Current Cardiovascular Risk Reports (2019) 13: 4
https://doi.org/10.1007/s12170-019-0598-9

ARRHYTHMIAS (J. BUNCH, SECTION EDITOR)

How to Choose Between His Bundle Pacing and Biventricular Pacing for Cardiac Resynchronization Therapy

Gaurav A. Upadhyay[1] · Pugazhendhi Vijayaraman[2]

Published online: 11 February 2019

Abstract

Purpose of Review The goal of this critical appraisal is to evaluate the role for His bundle pacing (HBP) in cardiac resynchronization, examine early clinical and physiologic data, as well as offer recommendations for selecting patients for HBP versus biventricular pacing for CRT.

Recent Findings Biventricular pacing with a left ventricular (LV) coronary sinus lead has been the primary mode of delivering cardiac resynchronization therapy (CRT) for over two decades. By fusing multiple wavefronts of activation, biventricular pacing shortens and homogenizes ventricular activation, increases left ventricular ejection fraction (LVEF), reduces mitral regurgitation, and is also associated with improved clinical outcomes, including reduced heart failure (HF) hospitalization and mortality. Despite these myriad benefits, approximately one-third of patients do not derive benefit from traditional CRT. HBP is a means of delivering CRT which restores electromechanical synchrony by activating the His-Purkinje system distal to the site of proximal bundle branch block. Early clinical data suggest that CRT with HBP may be associated with comparable clinical benefits to biventricular pacing in CRT-eligible patients, although randomized data are not yet available.

Summary The available data suggest that HBP is an alternative approach to biventricular pacing to achieve cardiac resynchronization by restoration of native Purkinje activation. The applicability is most clear in patients with typical BBB patterns. Further research and randomized studies are necessary to evaluate the role of HBP in CRT.

Keywords Cardiac resynchronization therapy · His bundle pacing · Biventricular pacing · Left bundle branch block

Abbreviations

AF	Atrial fibrillation
AV	Atrioventricular
BBB	Bundle branch block
CCB	Complete conduction block
CRT	Cardiac resynchronization therapy
CSP	Conduction system pacing
CS	Coronary sinus
HBP	His bundle pacing
HF	Heart failure
HPCD	His-Purkinje conduction disease
IPA	Intact Purkinje activation
IVCD	Intraventricular conduction delay
LBBB	Left bundle branch block
LV	Left ventricle or left ventricular
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
NYHA	New York Heart Association
RCT	Randomized controlled trial
RBBB	Right bundle branch block
RV	Right ventricular

This article is part of the Topical Collection on *Arrhythmias*

✉ Pugazhendhi Vijayaraman
pvijayaraman1@geisinger.edu; pvijayaraman@gmail.com

[1] From the Center for Arrhythmia Care at the University of Chicago Medicine, Chicago, IL, USA

[2] Geisinger Heart Institute, Geisinger Commonwealth School of Medicine, MC 36-10, 1000 E Mountain Blvd, Wilkes-Barre, PA 18711, USA

Introduction

Now close to a quarter-century after its initial case description, cardiac resynchronization therapy (CRT) is a mainstay device-based treatment for heart failure with reduced left ventricular ejection fraction (LVEF) and intraventricular conduction delay (IVCD) [1, 2]. The most common clinically utilized form of CRT is biventricular pacing with a transvenous left ventricular (LV) lead placed via the coronary sinus (CS). The goal of CRT is to improve left ventricular pump function through correction of mechanical dyssynchrony, particularly between the septal and lateral walls of the LV, which improves myocardial bioenergetics, increases LVEF, and reduces mitral regurgitation [3, 4]. Importantly, these physiologic changes have translated into improved hard clinical outcomes validated across multiple randomized controlled trials (RCTs), including significant reductions in heart failure (HF) hospitalization and greater survival [5]. Indeed, some CRT patients enjoy marked improvements after biventricular pacing (termed "super-response"), with normalization of LVEF and substantial improvement in functional HF symptoms [6]. Also unique among cardiovascular therapeutics, CRT shows benefit in women and men—indeed, female patients often demonstrated better outcomes after CRT relative to male patients in the RCTs that led to CRT approval. Predictors of super-response include female gender, wide QRS, classic left bundle branch block (LBBB) pattern at baseline, and history of nonischemic cardiomyopathy [6, 7]. Given these findings, CRT is a class I indication for patients with New York Heart Association (NYHA) class II, III, or ambulatory IV symptoms on guideline-directed medical therapy with LVEF ≤ 35%, sinus rhythm, and LBBB with a QRS duration ≥ 150 ms [8].

Despite the substantial benefits realized with CRT through biventricular pacing, however, considerable barriers remain to realizing benefit across all patients. Although agreement on what constitutes response to therapy is variable [9], a systematic review of nonresponse to CRT has shown that between 20 and 50% of CRT patients do not demonstrate detectable response to therapy, be it through hard outcome measures, remodeling measures, soft clinical function measures, or clinical composite scores [10, 11]. Given the marked degree of heterogeneity in response to traditional biventricular pacing with either CS or surgically placed epicardial LV leads, there has been ongoing work to improve CRT delivery, with the advent of multipoint pacing utilizing sequential therapy delivery across quadripolar leads, multisite pacing leveraging simultaneous activation with multiple LV leads, LV endocardial pacing through transseptal or "leadless" pacing approaches, and more recently, CRT delivery through targeted pacing of the conduction system, either with His bundle pacing (HBP) or through left bundle branch pacing [12]. Among these, HBP was recognized in the 2018 guidelines as a means to maintain physiologic ventricular activation over right particular pacing in patients with LVEF 36–50% and who are expected to require > 40% ventricular pacing (class IIa indication) [13••]. Although often identified as distinct from CRT, the goal of HBP is to restore electromechanical synchrony, and we would submit it is a means to achieve physiologic resynchronization in appropriate patients. The purpose of this critical appraisal is to focus on HBP as a means to deliver CRT: first, with a historical perspective on the rise of CRT and initial descriptions of corrective His pacing; second, an analysis of early clinical data for HBP in CRT-eligible patients; third, review possible mechanisms of QRS correction with HBP and discuss implications for how to select CRT-eligible patients for HBP; and, finally, to discuss future directions for HBP as a therapeutic modality for CRT.

Historical Perspective

In seminal work from the late 1960s, it had been observed that LBBB complicating myocardial infarction (MI) was associated with marked left ventricular pump dysfunction and increased mortality. The implication, however, was the majority of dysfunction was due to impaired contractility from MI rather than from altered electrical activation. The significance of delayed ventricular depolarization in LBBB leading to asynchronous right-left ventricular contraction—independent of underlying myopathy—was only recognized close to two decades later, and for which conventional medical therapies at the time were ineffective. The father of the modern implantable cardioverter-defibrillator, Dr. Morton Mower, also deserves credit for stimulating a field of development in cardiac pacing which represented a departure from traditional on-demand approaches of the era. He filed a US patent in 1989 for a "Method and apparatus for treating hemodynamic dysfunction" with a "bi-ventricular cardiac pacer" [14]. In contrast to prior devices focusing on demand or atrioventricular pacing, the concept of this device was to treat "bundle branch blocks or slow conduction in a portion of the ventricles." It is perhaps due to Dr. Mower's influence and the stated goal to utilize biventricular pacing to address the problem of poor pump function in conduction system block that led to its rapid uptake as a therapy in heart failure patients. In the ensuing decades, multiple RCTs were conducted which have shown that traditional biventricular pacing is associated with marked clinical benefits in patients with severe clinical heart failure and evidence of significant electrical conduction system delay.

In contrast to trials of biventricular pacing, early work in HBP in patients with bundle branch block (BBB) focused on the possible mechanism of QRS correction and its electrophysiologic rather than clinical impact. Indeed, the first two significant investigations of HBP to correct BBB, by Narula in 1977 [15] and El-Sherif and colleagues in 1978 [16], utilized temporary pacing at the His bundle to demonstrate QRS correction in patients with LBBB or right bundle branch block (RBBB), and did not focus on hemodynamic improvement. Their observations were seminal from an electrophysiologic perspective—they postulated that cardiac conduction system block was due to asynchronous conduction isolated to the level of the His bundle—and provided a theoretic framework for the mechanism of QRS correction with His bundle pacing which has largely been unchanged for the ensuing four decades. Further discussion regarding possible revision to this understanding based on newer data utilizing multielectrode mapping is presented further below. Irrespective, the work of Narula and El-Sherif and colleagues in corrective His pacing is critical in highlighting the fundamental premise that His bundle pacing might be utilized to overcome proximal block in the left-conduction system and thereby provide CRT by reengaging the His-Purkinje system distal to the site of proximal block.

Early Clinical Data for HBP in CRT-Eligible Patients

The first case series of *permanent* HBP for clinical use was in 2000 by Deshmukh and colleagues [17]. In their study, 18 patients with chronic atrial fibrillation, dilated cardiomyopathy, and normal QRS duration were evaluated for HBP and successful implant was achieved in 14 patients. It was not until 5 years later, however, that the first attempt for HBP in a CRT-eligible patient was reported by Moriña-Vázquez and colleagues in 62-year-old woman who had presented due to syncope [18]. Initial evaluation revealed sinus rhythm, LBBB, and LVEF 35% for which biventricular pacing utilizing a traditional CS lead was initially recommended. A focused electrophysiologic study was performed prior to implant and it was noted that high output pacing from the His catheter resulted in a narrow complex. When multiple attempts to cannulate the CS were later unsuccessful, decision was made to implant a Tendril 1488 T (St. Jude, Sylmar, CA, USA) at the His location. The patient demonstrated clinical improvement and repeat echocardiogram showed LV synchrony with only minimal delay at the left lateral wall.

Since this initial case, several subsequent case reports [19–25] and seven studies (see Table 1) [26, 27••, 28, 29••, 30••, 31••, 32••] on the use of HBP in CRT-eligible patient cohorts have been published in the literature, and will be reviewed briefly here. The first of these were published by Barba-Pichardo et al. [26], building upon the observation of their colleague Moriña-Vázquez. A total of 16 CRT-eligible patients with baseline LBBB in whom CS cannulation had failed were selected for attempt at HBP. Again, they utilized the Tendril family of leads (1488 T, 1788 TC, and 1888 TC; 52 cm length; St. Jude, Sylmar, CA, USA). Importantly, these 16 patients represented 14% of the total number of patients planned for CRT at their center and represent a real-world assessment of implant failure at the time. LBBB correction was noted in 13 patients, but in whom electrode fixation was unsuccessful in 4 patients (with final implant success in 9 of 16 patients, or 56%). No capture loss or lead dislodgement was noted over a mean follow-up of 31.3 ± 21.5 months, and mean LVEF improved, although assessment was not blinded.

Subsequent case series of HBP for CRT have primarily utilized the Medtronic 3830 lead (SelectSecure, Medtronic Inc., Minneapolis, MN, USA) which is distinct from traditional pacemaker and defibrillator leads in that it utilizes a fixed helix fixation system which requires the use of a lead delivery sheath (most commonly the fixed-curve C315His sheath or the deflectable C304SelectSite sheath; Medtronic Inc., Minneapolis, MN, USA). The first, and thus far only, study directly comparing HBP and CS LV leads for cardiac resynchronization was reported by Lustgarten and colleagues in 2015 [27••]. They utilized a cross-over study design in which patients were randomized in single, patient-blinded fashion to either HBP or biventricular pacing for 6 months and then crossed over to the other modality for another 6 months. Among 29 patients who were initially enrolled (28 LBBB and 1 atypical RBBB), 21 achieved QRS narrowing at the time of implant and 17 underwent implant. In follow-up, there were nonsignificant improvements in LV volumes, MR jet area, and LV outflow tract flow integral relative to baseline and the authors concluded that results between HBP and biventricular CRT were comparable. Importantly, however, there was significant dropout within the study with only 12 of 17 patients completing follow-up. In addition, due to the nature of the study design and use of a Y-adaptor, they were unable to exclude potential for stimulation at both sites. Lustgarten also reported a single HBP lead dislodgement on the day after the index procedure, which they reported as an unusual event.

In the same year, Su and colleagues reported on their results of HBP in 25 patients with LBBB and severe LV systolic dysfunction referred for CRT [28]. Of these, 16 patients underwent permanent HBP due inability to place a CS lead due to phrenic nerve stimulation, high capture threshold, or unfavorable CS anatomy where patients declined an epicardial LV lead implant. The remaining 9 patients underwent temporary HBP during testing and then underwent traditional CS placement. The primary focus of Su and colleagues was evaluating the impact of three distinct pacing and sensing configurations: (1) HB tip (−) to RV coil (+), (2) HB tip (−) to HB ring (+), and (3) HB tip (−) to pacemaker pocket (+). They found that utilization of the HB tip-to-RV ring configuration was associated with better R-wave sensing and lower thresholds in 3-month follow-up. They did not report on clinical outcomes of patients.

More recently, HBP for CRT in lieu of traditional biventricular pacing with an LV lead was first reported by Ajijola and colleagues in 2017 [29••]. Among 21 patients (17 LBBB, 4 RBBB) enrolled at two centers, permanent HBP was achieved in 16 patients (76%). At a median 12-month follow-up period, no lead dislodgements had been observed and with only 1 patient with loss of nonselective capture which was resolved with increased device output. Overall clinical and echocardiographic outcomes were

Table 1 Case series of His bundle pacing trials in patients meeting criteria for cardiac resynchronization

Author	Year	*n*	Indication	His bundle lead	LBBB (%)	Final QRS correction (%)	Clinical outcome
Barba-Pichardo et al.	2013	16	Unsuitable CS LV lead	Tendril family	100	56	During mean follow-up of 31.3 ± 21.5 months, NYHA class improved III➔II and LVEF improved from 29➔36% ($p < 0.05$)
Lustgarten et al.	2015	29	Cross-over study of HBP and BiV CRT	SelectSecure 3830	97	59	Patients demonstrated similar NYHA class reduction (2.0➔1.9, $p < 0.001$). Trend towards improvement in LV volumes did not reach significance
Su et al.	2015	25	Unsuitable CS LV lead	SelectSecure 3830	100	NR	HBP implant in 16 of 25. The cohort was composed only those with QRS narrowing, so number of non-narrowers is unknown. HB tip-to-RV coil best configuration
Ajijola et al.	2017	21	HBP in lieu of LV lead	SelectSecure 3830	81	76	NYHA class III➔II ($p < 0.001$) and LVEF improved from 27 ± 10% to 41 ± 13% ($p < 0.001$)
Sharma et al.	2018	106	Unsuitable CS LV lead *or* HBP in lieu of LV lead	SelectSecure 3830	34	92	Underlying BBB in 48 patients (33 of 36 LBBB and 11 of 12 non-LBBB corrected). NYHA class 2.8 ± 0.5➔1.8 ± 0.6 ($p = 0.0001$) and LVEF improved from 30 ± 10% to 43 ± 13% ($p = 0.0001$) among all patients
Sharma et al.	2018	39	Unsuitable CS LV lead *or* HBP in lieu of LV lead	SelectSecure 3830	0	74	Implant successful in 37 and BBB correction in 29 of 37 with remainder utilizing bifocal fusion. During a mean follow-up of 15 ± 23 months, LVEF improved from 31 ± 10% to 39 ± 13% ($p = 0.004$) and NYHA class improved from 2.8 ± 0.6 to 2 ± 0.7 ($p = 0.0001$)
Huang et al.	2018	74	HBP in lieu of LV lead	SelectSecure 3830	100	76	Acute LBBB correction achieved in 72 (97%) but permanent implant pursued in 56 (76%) due to high threshold or fixation failure. In patients with 3-year follow-up improved LVEF (32 ± 9% to 56 ± 11%, $p < 0.001$) and NYHA class (2.7 ± 0.6 to 1 ± 0.2, $p < 0.001$) observed

favorable, with the important caveat that there was no control population.

The largest retrospective cohort experience of HBP in CRT-eligible patients was reported by Sharma and colleagues in early 2018, compiling results from five centers [30••]. They combined two populations of patients: (group 1) patients with unsuccessful CS LV lead implant or nonresponders to CS LV lead pacing (33 patients); (group 2) patients in whom HBP was being utilized in lieu of an LV lead and were otherwise CRT-eligible (73 patients) due to high-degree AV block or AV junction ablation and narrow QRS, pre-existing BBB, or upgrade to CRT due to > 40% RV pacing. There was a high degree of implant success across centers (90%) and in patients with pre-existing BBB (92% correction in 48 patients). In addition, there was a low degree of lead-associated complications (7.4% with increased capture threshold and 7% with loss of bundle branch recruitment). Similar to other studies reporting on BBB correction, capture threshold for bundle branch correction was 2 ± 1.2 V at 1 ms. In follow-up over 14 months, there was significant improvement in LVEF and NYHA class noted, again assessed in a non-blinded manner without a control population as reference.

The first multicenter cohort experience in patients with RBBB morphology was also reported in 2018 by Sharma et al. [31••], combining data from five international sites. Patients were CRT-eligible and underwent HBP either as a first-line approach in place of a CS LV lead or as a bailout strategy after unsuccessful CS LV lead. Among 39 patients enrolled, implant was successful in 37 patients with bundle branch correction in 29 patients (74% of those enrolled). In the remainder, they utilized a novel strategy analogous to bifocal RV pacing in which the His and RV pacing timings were adjusted to generate the narrowest paced QRS. Echocardiographic and clinical outcomes were improved in follow-up over approximately 15 months. Additionally, data was presented using ECGi which demonstrated favorable ventricular activation with HBP.

The largest single-center report of HBP for LBBB correction in CRT-eligible patients was recently published by Huang and colleagues in 2018 [32••]. Among 74 patients enrolled, acute success was achieved in 72 patients (97%) and final HBP implant for CRT pursued in 56 (76%). Importantly, 30 patients had completed 3 years of follow-up and demonstrated marked improvements in LVEF as well as NYHA class, with stable thresholds over time (2.3 ± 0.9 V at 0.5 ms) and no lead dislodgements.

Taken together, these observational data (see Table 1) suggest that HBP may be associated with comparable improvements in LVEF and functional status as those receiving biventricular pacing for CRT, although randomized data are lacking and direct comparisons cannot be made. Distinct from traditional biventricular trials, there appears to be a signal for benefit in patients with RBBB, although the majority of data reported thus far are from patients with pre-existing LBBB.

QRS Correction and Implications for Patient Selection

CRT utilizing an LV lead requires fusion of up to three distinct wavefronts (intrinsic His-Purkinje, LV lead, and RV lead) to achieve resynchronization. As such, even in a patient with favorable LV lead position and long QLV time, the final paced QRS width may still be wide, and has a low degree of correlation with overall outcome after biventricular pacing (see Fig. 1). On the other hand, the final corrected QRS width is of paramount importance in patients receiving HBP for CRT. A multicenter collaborative work group has offered terminology to help standardize reporting of the paced QRS morphology after HBP [33••]. The situation is straightforward for patients with underlying narrow QRS. In this setting, the authors identify two distinct types of His bundle capture: selective and nonselective. Selective capture refers to situations in which the pacing stimulus only captures the His-Purkinje system—identified by an isoelectric stimulus to QRS interval—and nonselective capture occurs when there is fusion between capture of the His-Purkinje system and local ventricular myocardium leading to the appearance of pseudodelta wave.

In patients with pre-existing His-Purkinje conduction disease (HPCD), however, an additional nomenclature was proposed to categorize narrowing or QRS correction. QRS correction was defined as a final paced QRS morphology which is narrower than the pre-existing BBB. Here, a template of the patient's underlying QRS in the absence of BBB is not available, and voltage-dependent changes in QRS morphology must be noted at the time of QRS correction (to differentiate from upper septal capture only). In the example shown (see Fig. 2), the patient's LBBB has been corrected with nonselective HBP and restoration of the intrinsic R-wave forces is noted in the precordial leads.

Mechanism of BBB correction with HBP has been debated since Narula and El-Sherif's work in the 1970s. Three mechanisms have been predominant: (1) That BBB is due to longitudinal dissociation of the His fibers which is overcome by proximal HBP; (2) That BBB is a result of source-sink mismatch which is overcome by the supraphysiologic current load of pacing; (3) Proximal block at the bundle branch is leap-frogged by the virtual electrode of pacing.

Based upon observations James and Sherf [34] who had proposed a model of sinoventricular conduction—in which impulses are predestined from the sinus node to specific areas of the ventricle—Narula argued that longitudinally dissociated fibers at the His bundle were recruited by right-sided pacing just distal to a site of proximal block and that this was the mechanism of LBBB correction with His pacing. El-Sherif

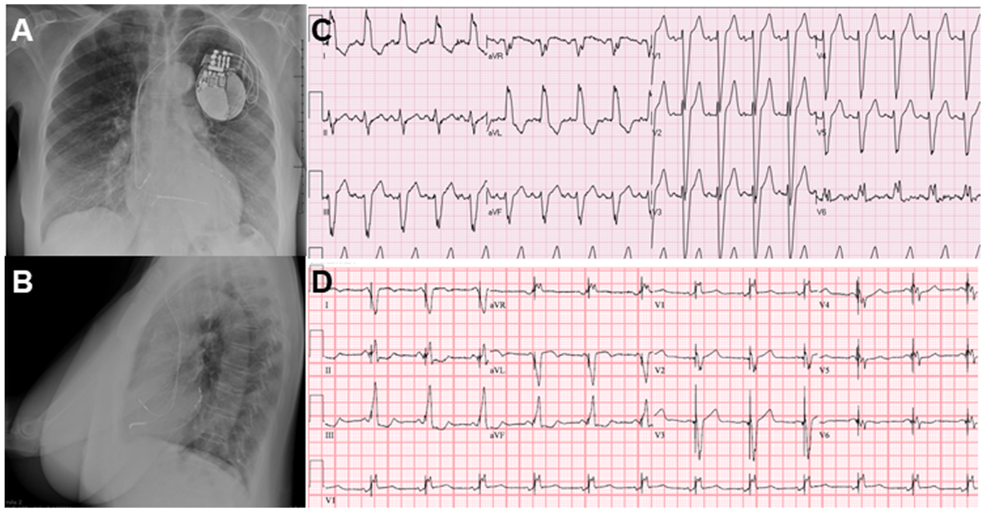

Fig. 1 Chest radiograph and ECGs for patient receiving biventricular device for CRT. Caption: Panels **a** and **b** demonstrate postoperative radiographs for patient who underwent CRT with transvenous LV lead placed into a posterolateral vein. Panel **c** shows pre-implant QRS morphology with typical LBBB pattern. Panel **d** shows biventricular paced QRS. Of note, this patient demonstrated long QLV (> 100 ms) and was a super-responder to biventricular pacing therapy

and colleagues built upon Narula's work with a study of 4 patients with acute RBBB secondary to anterior wall MI, 3 with chronic LBBB, and in a canine model with ligation of the anterior septal artery [16]. They observed evidence of intra-His conduction delay in some patients, and that patients exhibiting delay could be narrowed with pacing. Use of a plunge electrode could further normalize BBB in 67% of their canine model. They argued that selective depression of transverse interconnections in the pathologic His bundle led to BBB, and that this could be overcome with pacing at this location.

Contemporaries of El-Sherif, including Lazzara and colleagues [35] and Bailey and colleagues [36], challenged the notion of functionally significant longitudinal dissociation. In experimental models of canine and rabbit hearts, partial transections of the right or left bundle did not lead to distal block. Lazarra et al. suggested that functional transverse interconnections were robust within the His bundle and allowed for continuous propagation of an activation wavefront despite localized lesions. Fabregas and colleagues, however, reported conflicting data and found that rate-dependent block might occur with partial transection in an isolated canine heart model [37].

We sought to investigate the possibility of intra-His or inter-His delay by conducting multielectrode mapping of the LV septum in patients referred for HBP device implant and susbtrate mapping, primarily prior to ventricular tachycardia (VT) ablation [38••]. We hypothesized that right-to-left His block or delay would be present in patients with LBBB. We importantly observed that surface LBBB pattern reflected heterogeneous activation patterns of LV septal conduction, including intact Purkinje activation (IPA) and others with complete conduction block (CCB) (see Fig. 3). Importantly, high output HBP was not able to correct patients with IPA, and capture of the His-Purkinje system reproduced the patient's intrinsic QRS with variations of selective and nonselective

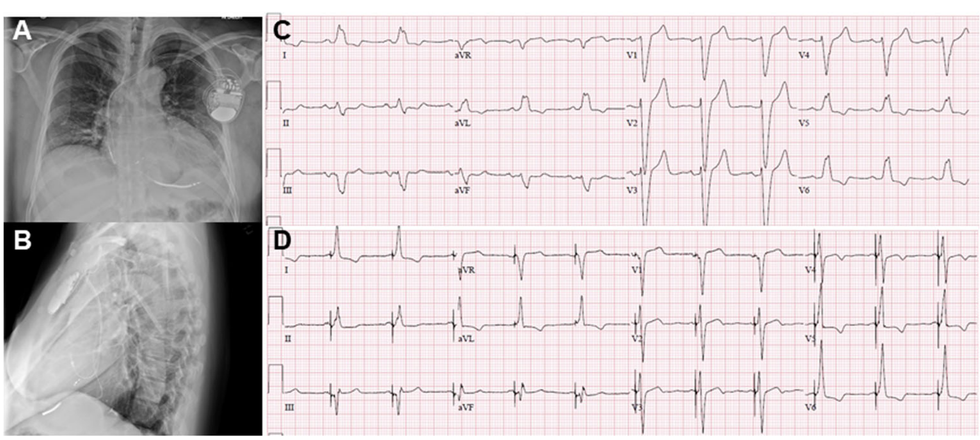

Fig. 2 Chest radiograph and ECGs for patient receiving HBP device for CRT. Caption: Panels **a** and **b** demonstrate postoperative radiographs for patient who underwent CRT with His bundle pacing lead. Panel **c** shows pre-implant QRS morphology with typical LBBB pattern. Panel **d** shows His bundle paced QRS. This patient demonstrated nonselective HBP with QRS correction and has demonstrated modest response in early follow-up (< 3 months since implant)

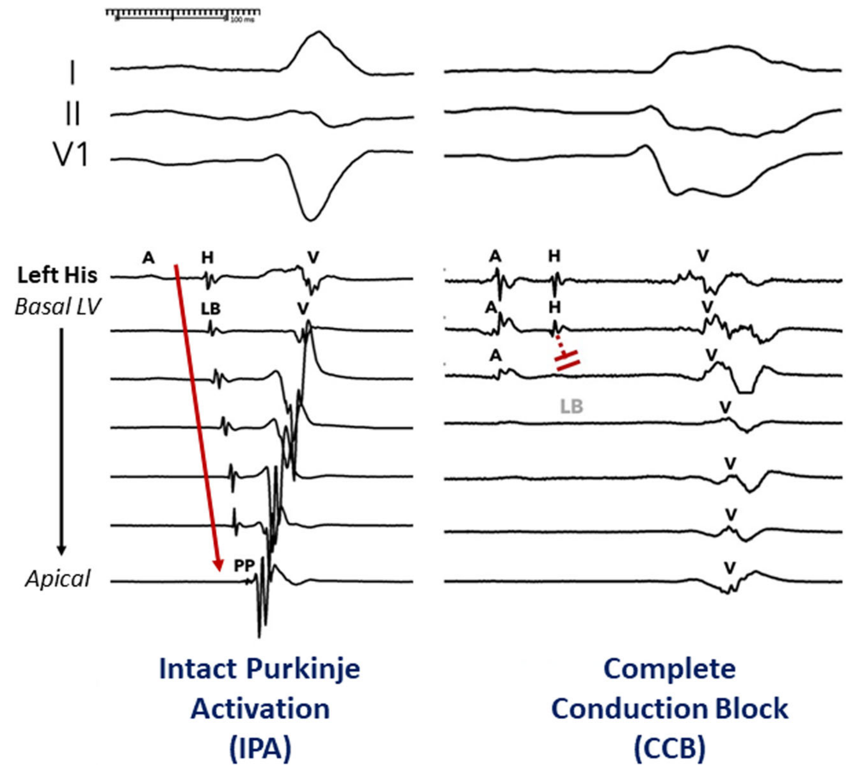

Fig. 3 LV septal intracardiac activation patterns in patients with LBBB by surface ECG. Caption: Two distinct activation patterns are found in patients with wide QRS and features meeting criteria for LBBB, including IPA and CCB. In IPA, His-Purkinje activation precedes the local ventricular electrogram. In patients with CCB, there is abrupt complete cessation of conduction, here at the proximal left-sided His fibers (i.e., left intra-Hisian block)

capture based on output. In patients with CCB, block at the level of the left-sided His fibers (i.e., left intra-Hisian block) was most amenable to QRS correction, with even slightly more distal block of the left bundle branch at the anteroseptum being associated with lower rates of correction. At times, upper septal capture without engagement of the His-Purkinje system was also noted, and this often produced a QRS morphology which was distinct from the patient's pre-existing wide QRS. The implication for patients referred for CRT is significant: based on these data, patients with IPA are less likely to benefit from HBP for CRT *and* it is critical to ensure that voltage-dependent changes in QRS morphology are noted to ensure selective or nonselective His capture is present in patients demonstrating QRS correction.

When viewed with respect to selecting patients for HBP versus biventricular pacing, the available data suggest that HBP is an alternative approach which may provide restoration of native Purkinje activation. The applicability is most clear in patients with typical BBB patterns, although there are limitations with respect to use of surface ECG criteria in predicting correction from HBP (as well as response to biventricular CRT). There is uncertain benefit in patients with IVCD and IPA. Importantly, some patients may demonstrate dual pathologies (i.e., BBB as well as diffuse myocardial disease and coexisting IVCD), and correction of QRS width may unmask underlying IVCD. Importantly, there are no currently available randomized data comparing primary HBP versus biventricular pacing, and we recommend a strategy of attempting HBP when conventional approach with biventricular pacing has not been successful or after close discussion with a patient regarding the risks and benefits of both approaches.

Future Directions

There has been ground swell of interest building in HBP for pacing indications over the past decade. The fundamental premise of HBP, to engage the native His-Purkinje system for conduction, is both intuitively attractive and now is enjoying a growing body of pathobiologic evidence to support its use. Beyond as an alternative to biventricular pacing, there are also data to suggest that His bundle pacing may be utilized in concert with an LV lead (i.e., His-optimized CRT [39•]) to improve outcome in some patients (perhaps those with dual pathology of BBB and IVCD) [40]. In addition to HBP, other forms of conduction system pacing, including intraseptal LV pacing, have also captured interest due to greater R-wave sensing and lower pacing thresholds [41•, 42].

With that noted, there is clearly a need to build on our evidence base with further data. It would be particularly compelling to compare HBP with traditional biventricular pacing utilizing traditional CS or epicardial LV leads, and the ongoing HIS-SYNC Pilot (NCT02700425) is evaluating this question. Other acute studies are underway such as the Electrical Resynchronization and Acute Hemodynamic Effects of Direct

His Bundle Pacing Compared to Biventricular Pacing study (NCT03452462), which will utilize ECGI at the time of implant, and His Bundle Pacing in Bradycardia and Heart Failure (NCT03008291) which will evaluate acute ECG metrics with HBP in patients undergoing CRT or dual-chamber implants. Other trials are exploring clinical outcomes use of HBP in CRT-eligible patients without BBB, such as HOPE-HF (NCT02671903) which is evaluating use of HBP in HF patients with long AV delay and without BBB, and the Comparison of His Bundle Pacing and Biventricular Pacing in Heart Failure With Atrial Fibrillation (NCT02805465). While traditional biventricular CRT has been validated across multiple large RCTs, these and other HBP studies are a first step to add to a growing body of prospective evidence evaluating the role of HBP for resynchronization [43].

There are many similarities with HBP today to the nascent period of biventricular pacing approximately two decades ago. There are open and evolving questions regarding appropriate patient selection, growing need for specialized tool sets to improve lead targeting and implant success, and rising awareness of the importance of post-implant care clinics focused on assessing His capture and correction in follow-up. As a modality for CRT, HBP offers an avenue to restore electromechanical synchrony through re-engaging the His-Purkinje system, and may be particularly suitable in nonischemic patients with prominent dyssynchrony. Questions remain regarding what thresholds should be accepted in patients with HBP for CRT, as these are often higher than those that are found in patients with narrow QRS. Noninvasive surface ECG assessment to assess correctability to HBP prior to implant would be desirable. Finally, there is a clear role for the development of dedicated HBP pacing systems which allow for altered programming in order to best optimize care in follow-up. Regardless, HBP is increasingly being utilized as an additional option for advanced heart failure patients, with a clearly reasonable role for patients in whom traditional biventricular pacing strategies have been attempted and were unsuccessful. While not a panacea, it is clear that HBP—and a focus on conduction system pacing—are physiologically motivated approaches which meaningfully add to our armamentarium in the care of heart failure patients.

Compliance with Ethical Standards

Conflict of Interest Pugazhendhi Vijayaraman reports grants and personal fees from Medtronic, personal fees from Boston Scientific, personal fees from Biotronik, personal fees from Abbott, outside the submitted work. In addition, Dr. Vijayaraman has a patent pending for a His bundle pacing delivery tool.

Gaurav Upadhyay declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey de Jr, Colvin MM, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2017;70(6):776–803.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129–200.
3. Leclercq C, Cazeau S, Le Breton H, et al. Acute hemodynamic effects of biventricular DDD pacing in patients with end-stage heart failure. J Am Coll Cardiol. 1998;32(7):1825–31.
4. Kass DA, Chen CH, Curry C, Talbot M, Berger R, Fetics B, et al. Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. Circulation. 1999;99(12):1567–73.
5. McAlister FA, Ezekowitz J, Hooton N, et al. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review. JAMA. 2007;297(22):2502–14.
6. Hsu JC, Solomon SD, Bourgoun M, McNitt S, Goldenberg I, Klein H, et al. Predictors of super-response to cardiac resynchronization therapy and associated improvement in clinical outcome: the MADIT-CRT (multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy) study. J Am Coll Cardiol. 2012;59(25):2366–73.
7. Cheng YJ, Zhang J, Li WJ, Lin XX, Zeng WT, Tang K, et al. More favorable response to cardiac resynchronization therapy in women than in men. Circ Arrhythm Electrophysiol. 2014;7(5):807–15.
8. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2013;127(3):e283–352.
9. Fornwalt BK, Sprague WW, BeDell P, Suever JD, Gerritse B, Merlino JD, et al. Agreement is poor among current criteria used to define response to cardiac resynchronization therapy. Circulation. 2010;121(18):1985–91.
10. Daubert C, Behar N, Martins RP, Mabo P, Leclercq C. Avoiding non-responders to cardiac resynchronization therapy: a practical guide. Eur Heart J. 2017;38(19):1463–72.
11. European Heart Rhythm A, European Society of C, Heart Rhythm S, et al. 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. Europace. 2012;14(9):1236–86.

12. Auricchio A, Prinzen FW. Enhancing response in the cardiac resynchronization therapy patient: the 3B perspective-bench, bits, and bedside. JACC Clin Electrophysiol. 2017;3(11):1203–19.
13.•• Kusumoto FM, Schoenfeld MH, Barrett C, et al. ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. Circulation. 2018;2018. https://doi.org/10.1161/CIR.0000000000000628 **These updated guidelines provide new indications for cardiac resynchronization therapy for patients with bradycardia and reduced left ventricular function utilizing physiologic pacing.**
14. Mower MM. Inventor. Method and apparatus for treating hemodynamic dysfunction. US patent 4,928,6881989.
15. Narula OS. Longitudinal dissociation in the His bundle. Bundle branch block due to asynchronous conduction within the His bundle in man. Circulation. 1977;56(6):996–1006.
16. El-Sherif N, Amay YLF, Schonfield C, et al. Normalization of bundle branch block patterns by distal His bundle pacing. Clinical and experimental evidence of longitudinal dissociation in the pathologic his bundle. Circulation. 1978;57(3):473–83.
17. Deshmukh P, Casavant DA, Romanyshyn M, Anderson K. Permanent, direct His-bundle pacing: a novel approach to cardiac pacing in patients with normal His-Purkinje activation. Circulation. 2000;101(8):869–77.
18. Morina-Vazquez P, Barba-Pichardo R, Venegas-Gamero J, Herrera-Carranza M. Cardiac resynchronization through selective His bundle pacing in a patient with the so-called InfraHis atrioventricular block. Pacing Clin Electrophysiol. 2005;28(7):726–9.
19. Dabrowski P, Kleinrok A, Kozluk E, Opolski G. Physiologic resynchronization therapy: a case of His bundle pacing reversing physiologic conduction in a patient with CHF and LBBB during 2 years of observation. J Cardiovasc Electrophysiol. 2011;22(7):813–7.
20. Manovel A, Barba-Pichardo R, Tobaruela A. Electrical and mechanical cardiac resynchronisation by novel direct His-bundle pacing in a heart failure patient. Heart Lung Circ. 2011;20(12):769–72.
21. Rehwinkel AE, Muller JG, Vanburen PC, Lustgarten DL. Ventricular resynchronization by implementation of direct his bundle pacing in a patient with congenital complete AV block and newly diagnosed cardiomyopathy. J Cardiovasc Electrophysiol. 2011;22(7):818–21.
22. Wu G, Cai Y, Huang W, Su L. Hisian pacing restores cardiac function. J Electrocardiol. 2013;46(6):676–8.
23. Shan P, Su L, Chen X, Xu L, Ni X, Huang W. Direct His-bundle pacing improved left ventricular function and remodelling in a biventricular pacing nonresponder. Can J Cardiol 2016;32: 1577.e1–1577.e4.
24. Ajijola OA, Romero J, Vorobiof G, Suh WM, Shivkumar K, Tung R. Hyper-response to cardiac resynchronization with permanent His bundle pacing: is parahisian pacing sufficient? HeartRhythm Case Rep. 2015;1(6):429–33.
25. Boczar K, Slawuta A, Zabek A, et al. Cardiac resynchronization therapy with His bundle pacing as a method of treatment of chronic heart failure in patients with permanent atrial fibrillation and left bundle branch block. J Electrocardiol. 2018;51(3):405–8.
26. Barba-Pichardo R, Manovel Sanchez A, Fernandez-Gomez JM, Morina-Vazquez P, Venegas-Gamero J, Herrera-Carranza M. Ventricular resynchronization therapy by direct His-bundle pacing using an internal cardioverter defibrillator. Europace. 2013;15(1): 83–8.
27.•• Lustgarten DL, Crespo EM, Arkhipova-Jenkins I, et al. His-bundle pacing versus biventricular pacing in cardiac resynchronization therapy patients: a crossover design comparison. Heart Rhythm. 2015;12(7):1548–57 **This is the only randomized, crossover study comparing His bundle pacing with biventricular pacing in patients requiring cardiac resynchronization therapy. Both biventricular pacing and His bundle pacing resulted in equivalent but significant improvement in functional class and LV ejection fraction compared to baseline.**
28. Su L, Xu L, Wu SJ, Huang WJ. Pacing and sensing optimization of permanent His-bundle pacing in cardiac resynchronization therapy/implantable cardioverter defibrillators patients: value of integrated bipolar configuration. Europace. 2016;18(9):1399–405.
29.•• Ajijola OA, Upadhyay GA, Macias C, Shivkumar K, Tung R. Permanent His-bundle pacing for cardiac resynchronization therapy: initial feasibility study in lieu of left ventricular lead. Heart Rhythm. 2017;14(9):1353–61 **This is the first study to demonstrate the feasibility of His bundle pacing as first-line therapy in patients requiring cardiac resynchronization therapy in place of LV lead placement.**
30.•• Sharma PS, Dandamudi G, Herweg B, et al. Permanent His-bundle pacing as an alternative to biventricular pacing for cardiac resynchronization therapy: a multicenter experience. Heart Rhythm. 2018;15(3):413–20 **This is the largest observational study of His bundle pacing in patients eligible for biventricular pacing. HBP was successful in 90% of patients with bundle branch block or AV conduction disease and cardiomyopathy with good response rates.**
31.•• Sharma PS, Naperkowski A, Bauch TD, et al. Permanent His bundle pacing for cardiac resynchronization therapy in patients with heart failure and right bundle branch block. Circ Arrhythm Electrophysiol. 2018;11(9):e006613 **This study demonstrated modest benefits of improvement in LV function and functional class in patients with right bundle branch block utilizing permanent His bundle pacing.**
32.•• Huang W, Su L, Wu S, et al. Long-term outcomes of His bundle pacing in patients with heart failure with left bundle branch block. Heart 2019;105(2):137–143. **This study demonstrated the role of His bundle pacing in improving long-term clinical outcomes in patients with cardiomyopathy and left bundle branch block. Majority of patients developed normalization of LV function uring three year follow-up.**
33.•• Vijayaraman P, Dandamudi G, Zanon F, et al. Permanent His bundle pacing: recommendations from a multicenter His bundle pacing collaborative working group for standardization of definitions, implant measurements, and follow-up. Heart Rhythm. 2018;15(3): 460–8 **This article discusses the nomenclature for permanent His bundle pacing in patients with normal His-Purkinje conduction and those with underlying His-Purkinje conduction disease.**
34. Sherf L, James TN. A new electrocardiographic concept: synchronized sinoventricular conduction. Dis Chest. 1969;55(2):127–40.
35. Lazzara R, Yeh BK, Samet P. Functional transverse interconnections within the His bundle and the bundle branches. Circ Res. 1973;32(4):509–15.
36. Bailey JC, Spear JF, Moore EN. Functional significance of transverse conducting pathways within the canine bundle of His. Am J Cardiol. 1974;34(7):790–5.
37. Fabregas RA, Tse WW, Han J. Conduction disturbances of the bundle branches produced by lesions in the nonbranching portion of His bundle. Am Heart J. 1976;92(3):356–62.
38.•• Upadhyay GA, Cherian T, Shatz D, et al. Intracardiac delination of left bundle branch block activation patterns: mechanistic evidence of left intra-Hisian block circumvented by His pacing. Heart Rhythm 2018;15:S641 **This article presents evidence for discrete conduction block in the distal His bundle or proximal left bundle in the majority of patients with left bundle branch block and predicts response to His bundle pacing using intrinsic ventricular activation patterns.**
39.• Vijayaraman P, Herweg B, Ellenbogen KA, Gazek J. His-optimized cardiac resynchronization therapy (HOT-CRT): a novel approach to enhance CRT response. Heart Rhythm 2018;15:supplement (abstract). **This abstract presents a novel concept of combining**

His bundle pacing and left ventricular pacing in patients with advanced cardiomyopathy and severe left Purkinje conduction disease.

40. Padeletti L, Pieragnoli P, Ricciardi G, et al. Simultaneous His bundle and left ventricular pacing for optimal cardiac resynchronization therapy delivery: acute hemodynamic assessment by pressure-volume loops. Circ Arrhythm Electrophysiol. 2016;9(5).

41.• Huang W, Su L, Wu S, et al. A novel pacing strategy with low and stable output: pacing the left bundle branch immediately beyond the conduction block. Can J Cardiol. 2017;33(12):1736 e1731–3 **This novel concept describes a innovative technique for pacing the left bundle branch beyond the site of block via transvenous, transseptal approach.**

42. Mafi-Rad M, Luermans JG, Blaauw Y, Janssen M, Crijns HJ, Prinzen FW, et al. Feasibility and acute hemodynamic effect of left ventricular septal pacing by transvenous approach through the interventricular septum. Circ Arrhythm Electrophysiol. 2016;9(3): e003344.

43. Sugrue A, Bhatia S, Vaidya VR, Kucuk U, Mulpuru SK, Asirvatham SJ. His bundle (conduction system) pacing: a contemporary appraisal. Card Electrophysiol Clin. 2018;10(3):461–82.