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Updates on His Bundle Pacing: The Road More Traveled Lately

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Abstract

His bundle pacing (HBP) has continued to evolve over the past decade and has started to become a global phenomenon. Evidence is mounting of its clinical benefits as compared to both right ventricular and left ventricular pacing. In this paper, we review recent data in support of His bundle pacing and some of the challenges facing us as we advocate its increasing role in clinical practice.

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Introduction

Right ventricular pacing (RVP) has remained as the standard pacing technique globally. However, over the past 2 decades, RVP has been shown to result in deleterious hemodynamic effects including higher rates of atrial fibrillation (AF), heart failure and mortality (DAVID and MOST trials) (1, 2). These negative hemodynamic effects result from an abnormal electrical and mechanical activation of the ventricles. In fact, the electrical effects of RVP are similar to those of left bundle branch block (LBBB). To solve this problem of ventricular dyssynchrony, alternative forms of pacing, including biventricular pacing (BiVP) and His bundle pacing (HBP), have emerged. Lately, HBP has started to grow in popularity due to its physiological benefits of recruiting the native His Purkinje system.

Implant success and procedure duration

The bundle of His is comprised of specialized cardiac muscle fibers that enhance the cardiac conduction properties. It is interspersed within collagen fibers and extends from the compact AV node through the membranous interventricular septum. Both the atrial (non-penetrating) and ventricular (penetrating) portions of the His bundle can be accessed for HBP. Stylet-driven, active fixation leads were used by early investigators to perform HBP. With time, the development of dedicated pacing lead and delivery sheaths has resulted in improved procedural success. A multipolar electrophysiology catheter may be used to locate the His bundle. However, it is not routinely necessary as the His bundle location can be successfully identified in 95% of the patients without the use of a mapping catheter (3-5). Recently, a systematic review and meta-analysis on permanent HBP comprising 26 articles demonstrated an overall average implant success rate of 84.8%; it increased to 92.1% with the use of catheter-delivered systems (P< 0.001) (6). With time and experience, procedural duration has also significantly improved from 3.7 ± 1.6 hr in 2000 to 80 mins in 2011 to 64 ± 10 mins in 2015 (4, 7, 8).

Pacing characteristics and thresholds

The average His bundle capture thresholds tend to be higher than RVP thresholds due to the inherent anatomical differences between the His bundle and the RV myocardium. Although His bundle capture thresholds are usually higher than RVP thresholds at implant, mean His-bundle capture thresholds remain stable during long-term follow up. Sharma et al. showed stable thresholds after 2 years of follow-up and Vijayaraman et al. obtained similar findings after 5 years of follow-up (3, 9). The development of new dedicated delivery sheaths has also resulted in improved capture thresholds. At this time, only one company has achieved FDA approval for using a specific lead to achieve successful HBP. The 3830 Select Secure MRI SureScan (Medtronic Inc., Minneapolis, USA) is an MRI conditional lead that has a solid core and a 1.8 mm exposed active helix. Along with the use of dedicated sheaths (a non-deflectable C315His sheath and a deflectable C304His sheath (Medtronic Inc., Minneapolis, USA), HBP implantations has resulted in better pacing thresholds. In a systematic review and meta-analysis on HBP, average pacing thresholds were 1.71 V at implant and 1.79 V at > 3 months follow up (6). Other investigators around the world have used regular pacing leads with shaped stylets and have reported longer term success rates as well (6).

One way to minimize capture thresholds in HBP patients who require cardiac resynchronization devices is to pace using His tip-RV coil pacing configuration rather than traditional bipolar pacing on the HB lead. In patients implanted with ICD/CRT-D, Su et al. showed lower capture thresholds could be obtained using the His-tip RV coil integration (1.13 ± 0.51 V at 0.5 ms) compared with HB unipolar (1.75 ± 0.83 V at 0.5 ms) and HB tip-ring (1.59 ± 0.71 V at 0.5 ms) (10). R waves also improved significantly with a His tip-RV coil (4.28 ± 2.27 mV) compared with HB unipolar (3.5 ± 1.82 mV) and HB tip-ring (2.56 ± 1.58 mV) (10).

Acute His bundle injury current obtained at the time of implantation is associated with better capture thresholds over the long term (4) (figure 1) . While obtaining a current of injury is desirable, there may be sites with good pacing threshold and little to no current of injury that remain stable at follow-up.

The inherent algorithms used at this time are not designed for His bundle pacing and careful attention to the programming algorithms should be undertaken to avoid unintended consequences. One such example was recently published by Padala et al. in a case report describing the auto-capture algorithms of HBP CRT devices in pacing-dependent patients (11). To conserve battery life, RV pacing output can be minimized in non-dependent patients who are achieving LBBB normalization with HBP. However, during atrial and ventricular capture management testing, the device switches to right ventricular-only pacing during ventricular support cycles for the duration of the test and does not pace from the left ventricular port in CRT devices. In patients receiving CRT devices with a His bundle lead in the LV port who are programmed to subthreshold RV outputs, this can lead to disastrous consequences. It is recommended to turn off these automated device tests to avoid ventricular asystole, especially in pacing-dependent patients. In all cases of loss of ventricular capture, a thorough device investigation and review of automated device algorithms is always warranted with HBP at this time. Such issues can be overcome with device algorithms specifically designed with HBP in mind.

Long-term lead performance

His bundle capture threshold can increase in ~ 10% of paced patients during follow-up (12). In most cases, the increase in capture threshold likely results from micro-dislodgement of the His lead. Lead revision may be necessary in 5% of patients due to progressive increase in thresholds. In this case, a new HBP lead is implanted in a distal location followed by removal of the old lead. The rates of lead dislodgement have improved over time from 17% (2/12) as reported by Deshmuskh et al. to none as reported by Ajijola in a 2017 study after a median 12 month follow up (7, 13). In a more recent study published by Vijayaraman et al. comparing HBP with RVP over 5-year follow-up, HBP was associated with higher rates of lead revisions (6.7% versus 3%) and generator changes due to premature battery depletion (9% versus 1%) (14). In a previous study, Vijayaraman et al. aimed to assess His bundle capture and its effects on LV function during medium to long-term follow up, and to determine His-Purkinje

conduction (HPC) at the time of generator change in patients with chronic HBP (9). HV intervals

remained stable as compared to initial implant (44 ± 4 ms vs 45 ± 4 ms). During HBP at 700 ms, 600 ms,

and 500 ms cycle lengths respectively, consistent 1:1 HPC was demonstrated. HBP QRS duration also

remained stable during follow-up (117 ± 20 ms vs 118 ± 23 ms). HBP thresholds at implant and generator

change were 1.9 ± 1.1 V and 2.5 ± 1.2 V at 0.5 ms respectively. Despite high pacing burden (77 ± 13%),

there was no deterioration in LVEF during follow up (50 ± 14% at implant vs 55 ± 6% at follow up;

P=0.06). As such, HBP was shown not to cause new HPC abnormalities. Battery longevity was longer in

this series of patients with HBP because back-up RV lead was not routinely used which limited battery

depletion. Even in patients with intra-His block, distal His-Purkinje conduction was preserved in patients

paced with HBP.

Selective versus Non-Selective HBP

Selective HBP (SHBP) is achieved by placing the pacing lead deep into the His bundle resulting

in His bundle capture only (figure 2). It is defined as ventricular activation occurring exclusively via His-

Purkinje system as evidenced by a QRS morphology being identical to baseline (if normal) and complete

recruitment of bundle branch blocks in patients with baseline bundle branch blocks. In these patients,

there is an isoelectric segment between the pacing spike and QRS complex which is equal to the intrinsic

HV delay in most cases. Nonselective HBP (NSHBP) is achieved when there is a significant amount of

myocardium surrounding the His bundle where pacing always results in fusion between HPC and local

myocardial capture (figure 3). In these patients, there is no isoelectric interval between the pacing

stimulus and QRS onset. A pseudo-delta wave is seen instead of an isoelectric line representing the septal

myocardial activation fusing with the His-Purkinje activation. Zhang et al. conducted a study assessing

the acute effect of SHBP, NSHBP and right ventricular septal pacing (RVSP) on electrical synchrony and

LV mechanical synchrony using electrocardiogram and phase analysis of gated single photon emission

computed tomography (SPECT) myocardial perfusion imaging (MPI) (15). HBP was performed in thirty-

seven patients: SHBP in 23 patients and NSHBP in 14 patients. Thirty-one patients simultaneously underwent back up RVSP. The paced QRS duration (QRS_d) in the SHBP low- and high-output mode and in the NSHBP high-output mode were similar to the baseline intrinsic QRS_d. QRS duration in the NSHP low-output mode was slightly longer than the baseline. SHBP and high-output NSHBP were shown to have better electrical and mechanical synchrony than RVSP (15).

His bundle pacing vs. right ventricular pacing

Several small studies have compared HBP with RVP and showed that HBP resulted in improved exercise tolerance, New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), and mitral and tricuspid regurgitation (table 1). Recently, Vijayaraman et al. published their 5-year follow up results comparing HBP to RVP and found that HBP is associated with reduction in death or heart failure hospitalization (HFH) during long-term follow up as compared to RVP patients with >40% ventricular pacing (32% vs 53%; hazard ratio 1.9; P=0.04) (14). This study also demonstrated that pacing-induced cardiomyopathy was significantly lower in HBP compared to RVP patients (2% vs 22%; P = 0.04). This reduction in the primary outcome associated with HBP may be explained by several factors including reduction in heart failure resulting from elimination of ventricular dyssynchrony, QRS narrowing and reduction in T peak to T end duration which is associated with increased risk of arrhythmias. Similarly, Abdelrahman et al. published a study comparing the clinical outcomes of HBP to RVP from the Geisinger HBP registry (16). HBP was successful in 92% of the patients in whom it was performed. The primary endpoint of death, HFH, or upgrade to BiVP was significantly lower in the HBP group (83 of 332 patients [25%]) compared to RVP (137 of 433 patients [32%]; hazard ratio [HR]: 0.71; 95% confidence interval [CI]: 0.534 to 0.944; p = 0.02). This difference was observed primarily in patients with ventricular pacing >20% (25% in HBP vs. 36% in RVP; HR: 0.65; 95% CI: 0.456 to 0.927; p = 0.02). The incidence of HFH was significantly reduced in the HBP group (12.4% vs. 17.6%; HR: 0.63; 95% CI: 0.430 to 0.931; p = 0.02). A trend toward reduced mortality was noted with HBP (17.2%

vs. 21.4%, respectively; p = 0.06). Among patients with ventricular pacing burden ≤20%, the primary outcome was similar in the HBP and RVP groups (22% vs 23.7%, respectively; p=0.34). Patients in the RVP group with baseline LVEF <50% had significantly increased risk for reaching the primary endpoint (HR: 1.785; 95% confidence interval [CI]: 1.054 to 3.023; p= 0.03) compared to patients with LVEF > 50%. This was not found in the HBP group when data were stratified according to LVEF. Another study supporting the beneficial effects of HBP in pacing dependent patients irrespective of the EF was published by Ye et al. (17). This study assessed the feasibility and intermediate follow-up results of upgrade to HBP in patients with long term RVP referred for pulse generator change. HBP was successful in 85.7% (12/14) of the patients in whom it was attempted. Nine patients had an EF≥40% and underwent upgrade to HBP whereas three patients had an EF <40% and underwent HBP and BiVP as well with coronary sinus lead placement. QRS_d was significantly reduced post-HBP implantation from 157.8 ± 13.3 ms to 109.3 ± 16.9 ms (p < 0.001). After 6 months follow-up, NYHA functional status significantly improved from 2.7 ± 0.6 to 1.8 ± 0.6 (p=0.007) and left ventricular internal diastolic diameter (LVIDd) was significantly reduced from 5.5 ± 0.4 cm to 5.3 ± 0.3 cm (p= 0.03). HBP improved HF symptoms in pacing dependent patients with preserved EF who previously had RVP. They concluded that HBP appears to be safe and feasible for upgrade in patients with long term RVP regardless of the LVEF. Another recent study was performed by Shan et al. to assess the clinical outcomes of upgrading to permanent HBP in patients with heart failure who underwent device upgrade from RVP (18). They demonstrated that in chronically paced patients with pacing induced cardiomyopathy (LVEF<50%), upgrade to HBP resulted in significant improvement in QRS duration and LVEF (from 36.1% ± 8.9% to 53.6% ± 10.3% at 1 year follow up; P<0.01). Other findings after HBP upgrade included improvement in mitral valve regurgitation, serum brain natriuretic peptide (BNP) concentrations, cardiothoracic ratios, and NYHA functional status (P<0.01 for all). Despite all these beneficial results, randomized controlled clinical trials comparing HBP with RVP are still lacking and are needed to further validate these findings.

HBP for cardiac resynchronization therapy (CRT) and bundle branch blocks

The concept of longitudinal dissociation of the His bundle has been postulated many decades ago. According to this concept, predestined fibers to the bundle branches are present within the proximal portions of the common His bundle and bundle branch blocks may be a manifestation of focal impulse blocks within the proximal portions of the common bundle. In such cases, HBP can overcome the block by pacing distal to the site of block resulting in a narrow QRS morphology (figure 3). Narula et al. first reported the normalization of BBB by distal HBP in the 1970s (19). Sharma et al. described two cases of left bundle branch delay with evidence of split His electrogram during unipolar mapping from the tip of the His bundle lead during pacemaker implantation (20). Pacing at these sites resulted in complete recruitment of the LBBB. CRT via BiVP is indicated in patients with severely reduced ejection fraction and wide bundle branch block. However, one third of these patients do not respond to conventional CRT (21, 22). Permanent atrial fibrillation is one of the reasons for not responding to CRT (23) . Lack of response to CRT was also seen in patients with normal QRS and those with right bundle branch block (RBBB). Indeed, the largest group of non-responders were HF patients with QRS duration < 130 msec (24, 25). In these patients, BiVP was associated with higher mortality incidence (26, 27). In patients with atrioventricular block and systolic dysfunction, equivocal results were demonstrated in two clinical trials (28, 29)**.** Furthermore, some patients have anatomical obstacles that hinder LV lead placement, including suboptimal coronary sinus venous branches and phrenic nerve stimulation. As such, CRT via BiVP fails to meet the needs of a significant group of patients and alternative pacing techniques are highly desired.

There are limited data on HBP as an alternative to BiVP for CRT. From a speculative point of view, in contrast to the non-physiologic BiVP in which ventricular activation occurs in response to RV endocardial and LV epicardial pacing, physiologic ventricular activation by activating previously dormant His-Purkinje tissue via HBP seems to be promising. In a crossover design trial, Lustgarten et. al was able to demonstrate successful recruitment of bundle branch blocks with His bundle pacing (46). They were also able to demonstrate improvement in clinical outcomes that were similar between His bundle pacing

and LV pacing. Several prospective cohort studies compared HBP to BiVP for CRT in patients with AV nodal block, patients who failed coronary sinus lead placement and others with lack of response to conventional CRT. The results of these studies were promising and demonstrated improvement in QRS duration, LVEF and NYHA functional status in patients with HBP (30) (table 2). The largest of these studies was a multicenter study by Sharma et al. (31). The study assessed HBP for CRT in CRT-eligible patients and BiVP non-responders. It demonstrated a 90% success rate with significant narrowing of QRS from 157 ± 33 ms to 117 ± 18 ms (P = .0001), increase in LVEF from 30% $\pm$ 10% to 43% $\pm$ 13% (P = .0001), and improvement in NYHA functional class from 2.8 ± 0.5 to 1.8 ± 0.6 (P = .0001) with HBP (31). Recently, Huang et al. published a study assessing the efficacy of HBP in correcting LBBB and its clinical outcomes in patients with LBBB and HF (32). They showed that HBP acutely corrected LBBB in 72 of 74 patients (97.3%). Thirty patients completed 3-year follow-up with LVEF increasing from a baseline of $32.4\pm8.9\%$ to $55.9\pm10.7\%$ (p<0.001), LVESV decreasing from a 137.9 ± 64.1 mL to 52.4 ± 32.6 mL (p<0.001) and NYHA Class improving from 2.73 ± 0.58 to 1.03 ± 0.18 (p<0.001) (32). The clinical feasibility and efficacy of HBP was also studied in patients with RBBB and HF by Sharma et al. (33). HBP was successful in 37 of 39 patients (95%) with narrowing of RBBB in 78% cases. During a mean follow-up of 15 ± 23 months, HBP resulted in a significant narrowing of QRS from 158 ± 24 to 127 ± 17 ms (P=0.0001), increase in LVEF from $31\pm10\%$ to $39\pm13\%$ (P=0.004), and improvement in NYHA functional class from 2.8 ± 0.6 to 2 ± 0.7 (P=0.0001) (33). Furthermore, Shan et al. demonstrated that in CRT non-responders, upgrade to HBP significantly reduced QRS_d and improved LVEF (from $34.6\% \pm 5.7\%$ to $51.1\% \pm 8.5\%$ at 1 year follow up; P<0.01) (18). However, none of these studies is a randomized controlled clinical trial with head-to-head comparison between HBP and BiVP. At this time, HBP is reserved for patients who are CRT non-responders, who have failed coronary sinus lead placement or patients with atrioventricular (AV) node disease requiring atrioventricular node ablation (AVNA). It should also be attempted in patients with anatomical challenges before considering surgical epicardial LV lead placement. Randomized controlled clinical trials comparing HBP with BiVP are

underway to better assess the efficacy of HBP in CRT (His-SYNC, HOPE-HF, and NCT02805465) (34-36).

Recently, the concept of trans-septal pacing with direct stimulation of the left bundle branch (LBB) fascicles has been entertained and demonstrated by a few clinical investigators (figure 4). It is possible to place a RV lead deep in the septum to try to capture the LBB fascicles directly. This may be a viable approach in the long run as the pacing thresholds seem to be significantly lower than direct His bundle pacing. This novel strategy was reported to correct LBBB with a low and stable output (37). More evidence is needed to confirm safety and long term efficacy of this approach.

His bundle pacing & Atrioventricular nodal ablation (AVNA)

Chronic AF with rapid ventricular rates where adequate rate control cannot be achieved pharmacologically can result in dilated cardiomyopathy and HF. Several small prospective studies compared chronic BiVP to RVP in patients undergoing ablation of the AV node for management of AF with rapid ventricular rates. These trials showed better clinical outcomes (NYHA functional status, quality of life, LVEF) with BiVP as compared to RVP. In patients undergoing AVNA, HBP can also be beneficial (figure 2). In fact, early studies of HBP were reported in patients with AF undergoing AVNA. A recent study by Huang et al. included 52 heart failure patients with narrow QRS who underwent AVNA for AF (38) . Compared to baseline, HBP significantly improved LVEF, left ventricular end diastolic pressure (LVEDP), and NYHA functional status. These benefits were more noticeable in patients with depressed LVEF. Similarly, Vijayaraman et al. studied the feasibility and safety of HBP in patients undergoing AVNA and its effect on LVEF (39). AVNA and HBP were successful in 95% of patients. Final HBP thresholds at implant was 1 ± 0.8 V at 1 ms and increased to 1.6 ± 1.2 V at 1 ms during a mean follow-up of 19 ± 14 months. Left ventricular ejection fraction increased from $43 \pm 13\%$ to $50 \pm 11\%$ (P = 0.01). NYHA functional status improved from 2.5 ± 0.5 to 1.9 ± 0.5 (P = 0.04). HBP seems to be ideally suited to this population if AVNA can be safely performed at the time of implant without increasing the pacing thresholds.

Conclusion

Recently, there has been mounting evidence supporting the role of HBP in various clinical settings. Studies have shown that HBP can be successfully utilized in almost all clinical scenarios, including RV pacing induced cardiomyopathy, AV nodal and infra-nodal heart blocks, AVNA for supraventricular arrhythmias, chronic bundle branch corrections in lieu of LV lead placement and prophylactically in patients who require permanent ventricular pacing. In all these subsets of patients, HBP has shown the ability to correct ventricular dyssynchrony and to improve outcomes. The allure of HBP lies in the fact that the intrinsic conduction system can be recruited and function as nature intended. Such claims cannot be made by both RV and LV pacing and account for their detrimental and limited benefits, respectively. However, lack of investments to develop better tools, leads and devices has resulted in slower progress. Large scale randomized trials and concomitant investments need to be undertaken to move the field forward and make HBP a permanent reality in the vast majority of patients who require ventricular pacing.

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Figure legend:
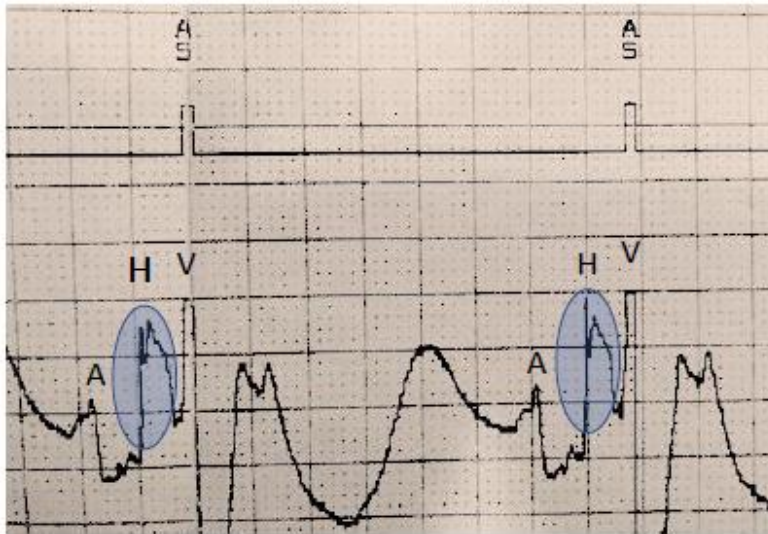
1. During implantation of a CIED, a His bundle lead is affixed into the tissue where a large His bundle electrogram (Egm) is recorded. The lead is connected in a unipolar fashion to the pacing system analyzer (PSA) during the procedure. Due to the annular location of the lead, a far field atrial Egm (A), a near field His Egm (H), and a ventricular egm (V) are recorded from the lead tip. The highlighted area depicts His bundle current of injury. AS represents ventricular sensing- the lead tip is connected to the atrial channel for better sensing (atrial channel settings are better optimized for sensing during His bundle implants through the Medtronic PSA).

2. A 54-year old female with Tetralogy of Fallot repair at a young age subsequently developed multiple atrial arrhythmias. After several ablations to treat her atrial arrhythmias, she underwent atrioventricular nodal ablation followed by CRT-P implantation. Pacing thresholds increased along with phrenic nerve capture and the lead was subsequently abandoned. Patient developed HF symptoms and LV EF reduced from 54% to 35% with RV pacing. Figure 2a demonstrates an atrial tachycardia with RV pacing. She underwent successful His bundle pacing 3 years later. This resulted in selective His bundle capture (2b). Note the isoelectric segments between the pacing stimulus to the QRS onset indicating recruitment of His bundle alone without any local ventricular fusion. Also, there are diffuse T wave changes related to T wave memory which normalize within a few weeks. The CXR displays atrial (A) and left ventricular (LV) leads that were abandoned (2c). A dual chamber was used in this case with the His lead plugged into the atrial port and the old RV lead plugged into the RV port. The device was programmed in the DVIR mode (RV lead acts as a back-up lead only in this mode). Her LV EF normalized in 3 months.
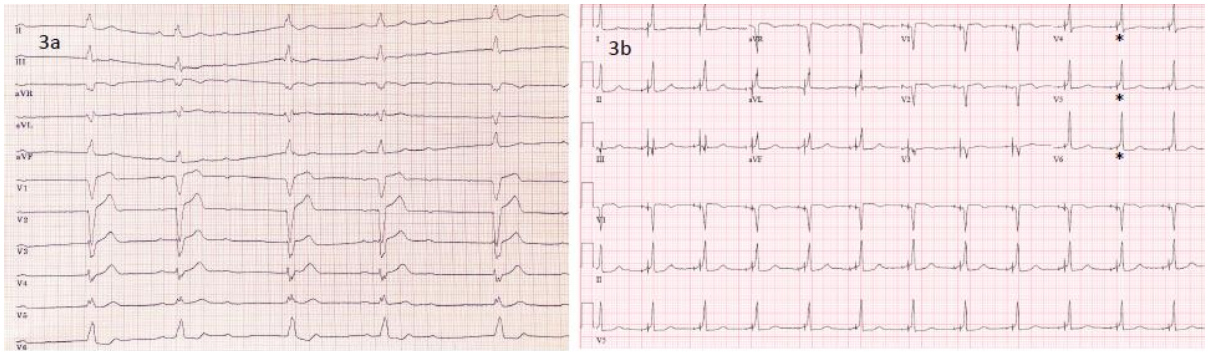
3. A 62-year old female presented with heart block and sudden cardiac arrest and underwent implantation of a dual chamber ICD. She developed HF symptoms over the next year and her LV EF reduced from 55% to 30%. She consented to undergoing HBP. Baseline ECG demonstrates underlying high degree heart block and wide LBBB (3a). Non-selective His bundle pacing was successfully achieved. Asterisk (*) denotes fusion between His bundle pacing and minimal local ventricular capture (pseudo delta wave). Her EF normalized in 4 months with resolution of HF symptoms.
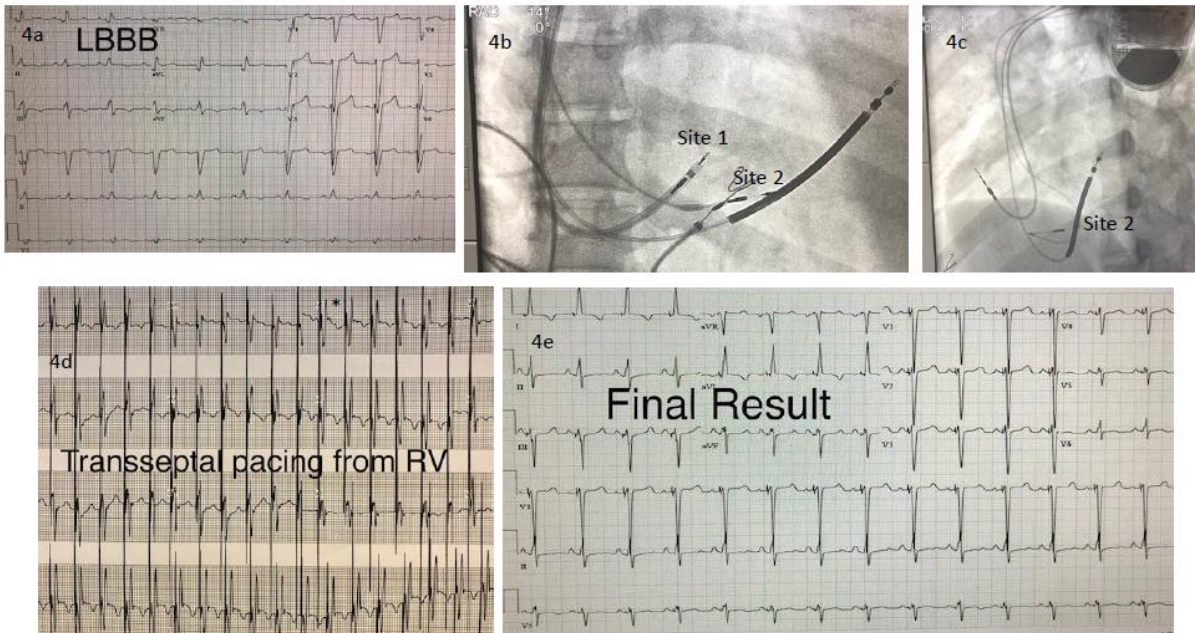
4. A 44-year old female with non-ischemic cardiomyopathy, LBBB and NYHA class III HF symptoms was referred for His bundle pacing due to failed LV lead placement (4a). During implant, LBBB was completely recruited at/above 4V @ 1 ms. Due to high pacing thresholds, trans-septal pacing was attempted. CXR shows the lead placement (4b & 4c). Site 1 is where LBBB recruitment was obtained at high pacing threshold. Site 2 is past the tricuspid annulus and the lead is screwed deep into the septum until pacing reveals a RBBB pattern in V1 (*), suggestive of direct LBB pacing (4d). With AV delays adjusted to allow for RBB conduction, the fused QRS is narrow with QRS < 120 ms (4e).

Table 1: His Bundle Pacing versus Right Ventricular Pacing				
Study	Patient population	Study design	N	Findings
Catanzariti et al. (2006) (40)	Patients with tachy-brady syndrome or supra-Hisian AV block	Comparative	24	Improvement in ventricular dyssynchrony, mitral regurgitation and left ventricular systolic function, Tei index (p<0.05) with HBP as compared to RVP.
Zanon et al. (2008) (41)	Patients with standard pacemaker indication	Crossover study design	12	Better perfusion score with HBP than with RVP (0.44 ± 0.5 vs 0.71 ± 0.53, respectively; p=0.011).
Kronborg et. al (2011) (42)	Patients with pacemaker indication due to AV block, LVEF>0.4, QRS duration <120 ms and sinus rhythm	Comparative	38	Mean QRS duration was 153 ± 12 ms with mid-septal pacing vs 161 ± 15 ms with apical pacing.
Catanzariti et al. (2013) (43)	Patients with standard pacemaker indication	Prospective cohort	26	Decreased EF ($50.1\pm8.8\%$ versus $57.3\pm8.5\%$, p<0.001); increased MR ($22.5\pm10.9\%$ vs $16.3\pm12.4\%$; p=0.018) and worsening interventricular delay (33.4 ± 19.5 ms vs 7.1 ± 4.7 ms, p=0.003) with RVAP, compared with HBP.
Pastore et al. (2014) (44)	Patients with standard pacemaker indication	Crossover study design	37	Increased left ventricular (LV) electromechanical delay (p=0.001) and intra-LV dyssynchrony (p=0.001); increased LV isovolumetric contraction time (p=0.001) and LV isovolumetric relaxation time (p=0.05); and decreased LV ejection time (p=0.033) with RVAP compared to HBP.
Sharma et al. (2015) (3)	Patients receiving pacemaker for the prevention or treatment of bradycardia	Prospective cohort	192	Similar fluoroscopy times (12.7 ± 8 min versus 10 ± 14 min; median 9.1 versus 6.4 min; p=0.14) and higher pacing thresholds in the HBP group vs the RVP group (1.35 ± 0.9 V vs 0.6 ± 0.5 V at 0.5 ms; p<0.001). Decreased HF hospitalization in the HBP group vs the RVP group (2% versus 15%; p=0.02) with no difference in mortality between the two groups.
Vijayaraman et al. (2018) (14)	Patients with standard pacemaker indication	Prospective cohort	192	Unchanged LVEF in the HBP group ($55\%\pm8\%$ vs $57\%\pm6\%$; p=0.13) vs decreased LVEF in the RVP group ($57\%\pm7\%$ vs $52\%\pm11\%$; p=0.002), lower incidence of pacing-induced cardiomyopathy in the HBP as compared to the RVP group ((2% vs 22%; p=0.04), lower mortality or HFH with HBP as compared to RVP with >40% ventricular pacing after 5 years of follow up (32% vs 53%; p=0.04).
Abdelrahman et al. (2018) (16)	Patients with standard pacemaker indication	Prospective cohort	765	Lower mortality, HFH or upgrade to BiV pacing with HBP (83 of 332 patients [25%]) compared to RVP (137 of 433 patients [32%]; hazard ratio [HR]: 0.71; 95% confidence interval [CI]: 0.534 to 0.944; p = 0.02).

Table 2: His Bundle Pacing for Cardiac Resynchronization Therapy				
Study	Patient population	Study design	N	Findings
Barba-Pichardo et al. (2013) (45)	CRT eligible patients with failed LV lead placement	Observational study	16	Improvement in functional class and LV function parameters including mean LVEDD/LVESD (65.9/55.4 vs 59.5/51.2; p<0.01), mean LVEF (29 vs 36; p<0.05), mean QRS (166 vs 97; p<0.001).
Lustgarten et al. (2015) (46)	CRT eligible patients (QRS>130 msec)	Crossover study design	29	QRS narrowing in 21 (72%) patients, improvement in clinical outcomes (EF, NYHA class, 6 min-walk and QOL score) for both pacing modes as compared to baseline.
Vijayaraman et al. (2016) (47)	CRT eligible patients	Observational study	32	QRS narrowing (165 ± 31 to 115 ± 19 ms; p< 0.05), improvement in mean LVEF (30 ± 10 to $47 \pm 11\%$; p<0.05) & NYHA class (2.9 to 1.6; p=0.05).
Ajijola et al. (2017) (13)	CRT eligible patients	Observational study	21	QRS narrowing (180 ± 23 to 129 ± 13 ms; p<0.0001), improvement in NYHA class, LVEF (27 ± 10 to $41 \pm 13\%$; p<0.001) & $LVID_d$ (5.4 ± 0.4 to 4.5 ± 0.3 cm; p<0.001).
Sharma et al. (2018) (31)	Patients with CRT indication or failed BiVP	Observational study	106	QRS narrowing (157 ± 33 to 117 ± 18 ms; p=0.0001), improvement in LVEF (30 ± 10 to $43 \pm 13\%$; p= 0.0001) & NYHA class (2.8 ± 0.5 to 1.8 ± 0.6; p=0.0001).
Shan et al. (2018) (18)	Patients with pacing-induced cardiomyopathy and CRT non-responders	Observational study	18	QRS narrowing (156.9 ± 21.7 to 107.1 ± 16.5 ms; p<0.01), improvement in LVEF ($35.7 \pm 7.9\%$ to $52.8 \pm 9.6\%$; p<0.01)& left ventricular end-diastolic dimensions (62.3 ± 6.9 to 55.5 ± 7.7 mm; p<0.01).
Huang et al. (2018) (32)	Patients with LBBB and heart failure	Observational study	74	Acute LBBB correction in 72 (97.3%) patients, improvement in LVEF ($32.4 \pm 8.9\%$ to $55.9 \pm 10.7\%$; p<0.001), LVESV (137.9 ± 64.1 mL to 52.4 ± 32.6 mL; p<0.001) & NYHA Class (2.73 ± 0.58 to 1.03 ± 0.18; p<0.001).
Sharma et al. (2018) (33)	Patients with RBBB and heart failure	Observational study	39	Successful HBP in 37 of 39 patients (95%) with QRS narrowing (158 ± 24 to 127 ± 17 ms; p=0.0001), improvement in LVEF ($31 \pm 10\%$ to $39 \pm 13\%$; p=0.004) & NYHA Class (2.8 ± 0.6 to 2 ± 0.7; p=0.0001).