Left bundle branch area pacing in mildly reduced heart failure: A systematic literature review and meta-analysis

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Abstract

Background: Although the beneficial effects of cardiac resynchronization therapy (CRT) in heart failure (HF) are fully established in HF with left ventricular ejection fraction (LVEF) ≤35%, CRT strategy for HF with mildly reduced ejection fraction (HFmrEF) is controversial. Left bundle branch area pacing (LBBAP) is an emerging pacing modality and an alternative option to CRT, and the efficacy and safety are promising so far. The aim of this analysis was to perform a systematic review of the literature and meta-analysis on impact of LBBAP strategy in HFmrEF, with LVEF between 35% and 50%. Methods: PubMed, Embase, and Cochrane Library were searched for full-text articles on LBBAP from inception to July 17, 2022. The outcomes of interest were QRS duration, and LVEF at baseline and at follow-up in mid-range HF. Data were extracted and summarized. A random-effect model incorporating the potential heterogeneity was used to synthesize the results. Results: Out of 1065 articles, 8 met the inclusion criteria for 211 mid-range HF patients with an implant LBBAP across the 16 centers. The average implant success rate with lumenless pacing lead use was 91.3%, and 19 complications were reported among all 211 enrolled patients. During the average follow-up of 9.1 months, average LVEF were 39.8% at baseline and 50.5% at follow-up (MD: 10.90%, 95% CI: 6.56 - 15.23 P < 0.01). Average QRS duration were 152.6ms at baseline and 119.3ms at follow-up (MD: -34.51ms, 95% CI: -60.00 to -9.02, P < 0.01). Conclusion: LBBAP could significantly reduce QRS duration and improve systolic function in patient with LVEF between 35 and 50%. Application of LBBAP as a CRT strategy for heart failure with mildly reduced ejection fraction may be a viable option.

1. Introduction

The advantageous effect of cardiac resynchronization therapy (CRT) are well known in heart failure (HF) patients with reduced left ventricular ejection fraction (LVEF) and prolonged QRS duration.¹⁻³ Current global guidelines suggest CRT for class I or IIA indications in patients with LVEF ≤35%, and symptomatic HF despite receiving optimal drug therapy.⁴⁻⁶ However, an LVEF cut-off of ≥35% was determined by the patient enrollment criteria in major CRT trials, and of note, was adopted from cut-off values in prior major implantable cardiac defibrillator trials, rather than from a prospective risk-benefit analyses of CRT for all LVEF ranges.

Although resynchronization therapy for HF patients with LVEF ≥35% is controversial and has not been clearly established, HF with LVEF >35% shows disease features similar to LVEF <35%, and treatment patterns are similar.⁷⁻⁸ Additionally, there are reports that long-term clinical outcomes were poor when HF with mildly reduced ejection fraction (HFmrEF) was accompanied by left bundle branch block (LBBB) versus without LBBB.⁹ Moreover, in a retrospective analysis of the PROSPECT trial database, CRT demonstrated significant clinical benefit among patients with an LVEF >35%.¹⁰ The BLOCK-HF trial proved that CRT provided clinical benefit over right ventricular pacing in patients with LVEF ≥50% and atrioventricular
block who require ventricular pacing, and almost 70% (483/691) of the study population had an LVEF of 36–50%.

Conduction system pacing that directly activates the specialized conduction system was developed, and left bundle branch area pacing (LBBAP)—which overcomes the limitations of the previously used His bundle pacing (HBP)—is emerging and widely used. Furthermore, the effectiveness and safety of LBBAP in patients with HF has also been reported. To date, LBBAP has been used as an alternative to CRT in indicated patients, as well as a first option for patients indicated for CRT or pacemaker implantation. LBBAP is more simple, convenient, and cheaper than biventricular CRT; therefore, there is increasing clinical interest in adopting wider LVEF ranges for LBBAP-CRT among patients with HF and a long QRS duration, especially in patients with an LVEF of 36–50%. Therefore, this study aimed to conduct a systematic review of the literature and meta-analysis on the impact of the LBBAP strategy in patients with HFmrEF with an LVEF between 35% and 50%.

2. Methods

2.1 Data sources and searches

This systematic review and meta-analysis were carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Searches were independently performed by two investigators (G.Y. and T.K.) who searched Embase, Medline (PubMed), and Cochrane’s Library databases for related articles, with the keywords: “left bundle branch pacing” OR “left bundle branch area pacing.” At the same time, references of the relevant original and review articles were manually sorted to undergo a comprehensive search. The search was restricted to research in humans published in English, and was completed on July 17, 2022.

2.2 Study selection and data extraction

Titles and abstracts were retrieved from articles searched using the keywords “left bundle branch pacing” or “left bundle branch area pacing.” Studies were included if the article was in English and met the following criteria: patients aged >18 years; included patients with an LVEF from 35–50%; LVEF or QRS duration follow-up was performed after the procedure; and for LBBAP CRT, both patients with pacing indications (de novo or upgrade), and with HF without pacing indications (de novo CRT), were included. Among studies satisfying the above criteria, a pooled analysis of patients with a baseline LVEF of 35–50% was used. Editorials, review articles, case reports/letters, and abstracts were excluded. The quality of the literature was evaluated by the above two researchers using the Newcastle-Ottawa scale criteria.

2.3 Statistical analyses

To evaluate the change in LVEF and QRS duration over time, means, standard deviations, and sample sizes were extracted from articles to estimate the overall average values and confidence intervals (CIs). Statistical heterogeneity was conducted by calculating Higgins $I^2$; $I^2 >50\%$ was considered to indicate significant heterogeneity. After confirming heterogeneity, we used a random effects model because the populations included in the individual studies were from different populations. Potential publication bias was assessed by visual inspection of the funnel plot and the Egger regression asymmetry test. If the P for bias was >0.05, it was judged that there was no publication bias. All tests with P-values <0.05 were considered to be statistically significant. Statistical analyses were performed using R programming version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1 Studies selection and evaluation

In total, 694 articles were retrieved after excluding duplicates. The title and abstract of the articles were screened, and 566 were excluded due to being editorials/review articles, case reports/letters, having no relevant outcome, and not being in English. The remaining 128 articles underwent full-text review, and 120
were excluded for not meeting the inclusion criteria; finally, eight studies were retrieved (Figure 1 and Table 1).

The eight articles included five single-arm studies, and three comparative studies, published between 2020 and 2022. After pooled analysis, the total population included 211 patients with HF and an LVEF of 35–50%, who underwent LBBAP at one of 16 centers in seven countries. The average age was 65.1 years (n=211; 95% CI: 58.4–71.8), and 52.4% (n= 211; 95% CI: 24.2–80.6) of patients were male. The average baseline QRS duration and LVEF were 152 ms (n=2; 95% CI: 133–172) and 40% (n=207; 95% CI: 38–41), respectively. The average follow-up period was 9.1 ± 3.8 months. Regarding quality assessment, the Newcastle-Ottawa scale criteria was used to evaluate the quality of observational studies (presented in Table 2).

3.2 Definition of LBBAP

The definition of LBBAP was described in seven studies and omitted in one. Confirmation of LBBAP was made by comprehensively reviewing the following findings: 1) the only criterion used in all seven studies was paced QRS morphology, presented with a right bundle branch block morphology pattern in lead V1; 2) abrupt shortening of Stim-LVAT (stimulus to peak of the R wave) in leads V5 and V6 was used in four studies; 3) observed left bundle branch potential in pacing leads was used in four studies; and 4) demonstration of the transition from nonselective LBBP to selective LBBP was used in two studies. Only one study used contrast to ensure the location of the lead in the interventricular septum.

3.3 Changes in QRS duration and left ventricular systolic function

Five studies presented both the baseline and follow-up QRS durations, with means and standard deviations. Pooled analysis with a random effects model showed that LBBAP was related with a significantly reduced QRS duration (MD: -34.51 ms, 95% CI: -60.00– -9.02; P<0.01, I²=92%; Figure 2A); the duration decreased from 152.6 ± 21.8 ms (n=42, 95% CI: 133.48–171.62 ms) at baseline, to 119.3 ± 10.9 ms (n=42, 95% CI: 109.75–128.85 ms) after LBBAP.

Seven studies presented both preimplant and postimplant LVEF values, with means and standard deviations (Table 3). The average LVEF among the seven studies was 39.8% ± 1.8% at baseline (n=207), and 50.5% ± 3.9% at follow-up (n=132). During the average follow-up of 9.1 ± 3.8 months, LVEF significantly improved (MD: 10.90%, 95% CI: 6.56–15.23; P<0.01, I²=87%; Figure 2B). Five studies included patients with HF with reduced ejection fraction (HFrEF). When HFrEF and HFmrEF were compared, the estimated increase was 59.3% for HFrEF ([average LVEF] baseline, 28.1 ± 1.1%; follow-up, 45.6 ± 7.9%) and 27.6% for HFmrEF ([average LVEF] baseline, 39.8 ± 1.8%; follow-up, 50.5% ± 3.9%; Figure 3). Only one study compared LVEF changes in HFmrEF and HF with preserved ejection fraction; the estimated increase was 19.4% for HFmrEF (40.3 ± 5.2 to 48.1 ± 9.5; P=0.002) and 3.9% for HF with preserved ejection fraction (59.1 ± 4.2 to 61.4 ± 4.3; P=0.009).

3.4 Complications and Clinical outcome

Among all studies, total complications related to the LBBAP procedure included 19 cases: 11 cases of reposition to another location in the left bundle branch area due to septal perforation during the procedure, three cases of pneumothorax, three cases of pocket infection requiring incision and drainage, and two cases of pocket hematoma requiring evacuation. During the follow-up period, five cases of lead dislodgements were observed.

One study reported both preimplant and postimplant New York Heart Association (NYHA) functional classes before and after LBBAP in patients with HFmrEF. In that study, during a mean follow-up of 10.4 months, NYHA functional status in patients with HFmrEF who underwent LBBAP improved from 2.5 ± 0.5 at baseline to 1.7 ± 0.8 at follow-up (P<0.01). One study reported hospitalization for HF after LBBAP in patients with HFmrEF; in this study, the HF hospitalization rate was 17.6% during a mean follow-up of 6.0 months after LBBAP.

3.5 Publication bias
According to Egger regression, the P for bias in QRS duration and LVEF were confirmed to be 0.126 and 0.433, respectively, indicating that there was no obvious publication bias. The funnel plots of the studies included in each analysis are presented in Figure 4.

4. Discussion

The clinical importance of cardiac resynchronization in patients with HF has already been demonstrated.\textsuperscript{1-3} Indications for CRT in patients with HFrEF with an LVEF <35\% are well established, whereas those for patients with HFmrEF and an LVEF of 35–50\% are less certain.\textsuperscript{4,5,33} In the PROSPECT prospective multicenter study, all echocardiograms were analyzed by a core laboratory; among patients with a NYHA functional Class III–IV status, and QRS>130 ms, those with a core laboratory-measured LVEF >35\% who underwent CRT demonstrated significant clinical benefit. Additionally, they exhibited both clinical and structural benefit from CRT.\textsuperscript{34,35} Meanwhile, among patients with HF and an LVEF <50\% who required pacing due to atrioventricular block, the BLOCK-HF trial showed that CRT was superior to right ventricular pacing regarding mortality and HF hospitalization.\textsuperscript{11} Based on these study results, guidelines state that HBP or biventricular pacing can be considered when the ventricular pacing burden exceeds 40\% in HFmrEF; still, the resynchronization strategy for HFrEF has not been clearly established.\textsuperscript{36} As the prevalence of HFmrEF increases, its clinical importance is emerging.\textsuperscript{37} Although researches have been reported to demonstrate the feasibility, efficacy, and safety of LBBAP adaptation to cardiac resynchronization (LOT-CRT, LBBAP-CRT),\textsuperscript{17,18} it is necessary to shed light on its role in the treatment of HFmrEF.

4.1 Feasibility of LBBAP in HFmrEF

All studies included in this meta-analysis performed LBBAP using lumenless pacing leads, with an average acute success rate of 91.3\%. In one case series wherein LBBAP was performed in patients with HFmrEF using stylet driven leads, the success rate was 100\% (n=4)\textsuperscript{38} Although procedure-related complications of septal perforation, pneumothorax, pocket infection, pocket hematoma, and lead dislodgements occurred during the follow-up period, no major implantation-related complications were observed.

4.2 LBBAP as a resynchronization strategy for HFmrEF

In this meta-analysis, during the average follow-up of 9.1 ± 3.8 months, the mean decrease in QRS duration after LBBAP in patients with HFmrEF was -34.51 ms (95\% CI: -60.00– -9.02; P<0.01). The mean LVEF increase was 10.9\% (95\% CI: 6.56–15.23, P<0.01), and the NYHA functional status improvement was -0.8 (only one article, P<0.01). This suggests that LBBAP is clinically beneficial for resynchronization therapy in the treatment of HFmrEF.

Interestingly, both HFrEF and HFmrEF exhibited significant improvements in LVEF after LBBAP. The LVEF attainment was 45.6\% ± 7.9\% for HFrEF and 50.5\% ± 3.9\% for HFmrEF, suggesting that intervention with more advanced cardiac remodeling before the LVEF reaches <35\% may be more beneficial.

Current findings reveal that about 30\% of patients for whom CRT is indicated are nonresponders.\textsuperscript{3,39,40} Moreover, among several studies that evaluated the effect of CRT in midrange HF with an LVEF >35\%, CRT did not significantly increase the LVEF or clinical composite score.\textsuperscript{34,41} Among these studies, it is encouraging that the resynchronization strategy applied with conduction system pacing—especially LBBAP, which overcomes some of the limitations of HBP—showed significant improvement in LVEF in patients with HFmrEF.

4.3 Limitations

This analysis has several limitations. First, there are currently no randomized controlled trials for LBBAP targeting HFmrEF; therefore, all studies included in this meta-analysis were retrospective and observational. Second, the sample size was small, with 16 centers and 211 patients (207 patients with LVEF followed-up before and after LBBAP, 42 patients with QRS duration followed-up before and after LBBAP) included in the analysis. Third, there was no long-term follow-up data. Fourth, in all studies included in the analysis, the pacing lead used for the procedure was a lumenless lead; therefore, there were no results for stylet-driven
leads. Finally, only one study reported clinical outcomes including HF hospitalization and mortality. Thus, large-scale randomized controlled trials with long-term observations are needed.

5. Conclusion

In all studies included in this meta-analysis, LBBAP in patients with HFmrEF was feasible and safe. In the pooled analysis, LBBAP was found to significantly shorten the QRS duration and improve cardiac systolic function in patients with an LVEF of 35–50%. This suggests that the application of LBBAP as a resynchronization strategy for patients with HFmrEF could be an acceptable option, especially in patients with both HFmrEF and dyssynchrony where a decrease in LVEF is anticipated. A randomized, prospective study is warranted to evaluate the effect of LBBAP-CRT on patients with HF and an LVEF >35% and [?]<35%.

References


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Figure legend

Figure 1. Flow diagram of selection process for articles included in the meta-analysis.

Figure 2. Forest plot for the meta-analysis comparing impact of LBBAP on QRS duration and LVEF. A. Changes in QRS duration before and after LBBAP. B. Changes in LVEF before and after LBBAP.

Plot demonstrating significant reduction in QRS duration and significant improvement in LVEF.

Square data markers represent mean difference of QRS duration (A) and LVEF (B) between pre implantation and post implantation, and horizontal lines represent 95% CIs.

LBBAP, left bundle branch area pacing; LVEF, left ventricular ejection fraction; SD, standard deviation; CI, confidence interval.

Figure 3. Average LVEF from implant to follow-up for baseline LVEF between 35% and 50% vs. LVEF <35%.

Both HFrEF and HFmrEF exhibited significant improvements in LVEF after LBBAP.

LVEF, left ventricular ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Figure 4. Begg’s funnel plots for LBBAP. A. QRS duration. B. LVEF.

The plot demonstrating there was no obvious publication bias.
Figure 1. Flow diagram of selection process for articles included in the meta-analysis

Figure 2. Forest plot for the meta-analysis comparing impact of LBBAP on QRS duration and LVEF
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Figure 4. Begg’s funnel plots for LBBAP

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