Usefulness of His Bundle Pacing to Achieve Electrical Resynchronization in Patients With Complete Left Bundle Branch Block and the Relation Between Native QRS Axis, Duration, and Normalization

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His Bundle pacing (HBP) restores electrical synchronization in left bundle branch block (LBBB); however, the underlying mechanisms are poorly understood. We examined the relation between native QRS axis in LBBB, a potential indicator of the site of block, and QRS normalization in patients with LBBB. Data from patients (n = 41) undergoing HBP at 3 sites were studied (68 ± 13 years, 13 women). Study criteria included strictly defined complete LBBB and successful implantation of a permanent HBP lead. Preprocedure and postprocedure electrocardiograms were reviewed independently by 2 blinded readers. QRS axis and duration were measured to the nearest 10° and 10 ms, respectively. QRS narrowing or normalization was the primary end point. Of 29 patients meeting study criteria, 9 had frontal plane QRS axes between −60° and −80°, 10 from −40° to 0°, and 10 from +1° to +90°. QRS narrowing occurred in 24 patients (83%, 44 ± 34 ms, p < 0.05). Percent QRS narrowing by axis were 26 ± 19%, 29 ± 25%, and 28 ± 23%, respectively. No correlation between prepacing QRS axis and postpacing narrowing was identified ($r^2 = 0.001, p = 0.9$). In patients with or without QRS normalization after HBP, mean QRS duration was 155 ± 21 vs 171 ± 8 ms, respectively, $p = 0.014$. HBP induces significant QRS narrowing in most patients and normalization in patients with shorter baseline QRS duration. In conclusion, the lack of correlation between native QRS axis and narrowing suggests that proximal His-Purkinje block causes most cases of LBBB, or that additional mechanisms underlie HBP efficacy. Further studies are needed to better understand how to predict those patients in whom HBP will normalize LBBB.  © 2016 Elsevier Inc. All rights reserved. (Am J Cardiol 2016;118:527–534)

Left bundle branch block (LBBB) causes asynchronous contraction of the left ventricle (LV), which may potentially lead to eventual global LV dysfunction.\textsuperscript{1–4} Cardiac resynchronization therapy has emerged as a technique to overcome this electrical delay and has been associated with a reduction in all-cause mortality and nonfatal heart failure events.\textsuperscript{5–8} The idea of resynchronization and its clinical benefits has been extrapolated to support His bundle pacing (HBP) in patients with LBBB and cardiomyopathy. HBP has been shown to achieve significant QRS narrowing, with improved LV ejection fraction, New York Heart Association functional class, and cardiopulmonary reserve.\textsuperscript{9} The mechanisms underlying HBP-mediated improvement in conduction remain poorly understood and have been explained by the concept of longitudinal dissociation that fibers within the His bundle are predestined for the left and right bundle branches (Figure 1). Given the well-described anatomy of the proximal His-Purkinje system,\textsuperscript{10–12} fibers exiting into the left posterior fascicle (LPF) before the site of block will result in earlier activation of the posterior-inferior LV, and hence, a left or extreme left axis deviation (Figure 1). Based on the concept of longitudinal dissociation and the anatomy of the HB, we hypothesized that preprocedure extreme left axis deviation indicates distal His-Purkinje block and a lower likelihood that HBP would normalize the QRS duration.

Methods

The study was approved by the institutional review board at the 3 centers. Data from 41 patients who underwent permanent HBP at these sites were evaluated retrospectively and included 17 patients from Geisinger Clinic (site 1), 14 from University of Vermont (site 2), and 10 from University of California, Los Angeles (site 3). The study period included 7 years of implantation (2008 to 2015). Patients who met a strict criteria for complete LBBB (QRS duration ≥140 ms in men or 130 ms in women; a QS or RS in leads

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Figure 1. His-Purkinje anatomy and theory of longitudinal dissociation. (A) His-Purkinje anatomy with longitudinal dissociation. Fibers are longitudinally oriented and “predestined” from the His bundle to the bundle branches. (B) Proximal LBBB, where the block is before the exit of any fibers of the LPF. (C) Distal LBBB, where some of the LPF fibers have exited before the level of the block. Sketch adapted from Rosenbaum. AVN = atrioventricular node; HB = His bundle; LAF = left anterior fascicle.

Figure 2. Strict criteria for complete LBBB. Sample 12-lead ECG of patient who meets strict LBBB criteria. In this example male patient, the QRS duration is >140 ms, there is an RS in lead V3, and there is mid-QRS slowing/notching in leads V1, V2, V5, and V6.
Programming was at the discretion of the implanting physician. Device placement to a site demonstrating a discrete His potential, (Minnesota), a SelectSecure 3830 lead (Medtronic) was advanced to the region of the His bundle and used to map a basis for selective HBP (after the His-ventricular, or “HV”, interval) and from the onset of steepest deflection in nonselective HBP (Figure 4).

Of the patients who met study criteria, pre-HBP procedure ECGs were evaluated by 2 blinded readers in an independent ECG core laboratory. Native QRS axis was measured to the nearest 10°, and preprocedural QRS duration was measured to the nearest 10 ms. Postprocedure ECGs were deidentified. The same 2 blinded readers measured postprocedural QRS to the nearest 10 ms. Any discordant measurements between readers were reread in a group conference where a third blinded reader was present. Postprocedural ECGs and electrophysiological tracings, QRS was measured from the onset of the first deviation from baseline for selective HBP (after the His-ventricular, or “HV”, interval) and from the onset of steepest deflection in nonselective HBP (Figure 4).

The primary study outcome was the degree of QRS narrowing with HBP (absolute narrowing and percent narrowing) relative to the mean QRS axis in LBBB at baseline. The secondary outcomes were the relation between QRS narrowing and QRS axis, and the relation between QRS narrowing and ischemic versus nonischemic cardiomyopathy.

Data are expressed as mean ± SD. All indexes reported were measured from consistent tracings without artifact or loss of capture. The study data were normally distributed, and paired comparisons were made using the Student t test. Data from ≥2 groups were compared using the one-way analysis of variance. A p value ≤0.05 was considered statistically significant. Correlation between QRS narrowing and mean native QRS axis or preprocedural QRS duration was determined using linear regression. Correlation between QRS narrowing and type of cardiomyopathy was determined using one-way analysis of variance, whereas normalization was evaluated using Fisher’s exact test. Analyses were performed using Systat Software, version 13 (San Jose, California).

Results

Of the 41 patients studied, 29 patients fulfilled study criteria (including strict LBBB as defined previously) and were included in the study (Figure 5). Sixteen patients were men and 13 were women. The frontal plane axis of 9 patients ranged from −60° to −80°, 10 from −40° to 0°, and 10 from +1° to +90° (Table 1).

In 24 of the 29 study patients (83%), HBP resulted in some degree of QRS narrowing, whereas 21 of 29 patients (72%) showed complete QRS normalization, as defined by a postprocedural QRS duration of ≤120 ms. Overall, the mean QRS duration from preprocedural to postprocedural decreased from 160 ± 16 ms to 115 ± 36 ms, respectively (p <0.0001). Figure 6 depicts the change in QRS duration from pre-to post-HBP procedure. Mean preprocedural QRS duration in patients who had QRS normalization was 155 ± 21 ms compared with those with no significant change or incomplete normalization with a mean preprocedural QRS duration of 171 ± 8 ms (p = 0.014), as shown in Figure 6. Mean QRS narrowing in patients with nonselective (n = 8) versus selective (n = 21) HBP was 68 ± 26 versus 36 ± 33 ms (p = 0.024).

Across the study population, there was no correlation between preprocedural QRS axis and postprocedural percent.
QRS narrowing \((r^2 = 0.001, p = 0.904, \text{Figure 6})\), absolute change in QRS duration \((r^2 = 0.001, p = 0.869, \text{Figure 6})\), or post-HBP QRS duration \((r^2 = 0.0001, p = 0.968, \text{Figure 6})\). In patients with a QRS axis ranging from \(-60^\circ\) to \(-80^\circ\), the QRS duration narrowed by 26 ± 19%, whereas in those with a QRS axis from \(-40^\circ\) to \(0^\circ\), the QRS duration narrowed by 29 ± 25%. In patients with a QRS axis of \(+1^\circ\) to \(+90^\circ\), QRS duration narrowed by 28 ± 23% with HBP. The means were not significantly different \((p = 0.958)\).

QRS percent narrowing and normalization by QRS axis category are depicted in Figure 7, respectively.

Likewise, there was no correlation between frontal plane axis and percent QRS narrowing when evaluated by individual study site \(\text{site 1: } r^2 = 0.19, p = 0.278; \text{site 2: } r^2 = 0.020, p = 0.663; \text{and site 3: } r^2 = 0.04, p = 0.627\).

In patients with ischemic cardiomyopathy, mean absolute narrowing was 60 ± 25 ms compared with 29 ± 31 ms in those with nonischemic cardiomyopathy \((p = 0.164)\), and postprocedure percent QRS narrowing was 38 ± 16% compared with 19 ± 20% in the ischemic and nonischemic groups, respectively \((p = 0.2)\).

**Discussion**

The major findings of the present study are (1) HBP results in QRS narrowing or normalization in a majority of patients with complete LBBB, independent of the site of block as estimated by the theory of longitudinal dissociation and (2) patients with mean QRS duration <155 ± 21 ms were more likely to normalize LBBB than those with greater QRS duration. We observed that 83% of the study subjects demonstrated QRS narrowing, whereas 71% had complete QRS normalization after HBP. Native QRS axis did not predict QRS narrowing or normalization.

Traditionally, the efficacy of HBP has rested on the theory of longitudinal dissociation, the concept that fibers within the HB are predestined for the left bundle or right bundle, and as such, conduction block within the HB can be bypassed by pacing distally.\(^{14-16}\) Although it is possible that the high success rate of HBP observed in this study and several other recent studies\(^{17,18}\) suggests that the site of block in patients with strict LBBBs is within the proximal HB, it also raises the possibility that other mechanisms may explain how HBP works.

To date, the mechanism by which HBP works rests on early descriptions of the structural organization and electrophysiological properties of the His-Purkinje system from the 1970s. James and Sherf\(^{11}\) posited that within the HB, there are longitudinally oriented cells that are separated by collagen sheaths that continue directly into the bundle branches. Narula showed that pacing the distal HB could restore native QRS, thereby suggesting the block was within the HB and could be bypassed. Distal lesions likely involve complete blockage of the left anterior fascicle and LPF, distal to where the HBP lead would be placed.\(^{15}\) Subsequent studies further demonstrated the potential and feasibility of HBP with the implantation of permanent HBP leads.\(^{18}\) Barba-Pichardo et al suggested the inability to narrow QRS in some patients was attributed to infra-Hisian block, possibly within the His or peripheral in the Purkinje system.
or bundles, the latter of which could not be bypassed and therefore not corrected. In the present study, we found no relation between baseline QRS duration and the degree of QRS narrowing in LBBB (Figure 6); however, the baseline QRS duration of patients who showed normalization compared with those who did not, a QRS duration \(<155 \pm 21\) ms was associated with QRS narrowing.

We examined whether frontal plane axis was predictive of a more proximal lesion within the His-Purkinje system. The LPF is composed of fibers dispersed over a broad area, exiting the His-Purkinje system as high as the level of the His bundle and extending down the left bundle. Accordingly, it would be expected that the more distal the level a block is, more fibers of the LPF have exited, resulting in an ECG with LBBB and leftward axis deviation pattern (Figure 1). As an extension, if the bulk of LPF fibers exit before the level of block, left anterior fascicular block would result and not LBBB. Such patients were not included in this study.

![Figure 5](image_url)

**Figure 5. Study population.** Schematic of inclusion data. Study site A refers to UCLA, study site B to Geisinger, and study site C to University of Vermont. CHB = complete heart block; IVCD = interventricular conduction delay; LAFB = left anterior fascicular block.

**Table 1**

<table>
<thead>
<tr>
<th>Demographics of patients included in study</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total pre-procedure patients included</td>
<td>29</td>
<td>100%</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>68±13</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>13</td>
<td>41%</td>
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<tr>
<td>LVEF (%)</td>
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<tr>
<td>&lt;25</td>
<td>9</td>
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<tr>
<td>25-35</td>
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<tr>
<td>36-45</td>
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<td>&gt;45</td>
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<tr>
<td>Cardiomyopathy</td>
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<td>Nonischemic</td>
<td>10</td>
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<td>28%</td>
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<td>Preserved ejection fraction</td>
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<tr>
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<td>7</td>
<td>24%</td>
</tr>
<tr>
<td>Frontal Plane Axis</td>
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<td></td>
</tr>
<tr>
<td>Extreme left axis deviation (-0° to -80°)</td>
<td>9</td>
<td>31%</td>
</tr>
<tr>
<td>Horizontal to left axis deviation (-40° to 0°)</td>
<td>10</td>
<td>34%</td>
</tr>
<tr>
<td>Normal axis (+10° to +90°)</td>
<td>10</td>
<td>34%</td>
</tr>
</tbody>
</table>
Figure 6. Relation between QRS axis, duration, and QRS narrowing with HBP. (A) Pre-HBP and post-HBP QRS duration for all included study patients. (B) Relation between QRS normalization and baseline QRS duration. (C) Correlation between QRS axis and percent QRS narrowing. (D) Correlation between QRS axis and change in QRS duration. (E) Correlation between baseline pre-HBP QRS duration and percent QRS narrowing.
In this study, there was no correlation between extreme left axis deviation and refractoriness to HBP. Instead, the data showed a reduction in QRS duration by an average of 44 ms, independent of frontal plane axis in 24 of 29 patients (72%). It is possible that the cases that did not narrow were attributable to block distal to the HB and that pacing anywhere along the HB would not be distal to that site of block, but it is also possible that the efficacy of HBP may not only depend on bypassing a structural block but in overcoming a functional block as well. An alternative or complementary mechanism may be related to the pacing output required to capture tissue (including normal myocardium and/or His-Purkinje tissue) just distal to the site of block. In a crossover comparison between HBP and biventricular pacing, 21 of 29 patients (72%) experienced QRS narrowing at the time of implant with HBP. Lustgarten et al \(^\text{7}\) noted that the HBP capture threshold was higher, although insignificantly, than the LV lead threshold. However, more recently, Vijayaraman et al \(^\text{21}\) demonstrated even better success rates with voltages as low as 1.3 ± 0.7 V. They specifically demonstrated significantly higher rates of success in infranodal blocks than previously noted. This may be operator dependent but may also reflect improved technology allowing better lead placement. A limitation of this study was its sample size. This also limits the ability to control for potential confounders, such as study site, variations in technique and equipment, and direct versus indirect capture. Likewise, of the 29 patients evaluated, it could not be determined in 7 of them whether they had ischemic cardiomyopathy, nonischemic cardiomyopathy, neither, or both.

**Acknowledgment:** The authors acknowledge the National Heart Lung and Blood Institutes of the National Institutes of Health for HL084261 to Dr. Shivkumar and HL125730 to Dr. Ajijola.

**Disclosures**

The authors have no conflicts of interest to disclose.


