His Bundle Pacing: A New Strategy for Physiological Ventricular Activation

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The specialized fibers of the His-Purkinje system are essential for the maintenance of the coordinated, synchronous ventricular contraction via endocardial to epicardial and apical to basal electrical activation. The right ventricle has been the most commonly used site to deliver artificial pacemaker stimuli since the 1950s, although pacing from both right ventricular (RV) apical and septal positions causes ventricular dyssynchrony, which is in turn associated with deleterious consequences including impaired myocardial perfusion,[1] mitral and tricuspid regurgitation,[2] an increased risk of atrial fibrillation, and systolic contractile dysfunction.[3] As a result, the risk of hospitalization for heart failure was strikingly increased in patients receiving a higher proportion of ventricular pacing in the DAVID (Dual Chamber and VVI Implantable Defibrillator) trial [4,5] and MOST (Mode Selection Trial)[6] alongside an increased risk of ventricular tachycardia/fibrillation.[7] Current guidelines[8] and pacemaker algorithms[9] therefore promote the minimization of right ventricular pacing wherever possible; however, excessive restriction of RV pacing with, for example, long atrioventricular delays impairs atrioventricular synchrony, increasing the risk of atrioventricular block at higher atrial rates and predisposing to mitral regurgitation. Furthermore, current strategies for the reduction of RV pacing have not improved clinical outcomes.[10]

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In patients with impairment of left ventricular (LV) systolic function and dyssynchrony attributable to left bundle branch block with a broad QRS duration, the benefits of at least partial restoration of ventricular synchrony with cardiac resynchronization therapy (CRT) from RV and coronary venous approaches are well established.[11,12] However, there remain patient groups for whom the indication for CRT is contentious, including those with right bundle branch block,[13] while ≈30% of patients meeting criteria for CRT implantation have a suboptimal clinical response.[14] The benefits of CRT are also less clear cut in patients with left bundle branch block and a relatively narrow QRS complex, and in a further group of patients it is not possible to achieve satisfactory placement of an left ventricular lead because of unfavorable anatomy of the coronary venous system.[15]

There exists a need for new pacing techniques that could reduce intraventricular and atrioventricular dyssynchrony by providing a more physiological pattern of ventricular electrical activation, with the aim of maintaining contractile function, optimizing atrioventricular synchrony and reducing the clinical complications of a high burden of RV pacing (RVP).

His bundle pacing (HBP) is an alternative approach to RV and biventricular pacing and is performed with the aim of maintaining a physiological pattern of ventricular activation via the native His-Purkinje system. One further potential advantage of HBP compared with RVP is a theoretical reduction in the risk of functional tricuspid regurgitation when the lead position lies on the atrial side of the tricuspid valve (as is the case in proximal His bundle implants). A reduction in tricuspid regurgitation has yet to be proven clinically with His bundle pacing, however, and would not be expected when His pacing is combined with transvalvular lead systems such as implantable cardioverter-defibrillator leads or with including RVP and distal His/conducting system implants.

The conceptual benefits of HBP compared with RVP in terms of improved QRS durations and ventricular activation patterns are increasingly recognized, while the feasibility of permanent HBP in patients was demonstrated in 2000.[16] The development of new leads and delivery catheters has dramatically reduced the learning curve for operators undertaking HBP, thus supporting wider clinical uptake. HBP is currently undergoing clinical trials to test whether it has potential clinical benefits over RVP or biventricular pacing.

Development and Early Experience of Human HBP

The His bundle lies in most people within the membranous portion of the interventricular septum, with a proportion of the proximal bundle lying on the right atrial portion of the septum, superior to the tricuspid valve annulus.[17] The His bundle is surrounded by fibrous connective tissue rather than myocardium, and then enters the muscular septum and divides to form the right and left bundles. Electrical recording and stimulation of the His bundle was first described using an open-chest model in dogs by Scherlag,[18] and subsequently by endocardial approaches in dogs[19] and humans.[20,21] It was also subsequently demonstrated that temporary transvenous HBP could reduce QRS duration and normalize electrocardiographic appearances in patients with bundle branch block.[22] Permanent HBP in dogs, in which an exposed screw lead was implanted through the fibrous tissue of the membranous septum to stimulate the His bundle, was described in 1992.[19]

The first description of permanent HBP in patients by Deshmukh[16] established the feasibility of implanting a transvenous pacemaker system with a lead directed to the His bundle and highlighted the potential for acute and chronic hemodynamic improvement with HBP relative to RVP. Their report included a series of 18 patients with chronic atrial fibrillation, narrow QRS complexes, and LV systolic dysfunction. HBP was successfully achieved in 12, while patients with a rapid ventricular rate also underwent atrioventricular node ablation. An electrophysiological mapping catheter was used to localize the His bundle, and an active fixation pacemaker lead with a nonretractable screw was affixed to the proximal intraventricular septum to activate the His bundle. When compared with baseline, improvements in LV dimensions and systolic function were observed. Similar results were reported in a larger series of 39 patients in 2004,[23] with acute improvements in hemodynamics and exercise performance demonstrated in a subgroup undergoing more detailed clinical investigation.

Delivering electrical stimulation at or adjacent to the His bundle can lead to either selective capture (in which only the His bundle is stimulated, also known as direct HBP) or nonselective capture (in which fusion capture between the His bundle and adjacent ventricular tissue occurs,[24] leading to a preexcitation-like pattern, also known as para-Hisian pacing). Selective HBP leads to a paced QRS complex that is similar to the native complex (Figure 1). Further criteria for the definition of selective HBP were initially established and validated by Deshmuk et al in their original and subsequent reports,[25,26] and have been subsequently modified[24] to improve their specificity when including patients with and without His bundle conducting system disease. This consensus definition is based around 4 criteria, including:

1. Relationship of the His-QRS and stimulus-QRS intervals.
2. Presence or absence of direct capture of the local ventricular electrogram on the pacing lead.
3. QRS duration and morphology.
4. Capture thresholds.

The extent to which selective HBP is preferable to nonselective His capture remains unclear and is a topic of ongoing investigation. Though a greater reduction in QRS width is seen with selective capture,[27] nonselective capture appears to result in similar LV activation time and pattern.

Acute and Chronic Effects of HBP

Acute Effects

While establishing the feasibility of HBP and identifying potential clinical benefits, the early case series' were not designed to directly compare outcomes from HBP to RV pacing.

Catanzariti et al[28] compared the electromechanical effects of RV apical pacing versus HBP in patients undergoing permanent implantation of a His bundle pacing lead. Marked improvements in echocardiographic indices of ventricular synchrony were demonstrated when the patients were assigned to HBP mode, along with a reduction in mitral regurgitation and improvement in LV systolic function. In a single-center, double-blind crossover study of a subgroup of 17 patients (reported as part of a series of 68 patients), improvements in exercise capacity were demonstrated when patients were assigned to HBP.[29] Mechanistically, HBP improved myocardial perfusion, dyssychrony, and mitral regurgitation in a 3-month crossover trial of 12 patients but had no effect on LV systolic function.[30] More recently, in patients with LV systolic dysfunction, first degree atrioventricular block and either right bundle branch block or narrow QRS complex, temporary HBP caused no increase in QRS duration (in contrast to temporary biventricular pacing) and led to acute hemodynamic benefit with a 4.1-mm Hg increase in systolic blood pressure compared with baseline using noninvasive averaged beat-to-beat recordings.[30] A series of case reports has also described sometimes dramatic clinical and cardiac functional improvement following HBP implant for a variety of indications.[31–35] In contrast to these reported benefits, Padelleti et al[36] performed a comparison of LV, RV, and His bundle pacing in the setting of an electrophysiological study and did not identify an improvement in dp/dt with HBP.

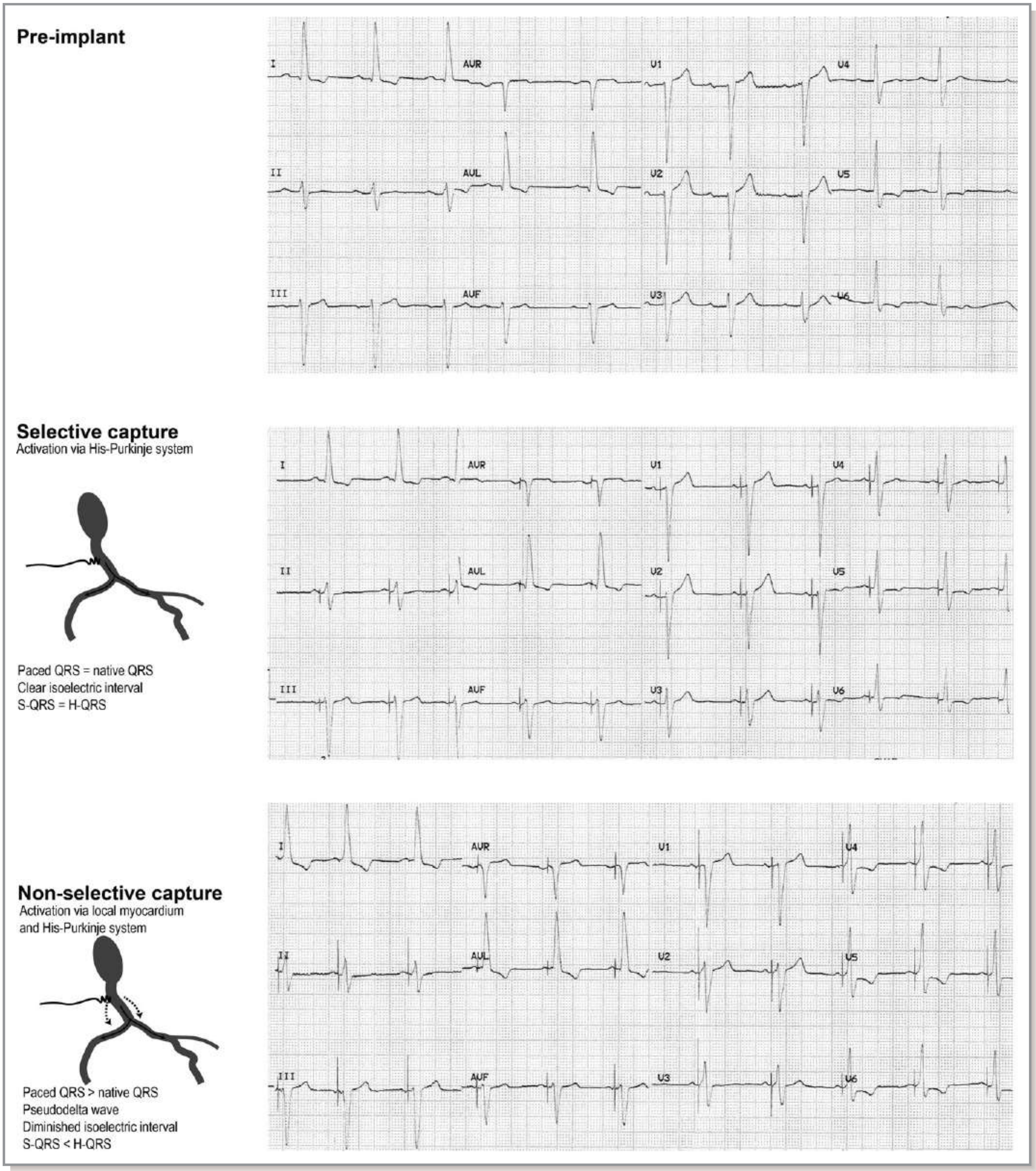

Figure 1. ECGs from the same patient demonstrating selective and nonselective ventricular capture according to pacing energy. Selective capture is seen at 4 V at 1 ms while nonselective capture occurs higher output (8 V at 1 ms; note the pseudodelta wave and absence of stimulus-QRS [S-QRS] isoelectric interval in nonselective capture). Depending on the lead position and His bundle anatomy, some patients (the majority in many series) will exhibit only nonselective capture regardless of pacemaker output. H-QRS indicates His electrogram to QRS interval.

The reasons for this apparent disparity may include the wide range of LV systolic function in patients within the study or possibly the narrow QRS durations and the lack of repeated hemodynamic measurements that are required to minimize the effect of spontaneous variations of the hemodynamic signal.

Chronic Effects

Fewer studies have addressed the question of whether HBP improves clinical outcomes in the medium to long term. In a relatively large series, outcomes between cohorts were retrospectively compared between 2 hospitals, 1 performing RVP and the other routinely attempting HBP implant.[37] At 2-year follow-up, no difference in heart failure hospitalization rate, mortality, or atrial fibrillation was demonstrated between the groups, though the subgroup of patients with high ventricular pacing burden (>40%) did demonstrate a reduction in heart failure hospitalization rate with low event rates. At 5-year follow-up, death or heart failure hospitalization was lower in the HBP group relative to the RVP group.[38] These authors recently reported clinical outcomes from a cohort of 765 patients, with 433 assigned to RVP and 332 to attempted HBP, with successful implant in 304. At a mean follow-up of 725±423 days, the composite primary outcome of death, heart failure hospitalization, or upgrade to biventricular pacing was significantly lower in the HBP group (hazard ratio, 0.71).[39] In a study of 26 patients who had undergone RV and His bundle lead placement, LV systolic function, indices of ventricular synchrony, and mitral regurgitation were all improved when the pacing mode was set to HBP relative to RVP at a mean of 36 months following the implant.[40] In a randomized crossover trial of RVP versus HBP in patients with narrow QRS duration and preserved LV systolic function, selective or nonselective HBP was associated with improved ventricular synchrony and a 5% absolute increase in systolic function relative to RVP after 12 months.[41]

Recent observational studies have reported excellent long-term results from HBP. In 74 patients with left bundle branch block and heart failure, improvements in LV systolic function and functional class were noted at mean follow-up of 37.1 months.[42] Furthermore, in the largest study to date (successful HBP in 304 patients within a total cohort of 765), the composite primary end point of death, heart failure hospitalization, or upgrade to CRT was significant reduced in the HBP group at mean 6 0.4±35 months.[39]

HBP in CRT Eligible Populations

HBP has most commonly been considered as an alternative to RVP but is increasingly considered in patients with bundle branch blocks or an indication for CRT (or as a rescue strategy if CRT is not possible). This is because it is frequently possible with HBP to recruit the native conducting system in many patients with advanced conducting system disease with bundle branch blocks (see example of right bundle branch block reversal in Figure 2). The mechanisms for the reduction in QRS duration with HBP remain to be fully elucidated but may include recruitment of fibers distal to the site of delay, longitudinal dissociation, capture attributable to higher pacing outputs, and hyperpolarizing dormant His bundle tissue.[43]

Vijayaraman et al[44] studied 100 patients with complete or advanced atrioventricular block (46% with atrioventricular nodal block and 54% with infranodal block; 23% of this cohort had left bundle branch block). Patients with infranodal block had a mean QRS duration of 143±18 ms at baseline, which was reduced to 134±17 ms with predominantly nonselective HBP in this group. In a study of 29 patients with CRT indication assigned to crossover comparison between HBP and biventricular pacing, clinical and functional parameter improvements were equivalent between the pacing modes in 12 patients completing the study at 1 year.[45] Ajijola et al[46] attempted HBP in 21 patients with a CRT indication, achieving technical implant success with narrowing of the QRS complex (from 180±23 to 129±13 ms) in 76% of patients, along with improvements in functional class and systolic function at median 12-month follow-up. In patients with a CRT indication or previous unsuccessful CRT implant, HBP was successful in 95 of 106 patients with significant reduction in QRS duration and improvement in systolic function and functional class.[47] A technique for direct left bundle branch pacing has been reported recently and may be an alternative strategy when bundle branch block cannot be overcome by HBP.[48]

The limited available evidence therefore supports HBP as an alternative strategy to CRT when this is not possible, though HBP has recently been shown to provide better ventricular activation times and a greater acute hemodynamic benefit than biventricular pacing in a CRT-eligible population,[49] and ongoing prospective trials will further evaluate this question.

New Leads and Delivery Catheters

Following its original description in patients, wider uptake of HBP was initially precluded by the technical difficulty of identifying the optimal target for delivering selective HBP (which is around 2 mm) and of subsequently maintaining a secure lead position.[16] In early studies, the His bundle was identified using electrophysiological mapping catheters, and the pacing lead was manipulated to this His bundle using reformed stylets and the risk of subsequent lead instability and displacement restricted His bundle pacing to a few expert centers.

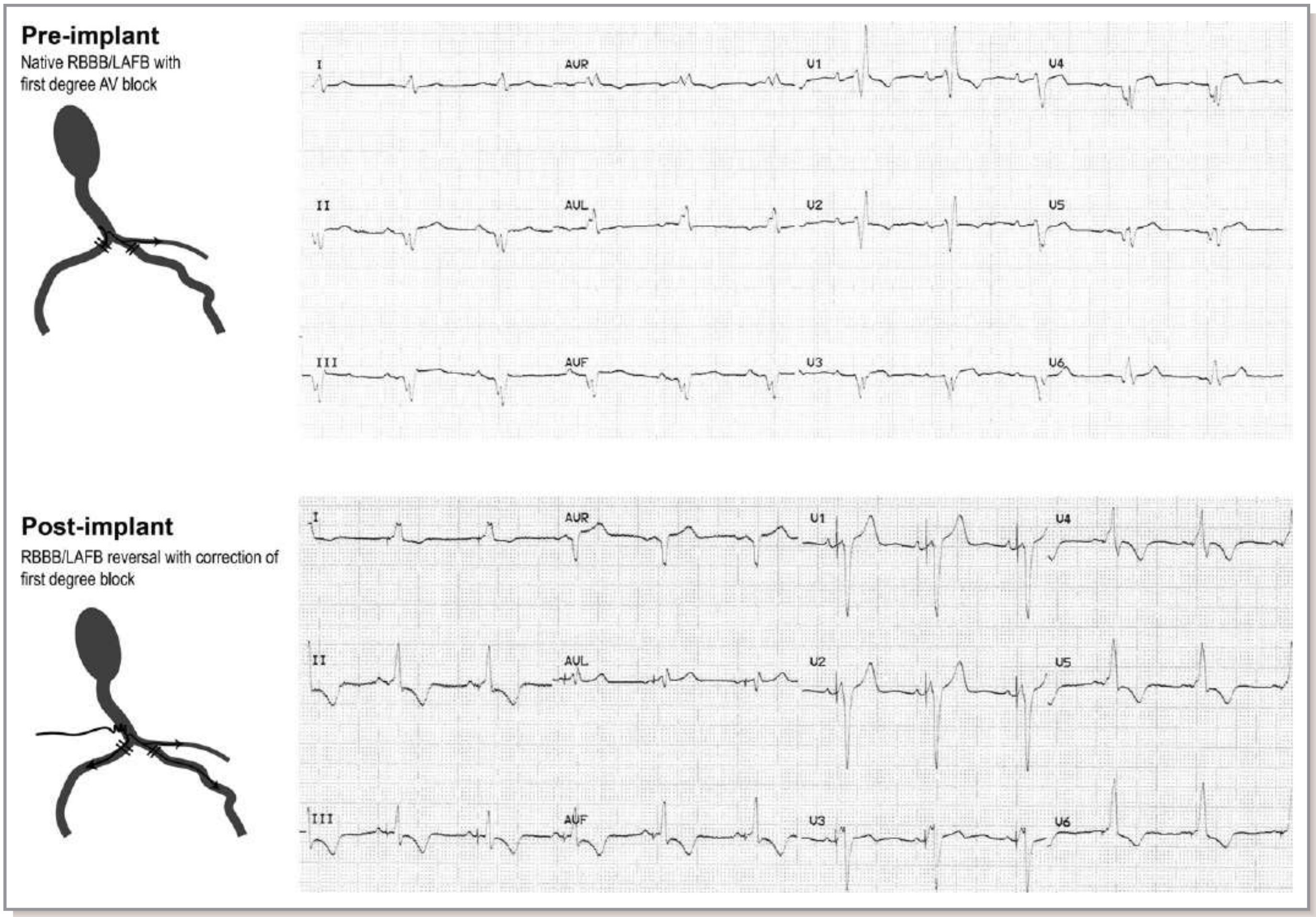

Figure 2. Correction of right bundle branch block (RBBB)/left anterior fascicular block (LAFB) with His bundle pacing (HBP) with nonselective capture, also enabling restoration of shorter atrioventricular (AV) conduction. The mechanisms by which HBP is able to correct bundle branch block remain contentious but are thought to include recruitment of fibers distal to the site of delay and improved capture relating to higher pacing output and suggest that bundle branch "block" is relative.

Unlike conventional active-fixation pacemaker leads, HBP is usually performed with a lead with a fixed helix screw mechanism. The use of a lead with a smaller electrode helps to maximize the likelihood of selective His bundle capture while minimizing local nonselective myocardial activation. In view of the technical difficulty of using preformed stylets, deflectable sheaths were devised to assist with lead placement. A high technical HBP success rate of 92% was reported in a single center using the combination of a steerable sheath (Medtronic C304 deflectable sheath, Medtronic, Minneapolis, MN) and fixed helix lead.[50]

HBP is now routinely performed using a specially designed preformed, nonsteerable sheath with dual-plane shaping (Medtronic C315 His, Medtronic, Minneapolis, MN), which is designed to direct the lead tip to the lower septal region of the right atrium and allows the rapid identification of His bundle electrograms in the majority of cases,[51] with deflectable catheters (Medtronic C304) reserved for cases with challenging or nonstandard anatomy. Many experienced operators no longer use separate mapping catheters, as mapping for the His bundle electrogram is performed using the catheter/lead system. The most commonly used lead is a non–stylet-driven exposed 4.1 Fr helical screw (Medtronic Select Secure 3830, Medtronic, Minneapolis, MN), which has good technical outcomes (Table[52–54]).

Potential Disadvantages of HBP

One current major barrier to more widespread uptake of HBP is that successful implantation with adequate capture threshold is more technically challenging than RVP because of the much smaller potential target area for lead placement. As a result, procedural and fluoroscopy times are prolonged when compared with RVP. Although all operators experience an initial learning curve with HBP that can be overcome, even the experienced operators in the largest published series

Table. Reported Technical Outcomes Using HPB With Medtronic 3830 SelectSecure™ Lead

Study	Number of Patients, n	Overall Reported Technical Success Rate, n (%)	Reported Selective HBP Rate, n (%)	Threshold at Time of Implant, V (0.5 ms Pulse)	Distribution of Heart Failure Within Study Population	Notes
Cantu et al 2006[26]	17	17 (100)	11 (65)	1.7±1.2 (selective) 3.1±1.6 (nonselective)	5 (29%) had EF <40%	All patients had suprahisian block
Catanzariti et al 2006[28]	24	23 (96)	17 (74)	1.61±0.55	13 (56%) reported to have heart disease	All patients had suprahisian block
Zanon et al 2006[50]	26	26 (100)	24 (92)	2.3±1.0	26 (100%) reported to have cardiomyopathy	All patients had preserved His-bundle conduction
Lustgarten et al 2010[53]	10	10 (100)	10 (100)	1.3±0.9	10 (100%) reported to have heart failure	All patients had conventional CRT indications
Kronborg et al 2011[41]	38	32 (84)	4 (13)	2.3±1.0 (selective) 1.5±1.2 (non-selective)	32 (100%) reported to have EF >40%	All patients had suprahisian block
Zanon et al 2011[54]	307	Not known	87 (28)	2.5±2.3 (selective) 1.3±1.1 (nonselective)	58 (19%) reported to have heart failure	All patients had suprahisian block
Lustgarten et al (2015)[45]	29	17 (59) achieved permanent HBP with QRS narrowing		3 to 4 (selective) 1 to 1.5 (nonselective)	21 (72%) reported to have cardiomyopathy	28 patients (97%) had left bundle branch block
Sharma et al 2015[37]	94	75 (80)	34 (45)	1.35±0.9	24 (32%) reported to have heart failure	44 (59%) had atrioventricular conducting system disease
Vijayaraman et al 2015[44]	100	84 (84)	22 (26)	1.4±1 V	Mean ejection fraction 54±10%	46 patients had atrioventricular nodal block, 54 patients had infranodal atrioventricular block
Ajijola et al 2017[46]	21	16 (76)	1 (6)	1.9±1.2 V at 0.6±0.2 ms	20 (95%) reported to have EF <35%	All patients reported to have an indication for CRT
Huang et al 2017[52]	52	42 (81)	38 (90)	1.5±1	42 (100%) reported to have heart failure	All patients had AF and underwent atrioventricular node ablation
Sharma et al 2018[47]	106	95 (90)	47 (50)	1.4±0.9 at 1 ms (His bundle capture) 2±1.2 at 1 ms (narrowing of BBB)	106 (100%) reported to have cardiomyopathy (LVEF 30±10% at baseline)	All patients had a CRT indication
Abdelrahman et al 2018[39]	332	304 (92)	115 (38)	1.30±0.85 at 0.79±0.26 ms	85 (26%) reported to have heart failure	Includes patients with wide range of pacemaker indications

AF indicates atrial fibrillation; BBB, bundle branch block; CRT, cardiac resynchronization therapy; EF, ejection fraction; HBP, His bundle pacing; LVEF, left ventricular ejection fraction.

reported a 27% increase in procedure time (70.2±34 versus 55.0±25 minutes) and 39% increase in fluoroscopy duration (10.3±6.5 versus 7.4±5.1). Although this may be mitigated with further developments in delivery systems and techniques, it is likely that average HBP implant times will always exceed those of RVP.

A further disadvantage of HBP is that higher pacemaker energies tend to be needed to achieve His bundle capture compared with RV capture (frequently with discrete selective and nonselective capture thresholds), which will tend to cause more rapid battery depletion. In the same large series, capture threshold was increased compared with RVP (1.30±0.85 V at 0.79±0.26 ms versus 0.59±0.42 V at 0.5±0.03 ms) and in a separate report by the same group, premature generator unit replacement was required because of a high threshold in 3 of 75 patients undergoing HBP 4.2±0.4 years[38] (a further 3 patients in the HBP group in this series underwent premature generator unit replacement because of a manufacturer advisory notice; 1 patient underwent upgrade to CRT). Finally, His bundle leads tend to be initially less stable than RV leads, leading to a higher incidence of need for early lead revision (4.2% versus 0% in the Geisinger report[39]) though, balanced against this, tend to have low rates of pericardial effusion requiring pericardiocentesis. Long-term performance of the leads and generator units following successful implant appear to be excellent though concerns about the performance of HBP following subsequent development of low infra-Hisian block remain.[39,42] Ultimately, the results from ongoing and future randomized controlled trials will determine whether these disadvantages will be outweighed by the potential clinical benefits.

Ongoing Trials of His Bundle Pacing

HBP appears to have particular promise as a therapy for patients with heart failure who are ineligible for CRT and as discussed is increasingly regarded as a potential alternative to CRT even in conventionally eligible patients. Three ongoing trials will evaluate the efficacy of HBP in these situations.

HOPE-HF Trial

In the UK-based HOPE-HF (His Optimised Pacing Evaluated for Heart Failure) trial, the potential role for atrioventricular optimized HBP will be tested in patients with heart failure and first-degree atrioventricular block who are ineligible for CRT on the basis of either narrow QRS duration or right bundle branch block. One hundred sixty patients will be randomized to 6-month blocks of receiving either no pacing or atrioventricular optimized HBP, with a primary outcome measure of change in exercise capacity[55] (ClinicalTrials.gov NCT02 671903).

His-SYNC Trial

In the US-based His-SYNC (His Bundle Pacing Versus Coronary Sinus Pacing for Cardiac Resynchronization Therapy) trial, 40 patients with a conventional CRT indication (ie, LV ejection fraction <35% and QRS duration >120 ms), will be randomly assigned to CRT with a lead placed in either the coronary sinus or His bundle.

The coprimary outcome measures are the change in LV ejection fraction measured by echocardiography at 6 months, change in QRS duration, and time to first hospitalization or death (ClinicalTrials.gov NCT02700425).

Comparison of His Bundle Pacing and Bi-Ventricular Pacing in Heart Failure With Atrial Fibrillation Trial

The China-based Comparison of His Bundle Pacing and Bi-Ventricular Pacing in Heart Failure With Atrial Fibrillation trial will enroll 50 patients with atrial fibrillation, a need for atrioventricular node ablation and an LV ejection fraction of <40%. Participants will undergo placement of an RV lead as well as both a coronary sinus lead and a His bundle lead. Participants will then undergo 1:1 randomization to either HBP or CRT for 9 months, switching to the other pacing mode for a further 9 months. The primary end point is change in LV ejection fraction (ClinicalTrials.gov NCT02805465).

Conclusions

Permanent His bundle pacing is an emerging technique to deliver a more physiological pattern of ventricular pacing and has the potential to mitigate the adverse consequences of chronic right ventricular pacing and promote atrioventricular and intraventricular synchrony. The development of new delivery systems and leads has led to excellent long-term technical outcomes and reduced the operator learning curve. As a result, HBP has undergone wider clinical uptake and is now undergoing larger-scale clinical trials to evaluate its potential role in patients with heart failure who are not eligible for CRT, but also as an alternative to CRT, and may become a mainstream approach for patients undergoing pacemaker implant.

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Dr Keene has received honoraria from Medtronic. Dr Foley has received a travel grant for training from Medtronic and has

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