

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

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Abstract

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 & Results:** 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). 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.

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

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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 func-

tional capacity and quality of life and reduces morbidity and mortality among patients with heart failure with reduced ejection fraction (HFrEF) with left bundle branch block (LBBB) > 150 msec. However, BVP is hindered by cardiac venous anatomy and difficulty in LV lead positioning, and thus, up to 30% of patients are CRT non-responders [1-3]. Several studies have shown that left bundle branch area pacing (LBBAP), which is reverse LV remodeling in patients with HFrEF indicated for CRT, is practical in patients with HF and bradycardia [4,5]. LBBAP can lead to a relatively narrow QRS duration (QRSd) and rapid left ventricular activation with direct excitation distal to the LBBB site, thus improving clinical and echocardiographic findings [6].

Thus, the benefits of LBBAP, such as improvement in clinical and echocardiographic findings and fewer complications, have gained interest as a potential alternative to BVP [7-21]. However, the data to support these notions remain controversial. Accordingly, 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 May 2021 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 study. The qualified studies must have statistical outcomes in the form of mean \pm 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. 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 dia-

meter (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. 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 $I^2 > 25\%$); otherwise, an inverse variance fixed-effect model was used [24]. 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 eliminated from the study. 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, $p = 0.14$).

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 msec [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. There was a mean LVEF difference of 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 versus 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 1**.

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) causes worsening of LV systolic function. Initially, RVP has been indicated for severe bradyarrhythmia resulting from complete heart block, but nowadays, there are more indications for RVP implantation in the general population. This pacing causes 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, this is a non-physiological activation that is limited by its reliance on myocardial cell conduction, and 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. Thus, 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 conducting electrical cardiac resynchronization, 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 undergoing RVP. This works by bypassing the blocking zone and delivering the electrophysiological signal inside the LV endocardium area, resulting in reverse LV function, narrow 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.

According to our findings, LBBAP caused a significant narrowing in QRSd, which is an important indicator of electrical conduction disturbance correction and is now 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 $T_{\text{peak-Tend}}$ duration and corrected QT interval relative to baseline, followed by a further decrease after memory T-wave resolution. It was also found that $T_{\text{peak-Tend}}/QTc$ 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, but this 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 noteworthy limitations. First, majority of the studies included are prospective and retrospective observational studies, meaning that 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, additional studies 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.

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.

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Conflict of interest statement

The authors declare no conflict of interest.

Figure legend

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

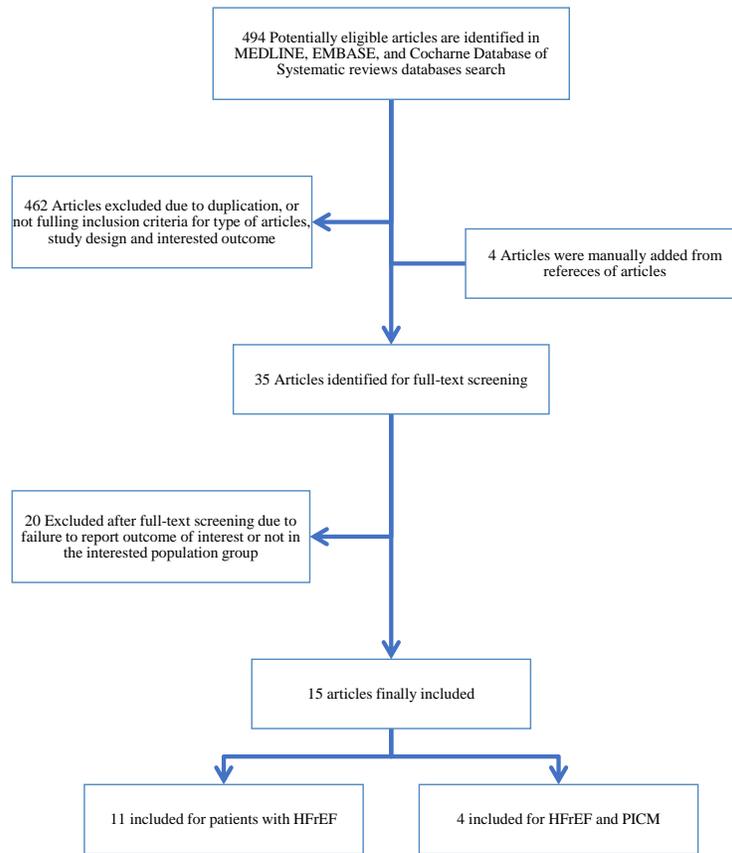


Figure 1 Flow diagram indicating the number of articles considered for inclusion and number of articles excluded.

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Tables.docx available at <https://authorea.com/users/489239/articles/573039-reverse-left-ventricular-remodeling-with-left-bundle-branch-area-pacing-in-heart-failure-patients-with-dyssynchrony-systematic-review-and-meta-analysis>