In 1986, Burkhoff and Sagawa\(^1\) observed that left ventricular pressure decreased linearly as the QRS duration (QRSd) increased in a pacing experiment. Consequently, it became recognized that either left bundle branch block (LBBB) or right ventricular pacing could result in prolonged QRSd, with potential deleterious effects on cardiac function and increased risk of atrial fibrillation (AF), heart failure, and mortality.\(^2\) Although previous clinical trials have demonstrated that patients with LBBB and heart failure could benefit from biventricular pacing (ie, biventricular cardiac resynchronization therapy [BiV-CRT]), 30% to 40% of such patients do not respond to BiV-CRT and approximately an additional 10% of patients remain untreated owing to an unsuitable coronary sinus vein. With the development of appropriate implant tools, His bundle pacing (HBP) has become increasingly important to enhance pacing as an adjunctive therapy in heart failure treatment. Various studies have demonstrated that CRT utilizing HBP (His-CRT) may be valuable in patients with no response or failure to place a BiV-CRT. However, HBP has higher pacing threshold and lower R-wave amplitude shortcomings and cannot correct LBBB in patients with distal conduction system disease.

In 2017, Huang et al\(^3\) first reported a patient with LBBB and heart failure in whom both BiV-CRT and His-CRT procedures failed, but in whom cardiac resynchronization by left bundle branch area pacing (LBBAP) (Lbb-CRT) was achieved with low and stable output; clinical outcomes showed significant improvement over 1 year of follow-up. Thereafter, other researchers have reproduced the feasibility and safety of LBBAP in patients with normal QRS complex and symptomatic bradyarrhythmia such as sinus sick syndrome (SSS) or ativoventricular block (AVB).\(^4\) However, the effectiveness of LBBAP has not been widely evaluated in a cohort of patients with LBBB. Consequently, this study was undertaken to investigate whether LBBAP can shorten the QRSd and improve cardiac function in pacing-indicated patients with LBBB.

Consecutive pacing-indicated patients with LBBB were prospectively enrolled from the First Affiliated Hospital of Nanjing Medical University between October 2017 and December 2019. The study protocol was approved by the Hospital Institutional Review Board, and all patients gave written informed consent to participate in the study.

The technique of LBBAP procedure has been described in previous reports and is depicted in Figure 1A-1C. Successful LBBAP was defined as unipolar paced QRS morphology present as right bundle branch block pattern and QRSd \(\leq 130\) ms. The patients with successful LBBAP were directly implanted with dual-chamber sensing and pacing, both triggered and inhibited or ventricle sensing and pacing, inhibited (patients with persistent AF) pacemakers. If successful LBBAP could not be achieved after five attempts of lead positioning or fluoroscopy duration exceeded 30 min, then left ventricular septum pacing (LVSP) is accepted. If the patients still have the Biv-CRT indication, then CRT pacemaker should be performed.

The baseline and LBBAP paced ECG were interpreted by two cardiologists. The stimulus to peak LV activation time (SPLVAT), defined as the duration between the ventricular stimulation signal and R peak in lead V5, was measured; the latter served as evidence that LBBAP directly captured either the main LB or its branches as previously described. Echocardiography was performed before and after the procedure. The parameters included were left atrial dimension (LAD), left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), and left ventricular ejection fraction (LVEF). The implant depth and distance to tricuspid attachment of LBBAP lead were measured.
Continuous variables were expressed as mean ± standard deviation (SD) and compared using analysis of variance (ANOVA) or paired t-test. Categorical variables were expressed as observed number and percentage values and compared using chi-square or Fisher exact test. All P values were two-tailed and P values < 0.05 were considered significant. Statistical analysis was performed using SPSS version 20.0 software.

Finally, 39 LBBB patients underwent an attempted LBBAP. In the end, based on the definition of success provided above, successful LBBAP was achieved in 31/39 (79.5%) of cases. Eight patients failed with LBBAP and LVSP was used instead. CRT devices were implanted in two patients with paced QRSd still > 150 ms. Ten patients had AF, three were persistent AF, and seven were paroxysmal AF. Among patients with persistent AF, one had three-degree AVB and two had HF; for seven patients with paroxysmal AF, metoprolol was given to control the AF event. Among the 31 patients with successful LBBAP (average age 66 ± 13 years, 16 male), the thickness of the IVS was 10 ± 1 mm. There were 16 LBBB patients with LVEF < 50%, 15 LBBB patients with LVEF ≥ 50% (7 SS and 8 AVB).

In LBBAP patients with LVEF < 50%, the QRSd significantly decreased from 175 ± 18 ms to 115 ± 8 ms (P < 0.001) and the SPLVAT was 75 ± 11 ms. In LBBAP patients with normal LVEF, the QRSd was also significantly reduced by LBBAP. All successful LBBAP patients were implanted with dual-chamber sensing and pacing, both triggered and inhibited (28 patients) device or ventricle sensing and pacing, inhibited (3 patients with persistent AF). One patient (3.2%, 1/31) had lead micro-perforation requiring lead reposition, but there was no sequela. No acute complications (e.g., chest pain, pneumothorax, or pericardial effusion) were encountered during the procedures. The depth of 3830 lead was 9 ± 2 mm in IVS, and the distance from lead tip to tricuspid valve attachment was 21 ± 6 mm.

During a mean follow-up of 6 ± 3 months, there were no complications associated with LBBAP such as lead perforation and dislodgement, device infection, pneumothorax, pericardial effusion, or thromboembolism. The clinical outcomes and echocardiography parameters showed significant improvement in LBBAP patients with LVEF < 50%. Furthermore, LBBB was corrected in all LBBAP patients and the mean QRSd reduction was 60 ± 10 ms. New York Heart Association functional class improved from 2.4 ± 0.8 to 1.7 ± 0.6 and amino-terminal pro-brain natriuretic peptide decreased from 1823 ± 1641 ng/L to 829 ± 222 ng/L (all P < 0.05). In 6/16 patients (37.5%), we observed super-response to LBBAP. Among 15 LBBAP patients with baseline normal LVEF and 8 LVSP patients with LVEF < 50%,
cardiac function parameters were also improved, although not significantly.

In this prospective cohort study assessing the ability of LBBAP for LBBB correction (Lbb-CRT), we found that LBBAP could significantly shorten the QRSd and improve the cardiac function in LBBB patients with reduced LVEF. American College of Cardiology/American Heart Association and European Society of Cardiology guidelines emphasized that both QRSd (>150 ms) and morphology (LBb) are the major predictors of BiV-CRT response. The echoCRT trial showed potential harm of BiV-CRT in patients with QRSd < 130 ms. Thus, the European Society of Cardiology guideline clearly states that BiV-CRT implantation is contraindicated (III) in patients with a QRSd < 130 ms (120 ms, American College of Cardiology/American Heart Association). The meta-analysis demonstrated that average QRS narrowing was only – 19 ms in BiV-CRT responders.

The average increase in LVEF in the large BiV-CRT trials (MIRACLE-ICD, CARE-HF, REVERSE, and MADIT-CRT) ranged from 2% to 11%, and the super-response was only 16%. Our study demonstrates that a high successful LBBAP rate is achievable (79.5%, 31/35 in this report) in pacing-indicated patients with LBBB. The average QRS narrowing was – 60 ms. In patients who failed LBBAP, atypical LBb morphology was often observed. Actually, patients with atypical LBb usually had worse LVEF, LVEDD, and LAD than patients with typical LBb in this study, which suggested different underlying cardiac substrates may impact the success of QRS correction by LBBAP in these patients.

According to the current BiV-CRT guideline mentioned above, the patients with LBBB corrected by LBBAP (average paced QRSd 115 ms) no longer had a BiV-CRT indication. Furthermore, LVEF was significantly improved by successful LBBAP in a mean follow-up of 6 ± 3 months. Among all the patients, 16 LBBB patients with heart failure, LVEF increased from 34.6 ± 7.9% to 45.8 ± 12.4% (P < 0.001), and 37.5% (6/16) had super-response to LBBAP. In addition, LBBAP (LBb-CRT) was achieved by single- or dual-chamber device and revealed a better cost-effectiveness ratio.

The degree of QRSd reduction and cardiac function improvement were determined by the various CRT modes in patients with LBBB and heart failure. The BiV-CRT combined pacing of left ventricular epicardium and right ventricular endocardium to achieve cardiac resynchronization effects, but His-CRT and Lbb-CRT utilized heart itself conduction system. The pulse propagation velocity in the cardiac conduction system is fast 5 to 10 times than myocardium (2.0–3.0 vs. 0.3–0.4 m/s). So the efficacy of His-CRT and Lbb-CRT is superior to BiV-CRT. However, due to special anatomy of His bundle located in central fibrous body of membranous interventricular septum, HBP has some inherent limitations such as higher capture threshold, lower R amplitudes, and lead stable problem. Furthermore, HBP may not be performed successfully in patients with distal disease of His bundle and proximal site of LBBB or unacceptable high threshold for LBBB correction. LBBAP could overcome these shortcomings of HBP. The effects of narrowing QRSd and improving cardiac function in successful LBBAP are similar to HBP.

The LBBAP procedure proved to be safe. One patient had lead micro-perforation during procedure and underwent lead repositioning. No late LBBAP related complications were observed in this study. Li et al. and Vijayaraman et al. reported that 1/33 and 3/100 patients had acute lead perforation and required lead repositioning, respectively.

In conclusion, LBBAP significantly shortened QRSd in pacing-indicated patients with LBBB and also improved cardiac function during short-term follow-up in patients with LBBB and heart failure. Findings were most marked in those individuals with low baseline LVEF. Thus, LBBAP may be a promising technique for improving hemodynamic responses to cardiac pacing.

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Conflicts of interest

None.

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