



# His Bundle Pacing in Heart Failure—Concept and Current Data

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## Abstract

**Purpose of Review** His bundle pacing (HBP) has continued to emerge as a viable alternative to both right ventricular pacing (RVP) and cardiac resynchronization therapy. In recent years, a considerable amount of research has been published with regard to using HBP to treat congestive heart failure (CHF) and this article presents a concise yet comprehensive review of this literature.

**Recent Findings** Studies have demonstrated that HBP is useful for CHF patients who are non-responders to biventricular pacing (BiVP) or have a history of previously failed coronary sinus lead placement, right/left bundle branch block cardiomyopathy, or pacing-induced cardiomyopathy. Additionally, HBP is useful in patients with an indication for pacing who are expected to have a RVP burden exceeding 20%.

**Summary** The theoretical benefit of utilizing the native His Purkinje system to excite cardiac tissue is appealing as it can result in true cardiac resynchronization. Limited studies have shown its benefit in reducing heart failure symptoms and improving cardiac function. Larger randomized clinical trials and further investments into developing better technologies are highly desired to make its clinical use sustainable in the long run.

**Keywords** His bundle pacing · Cardiac resynchronization therapy · Heart failure · Cardiac dyssynchrony · Pacing-induced cardiomyopathy

## Cardiac Resynchronization for Congestive Heart Failure

Since the introduction of cardiac resynchronization therapy (CRT) for the treatment of congestive heart failure (CHF) in 1993, considerable research has been conducted in this arena to justify its use in the CHF population [1]. Leclercq et al. provided compelling hemodynamic evidence, in the form of both reduced pulmonary capillary wedge pressure and increased cardiac index, that biventricular pacing (BiVP) was superior to either atrial or right ventricular pacing for heart failure patients [2]. In 2002, Abraham et al. demonstrated in the first double-blind study of its kind that CHF patients undergoing CRT not only benefited from symptomatic improve-

ment of their disease, but also experienced some degree of reverse remodeling with a significant increase in their left ventricular ejection fraction (LVEF) [3]. This was followed by a number of prospective, randomized, and double-blinded trials confirming mortality benefit for CHF patients with New York Heart Association (NYHA) classes II–IV in the latter half of that decade [4–6]. The mountain of evidence in support of CRT, which runs the gamut of small, pilot, and hemodynamic studies all the way to large, prospective, and randomized clinical trials, has led to its entrenchment in our guidelines as a class 1a indication for the treatment of CHF with significant dyssynchrony [7].

## Origin and Concept of His Bundle Pacing

His bundle recording and pacing had its nascent beginnings as a form of diagnostic testing in the field of electrophysiology back in the 1960s [8]. It was not until the late 1970s that researchers discovered that Purkinje fibers could be recruited by pacing the common His bundle resulting in a narrow QRS despite a baseline left bundle branch block (LBBB) or right bundle branch block (RBBB) [9]. The physiological basis of

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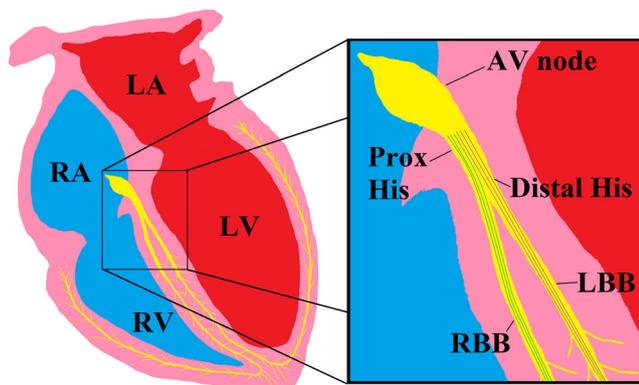
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this phenomenon was “longitudinal dissociation” of the fibers; fibers predestined to the bundle branches originating within the common His bundle, along with lesions that are focal in nature and within the proximal His bundle, could manifest as bundle branch blocks. Narula et al. demonstrated in the 1970s that LBBB could be recruited by pacing distal to the site of block within the common His bundle [9] (Fig. 1). This could abolish the bundle branch block, resulting in a narrow QRS complex. The first reported application of this novel pacing strategy on a permanent basis in humans occurred right around the time CRT was being investigated for the treatment of CHF at the turn of the century by Deshumkh et al. [10]. While Deshumkh et al. demonstrated improvement in left ventricular function and dimensions with His bundle pacing (HBP) in their small cohort of patients, this strategy of pacing did not achieve the same level of notoriety as BiVP did. Over the years, the strength of evidence supporting BiVP has been substantially greater compared to HBP for CRT. However, over the past 10 years, there has been increasing interest in this more physiological modality of pacing, and the strength of evidence supporting its use has grown proportionally with regard to a variety of clinical scenarios.

## Applications of HBP

Based on current evidence (summarized in Table 1), there are now a number of compelling scenarios where HBP is considered a suitable alternative for CRT:



**Fig. 1** Anatomy of the His Purkinje system in relation to the heart. RA right atrium, LA left atrium, RV right ventricle, LV left ventricle, Prox His proximal His, RBB right bundle branch, LBB left bundle branch. Note how the compact AV node and the His bundle can be accessible from within the right atrium. A discrete lesion at the prox His can potentially result in RBB, LBB, or complete heart block depending on which fibers are affected (green fibers are predestined RV fibers while purple fibers are predestined LV fibers). However, pacing distal to this lesion at the distal His bundle can recruit all of the predestined Purkinje fibers past this lesion and still result in a normal QRS complex

### 1. Cardiac Resynchronization Therapy for Non-responders, Failed Coronary Sinus Lead Placement, and Cardiomyopathies with Chronic Bundle Branch Blocks

Perhaps one of the most useful applications of HBP is in patients who need CRT but have failed coronary sinus lead implantation due to the inability to cannulate the CS or its branches, inability to find suitable targets, or clinical non-responders. Coronary sinus lead placement failure varies between 2 to 8% of patients according to previous studies [3, 11]. Barba-Pichardo et al. successfully instituted HBP in 9 of 16 patients that had previously failed coronary sinus lead placement. In these 9 patients, NYHA functional class improved, the mean EF increased from 29 to 36%, and the left ventricular end diastolic dimension decreased from 66 to 60 mm [12]. Recently, Sharma et al. reported on a multicenter experience involving 33 patients who had either failed coronary sinus lead patients or were considered BiVP non-responders that subsequently underwent HBP rescue therapy [13]. Permanent HBP was successful in 91% of these patients (30), and these patients experienced a mean EF improvement from 26 to 40% with reduction in left ventricular end diastolic dimension (LVEDD) from 57.0 to 53.5 mm. These patients also had improvement in their NYHA functional class, from an average of 2.8 to 1.9.

Patients who are non-responsive to BiVP are defined as having less than 15% decrease in left ventricular systolic volume after institution of CRT, and this is estimated to occur in up to 30% of patients receiving traditional BiVP CRT [4, 14]. Recently, Shan et al. reported on 5 patients who were CRT non-responders that subsequently underwent HBP [15]. At 24-month follow-up, these 5 patients had an improvement in LVEF from 34.6 to 55.1% with reduction in LVEDD from 65.8 to 56.6 mm. Mean QRS duration improved from 169.4 to 119 ms in these 5 patients. In the HBP rescue group by Sharma et al., there were 8 non-responders to CRT, and 7 of the 8 experienced improvement in NYHA functional class, and 6 of the 8 experienced improvement in LVEF from 30 to 38% [13].

Recently, in a large cohort of HBP patients, the authors reported that in a subset of patients with bundle branch block wherein HBP was used as the primary form of CRT, permanent HBP was successfully performed in 25 of these 27 patients [13]. In these 25 patients, the mean QRS duration narrowed from 163 to 116 ms, and in those with LBBB only, there was a significant improvement in mean LVEF from 26 to 41%. The efficacy of permanent HBP in this form of non-ischemic cardiomyopathy is not surprising considering the pathogenesis of LBBB-related cardiomyopathy is directly related to cardiac dyssynchronization. LBBB-mediated cardiomyopathy is a type of non-ischemic cardiomyopathy characterized by a history of LBBB with normal LVEF (> 50%) for a number of years with subsequent development of clinical CHF symptoms and decreased LVEF to less than 40% with

**Table 1** Summary of studies of HBP in CHF patients

Study	No. of patients and inclusion criteria	Trial design	Objective	Observations
Cardiac resynchronization therapy non-responders, failed coronary sinus lead placement, and cardiomyopathies with chronic bundle branch blocks Barba-Pichardo et al. [12•]	16 patients Failed CS lead placement	Prospective observational	HBP feasibility	
Sharma et al. [13]	33 patients (group 1, failed CS lead or non-responders)	Retrospective observational	Assess the feasibility and outcomes of HBP in CRT eligible or failed patients	9/16 (56%) successful with loss of LBBB; NYHA functional class improved, the mean EF increased
Ajjola et al. [37•]	21 patients with indications for CRT	Retrospective observational	Assess the feasibility of incorporating HBP for CRT in lieu of a CS lead	30/33 (91%) successful; significant narrowing of QRS; increase in LVEF, and improvement in functional class
Lusgarten et al. [40]	29 patients with indications for CRT	Prospective crossover design	Feasibility of, and clinical response to HBP as an alternative to BiVP	16/21 (76%) successful; significant narrowing of QRS; increase in LVEF, and improvement in functional class
Sharma et al. [13]	73 patients (group 2) with indications for CRT	Retrospective observational	Assess the feasibility and outcomes of HBP in CRT eligible or failed patients	21/29 (72%) successful; clinical outcomes, quality of life, functional class, 6-min hall walk test, LVEF significantly improved for both pacing modes
Pacing-induced cardiomyopathy (PICM) Shan et al. [15]	18 patients with pacing-induced cardiomyopathy	Prospective observational	Assess clinical outcomes	65/73(89%) successful; significant narrowing of QRS; increase in LVEF, and improvement in functional class
Ye et al. [23]	12 patients with pacing-induced cardiomyopathy	Prospective observational	Assess clinical outcomes	16/18 (90%) successful; improvement in LVEDD, LVEF, mitral valve regurgitation, BNP levels, cardiothoracic ratios, and functional class
High right ventricular (RV) pacing burden Sharma et al. [28•]	192 patients with indication for pacemaker. Patients at one center receiving HBP and patients at another center receiving RVP	Case control study 2-year follow-up	Asses feasibility, safety, and clinical outcomes of permanent HBP in an unselected population as compared to RVP	12/14 (86%) successful; significant improvement in QRS duration, NYHA class, and LVIDD
Vijayaraman et al. [29]	192 patients with indication for pacemaker. Patients at one center receiving HBP and patients at another center receiving RVP	Case control study 5-year follow-up	Assess long-term performance and compare the clinical outcomes of permanent HBP vs RVP	75/94 (80%) successful; 107 patients (> 60%) had RV pacing burden >40%. HFH was significantly reduced; no difference in mortality
Abdelrahman-an et al. [30•]	765 patients with an indication for pacemaker. Patients at one center receiving HBP and patients at another center receiving RVP	Case control study	Assess primary outcome of combined endpoint of death, HFH, or upgrade to BiVP	Higher incidence of PICM (2% vs 22%) in HBP vs RVP. Death or HFH was significantly lower in HBP compared to RVP patients; the need for lead revisions was higher in the HBP group
Deshmukh et al. [10]	18 patients with AF, DCM. 10 patients underwent AV node ablation	Prospective observational	Assess HBP feasibility in humans	304/332 (92%) successful; primary endpoint was significantly reduced in the HBP group; observed primarily in patients with ventricular pacing > 20%; a trend toward reduced mortality in HBP
Deshmukh et al. [43]	54 patients; narrow QRS complex of ≤120 ms, persistent AF requiring AV nodal ablation and DCM	Prospective observational	Long-term outcomes with HBP	12/18 (60%) successful; significant improvement in LVEDD, LVESD, LVEF, cardiothoracic ratios
Kronborg et al. [44]	38 patients with high-grade AV block, narrow QRS and EF > 40%	Prospective, randomized, crossover design	Primary outcome, LVEF	39/54 (72%) successful; improved EF (23 to 33%), increased cardiopulmonary reserve
Huang et al. [31•]	52 patients with CHF (HFpEF and HFrEF), persistent AF and AV node ablation	Prospective observational	Assess clinical outcomes	32/38 (84%) successful; significantly lower after 12 months with RVP. No difference in functional class, 6-min walk test
CRT with HBP in RBBB and CHF Sharma et al. 2018 [33]	39 patients with indications for CRT	Retrospective observational	Assess the feasibility and outcomes of HBP in patients with RBBB and heart failure	42/52 (80%) successful; improved echocardiographic measurements, functional class and reduced diuretics use

Abbreviations: AF atrial fibrillation, BiVP biventricular pacing, CRT cardiac resynchronization therapy, CS coronary sinus, DCM dilated cardiomyopathy, EF ejection fraction, HBP His bundle pacing, HFH heart failure hospitalizations, HFpEF heart failure with preserved ejection fraction, HFrEF heart failure with reduced ejection fraction, LBBB left bundle branch block, LVEDD left ventricular end-diastolic diameter, LVEF left ventricular ejection fraction, LVIDd left ventricular internal diameter diastole, NYHA New York heart association, RBBB right bundle branch block, RVP right ventricular pacing

no explainable reason other than significant ventricular dyssynchrony [16]. The etiology of this condition has been attributed to the redistribution of both myocardial blood flow as well as workload of myocardial contractility from the septum to the lateral wall of the left ventricle [17]. Both of these phenomena are thought to herald the start of left ventricular remodeling after development of LBBB. While this form of non-ischemic cardiomyopathy is thought to account for only a small percentage of patients with cardiomyopathy, it is important to recognize this clinical entity given its responsiveness to cardiac resynchronization [16]. For the first time, HBP is able to prove that LBBB-induced cardiomyopathy is a real entity and direct correction of the underlying LBBB with HBP can result in resolution of the cardiomyopathy despite years of guideline-directed optimal medical therapy (Fig. 2). As HBP engenders a more physiologic form of ventricular activation versus BiVP, theoretically it should work just as well, if not better than BiVP for LBBB-related cardiomyopathy.

## 2. Pacing-Induced Cardiomyopathy

Pacing-induced cardiomyopathy (PICM) is an important and under-recognized cause of cardiomyopathy in some populations. Defined as right ventricular (RV) pacing causing greater than 10% decline in LVEF, it is postulated to occur in up to 15% of patients who are chronically RV paced [18–20]. Though the mechanism is not entirely clear, many large, prospective studies have documented this phenomenon. In the DAVID trial, patients with indications for ICD who were randomized to dual chamber pacing at a base rate of 70 beats per minute (BPM) experienced more heart failure events than those who were randomized to backup ventricular pacing at a rate of 40 bpm [21]. In that study, 57% of these patients had CHF at baseline. Lamas et al. demonstrated that the risk for hospitalization of CHF increased by 20% for every 10% increase in pacing burden [22]. Shan et al. reported on 11 patients with previously normal LVEF (average 62.1%) who received RV pacing for sinus nodal dysfunction or advanced atrial-ventricular (AV) block [15]. After RV pacing, their average LVEF decreased to 36.1%, and with institution of permanent HBP, at 24-month follow-up, average LVEF had improved to 53.0%. Additionally, LVEDD decreased from 60.6 to 56.9 mm at 24-month follow-up. Ye et al. studied patients referred for pulse generator changes who were chronically paced [23]. Nine patients had LVEF  $\geq$  40% and underwent successful upgrade to HBP while three pts. had LVEF  $<$  40% and underwent both HBP and LV lead placement. QRS duration was significantly reduced from  $157.8 \pm 13.3$  to  $109.3 \pm 16.9$  ms and at 6 months, there was improvement in NYHA class ( $2.7 \pm 0.6$  to  $1.8 \pm 0.6$ ,  $P =$

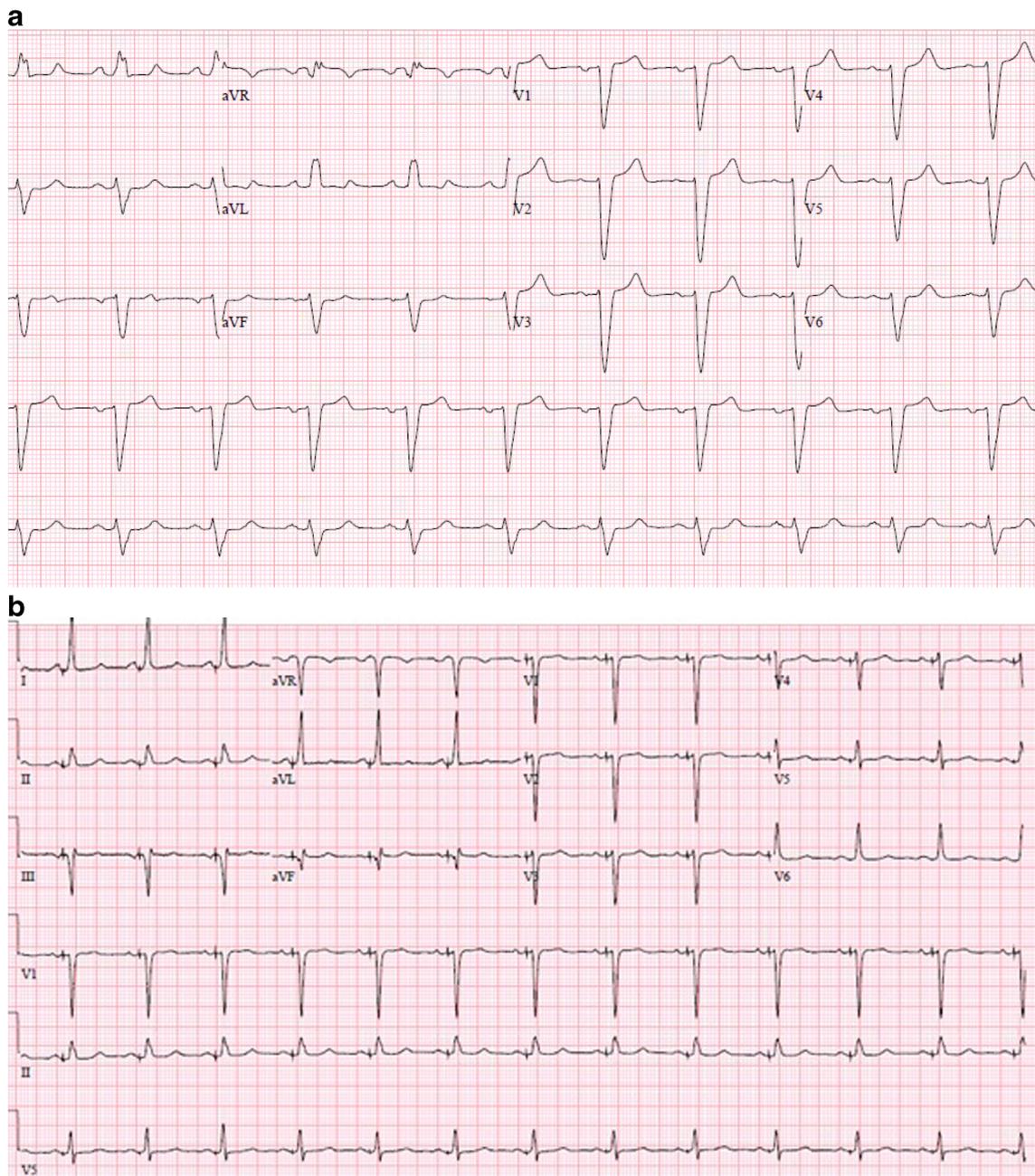
$0.007$ ) and left ventricular internal diastolic diameter ( $5.5 \pm 0.4$  cm to  $5.3 \pm 0.3$  cm,  $P = 0.03$ ). An extreme example of pacing-induced cardiomyopathy in a 17-year-old male is described (Fig. 3).

## 3. Anticipated High Ventricular Pacing Burden

Another compelling indication for HBP is patients with advanced AV conduction disease who need a pacemaker and are expected to require a high burden of RV pacing ( $> 20$ – $40\%$ ). These patients are believed to be particularly vulnerable to development of CHF and the institution of CRT appears to mitigate this risk, especially once RV pacing burden exceeds 40% [24]. In BLOCK-HF, Curtis et al. demonstrated that in 691 patients who had complete HB, those that were randomized to a CRT arm with BiVP, experienced less events (mortality, CHF visits, and increase in left ventricular end systolic volume by 15%) than the group randomized to RV pacing, (45.8% versus 55.6%) [25]. This improvement in event-free survival in the BiVP arm was primarily driven by an increase in LVESV in the RV pacing arm. The median percentage of pacing in this study was upwards of 97% for all patients. The BIOPACE trial was a similar trial to BLOCK-HF performed in Europe and was three times the size of BLOCK-HF and did not show any significant benefit with BiVP vs. RV pacing [26]. This study is yet to be published in print form. Also, in contrast to DAVID where dual chamber pacing at 70 bpm increased incidence of CHF versus backup pacing at 40 bpm, DAVID 2 demonstrated that pacing from the atrium at 70 bpm with subsequent conduction down the native conduction system did not result in an increased CHF incidence compared to backup pacing at 40 bpm [21, 27].

In 2015, Sharma et al. described the results of (RVP) versus HBP in a large cohort of patients (192 patients) who required permanent pacemaker implantation for prevention or treatment of bradycardia [28•]. In patients who required pacing greater than 40% of the time hospitalization for CHF was considerably less in the HBP versus the RV pacing group (2% vs 15%). There were no differences in mortality (13% in the HBP group vs 18% in the RVP group). In 2017, long-term follow-up of this cohort revealed more striking differences, both clinically as well as echocardiographically, between these two study groups [29]. In the HBP group, the average LVEF was 55% at baseline and 57% at follow-up, whereas the LVEF in the RVP group was 57% at baseline and 52% at follow-up. There was a significantly higher incidence of PICM (22% vs 2%) and composite of death and CHF hospitalizations (53% vs 32%) in the RVP group compared to the HBP group.

Recently, Abdelrahman et al. published one of the largest series of HBP patients (322) followed in a registry [30•]. HBP was successfully accomplished in 92% of the attempted



**Fig. 2** A 44-year-old female has a long-standing history of non-ischemic cardiomyopathy and 4 years ago, developed worsening HF symptoms and LBBB (Fig 2a). She was treated on guideline-directed medical therapy including beta blockers, ACE inhibitors, and aldosterone antagonists. She presented 4 years later for consideration for CRT-D therapy. Her LVEF was 25% at that time with NYHA class II–III

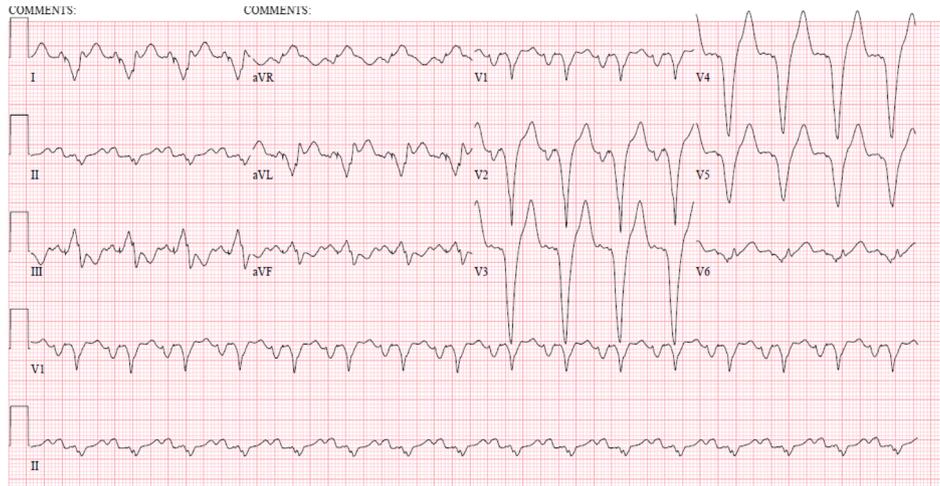
patients in the Geisinger registry. When compared to RVP, HBP significantly lowered the composite endpoint of death, CHF hospitalizations, or upgrade to BiVP (25% vs 32%, HR 0.71,  $P=0.02$ ). When stratified based on ventricular pacing > 20%, this difference was even larger (25% vs 36%, HR 0.65,  $P=0.02$ ). Also, the incidence of CHF was significantly reduced in the HBP group compared to the RVP group (12.4% vs 17.6%, HR 0.63). There was a trend toward reduced

symptoms. She underwent His bundle pacing with complete recruitment of her LBBB (Fig 2b). Three months later, her HF symptoms improved significantly (NYHA class I) and her LVEF improved to 54%. This case highlights that optimal medical therapy is not sufficient in some cases and correction of LBBB results in improvement of cardiomyopathy

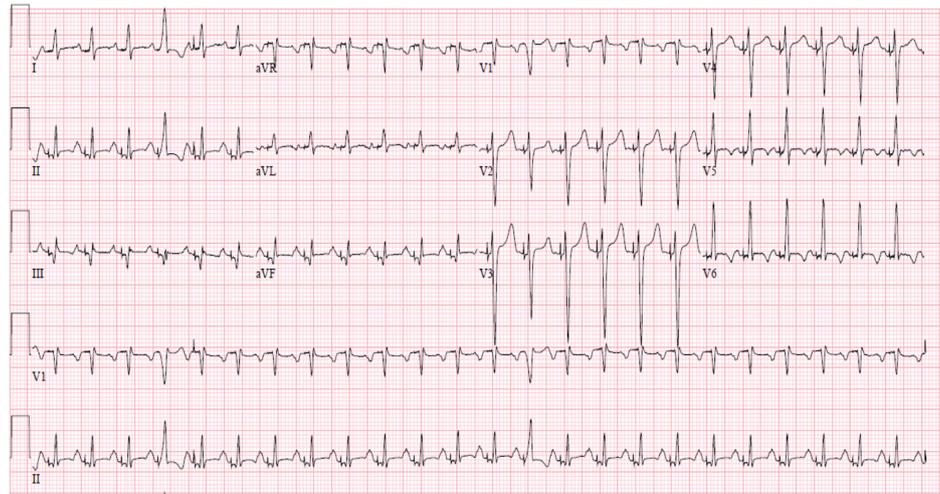
mortality favoring HBP that did not reach statistical significance (17.2% vs 21.4%).

There is some evidence in the literature to support the use of HBP as a pacing strategy in patients with chronic atrial fibrillation who undergo AV node ablation. In the initial permanent HBP study by Deshmukh et al., HBP was implemented in 12 out of 18 patients with chronic atrial fibrillation [10]. Ten of these patients underwent AV node ablation prior to the

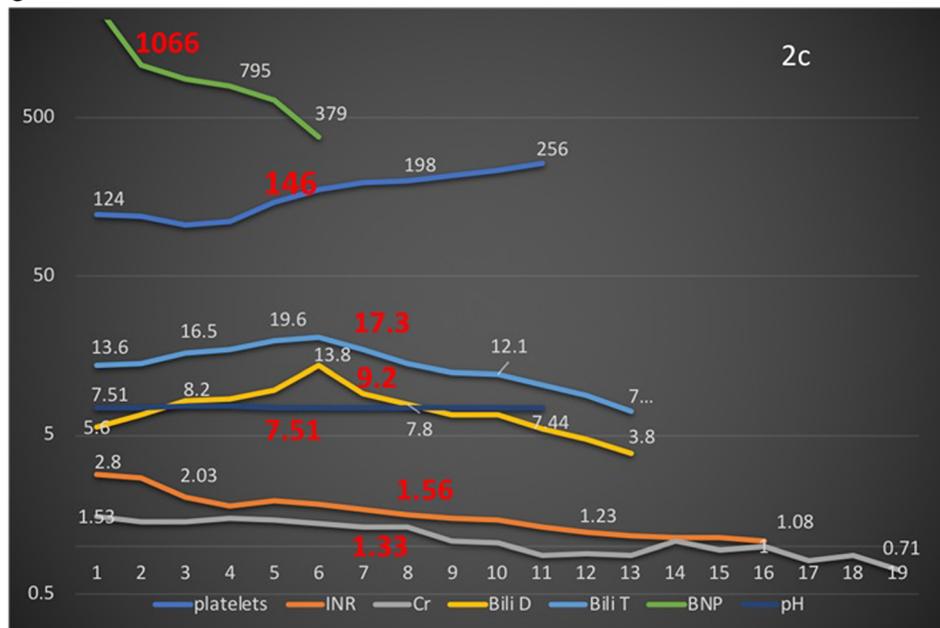
**a**



**b**



**c**



◀ **Fig. 3** A 17-year-old male with congenital heart block underwent implantation of a dual chamber pacemaker for symptoms. Two years later, he was admitted with multisystem organ failure and severe biventricular heart failure with LVEF of 14%, and for emergent consideration for left ventricular assist device. Pacing-induced cardiomyopathy was considered as a potential cause due to significant ventricular dyssynchrony (QRS > 200 ms, Fig. 3a). His device was upgraded to His bundle pacing (HBP) with complete recruitment of his native His Purkinje system (QRS 110 ms, Fig. 3b). Over the next few days, he showed dramatic improvement in his symptoms and his metabolic profile (Fig. 3c; red numbers denote the day HBP was initiated). He was successfully weaned off inotropes and discharged home a few days later on oral medications and his LVEF subsequently normalized

implantation of HBP due to rapid ventricular response. In the 12 patients that underwent successful permanent HBP, average LVEDD was reduced from 59 to 52 mm and LVEF improved from 20 to 31% at a mean follow-up of 24 months. In a larger cohort of 52 patients with chronic atrial fibrillation undergoing AV node ablation, Huang et al. were able to successfully perform HBP in nearly 42 of these patients (81%) [31]. In these 42 patients, average QRS duration was essentially unchanged at baseline and follow-up (107 ms vs 105 ms). After 12 months, average LVEDD decreased from 55.8 mm at baseline to 50.6 mm at follow-up, and LVEF also improved from an average of 44.9% at baseline to 59.7% at follow-up. These differences were even more significant in the patients with reduced LVEF at baseline, who had an improvement of LVEDD from 60.6 to 52.3 mm, and improvement in LVEF of 32.2 to 55.7% at 1 year. Vijayaraman et al. also reported improvement in LVEF ( $43 \pm 13$  to  $50 \pm 11\%$ ,  $P = 0.01$ ) and NYHA class ( $2.5 \pm 0.5$  to  $1.9 \pm 0.5$ ,  $P = 0.04$ ) in a series of patients who underwent AV nodal ablation followed by HBP [32].

### Possible Indications in the Pipeline

There are a number of specific indications for HBP in the treatment of heart failure under investigation with promising but, as of yet, limited evidence: CHF patients with RBBB and CHF patients with prolonged PR interval with normal QRS duration. Current guidelines suggest patients with RBBB and QRS duration  $\geq 150$  ms, and even those with QRS duration of 120 to 150 ms, may benefit from BiVP for CRT although evidence in this regard is limited. Recently, Sharma et al. described the role of CRT with HBP in these patients [33]. In this study, there was significant narrowing of QRS from  $158 \pm 24$  to  $127 \pm 17$  ms ( $P = 0.0001$ ), increase in LV ejection fraction from  $31 \pm 10$  to  $39 \pm 13\%$  ( $P = 0.004$ ), and improvement in New York Heart Association functional class from  $2.8 \pm 0.6$  to  $2 \pm 0.7$  ( $P = 0.0001$ ) with HBP.

Another specific population under investigation is CHF patients with a prolonged PR interval and normal QRS

duration. A prolonged PR interval is associated with higher heart failure hospitalizations and mortality in CHF patients [34]. In the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, patients with a prolonged PR interval benefited more than those with normal PR intervals, with relative reduction of 17% in heart failure admissions and death [35]. In patients with normal QRS duration, CRT can be detrimental. CRT with BiVP creates dyssynchrony in these patients although it shortens PR interval. HBP appears to be a sound strategy in these patients. Sohaib et al. demonstrated that acute hemodynamic function is improved with AV optimized HBP in patients with heart failure and PR prolongation with either a normal QRS or RBBB [36]. A randomized trial (His Optimised Pacing Evaluated for Heart Failure trial, HOPE-HF) is specifically looking into the role of HBP in PR interval prolongation and CHF (Table 2).

### Can HBP Replace CRT in the Long Run?

While HBP is emerging as a promising new alternative to BiVP for CRT, the body of evidence in support for HBP is limited when compared to CRT. From a procedural standpoint, one of the potential limitations of HBP is the initial success rates. When Deshmukh et al. attempted permanent HBP in 2000, they were only successful in 12/18 patients [10]. Since then, the success rates of permanent HBP implantation reported in the literature have risen from 56% in 2013 [12], to 76–80% in 2015 [28, 37], to roughly 90% in 2017 [13, 15]. The most likely explanation for this dramatic increase of success rate in recent years is operator experience, coupled with relatively standardized deployment tools and methods [38, 39]. Assuming this current trajectory of success rates, it would not be unreasonable to predict that successful implantation rates of HBP will match those of BiVP in the future.

Another concern of HBP is high capture thresholds leading to lead revisions or more frequent generator changes. Vijayaraman et al. recently reported 5-year results and found that there were an increased number of lead revisions (6.7% vs 3%) and generator changes (9% vs 1%) compared to the group that underwent standard RV pacing [29]. Compared to BiVP, HBP capture thresholds are likely modestly high as shown in a small cohort of patients who simultaneously received a His bundle lead as well as a coronary sinus lead [40]. Su et al. demonstrated that a His bundle tip to RV coil configuration resulted in the highest R wave amplitude and lowest capture threshold in a device with defibrillation capabilities [41]. Vijayaraman et al. showed that current of injury at the implantation site of a HIS bundle lead strongly predicts lower capture thresholds over time [42].

**Table 2** On-going clinical trials of HBP in CHF patients

Study	Trial design and inclusion criteria	No. of patients in the study	Study groups	Follow-up duration	Primary outcome
HIS-SYNC NCT02700425	Randomized, single-blinded study All patients with CRT indication	40	BiVP vs HBP	12 months	Change in LVEF, QRS duration, time to first CV hospitalization or death
NCT02805465	Prospective, randomized crossover study HFrEF patients with AF who need AV node ablation	50	BiVP and HBP group for 9 months and then crossover for another 9 months	18 months	Change in LVEF from baseline
HOPE-HF NCT02671903	Prospective randomized double-blinded crossover study HFrEF patients with PR $\geq$ 200 and narrow QRS or RBBB	160	2-month run in period after implantation. Active pacing vs back-up pacing for 6 months and then crossover	12 months	Changes in exercise capacity
HIS Alternative NCT03614169	Randomized, parallel assignment, double-blinded study HFrEF with true LBBB	50	BiVP vs HBP	6 months	Success rate of implanting HBP lead with narrowing of the QRS duration and maintaining this effect during the course of the study
NCT03452462	Prospective, randomized single-blinded, crossover study All patients with CRT indications	20	BiVP vs HBP	5 min	Acute changes in LV activation time

As described earlier, there is limited data to date comparing CRT with LV leads and HBP. Most studies have been either retrospective, prospective without head to head comparison or registries where an LV lead could not be placed. At this time, there is only one small randomized crossover study by Lustgarten et al. where 12 patients were able to achieve permanent and simultaneous His bundle and coronary sinus lead implantation [40]. This study demonstrated that there were no differences in LVEF, NYHA functional class, quality of life, or any other echocardiographic parameters at the end of each 6-month period of HBP or BiVP when compared to each other in a crossover fashion.

Based on the current body of evidence, HBP should not supplant BiVP as a first-line strategy for CRT except for the following clinical scenarios: (1) those failing coronary sinus lead placement or BiVP non-responders where HBP may be considered prior to epicardial LV lead placement, (2) pacing-induced cardiomyopathy where HBP can result in electrical resynchronization, (3) anticipated pacing burden  $> 20$ – $40\%$ , and (4) planned AV nodal ablation and ventricular pacing. Although there is growing evidence to attempt HBP in patients with LBBB and CHF who qualify for CRT, there is no long-term data regarding safety and efficacy in this population. BiVP has clearly demonstrated morbidity and

mortality benefit in patients with cardiomyopathy, CHF, and wide LBBB in multiple trials and should continue to be the first-line therapy for cardiac resynchronization in the near future. Randomized studies are underway to assess the role of HBP in CRT eligible patients and these studies will help us better understand the role of HBP in the future (Table 2).

## Conclusion

HBP has started to emerge as a sustainable option for permanent ventricular pacing in daily clinical practice. It offers true physiological pacing without the detrimental effects of cardiac dyssynchrony. It is very elegant in its nature and current data in CHF patients has been very promising. With results from larger randomized trials and continued development of the requisite tools, it is likely to gain an increased role in clinical practice.

## Compliance with Ethical Standards

**Conflict of Interest** Philip L Mar and Subodh R Devabhaktuni each declare no potential conflicts of interest. Gopi Dandamudi is a consultant

and on the advisory board for Medtronic, Inc. and on the advisory board for Biotronik, Inc.

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- Of importance
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