Recording an isoelectric interval as an endpoint of left bundle branch pacing with continuous paced intracardiac electrogram monitoring

Hao Wu, Longfu Jiang, Jiabo Shen

Department of Cardiology, HwaMei Hospital, University of Chinese Academy of Sciences, Ningbo, Zhejiang, China

ABSTRACT

Background: The present study aimed to evaluate the feasibility and safety of the novel left bundle branch pacing (LBBP) procedure that uses isoelectric interval as an endpoint for lead implantation.

Methods: A total of 41 patients with indications for pacing were enrolled. All patients underwent a novel LBBP procedure guided by recording an isoelectric interval as an endpoint for lead implantation. The procedural details and electrophysiological characteristics were then analyzed.

Results: A total of 38/41 (92.7%) cases were confirmed of left bundle branch (LBB) capture. An isoelectric interval was observed in 36/41 cases (87.8%). A total of 36/41 (87.8%) cases with LBB potential were observed. The mean unipolar LBBP threshold at the implant was 0.5 ± 0.2 V. The mean sensed amplitude of the R wave and the pacing impedance at the implant were 12.9 ± 5.0 mV and 723.5 ± 117.1 Ω. During the final threshold testing, a transition from non-selective to selective LBBP (S-LBBP) was demonstrated in 26 patients. A transition from non-selective LBBP (NS-LBBP) to left ventricular septal myocardial capture was observed in 12 patients.

Conclusion: Using an isoelectric interval as an endpoint to guide the LBBP was feasible in a high proportion of captured LBB cases.

Key words: conduction system pacing, isoelectric interval, intracardiac electrogram, John Jiang's connecting cable, left bundle branch pacing

INTRODUCTION

Left bundle branch pacing (LBBP) is a novel physiological pacing modality that is based on the transventricular septal left ventricular (LV) pacing method [1]. This technique has been widely adopted by medical centers in different countries since it was reported in 2017 [2]. Prior research has demonstrated its feasibility and effectiveness [3–6]. Previous studies usually use electrocardiogram (ECG) characteristics, such as paced right bundle branch block (RBBB) pattern, time from stimulus to R-wave peak time (RWPT) in V4–V6, and LBB potential as a guide to performing LBBP [2]. However, these ECG characteristics were not precise enough to tell when to stop screwing the lead. Using a mechanically induced premature ventricular complex (PVC) to guide LBBP, has been reported [7], but PVC cannot exist persistently. The implantation procedure for LBBP is still in the empirical stages and therefore lacks a precise endpoint for lead implantation.

Continuous pacing while lead screwing in LBBP was reported by Jastrzębski et al. [8, 9]. With no doubt, the ability to monitor in real-time the paced QRS morphology is very helpful in LBBP, but it is not easy to achieve by the traditional connecting cable. Our center (Department of Cardiology, HwaMei Hospital, University of Chinese Academy of Sciences) began using John Jiang’s connecting cable for LBBP in July 2019. It allows for simultaneous monitoring and recording of ECG and intracardiac electrogram (EGM) during lead deployment. Recently, our group reported
on a case where John Jiang’s connecting cable was used for LBBP and found that a distinct isoelectric interval was recorded in intracardiac EGM during selective LBBP (S-LBBP) [10]. We then developed a novel LBBP lead implantation technique assisted by John Jiang’s connecting cable to record an isoelectric interval in the pacing lead as an endpoint for lead implantation with continuous monitoring of paced EGM. Herein, we report on the novel LBBP technique that uses isoelectric interval as an endpoint for lead implantation. The feasibility and safety of the novel procedure were also evaluated.

**METHODS**

**Study design and patient population**

This study involved patients referred for permanent pacemaker implantation therapy between April and August 2021 at the HwaMei Hospital, Ningbo. All enrolled patients underwent a novel LBBP procedure. All patients were indicated for pacing therapy according to the current guidelines [11]. The Institutional Review Board approved the study protocol (no. SL-KYSB-NBEY-2021-079-01), and all patients provided written informed consent.

**Implantation procedure**

**Preparation**

A 3830 (SelectSecure, 69 cm, Medtronic, Minneapolis, MN, US) pacing lead was delivered using a C315 HIS (Medtronic, Minneapolis, MN, US) sheath via left subclavian or left axillary vein access and connected by John Jiang’s connecting cable. The modified connecting cable had a special rotating device with an IS-1 connector port, which was connected to the distal pin of the lumenless Medtronic 3830 lead (cathode). The special rotating device was like a double-layer metal ring, and the mechanism of the device was similar to that of bearings, allowing components to move with respect to each other. Twelve-lead ECG along with EGM from the pacing lead were continuously recorded with an EP-Workmate™ recording system (Abbott Laboratories, Chicago, IL, US). The band-pass filter for the pacing lead was set to: “High Pass-200 Hz/Low Pass-500 Hz”.

**Lead implantation**

A C315 HIS sheath in the right anterior oblique (RAO) 30° was advanced into the right ventricle. The sheath was then slowly withdrawn until the tip reached the area just across the tricuspid valve annulus (TVA). About 20 ml of the contrast medium were then injected via the sheath for right ventriculography to visualize the TVA. A TVA image was saved as a reference marker to help locate the target entry site without searching for a HIS potential or the typical paced morphology with an electrocardiographic “W”pattern in lead V1. A previous study has demonstrated that the HIS bundle travels in the membranous part of the atrioventricular septum and penetrates the posterior site of the basal interventricular septum (IVS) just inferior to the tricuspid septal leaflet [12]. The target site for LBBP was identified in the proximal interventricular septum 2.0–2.5 cm below the summit of the tricuspid, along an imaginary line connecting the summit of the tricuspid to the right ventricular apical (RVA) in the RAO 30° fluoroscopic view.

Continuous unipolar pacing at 2 V/0.5 ms was performed during the whole period of lead implantation. At the beginning of implantation, the lead was screwed on rapidly, and the R-wave in the precordial lead R/S transition was elevated while the impedance increased (Figure 1), indicating that the lead had begun to enter the right side of the ventricular septum. The most common precordial lead where R/S transition occurred was V3 or V4.

As the lead reached the left side of the ventricular septum, the R/S transition zone gradually advanced to lead V1 (Figure 1), while the impedance began to decrease gradually. The output was intermittently increased to 5 V/0.5 ms to monitor whether the V5 RWPT shortens abruptly compared to the initial pacing output (2 V/0.5 ms). This means that the lead was closer to the conduction system, slowing down the screwing speed and increasing the measuring impedance frequency.

The V5 RWPT for two adjacent paced beats first shortened abruptly to ≥10 ms with the same output (2 V/0.5 ms), and the lead was screwed in very slowly (Figure 2), gradually decreasing the pacing output. The lead screwing was stopped if an isoelectric interval was directly observed in
**Figure 1.** Electrophysiological characteristics during the whole period of lead implantation. The overall total lead screwing procedural time was 35 seconds. The precordial R/S transition zone gradually advanced to lead V1 as the lead traversed from the right to left side of the septum. A distinct isoelectric interval was observed at the end of lead screwing. LBB potential can be recorded in intrinsic rhythm.

Abbreviations: LBB, left bundle branch

**Figure 2.** Electrophysiological characteristics at the end of lead implantation. As the lead almost reached to the LBB, the V5 RWPT for two adjacent paced beats was suddenly shortened from 102 ms to 67 ms with the same output (2 V/0.5 ms). And after the lead reach to the LBB, a distinct isoelectric interval was observed in the LBBP lead and V5 RWPT remained the same (67 ms), V1 RWPT increased from 129 ms to 141 ms.

Abbreviations: LBBP, left bundle branch pacing; RWPT, R-wave peak time; other — see Figure 1
intracardiac EGM with the initial pacing output (2 V/0.5 ms) or during a decrease in pacing output (Figure 2). If the isoelectric interval still cannot be observed, screw the lead very slowly with near-threshold output until the unipolar impedance decreases to 600 Ω or the amplitude of current of injury (COI) starts to decrease.

**Final threshold test and pacemaker implantation**

After the lead was in place, the LBB potentials were recorded. In the left anterior oblique 45° fluoroscopy view, about 5 ml of the contrast agent were injected through the sheath to delineate the right ventricular (RV) septal wall and to demonstrate the lead depth in the interventricular septum. Lead tension was adjusted and then the sheath was removed. The pacing lead was fixed, and the final threshold test was performed before connecting the pacemaker. After it was connected, the pacemaker was placed in a prefabricated bag and the skin was sutured.

**Strict criteria for confirming LBB capture**

LBB capture is confirmed by paced QRS morphology of RBB delay pattern (qR or rSR in lead V1) along with all of the following criteria: (1) demonstration of non-selective left bundle branch (NS-LBB) to selective left bundle branch (S-LBB) capture or NS-LBB to left ventricular septal (LVS) myocardial capture transition during threshold testing; (2) differential pacing at 8 V and 2 V produce short and constant RWPT as measured in leads V5 (preferably <70 ms).

**Data collection**

Baseline patient characteristics and indications for pacing were documented in addition to baseline QRS duration and echocardiographic data. Pacing thresholds (unipolar pacing), R-wave amplitudes, and impedances were recorded. The presence of isoelectric interval and intracardiac isoelectric stimulus-ventricular potential interval (S-V interval) was noted. Abrupt shortening to ≥10 ms in two adjacent paced beats with the same output (2 V/0.5 ms) of the VS RWPT and shortening duration were also recorded in addition to the presence of LBB potential and its amplitude. The characteristics of different changes in ECG and EGM morphology during the final threshold test and the RWPT (stimulus — the peak of the R wave in surface leads V1, V6) with different outputs (threshold, 2 V, and 8 V) were determined (measured using the electrophysiology recording system at a speed of 600 mm/s). The length of the septum lead from the RV to LV wall along the course of the lead was measured. The lead implantation procedural duration was recorded and was defined as the time from the TVA visualization to the removal of the C315 HIS sheath.

Acute procedure-related complications, such as lead dislodgement, pneumothorax, pericardial effusion, pocket hematoma, and loss of capture were recorded.

### Table 1. Basic study group characteristics (n = 41)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>73.7 (9.2)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>25 (60.9)</td>
</tr>
<tr>
<td>Pacing indication, n (%)</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>3 (7.3)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>13 (31.7)</td>
</tr>
<tr>
<td>Sinus node</td>
<td>23 (56.1)</td>
</tr>
<tr>
<td>Atrial arrhythmia</td>
<td>18 (43.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27 (65.8)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>27 (65.8)</td>
</tr>
<tr>
<td>Nonspecific intraventricular conduction</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Nonspecific intraventricular conduction</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Narrow, n (%)</td>
<td>27 (65.8)</td>
</tr>
<tr>
<td>RBBB, n (%)</td>
<td>9 (22.0)</td>
</tr>
<tr>
<td>LBBB, n (%)</td>
<td>4 (9.8)</td>
</tr>
<tr>
<td>NIVCD, n (%)</td>
<td></td>
</tr>
<tr>
<td>Native QRS duration, ms, mean (SD)</td>
<td>107.5 (33.2)</td>
</tr>
</tbody>
</table>

Abbreviations: LBBB, left bundle branch block; NIVCD, non-specific intraventricular conduction disturbances; RBBB, right bundle branch block

### Statistical analysis

Continuous variables were reported as mean (standard deviation [SD]). Categorical variables were expressed as percentages. Repeated measures ANOVA was used for more than two-group comparisons with an LSD post hoc test for two-group comparisons. A \( P \)-value of <0.05 was considered significant. Statistical analysis was performed using IBM SPSS Statistics for Macintosh (version 26.0, IBM Corp, Armonk, NY, US).

**RESULTS**

### Baseline characteristics

A total of 41 patients with LBBP were screened. The baseline characteristics of the study population are shown in Table 1. The mean age was 73.7 (9.2) years and 60.9% of patients were men. Indications for pacing included atrioventricular block (65.9%), sick sinus syndrome (24.3%), atrial fibrillation with bradycardia (4.9%), and heart failure (4.9%). The main comorbidities were hypertension (56.1%), diabetes mellitus (43.9%), and atrial fibrillation (31.7%). The mean LV ejection fraction was 64.6 (7.4)%. The mean LV end-diastolic dimension was 50.4 (6.1) mm. The mean native QRS duration was 107.5 (33.2) ms. The native QRS type was narrow (65.8%), RBBB (22%), LBBB (9.8%), and non-specific intraventricular conduction disturbance (2.4%).

### Procedural characteristics and complications

Among 41 patients who underwent the LBBP procedure, a total of 36 cases (87.8%) reached the endpoint during...
Abrupt V5 RWPT shortening to ≥10 ms, n (%) 38 (92.7)
Mean duration of shortening, ms, mean (SD) 18.1 (5.2)
Isoelectric interval, n (%) 36 (87.8)
Be observed directly, n (%) 16 (39.0)
Be observed during decreasing the pacing output, n (%) 20 (48.8)
S-V interval, ms, mean (SD) 30.6 (5.7)
LBB potential, n (%) 36 (87.8)
LBB potential amplitude, µV, mean (SD) 12.9 (5.0)
Sensing, µV, mean (SD) 0.2 (0.1)
Threshold, V, mean (SD) 0.5 (0.2)
Impedance, V, mean (SD) 723.5 (117.1)
Lead depth, mm, mean (SD) 13.0 (2.1)
Lead implantation procedural duration, min, mean (SD) 40.2 (23.8)

Table 3. Different changes in near-threshold output and electrophysiological characteristics at the final threshold test

<table>
<thead>
<tr>
<th>The changes in near-threshold outputs</th>
<th>Patients</th>
<th>V1 RWPT</th>
<th>P</th>
<th>V5 RWPT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Threshold output, ms, mean (SD)</td>
<td>2V output, ms, mean (SD)</td>
<td>8V output, ms, mean (SD)</td>
<td>Threshold output, ms, mean (SD)</td>
<td>2V output, ms, mean (SD)</td>
</tr>
<tr>
<td>NS-LBB to S-LBB to S-LBBP (n = 26)</td>
<td>119.2 (15.9)</td>
<td>106.6 (10.8)</td>
<td>104.2 (9.6)a</td>
<td>&lt;0.001</td>
<td>69.1 (7.4)</td>
</tr>
<tr>
<td>NS-LBB to LV-septal (n = 12)</td>
<td>112.0 (13.8)</td>
<td>105.0 (13.0)</td>
<td>102.4 (10.8)</td>
<td>0.071</td>
<td>87.1 (10.1)</td>
</tr>
<tr>
<td>No changes (n = 3)</td>
<td>107.0 (32.5)</td>
<td>109.5 (24.7)</td>
<td>98.5 (19.1)</td>
<td>0.082</td>
<td>98.0 (8.0)</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; other — see Figures 2 and 4

**Electrophysiological characteristics and different morphological changes in paced QRS and EGM at the final threshold test**

Before the pacemaker was implanted, the final threshold test was performed in 41 patients. An isoelectric interval with the initial pacing output (2 V/0.5 ms) could not be recorded in any patient. There were different morphological changes in paced QRS and EGM during the final threshold test. The electrophysiological characteristics are shown in Table 3. Different changes in ECG and EGM during different periods of the LBBP procedure are shown in Figure 3.

During the final threshold testing, a transition from NS-LBB to S-LBB capture was demonstrated in 26 patients (Figure 4A). An isoelectric interval in the LBBP lead was observed, while V1 RWPT was prolonged due to the loss of direct LV septal myocardial activation, which was reported by a previous study [14]. The LV septal myocardial capture threshold was 0.8 (0.3) V, the LBB capture threshold was 0.4 (0.2) V. The V5 RWPT remained short and constant at different pacing outputs (the V5 RWPT with threshold output [LBB capture threshold] vs. that with low output [2 V/0.5 ms] vs. that with high output [8 V/0.5 ms]): (69.1 [7.4] ms vs. 68.7 [7.4] ms vs. 68.3 [7.1] ms). The V1 RWPT with the threshold output (LBB capture threshold) was significantly higher than that with low output (2 V/0.5 ms): (119.2 [15.9] ms vs. 106.6 [10.8] ms; P < 0.001). There were no significant differences between the V1 RWPT with high output (8 V/0.5 ms) and that with low output (2 V/0.5 ms): (104.2 [9.6] ms vs. 106.6 [10.8] ms).

In 12 patients, a transition from NS-LBB to LVs capture was observed during the final threshold testing (Figure 4B). This presented as an abrupt V5 RWPT prolongation with near-threshold output due to the loss of LBB activation, and the isoelectric interval could not be observed. Specifically, the LBB capture threshold was 1.1 (0.3) V and the LV septal myocardial capture threshold was 0.4 (0.1) V. The V5 RWPT with threshold output (LV septal myocardial capture threshold) was significantly higher than that with low output (2 V/0.5 ms): (87.1 [10.1] ms vs. 65.9 [6.3] ms; P < 0.001). The V5 RWPT remained the same at the output of 8V to 2V: the V5 RWPT with high output (8 V/0.5 ms) vs. that...
Figure 3. Flowchart for different changes in electrocardiogram and electrogram during different stages of the LBBP procedure
Abbreviations: see Figure 2

Figure 4. Different changes in electrocardiogram and LBBP lead electrogram morphology during a decrease in pacing output in the final threshold test. A. Non-selective LBBP transfer to selective LBBP. Decreasing the output from 0.3 V to 0.2 V changes to selective LBB capture and a distinct isoelectric interval observed in the LBBP lead. V5 RWPT remains the shortest (69 ms), V1 RWPT increases from 103 ms to 107 ms. B. Non-selective LBBP transfer to left ventricular septum capture. Decrease in output from 1 V to 0.9 V changes to septal myocardial activation. V5 RWPT increases from 67 ms to 88 ms, while V1 RWPT remains the same (107 ms). Electrogram in LBBP lead shows no discernible change
Abbreviations: LV, left ventricular; NS-LBBP, non-selective LBBP; S-LBBP, selective LBBP; other — see Figure 2
with low output (2 V/0.5 ms): [64.9 [6.0] ms vs. 65.9 [6.3] ms]. There were no significant differences between the V1 RWPT with different outputs (V1 RWPT with threshold output [LV septal myocardial capture threshold] vs. that with low output [2 V/0.5 ms] vs. that with high output [8 V/0.5 ms]): (112.0 [13.8] ms vs. 105.0 [13.0] ms vs. 102.4 [10.8] ms).

Three patients showed no discernible change in QRS or local EGM morphology during the final threshold testing. A sizeable shortening in V5 RWPT at high outputs (8 V/0.5 ms) was observed, although it was not statistically significant, likely because the sample size was too small. This suggests that only LV septal myocardial capture was performed.

**DISCUSSION**

This study first reports a novel LBBP lead implantation technique, which uses the isoelectric interval as an endpoint for lead implantation and was feasible in 87.8% of patients. There were no lead-related complications in this study. This study preliminarily indicates that this novel LBBP lead implantation technique is feasible and safe. The LBB capture rate with strict criteria (demonstration of NS-LBB to S-LBB capture or NS-LBB to LVS capture transition during threshold testing) was reported as 124/468 (26.4%) [14] or 21/51 (41%) [15] in prior studies. In this study, a total of 36 cases (87.8%) reached the endpoint, all of which were confirmed as diagnosis of LBB capture during the threshold testing, which may indicate that this novel LBBP lead implantation technique can increase the LBB capture rate.

The past study has shown that the physiological Purkinje activation was like distal to proximal activation of the ventricular component [16]. An isoelectric interval in the pacing lead can be recorded because direct myocardial capture is absent and therefore ventricular activation over the pacing lead occurs late following initial conduction only over the LBB-Purkinje system. Recording an isoelectric interval was defined as S-LBBP and had a specificity of 100% for confirmation of LBB capture, which was demonstrated by a previous study [17]. That novel endpoint is precise because patients who reach the endpoint were all diagnosed as LBB capture in our study.

Although this novel LBBP lead implantation technique can offer such a precise endpoint, it also has a limitation – not every patient can get the isoelectric interval even if they have LBB capture. In our study, two patients did not reach the endpoint but still were shown as LBB capture during the threshold testing. We think LBB should have a different capture threshold with the left septal myocardium, and that an isoelectric interval can only be recorded when the left septal myocardial threshold is higher than the LBB threshold. By contrast, when the LBB threshold is higher than the left septal myocardial threshold, the isoelectric interval cannot be recorded. That is why these two patients cannot get the isoelectric inter-

val even if they have LBB capture. It reminds us that when applying this novel LBBP lead implantation technique in clinical practice, other electrophysiological characteristics, like impedance and COI, should also be monitored to help to determine the depth of the lead to avoid perforation. Sometimes we need to give up seeking the isoelectric interval to ensure the safety of patients. In addition, the isoelectric interval with near-threshold pacing output during the final threshold test was consistently recorded in only 26/41 (63.4%) patients. We hypothesize that there are two possible reasons. One reason is that the lead would displace proximally during sheath withdrawal or manipulation of the atrial lead, which can result in making the LBB threshold higher than the left septal myocardial threshold. The mean LBB threshold in the patients who had the transition from NS-LBB to LVS capture was 1.1 V although it was higher than that in the patients with the transition from NS-LBB to S-LBB capture, but still it had an acceptable value. Another reason is that the left septal myocardial threshold may transiently rise after the lead approaches the LBB area, which was a visible COI on the unipolar electrogram in most of the patients. This causes a higher left septal myocardial in comparison with the LBB capture threshold and results in a transient recording of the isoelectric interval in most of the patients at the end of the lead screwing procedure. With improvement in injury, reduction in the left septal myocardial threshold below the LBB threshold might have resulted in less selective LBB capture later.

In addition, our study showed that the V5 RWPT for two adjacent paced beats shortens abruptly to ≥10 ms with the same output (2 V/0.5 ms) in the process of lead screwing. This was recorded in 38 cases, all of which were confirmed as LBB capture. It may indicate that when the V5 RWPT for two adjacent paced beats shortens abruptly to ≥10 ms with the same output (2 V/0.5 ms), the lead captures the LBB as NS-LBB. It seems the shortening of V5 RWPT on 2V was also a good endpoint for lead screwing. But in some patients, we can see more than one shortening of V5 RWPT, and the shortening was not easy to recognize using the monitor alone, it always needed measuring. It is obvious that the isoelectric interval is a more visible marker than the shortening of V5 RWPT. What is more, the isoelectric interval can guide the lead more closely to LBB than using the shortening of V5 RWPT as an endpoint, and it can achieve a lower LBB threshold.

**Study limitations**

This study should be interpreted in the context of several limitations. First, this study was performed at a single center with small sample size. Further prospective multi-center randomized controlled clinical trials are needed to validate the novel endpoint for lead implantation. Second, long-term follow-up for the evaluation of clinical outcomes and adverse events is lacking.
CONCLUSION

This study showed that this novel LBBP lead implantation technique, which uses the isoelectric interval as an endpoint for lead implantation, is feasible and safe. As a result, a high proportion of LBB cases with a low LBB capture threshold were revealed. This method can provide a precise endpoint for lead implantation and help facilitate LBBP implantation.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: The corresponding author owns the patent for John Jiang’s connecting cable, which allows for monitoring and recording of electrocardiograms and intracardiac electrograms during the transseptal placement of the pacing lead. The other author declares no conflict of interest.

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