Reverse of left ventricular remodeling in heart failure patients with left bundle branch area pacing: Systematic Review and Meta-Analysis

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Background: Left bundle branch area pacing (LBBAP) has recently become a promising option for the near-natural restoration of electrical activation. However, the clinical relevance of therapeutic effects in individuals with heart failure with reduced ejection fraction (HFrEF) and dyssynchrony remains unknown.

Methods: MEDLINE, EMBASE, and Cochrane databases were searched from inception until June 2022. Data from each study was combined using a random-effects model, the generic inverse variance method of DerSimonian and Laird, to calculate standard mean differences and pooled incidence ratio, with 95% confidence intervals (CI).

Results: A total of 772 HFrEF patients were analyzed from 15 observational studies per protocol. The success rate of LBBAP implantation was 94.8% (95% CI 89.9 to 99.6, I^2 = 79.4%), which was strongly correlated with shortening QRS duration after LBBAP implantation, with a mean difference of −48.10 msec (95% CI −60.16 to −36.05, I^2 = 96.7%). Over a period of 6–12 months of follow-up, pacing parameters were stable over time. There were significant improvements in left ventricular ejection fraction (LVEF), left ventricular end-systolic volume (LVESV), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-diastolic volume(LVEDV) with mean difference of 16.38%(95% CI 13.13 to 19.63 I^2 = 90.2 %), −46.23 mL(95% CI −63.17 to −29.29, I^2 = 86.82%), −7.21 mm(95% CI −9.71 to −4.71, I^2 = 84.6%), and −44.52 mL(95% CI −64.40 to −24.64, I^2 = 85.9 %), respectively**.**

Conclusions: LBBAP was associated with improvements in both cardiac function and electrical synchrony. The benefits of LBBAP in individuals with HFrEF and dyssynchrony should be further validated by randomized studies.

Keywords: left bundle branch area pacing, reverse left ventricular remodeling, heart failure, cardiac resynchronization therapy, pacing-induced cardiomyopathy

Abbreviation:

LBBAP; Left bundle branch area pacing

HFrEF; Heart failure with reduced ejection fraction

LVEF; Left ventricular ejection fraction

LVESV; Left ventricular end-systolic volume

LVEDD; left ventricular end-diastolic diameter

LVEDV; Left ventricular end-diastolic volume

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Introduction

Cardiac resynchronization therapy (CRT) is the first-line treatment for patients with systolic dysfunction heart failure (HF) and ventricular asynchrony **[1].** Biventricular pacing (BVP) substantially improves functional capacity and quality of life while reducing morbidity and mortality among patients. These health benefits are usually observed among heart failure with reduced ejection fraction (HFrEF) patients with left bundle branch block (LBBB) > 150 msec. However, BVP is hindered by cardiac venous anatomy and difficulty in LV lead positioning. Thus, up to 30% of patients are CRT non-responders **[1-3]**. Studies have demonstrated that HFrEF patients with bradycardia receive beneficial effects from left bundle branch area pacing (LBBAP), similar to reverse LV remodeling effects from CRT **[4,5]**. LBBAP can result in a relatively short QRS duration (QRSd), and rapid left ventricular activation with direct excitation distal to the LBBB site, thus improving clinical and echocardiographic findings **[6].**

As a result, the advantages of LBBAP, including favorable clinical outcomes, improved echocardiographic findings, and fewer complications, have attracted the attention of clinicians as a potential alternative to BVP **[7-21]**. However, the data to support these notions are not well established. Therefore, this systematic review and meta-analysis aimed to determine the benefits in patients with HFrEF who underwent LBBAP implantation.

Materials & Methods

Literature review and search strategy

A systematic literature search was conducted, including studies up until June 2022 in the databases MEDLINE (via PubMed), EMBASE (via Scopus), and the Cochrane Database of Systematic Reviews. We aimed to identify studies that analyzed how individuals with HFrEF, particularly pacing-induced cardiomyopathy (PICM), responded to LBBAP

implantation. Two investigators (N.S. and R.C.) separately compiled the systematic literature review using a search strategy that included the terms “left bundle branch pacing” and (“heart failure” or “pacing-induced cardiomyopathy”) (**Supplementary 1**). There were no language restrictions. Reference lists of recognized studies were manually searched for relevant research as well. This systematic review and meta-analysis followed the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) standards and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Selection criteria

To qualify for analysis, studies must include randomized controlled trials, cross-sectional studies, case-control studies, or cohort studies evaluating the outcomes of LBBAP implantation in HFrEF patients. Case reports and case series were excluded from the analysis. The qualified studies must have statistical outcomes in the form of mean ± standard deviation (SD) or median (interquartile range Q1–Q3) with p-values to determine the level of significance in the statistical hypothesis test. The inclusion of studies was not limited by sample size or ethnicity of the population. Any disagreements concerning study choices were settled through a collaborative discussion between the two investigators (R.C. and N.S.). The Newcastle-Ottawa quality assessment scale and the modified Newcastle-Ottawa scale were used to assess the quality of study for case-control studies and the result of interest for cohort and cross-sectional studies (Tables 1–2) **[22]**. The evaluation was conducted in three domains: four items of study group selection (S), two items of group comparability (C), and three items of exposure and outcome (O). The bias assessment results were displayed as a number, with the S, C, and O domains receiving a maximum of 4, 2, and 3, respectively.

Data abstraction

Using a structured data record form, the following information was collected from each study:

(1) Basic information of literature: title, year of the study, name of the first author, publication year, and the country where the study was conducted

(2) Patient baseline characteristics, demographic data, and underlying diseases

(3) Outcomes: the success rate of LBBAP implantations, QRSd, echocardiographic findings including left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), New York Heart Association (NYHA) classification, B-type natriuretic peptide (BNP) level, and pacing parameters (LBB capture threshold, lead impedance, and R-wave amplitude)

Statistical analysis

Data was analyzed using the R program and STATA version 15 (College Station, TX). Previously proposed and widely used algorithms described by former investigators were used to convert median and quartile into means and SDs, if necessary. DerSimonian and Laird's generic inverse variance technique was used to calculate adjusted point estimates from each study, which assigned a weight to each study based on its variance **[23]**. The Cochran's Q test was used to examine and quantify variation in prevalence across studies. The DerSimonian and Laird technique was used if there was heterogeneity ($P < 0.1$ or $I2 > 25\%$); otherwise, an inverse variance fixed-effect model was used **[24]**. Sensitivity analysis was performed to test the study robustness, by "leave-one-out method". Afterward, meta-regression and subgroup analysis were performed to identify sources of heterogeneity, such as clinical and methodological variations. The Egger test was used to determine whether there is publication bias **[25]**.

Results

After filtering out duplicate studies, our search strategy yielded 493 articles. After screening the abstracts, 458 studies that were case reports, case series, review articles, in vitro studies, animal studies, or interventional studies were omitted. The full text of 35 studies was reviewed. The remaining 20 studies were later excluded due to lack of a target population or failure to report outcomes of interest. As a result, the final analysis included 15 observational cohort studies **[7-21]** with 772 individuals with HFrEF who underwent LBBAP implantation. The included articles were classified into 2 categories: patients with PICM (4 articles, 62 patients) **[7-10]** and patients without PICM (11 articles, 710 patients) **[11-21]**.

Figure 1 shows the literature review's inclusion and exclusion process. **Tables 1, and 2** show the characteristics and quality assessment of the included studies.

Definition of patients with PICM

According to the literature review **[7-10]** (**Table 1**), the diagnosis of PICM is made in the presence of a ≥ 10% decrease in LVEF after chronic RV pacing with resultant LVEF ≤ 50% without other causes of cardiomyopathy.

The success rate of a procedure

The success rate of LBBAP implantation in patients with HFrEF was evaluated in nine studies. The pooled success rate of individuals was 94.8% (95% CI 89.9 to 99.6, I^2 = 79.4%).

Effects of LBBAP on QRSd

The pre- and post-procedural effects of LBBAP on QRSd were compared in 14 studies. LBBAP was significantly associated with shortened QRSd, with a mean difference of -48.10 msec (95% CI -60.16 to -36.05, I^2 = 96.7%) compared with the baseline of the patients. Notably, there were no

differences among PICM versus non-PICM patients (-58.67 vs. -45.49, p = 0.10) nor in the Chinese versus non-Chinese population (-53.58 vs. -34.94, p = 0.14).

To assess overall study robustness given the heterogeneity in different populations, sensitivity analysis was performed, by leave-one-out method. According to our analysis, the degree of QRS changes did not substantially alter after each study was excluded as shown in **Supplementary 1**.

Effects of LBBAP on pacing parameters

Over a period of 6 – 12 months of follow-up, pacing parameters were stable over time, including pacing threshold (mean difference: 0.01 volts [95% CI -0.05 to 0.07, I^2 = 81.5%]), impedance (mean difference: -119.52 Ω [95% CI −163.44 to -75.60, I^2 = 83.0%]), and sensing (mean difference: 1.72 mV [95% CI 0.93 to 2.52, I^2 = 21.2%]).

Associations between LBBAP and echocardiographic parameters

There was a statistically significant increase in LVEF after LBBAP implantation. Mean LVEF difference is 16.38% (95% CI 13.13 to 19.63 I^2 = 90.2 %) after the procedure compared with the patient's baseline, with a marginal difference between the PICM and non-PICM group (12.77% vs. 17.60%, p = 0.07) but not between Chinese and non-Chinese populations (17.16% vs. 14.97%, p = 0.54). Moreover, significant improvements were also seen in LVESV, LVEDD, LVEDV and LVESD with respective mean differences before and after treatment of −46.23 mL (95% CI -63.17 to -29.29, I^2= 86.82%), -7.21 mm (95% CI -9.71 to -4.71, I^2 = 84.6%), -44.52 mL (95% CI -64.40 to -24.64, I^2 = 85.9 %) and -12.15 mm (95% CI -14.87 to -9.43, I^2 = 38.64%).

Treatment outcomes of the LBBAP

Six studies assessed the effects of LBBAP on NT-pro BNP levels between pre- and post-procedural treatment. LBBAP significantly lowered NT-pro BNP levels, with mean difference of -674.89 pg/ml (95% CI -1103.72 to -246.06, I^2 = 93.8%). Furthermore, 13 studies assessed the effects of LBBAP on NYHA classification between pre- and post-procedural treatment over 6 – 12 months of follow-up. LBBAP was also associated with a significant improvement of NYHA classification, with a mean difference of -1.25 (95% CI -1.46 to -1.04, I^2 = 87.9%), with no differences between the Chinese and non-Chinese population (-1.27 vs. -1.24, p= 0.90) and the PICM and non-PICM patients (-1.02 vs. -1.31, p = 0.28).

Evaluation of publication bias

Due to the limited amount of data, the power of the test was too low to distinguish between chance and actual asymmetry. Hence, a funnel plot was not produced **[26]**. For the correlations of LBBAP implantation with outcomes, Egger's regression asymmetry revealed no publication bias. **Table 3** shows these results.

Discussions

Our study demonstrated that LV systolic function was significantly improved after LBBAP implantation in patients with HFrEF. Specifically, LBBAP implantation resulted in a greater reduction in paced QRS and improved echocardiographic findings (i.e., LVEF, LVESV, LVESD, LVEDD, and LVEDV). Furthermore, LBBAP implantation significantly improved NYHA classifications and NT-pro BNP levels. Regarding pacing durability, pacing parameters were stable over time. The results were demonstrated in **Supplementary 2**.

The decline in LV systolic function is multifactorial. In clinical practice, this is generally categorized into device-related LV systolic function and others. For device-related LV systolic dysfunction or PICM, chronic RV pacing (RVP) can cause worsening of LV systolic function. RVP can

cause several adverse events, including cardiac contraction asynchrony, which is linked to PICM and higher mortality. On the other hand, BVP has the potential to reverse LV remodeling and can improve clinical outcomes in patients with PICM. However, BVP is a non-physiological activation that is limited by its reliance on myocardial cell conduction, thus, there is a significant proportion of CRT non-responders, at around 30% to 40%. Barba-Pichardo et al. found that HBP could correct LBBB and improve clinical HF symptoms and outcomes in patients with unsuccessful LV lead replacement. Therefore, HBP has been explored for several years as an alternative to CRT **[27]**, and various studies comparing the efficacy and results of HBP and BVP have been discussed **[28,29]**. These studies found that HBP is superior in correcting dyssynchrony, but the pacing output of HBP was substantially high and unstable during long-term follow-up. To overcome the increasing trend of pacing thresholds by HBP, LBBAP was developed as a new pacing strategy to correct PICM after RVP. This works by bypassing the blocking zone and delivering the electrophysiological signal inside the LV endocardium area, resulting in improving dyssynchrony/LV function, narrower QRSd, LBBB correction, and a low and consistent pacing output **[30,31]**.

Our results were consistent with those of previous meta-analyses, which reported that patients with LBBAP had a greater reduction in paced QRS (mean difference: 27.91 msec; 95% CI, 22.33 to 33.50), as well as a greater improvement in NYHA class (mean difference: 0.59; 95% CI, 0.28 to 0.90) and LVEF (mean difference: 6.77 %; 95% CI, 3.84 to 9.71) **[32]**. Nevertheless, we included 14 papers in our updated systematic review and meta-analysis, which studied at the clinical outcomes and efficacy of LBBAP in HFrEF. Furthermore, this is the first study to compare the PICM and non-PICM groups. To our knowledge, this is the single largest and most comprehensive meta-analysis on LBBAP for CRT to date.

LBBAP caused a significant narrowing in QRSd, which is an important indicator of electrical conduction disturbance correction, according to our findings. It is also the most relevant measure of the influence of CRT on electromechanical resynchronization. High-

output unipolar pacing, according to Kailun et al., overcomes the resistivity of longitudinal dissociation fibrous sheaths and captures RBB by overcoming the obstruction via transverse connectivity **[33].** Moreover, Ponnusamy et al. **[17]** discovered that LBBAP was linked to an initial drop in T_{peak}-T_{end} duration and corrected QT interval relative to baseline, followed by a further decrease after memory T-wave resolution. It was also found that Tpeak-Tend/QTc ratio, a better indicator of arrhythmogenesis, reduced from 0.22 ± 0.02 to 0.17 ± 0.01 immediately after LBBAP. This eventually reduced to 0.16 ± 0.01 after 6 weeks, implying that there may be a secondary benefit of reduced arrhythmic risk. T-wave memory impairments were observed in all patients shortly after LBBAP, which disappeared after 6 weeks.

Interestingly, no statistically significant differences were found in QRSd shortening, pacing parameters, and NYHA class improvements among PICM versus non-PICM groups. Furthermore, we aimed to explore the impact of Chinese outcomes due to their recognition as a pioneer of the LBBAP procedure, but no racial difference was demonstrated in our meta-analysis. Aside from the clinical benefits and electrical synchrony, pacing parameters were also important in pacing treatments, such as pacing threshold and impedance. The pacing thresholds/impedances of the LBBAP group remained relatively stable at 6–12 months of follow-up.

This meta-analysis has several noticeable limitations to be mentioned. First, majority of the studies included are prospective and retrospective observational studies, meaning that the value of the meta-analysis is limited. Therefore, a causal association between improved clinical and echocardiographic outcomes after LBBAP implantation cannot be concluded. Second, only a limited number of studies and patients were included. As a result, the data may not be applicable to a broad range of populations, and additional research may be required to support these findings. Finally, there was a discrepancy in the definition of QRSd after completion of LBBAP implantation, which represents the correction of electrical

dyssynchrony. Nonetheless, this study can add value and broaden our perspective on this novel technique.

Conclusion

In this meta-analysis, LBBAP improved clinical and echocardiographic parameters in HFrEF with dyssynchrony, implying that LBBAP has a role in reverse LV remodeling. Further well-designed studies and randomized controlled trials on LBBAP in HF patients are required to confirm our findings.

Authors' Contribution: NS, RC, NP, AH, LN, WC and KJ designed and conceptualized the study design. NS conducted a systematic search. NS and RC performed abstract screening and full-article review. NS and RC extracted the data and performed the quality assessment. NS, RC, TP and WS drafted the initial manuscript. NT, RC and WS created tables and figures. RC and NP analyzed and interpreted the data. RC, NP, AH, LN, WC and KJ critically reviewed the manuscript. All authors have read and approved the final manuscript.

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Conflict of interest statement

The authors declare no conflict of interest.

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Table 1 Characteristics of HFrEF with PICM studies included in the meta-analysis.

Author	**Zhiyong al.**	**Yang ye et al.**	**Leonard et al.**	**Huacheng et al.**
Year	2020	2021	2022	2021
Country	China	China	The Netherlands	China
Study design	single center prospective cohort study	multicenter retrospective cohort study	single center prospective cohort study	single center prospective cohort study
Population	PICM patients with symptomatic HF	PICM patients with pacing percentage <40% and infranodal AV block	PICM patients who upgraded to LBBP	PICM patients with successful LBBP pacing operation
Total number	13	19	20	10
Mean age (years) ± SD	75.8 ±6.8	70.2 ± 8.6	77 ± 10	70.8 ± 7.9
Male sex (%)	9 (69.2)	11 (57.9)	14 (70)	5 (50)
CAD (n, (%))	3 (23.1)	1 (5.3)	10 (50)	0
HT (n, (%))	8 (61.5)	6 (31.6)	14 (70)	7 (70)
DM (n, (%))	1 (7.7)	*	2 (10)	1 (10)
AF (n, (%))	6 (46.2)	2 (10.5)	11 (55)	5 (50)
Duration of ventricular pacing (months)	128.4 ± 58.8	75.5 ± 33.3	45.6 (18.9-92.4)	82.76 ± 45.21
Quality assessment (Newcastle-Ottawa scale)	S4, C1, O2	S4,C1, O2	S3, C1, O2	S3, C1, O2

*; data not available

PICM; Pacing-Induced Cardiomyopathy, HF; Heart failure, LBBB; Left bundle branch block, LBBP; Left bundle branch pacing, AV; Atrioventricular, LVEF; Left ventricular ejection fraction, CAD; Coronary artery disease, HT; Hypertension, DM; Diabetes Mellitus, AF; Atrial Fibrillation

Table 2 Characteristics of HFrEF studies included in the meta-analysis.

Author	Weiwei Zhang	Huang	Chen	Yuqiu Li	Xiaofei Li	Vijayaraman	Ponnusamy	Shengjie Wu	Jincun Guo	Yao Wang	Pugazhendhi Vijayaraman
Year	2019	2020	2022	2020	2020	2021	2021	2021	2020	2020	2022
Country	China	China	China	China	China	International	International	China	China	China	International
Study design	single center prospective cohort study	multi center prospective cohort study	multi center prospective cohort study	single center prospective cohort study	multi center prospective cohort study	multi center prospective cohort study	multi center prospective cohort study	single center prospective cohort study	single center prospective cohort study	single center prospective cohort study	multicenter retrospective cohort study
Population	Symptomatic HF patients with LVEF ≤ 40 with LBBB	LBBB patients with non-ischemic cardiomyopathy and HF symptoms	LBBB patients with symptomatic HF	LBBP patients with symptomatic HF	LBBP patients with symptomatic HF	LBBP patients with LVEF <50 %, and indication for pacing	patients undergone CRT with criteria for LIC	LBBB patients with symptomatic HF	LBBB patients with symptomatic HF and successful CRT	CRT indicated patients	RBBB with HF, with indication for CRT
Total nu	11	63	49	25	37	325	13	32	24	10	121

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Mean age (years) ± SD	67.36 ± 13.73	67.8 ± 11.1	67.14 ± 8.88	59.3 ± 12.5	56.8 ± 10.1	71 ± 12	63.2 ± 16.4	67.2 ± 13	66.1 ± 9.7	64.80 ± 7.25	74 ± 12
Male sex (%)	6 (54.55)	33 (52.4)	24 (49.98)	13 (52)	22 (59.5)	212 (65)	4 (30.8)	14 (43.8)	9 (42.9)	9 (90)	91 (75)
CAD (n, (%))	2 (18.18)	13 (20.6)	*	4 (16)	7 (18.9)	161 (50)	3 (23)	1 (3.1)	2 (9.5)	1 (10)	69 (57)
HT (n, (%))	*	33 (52.4)	14 (28.57)	*	10 (27.0)	224 (69)	8 (62)	16 (50.0)	9 (42.9)	*	91 (75)
DM (n, (%))	*	16 (25.4)	12 (24.49)	*	6 (16.2)	113 (35)	5 (38)	12 (37.5)	8 (38.1)	*	44 (36)
AF (n, (%))	1 (9.09)	18 (28.5)	4 (8.16)	7 (28)	7 (18.9)	184 (57)	0	7 (21.9)	3 (14.3)	0	50 (41)
Quality assesment (Newcastle-	S3, C0, O3	S4, C1, O2	S3, C1, O1	S3, C1, O2	S4, C1, O3	S3, C1, O3	S4, C1, O3	S4, C1, O3	S4, C1, O3	S3, C1, O3	S4, C1, O3

Ottawa scale)

*; data not available

HF; Heart failure, LBBB; Left bundle branch block, LBBP; Left bundle branch pacing, LVEF; Left ventricular ejection fraction, CRT; Cardiac resynchronization therapy, LIC; Left Bundle Branch Block-Induced Cardiomyopathy, CAD; Coronary artery disease, HT; Hypertension, DM; Diabetes Mellitus, AF; Atrial Fibrillation

Table 3 Egger's regression asymmetry test with p-value for the associations of LBBAP and clinical outcomes.

Egger's test	P-value
Success rate	0.8410
QRS Duration	0.1342
LVEF	0.8757
LVESV	0.0445
LVESD	0.5063
LVEDV	0.0053
LEVDD	0.2446
Pacing threshold	0.7062
R-wave amplitude	0.2452
Lead impedance	0.4020
NYHA Classification	0.7071
NT-ProBNP	0.0013

(LVEF; Left ventricular ejection fraction, LVESV; Left ventricular end systolic volume, LVESV; Left ventricular end systolic diameter, LVEDV; Left ventricular end diastolic volume, LVEDV; Left ventricular end diastolic diameter, NYHA; New York Heart Association)

Figure legend

Figure 1 Flow diagram indicating the number of articles considered for inclusion and number of articles excluded.