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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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Abstract

His Bundle pacing (HBP) restores electrical synchronization in left bundle branch block (LBBB), however, the underlying mechanisms are poorly understood. We examined the relationship 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 three sites were studied (68±13 years, 13 females). Study criteria included strictly defined complete LBBB, and successful implantation of a permanent HBP lead. Pre- and post-procedure electrocardiograms were reviewed independently by two blinded readers. QRS axis and duration were measured to the nearest 10° and 10ms, respectively. QRS narrowing or normalization was the primary endpoint. Of 29 patients meeting study criteria, 9 had frontal plane QRS axes between -60° and -80° , 10 from -40° to 0° , and 10 from $+1^{\circ}$ to $+90^{\circ}$. QRS narrowing occurred in 24 patients (83%, 44 ± 34 ms, p<0.05). Percent QRS narrowing by axis were $26\pm19\%$, $29\pm25\%$, and $28\pm23\%$, respectively. No correlation between pre-pacing QRS axis and post-pacing narrowing was identified ($r^2 = 0.001$, p = 0.9). In patients with or without QRS normalization following HBP, mean QRS duration were 155±21ms vs. 171±8ms, 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

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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.

Keywords

His Bundle Pacing; QRS resynchronization; left bundle branch block

INTRODUCTION

Left bundle branch block (LBBB) causes asynchronous contraction of the LV, which may potentially lead to eventual global LV dysfunction.¹⁻⁴ Cardiac resynchronization therapy (CRT) has emerged as a technique to overcome this electrical delay and has been associated with a reduction in all-cause mortality and non-fatal heart failure events.^{5–7,8} 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 ORS narrowing, with improved LV EF, New York Heart Association (NYHA) functional class, and cardiopulmonary reserve.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 (Figure 1A) bundle branches. Given the well-described anatomy of the proximal His Purkinje system^{10–12}, fibers exiting into the left posterior fascicle (LPF) prior to the site of block will result in earlier activation of the posterior-inferior LV, and hence a left or extreme left axis deviation (Figure 1B–C). Based on the concept of longitudinal dissociation and the anatomy of the HB, we hypothesized, that pre-procedure 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 (IRB) 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 greater than or equal to 140milliseconds (ms) in men or 130ms in women; a QS or RS in leads v1 or v3; and a mid QRS slowing or notching in 2 of the leads V1, V2, V5, V6, I, or aVL)¹³, had an indication for pacing or cardiac resynchronization, and who underwent a successful implantation of an HBP lead were included in this study (Figure 2). Criteria for LBBB were made from a standard 12-lead electrocardiogram (25mm/s paper speed) or electrocardiograms recorded using an electrophysiological mapping system (Cardiolab, GE Healthcare, OH, USA).

After femoral venotomy, a multipolar catheter was advanced to the region of the His bundle, and used to map a discrete His potential. Using standard lead and device implantation techniques, a defibrillator lead was placed into the right ventricle for patients undergoing CRT-D implantation. Next, using a SelectSite C304 or C315 catheter system (Medtronic,

Minneapolis, MN, USA), a SelectSecure 3830 lead (Medtronic, Minneapolis, MN, USA) was secured to a site demonstrating a discrete His potential, guided by the multipolar catheter (Figure 3A). An atrial lead and generator were placed in the standard fashion. Device programming was at the discretion of the implanting physician.

Of the patients who met study criteria, pre-HBP procedure ECGs were evaluated by 2 blinded readers in an independent ECG Core Lab. Native QRS axis was measured to the nearest 10 degrees, and pre-procedure QRS duration was measured to the nearest 10ms. Post-procedure ECGs were de-identified. The same 2 blinded readers measured post-procedure QRS to the nearest 10ms. Any discordant measurements between readers were reread in a group conference where a third blinded reader was present. On post-procedure ECGs and EP tracings, QRS was measured from the onset of the first deviation from baseline for selective HBP (after the "HV" interval) and from the onset of steepest deflection in non-selective 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 relationship between QRS narrowing and QRS axis, and the relationship between QRS narrowing ischemic versus nonischemic cardiomyopathy.

Data are expressed as mean ± standard deviation. All indices 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 (ANOVA). A p value 0.05 was considered statistically significant. Correlation between QRS narrowing and mean native QRS axis or pre-procedure QRS duration was determined using linear regression. Correlation between QRS narrowing and type of cardiomyopathy was determined using one-way ANOVA, while normalization was evaluated using Fisher's exact test. Analyses were performed using Systat version 13 (San Jose, CA, USA).

Results

Of the 41 patients studied, 29 patients fulfilled study criteria (including strict LBBB as defined above), and were included in the study. Sixteen patients were male and 13 were female (Figure 5). The frontal plane axis of 9 patients ranged from -60° to -80° , 10 from -40° to 0° , and 10 from $+1^{\circ}$ to $+90^{\circ}$.

In 24 of the 29 study patients (83%), HBP resulted in some degree QRS narrowing, while 21 of 29 patients (72%) showed complete QRS normalization, as defined by a post-procedure QRS duration of 120ms. Overall, the mean QRS duration from pre- to post-procedure decreased from $160\pm16ms$ to $115\pm36ms$ respectively (p < 0.0001). Figure 6A depicts the change in QRS duration from pre- to post-HBP procedure. Mean pre-procedure QRS duration in patients who had QRS normalization was $155\pm21ms$ compared to those with no significant change or incomplete normalization with a mean pre-procedure QRS duration of $171\pm8ms$ (p = 0.014), as shown in Figure 6B. Mean QRS narrowing in patients with non-selective (n=8) vs. selective (n=21) HBP was $68\pm26ms$ vs. $36\pm33ms$ (p=0.024).

Across the study population, there was no correlation between pre-procedure QRS axis and post-procedure percent QRS narrowing ($r^2 = 0.001$, p = 0.904, Figure 6C), absolute change in QRS duration ($r^2 = 0.001$, p = 0.869, Figure 6D), or post-HBP QRS duration ($r^2 = 0.0001$, p = 0.968, Figure 6E). In patients with a QRS axis ranging between -60° and -80° , the QRS duration narrowed by $26\pm19\%$, while in those with a QRS axis between -40° and 0° , the QRS duration narrowed by $29\pm25\%$. In patients with a QRS axis of $+1^{\circ}$ to $+90^{\circ}$, QRS duration narrowed by $28\pm23\%$ with HBP. The means were not significantly different (p=0.958). QRS percent narrowing and normalization by QRS axis category are depicted in Figures 7A and 7B respectively.

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

In patients with ischemic cardiomyopathy mean absolute narrowing was 60 ± 25 ms compared to 29 ± 31 ms in those with non-ischemic cardiomyopathy (p=0.164), and post-procedure percent QRS narrowing was $38\pm16\%$ compared to $19\pm20\%$ 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±21ms were more likely to normalize LBBB than those with greater QRS duration. We observed that 83% of the study subjects demonstrated QRS narrowing, while 71% had complete QRS normalization following 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 LB or RB, and as such, conduction block within the HB can be bypassed by pacing distally^{14–16}. While it is possible that the high success rate of HBP observed in this study and several other recent studies¹⁷¹⁸ 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 posited that within the HB, there are longitudinally-oriented cells that are separated by collagen sheaths that continue directly into the bundle branches¹¹. 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 LAF and LPF, distal to where the HBP lead would be placed¹⁵. Barba-Pichardo *et al.* further demonstrated the potential and feasibility of HBP with the implantation of permanent HBP leads^{18,19}. 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 corrected¹⁹. In the present study, we found no relationship between baseline QRS duration and the degree of QRS narrowing in LBBB (Figure 6D), however, the baseline QRS duration of patients who showed normalization compared to those who did not, a QRS duration < 155 ± 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^{12,20}. 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 1B). As an extension, if the bulk of LPF fibers exit prior to the level of block, LAFB would result, and not LBBB. Such patients were not included in this study.

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 44ms, independent of frontal plane axis in 24 of 29 patients (83%). 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 (72%) of patients experienced QRS narrowing at the time of implant with HBP. Lustgarten et al. noted that the HBP capture threshold was higher, though insignificantly, compared to the LV lead threshold¹⁷. However, more recently, Vijavaraman et al. demonstrated even better success rates with voltages as low as $1.3 \pm 0.7 V^{21}$. 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.

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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 left bundle branch block (LBBB), where the block is prior to the exit of any fibers of the left posterior fascicle (LPF). C) Distal LBBB, where some of the LPF fibers have exited before the level of the block. Sketch adapted from Rosenbaum. AVN=AV node, HB=His bundle, LBB=Left bundle branch, LPF=Left posterior fascicle, LAF=L anterior fascicle, RBB=Right bundle branch



FIGURE 2. Strict Criteria for Complete Left Bundle Branch Block

Sample 12-lead ECG of patient who meets strict LBBB criteria. In this example male patient, the QRS duration is >140ms, there is an RS in lead v3, and there is mid-QRS slowing/notching in leads v1, v2, v5, and v6.



FIGURE 3. His Bundle Lead Placement and QRS Response to pacing

A) Fluoroscopy image following His bundle lead placement. Also shown are the right ventricular (RV) defibrillator lead), and the right atrial (RA) lead. The fluoroscopic image is shown in the antero-posterior (AP) projection. B) Representative example of 12-electrocardiogram showing QRS narrowing pre- and C) post-His bundle Pacing.



FIGURE 4. Quantification of QRS Duration in Nonselective and Selective His Bundle Capture Example of non-selective (A) and selective (B) His bundle pacing (HBP). In non-selective HBP cases, QRS was measured following the area of periventricular capture represented by a slurred area between the pacing spike and the steep deflection of the QRS. In selective pacing cases, QRS was measured at the start of the first deflection from the isoelectric period following the pacing spike.



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.











FIGURE 6. Relationship between QRS axis, duration and QRS narrowing with His bundle pacing

A) pre- and post-His bundle pacing (HBP) QRS duration for all included study patients. B) Relationship 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.



FIGURE 7. Relationship between QRS axis and QRS normalization

A) Percent QRS narrowing by QRS axis categorized by range. B) Normalization of QRS following HBP by QRS axis categorized by range.

Table 1

Demographics of patients included in study

	Number	%
Total pre-procedure patients included	29	100%
Age (Years)	68±13	
Women	13	41%
LVEF (%)		
• <25	9	
• 25–35	9	
• 36–45	3	
• >45	6	
Cardiomyopathy		
Nonischemic	10	34%
• Ischemic	8	28%
Preserved ejection fraction	4	14%
• Unknown	7	24%
Frontal Plane Axis:		
• Extreme left axis deviation (-0° to -80°)	9	31%
\bullet Horizontal to left axis deviation (–40° to 0°)	10	34%
• Normal axis (+10° to +90°)	10	34%