsequently causes left ventricular contraction dysfunction and HF (2). In addition, long-term right ventricular pacing (RVP), which mimics LBBB, can also lead to pacing-related cardiomyopathy and subsequent HF. According to epidemiological data, approximately one-third of HF patients have a QRS longer than 120 ms, among which 25% have LBBB (3). Therefore, it is of great importance to correct electrical disturbance and ventricular dyssynchrony, especially that caused by LBBB, in HF patients despite the optimized medication options. Since the early 21st century, cardiac resynchronization therapy (CRT) has been recognized as effective non-pharmacological management for moderate to severe HF. Currently, conventional biventricular pacing (BVP) is the first-line therapy for delivering CRT, which improves cardiac function and exercise tolerance and reduces HF-related symptoms, hospitalizations, and mortality by reversing ventricular remodeling (4, 5). However, BVP activates the ventricles non-physiologically, and up to 30–40% of patients do not respond to this pacing method (6). Alternative pacing methods requiring a more physiological mode are needed either for primary or rescue therapy for CRT.

Conduction system pacing (CSP) has gradually attracted public attention in recent years as it directly activates the His-Purkinje system, providing the maximum physiological stimulation to ensure ventricular synchrony, which includes His bundle pacing (HBP) and left bundle branch pacing (LBBP) (7). In 2000, Deshmukh et al. (8) first applied HBP to HF patients with dilated cardiomyopathy and chronic atrial fibrillation (AF). Since then, growing evidence has confirmed the feasibility and safety of HBP in clinical use. In current guidelines, HBP is recommended as a class IIb pacing indication for patients with a mildly reduced left ventricular ejection fraction (LVEF: 36–50%) who need >40% ventricular pacing (9). His capture distal to the intra-Hisian delay site can recruit fibers predestined to be the bundle branches, thereby correcting LBBB and improving HF; this process is also called the "longitudinal dissociation" phenomenon (10). However, the anatomic His bundle area is small and variable and is enfolded by a dense layer of fibrous tissue, making HBP technically challenging with high pacing thresholds and low R wave sensing, as well as disabilities, to correct distal conduction system diseases (11). Moreover, His bundle anatomy increases lead dislocation rates of HBP, and elevated thresholds consequently lead to short battery life, limiting its long-term use (12). In this regard, another novel form of CSP, namely, LBBP stands out. LBBP was initially reported by Huang et al. (13) in 2017 as a rescue pacing therapy for an HF patient with LBBB who failed to achieve both BVP and HBP. Subsequently, LBBP has been expanded

Abbreviations: AF, atrial fibrillation; ANS, anodal stimulation; BNP, B-type natriuretic peptide; BVP, biventricular pacing; COI, current of injury; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; CSP, conduction system pacing; ECGs, electrocardiograms; EGMs, electrograms; GCW, global constructive work; GWE, global work efficiency; GWI, global work index; HBP, His bundle pacing; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; IVCDs, intraventricular conduction defects; IVMD, interventricular mechanical delay; IVS, interventricular septum; LAO, left anterior oblique; LBB, left bundle branch; LBBAP, left bundle branch area pacing; LBBB, left bundle branch block; LBBP, left bundle branch pacing; LLL, lumen-less pacing lead; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; LVSP, left ventricular septal pacing; MRI, magnetic resonance imaging; NS-LBBP, non-selective left bundle branch pacing; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; pLVAT, stimulus-to-peak left ventricular activation time; PSD, peak strain dispersion; QRSd, QRS duration; RAO, right anterior oblique; RBB, right bundle branch; RBBB, right bundle branch block; RVP, right ventricular pacing; SDL, stylet-driven pacing lead; S-LBBP, selective left bundle branch pacing.

and used as a rescue and even a primary strategy for ventricular synchronization in selected patients, including HF patients. Observational studies have shown excellent pacing parameters, narrow QRS duration (QRSd), and improvements in cardiac function by LBBP. However, whether LBBP is superior to BVP for delivering CRT in HF patients remains uncertain. In this review, we will summarize the current knowledge of LBBP, compare it with BVP, and explore the possibility of LBBP as a promising alternative therapy to achieve cardiac resynchronization.

Novel left bundle branch pacing strategy for cardiac pacing

As more physiological cardiac pacing modalities are in great need to realize cardiac resynchronization, pacing directly through the conduction system has become the focus of attention, especially the novel LBBP with excellent pacing parameters and clinical benefits, which had been gradually put into use in the past 5 years.

Procedure description

The left bundle branch (LBB) is located underneath the endocardium of the left interventricular septum (IVS) with two main branches, the anterior and the posterior branches, presenting a fan-shaped distribution (14). LBBP is defined as pacing the left bundle trunk or the proximal sites of its branches at the low output (<1.0 V/0.4 ms). Huang et al. (13, 15) first introduced the primary implant technique using Medtronic 3,830 lead [a lumen-less pacing lead (LLL)] and the C315 or C304-His sheath *via* the transseptal way. Routine echocardiography should be performed before implantation to evaluate the thickness of the base IVS as well as the degree of septal scar and fibrosis. in addition, cardiac magnetic resonance imaging (MRI) also presents an available option (16). Twelve-lead surface electrocardiograms (ECGs) and intracardiac electrograms (EGMs) were continuously recorded during the operation. Key steps are described and summarized below.

Determining the proper initial site

First of all, the determination of the screwing site on the right side of IVS is a pivotal and initial procedure to endure later success. The 3,830 lead is positioned on the distal His bundle under the right anterior oblique (RAO) view, and the fluoroscopic position is saved as a landmark for identifying the target area unless it is so difficult to locate that the tricuspid annulus is used as a reference. The ideal site to implant LBBP lead is 1.0 to 1.5 cm distal to the saved fluoroscopic lead position, marking the His bundle toward the right ventricular apex on the upper mid-septum under fluoroscopic RAO 30° view (15). Unipolar pacing is performed, and the initial site is identified until a typical "W" pattern with a notch at the nadir of the QRS in lead V1, a positive R waveform in lead II, and an "RS" or "rS" waveform in lead III appear (16). Likewise, discordant aVR/aVL (negative aVR and positive aVL) is used to determine the initial site (17, 18). Recently, another stand stylet-driven pacing lead (SDL) was introduced for LBBP. The process of sheath delivery and lead positioning with SDL is similar to LLL, yet there are still some differences. For example, the lead body of the SDL is wider than that of the LLL due to the presence of an inner lumen, and the SDL is stiffer with the stylet inserted in this lumen (19). Growing evidence supports that LBBP using SDL can achieve a success rate, pacing parameters, and procedural safety comparable to those of LLL (19). However, studies reporting the use of SDL remain limited, and an increasing number of large studies are required to confirm its feasibility. Delivery tools and pacing leads specifically designed for LBBP require further exploration.

Penetrating the septum and fixing the lead

Once the initial site is identified, the sheath is rotated counterclockwise to guarantee that the lead tip is perpendicular to the right surface of the septum. Then, the lead is advanced gently toward the left side of the septum with repeated rapid rotation for three to five turns in every attempt to screw it into place. The contrast is injected through the sheath to determine the depth of the lead under a left anterior oblique (LAO) 30° fluoroscopic view (15). Unipolar cathode pacing is intermittently applied during the lead advancement with R wave amplitude, pacing impedance, and paced QRS morphology monitored. Progressive lead advancement results in gradually increasing pacing impedance and an ascending of the notch at the nadir of QRS to form a terminal R wave in lead V1, ultimately presenting a right bundle branch block (RBBB) morphology (a "M" pattern or qR/rsR′) when LBBP is achieved. Unipolar anode pacing was performed to confirm the ring electrode position in the right ventricular septum and estimate the lead depth (18). Septal perforation is one of the most remarkable complications in this process, requiring lead repositioning. To avoid this complication, it is necessary in performing sheath angiography, monitoring QRS morphology, and pacing impedance or monitoring current of injury (COI) during lead advancement (5). A sudden decrease in impedance or sudden disappearance of COI may indicate IVS perforation. Recently, several researchers proposed a fixation beat-guided lead deployment technique, which is defined as premature ventricular contractions (PVCs) with narrow QRS complexes of qR/rsR′ morphology in lead V1. A fixation beat appears when the lead reaches the LBB area and may represent a promising marker for final lead positioning and LBB capture, thus better avoiding septal perforation (20).

Confirming the achievement of left bundle branch pacing and sheath removal

To confirm LBB capture, low and high output pacing is performed. Electrical criteria for LBBP are as follows: (1) narrowing of QRS complex (typically ≤130 ms) and a paced RBBB QRS morphology (qR or rSR′ in lead V1); (2) the stimulus-to-peak LV activation time (pLVAT, defined as the interval between pacing stimulus and the peak of R wave in lead V5, V6) remains short (typically <80 ms) and constant regardless of high (5 V) or low (1 V) pacing output; (3) recording LBB potential in patients without LBBB (of note, LBB potential can be recorded only after LBB conduction correction in patients with LBBB); (4) selective (S) or non-selective (NS) LBBP (S-LBBP captures only the LBB with latency from stimulus to QRS and an isoelectric interval, whereas NS-LBBP captures LBB and the adjacent myocardium with no stimulus-QRS latency and isoelectric interval); and (5) recording retrograde His potential or anterograde distal LBB potential (not necessary) (15). Generally, once criterion (1) and at least one of criteria (2) to (5) are achieved, LBB capture is thought to be confirmed, although there is still no consensus. After confirming the LBB capture, further lead advancement is stopped, and the sheath is removed to allow lead slack. Unipolar and bipolar pacing is performed to test the electrical parameters, such as pacing threshold, sensing, and impedance. Resolution of RBBB QRS morphology is seen during unipolar cathode pacing because of retrograde right bundle branch (RBB) activation in some patients. However, in other patients who do not have retrograde RBB stimulation, anodal stimulation (ANS) during bipolar pacing can partially compensate for RBB conduction delay *via* a fusion of LBBP and right ventricular septal capture (21).

Benefits of left bundle branch pacing in heart failure patients requiring cardiac resynchronization therapy

Heart failure is always accompanied by conduction abnormalities, especially LBBB (3). According to epidemiological data, approximately one-third of HF patients have a QRS longer than 120 ms, among which 25% have LBBB (3). Thus, heart failure with reduced ejection fraction (HFrEF) and LBBB account for the majority of patients requiring CRT (22). Since Huang et al. (13) first applied LBBP in an HF patient with dilated cardiomyopathy and LBBB who failed to achieve both BVP and HBP in 2017, an increasing number of subsequent observational studies have been conducted to explore the feasibility and safety of LBBP in selected patients in need of ventricular pacing. In a prospective study to evaluate the feasibility of permanent LBBP, Li et al. (23) achieved 68.7% (11/16) success in correcting LBBB or RBBB with the paced QRSd narrowed compared with baseline (122.2 ± 9.9 vs. 153.3 ± 27.8 ms). Vijayaraman et al. (24) also found a significantly narrower QRSd from 162 ± 21 to 137 ± 19 ms ($P < 0.001$) after LBBP in HF patients with LBBB who were indicated for CRT [success rate: 88% (21/24)] in their study, whereas QRSd widened from 97 ± 12 to 131 ± 15 ms ($P < 0.001$) in baseline narrow QRS patients, providing a clue for LBBP to realize ventricular electrical resynchronization only if the ventricles were originally asynchronous. Later, increasing evidence merged to support that LBBP benefits ventricular conduction abnormalities. Padala et al. (25) demonstrated narrower paced QRSd compared with baseline (115 ± 12 vs. 144.5 ± 19 ms, $P < 0.001$) by LBBP in patients with the infra-Hisian disease. Similarly, Ravi et al. (26) reported a significantly reduced QRSd *via* LBBP in patients with LBBB (ΔQRSd: 47 ms, $P < 0.001$), RBBB (ΔQRSd: 46 ms, $P < 0.001$), and intraventricular conduction defect (IVCD) (ΔQRSd: 18 ms, $P = 0.006$). Recently, Su et al. (27) conducted a large single-center study with long-term follow-up to evaluate the feasibility of LBBP. Their results similarly revealed a remarkable decrease in paced QRSd in baseline LBBB patients (124.02 ± 24.15 vs. 167.22 ± 18.99 ms, $P < 0.001$) and improvement in LVEF from 48.82 ± 17.78 to 58.12 ± 13.04% ($P < 0.001$) in patients with QRS ≥120 ms. However, most of these studies applying LBBP in bradyarrhythmia indications revealed preserved LVEF or NYHA class but not a significant improvement, which is in contrast with that noted for CRT-indicated patients described in the following part. These studies provide preliminary evidence that LBBP can correct conduction disorders and normalize ventricular electrical synchrony, making it possible to apply LBBP in HF patients requiring CRT.

Several studies were specifically conducted for CRT in HF patients *via* LBBP. Zhang et al. (28) enrolled 11 patients with reduced LVEF and LBBB. They revealed both electrical resynchronization and mechanical resynchronization by LBBP as evidenced by narrowed QRSd (129.09 ± 15.94 vs. 180.00 ± 15.86 ms, $P < 0.01$) and shortened interventricular mechanical delay (IVMD) (14.45 ± 6.38 vs. 61.18 ± 19.46 ms, $P < 0.0001$), respectively. In addition, they observed significant improvement in echocardiographic parameters [LVEF, left ventricular end-systolic diameter (LVESD), $P < 0.05$] and clinical New York Heart Association (NYHA) functional class ($P < 0.05$). Plasma B-type natriuretic peptide (BNP) levels were similarly reduced from 876.00 ± 792.62 to 242.18 ± 267.37 pg/ml ($P = 0.0067$). Huang et al. (29) demonstrated a 97% (61/63) success rate of performing LBBP in HF patients with non-ischemic cardiomyopathy and LBBB. Comparing electrical parameters, LBBP resulted in a pronounced decrease in QRSd (118 ± 12 vs. 169 ± 16 ms, $P < 0.001$) to provide maximum electrical synchrony. At the 1-year follow-up, a significant increase in LVEF (55 ± 10 vs. 33 ± 8%, $P < 0.001$) and a reduction in left ventricular end-systolic volume (LVESV) (67 ± 39 vs. 123 ± 61 ml, $P < 0.001$) were observed. In parallel, LBBP remarkably improved the NYHA class (1.4 ± 0.6 vs. 2.8 ± 0.6, $P < 0.001$) at 1 year. This multicenter study revealed both electric resynchronization and clinical benefits of LBBP for CRT. Similar benefits were

demonstrated in the study conducted by Li et al. (30). LBBP shortened QRSd (123.0 ± 10.8 vs. 163.6 ± 29.4 ms, $P < 0.001$), increased LVEF (46.9 ± 10.2 vs. 35.2 ± 7.0%, $P < 0.001$), decreased LV end-diastolic diameter (LVEDD) (56.8 ± 9.7 vs. 64.1 ± 9.9 mm, $P < 0.001$), and improved NYHA class (1.4 ± 0.6 vs. 2.6 ± 0.6, $P < 0.001$) in CRT-indicated patients at a mean follow-up of 9.1 months. In another international, multicenter, collaborative study performed by Vijayaraman et al. (31), LBBP was applied for delivering CRT with an 85% success rate. Notably, a significant QRS narrowing (137 ± 22 vs. 152 ± 32 ms, $P < 0.01$), obvious improvement of LVEF (44 ± 11 vs. 33 ± 10%, $P < 0.01$), and high clinical (72%) and echocardiographic (73%) responses were observed after LBBP. In addition, LBBP showed low and stable pacing thresholds and high R-wave sensing, providing a promising alternative option for delivering CRT in HF patients. Data from Qian et al. (32) evaluating the effects of LBBP in HF caused by chronic RVP also supported these findings. They revealed that LBBP was effective in improving pacing-induced HF by improving cardiac function (LVEF increasing: 48.1 ± 9.5 vs. 40.3 ± 5.2%, $P = 0.002$), improving NYHA class (1.7 ± 0.8 vs. 2.5 ± 0.5, $P < 0.0001$), decreasing N-terminal pro-brain natriuretic peptide (NT-proBNP) levels (1,840 ± 2,261 vs. 3,178 ± 2,974 pg/ml, $P = 0.005$), and normalizing electrical synchrony (QRSd narrowing: 116.6 ± 11.7 vs. 174.1 ± 15.8 ms, $P < 0.0001$). No lead-related complications occurred in this study. In elderly patients who are typically precluded from BVP due to their frailty, LBBP seems to be a better option with a lower risk of CRT complications. Grieco et al. evaluated the feasibility and safety of LBBP-CRT in elderly patients. The study compared electrical parameters, echocardiographic parameters, lead parameters, and complications, revealing that LBBP achieved comparable efficacy between elderly patients and younger patients with narrow QRS, satisfactory pacing threshold, impedance and sensing, low rates of complication, and improved LVEF (33). In summary, LBBP is a promising option for delivering CRT in HF patients, providing excellent ventricular resynchronization, improved cardiac function, and great clinical benefits with a high success rate, low and stable pacing thresholds, and fewer complications.

Comparison of left bundle branch pacing with biventricular pacing as a treatment for heart failure

Current studies comparing left bundle branch pacing with biventricular pacing

Biventricular pacing has long been a standard method for delivering CRT in symptomatic HF patients for approximately 20 years, yet LBBP has recently emerged as a promising alternative modality. Several non-randomized observational studies have shown the advantages of LBBP over conventional BVP by comparing electrical parameters, echocardiographic parameters, and clinical outcomes. These results are summarized in **Table 1**. Li et al. (34) prospectively compared the efficacy of LBBP and BVP in HF patients during a 6-month follow-up period. The results showed that LBBP required less X-ray exposure time (16.9 ± 6.4 vs. 39.6 ± 9.2 min, $P < 0.001$) than BVP at the implant, indicating better safety for the operator and patients. Their results also revealed a much more significant decrease in paced QRSd (58.0 vs. 12.5 ms, $P < 0.001$) in the LBBP group than in the BVP group, as well as enhanced LVEF improvement (15.6 vs. 7.0%, $P < 0.001$) during the 6-month follow-up. Another non-randomized study performed by Wu et al. (35) recruited CRT-indicated patients for BVP, HBP, or LBBP. In this study, BVP or HBP was applied as the primary therapy, whereas LBBP was used as rescue therapy for HBP-failed patients. The paced QRSd was significantly decreased both in the LBBP group (ΔQRSd = 56 ms, $P < 0.001$) and the BVP group (ΔQRSd = 26 ms, $P < 0.001$). A comparison of LBBP with BVP was not shown, although there was a trend toward a greater reduction in QRSd in the LBBP group. Echocardiographic benefits were greater in the LBBP group than in the BVP group, as evidenced by greater LVEF improvement (ΔLVEF) in the LBBP group than in the BVP group (24.0 ± 10.9 vs. 16.7 ± 14.6%, $P = 0.015$) and a considerably improved echocardiographic response in the LBBP group than in the BVP group (ΔLVEF ≥10%, 93.3 vs. 61.2%, $P = 0.004$; ΔLVEF ≥15%, 76.7 vs. 53.1%, $P = 0.036$; final LVEF ≥50%, 70.0 vs. 44.9, $P = 0.030$) at the 1-year follow-up. LBBP also resulted in greater improvement in NYHA class ($P = 0.002$) and a trend toward greater improvement in BNP levels ($P = 0.099$) compared with the BVP group, indicating a better clinical response. Supportively, the BVP group exhibited a higher adverse event rate. Specifically, three patients experienced HF hospitalization and two patients were transferred to HBP. In contrast, none of these events occurred in the LBBP group. Similarly, Wang et al. (36) compared the efficacy of LBBP with BVP in HF patients with complete LBBB. LBBP shortened QRSd much more than BVP (60.80 ± 20.09 vs. 33.00 ± 21.48 ms, $P = 0.0009$). The echo-LVEF exhibited better improvements in the LBBP group than in the BVP group, although the difference was not statistically significant ($P = 0.11$). Changes in clinical NYHA class were significant, and more patients were classified as NYHA I/II in the LBBP group than in the BVP group (median 1.5 vs. 2.0, $P = 0.029$) at the 6-month follow-up. Consistently, Guo et al. (37) demonstrated a greater QRSd reduction (56.0 ± 14.7 vs. 32.3 ± 14.6 ms, $P < 0.0001$) in the LBBP group than in the BVP group, whereas no significant difference was observed in echocardiographic parameters or clinical NYHA class change (although there was a trend toward better improvement *via*

LBBP), which may be due to a relatively small sample size. Advantages in LBBP were noted compared with BVP with lower and stable pacing thresholds (0.48 ± 0.22 V at 0.4 ms vs. 1.12 ± 0.46 V at 0.4 ms, $P < 0.0001$). Recently, Zu et al. (38) evaluated and compared the feasibility of LBBP with BVP for delivering CRT. Shorter operation time (90.08 ± 33.40 vs. 158.05 ± 19.05 min, $P < 0.01$) and X-ray exposure time (20.46 ± 7.36 vs. 43.53 ± 10.36 min, $P < 0.01$) were achieved in the LBBP group. Better electrical resynchronization was observed in the LBBP group as evidenced by greater QRS shortening (50.30 ± 23.79 vs. 33.15 ± 20.22 ms, $P = 0.036$) compared with the BVP group. At the 12-month follow-up, LVEF improved more in the LBBP group compared with the BVP group (48.92 ± 8.06 vs. 42.53 ± 4.89%, $P < 0.05$). The increased safety and feasibility of LBBP compared with BVP were further confirmed in a multicenter study conducted by Chen et al. (39) in HF patients with LBBB. Their results showed a high success rate in both groups (98.00% in the LBBP group and 91.07% in the BVP group). The LBBP group exhibited a shortened QRSd as compared to the BVP group (102.61 ± 9.66 vs. 126.54 ± 11.67 ms, $P < 0.001$) and better improvement in LVEF both during the 6-month (47.58 ± 12.02 vs. 41.24 ± 10.56%, $P = 0.008$) and 1-year follow-ups (49.10 ± 10.43 vs. 43.62 ± 11.33%, $P = 0.021$). A stable and lower pacing threshold was observed in the LBBP group both at implant ($P < 0.001$) and the 1-year follow-up ($P < 0.001$). Adverse clinical outcomes and complications were comparable in the LBBP and BVP groups. The studies above evaluated left ventricular electrical synchrony; however, mechanical resynchronization of LBBP was less explored and compared. In a multicenter, prospective cohort study, Liu et al. (40) specifically evaluated the mechanical synchrony of LBBP and compared it with that of BVP. HF patients with complete LBBB who underwent LBBP or BVP were enrolled in the study. Compared with BVP, LBBP resulted in better QRS shortening (64.1 ± 18.9 vs. 32.5 ± 22.3 ms, $P < 0.001$). The interventricular and intraventricular mechanical synchronization, reflected by IVMD and peak strain dispersion (PSD), respectively, were better improved in the LBBP group compared with the BVP group (ΔIVMD: 27.4 ± 28.7 vs. 18.6 ± 27.9 ms, $P = 0.013$; ΔPSD: 50.9 ± 56.8 vs. 26.9 ± 63.9 ms, $P = 0.036$). Moreover, global and segmental myocardial work were evaluated in both groups. Global work efficiency (GWE), global work index (GWI), and global constructive work (GCW) were better improved in the LBBP group compared with the BVP group ($P < 0.05$). For each LV segment myocardial work, LBBP showed more improvements in most segments than in the BVP group, especially the lateral ($P = 0.006$) and posterior ($P = 0.068$) segments. Taking all these studies together, we hypothesize better electrical resynchronization, mechanical synchrony, and clinical benefits of LBBP in HF patients requiring CRT than conventional BVP. Furthermore, we searched studies comparing LBBP with BVP in HF patients with AF and narrow QRS in need of atrioventricular node ablation. Ivanovski et al. (41) found shorter-paced QRSd in the LBBP group compared with the BVP group (127.0 ± 13.0 vs. 172.0 ± 13.0 ms, $P < 0.001$), whereas no significant difference in baseline QRSd was noted. Echocardiographic results showed improved LVEF ($P = 0.041$) and decreased indexed LV volumes ($P = 0.004$) in the LBBP group during follow-up, but no significant change was observed in the BVP group ($P = 0.916$ for LVEF; $P = 0.551$ for indexed LV volumes). Regarding clinical outcomes, the follow-up NYHA class did not differ from the baseline NYHA class in the BVP group ($P = 0.096$). However, in the LBBP group, NYHA class was significantly improved at the 6-month follow-up ($P = 0.008$). NT-proBNP levels were reduced at follow-up in the LBBP group ($P = 0.047$) but remained unchanged in the BVP group ($P = 0.331$). Therefore, LBBP is not only beneficial for HF patients requiring CRT with wide QRS but also provides superior electrical, symptomatic, and echocardiographic improvements than BVP in HF patients with AF and narrow QRS who require atrioventricular node ablation. Recently, the first prospective, randomized trial performed by Wang et al. compared LBBP with BVP for CRT (42). Consistent with the observational studies above, LBBP showed higher LVEF improvement than BVP (21.08 ± 1.91 vs. 15.62 ± 1.94%, $P = 0.039$) and a trend toward a greater decrease in LVESV (77.74 ± 7.80 vs. 55.58 ± 8.80 ml) and NT-proBNP (1,768.36 ± 217.91 vs. 1,181.05 ± 216.75 pg/ml). However, there were comparable changes in QRSd, NYHA class, and the 6-min walk distance between the two groups.

Clinical limitations of biventricular pacing for heart failure management

Despite the long history of the use of BVP as a standard CRT modality, some challenges continue to emerge regarding the growing need for a more ideal cardiac pacing strategy. First of all, BVP is a non-physiological pacing mode unable to realize effective ventricular synchronization due to epicardial LV pacing, which forces the ventricle to depolarize from the epicardium to the endocardium, in contrast to the physiologic way and predisposes to torsade de pointes tachycardias (43, 44). In addition, long-term RVP does not meaningfully improve RV systolic function and even worsens RV asynchrony, thus causing RV remodeling and aggravating HF or leading to ventricular arrhythmias, including AF (45). Approximately 30–40% of patients remain non-responsive to BVP due to ischemic heart disease, remarkable left atrial dilation, advanced mitral regurgitation, and NYHA class IV. (46). In addition, coronary sinus anatomy and venous malformation limit the intravenous implantation of epicardial LV leads (47) despite improvements in delivery leads and tools and refinements in implant technique. Transvenous LV lead implantation also

TABLE 1 Studies comparing LBBP with BVP.

References	Design	*N*	Success rate of LBBP	Rescue LBBP (*n*)	Cross-over from CSP to BVP (*n*)	Criteria of inclusion/ exclusion	Patients with AVB	Follow-up (m)	Pacing parameter	Electrical or mechanical changes	Echocardiographic changes	Clinical changes
Li et al. (34)	Prospective, multicenter, observational	27 vs. 54	73.0% (27/37)	9	4	Inclusion: HF symptoms, LVEF ≤35% with LBBB	Not mentioned	6	Threshold: 0.81 vs. 1.22 V Impedance: 644.9 vs. 817.5 Ω	Baseline QRSd: 178.2 ± 18.8 vs. 180.9 ± 29.7 ms Paced QRSd: 121.8 ± 10.8 vs. 158.2 ± 21.5 ms ΔQRSd: 58.0 vs. 12.5 ms Baseline QRS morphology: LBBB	Baseline LVEF: 28.8 ± 4.5 vs. 27.2 ± 4.9% Follow-up LVEF: 44.3 ± 8.7 vs. 35.0 ± 10.5% ΔLVEF: 15.6 vs. 7.0% ΔLVEDD: 8.0 vs. 0.5 mm Echocardiographic response: 88.9 vs. 66.7% Super response: 44.4 vs. 16.7%	Baseline NYHA: 3.1 ± 0.7 vs. 3.0 ± 0.7 Follow-up NYHA: 1.5 ± 0.5 vs. 2.3 ± 0.7 clinical response: 96.3 vs. 75.9%
Wu et al. (35)	Prospective, non-randomized, single-center	32 vs. 54	100% (32/32)	32	15	Inclusion: LVEF ≤40% and typical LBBB	3.1 vs. 3.7%	12	Threshold: 0.49 (LBBP) vs. 0.61 (RV lead)/0.93 V (CS lead) Sensing: 11.2 vs. 14.1 mV	Baseline QRSd: 166.2 ± 16.2 vs. 161.1 ± 18.2 ms Paced QRSd: 110.8 ± 11.1 vs. 135.4 ± 20.2 ms ΔQRSd: 56.0 vs. 26.0 ms Baseline QRS morphology: LBBB	Baseline LVEF: 30.4 ± 7.1 vs. 29.7 ± 5.1% Follow-up LVEF: 54.4 ± 9.8 vs. 46.5 ± 16.9% ΔLVEF: 24.0 vs. 16.7% LVESV: 54.6 vs. 84.8 ml	Baseline NYHA: 2.8 ± 0.5 vs. 2.8 ± 0.6 Follow-up NYHA: 1.3 ± 0.5 vs. 1.9 ± 0.9
Wang et al. (36)	Matched case–control study	10 vs. 30	100% (10/10)	0	0	Inclusion: HF, LBBB with QRSd > 140 ms in men and > 130 ms in women, LVEF ≤35%, and NYHA II to IV	Not mentioned	6	Threshold: 0.54 vs. 1.00 V	Baseline QRSd: 183.60 ± 19.27 vs. 174.60 ± 19.48 ms Paced QRSd: 122.80 ± 17.24 vs. 141.60 ± 15.38 ms ΔQRSd: 60.8 vs. 33.0 ms Baseline QRS morphology: LBBB	Baseline LVEF: 26.80 ± 3.85 vs. 26.38 ± 5.27% Follow-up LVEF: 45.66 ± 9.22 vs. 39.35 ± 12.29% ΔLVEF: 18.86 vs. 12.97% Response rate: 100.00 vs. 63.33%	Baseline NYHA: 2.90 ± 0.74 vs. 3.07 ± 0.74 Follow-up NYHA: 1.50 ± 0.55 vs. 1.97 ± 0.61
Guo et al. (37)	Prospective, observational	21 vs. 21	87.5% (21/24)	0	3	Inclusion: HF, LBBB morphology, with LVEF ≤35%, NYHA II to IV	Not mentioned	6	Threshold: 0.48 (LBBP) vs. 0.57 (RV lead)/1.12 V (CS lead)	Baseline QRSd: 167.7 ± 14.9 vs. 163.6 ± 13.8 ms Paced QRSd: 111.7 ± 12.3 vs. 130.1 ± 14.0 ms ΔQRSd: 56.0 vs. 32.3 ms Baseline QRS morphology: LBBB	Baseline LVEF: 30.0 ± 5.0 vs. 29.8 ± 4.1% Follow-up LVEF: 50.9 ± 10.7 vs. 44.4 ± 13.3% LVEF: 50.9 vs. 44.4% Super response: 80.9 vs. 57.1%	Baseline NYHA: 3.0 ± 0.7 vs. 3.0 ± 0.7 Follow-up NYHA: 1.3 ± 0.9 vs. 1.5 ± 0.7

(Continued)

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TABLE 1 (Continued)

References	Design	*N*	Success rate of LBBP	Rescue LBBP (*n*)	Cross-over from CSP to BVP (*n*)	Criteria of inclusion/ exclusion	Patients with AVB	Follow-up (m)	Pacing parameter	Electrical or mechanical changes	Echocardiographic changes	Clinical changes
Zu et al. (38)	Observational	13 vs. 19	100% (13/13)	3	0	Inclusion: DCM complicated with HF and LBBB, ischemic cardiomyopathy was excluded	30.8 vs. 10.5%	12	Comparison not mentioned	Baseline QRSd: 167.46 ± 28.11 vs. 163.47 ± 21.66 ms Paced QRSd: 117.15 ± 9.91 vs. 130.32 ± 12.41 ms ΔQRSd: 50.30 vs. 33.15 ms Baseline QRS morphology: LBBB	Baseline LVEF: 30.62 ± 6.983 vs. 29.11 ± 4.818% Follow-up LVEF: 48.92 ± 8.06 vs. 42.53 ± 4.89%	Not mentioned
Chen et al. (39)	Prospective, multi-center, observational	49 vs. 51	98.0% (49/50)	5	1	Inclusion: HF, NYHA II–IV, LVEF ≤35%, QRSd >150 ms, typical LBBB Exclusion: PR interval >200 ms, persistent AF and IVCD	Not mentioned	12	Threshold: 0.92 vs. 1.45 V	Baseline QRSd: 180.12 ± 15.79 vs. 175.70 ± 11.29 ms Paced QRSd: 102.61 ± 9.66 vs. 126.54 ± 11.67 ms ΔQRSd: 59.16 vs. 31.00 ms Baseline QRS morphology: LBBB	Baseline LVEF: 29.05 ± 5.09 vs. 28.36 ± 5.30% Follow-up LVEF: 49.10 ± 10.43 vs. 43.62 ± 11.33% ΔLVEF: 20.9 vs. 15.2% LVEDD: 54.50 vs. 60.99 mm LVESD: 41.78 vs. 48.33 mm Super response: 61.22 vs. 39.22%	Baseline NYHA (percentage of III–IV): 91.48 vs. 88.24% Follow-up NYHA (percentage of III–IV): 4.08 vs. 19.61%
Liu et al. (40)	Prospective, multicenter, cohort study	27 vs. 35	79.4% (27/34)	0	7	Inclusion: HF, LVEF ≤35%, LBBB morphology and QRSd ≥130 ms Exclusion: narrow QRS or non-LBBB morphology	Not mentioned	3–6	Not mentioned	Baseline QRSd: 177.1 ± 16.7 vs. 168.8 ± 16.8 ms Paced QRSd: 113.0 ± 18.4 vs. 136.3 ± 20.1 ms ΔQRSd: 64.1 vs. 32.5 ms Baseline QRS morphology: LBBB Better mechanical synchrony reflected by IVMD, PSD, GWE, GWI, GCW, MWE	Baseline LVEF: 29.9 ± 4.8 vs. 29.5 ± 4.9% Follow-up LVEF: 47.1 ± 8.3 vs. 43.1 ± 11.0% ΔLVEF: 17.2 ± 9.3 vs. 13.7 ± 11.5% Echocardiographic response: 88.9 vs. 68.6%	Baseline NYHA: 3.0 ± 0.5 vs. 2.8 ± 0.6 Follow-up NYHA: 1.6 ± 0.6 vs. 2.2 ± 0.8 ΔNYHA: 1.6 ± 0.6 vs. 0.9 ± 0.8

(Continued)

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TABLE 1 (Continued)

References	Design	*N*	Success rate of LBBP	Rescue LBBP (*n*)	Cross-over from CSP to BVP (*n*)	Criteria of inclusion/ exclusion	Patients with AVB	Follow-up (m)	Pacing parameter	Electrical or mechanical changes	Echocardiographic changes	Clinical changes
Ivanovski et al. (41)	Retrospective, single-center, observational	10 vs. 13	100% (10/10)	0	0	Inclusion: severely symptom AF with rapid ventricular rate, tachycardia-induced cardiomyopathy, LVEF <50%, NYHA II–IV, narrow QRSd ≤120 ms	Not mentioned	6	Threshold: 0.80 vs. 1.40 V Impedance: 749.0 vs. 760.0 Ω	Baseline QRSd: 105 ± 15 vs. 98 ± 7 ms Paced QRSd: 127 ± 13 vs. 172 ± 13 ms ΔQRSd: −29.0 vs. −74.0 ms Baseline QRS morphology: LBBB	Baseline LVEF: 28.0 vs. 38.0% Follow-up LVEF: 40.0 vs. 37.0% ΔLVEF: 12.0% vs. −1.0%	Baseline median NYHA: 3.0 vs. 3.0 Follow-up median NYHA: 2.0 vs. 3.0 ΔNT-proBNP: 1,057.0 vs. 52.0 pg/ml
Wang et al. (42)	Prospective, randomized trial	22 vs. 18	91.7% (22/24)	4	2	Inclusion: age 18–80 years, sinus rhythm, complete LBBB meeting Strauss's standard definition (QRSd >140 ms for men or >130 ms for women), LVEF ≤40%, and NYHA class II to IV Exclusion: (1) ischemic cardiomyopathy; (2) non-LBBB QRS morphology including RBBB or IVCD; (3) persistent AF; or (4) pregnancy	Not mentioned	6	Threshold: 0.82 vs. 1.12 V Impedance: 476.0 vs. 592.0 Ω	Baseline QRSd: 174.6 ± 14.3 vs. 174.7 ± 14.1 ms Paced QRSd: 131.5 ± 12.5 vs. 136.6 ± 12.9 ms Baseline QRS morphology: LBBB	Baseline LVEF: 28.3 ± 5.3 vs. 31.1 ± 5.6% Follow-up LVEF: 49.4 ± 13.2 vs. 46.5 ± 9.4% ΔLVEF: 21.08 ± 1.91 vs. 15.62 ± 1.94% Super response: 65.0 vs. 42.1%	Baseline NYHA: 2.40 ± 0.50 vs. 2.45 ± 0.51 ΔNYHA: 1.22 ± 0.11 vs. 1.10 ± 0.11 Δ6-min walk distance: 100.69 ± 14.14 vs. 80.56 ± 15.92 m ΔNT-proBNP: 1,768.36 ± 217.91 vs. 1,181.05 ± 216.75 pg/ml

LBBB, left bundle branch block; LBBP, left bundle branch pacing; BVP, biventricular pacing; CSP, conduction system pacing; AVB, atrioventricular block; IVCD, intraventricular conduction defect; AF, atrial fibrillation; LV, left ventricle; RV, right ventricle; CS, coronary sinus; Δ, change of parameters; QRSd, QRS duration; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; IVMD, interventricular mechanical delay; PSD, peak strain dispersion; GWE, global work efficiency; GWI, global work index; GCW, global constructive work; MWE, myocardial work efficiency; NYHA, New York Heart Association. NT-proBNP, N-terminal pro-brain natriuretic peptide. All the numerical values ahead of "vs." represents the LBBP group while numerical values that comes after "vs." represents the BVP group. The symbol "−" in the "Electrical or mechanical" column represents an increase in QRSd.

10.3389/fcvm.2022.901046

leads to a chronic increase in the capture threshold, a high lead dislocation rate (up to 5–10%) (48), and phrenic nerve stimulation. Furthermore, BVP fails to stimulate myocardial scar or severely diseased myocardium (4). To address some of these issues, several new target approaches, such as multipoint LV pacing and endocardial LV pacing, have been proposed. Multipoint LV pacing is realized by a multipolar (typically quadripolar) LV lead which is positioned from the coronary sinus branch (49). Three ring electrodes are located at 20, 30, and 47 mm from the tip (50) to achieve multi-site pacing, which can better avoid tissue scar, thereby achieving better electrical synchrony than conventional BVP (51). The Multi-Point Pacing Study (52) and the LV Multi-spot Pacing for CRT (iSPOT) study (53) revealed the non-inferiority of multipoint pacing compared with conventional BVP. However, the feasibility of multipoint pacing remains uncertain, and battery longevity is reduced (6, 54). Moreover, still positioning from the coronary sinus branch as BVP (49), multipoint LV pacing is essentially a type of epicardial LV pacing and thus not an ideal physiological pacing modality. Endocardial LV pacing through a transseptal approach delivers a more rapid and physiological stimulation of LV eliminating phrenic nerve stimulation compared with conventional epicardial LV pacing (55), and it has been proven in the ALSYNC (Alternate Site Cardiac Resynchronization) study to be non-inferior and even superior to conventional BVP with improved hemodynamic response and clinical outcomes even noted in conventional BVP non-responders (56). However, the thromboembolic event rate in this study remained high despite the use of anticoagulants (57). Later, leadless LV pacing was developed to address some of the lead-related complications, which are still under research. Using this method, LV pacing is achieved wirelessly by converting acoustic energy to pacing energy with a receiving electrode in the LV wall (58). A meta-analysis conducted recently concluded that leadless LV pacing could serve as a second-line therapy for conventional CRT non-responders (59). In recent years, BVP has been expanded from severe HF (NYHA III/IV) to mild to moderate HF (NYHA I/II), yet HF patients with a narrow QRS (<130 ms) do not respond to it or benefit from it in most cases. BVP is recommended only as a class III, level A indication in the 2021 ESC guidelines (55). Moreover, CRT-indicated patients are typically those with LVEF ≤35%, but rare patients with LVEF >35% [heart failure with mildly reduced ejection fraction (HFmrEF)] are indicated for conventional CRT or benefit from it. In the 2018 ACC/AHA/HRS guidelines, HF patients with mild to moderate reduced LVEF (36–50%) are recommended as a class IIb, and level C CRT indication only if they have LBBB (QRS ≥150 ms) (9). These limitations above restrain the clinical use of BVP for HF or expanded patients.

Potential advantages of left bundle branch pacing over biventricular pacing

Left bundle branch area pacing (LBBAP) may partially solve some of the obstacles mentioned above, including left ventricular septal pacing (LVSP) and LBBP. LVSP is defined by pacing at the left side of the interventricular septum (IVS), which

TABLE 2 Comparison of advantages and disadvantages between LBBP and BVP.

	LBBP	BVP
Anatomy	Wide target zone underneath the endocardium of left side of IVS	Coronary sinus anatomy variation and venous malformation limits LV lead implantation
Safety	Safer for operators and patients with shorter operation and fluoroscopy time	Prolonged operation and X-ray exposure time
Costs	Fewer costs because of a dual chamber system in CRT-P, yet comparable costs with BVP in scenario that needs a CRT-D	Greater costs for a triple chamber system
Technical difficulty	Relatively easier	A little more difficult due to various coronary sinus anatomy
Delivery tools and leads	Limited and still using leads designed for HBP	Numerous as endocardial LV pacing, multi-point LV pacing developing
Success rate	85–100% (4)	85–95% (4)
Respond rate	Not clear	Around 70% (6, 11)
Pacing parameters	Lower and stable threshold, high R wave sensing	Higher threshold *via* CS lead
Cardiac synchrony	Better electromechanical synchronization with a narrower QRS	A degree of LV dyssynchrony because of non-physiological pacing with a wider QRS
Indication range	Wider, including HFmrEF and HF with narrow QRS such as AF patients with atrioventricular node ablation	Narrower, with wide QRS (≥130 ms) and usually those whose LVEF ≤35% in most cases
Complications	Comparable, septal perforation	Comparable, phrenic nerve stimulation

LBBP, left bundle branch pacing; BVP, biventricular pacing; CRT-P, cardiac resynchronization therapy-pacemaker; CRT-D, cardiac resynchronization therapy-defibrillator; HBP, his bundle pacing; LV, left ventricle; RV, right ventricle; CS, coronary sinus; IVS, interventricular septum; LVEF, left ventricular ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction.

was first proposed by Mafi-Rad et al. (60). Later, LVSP showed acute hemodynamic and electrophysiological benefits equal to BVP in a study performed by Salden et al. (61), but the long-term clinical outcomes have not been investigated. The difference between LBBP and LVSP is whether they capture the LBB (only LBBP does) (62). However, there areno definite criteria for LVSP. Both pacing modes provide nearly physiological LV activation (63) by endocardial pacing and stimulating the left side of the IVS first. LBBP activates the ventricles more physiologically than LVSP by directly stimulating the conduction system, resulting in a shorter pLVAT (64). Emerging studies pay attention to the clinical use of LBBP, and the potential advantages of LBBP compared with conventional BVP are listed in **Table 2**. First, LBBP provides physiological LV activation starting at the IVS, from the endocardium to the epicardium, which provides maximum ventricular synchronization with a narrower QRS (65). Given that electrical synchronization is achieved more effectively, LBBP achieves considerably improved ventricular mechanical synchrony than BVP to ensure normal electromechanical coupling of the myocardium. The success rates of LBBP (85–100%) (4) and BVP (85–95%) (4) are comparable, yet approximately 30% of patients do not respond to BVP (6, 11). Advancing the lead *via* the transseptal approach, implantation of LBBP is rarely influenced by the anatomic variation of the vessels, making it easier to perform with high success rates. In addition, the procedure is safer for the operators and patients given the short procedure time and X-ray exposure time. Although septal perforation, thromboembolism, lead dislodgement, and other complications might probably occur (17), previous studies (23, 25, 27, 66) reported few complication events, and these events could be avoided or reduced by cautious operation with rare long-term damage. Relatively speaking, LBBP has a lower and more stable capture threshold during the procedure and in long-term follow-up, whereas fewer lead dislocation events are noted compared with BVP. Based on its application in patients with HFmrEF in several studies (29–32), LBBP is considered effective in an expanded group of patients for wider indications. In addition, LBBP has also been used in HF patients with narrow QRS and AF in need of atrioventricular node ablation, suggesting its benefits despite QRSd and providing a wider indication for the application of LBBP in HF patients. Moreover, in elderly patients who are typically precluded from BVP due to CRT complications, LBBP seems to represent a better option. Nevertheless, in scenarios in which patients do not respond to BVP, such as ischemic heart disease, marked left atrial dilation, advanced mitral regurgitation, and severely diseased myocardium, LBBP may not serve as an ideal pacing strategy to solve these obstacles either. Moreover, delivery tools and leads of LBBP are quite limited, and leads designed for HBP are currently being used.

Left bundle branch area pacing-optimized cardiac resynchronization therapy for severe heart failure

In patients with more advanced HF, severe electrical asynchrony may exist such as distal conduction delay and IVCDs. In these scenarios, LBBAP alone may not achieve ideal ventricular electrical synchronization. Instead, BVP can partially offset those conduction abnormalities. Therefore, LBBAP combined with BVP (sequential LV pacing) might provide better synchronization and clinical outcomes in these patients. Jastrzebski et al. (67) conducted a prospective observational multicenter study for left bundle branch area pacing-optimized cardiac resynchronization therapy (LOT-CRT) in CRT-indicated patients or non-responders to BVP alone. Patients recruited had severe ventricular dyssynchrony with a wide baseline QRSd of 181 ± 26 ms. Greater QRS narrowing *via* LOT-CRT was noted compared with either BVP or LBBAP alone (144 ± 22 vs. 170 ± 30 vs. 162 ± 23 ms, $P < 0.0001$), suggesting better electrical synchrony when these two approaches are combined for selected patients. For echocardiographic benefits, LOT-CRT improved LVEF (37.2 ± 12 vs. 28.5 ± 9.9%, $P < 0.0001$) and decreased left ventricular end-diastolic volume (LVEDV, 171.4 ± 83 vs. 209.8 ± 99, $P < 0.0001$) and LVESV (110.6 ± 69 vs. 149.5 ± 84, $P < 0.0001$) compared to baseline. Furthermore, the NYHA class was improved from 2.9 ± 0.6 to 1.9 ± 0.6 ($P < 0.0001$), and serum NT-proBNP levels decreased from 5,668 ± 8,249 pg/ml to 2,561 ± 3,555 pg/ml ($P < 0.0001$) during the 3-month follow-up. In subgroup analysis, using LBBP for LBBAP provided a greater reduction of QRSd (141 ± 20 vs. 152 ± 25 ms, $P = 0.028$) and greater improvement of LVEF (ΔLVEF: 11.1 ± 11.3 vs. 4.7 ± 7.5, $P = 0.0196$) than LVSP, indicating the advantages of the LBBP-BVP combined LOT-CRT strategy compared with LVSP-BVP strategies.

Limitations and future directions

To date, BVP remains the standard CRT option supported by evidence-based medicine and recommended in guidelines. However, LBBP has quickly developed and spread, especially in China, during the last 5 years. LBBP still serves as a rescue therapy for BVP-failed patients and is not routinely used in clinical practice. Long-term safety and complications, including arrhythmias, require further exploration in large-scale random controlled trials. More prospective, large-scale studies comparing LBBP with conventional BVP with a longer follow-up period

and definite clinical endpoints are required to decide which pacing modality is superior for HF patients. Obstacles in determining precise indications for LBBP or BVP must be solved perhaps by recruiting more HF patients who have ischemic cardiomyopathy or non-specific IVCDs, not only typical LBBB. Moreover, LBBP alone is less likely to achieve ideal electrical synchrony in patients with severe electrical dyssynchrony such as IVCD, whereas BVP can partially solve these problems. Thus, LOT-CRT combining LBBP and BVP is required in the treatment of more advanced HF in future, and more studies involving LOT-CRT should be conducted to further verify its clinical efficacy and long-term safety. Finally, improvements or special designs in delivery leads, sheaths, and devices for better adaptation to LBBP are also a matter of concern given that a set of delivery tools suitable for HBP is continuously used in LBBP currently.

Conclusion

Left bundle branch pacing represents a novel CSP modality that demonstrates promise for replacing the standard application of conventional BVP for CRT in HF patients in future, offering physiological activation of the ventricles. Advantages of LBBP have emerged in recent years over BVP, including better ventricular electrical and mechanical resynchronization and improvements in cardiac function, NYHA function class, and clinical outcomes. Further prospective randomized trials involving larger populations are required to provide further evidence for the safety and feasibility of LBBP and expand its primary clinical use.

Author contributions

QZ and XQ provided the idea and technical guidance and revised the manuscript. YF wrote the manuscript. PL, LJ, YL, and YZ made the tables and figure. All authors reviewed and approved the manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (Grant Numbers: 81870257 and 31871172).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Abraham WT. Cardiac resynchronization therapy. *Prog Cardiovasc Dis.* (2006) 48:232–8. doi: 10.1016/j.pcad.2005.11.001

2. Prinzen FW, Auricchio A, Mullens W, Linde C, Huizar JF. Electrical management of heart failure: from pathophysiology to treatment. *Eur Heart J.* (2022) 43:1917–27. doi: 10.1093/eurheartj/ehac088

3. Zannad F, Huvelle E, Dickstein K, van Veldhuisen DJ, Stellbrink C, Kober L, et al. Left bundle branch block as a risk factor for progression to heart failure. *Eur J Heart Fail.* (2007) 9:7–14. doi: 10.1016/j.ejheart.2006.04.011

4. Herweg B, Welter-Frost A, Vijayaraman P. The evolution of cardiac resynchronization therapy and an introduction to conduction system pacing: a conceptual review. *Europace.* (2021) 23:496–510. doi: 10.1093/europace/euaa264

5. Wu S, Sharma PS, Huang W. Novel left ventricular cardiac synchronization: left ventricular septal pacing or left bundle branch pacing? *Europace.* (2020) 22(Suppl_2.):ii10–8. doi: 10.1093/europace/euaa297

6. Wang Z, Wu Y, Zhang J. Cardiac resynchronization therapy in heart failure patients: tough road but clear future. *Heart Fail Rev.* (2021) 26:735–45. doi: 10.1007/s10741-020-10040-2

7. Wouters PC, Vernooy K, Cramer MJ, Prinzen FW, Meine M. Optimizing lead placement for pacing in dyssynchronous heart failure: the patient in the lead. *Heart Rhythm.* (2021) 18:1024–32. doi: 10.1016/j.hrthm.2021.02.011

8. Deshmukh P, Casavant DA, Romanyshyn M, Anderson K. Permanent, direct his-bundle pacing: a novel approach to cardiac pacing in patients with normal his-purkinje activation. *Circulation.* (2000) 101:869–77. doi: 10.1161/01.cir.101.8.869

9. Writing Committee M, Kusumoto FM, Schoenfeld MH, Barrett C, Edgerton JR, Ellenbogen KA, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart rhythm society. *Heart Rhythm.* (2019) 16:e128–226. doi: 10.1016/j.hrthm.2018.10.037

10. Sharma PS, Huizar J, Ellenbogen KA, Tan AY. Recruitment of bundle branches with permanent his bundle pacing in a patient with advanced conduction system disease: what is the mechanism? *Heart Rhythm.* (2016) 13:623–5. doi: 10.1016/j.hrthm.2015.11.012

11. Vijayaraman P, Chung MK, Dandamudi G, Upadhyay GA, Krishnan K, Crossley G, et al. His bundle pacing. *J Am Coll Cardiol.* (2018) 72:927–47. doi: 10.1016/j.jacc.2018.06.017

12. Teigeler T, Kolominsky J, Vo C, Shepard RK, Kalahasty G, Kron J, et al. Intermediate-term performance and safety of his-bundle pacing leads: a single-center experience. *Heart Rhythm.* (2021) 18:743–9. doi: 10.1016/j.hrthm.2020.12.031

13. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, et al. A novel pacing strategy with low and stable output: pacing the left bundle branch immediately beyond the conduction block. *Can J Cardiol.* (2017) 33:1736.e1–1736.e3. doi: 10.1016/j.cjca.2017.09.013

14. Tan NY, Witt CM, Oh JK, Cha YM. Left bundle branch block: current and future perspectives. *Circ Arrhythm Electrophysiol.* (2020) 13:e008239. doi: 10.1161/CIRCEP.119.008239

15. Huang W, Chen X, Su L, Wu S, Xia X, Vijayaraman PA. Beginner's guide to permanent left bundle branch pacing. *Heart Rhythm.* (2019) 16:1791–6. doi: 10.1016/j.hrthm.2019.06.016

16. Ponnusamy SS, Arora V, Namboodiri N, Kumar V, Kapoor A, Vijayaraman P. Left bundle branch pacing: a comprehensive review. *J Cardiovasc Electrophysiol.* (2020) 31:2462–73. doi: 10.1111/jce.14681

17. Cano O, Vijayaraman P. Left bundle branch area pacing: implant technique, definitions, outcomes, and complications. *Curr Cardiol Rep.* (2021) 23:155. doi: 10.1007/s11886-021-01585-1

18. Padala SK, Ellenbogen KA. Left bundle branch pacing is the best approach to physiological pacing. *Heart Rhythm O2.* (2020) 1:59–67. doi: 10.1016/j.hroo.2020.03.002

19. De Pooter J, Wauters A, Van Heuverswyn F, Le Polain de Waroux JB. A guide to left bundle branch area pacing using stylet-driven pacing leads. *Front Cardiovasc Med.* (2022) 9:844152. doi: 10.3389/fcvm.2022.844152

20. Jastrzębski M, Kiełbasa G, Moskal P, Bednarek A, Kusiak A, Sondej T, et al. Fixation beats: a novel marker for reaching the left bundle branch area during deep septal lead implantation. *Heart Rhythm.* (2021) 18:562–9. doi: 10.1016/j.hrthm.2020.12.019

21. Chokesuwattanaskul R, Jongnarangsin K. Left bundle branch pacing: unexpected resynchronization effect of anodal capture. *J Innov Card Rhythm Manag.* (2022) 13:4933–5. doi: 10.19102/icrm.2022.130303

22. Murphy SP, Ibrahim NE, Januzzi JL Jr. Heart failure with reduced ejection fraction: a review. *JAMA.* (2020) 324:488–504. doi: 10.1001/jama.2020.10262

23. Li X, Li H, Ma W, Ning X, Liang E, Pang K, et al. Permanent left bundle branch area pacing for atrioventricular block: feasibility, safety, and acute effect. *Heart Rhythm.* (2019) 16:1766–73. doi: 10.1016/j.hrthm.2019.04.043

24. Vijayaraman P, Subzposh FA, Naperkowski A, Panikkath R, John K, Mascarenhas V, et al. Prospective evaluation of feasibility and electrophysiologic and echocardiographic characteristics of left bundle branch area pacing. *Heart Rhythm.* (2019) 16:1774–82. doi: 10.1016/j.hrthm.2019.05.011

25. Padala SK, Master VM, Terricabras M, Chiocchini A, Garg A, Kron J, et al. Initial experience, safety, and feasibility of left bundle branch area pacing: a multicenter prospective study. *JACC Clin Electrophysiol.* (2020) 6:1773–82. doi: 10.1016/j.jacep.2020.07.004

26. Ravi V, Hanifin JL, Larsen T, Huang HD, Trohman RG, Sharma PS. Pros and cons of left bundle branch pacing: a single-center experience. *Circ Arrhythm Electrophysiol.* (2020) 13:e008874. doi: 10.1161/CIRCEP.120.008874

27. Su L, Wang S, Wu S, Xu L, Huang Z, Chen X, et al. Long-term safety and feasibility of left bundle branch pacing in a large single-center study. *Circ Arrhythm Electrophysiol.* (2021) 14:e009261. doi: 10.1161/CIRCEP.120.009261

28. Zhang W, Huang J, Qi Y, Wang F, Guo L, Shi X, et al. Cardiac resynchronization therapy by left bundle branch area pacing in patients with heart failure and left bundle branch block. *Heart Rhythm.* (2019) 16:1783–90. doi: 10.1016/j.hrthm.2019.09.006

29. 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) 6:849–58. doi: 10.1016/j.jacep.2020.04.011

30. Li Y, Yan L, Dai Y, Zhou Y, Sun Q, Chen R, et al. Feasibility and efficacy of left bundle branch area pacing in patients indicated for cardiac resynchronization therapy. *Europace.* (2020) 22(Suppl_2.):ii54–60. doi: 10.1093/europace/euaa271

31. 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) 7:135–47. doi: 10.1016/j.jacep.2020.08.015

32. Qian Z, Wang Y, Hou X, Qiu Y, Wu H, Zhou W, et al. Efficacy of upgrading to left bundle branch pacing in patients with heart failure after right ventricular pacing. *Pacing Clin Electrophysiol.* (2021) 44:472–80. doi: 10.1111/pace.14147

33. Grieco D, Bressi E, Sedláèek K, Čurila K, Vernooy K, Fedele E, et al. Feasibility and safety of left bundle branch area pacing-cardiac resynchronization therapy in elderly patients. *J Interv Card Electrophysiol.* (2022). [Epub ahead of print]. doi: 10.1007/s10840-022-01174-4

34. Li X, Qiu C, Xie R, Ma W, Wang Z, Li H, et al. Left bundle branch area pacing delivery of cardiac resynchronization therapy and comparison with biventricular pacing. *ESC Heart Fail.* (2020) 7:1711–22. doi: 10.1002/ehf2.12731

35. Wu S, Su L, Vijayaraman P, Zheng R, Cai M, Xu L, et al. Left bundle branch pacing for cardiac resynchronization therapy: nonrandomized on-treatment comparison with his bundle pacing and biventricular pacing. *Can J Cardiol.* (2021) 37:319–28. doi: 10.1016/j.cjca.2020.04.037

36. Wang Y, Gu K, Qian Z, Hou X, Chen X, Qiu Y, et al. The efficacy of left bundle branch area pacing compared with biventricular pacing in patients with heart failure: a matched case-control study. *J Cardiovasc Electrophysiol.* (2020) 31:2068–77. doi: 10.1111/jce.14628

37. Guo J, Li L, Xiao G, Ye T, Huang X, Meng F, et al. Remarkable response to cardiac resynchronization therapy via left bundle branch pacing in patients with true left bundle branch block. *Clin Cardiol.* (2020) 43:1460–8. doi: 10.1002/clc.23462

38. Zu L, Wang Z, Hang F, Jiang Y, Wang X, Cheng L, et al. Cardiac resynchronization performed by Lbbap-Crt in patients with cardiac insufficiency and left bundle branch block. *Ann Noninvasive Electrocardiol.* (2021) 26:e12898. doi: 10.1111/anec.12898

39. Chen X, Ye Y, Wang Z, Jin Q, Qiu Z, Wang J, et al. Cardiac resynchronization therapy via left bundle branch pacing vs. optimized biventricular pacing with adaptive algorithm in heart failure with left bundle branch block: a prospective, multi-centre, observational study. *Europace.* (2021) 24:807–16. doi: 10.1093/europace/euab249

40. Liu W, Hu C, Wang Y, Cheng Y, Zhao Y, Liu Y, et al. Mechanical synchrony and myocardial work in heart failure patients with left bundle branch area pacing and comparison with biventricular pacing. *Front Cardiovasc Med.* (2021) 8:727611. doi: 10.3389/fcvm.2021.727611

41. Ivanovski M, Mrak M, Meznar AZ, Zizek D. Biventricular versus conduction system pacing after atrioventricular node ablation in heart failure patients with atrial fibrillation. *J Cardiovasc Dev Dis.* (2022) 9:209. doi: 10.3390/jcdd9070209

42. Wang Y, Zhu H, Hou X, Wang Z, Zou F, Qian Z, et al. Randomized trial of left bundle branch vs biventricular pacing for cardiac resynchronization therapy. *J Am Coll Cardiol.* (2022) 80:1205–16. doi: 10.1016/j.jacc.2022.07.019

43. Fish JM, Di Diego JM, Nesterenko V, Antzelevitch C. Epicardial activation of left ventricular wall prolongs Qt interval and transmural dispersion of repolarization: implications for biventricular pacing. *Circulation.* (2004) 109:2136–42. doi: 10.1161/01.CIR.0000127423.75608.A4

44. Bordachar P, Derval N, Ploux S, Garrigue S, Ritter P, Haissaguerre M, et al. Left ventricular endocardial stimulation for severe heart failure. *J Am Coll Cardiol.* (2010) 56:747–53. doi: 10.1016/j.jacc.2010.04.038

45. Gillis AM. Optimal pacing for right ventricular and biventricular devices: minimizing, maximizing, and right ventricular/left ventricular site considerations. *Circ Arrhythm Electrophysiol.* (2014) 7:968–77. doi: 10.1161/CIRCEP.114.001360

46. Daubert C, Behar N, Martins RP, Mabo P, Leclercq C. Avoiding non-responders to cardiac resynchronization therapy: a practical guide. *Eur Heart J.* (2017) 38:1463–72. doi: 10.1093/eurheartj/ehw270

47. Ailawadi G, Lapar DJ, Swenson BR, Maxwell CD, Girotti ME, Bergin JD, et al. Surgically placed left ventricular leads provide similar outcomes to percutaneous leads in patients with failed coronary sinus lead placement. *Heart Rhythm.* (2010) 7:619–25. doi: 10.1016/j.hrthm.2010.01.014

48. Wu HY, Li SJ, Yang Z, Chen HC, You PH, Cheng GA. Novel approach for repetitive dislocation of transvenous left ventricular leads during cardiac resynchronization therapy implantation by the loop technique. *Front Cardiovasc Med.* (2022) 9:836514. doi: 10.3389/fcvm.2022.836514

49. Menardi E, Ballari GP, Goletto C, Rossetti G, Vado A. Characterization of ventricular activation pattern and acute hemodynamics during multipoint left ventricular pacing. *Heart Rhythm.* (2015) 12:1762–9. doi: 10.1016/j.hrthm.2015.04.029

50. Sohal M, Chen Z, Sammut E, Jackson T, Behar J, Carr-White G, et al. New developments in the delivery of cardiac resynchronization therapy: targeted lead placement, multi-site and endocardial pacing. *Expert Rev Med Devices.* (2014) 11:295–304. doi: 10.1586/17434440.2014.885320

51. Rinaldi CA, Burri H, Thibault B, Curnis A, Rao A, Gras D, et al. A review of multisite pacing to achieve cardiac resynchronization therapy. *Europace.* (2015) 17:7–17. doi: 10.1093/europace/euu197

52. Niazi I, Baker J II, Corbisiero R, Love C, Martin D, Sheppard R, et al. Safety and efficacy of multipoint pacing in cardiac resynchronization therapy: the multipoint pacing trial. *JACC Clin Electrophysiol.* (2017) 3:1510–8. doi: 10.1016/j.jacep.2017.06.022

53. Sterlinski M, Sokal A, Lenarczyk R, Van Heuverswyn F, Rinaldi CA, Vanderheyden M, et al. In heart failure patients with left bundle branch block single lead multispot left ventricular pacing does not improve acute hemodynamic response to conventional biventricular pacing. A multicenter

prospective, interventional, non-randomized study. *PLoS One.* (2016) 11:e0154024. doi: 10.1371/journal.pone.0154024

54. Akerstrom F, Narvaez I, Puchol A, Pachon M, Martin-Sierra C, Rodriguez-Manero M, et al. Estimation of the effects of multipoint pacing on battery longevity in routine clinical practice. *Europace.* (2018) 20:1161–7. doi: 10.1093/europace/eux209

55. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, et al. 2021 Esc guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J.* (2021) 42:3427–520. doi: 10.1093/eurheartj/ehab364

56. Morgan JM, Biffi M, Geller L, Leclercq C, Ruffa F, Tung S, et al. Alternate site cardiac resynchronization (Alsync): a prospective and multicentre study of left ventricular endocardial pacing for cardiac resynchronization therapy. *Eur Heart J.* (2016) 37:2118–27. doi: 10.1093/eurheartj/ehv723

57. Chatterjee NA, Heist EK. Cardiac resynchronization therapy-emerging therapeutic approaches. *Curr Treat Options Cardiovasc Med.* (2018) 20:20. doi: 10.1007/s11936-018-0614-2

58. Mullens W, Nijst P. Leadless left ventricular pacing: another step toward improved crt response. *J Am Coll Cardiol.* (2017) 69:2130–3. doi: 10.1016/j.jacc.2017.03.534

59. Wijesuriya N, Elliott MK, Mehta V, Sidhu BS, Behar JM, Niederer S, et al. Leadless left ventricular endocardial pacing for cardiac resynchronization therapy: a systematic review and meta-analysis. *Heart Rhythm.* (2022) 19:1176–83. doi: 10.1016/j.hrthm.2022.02.018

60. Mafi-Rad M, Luermans JG, Blaauw Y, Janssen M, Crijns HJ, Prinzen FW, et al. Feasibility and acute hemodynamic effect of left ventricular septal pacing by transvenous approach through the interventricular septum. *Circ Arrhythm Electrophysiol.* (2016) 9:e003344. doi: 10.1161/CIRCEP.115.003344

61. Salden F, Luermans J, Westra SW, Weijs B, Engels EB, Heckman LIB, et al. Short-term hemodynamic and electrophysiological effects of cardiac resynchronization by left ventricular septal pacing. *J Am Coll Cardiol.* (2020) 75:347–59. doi: 10.1016/j.jacc.2019.11.040

62. Huang W, Zhou X, Ellenbogen KA. Pursue physiological pacing therapy: a better understanding of left bundle branch pacing and left ventricular septal myocardial pacing. *Heart Rhythm.* (2021) 18:1290–1. doi: 10.1016/j.hrthm.2021.05.013

63. Curila K, Jurak P, Jastrzebski M, Prinzen F, Waldauf P, Halamek J, et al. Left bundle branch pacing compared to left ventricular septal myocardial pacing increases interventricular dyssynchrony but accelerates left ventricular lateral wall depolarization. *Heart Rhythm.* (2021) 18:1281–9. doi: 10.1016/j.hrthm.2021.04.025

64. Vijayaraman P, Nayak HM, Ellenbogen KA. Left ventricular septal versus left bundle branch pacing: a new beginning in cardiac resynchronization therapy? *J Am Coll Cardiol.* (2020) 75:360–2. doi: 10.1016/j.jacc.2019.11.041

65. Mittal S, Bhatt AG. Left bundle branch pacing: a contender emerges to challenge the 25-year run of cardiac resynchronization therapy. *JACC Clin Electrophysiol.* (2020) 6:859–62. doi: 10.1016/j.jacep.2020.05.006

66. Hou X, Qian Z, Wang Y, Qiu Y, Chen X, Jiang H, et al. Feasibility and cardiac synchrony of permanent left bundle branch pacing through the interventricular septum. *Europace.* (2019) 21:1694–702. doi: 10.1093/europace/euz188

67. Jastrzebski M, Moskal P, Huybrechts W, Curila K, Sreekumar P, Rademakers LM, et al. Left bundle branch-optimized cardiac resynchronization therapy (Lot-Crt): results from an international lbbap collaborative study group. *Heart Rhythm.* (2022) 19:13–21. doi: 10.1016/j.hrthm.2021.07.057

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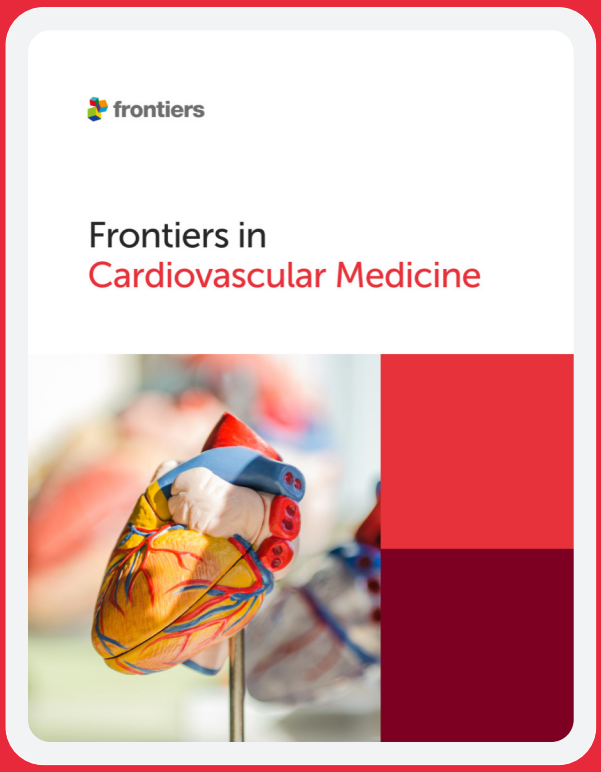

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