Systematic Review and Meta-Analysis

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Safety and efficacy of left bundle branch pacing in comparison with conventional right ventricular pacing

A systematic review and meta-analysis

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Abstract

Background: Right ventricular pacing (RVP) has been widely accepted as a traditional pacing strategy, but long-term RVP has detrimental impact on ventricular synchrony. However, left bundle branch pacing (LBBP) that evolved from His-bundle pacing could maintain ventricular synchrony and overcome its clinical deficiencies such as difficulty of lead implantation, His bundle damage, and high and unstable thresholds. This analysis aimed to appraise the clinical safety and efficacy of LBBP.

Methods: The Medline, PubMed, Embase, and the Cochrane Library databases from inception to November 2020 were searched for studies comparing LBBP and RVP.

Results: Seven trials with 451 patients (221 patients underwent LBBP and 230 patients underwent RVP) were included in the analysis. Pooled analyses verified that the paced QRS duration (QRSd) and left ventricular mechanical synchronization parameters of the LBBP capture were similar with the native-conduction mode ($P > .7$),but LBBP showed shorter QRS duration (weighted mean difference [WMD]: −33.32; 95% confidence interval [CI], −40.44 to −26.19, $P < .001$), better left ventricular mechanical synchrony (standard mean differences: −1.5; 95% CI: −1.85 to −1.14, $P < .001$) compared with RVP. No significant differences in Pacing threshold (WMD: 0.01; 95% CI: −0.08 to 0.09, $P < .001$), R wave amplitude (WMD: 0.04; 95% CI: −1.12 to 1.19, $P = .95$) were noted between LBBP and RVP. Ventricular impedance of LBBP was higher than that of RVP originally (WMD: 19.34; 95% CI: 3.13–35.56, $P = .02$), and there was no difference between the 2 groups after follow-up (WMD: 11.78; 95% CI: −24.48 to 48.04, $P = .52$). And follow-up pacing threshold of LBBP kept stability (WMD: 0.08; 95% CI: −0.09 to 0.25, $P = .36$). However, no statistical difference existed in ejection fraction between the 2 groups (WMD: 1.41; 95% CI: −1.72 to 4.54, $P = .38$).

Conclusions: The safety and efficacy of LBBP was firstly verified by meta-analysis to date. LBBP markedly preserve ventricular electrical and mechanical synchrony compared with RVP. Meanwhile, LBBP had stable and excellent pacing parameters. However, LBBP could not be significant difference in ejection fraction between RVP during short- term follow-up.

Abbreviations: BBB = bundle branch block, CI = confidence interval, CRT = cardiac resynchronization therapy, HBP = His-bundle pacing, LBBB = left bundle branch block, LBBP = left bundle branch pacing, LV = left ventricular, LVEF = left ventricular ejection fraction, QRSd = QRS duration, RVAP = right ventricular apical pacing, RVP = right ventricular pacing, RVSP = right ventricular septal pacing, SMD = standard mean differences, Stim-LVAT = stimulus to peak left ventricular activation time, WMD = weighted mean difference.

Keywords: efficacy, his-bundle pacing, left bundle branch pacing, right ventricular pacing, safety

Editor: Neil Patel.

Funding/support: This study was supported by Science and Technology Department of Hunan Province in China (2018SK52104).

Data Availability: The data used to support the findings of this study are included within the article.

The authors report no conflicts of interest.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Liu X, Li W, Wang L, Tian S, Zhou X, Wu M. Safety and efficacy of left bundle branch pacing in comparison with conventional right ventricular pacing: a systematic review and meta-analysis. Medicine 2021;100:27(e26560).

Received: 9 January 2021 / Received in final form: 9 June 2021 / Accepted: 12 June 2021

http://dx.doi.org/10.1097/MD.0000000000026560

1. Introduction

Pacemaker therapy has been used for more than half a century as a treatment for patients with bradycardia arrhythmias. Conventional right ventricular pacing (RVP) including right ventricular apical pacing (RVAP), right ventricular septal pacing (RVSP), or right ventricular outflow tract pacing are widely accepted, which have the advantages of convenient installation, good pacing parameters, and less lead dislodgement. However, RVP causes cardiac electromechanical asynchrony, which is relate to an increased risk for hospitalization due to heart failure and atrial fibrillation.[1–3] Cardiac resynchronization therapy (CRT) can shorten the left and right ventricular delays and improve ventricular systolic function, which is especially suitable for patients with heart failure reduced ejection fraction combined with complete left bundle branch block.[4] But, 30% and 40% of patients implanted with biventricular pacing have no clinical benefit or no response to CRT[5]; moreover, there was no significant improvement in cardiac function in patients with right bundle branch block,[6] even leading to deterioration of cardiac function in patients with narrow QRS duration.[7]

His bundle pacing (HBP) ensures rapid activation in left and right ventricles and synchronized contraction via pacing His-Purkinje system directly, emerging as a viable alternative for CRT with physiological restoration of electrical synchrony.[8] However, there are still some limitations of HBP, including difficult implantation, high capture thresholds and lower success rates particularly in patients with bundle branch block (BBB) or infranodal block.[9,10] Thus, alternative pacing sites have been sought. Left bundle branch pacing (LBBP) is defined as capture of the left bundle trunk or its proximal fascicles, usually with septal myocardium capture,[11] which overcomes clinical deficiencies mentioned above of HBP. Previous studies reported that the surgery time was significantly increased for the LBBP compared with RVP.[12,13] But recent study revealed that the surgery method via the ventricular RAO fluoroscopic image was divided into 9 parts ("nine partition method") and without the guidance of intracardiac electrograms could save the operation time.[14] Recently, it still lacked study to systemically summarize and comprehensively evaluate the effects of LBBP. Therefore, this study represented the first systematic review and meta-analysis on safety and efficacy of LBBP in comparison with RVP.

2. Methods

2.1. Search strategy

An all-round search was searched in the Medline, PubMed, Embase, and the Cochrane Library databases from inception up to November 2020 by 2 reviewers independently. Only articles in English were included. The search strategy used the following relevant keywords, including the following: ([left bundle branch] OR [LBBP]) and ([right ventricular apical] OR [right ventricular septal] OR [right ventricular] OR [RVP]). And reviews and reference lists of retrieved articles were hand searched for potentially relevant publications not being identified previously.

All analyses were based on previous published studies, thus no ethical approval and patient consent are required in this study.

2.2. Inclusion and exclusion criteria

Two investigators filtrated and identified researches that fulfilled the following inclusion criteria: full-text studies of controlled experiments about LBBP versus RVP; RVP group included RVSP, RVAP, or right ventricular outflow tract pacing; randomized control trials, case-control, cohort, and observational studies; studies wanted to provide some dependable information with QRS duration (QRSd), mechanical synchronization parameters, pacing parameters, left ventricular ejection fraction (LVEF) and complications in both groups. The exclusion criteria were as follows: studies that did not offer plentiful data to analyze the procedural efficacy and safety; animal studies, conference abstracts, case reports, review articles, editorials, or non-English language articles.

2.3. Data extraction

Data were extracted using standardized protocol and reporting forms, including name of the first author, year of publication, country of origin, sample size, baseline characteristics (age, sex, LVEF, QRSd), selection of patients and pacing parameters, and so on. Estimating the sample mean and standard deviation from commonly reported quantiles.[15] This data extraction process was independently performed by 2 investigators. Discrepancies between them were resolved by a third reviewer.

2.4. Quality assessment

The study quality was evaluated by two investigators using the Newcastle–Ottawa Scale (NOS) for nonrandomized studies. The NOS uses a star system (0–9) to evaluate studies. A research with NOS ≥7 was judged to be a study of good quality.[16]

2.5. Statistical analysis

Dichotomous variables and outcome endpoints were reported as a risk ratio (RR) with 95% confidence intervals (CIs). The continuous variables were analyzed using weighted mean differences (WMD) or standard mean differences (SMD). The between-study heterogeneity was reflected by $I^2 > 50\%$, with a $P < 0.05$ deemed statistically significant. In cases of heterogeneity (defined as $I^2 > 50\%$), random-effects models were used; otherwise ($I^2 \leq 50\%$), fixed-effects models were used. In cases of statistical heterogeneity, subgroup analysis or sensitivity analyses was used. Sensitivity analysis was performed to check the consistency of the overall effect estimate. When the pooled analysis still yielded significant heterogeneity, descriptive analysis was used. All statistical testing was 2-tailed with a statistical significance set at $P < .05$. The presence of publication bias was evaluated by the use of funnel plots. The statistical analysis was performed using the Revman5.4 soft-ware.

3. Results

3.1. Study and data selection

Our search strategy yielded 177 potentially relevant articles (21 articles from PubMed, 25 articles from EMBASE, 91 articles from Cochrane Library, 40 articles from Medline). The results of the search and selection process are illustrated in Figure 1. Initially, the exclusion of 50 duplicated articles, 92 articles underwent title and abstract review. Of the remaining 5 studies were excluded as topics were conducted in animals and conference, leaving a total of 30 articles for reading the full text. Next, 23 studies were excluded for the following reasons: 6 were uncontrolled studies, 8 lacked study endpoints, and 7

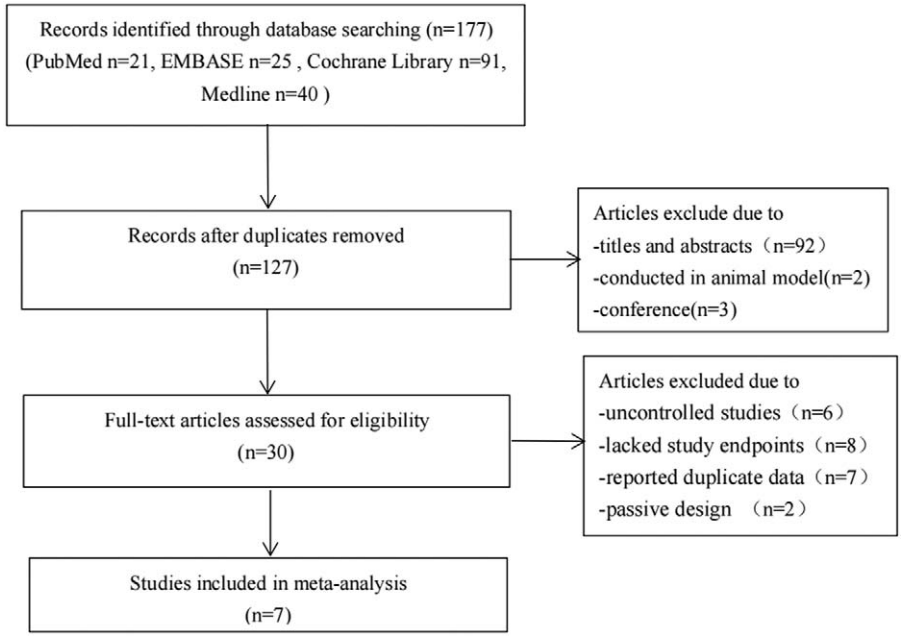

Figure 1. Flow diagram of study selection process.

reported duplicate data. And then, 1 trail by Hou et al[17] was excluded because RVSP justly acted as backup pacing in HBP group. Another trail by Li et al[18] was excluded because patients of LBBP implantation failure received RVSP. No additional articles were added through manual search. Thus, 7 articles were finally selected in this meta-analysis.[12,13,19–23]

3.2. Study characteristics and quality assessment of included studies

Baseline and procedural characteristics of included studies are shown in Table 1. A total of 451 patients were enrolled in these trials (221 in the LBBP group and 230 in the RVP group). The mean ages of the study participants ranged from 61.64 ± 5.40 to 73.6 ± 8.9 years, and the mean follow-up duration was from 0 to 6 months. In this meta-analysis, 2 studies[12,19] included RVSP in RVP group, only 1 study[21] included RVAP, the remaining studies[12,20,22,23] included RVAP or RVSP. Only 1 study[19] selected patients who were sick sinus syndrome with narrow QRSd; the rest[12,13,20–23] included sick sinus syndrome or atrioventricular block. The mean success rate of LBBP in the included study was 94.0%, and the average probability of recording LBB potential is 64.7%. Six of seven were prospective

Table 1

Baseline and procedural characteristics of included studies.

Study	Country	Study type	Treatment group	Patients (n)	Follow, mo	Age, y	Male, n (%)	Hy, n (%)	CAD, n (%)	LVEF (%)	QRSd	Bundle branch block, n (%)	Surgical success rate (%)	LBB potential (%)	Correction of BBB (%)
Chen et al, 2019[20]	China	Prospective cohort trial	LBBP	20	3	66.90 ± 7.49	7 (35.0)	13 (65.0)	6 (30)	60.00 ± 10.60	110.00 ± 33.38	3 (15.0)	100	55	100
			RVP	20	3	71.65 ± 7.80	9 (45.0)	14 (70.0)	14 (70)	60.70 ± 6.08	106.25 ± 21.53	3 (15.0)	100		
Cai et al, 2020[19]	China	Observational trial	LBBP	40	0	65.93 ± 9.99	13 (32.5)	14 (35.0)	5 (13)	65.44 ± 7.84	91.06 ± 14.17	NR	90.4	80	NR
			RVP	38	0	68.61 ± 9.83	14 (36.8)	23 (60.5)	10 (26)	68.84 ± 8.15	83.75 ± 14.82	NR	100		
Das et al, 2020[21]	India	Prospective cohort trial	LBBP	22	6	63.36 ± 7.82	12 (54.5)	NR	NR	61.15 ± 4.04	131.64 ± 17.80	13 (59.1)	88	40.9	84.6
			RVP	28	6	61.64 ± 5.40	16 (57.1)	NR	NR	62.50 ± 4.00	132.73 ± 16.71	18 (64.3)	100		
Liu et al, 2020[22]	China	Prospective cohort trial	LBBP	42	1/4	65.36 ± 13.08	20 (47.6)	28 (66.7)	NR	NR	109.48 ± 25.58	NR	100	NR	NR
			RVP	42	1/4	68.19 ± 9.52	10 (23.8)	29 (69.1)	NR	NR	97.36 ± 22.20	NR	100		
Wang et al, 2019[12]	China	Prospective cohort trial	LBBP	66	6	71.12 ± 13.14	38 (57.6)	34 (51.5)	10 (15.2)	61.3 ± 5.7	99.24 ± 13.60	NR	92.4	75.4	NR
			RVP	65	6	72.03 ± 12.11	41 (63.1)	37 (56.9)	12 (18.5)	62.1 ± 6.3	101.88 ± 11.72	NR	100		
Zhang et al, 2019[13]	China	Prospective cohort trial	LBBP	23	0	64.61 ± 12.65	17 (73.9)	11 (47.8)	4 (17.4)	45.75 ± 18.47	131.83 ± 41.68	7 (35.0)	87	NR	100
			RVP	21	0	65.76 ± 13.53	10 (47.6)	9 (42.9)	6 (28.6)	65.93 ± 4.16	93.62 ± 8.28	NR	100		
Sun et al, 2020[23]	China	Prospective cohort trial	LBBP	16	1/4	71.4 ± 14.4	7 (43.8)	4 (25.0)	1 (6.3)	68.69 ± 3.14	106.25 ± 25.00	3 (18.8)	100	50	NR
			RVP	16	1/4	73.6 ± 8.9	5 (31.3)	4 (25.0)	2 (12.5)	66.13 ± 4.50	107.50 ± 28.17	5 (31.3)	100		

BBB = bundle branch block, CAD = coronary artery disease, Hy = hypertension, LBBP = left bundle branch pacing, LBB = left bundle branch, LVEF = left ventricular ejection fraction, NR = not recorded, QRSd = QRS duration, RVP = right ventricular pacing.

Table 2

Quality assessment of the included studies according to the Newcastle-Ottawa Scale.

Study	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total stars
Chen et al, 2019[20]	*	*	*	*	**	*		*	8
Cai et al, 2020[19]	*	*	*	*	**	*			7
Das et al, 2020[21]	*	*	*	*	**	*	*	*	9
Liu et al, 2020[22]	*	*	*	*	**	*			7
Wang et al, 2018[12]	*	*	*		**	*	*	*	8
Zhang et al, 2019[13]	*	*	*	*	**	*			7
Sun et al, 2020[23]	*	*	*	*	**	*			7

studies,[12,13,20–23] and 1 was observational study.[19] It is worth noting that left ventricular (LV) mechanical synchrony was measured in different ways. In Cai et al study,[19] it was measured by SD-Tmsv-16; In Das et al's study,[21] it was measured by standard pulsed wave Doppler echocardiography as the interval between the onset of the QRS and the onset of the aortic and pulmonary ejection; In Sun et al study,[23] it was measured by standard deviation of 18-segment systolic times to peak 2-D strain.

The Newcastle–Ottawa scales (NOS) of the included studies are described in Table 2.

3.3. Ventricular electrical synchrony

All studies[12,13,19–23] recorded the baseline of QRSd. In the LBBP group, the paced QRSd in LBBP capture was no significant difference with the native-conduction mode (WMD: −1.69; 95% confidence interval [CI]: −14.25 to 10.86, $I^2=94\%$, $P=.79$; Fig. 2A). However, compared with RVP, LBBP showed shorter QRSd ([WMD]: −33.32; 95% [CI], −40.44 to −26.19, $I^2=90\%$, $P<.001$; Fig. 2B), which represented a better electrical synchrony resulting from LBBP. Considering the high heterogeneity, random-effects model was used for analyses. According to existence of LBB potentials, the LBBP group was divided into two different subgroups as follows: LBB potential (potential +) and without LBB potential (potential −). Three studies[19–21] were included in this analysis and 2 studies[19,20] compared the stimulus to peak left ventricular activation time (Stim-LVAT) in lead V5. And there were no statistically significant differences in paced QRSd (WMD: −2.93; 95% CI: −7.40 to 1.55, $I^2=0\%$, $P=.20$; Fig. 3A) and Stim-LVAT (WMD: −3.45; 95% CI: −8.89 to 1.99, $I^2=0\%$, $P=.21$; Fig. 3B) by a fixed-effect model in 2 subgroups. The sensitivity analysis showed the all results were not driven by any single study.

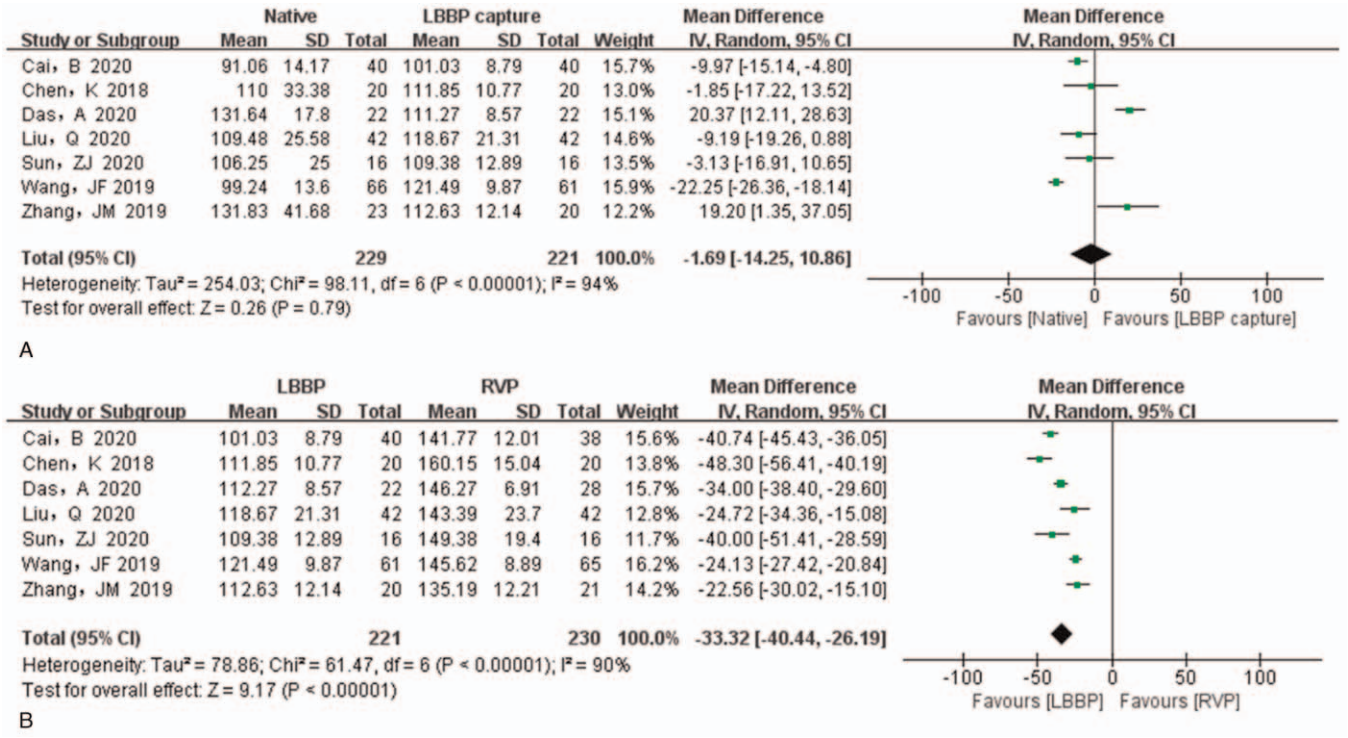

Figure 2. Forest plots of QRSd. (A) for native vs LBBP capture; (B) for LBBP vs RVP. LBBP = left bundle branch pacing, QRSd = QRS duration, RVP = right ventricular pacing.

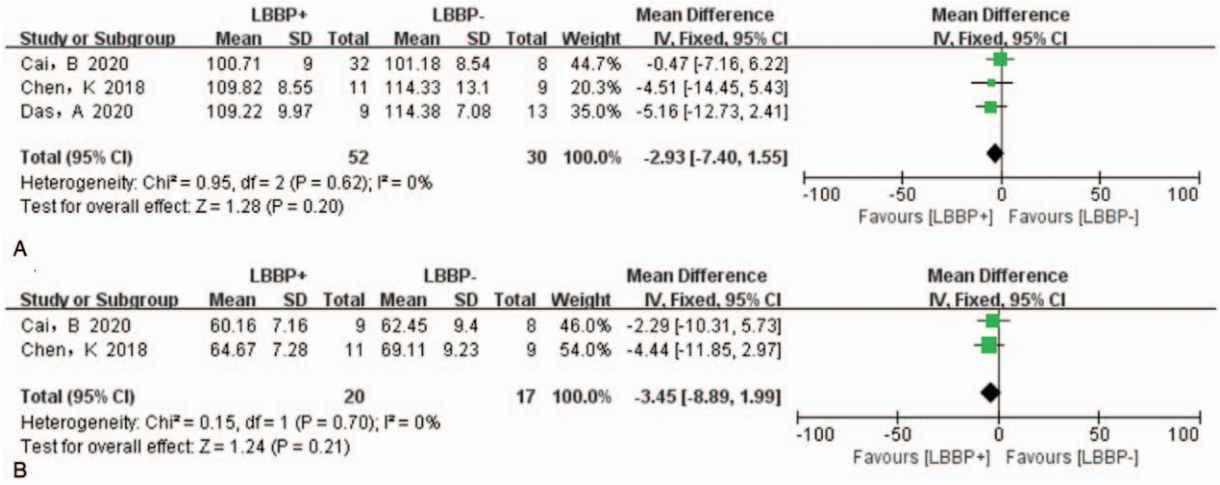

Figure 3. Forest plots of LV electrical synchrony in LBBP+ compared with LBBP−. (A) QRSd; (B) Stim-LVAT. LBB = left bundle branch, LBBP = left bundle branch pacing, LBBP+ = with LBB potential, LBBP- = without LBB potential, QRSd = QRS duration, Stim-LVAT = the stimulus to peak left ventricular activation time.

3.4. LV mechanical synchrony

The baseline of LV mechanical synchrony measured by different ways was summarized from 3 studies[19,21,23] and the heterogeneity was low (I^2 = 45%), taking a fixed-effect model and the continuous variables were analyzed using SMD. In the LBBP group, LV mechanical synchronization parameter of the LBBP capture was similar with the native-conduction mode (WMD: −0.01; 95% CI, −0.33 to 0.31, P = .95; Fig. 4A). But, the LV mechanical synchronization parameter in LBBP capture mode was superior to that of the RVP group (SMD: −1.5; 95% CI: −1.85 to −1.14, P < .001; Fig. 4B). And low statistical heterogeneity was observed (I^2 = 41%), taking a fixed-effect model. Meanwhile, the results of the sensitivity analysis were not changed by removing any individual study from the analysis.

3.5. LVEF assessment

The baseline LVEF assessment was reported among most of the included studies. Postoperative LVEF was assessed in only three studies.[19,21,23] In the LBBP group, LVEF of the LBBP were similar with RVP mode during short-term follow-up by a random-effect model (WMD: 1.41; 95% CI: −1.72 to 4.54, I^2 = 77%, P = .38; Fig. 5).

3.6. Pacing parameters

3.6.1. Pacing threshold. The pacing threshold was assessed in all studies[12,13,19–23] and the heterogeneity was high (I^2 = 85%), taking a random-effect model. Pacing threshold in LBBP group was low and similar with RVP group (WMD: 0.01; 95% CI: −0.08 to 0.09, P = .9; Fig. 6A). Upon sensitivity analysis by removing any individual study, the point estimate or CI in the

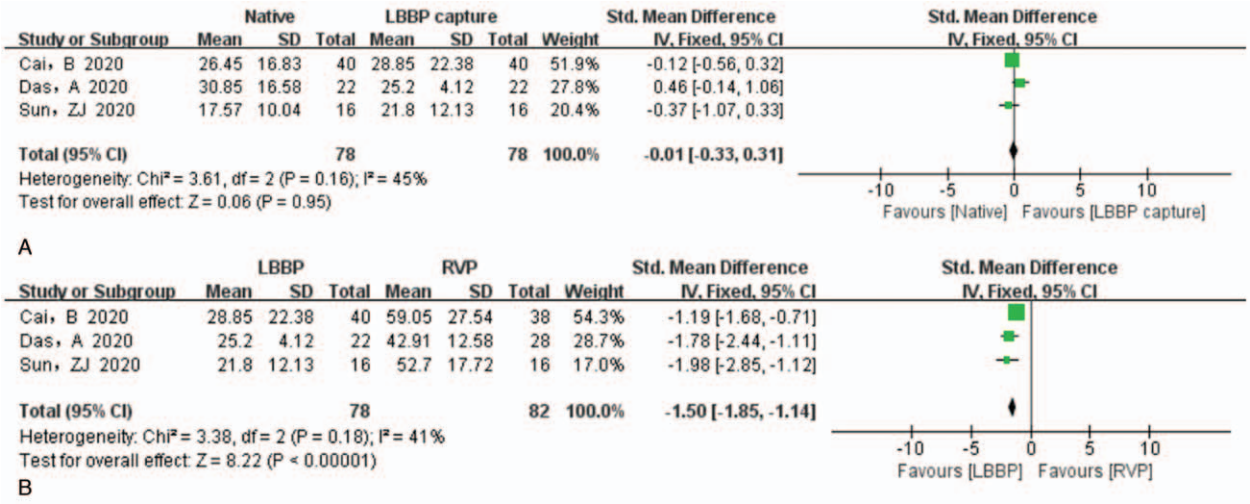

Figure 4. Forest plots of LV synchrony. (A) For native vs LBBP capture; (B) for LBBP vs RVP. LBBP = left bundle branch pacing, LV = left ventricular, RVP = right ventricular pacing.

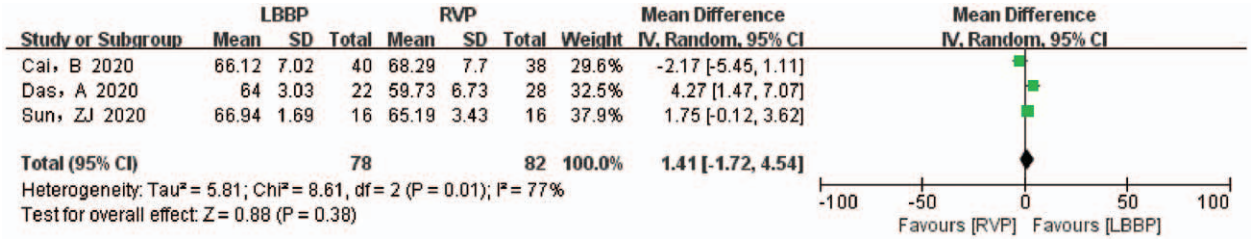

Figure 5. Forest plots of LVEF, for LBBP vs RVP. LBBP = left bundle branch pacing, LVEF = left ventricular ejection fraction, RVP = right ventricular pacing.

result was not appreciably altered. And pacing threshold was assessed at short-term follow-up (from 7 days to 6 months) in 4 studies[12,20–22] by a random-effect model, pacing threshold maintain stability in the LBBP group (WMD: 0.08; 95% CI: −0.09 to 0.25, I^2 = 92%, P = .36; Fig. 6B).

3.6.2. Ventricular impedance. Ventricular impedance was reported in 5 studies[12,13,21–23] and the heterogeneity was low (I^2 = 0%), taking a fixed-effect model. Patients receiving LBBP showed a higher ventricular impedance at implantation compared with the RVP group (WMD, 19.34; 95% CI 3.13–35.56; P = .02; Fig. 7A). However, ventricular impedance of the LBBP group in 3 studies,[12,21,22] at short-term follow-up was significantly lower than at implantation (WMD, 122.09; 95% CI 12.06–232.12, I^2 = 95%, P = .03; Fig. 7B), that was not different from RVP group (WMD, 11.78; 95% CI −24.48 to 48.04, I^2 = 58%, P = .52; Fig. 7C). Considering the high heterogeneity, random-effects model was used for these analyses. By sensitivity analysis by removing any individual study, the results did not change, indicating that the results were stable.

3.6.3. R-wave amplitude. Five studies[12,13,19,21,23] compared R-wave amplitude by a random-effect model. Compared with RVP patients, R-wave amplitude in LBBP patients had no different at implantation (WMD 0.04; 95% CI −1.12 to 1.19, I^2 = 59%, P = .95; Fig. 8), but no follow-up was recorded. The sensitivity analysis showed the results were stable by any single study.

3.7. Complications

Complications mainly referred to pocket infection and hematoma, lead perforation and lead dislodgement were reported in 5 studies.[12,13,21–23] There were no complications in 4 studies.[13,21–23] In Wang et al research[12], the LBBP group had 3 cases of the mild pocket hematoma, 1 septal lead perforation (1.6% vs 0%; P = .30), and 2 cases of the mild pocket hematoma was observed in the RVSP group within 1 month after procedure (4.9% vs 3.1%; P > .59). One case of lead dislodgement occurred 2 months and 4 months after implantation in the LBBP group, while one lead dislodgement

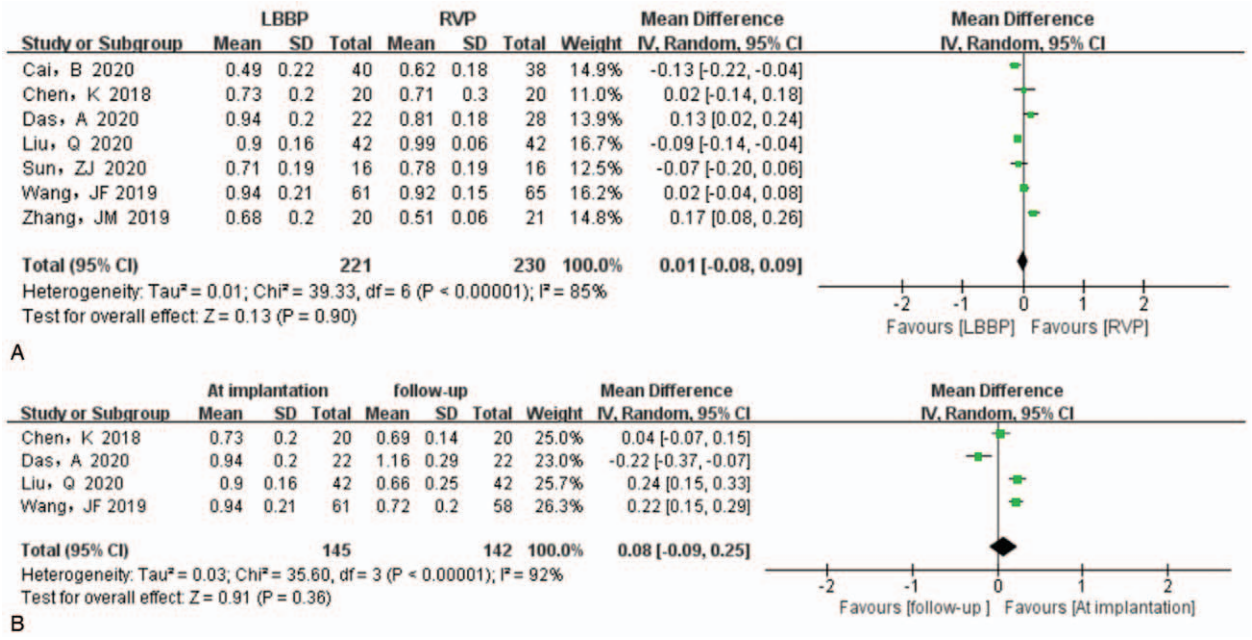

Figure 6. Forest plots of pacing threshold. (A) For LBBP vs RVP; (B) for at implantation vs follow-up in LBBP group. LBBP = left bundle branch pacing, RVP = right ventricular pacing.

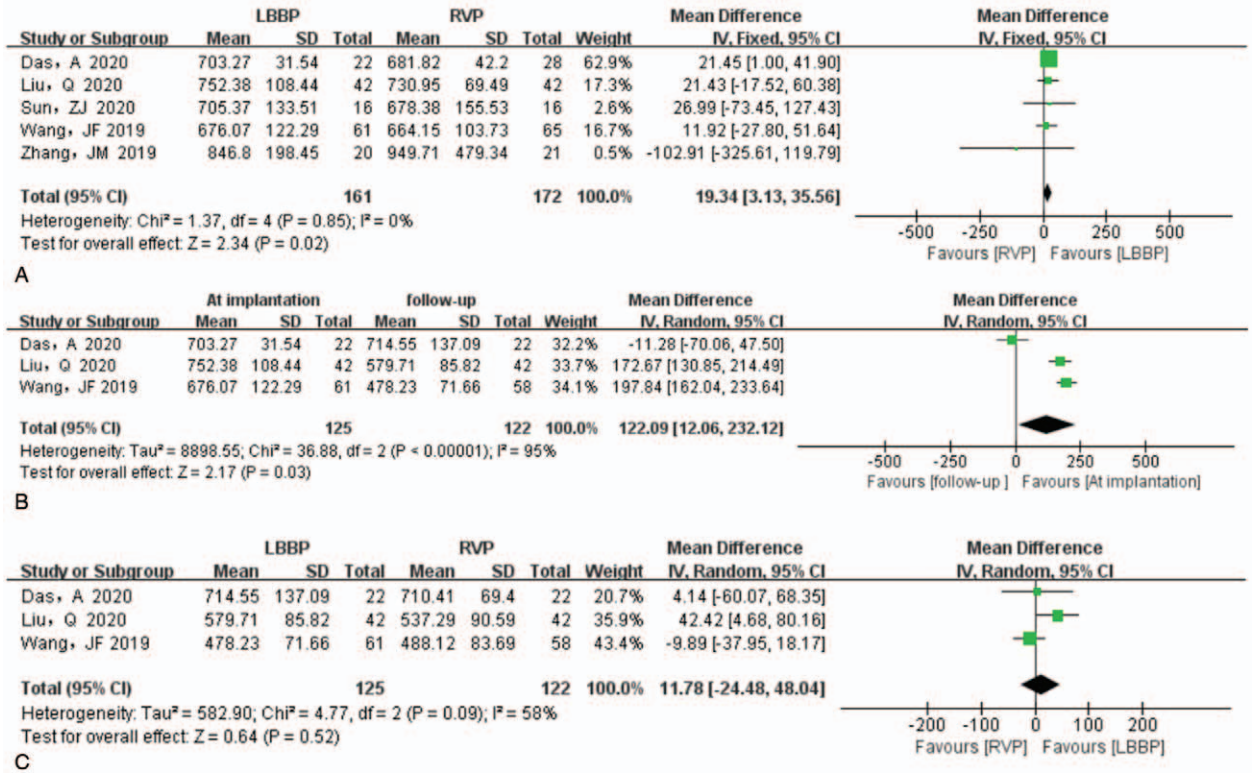

Figure 7. Forest plots of ventricular impedance. A) for LBBP vs RVP at implantation; B) for at implantation vs follow-up in LBBP group; C) for LBBP vs RVP at short follow-up. LBBP = left bundle branch pacing, RVP = right ventricular pacing.

occurred 2 months post-implant in RVSP group (1.5% vs 3.3%; $P > .52$).

3.8. Publication bias

We intended to investigate potential publication bias via the funnel plot. However, as we only had up to 7 studies in our analysis, the number was insufficient to reject the assumption of no funnel plot asymmetry. Thus, we did not perform a funnel plot.[24,25]

4. Discussion

This study represented the first systematic review and meta-analysis on the comparison between LBBP and RVP. The main findings were as follows: the paced QRSd in LBBP capture was no significant difference with the native-conduction mode, whereas it was obviously shorter than the QRSd induced by RVP; regarding of QRSd and Stim-LVAT, there were no statistically significant differences between the potential + and potential- subgroups; LV mechanical synchronization parameter of the LBBP capture was similar with the native-conduction mode, however was superior to that of the RVP group; neither LBBP capture mode nor RVP capture mode had significant change in ejection fraction during short term follow-up; LBBP showed stable low pacing threshold, high R wave amplitude and there was no significant difference compared to RVP. LBBP showed a higher ventricular impedance at implantation compared with the RVP group, but it was not different from RVP group at short-term follow-up; Complications of LBBP was low and similar with RVP.

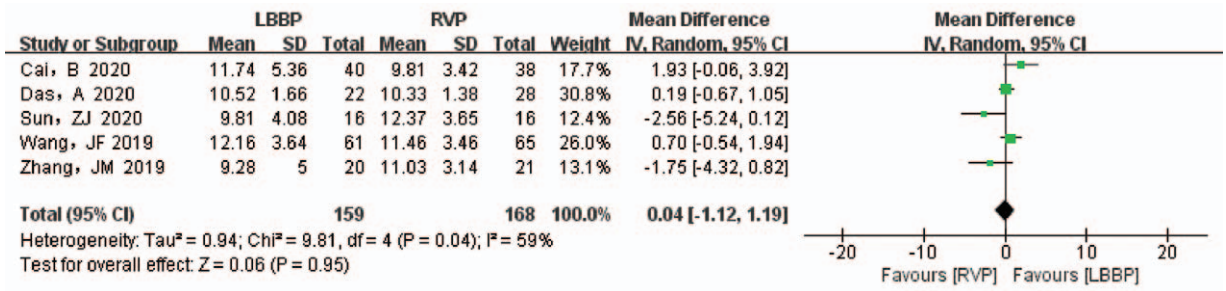

Figure 8. Forest plots of R wave amplitude, for LBBP vs RVP. LBBP = left bundle branch pacing, RVP = right ventricular pacing.

HBP as a physiological pacing utilizes the intrinsic His bundle-Purkinje conduction system that results in ventricular synchronized contraction, whereas LBBP can produce true conduction system pacing by bypassing pathological or disease-vulnerable region in the conduction system.[26] LV synchrony caused by HBP has been demonstrated, and some studies have even suggested that HBP may serve as the first-line treatment for patients with heart failure combined with LV asynchrony.[8,27,28] Meanwhile, recent researches showed that LV synchrony in the LBBP group was similar to that in HBP group,[17,29,30] and LBBP has also been shown to be effective in the treatment of heart failure combined with bundle branch block.[31] However, LBBP is easier to operate than HBP because of wide spread of fascicules of LBB in the subendocardium of the left side and limitation of His bundle.[32] Moreover, LBBP exhibited stable parameters of higher R-wave amplitudes and lower capture thresholds than those of HBP.[17] Importantly, LBBP can correct left bundle branch block (LBBB) and right bundle branch block at a low capture threshold.[20] But HBP required a high pacing output to correct LBBB,[10] which means the electrical current must penetrate the pathological region to reach normal left bundle branch for LBBB correction. And LBBP can theoretically perform cardiac resynchronization in patients blocked in His bundle.[26] Therefore, LBBP can effectively produce a better ventricular synchronization and may be superior to CRT based on biventricular pacing. Nonetheless, it is necessary to further verify safety and efficacy of LBBP by randomized clinical studies directly comparing HBP and LBBP with CRT in patients.

On the contrary, a good LV electrical and mechanical synchrony that is similar to that of native conduction. It is well known that the QRSd has been accepted as an indicator for the evaluation of electrical synchrony. Our analysis showed the paced QRSd and LV mechanical synchronization parameter measured by echocardiography in LBBP capture were similar with the native-conduction mode, which indicates LBBP can bring about synchronization of ventricular contraction. Inversely, compared with RVP group, LV electrical and mechanical synchronization was significantly better in LBBP group, for pacing from the RV causes an abnormal late activation of the LV free and lateral wall and consequent electromechanical dyssynchrony.[3] This also explains the clinical adverse events associated with RVP, such as heart failure, atrial fibrillation, and pacemaker cardiomyopathy. Interestingly, LBB potential can be recorded during the implantation procedure, an indication of direct LBBP, but not all LBBP can observe LBB potential. Studies showed that approximately 50% to 80% of implants can record LBB potential,[18,33] which was similar with our result of 64.7%. In Hou et al's study,[17] patients with LBBP with LBB potentials had shorter Stim-LVAT and better LV mechanical synchrony than those without potentials. However, our analysis found Stim-LVAT and paced QRSd in LBBP capture were irrelevant with whether the existence of LBB potentials. The mechanism may be that stimulation initially activates the LV septal sub-endocardium and then propagates to nearby conductive tissue or directly to the conduction system, so large sample size and randomized multicenter study with longer-term follow-up is needed for conclusive evidence. However, since pacing is intended to correct conduction disease or stimulate the bundle branch to produce rapid conduction with normal or near-normal electrocardiogram, it may not be necessary to record LBB potential. Consequently, surgical method of LBBP reported by Zhang et al[14] without the guidance of intracardiac electrograms proved to be effective.

Theoretically, LV function in patients with LBBP should be superior to RVP because of LV synchrony in LBBP group was significantly better than RVP group. However, no statistical difference existed in ejection fraction between the 2 groups during short-term follow-up in our meta-analysis. The result of one of our included studies showed that LBBP is associated with better LV function (higher LVEF 64.00 ± 3.03 vs 59.73 ± 6.73, $P = 0.01$) during 6 months' follow-up in comparison to RVP.[21] A major difference from other included studies was that up to 64% of patients combined with BBB, and the BBB was corrected in 84% of these patients in LBBP group. And the paced QRSd in LBBP capture was significant shorter than the baseline (112.27 ± 8.57 vs 131.64 ± 17.8),[21] indicating significant improvement in postoperative LV synchronization, so LVEF of LBBP group was increased compared with RVP. Moreover, more and more studies reported that patients with HF and BBB can benefit significantly from LBBP.[26,31,33] So there are 2 possible reasons for the result: one reason may be the small sample size and short follow-up time; LBBP mainly may improve LVEF of patients with HF combined with BBB, while LBBP and RVP have little effect on LVEF in patients with normal cardiac function and narrow QRSd during short-term follow-up.

The cathode ring of LBBP is also embedded in the myocardium as same as RVP. So, LBBP showed stable low pacing threshold and high R wave amplitude in our analysis, and a higher ventricular impedance at implantation compared with the RVP group, but it was not different from RVP group at short term follow-up. It may be that electrode tip of LBBP causes more myocardial injuries, then excessive myocardial edema in the early stage made the electrode impedance high at implantation. When the edema was reduced, the impedance gradually decreased and tended to be stable. Other studies also confirmed good pacing parameters for LBBP.[17,18,33] The complications of LBBP were low and no difference with RVP in our analysis. In one[12] of the studies we included, one lead perforation was observed in LBBP group mainly because of the rapid decline of impedance during the operation. So, it is necessary for us to timely monitor the change of electrode impedance to avoid acute or delayed ventricular septal perforation and ensure capture of the LBB. Except for this method, recent documents proposed several methods to monitor lead depth: fulcrum sign, sheath angiography, changes in the QRS notch in V1 lead, pacing from the ring electrode and observing fixation beats (the ectopic beats of qR/rsR' morphology in V1 lead).[34] In addition, myocardial damage deserves our attention in LBBP. The recent study[35] showed the number of attempts at lead position was an independent risk factor related to the myocardial damage, so excessive number of attempts should be avoided. It is worth noting that patients with intraventricular block, hypertrophic cardiomyopathy and ventricular septal infarction should not be treated with LBBP.

4.1. Limitation

This meta-analysis has some limitations. First, there were several indicators with high heterogeneity, but the sensitivity analysis indicated that it did not affect the reliability of the results. This may be attributed to different diagnosis of patients, multiple right ventricular pacing sites, and different operator experiences and methodological quality. The inconsistency of RVP location in the included studies may have caused some heterogeneity in the

results. Second, the small sample size of the included study may affect the stability of the result indicators, reduce the detection efficiency, and possibly lead to the bias of the study results. Third, the included studies were followed for a short period of time, with only 2 studies being followed for 6 months. Four, only 7 studies were included in our meta-analysis, and no randomized controlled trial were included. Thus, more well-designed and large-scale RCTs with longer-term follow-up are demanded to validate the results.

5. Conclusions

Our systematic review and meta-analysis confirmed that LBBP was a safe and effective method for bradycardia arrhythmias. Compared with RVP, LBBP markedly preserve ventricular electrical and mechanical synchrony. In addition, LBBP showed stable low pacing threshold, high R wave amplitude, and there was no significant difference compared to RVP. However, LBBP and RVP have little effect on LVEF in patients during short-term follow-up.

Acknowledgments

The authors thank the Science and Technology Department of Hunan Province in China (2018SK52104) for the support.

Author contributions

Xing Liu and Mingxing Wu conceived and designed research; Xing Liu, Wenbin Li, and Lei Wang collected data and conducted research; Xing Liu, Lei Wang, Shaohua Tian and Xiaolin Zhou analyzed and interpreted data; Xing Liu wrote the initial paper; Mingxing Wu revised the paper; Xing Liu had primary responsibility for final content. All authors read and approved the final manuscript.

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References

[1] Cicchitti V, Radico F, Bianco F, et al. Heart failure due to right ventricular apical pacing: the importance of flow patterns. Europace 2016;18:1679–88.
[2] Pastore G, Zanon F, Baracca E, et al. The risk of atrial fibrillation during right ventricular pacing. Europace 2016;18:353–8.
[3] Vijayaraman P, Huang W. Atrioventricular block at the distal His bundle: electrophysiological insights from left bundle branch pacing. HeartRhythm Case Rep 2019;5:233–6.
[4] Ponikowski P, Voors AA, Anker SD, 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.
[5] Daubert C, Behar N, Martins RP, et al. Avoiding non-responders to cardiac resynchronization therapy: a practical guide. Eur Heart J 2017; 38:1463–72.
[6] Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329–38.
[7] Kutyifa V, Stockburger M, Daubert JP, et al. PR interval identifies clinical response in patients with non-left bundle branch block: a Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy substudy. Circ Arrhythm Electrophysiol 2014;7:645–51.
[8] Sharma PS, Dandamudi G, Herweg B, 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.
[9] Zanon F, Ellenbogen KA, Dandamudi G, et al. Permanent His-bundle pacing: a systematic literature review and meta-analysis. Europace 2018;20:1819–26.
[10] Huang W, Su L, Wu S, et al. Long-term outcomes of His bundle pacing in patients with heart failure with left bundle branch block. Heart 2019; 105:137–43.
[11] Huang W, Chen X, Su L, et al. A beginner's guide to permanent left bundle branch pacing. Heart Rhythm 2019;16:1791–6.
[12] Wang J, Liang Y, Wang W, et al. Left bundle branch area pacing is superior to right ventricular septum pacing concerning depolarization-repolarization reserve. J Cardiovasc Electrophysiol 2020;31:313–22.
[13] Zhang J, Wang Z, Cheng L, et al. Immediate clinical outcomes of left bundle branch area pacing vs conventional right ventricular pacing. Clin Cardiol 2019;42:768–73.
[14] Zhang J, Wang Z, Zu L, et al. Simplifying physiological left bundle branch area pacing using a new nine-partition method. Can J Cardiol 2021;37:329–38.
[15] McGrath S, Zhao X, Steele R, et al. Estimating the sample mean and standard deviation from commonly reported quantiles in meta-analysis. Stat Methods Med Res 2020;962280219889080.
[16] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
[17] Hou X, Qian Z, Wang Y, et al. Feasibility and cardiac synchrony of permanent left bundle branch pacing through the interventricular septum. Europace 2019;21:1694–702.
[18] Li Y, Chen K, Dai Y, et al. Left bundle branch pacing for symptomatic bradycardia: Implant success rate, safety, and pacing characteristics. Heart Rhythm 2019;16:1758–65.
[19] Cai B, Huang X, Li L, et al. Evaluation of cardiac synchrony in left bundle branch pacing: Insights from echocardiographic research. J Cardiovasc Electrophysiol 2020;31:560–9.
[20] Chen K, Li Y, Dai Y, 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.
[21] Das A, Islam SS, Pathak SK, et al. Left bundle branch area. A new site for physiological pacing: a pilot study. Heart Vessels 2020;35:1563–72.
[22] Liu Q, Yang J, Bolun Z, et al. Comparison of cardiac function between left bundle branch pacing and right ventricular outflow tract septal pacing in the short-term: a registered controlled clinical trial. Int J Cardiol 2021;322:70–6.
[23] Sun Z, Di B, Gao H, et al. Assessment of ventricular mechanical synchronization after left bundle branch pacing using 2-D speckle tracking echocardiography. Clin Cardiol 2020;43:1562–72.
[24] Debray TPA, Moons KGM, Riley RD. Detecting small-study effects and funnel plot asymmetry in meta-analysis of survival data: a comparison of new and existing tests. Res Synth Methods 2018;9:41–50.
[25] Simmonds M. Quantifying the risk of error when interpreting funnel plots. Syst Rev 2015;4:24.
[26] Huang W, Su L, Wu S, 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;33:1736e1731-1736.e1733.
[27] Arnold AD, Shun-Shin MJ, Keene D, 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.
[28] Shan P, Su L, Zhou X, 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.
[29] Chan JYS, Huang WJ, Yan B. Non-invasive electrocardiographic imaging of His-bundle and peri-left bundle pacing in left bundle branch block. Europace 2019;21:837.

[30] Salden F, Luermans J, Westra SW, et al. Short-term hemodynamic and electrophysiological effects of cardiac resynchronization by left ventricular septal pacing. J Am Coll Cardiol 2020;75: 347–59.
[31] Zhang W, Huang J, Qi Y, 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.
[32] Anderson RH, Yanni J, Boyett MR, et al. The anatomy of the cardiac conduction system. Clin Anat 2009;22:99–113.
[33] Li X, Li H, Ma W, et al. Permanent left bundle branch area pacing for atrioventricular block: feasibility, safety, and acute effect. Heart Rhythm 2019;16:1766–73.
[34] Jastrzębski M, Kiełbasa G, Moskal P, 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.
[35] Wu Y, Chen Y, Chen M, et al. Quantification of acute myocardial damage secondary to implantation of electrodes for the left bundle branch area pacing. Rev Invest Clin 2020;[Online ahead of print].