

Cardiac Resynchronization Therapy using Left-Bundle-Branch Area and Left Ventricular Pacing

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Abstract

Introduction: Cardiac resynchronization therapy via biventricular pacing is an established therapy for patients with heart failure. However, high nonresponder rates and inability to predict response remains a challenge. Recently left bundle branch area pacing (LBBAP) has been shown to be feasible and may also improve clinical outcomes. In this article we describe sequential LBBAP followed by left ventricular (LV) pacing (LOT-CRT) and assess the feasibility of LOT-CRT. **Methods:** The RV implantation site was positioned and the LBBAP lead was implanted using our methods. The QRS duration (QRSd) at baseline, during LBBAP, biventricular pacing, and LOT-CRT was measured. **Results:** LOT-CRT was successful in 5 patients (age 71.8 ± 5.1 years, men 3, ischemic 3). The QRSd at baseline was 158.0 ± 13.0 ms and significantly narrowed to 117.0 ± 6.7 ms during LOT-CRT ($P < 0.01$). During 3-month follow-up, LV ejection fraction improved from 32.8 ± 5.2 % to 45.0 ± 5.1 % ($P < 0.01$), and New York Heart Association functional class changed from 3.25 ± 0.5 to 2.5 ± 0.6 ($P < 0.05$). A decrease in left ventricular end-diastolic dimension was observed, with widening from (68.2 ± 12.3) mm at baseline to (62.2 ± 11.3) mm at pacing ($P < 0.05$). The length of operation time was (152.0 ± 31.1) min. **Conclusions:** The study demonstrates that LOT-CRT is clinically feasible in patients with systolic HF and LBBB. LOT-CRT was associated with significant narrowing of QRSd and improvement in LV function, especially in patients with ischemic cardiomyopathy.

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INTRODUCTION

Cardiac resynchronization therapy (CRT) via biventricular pacing (BVP) is known to improve clinical outcomes, and decreases all-cause mortality, particularly in patients with left bundle branch block (LBBB), and reduced left ventricular function^{1,2}. Permanent His bundle pacing (HBP) has been shown to overcome LBBB, and is being considered as a viable alternative to BVP in patients requiring CRT³. However, HBP may be associated with high pacing thresholds to capture the distal His bundle and/or correct LBBB⁴.

Recently several groups have shown the feasibility of left bundle branch area pacing (LBBAP) as an alternative choice to HBP in patients with LBBB by pacing the LBB region beyond the block site with a stable threshold and narrow QRS duration (QRSd)⁵⁻⁷. However, it is unknown whether the clinical efficacy of LBBAP with an appropriate AV delay would be the same as or better than LV epicardial pacing or cardiac resynchronization therapy.

We hypothesized that electrical resynchronization measured by narrowing of the QRS complex can be accomplished more effectively by LBBAP followed by sequential LV pacing (LBB-Optimized LV pacing, LOT-CRT). The aim of our study is to assess the feasibility and efficacy of LOT-CRT to improve electrical resynchronization in patients qualifying for CRT and evaluate clinical and echocardiographic response rates.

2. METHODS

This study was approved by Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiao tong University School of Medicine (approval number: XHEC-D-2020-148) and performed in accordance with the Declaration of Helsinki.

2.1 Patient's selection

Patients with chronic LBBB by Strauss criteria⁸, optimal medical therapy-refractory New York Heart Association (NYHA) class III to IV heart failure(HF) symptoms and a baseline left ventricular ejection fraction (LVEF, calculated by Simpson method) [?] 35% were enrolled in Shanghai Xinhua Hospital from April 1, 2019 to June 1, 2020.

Patients were excluded if they had a history of previous valve intervention, end-stage renal disease, previous heart transplantation, left ventricular assist device, metastatic cancer, moderate or severe valve disease, life-expectancy less than 1 year.

All patients submitted written informed consent and demonstrated an understanding of LOT-CRT as a nonstandard approach to achieve physiologic pacing, and their data were analyzed prospectively.

2.2 Procedural Details

The RV defibrillator lead was first implanted in the RV to provide backup ventricular pacing should the patient develop transient complete atrioventricular block during the LBBAP lead placement. Subsequently, the LV lead was implanted in the standard fashion targeting sites with maximal LV delay. Then, LBBAP was performed using the Select Secure pacing lead. The fluoroscopy duration for the entire procedure, LBBAP lead implant and LV lead implant were separately recorded.

2.3 LBBAP lead implantation technique

As previously described⁹⁻¹², a Select Site C315 His sheath and a Select Secure 3830 pacing lead (Medtronic Inc, Minneapolis, MN, USA) were advanced to the implantation site. Right ventricular septal location for LBBAP is identified using the anatomical location and pacing localization in nine-grid system¹³. Once

this site is identified, the pacing lead is advanced deep into the septum while monitoring unipolar pacing impedance, electrogram characteristics and paced QRS morphology.

Additionally, the lead orientation can be displayed in various projections. During the initial LBBAP lead fixation, if the lead torques back, it will mean that the lead and sheath are not oriented orthogonal to the RV septum. Generally, the sheath and the lead are oriented such that the lead is pointing towards 12-1 O'clock direction right anterior oblique 30° view and 2-3 O'clock direction in left anterior oblique 30° view¹⁴.

In addition to fluoroscopic views, significant rise in unipolar pacing impedance above 900 Ohms would suggest that the lead is directing to an oblique direction and need re-oriented. If several attempts were made to achieve LBBAP, prior sites were tagged in the mapping system or fluoroscopic view to prevent re-engaging in the same site. Once the lead position was finalized, 1-2 ml of contrast was injected through the delivery sheath to visualize the septal wall and the approximate depth of the lead under left anterior oblique fluoroscopic view.

2.4 Device Connection and Programming

In patients with normal sinus rhythm undergoing CRT-defibrillators, the LBBAP lead was connected to the pace-sense portion of RV port and a bipolar LV lead in the LV port. The pace-sense portion of the spliced ICD lead (DF-1) was capped. In patients with normal sinus rhythm undergoing CRT-pacemakers (P), the LBBAP lead was connected to the RV port and the LV lead to the LV port.

2.5 Implant Measurements

The pacing output required to maximally narrow the QRS (BBB correction threshold) and LBB capture threshold (without BBB correction) was assessed and recorded at a pulse width of 1.0 ms. The QRSd at baseline, during LBBAP, BVP (via RV defibrillator lead, when available) and LBB-Optimized LV pacing were measured on the EP recording system at 100 mm/s. The interval from the onset of QRS to the maximal deflection of LV electrogram (LVAT) during native LBBB pacing and during LBBAP was documented.

2.6 Clinical follow-up

Patients were seen for routine clinical follow-up at standard time periods (every 3 months). Functional status was assessed by NYHA classification. Device thresholds were checked and adjusted as needed to maximize battery longevity. The pacing threshold, impedance and R wave amplitude were measured. According to previous literature¹⁵, the high pacing threshold was defined as pacing threshold over 2.5 V/0.4 ms, increased threshold over 1.0 V compared with the baseline after the procedure and at follow-up. Echocardiographic indices, including LVEF, LV end-diastolic dimensions, pulmonary artery systolic pressure were recorded pre-implant and at follow-up.

2.7 Statistical analysis

Continuous variables were given as mean \pm SD or median. Paired comparisons were made using a Student t test if the data were normally distributed, and with the Wilcoxon signed-rank test for nonparametric data. Paired categorical data (NYHA functional class) were compared using the Wilcoxon test. P [?] 0.05 was considered significant.

3. RESULTS

Seven out of the 12 screened patients were excluded from the study according to the exclusion criteria. Consequently, 5 patients were registered into the LOT-CRT cohort.

3.1 Baseline characteristics

Among 5 patients, three patients (60%) were male. All patients had cardiomyopathy (2 with nonischemic and 3 with ischemic), and 2 patients had paroxysmal atrial fibrillation. Hypertension was present in all the patients. The mean age was 71.8 \pm 5.1 years, and the baseline characteristics of patients are provided in

Table 1. The baseline LVEF and the baseline QRSd with LBBB were $32.8 \pm 5.2\%$ and 158.0 ± 13.0 ms respectively (Figure 1A).

All patients had at least 1 HF hospitalization 3 months before LBBAP implantation. ENTRESTO (sacubitril / valsartan), β -blockers, and loop diuretics were prescribed in all patients.

3.2 Procedural Outcomes

LOT-CRT was successfully achieved in all 5 patients. The acute success rate was 100 %. The operation duration was 152.0 ± 31.1 min. The time of X-ray fluoroscopy was 26.2 ± 5.9 min. Biventricular ICD (CRT-D) was implanted in 4 patients (Figure 2A, 2B) and CRT-pacemakers in the remaining 1 patient (Table 1).

Both LBBAP and LV capture thresholds remained stable during follow-up (1.3 ± 0.6 V at 0.4 ms vs 1.6 ± 0.7 V at 0.4 ms). Bipolar LBBAP resulted in partial, but significant narrowing of QRSd (BBB correction) in 5 patients (Figure 1B).

3.3 ECG characteristics and pacing parameters

Individual electrocardiographic responses to RV, LV, and LBBAP at the time of implantation are shown in Table 2. Among 5 patients, the baseline QRSd was 158.0 ± 13.0 ms. After unipolar LBBAP, 5 patients demonstrated an RBBB pattern with a paced QRSd of 123.0 ± 5.7 ms ($P = 0.001$ vs. baseline). LBB potential could be recorded in 3 patients from the LBB lead (60%). The LVAT for all LBBAP patients was 72.5 ± 9.4 ms, and the R wave amplitude, pacing impedance, and unipolar pacing capture threshold were 9.9 ± 7.2 V, 678 ± 102 Ω , and 0.84 ± 0.17 V / 0.4 ms respectively after implantation.

BVP resulted in significant narrowing of QRSd from 158.0 ± 13.0 ms at baseline to 132.0 ± 4.5 ms ($P=0.019$). Compared with BVP, unipolar LBBAP resulted in further narrowing of QRSd to 123.0 ± 5.7 ms ($P=0.006$ versus baseline and $P=0.021$ versus BVP). However, LOT-CRT resulted in more significant narrowing of QRSd to 117.0 ± 6.7 ms ($P < 0.01$ versus baseline, BVP, or bipolar LBBAP).

3.4 Follow-up

The mean follow-up time was 296 ± 201 days. Overall, LBBAP capture threshold, R-wave amplitude, and lead impedance were 0.74 ± 0.25 V, 13.36 ± 5.23 mV, and 533.73 ± 32.31 Ω during 1-month follow-up ($P > 0.05$, respectively, between at the time of device implantation and at the follow-up visit). During LOT-CRT, QRSd was stable and no significant difference was observed between at the 3-month follow-up visit and at the time of device implantation ($P > 0.05$). The ventricular pacing rates were 99%. The latest success rate was 100%. No patients showed signs of dislodgement, loss of capture, infections, embolism, or stroke associated with the implantation.

Transthoracic echocardiogram (Figure2C) evaluation data at baseline and 1-month follow-up, 3-month follow-up were available in all 5 patients receiving successful LOT-CRT. As shown in Table 3, the left ventricular end-diastolic dimension (68.2 ± 12.3 mm vs. 62.2 ± 11.3 mm, $P=0.017$) and LVEF ($32.8 \pm 5.2\%$ vs. $45.0 \pm 5.1\%$, $P=0.008$) were improved at the 3-month follow-up visit. The symptoms and the median NYHA classification score were improved significantly from 3.2 ± 0.45 to 2.4 ± 0.55 ($P=0.016$).

4. DISCUSSION

4.1 Major findings

The present study demonstrated the following merits. (1) LOT-CRT was feasible in a small nonrandomized, nonconsecutive series of patients with reduced LVEF and LBBB. At the time of the device implantation, ECG changes during LOT-CRT were characterized with LBBB correction, narrower QRSd, and short LVAT. (2) Significant improvements in clinical and echocardiographic assessments were achieved during the mean follow-up period of 3 months. (3) There were no major implantation-related adverse events during perioperative period and follow-up.

4.2 Anatomical definition

CRT using BVP (BVP-CRT) is as an integral part of the therapy for patients with HF with reduced LVEF and BBB, particularly LBBB¹⁶. However, up to a third of patients treated with BVP-CRT are still considered non-responders¹⁷. The reasons for BVP-CRT nonresponse are many but include LV scar burden and distribution, suboptimal LV stimulation site, sex, and limited electrical or mechanical dyssynchrony¹⁸. Patients with ischemic cardiomyopathy experience a similar response rate to BVP-CRT as their nonischemic counterparts¹⁹. However, higher overall scar burden, a larger number of severely scarred segments, and greater scar density near the LV lead tip portend an unfavorable response to BVP-CRT in ICM patients²⁰. There is evidence that CRT is not salutary in patients with posterolateral scar²¹.

4.3 Electrophysiological definition

Permanent LBBAP is an effective form of physiologic pacing with high success rates in patients with intact His-Purkinje conduction⁷. LBBAP can be a new CRT technique to correct LBBB, provide ventricular synchrony, and improve clinical symptoms with LV reverse remodeling²².

There is evident in LV activation time studies where LV activation time is only minimally increased in RBBB but significantly increased in LBBB²³. During unipolar LBBAP, as the right ventricle is predominantly activated via myocardial conduction, RV dyssynchrony may be present compared to HBP. While it does not cause LV dyssynchrony since LV activation occurs via the His-Purkinje system. So, in patients undergoing permanent LBBAP, synchronization of delayed RV activation and normal LV activation is feasible.

4.4 LOT-CRT advantage

However, in patients with intraventricular block or higher overall scar burden, success rates are somewhat limited depending on the site of block and the scar burden and distribution of interventricular septum²⁴. Intra or inter-ventricular dyssynchrony cannot be reduced utilizing LBBAP. LBBAP achieved only partial narrowing of QRSd in those patients with the baseline surface ECG of atypical LBBB morphology²⁴. LOT-CRT offers the advantage to use the LV lead in addition to LBBAP in a potential scenario of progression of conduction disease.

In patients with LBBB and cardiomyopathy, LOT-CRT resulted in significant electrical resynchronization in these patients. In our study, which included 60 % of patients with severe ischemic cardiomyopathy, LOT-CRT resulted in high clinical and echocardiographic response rates. Our results indicated that those patients with LBBB and higher overall scar burden might be the desired candidates of LOT-CRT.

4.5 Limitations

First, it is time consuming. The duration of operation time was 152 ± 31 min, and the time of X-ray fluoroscopy was 26.2 ± 5.9 min, both are longer than previous report (117 ± 48 and 16.4 ± 12.3 min)⁷. Second, this study includes a small sample in a single center. Third, this study had a short follow-up interval. We expect long-term favorable clinical benefits. Furthermore, this study enrolled only 3 ischemic patients. Although this uncontrolled nonrandomized study does not provide sufficient data to support this conclusion, we observed significant echocardiographic and clinical improvement in these patients with HF treated with LOT-CRT.

5. CONCLUSIONS

The study demonstrates that LOT-CRT is clinically feasible in patients with systolic HF and LBBB. LOT-CRT was associated with significant narrowing of QRS duration and improvement in LV function, especially in patients with ICM.

Conflict of interest statement

The authors declare no Conflict of Interest for this article.

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Data Availability Statement

Datasets analyzed in this study are available from the corresponding author upon reasonable request due to privacy or other restrictions.

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Table and Figure Legends

Table 1 . Baseline characteristics of patients for LBBAP with a CRT device

LBBAP, left bundle branch area pacing; ICM, ischemic cardiomyopathy; AF, atrial fibrillation; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction

Table 2 . Pacing parameters of LOT-CRT during the procedure

LBBAP, left bundle branch area pacing; LV, left ventricle; RV, right ventricle

Table 3. Comparison of the pre- and post-operation TTE parameters (mean \pm SD)

LVEDD, left ventricular end diastolic diameter, LVEF, left ventricular ejection fraction

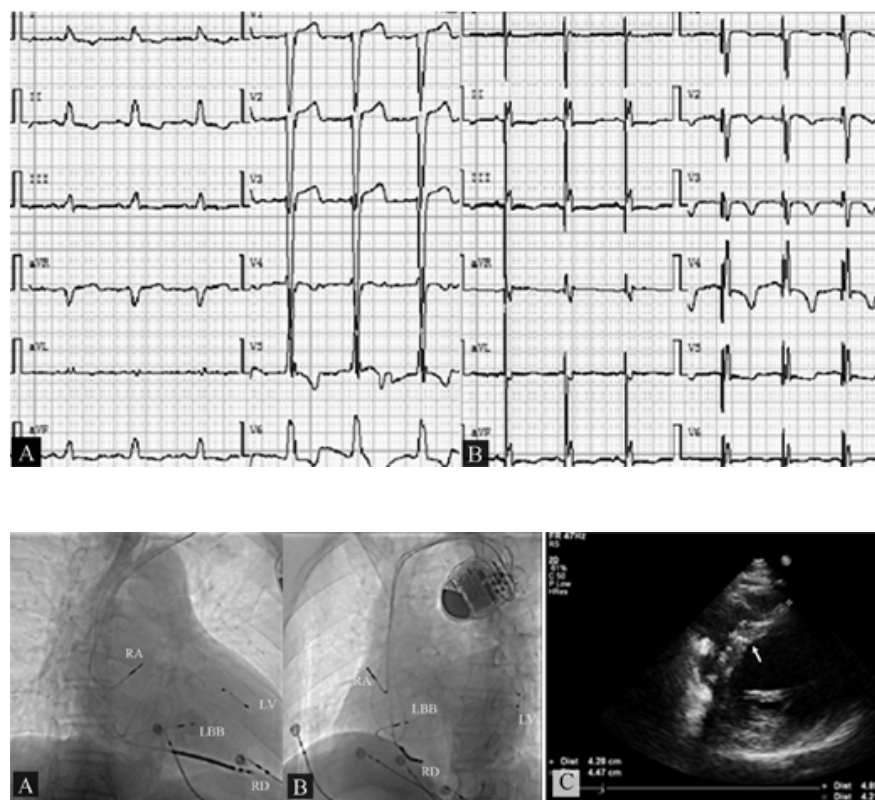
Figure 1. Left-bundle-branch-optimized cardiac resynchronization therapy in a patient with ischemic cardiomyopathy.

A, Baseline ECG shows LBBB with QRS duration of 160 ms. B, During pacing with LOT-CRT, left bundle branch block correction pattern with QRS duration of 115 ms is seen.

Figure 2. Fluoroscopic image and echo image of LOT-CRT in a patient with ischemic cardiomyopathy

A and B Fluoroscopic image in the LAO 40° and RAO 30° projection. These images showed the final lead position in the IVS. RA, right atrial lead; LV, left ventricular lead; LBB, left bundle branch lead; RD, right defibrillator lead.

C Intracardiac echocardiography image. Parasternal short-axis view demonstrating the depth of the lead in the interventricular septum. Arrow, left bundle branch lead.



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