His Bundle Pacing: Hemodynamics and Clinical Outcomes.

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His Bundle Pacing

Hemodynamics and Clinical Outcomes

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Abstract: From 1993 to 2009, nearly 2.9 million pacemakers were implanted in the United States; the majority of which were dual-chamber pacemakers. One of the major physiologic advantages of dual-chamber pacing over single-chamber ventricular pacing is atrioventricular synchrony, which prevents the pacemaker syndrome. However, patients who are pacemaker dependent or use right ventricle (RV) apical pacing more than 40% of the time are at a risk of developing heart failure from electromechanical dyssynchrony. Studies have also shown that RV pacing results in nonphysiological activation of the left ventricle, leading to adverse clinical outcomes. Hence, alternative pacing sites, including the RV outflow tract, the high-RV septal region, bi-ventricular pacing, or His bundle pacing, have been explored for a better physiological electromechanical coupling of the ventricles. Although His bundle pacing has gained attention due to favorable data and clinical outcomes, it has not gained widespread acceptance into clinical practice. Hence, we aim to review the current experience with His bundle pacing and its clinical implications in this article.

Key Words: His bundle, selective His bundle pacing, nonselective His bundle pacing, QRS duration

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From 1993 to 2009, nearly 2.9 million pacemakers were implanted in the United States; the majority of which were dual-chamber pacemakers.[1] One of the major physiologic advantages of dual-chamber pacing over single-chamber ventricular pacing is atrioventricular (AV) synchrony, which prevents the pacemaker syndrome.[2] However, patients who are pacemaker dependent, or who use right ventricle (RV) apical pacing more than 40% of the time, are at an increased risk of developing heart failure from electromechanical dyssynchrony.[3] As a result, the 2012 American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society guidelines on device-based therapy recommend cardiac resynchronization therapy (CRT) in patients with a reduced left ventricular ejection fraction (LVEF, ≤35%) with anticipated ventricular pacing of more than 40%.[4] Despite this, 30–40% patients do not have an overall benefit (of symptoms, LV remodeling, or mortality) from CRT therapy.[5]

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Studies have also shown that RV pacing results in nonphysiological activation of the LV, leading to adverse clinical outcomes.[6] Hence, alternative pacing sites, including the RV outflow tract, the high RV septal region, bi-ventricular or His bundle pacing (HBP), have been explored for a better physiological electromechanical coupling of the ventricles. Although HBP has gained significant attention in recent years, it has not been widely accepted in clinical practice. Hence, we aim to review the current experience with permanent HBP and the clinical implications resulting from this approach in this article.

THE ATRIOVENTRICULAR NODE AND HIS BUNDLE

In the mid-19th century, Stannius proposed that electrical conduction in the heart was carried out by specialized myocardial tissues.[7] However, it was not until 1906 when the existence of the His Bundle (HB) was confirmed by Sunao Tawara.[8] Tawara also recognized the connection between the right atrium, the AV node, the HB, the ventricle, and Purkinje cells.[8,9] The AV node is located at the base of atrial septum and within the triangle of Koch.[10] The HB (or Bundle of His) is a continuation of the AV node perforating the central fibrous body and then dividing into the right and left bundle branches. Even though they are specialized myocardial tissues, there are histological differences within these tissues that are different from the myocardium.[9] A detailed histological description of the AV node and HB is beyond the scope of this article. An understanding of the basic flow of conduction is clinically relevant when treating patients with conduction disorders. To summarize, an impulse generated by the sino-atrial node is carried to the AV node by specialized fibers, then through the HB and bundle branches. It is well known that if one of the bundle branches is diseased, potential electrical, as well as mechanical, dyssynchrony can ensue, leading to heart failure.[11] Theoretically speaking, HB provides the last point in the cardiac conduction system where an impulse can travel to both branches (assuming they are intact) without electrical or mechanical dyssynchrony. This forms the basis of HBP.

HIS BUNDLE PACING

Although the concept of HBP was first studied in animal models by Scherlag et al,[12,13] it was first tested in humans in 1970.[14] Nonetheless, the proper selection of para-Hisian sites of pacing and technical difficulties needed to be overcome. In 1977, Narula[15] demonstrated that proximal HB stimulation was associated with wide QRS complexes or axis deviation, whereas distal HB stimulation was associated with a narrow QRS complex or abolition of the left axis deviation in 27 patients with preexisting left bundle branch block (LBBB) or isolated left axis deviation. Distal HBP results in a narrow QRS complex in patients with bundle branch block (BBB) as the bundle branch fibers are committed in the proximal His. With injury, conduction across the transverse interconnections suffers a more selective depression in the pathologic HB, causing longitudinal dissociation. Due to the distal HB being intact in the majority of HB injuries, pacing from the HB distal to the site of severely depressed conduction can result in synchronous activation of the bundle branches as opposed to pacing from the proximal location, hence, resulting in a narrow QRS.[16] In 1978, El-Sherif et al[16] showed a reversal of preexisting BBB with temporary HB stimulation, both in canine and human models. In 1999, Amitani et al[17] demonstrated the feasibility of performing permanent HBP using an anchoring screw-in lead at the HB region in 6 adult beagles. They observed no histological influence on the conduction system in the autopsy after 2 months of pacing follow-up. In 2000, Deshmukh et al[18] conducted a study of 18 patients with permanent atrial fibrillation and dilated cardiomyopathy who underwent permanent HBP. They demonstrated an improvement in long-term reduction of LV dimensions and cardiac function. Since then, HBP has caught the attention of numerous clinicians as an alternate pacing site, and multiple studies and case reports have been published displaying its efficacy in humans.

CLINICAL DATA

Initial Reports

The clinical data on HBP are limited to smaller studies, case reports, and case series. To date, a large, randomized, control trial is lacking. In the study performed by Deshmukh et al,[18] 14 of the 18 patients had reliable HBP based on the use of a mapping catheter. All patients had systolic dysfunction (LVEF < 40%), a narrow QRS, and permanent atrial fibrillation; they underwent pacing using fixed screw-in leads and a single-chamber rate responsive pacemaker. Lead-related nonfatal complications occurred in 2 patients. During follow-up (mean 23 months), 11 patients retained capture, whereas 3 patients had widening of the QRS (>20%) from the baseline, which was thought to be from muscle–muscle activation before HB activation. From a clinical standpoint, there was a marked overall improvement in LVEF (18%–29%; $P < 0.01$) and in LV dimensions, including the LV end-diastolic diameter (LVEDD) and systolic diameter (LVESD), with a 1-year mortality rate of 9% (n = 2, due to worsening heart failure).

In another series consisting of 12 patients,[19] 8 of the 12 patients had an acceptable pacing threshold with HBP. At 3-month follow-up, the authors reported no significant echocardiographic or clinical deterioration and concluded that HBP could be a long-term option in patients with a normal His conduction system.

ELECTROCARDIOGRAPHIC PARAMETERS DEFINING HIS BUNDLE PACING

The following criteria define HBP:[20]

- The morphology and duration of the QRS from HBP should be identical to those of the native QRS. An underlying right bundle branch block (RBBB) or LBBB can be normalized to a narrow QRS complex by HBP in the majority (>90%) of patients who have indications for permanent pacing.[21,22] Figure 1[23] shows an electrocardiogram (ECG) of a patient who underwent selective HBP, with the following characteristics: (1) the local ventricular electrogram is seen after HB capture on the His electrogram; (2) the timing of the local ventricular electrogram is the same for native and paced QRS complexes (red arrow); (3) the native HV interval is similar to the stimulation-earliest QRS; (4) the stimulation-earliest QRS interval is isoelectric in all leads; and (5) the paced QRS morphology is narrow and similar to a native QRS complex with a similar QRS axis.
- Nonselective HBP (Fig. 2)[23] has the following characteristics: (1) the absence of a local ventricular electrogram as compared to the native QRS on the His electrogram (red arrow); (2) HBP resulting in local ventricular myocardial and HB capture, thus, generating a pseudo-delta wave pattern similar to an anteroseptal accessory pathway—not seen in the native QRS complex; (3) a QRS axis of the paced QRS complex similar to the native QRS; and (4) the HB spike to QRS end is similar to the stimulation-QRS end (135 ms).

HEMODYNAMIC CONSEQUENCES OF HIS BUNDLE PACING

In a study by Deshmukh and Romanyshyn,[24] 54 patients with persistent atrial fibrillation, narrow QRS complexes (<120 ms), and dilated cardiomyopathies with a mean LVEF of 23% underwent HBP. At follow-up, nearly two-thirds of the patients were noted to have improvement in LVEF. In 2006, Occhetta et al[25] published outcomes on 16 patients who underwent HBP after AV node ablation for permanent atrial fibrillation. The study aimed to evaluate the feasibility and effects of HBP compared with conventional RV apical pacing. The study demonstrated a worsening of mitral and tricuspid regurgitation in patients with conventional RV apical pacing versus HBP, which according to the authors was secondary to an improvement in interventricular dyssynchrony (observed by QRS shortening in the HBP group). However, no significant difference was seen in terms of LVEF.

Later, in a study of 38 patients with a high-grade AV block and a narrow QRS complex, Kronborg et al[26] demonstrated that HBP was associated with preservation of LV systolic performance (as measured by LV outflow tract velocity–time integral) as compared with RV apical pacing. In 2013, Catanzariti et al[27] performed a prospective trial enrolling 26 patients who underwent HBP (with backup RV apical pacing). In their study, all devices were programmed to perform HBP postimplantation, and after 3 years, the pacing modality was temporarily switched to RV apical pacing. A significant reduction in LVEF and an increase in mitral regurgitation with RV apical pacing was observed. Although no difference in the myocardial performance index was seen, significant dyssynchrony was present during RV apical pacing versus none with HBP. In 2014, Kronborg et al[28] published the long-term results from 38 patients with a high-grade AV block, a narrow QRS, and an LVEF >40% who underwent HBP and RV septal pacing in a 12-month crossover study. The study demonstrated that HBP or para-Hisian pacing (defined as (1) the His potential in the permanent lead was identical to the His potential in the diagnostic electrophysiology catheter, and (2) a shortening of the QRS at high output pacing) was associated with a preserved LVEF and mechanical synchrony compared with RV septal pacing. In 2014, Pastore et al[29] reported electromechanical delays and LV dyssynchrony during systole and diastole with RV apical pacing compared with HBP. LVEF and LV diameters did not show a significant difference between the 2 groups.

CLINICAL OUTCOMES FOLLOWING HIS BUNDLE PACING

In a study by Sharma et al[30] designed to assess the feasibility, safety, and clinical outcomes of patients who underwent HBP versus RV pacing, permanent HBP was accomplished in 75 out of 92 patients. A long procedure time was observed in the HBP group (79 ± 25 min for HBP vs 64 ± 25 min for RV pacing); however, no significant differences were observed for fluoroscopy time (12.7 ± 8 min vs 10 ± 14 min, respectively). Higher pacing thresholds were observed in the HBP group (although they remained stable over the 2-year follow-up period) as compared to RV pacing (1.35 ± 0.9 V vs 0.6 ± 0.5 V at 0.5 ms; $P < 0.001$, respectively). Forty-six percent of the patients had >40% ventricular pacing. In this subgroup, reduced heart failure hospitalizations were observed with HBP as compared

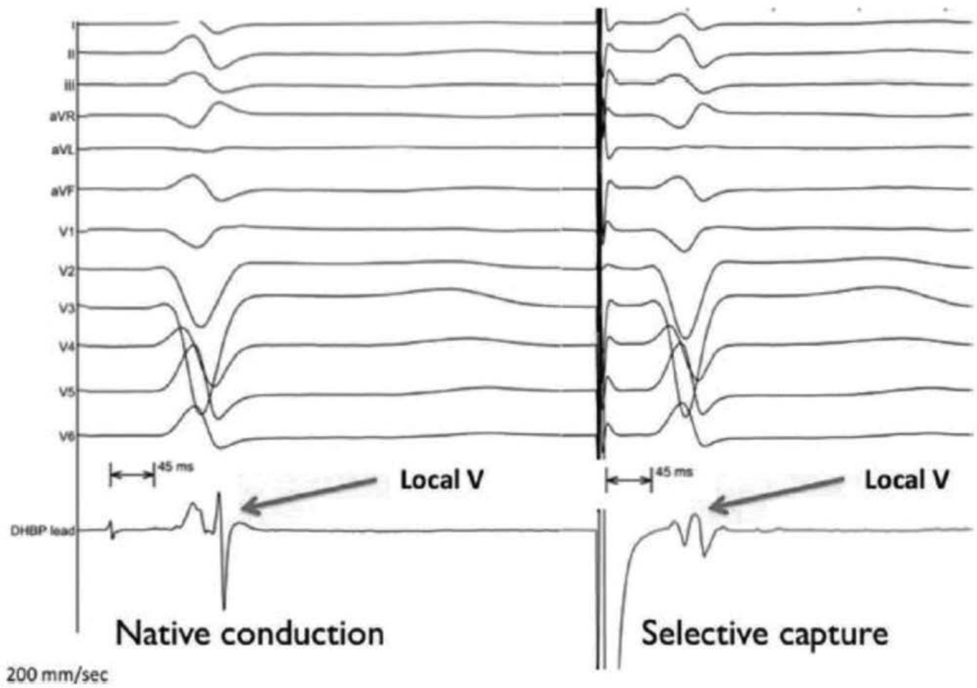

FIGURE 1. Electrocardiogram demonstrates selective His bundle pacing (HBP) with following characteristics: (1) local ventricular electrogram is seen after His bundle capture on the His electrogram; (2) the timing of the local ventricular electrogram is the same for native and paced QRS complexes (red arrow); (3) native HV interval is similar to stimulation-earliest QRS; (4) stimulation-earliest QRS interval is isoelectric in all leads; (5) paced QRS morphology is narrow and similar to native QRS complex with similar QRS axis. Adapted with permission from Lustgarten.[23]

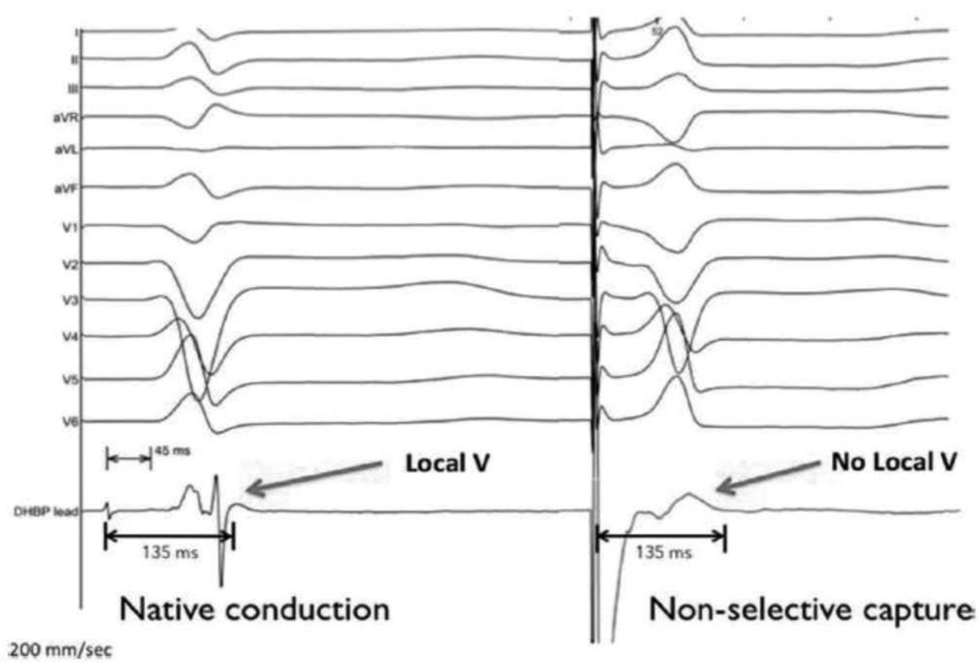

FIGURE 2. Electrogram demonstrates nonselective His bundle pacing (HBP) with following characteristics: (1) absence of local ventricular electrogram as compared to native QRS on His electrogram (red arrow); (2) HBP resulting in local ventricular myocardium and His bundle (HB) capture, thus, generating pseudo-delta wave pattern demonstrated similar to anteroseptal accessory pathway—not seen in native QRS complex; (3) QRS axis of paced QRS complex similar to native QRS; (4) The HB spike to QRS end is similar to the stimulation QRS end (135 ms). Adapted with permission from Lustgarten.[23]

TABLE 1. The Definitions of HBP and Para-Hisian Pacing

Parameter	His Bundle Pacing	Para-Hisian Pacing
QRS complex	Identical to native QRS	Paced QRS complex should be 50 ms shorter than RV apical paced QRS complex QRS axis should be concordant with native QRS axis (or within 20–30 degrees)
HV interval	Pacer spike to QRS duration should be within 10 ms of native HV interval	—
Pacing threshold	At least 2 V	Lower than 1 V as interventricular septum's muscular portion was also captured

HBP indicates His bundle pacing; RV, right ventricle.

with RV pacing (2% vs 15%; $P = 0.02$, respectively). No significant mortality difference was observed between the 2 groups (13% with HBP vs 18% with RV pacing; $P = 0.45$). Table 1 summarizes the definitions of HBP and para-Hisian pacing.

DISEASE-SPECIFIC USE OF HIS BUNDLE PACING

Sinus and AV Nodal Disease With Preserved Ejection Fraction

From 1993 to 2009, there was an increasing trend for implantation of dual chamber (DDD) pacemakers and a significant decline in the number of implanted single chamber (AAI) ventricular pacemakers.[1] In The Danish Multicenter Randomized Trial on AAIR versus dual-chamber pacing (DDDR) in sick sinus syndrome (DANPACE) trial,[31] no mortality benefit was observed using the DDD pacer mode; however, there was a significant reduction in the incidence of atrial fibrillation as compared to the AAI mode. One of the risks of aggressive RV pacing is AV dyssynchrony. When the atria and ventricles are electrically dissociated, especially in the case of RV pacing, it may result in the pacemaker syndrome (affected patients may experience heart failure). In the MOde Selection Trial, nearly 20% of patients experienced the pacemaker syndrome and improved with DDD reprogramming.[32] This suggests the importance of AV synchrony in pacemaker-dependent patients. In a subgroup analysis of the MOde Selection Trial, patients with a normal baseline QRS duration and higher RV pacing (>40%) were at an increased risk for pacemaker syndrome despite AV synchrony.[3] Putting this together, synchronous right atrium and ventricular pacing, without causing the pacemaker syndrome, is essential for improving patient outcomes. Thus, HBP is an excellent alternative option for sick-sinus syndrome patients who are anticipated to have a higher ventricular pacing requirement (>40%). However, there is no head-to-head randomized trial comparing the DDD mode RV apical site versus HBP in sick-sinus syndrome patients.

In a retrospective study of 100 patients, Vijayaraman et al[33] demonstrated the technical feasibility of HBP pacing (both selective HBP and nonselective HBP: i.e., pacing of the HB in combination with the atrium and/or ventricular septum) in patients with AV node disease. The authors studied 100 patients with advanced degree AV block; 46 patients had AV nodal block and 54 patients had infranodal AV block. The success rate of HBP in each group was 93% and 76%, respectively. There was no increase in fluoroscopy time between the groups. This study, however, was a retrospective analysis not initially intended to report the clinical outcomes.

The use of HBP is still in its infancy, and its utility is currently being explored in special circumstances, such as in congenital complete heart block, and with the use of an implantable cardioverter defibrillator (ICD) in an adult patient with complete heart block and monomorphic ventricular tachycardia.[34,35]

PREEXISTING ELECTRICAL DYSSYNCHRONY AND CARDIOMYOPATHY

As discussed previously, a higher percentage of RV pacing can be detrimental for patients, and hence, HBP is an excellent alternative. However, patients with preexisting cardiomyopathy may pose 2 challenges: (1) a need for resynchronization if they have wide QRS complexes; and (2) patients with severely reduced EFs may also require primary or secondary prevention ICDs.

Studies have shown that the bundle branches are longitudinally dissociated by collagen strands and intercellular junctions,[36] and when injury or block occurs at any microfocal point, the disruption may result in either RBBB or LBBB. Hence, if the HB is reactivated distal to the site of injury or block, it could potentially resolve the BBB. In a study by Barba-Pichardo et al[37] that incorporated 7 patients with infra-Hisian block and dual-chamber pacemaker use with HBP, 4 patients had chronic RBBB, one of which also had first-degree AV block; 2 had chronic LBBB, and 1 had complete infra-Hisian AV block. Interestingly, 2 of the patients with chronic RBBB and both patients with chronic LBBB had disappearance of their respective BBBs, with normalization of the QRS morphology with HBP. In a subsequent study, Barba-Pichardo et al also demonstrated a reduction in mean QRS duration (166 ± 8 to 97 ± 9 ms) in patients with cardiomyopathy and in CRT nonresponders. Also, there was a statistically significant improvement in New York Heart Association functional class and an improvement in LVEF and LV dimensions in patients who underwent CRT with HBP.[38] Lustgarten et al[5] demonstrated that HBP, either selective or nonselective, can narrow the QRS complex to a capacity similar to bi-ventricular pacing, although not all patients demonstrated an expectant narrower QRS post HBP. One of the possible explanations could be that the pacing site was proximal to the level of block. Hence, it is essential to identify the level of block before securing an HBP lead into the myocardium. To address this issue, Barba-Pichardo et al[38] studied 16 patients with a dilated LV and chronic LBBB who were candidates for conventional CRT defibrillator. Thirteen of the 16 patients had their chronic LBBB corrected, though only 9 of them had fixation of the electrodes. Three out of 9 patients had "pure" HBP, while the remaining patients had fusion of HBP and a wider QRS. At mean follow-up of 31.3 ± 21.5 months, 9 out of 16 patients (who underwent permanent HBP) demonstrated a statistically significant reduction in LVEDD (65.9 vs 59.5 mm; $P < 0.01$) and LVESD (55.4 vs 51.2; $P < 0.05$), an improvement in LVEF (29% vs 36%; $P < 0.05$), and QRS duration (166 vs 97 ms; $P < 0.01$). There was no significant change in left atrial dimension (56.3 vs 52.9 mm), and none of the patients had any ICD shocks during the follow-up. These results corroborated with the results of the first study reported by Deshmukh et al[18] demonstrating a significant improvement in LVEDD, LVESD, fractional shortening, and LVEF in the majority of the patients.

Of note, we recently published a meta-analysis of 3731 patients, demonstrating no difference between the use of an apical and nonapical RV ICD lead position regarding the total number of shocks delivered, the number of appropriate and inappropriate shocks, the cut-to-suture time, and all-cause mortality at 1 or 3 years of follow-up (although trials with HBP were not included in our study).[39] However, the majority of ICD leads in the nonapical RV group were placed in the RV outflow tract or mid-septal. Nonetheless, our study demonstrates the noninferiority of nonapical RV ICD lead position compared to the apical position. Further studies are needed to evaluate the safety and efficacy of an HB-implanted defibrillator lead in selected patients.

Ploux et al[40] demonstrated that although bi-ventricular pacing results in a moderate reduction in interventricular dyssynchrony, it does not eliminate electrical dyssynchrony induced by LBBB as compared with a normal QRS. This suggests that there is a potential for improvements in CRT. Thus, HBP as an alternative for CRT (especially when HB pacing can be performed distal to the site of block, resulting in the recruitment of a normal conduction system) is a promising approach, with favorable short-term, electrical, and clinical outcomes, although long-term stability outcomes, especially pacing threshold and the persistent correction of BBB, still needs to be evaluated. In a recent study by Vijayaraman et al[41] assessing HB capture and LV function at the time of generator change at a mean follow-up of 70 months, HV intervals remained unchanged (44 ± 4 ms at the time of implant vs 45 ± 4 ms at the time of generator change). Despite a high pacing burden, there was no significant difference in LVEF at the time of follow-up, with no significant worsening of valve regurgitation.[41]

It still remains unanswered as to who are the most suitable candidates for CRT with permanent HBP. In our opinion, the patients who are CRT nonresponders who have failed coronary sinus lead placement, or patients with AV nodal disease requiring AV node ablation, would benefit from HBP.

The His Optimized Pacing Evaluated for Heart Failure Trial (NCT02671903) is an ongoing multicentered, prospective, randomized, double-blinded, crossover study recruiting patients with a history of heart failure and those who are candidates for CRT with at least 1 lead positioned at the HB to obtain direct HB capture. After a 2-month run-in period (when the device is not active), the patients will then be randomized to a 6-month treatment period of either "no pacing" or "AV optimized distal HBP". The primary end point of the study is to assess the difference in the exercise capacity measured, using peak oxygen uptake.

The HBP versus Coronary Sinus Pacing for Cardiac Synchronization Therapy study (NCT02700425) is currently an ongoing study with a hypothesis that QRS narrowing with HBP will be superior for improving systolic function as assessed by echocardiographic indices (ejection fraction and strain), quality of life, and decreased hospitalization rates and mortality.

LIMITATIONS OF HIS BUNDLE PACING

One of the biggest limitations of HBP is the inability to map HB in 10%–20% of cases. This is especially true in patients with dilated atria or in patients with structural heart disease where delivery of the HB lead can be challenging. Also, due to high pacing thresholds, increased pacing outputs might also result in decreased battery longevity. Hence, multicenter randomized studies will be necessary to change current clinical practice and guidelines.

CONCLUSIONS

From the currently available data on HBP, it appears to be a safe and feasible pacing technique that reduces electromechanical uncoupling of the LV as compared to traditional RV apical pacing. Multiple studies have also demonstrated favorable hemodynamic profiles with improvements in clinical parameters such as LVEF, QRS durations, and LV dimensions in patients with HBP. It should be noted that HBP is not currently a routine practice and the evidence exists only from case reports, case series, or small, nonrandomized studies. The potential problems observed in HBP include a procedural learning curve, a longer procedure time, and a higher pacing threshold (decreased battery longevity). Despite these limitations, we believe that HBP can be ideal in patients who are pacemaker dependent who require higher cumulative percentages of RV pacing (>40%). Further studies are needed to explore this novel and more physiological form of pacing in patients with both narrow and wide QRS complexes, as well as in those patients who are candidates for an ICD.

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