

## Review

### His Bundle Pacing – Stand-alone or adjunctive physiological pacing: a systematic review

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#### Abstract

His-bundle pacing (HBP) appears to be a viable stand-alone or adjunctive physiological pacing therapy in pacemaker dependent patients. It could also serve as an effective adjunct or alternative pacing therapy for heart failure patients who require cardiac resynchronization therapy or pacemaker upgrade. His-bundle pacing has demonstrated improvement of His-Purkinje conduction, left ventricular electrical / mechanical synchronization, and left ventricular ejection fraction (LVEF) compared with right ventricle pacing. Patients who have high pacing dependence and/or LVEF impairment would benefit most from HBP in terms of heart failure hospitalization and LVEF improvement. Mortality benefit has not been consistently demonstrated in latest meta-analysis. The long-term clinical benefit and safety profile of HBP remains to be explored in future studies.

**Key words:** His bundle pacing, physiologic pacing, upgrade pacing

(Heart Vessels Transplant 2021; 5: doi: 10.24969/hvt.2020.248)

#### Introduction

##### *His Bundle Pacing / Physiologic pacing*

In conventional right ventricular pacing (RVP), the pacing lead is generally positioned at the right ventricular apex or right ventricular septum (1). However, right ventricular apical (RVA) or right ventricular septal pacing is associated with non-physiological electrical activation and electro-mechanical dyssynchrony. Right ventricular pacing >20-40% is associated with increased risk of heart failure (HF) hospitalization, pacing-induced cardiomyopathy (PICM), atrial fibrillation (AF) and mortality (2-6). Various physiological pacing techniques including cardiac resynchronization therapy (CRT) and His-bundle

pacing (HBP) have been developed to minimize the adverse cardiovascular effect of RVP. In CRT, apart from the conventional right ventricular lead, an additional left ventricular lead is positioned in the coronary sinus to pace the left ventricle simultaneously, in order to achieve biventricular electro-mechanical synchronization in heart failure patients with electro-mechanical dyssynchrony. However, among CRT recipients, the clinical non-responder rate remains as high as 30% (7). Besides, CRT has not demonstrated consistent cardiovascular benefit in patients with narrow QRS, right bundle branch block (8), or preserved left ventricular ejection fraction (LVEF) (9, 10).

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**Received:** 04.01.2021 **Revised:** 28.02.2021 **Accepted:** 02.03.2021

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His bundle pacing is a physiological pacing technique aiming to preserve the electrical conduction of His-Purkinje system and ventricular mechanical synchrony by selectively or non-selectively pacing the His bundle area. It was first reported by Deshmukh et al (11) in 2000. Among patients with chronic AF and dilated cardiomyopathy with narrow QRS complexes, HBP was associated with left ventricular reverse remodelling and improvement of LVEF from  $20\pm 9\%$  to  $31\pm 11\%$  ( $p=0.01$ ) (11). Over the past few years, HBP has evolved into both a stand-alone physiological pacing therapy or as an adjunct to CRT.

The objective of the review is to evaluate the implant success rate, long-term safety and clinical benefit of HBP in HF patients requiring CRT and non-heart failure patient with pacing indications.

## Methods

### **Search strategy (Fig. 1)**

A comprehensive literature search was conducted in PubMed (including Medline) online database.

Literature search was performed using the key word "His bundle pacing" in PubMed (including Medline). Journal articles published between 1st January 2000 to 8th March 2021 were included.

Exclusion criteria include review articles, systematic reviews, case reports, non-human studies, abstracts, studies involving patients under the age of 18 and other studies not fulfilling the inclusion criteria. Inclusion criteria include clinical trials, observational studies, multicenter studies, randomized control trials and meta-analysis. Articles involving left bundle branch pacing, electrophysiology study, and observational HBP studies in non-heart failure population with sample size less than 100 patients were further excluded.

## Results

A total of 967 articles were screened (Fig. 1). Nine hundred and one articles were excluded. A total of 72 studies fulfilled the inclusion criteria. Thirty-five studies were further excluded based. Finally, 37 studies were included in the systematic review.

### ***HBP as an adjunct therapy to CRT in heart failure patients***

We reviewed 4 studies (72 patients) (Table 1) which explored the effect of HBP as an adjunct to CRT in heart failure patients. In patients with HF and bundle branch block (BBB), HBP with or without left ventricular pacing (LVP) has been shown to improve invasive blood pressure (12). His-optimized CRT (HOT-CRT) improved LVEF and hemodynamic parameters measured by pressure-conductance volume catheter (13). Among CRT eligible candidates, both HBP and CRT resulted in QRS narrowing, improvement of quality of life (QoL), New York Heart Association (NYHA) functional class, 6-minute walk test (6MWT) and LVEF (1). Lustgarten et al (14) demonstrated that in 10 patients with CRT indications, HBP resulted in more significant QRS narrowing compared with biventricular pacing, with satisfactory pacing threshold. However, they did not report long-term clinical outcome data. Boczar et al. (15) showed that in 14 CRT eligible patients with permanent AF, heart failure, BBB, widened QRS  $>130\text{ms}$  and impaired LVEF, HBP as an adjunct to CRT resulted in improvement of LVEF, NYHA functional class and reduction of left ventricular end-diastolic dimension at 14.4 months follow-up.

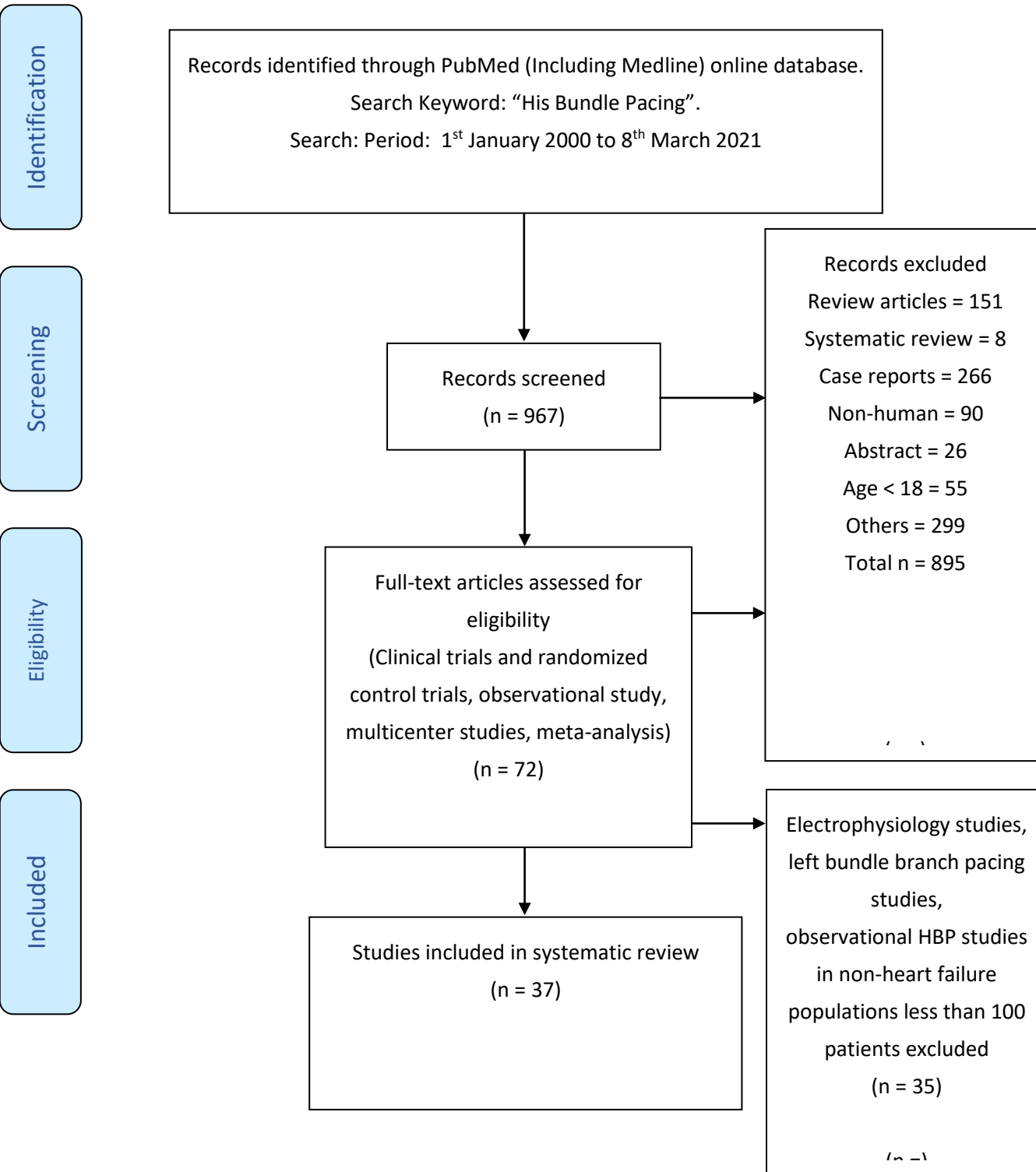


Figure1. Evidence search strategy

Table 1. Studies of HBP as an adjunct to CRT in heart failure patients										
Study	Year	Pts n=72	Age, yrs	Patient selection	Study design	FU, mo	Success Rate, n(%)	Pacing threshold	QRS width, ms	Long-term outcome
Lustgarten (14)	2010	10	NR	All pts with CRT indications (HBP + CRT)	Prospective cohort	NR	10/10 (100)	HBP 3.1 ± 1.1 V at 0.5ms BiVP 1.3 ± 0.9 V at 0.5ms	Intrinsic: 171 ± 13 HBP: 148 ± 11 BiVP: 158 ± 21 p < 0.0001	NR
Boczar (15)	2019	14	67.35 ± 10	CRT eligible patients with permanent AF, CHF, BBB, QRS > 130ms, impaired LVEF	Prospective cohort Multicenter	14.4	14/14 (100)	NR	Intrinsic: 159 ± 29 HBP/BiVP: 128	1 of 13 patients died of CHF. LVEF, NYHA improved, LVEDD decreased
Vijayaraman (HOT-CRT) (16)	2019	27	72 ± 15	LBBB, IVCD, RVP with CRT indication	Prospective cohort Multicenter	14 ± 10	25/27 (93)	At implant: HBP 1.7 ± 0.9 V at 1.0 ms LVP 1.5 ± 0.5 V at 0.6 ms at implant  At FU HBP 1.8 ± 1.1 V at 1 ms LVP 1.6 ± 0.8 V at 0.6 ms	Intrinsic 183 ± 27 BiVP 162 ± 17 p = 0.003  HBP 151 ± 24 p < 0.0001	Improved LVEF, NYHA & CRT clinical response rate
Deshmukh (17)	2020	21	70.7 ± 9.9	CRT candidates (sequential HBP & LV pacing when HBP did not correct QRS)	Prospective cohort	32	21/21 (100)	At implant: HBP 1.7 ± 0.7 V at 0.8 ± 0.4 ms At FU: 3.0 ± 2.3 V at 0.8 ± 0.4 ms	Intrinsic 157 ± 16 HBP+LV 110 ± 14 p < 0.0005	Improved LVEF and NYHA functional class

AF - atrial fibrillation, BBB - bundle branch block, BiVP - biventricular pacing, CHF - congestive heart failure, CRT - cardiac resynchronization therapy, FU – follow-up, HBP - His bundle pacing, IVCD - interventricular conduction delay, LBBB - left bundle branch block, LVEF - left ventricular ejection fraction, LV P- left ventricular pacing, mo – months, NR - not reported, NYHA - New York Heart Association, Pts – patients, RVP - right ventricular pacing, yrs-years

Vijayaraman et al (16) performed HOT-CRT in 27 CRT candidates with a high success rate of 93%. His-optimized CRT resulted in significant QRS narrowing ( $120\pm 16$  ms) compared with baseline ( $183\pm 27$ ms) and CRT alone ( $162\pm 17$  ms), ( $p<0.0001$ ). The LVEF improved from  $24\pm 7\%$  to  $38\pm 10\%$  ( $P<0.0001$ ) at  $14\pm 10$  months follow-up. The clinical response rate (84%) and echocardiographic response rate (92%) were higher compared with conventional CRT. Deshmukh et al. (17) studied 21 CRT eligible patients who received HBP as an adjunct to biventricular pacing. His bundle pacing plus LVP resulted in significant QRS narrowing, improvement in LVEF and NYHA at 32 months follow-up.

***HBP as an alternative therapy to CRT in patients with CRT indications (De novo HBP implant or HBP upgrade)(Table 2)***

We reviewed 13 studies (1, 11, 18-28) (651 patients) (Table 2) which explored the effect of HBP as an alternative to CRT in patients with CRT indications.

The largest study was reported by Sharma et al (28). They studied 106 patients with CRT indications. His-bundle pacing was successful in 95 patients. Thirty patients had failed previous CRT attempt while 65 adopted de novo HBP as an alternative to CRT. Patients were followed-up for 14 months. His bundle pacing resulted in significant narrowing of QRS from  $157 \pm 33$  ms to  $117 \pm 18$  ms ( $p=0.0001$ ). The LVEF increased from  $30\pm 10\%$  to  $43\pm 13\%$  ( $p=0.0001$ ). The NYHA functional class improved from  $2.8\pm 0.5$  to  $1.8\pm 0.6$  ( $p=0.0001$ ). Lead-related complications occurred in 7% of patients. Huang et al. (23) performed HBP in 74 potential CRT candidates with HF and left bundle branch block (LBBB). The acute LBBB correction rate was 97.3%. Permanent HBP was successful in 75.7% of patients. Rest of the patients received CRT due to failed LBBB correction, high LBBB correction threshold or failed HBP lead

fixation. Among the 56 patients who had successful permanent HBP, 54% completed 3 years follow-up. His-bundle pacing improved LVEF (from  $32.4\pm 8.9\%$  to  $55.9\pm 10.7\%$ ,  $p<0.001$ ), left ventricular end-systolic volume (from  $137.9\pm 64.1$  mL to  $52.4\pm 32.6$  mL,  $p<0.001$ ) and NYHA functional class (from  $2.73\pm 0.58$  to  $1.03\pm 0.18$ ,  $p<0.001$ ). The LBBB acute correction threshold was  $2.13\pm 1.19$  V @0.5 ms and remained stable at  $2.29\pm 0.92$  V@0.5 ms at 3 years follow-up ( $p>0.05$ ). Vijayaraman et al. (25) conducted a multicenter cohort study involving 85 CRT eligible patients with atrioventricular block (AVB), chronic RVP and/or PICM. At  $25\pm 24$  months following, HBP resulted in improvement of LVEF and narrowing of QRS ( $123\pm 32$  ms at baseline vs  $177\pm 17$ ms with RVP vs  $115\pm 20$ ms with HBP,  $p<0.001$ ). Pacing threshold was  $1.47 \pm 0.9$  V @1 ms at implant and  $1.9 \pm 1.3$  V @ 1 ms at  $25\pm 24$  months follow-up. Among the 60 patients with PICM, LVEF improved from  $34.3\pm 9.6\%$  to  $48.2\pm 9.8\%$  ( $p<0.001$ ) after HBP. Su et al. (26) studied 94 AF patients with HF and narrow QRS who received atrioventricular node (AVN) ablation and HBP. Acute HBP success was 94.7%. The LVEF improved from  $44.9 \pm 14.9\%$  to  $57.6 \pm 12.5\%$  at median follow-up of 3 years ( $p<0.001$ ). The HBP capture threshold was  $1.0\pm 0.7$ V at 0.5ms at implant and remained stable at follow-up. Heart failure hospitalization or all-cause mortality occurred in 35.9% of patients.

There were 2 randomized control trials (RCT) studying the effect of HBP as an alternative to CRT. The first single-blinded RCT was conducted by Lustgarten et al. (1). They studied 29 CRT eligible candidates (97% had LBBB). Patients were randomized to either HBP or biventricular pacing (BiVP). Patients were crossed over to the other pacing modality after 6 months. The HBP implant success rate was 96.6%.

**Table 2. Studies of HBP as an alternative therapy to CRT in patients with CRT indications (De novo HBP implant or HBP upgrade)**

Study	Year	Pts n= 651	Age, yrs	Patient selection	Study design	FU, mo	Success Rate, n (%)	Pacing threshold	QRS duration, ms	Long-term outcome
Deshmukh (11)	2000	18	69±10	Chronic AF, dilated CMP, QRS<=120 ms ± AVN ablation  De novo HBP	Observational	23.4 ±8.3	12/14 (86)	2.4±1.0 V at 0.5 ms	Intrinsic 95±13  HBP 92.8±11  P = NS	Reduced: LVEDD, LVESD Improved LVEF 20±9% to 31±11%, p<0.01 1 lead dislodgement; 1 high pacing threshold
Deshmukh (18)	2004	54	70±8	CMP LVEF 23±11%, persistent AF, QRS <120ms De novo HBP	Observational	42	39/54 (72) (12 pts - RV apical lead)	NR	None had QRS widening	LVEF improved from 23 ± 11% to 33 ± 15% dP/dt, NYHA, exercise time, oxygen uptake all improved
Barba-Pichardo (19)	2012	16	67.56 ± 5.81	CHF population CRT indication (failed LV lead implantation) CRT Alternative	Prospective cohort	31.33±21	9/16 (56.3)	3.09±0.44V at implant;  3.7±0.54V at follow-up	Intrinsic 166±9  HBP 97±9 P = 0.01	HBP corrected conduction disturbance in 81%. Improved NYHA, LV dimension, LVEF
Lustgarten (1)	2015	29	NR	CRT candidate QRS >130ms 97% had LBBB  CRT alternative	RCT  Single blinded HBP vs BiVP	12	28/29 (96.6)	At implant: HBP <1.5V RVP <1V LVP <1.5V At FU: HBP <2.5V, RVP <1V, LVP <2V	Intrinsic 169±16 NS HBP 160±25  Selective HBP 131±35	Improved NYHA class, LVEF with both BiVP and HBP No significant difference between BiVP and HBP
Ajjola (20)	2017	21	62±18	All patients with CRT indication (BBB, HF)  CRT alternative	Observational	12	12/16 (75)	1.9±1.2 at 0.6±0.2ms	Intrinsic 180±23  HBP 129±13  p<0.0001	Improved NYHA class and LVEF from 27±10% to 41±13% (p<0.001) Decreased LV dimension; No lead dislodgment
Shan (21)	2017	18	70.6 ± 12.9	PICM LVEF<50% requiring CRT upgrade  (5/16 were CRT non-responders)  CRT alternative	Observational	36.2	16/18 (88.9)	At implant: PICM group 0.8±0.4V BiVP non-responder group 1.1±0.6V At FU: PICM group 1.2±0.8V BiVP non-responder group 1.7±0.8V	QRS baseline 156.9±21.7ms to 107.1±16.5 ms; P <0.01)	HBP associated with decreased LVEDD, improved LVEF, improved MR, decreased BNP, improved NYHA class

Table 2. Continued from page 55

Study	Year	Pts n= 651	Age, yrs	Patient selection	Study design	FU, mo	Success Rate, n (%)	Pacing threshold	QRS duration, ms	Long-term outcome
Sharma (28)	2018	106	71± 12	All patients with CRT indication (Failed CRT or new implant) CRT alternative	Multicent er cohort	14	95/106 (90)	1.4±0.9 at 1ms (HBP) 2±1.2 at 1ms (narrowing of BBB)	Intrinsic 157±33  HBP 117±18	Improved NYHA class and LVEF in both groups. <sup>7</sup> Lead related complications
Sharma (22)	2018	39	72+ /10	Impaired LVEF, RBBB, QRS≥120ms , NYHA II-IV CRT alternative	Retrospec tive observatio nal multicent er cohort	15± 23	37/39 (95)	At implant HBP 1.1±0.6V at 1ms At FU 1.3±0.9V at 1ms	Intrinsic 158±24  HBP 127±17	Improved NYHA class, LVEF, narrowing of RBBB in 78%
Huang (23)	2019	74	69.6 ±9	CHF and LBBB  CRT alternative	Single center cohort	37.1	72/74 (97.3)	At implant: LBBB correction threshold: 2.13±1.19 V at 0.5 ms At FU: 2.29±0.92 V at 0.5 ms p>0.05	Intrinsic 170.9±18 ms vs 113.8±24 ms after HBP (p<0.001)	Improved NYHA, decreased LVESV, and improved LVEF.
Upadhyay (24)  (His-Sync)	2019	41	64± 13	CHF, wide QRS, CRT candidate  CRT alternative	RCT  Single- blinded  His-CRT vs BiVP-CRT	6.2	40/40	His-CRT: 1.7 V  BiVP-CRT 0.9 V  p=0.046;  Threshold stable at 12- months follow-up	Intrinsic 172±16  His-CRT 144±30  p=0.002  but no QRS shortenin g in BiVP- CRT	Improved LVEF with both His- CRT and BiVP- CRT. His-CRT was not superior to BiVP-CRT with regard to LVEF improvement or rate of echo response. No lead dislodgement. No difference in CV hospitalization or death
Vijayaraman (25)	2019	85	72.4 ±13. 2	AVB and chronic RVP and/or PICM in need for CRT  CRT alternative	Multi- center cohort	25± 24	79/85 (93)	At implant: 1.47±0.9V at 1ms At FU: 1.9±1.3V at 1ms	Intrinsic 123±31 RVP 177±17 HBP 115±20 p<0.001	Improved LVEF

**Table 2. Continued from page 55**

Study	Year	Pts n= 651	Age, yrs	Patient selection	Study design	FU, mo	Success Rate, n (%)	Pacing threshold	QRS duration, ms	Long-term outcome
Su (26)	2020	94	70.1 ± 10.5	AF with CHF and narrow QRS requiring AVN ablation  CRT alternative	Observational cohort	36	89/94 (94.7)	At implant 1±0.7V at 0.5ms Stable threshold during FU	NR	Improved LVEF Heart failure hospitalization or all-cause mortality occurred in 21 (25.9%)
Singh (27)	2020	7	59	CRT eligible candidates LBBB mediate CMP  CRT alternative	Multicenter observational cohort	14.5	7/7 (100)	At implant 1.99V at 1ms  At follow-up 2V at 1ms	Intrinsic 152  HBP 115	LVEF improvement from 25% to 50% p=0.0001; LVESD & LVEDD decreased, improved NYHA class

AF - atrial fibrillation, AVB - atrioventricular block, AVN - atrioventricular node, BBB - bundle branch block, BIVP - biventricular pacing, CMP - cardiomyopathy, CRT - cardiac resynchronization therapy, FU – follow-up, HBP - His bundle pacing, IVCD - interventricular conduction delay, LBBB - left bundle branch block, LVEDD - left ventricular end-diastolic diameter, LVEF - left ventricular ejection fraction, LVESD - left ventricular end-systolic diameter, LV P- left ventricular pacing, mo-months, NYHA - New York Heart Association, NS - non-selective, NR - not reported, PICM - pacing induced cardiomyopathy, pts – patients, RVP - right ventricular pacing, yrs- years

Electrical resynchronization with QRS narrowing was achieved in 72% of patients at implant.

Quality of life, NYHA class, 6MWT and LVEF were significantly improved in both pacing modes compared with baseline. The other single-blinded RCT, the His-Sync study, was conducted by Upadhyay et al (29). They studied 41 CRT eligible candidates. Patients were randomized to His-CRT and biventricular pacing CRT (BiV-CRT). Cross over occurred in 48% of His-CRT arm and 26% in the BiV-CRT arm. At median follow-up of 6.2 months, His-CRT resulted in significant QRS narrowing (172±16 ms to 144±30 ms, p=0.002), while BiV-CRT did not. Both His-CRT and BiV-CRT resulted in similar improvement in LVEF (median +9.1% (5-14.4%) vs +5.2% (1.5-11.3%), p=0.33). The His-CRT group had higher pacing threshold than BiV-CRT group (median 1.7V versus 0.9V, p=0.046). Overall, cardiac event rates were

low (6 cardiovascular hospitalizations and 2 deaths). There was no lead dislodgement reported. The study was underpowered to detect clinical outcome difference. Other studies (19-22, 27) recruited CRT eligible patients with heterogeneous backgrounds including heart failure with BBB, PICM and AF post AVN ablation, with narrow or wide QRS complexes. The longest follow-up periods were up to approximately 3 years (19, 21, 23).

Most studies have demonstrated that HBP results in electrical resynchronization (QRS narrowing or normalization of BBB), improvement of NYHA class, LVEF, and left ventricular reverse remodelling in CRT eligible candidates. However, these studies had small sample-sizes and were underpowered to detect statistically significant difference in clinical outcome in terms of mortality and heart failure hospitalization.



### ***HBP as a stand-alone therapy in non-heart failure patients with pacing indications***

To study the effect of HBP as a stand-alone therapy in non-HF patients with pacing indications, we reviewed 11 observational cohort studies (Table 3) (30-40) (with sample size >100 patients) involving 3195 patients (conducted over the past 10 years) and 3 RCTs (Table 4)(41-43) involving 122 patients.

#### ***Observational cohorts on HBP (Table 3)***

The largest multicenter observational cohort was conducted by Zanon et al. (36). Eight hundred and forty-four patients (AVB in 41.2%, sinus node dysfunction in 17.4%, AF with bradycardia in 39.7% and CRT in 1.7%) received HBP. The mean HBP pacing threshold was 1.6V at implant and 2V at follow-up. In the first 368 patients, HBP was achieved using deflectable curve delivery sheaths. In the subsequent 476 patients, HBP was achieved using fixed-curve delivery system ( $p<0.001$ ). The fixed-curve delivery system was associated with lower pacing threshold ( $1.7\pm 1.1$  V vs  $2.4\pm 1.0$  V,  $p<0.001$ ) and lower complication rate (4.2% vs 11.9%,  $p<0.001$ ). The paced QRS was  $123\pm 29$  ms vs  $112\pm 28$  ms at baseline. The 64 (7.6%) patients had interruption of HBP pacing at 3 years follow-up due to elevated capture thresholds, sensing issues, infection, lead dislodgement, lead fracture and upgrade to biventricular devices.

Keene et al. (35) conducted a multicenter observational cohort study involving 529 patients with persistent or intermittent high grade AVB. His bundle pacing was successful in 87% of patients. Pacing threshold was  $1.4\pm 0.9$ V at  $0.8\pm 0.3$ ms at implant and  $1.3\pm 1.2$ V at  $0.9\pm 0.2$ ms at follow-up. His bundle pacing preserved electrical synchrony (Intrinsic QRS  $116 \pm 31$  ms vs HBP paced QRS  $115 \pm 24$  ms ( $p=0.5$ )). Lead re-intervention or deactivation rate was 7.5% at  $7.2\pm 10$  months follow-up

(mostly related to lead dislodgement or rise in capture threshold). Five patients died within the follow-up period (3 died of progressive heart failure, 2 died of unknown cause). Zanon et al. (33) conducted a prospective cohort of 307 patients with pacemaker indications. Selective HBP and para-Hisian HBP were performed in 87 and 220 patients respectively. The capture thresholds for selective HBP and para-Hisian HBP were  $2.5\pm 2.3$ V and  $1.3\pm 1.1$ V at implant, and  $3.2\pm 2.9$ V and  $1.6\pm 1.5$ V at 24 months (at 0.5ms) respectively. His bundle pacing resulted in narrow paced QRS ( $108\pm 21$ ms vs intrinsic QRS  $104\pm 31$ ms). Lead complication rate was 3.9% at  $20\pm 10$  months follow-up. Beer et al. (30) performed HBP in 294 patients with pacing indications. Pacing threshold was  $1.6\pm 1$ V at implant. Six percent of patients required lead revision at follow-up. His bundle capture threshold remained stable in 85% of patients. Vijayaraman et al. (31) studied 100 patients with advanced AVB and preserved LVEF. His bundle pacing normalized His-Purkinje conduction in 76% of patients with infra-nodal block. However, these 5 large HBP observational cohorts did not include control groups to assess the comparative benefit of HBP over conventional RVP, in terms of HF hospitalization, LVEF improvement, left ventricular reverse remodelling and mortality.

#### ***Observational HBP studies reporting clinical outcome, in non-heart failure patients with pacing indications***

Abdelrahman et al. (34) performed HBP in 332 consecutive pacemaker recipients. Pacemakers were indicated for sinus node dysfunction and AVB in 35% and 65% of patients respectively. The implant success rate was 92%. The clinical outcome was compared with 443 RVP patients.

**Table 3. Studies of HBP as a stand-alone therapy in non-heart failure patients with pacing indications**

Study	Year	Pts n = 3195	Age, yrs	Patient selection	Study Design	FU, mo	Success Rate, n(%)	Acute / Chronic threshold	QRS duration	Long-term outcome
Zanon (33)	2011	307	72±12	Pacemaker indications	Prospective cohort	20±10	HBP 87/307 (28)  NS HBP 220/307 (72%)	At implant Selective HBP 2.5±2.3 V NS HBP 1.3±1.1 V At FU: Selective HBP 3.2±2.9V NS HBP 1.6±1.5V at 0.5ms	Intrinsic 104±31  HBP 108±21	Lead related complications  12/307 (3.9%)
Vijayaraman (31)	2015	100	75+ /12	46% AVN block; 54% infranodal block, or AVN ablation; narrow and wide QRS	Single center cohort	19±12	84/100 (84)	At implant  HBP 1.3±0.9V  At FU 1.7±1V at 0.5ms	Intrinsic 122±27  HBP 124±22	His Purkinje conduction normalized in 76% patients with infranodal block
Pastore (32)	2016	148	74+ 8.5	Complete / advanced AVB	Retrospective observational	58.5±26.5	148/148 (100)	NR	NR	HBP associated with lower risk of AF vs RVP HR = 0.28 p=0.0001
Abdelrahman (34)	2018	332	76±11	All pts requiring pacemaker implant	Multicenter prospective cohort Non-randomized HBP 332 vs RVP 433	24	304/332 (92)	At implant: HBP 1.3±0.85 RVP 0.59±0.42V  At FU: HBP 1.56±0.95V RVP 0.76±0.29V	Intrinsic 105-110  HBP 128±27  RVP 166±22	HBP reduced CHF hospitalization (primarily in pts with VP >20%), a trend towards reduced mortality
Bhatt (40)	2018	101	76 ± 9.8	All pts with pacing indication	Single center observational	24	76/101 (75)	At implant: 1.2 ±0.8 V at 1.0 ms At FU: 1.8 ± 1.5V at 0.6 ± 0.2ms	Intrinsic (with BBB) 156 +/- 48ms;  HBP 83+/- 2ms	Narrowing of QRS in pts with BBB. Rising threshold in 30% and lead intervention in 8%

**Table 3. Continued from page 58**

Study	Year	Pts n = 3195	Age, yrs	Patient selection	Study Design	FU, mo	Success Rate, n(%)	Acute / Chronic threshold	QRS duration	Long-term outcome
Keene (35)	2019	529	75 ± 11	Persistent or intermittent high grade AVB	Multi- center observati onal study (7 centers)	7.2± 10	332/410 (81)	At implant 1.4±0.9V at 0.8±0.3 ms  At FU 1.3±1.2V at 0.9±0.2ms	Intrinsic 116 ± 31 ms  HBP 115 ± 24 ms p=0.5	HBP lead re- intervention or deactivation rate of 7.5% (lead dislodgement or rise in threshold). Death (n=5); progressive heart failure, 2 unknowns)
Zanon (36)	2019	844	75± 9	AVB 41.2% SND 17.4% AF with bradycardi a 39.7%	Multicen ter cohort	36	844/844 (100)	2.4+/1V (with deflectable curve delivery system) 1.7±1.1V with fixed curve sheath p<0.001	Intrinsic 112 ± 28  HBP 123 ± 29ms	Complication rate 8.4%
Beer (30)	2020	294	75± 11	Bradycardi a / pacing indication	Single center cohort	39.5 ±16. 8	294/294 (100)	At implant 1.6±1V  At FU 1.6±0.8V	NR	Threshold increase 41% by 8 weeks, 66% by 1y; 6% require lead revision HBP capture threshold stable in 85% patients
Dawson (37)	2020	140	76	Pts with pacing indications	Multicen ter cohort	0.5- 2	122/140 (87)	At implant 0.8V@1ms	Intrinsic 110 HBP 110	NR
Ravi (38)	2020	105	72.6 5±1 1.04	Pts with pacemaker indications: HBP (105) vs RVP (120)	Observati onal cohort	23.4 ±10. 8	105/105 (100)	NR	NR	HBP lowered risk of new-onset AF in pts with >20% pacing dependence. HBP -lower risk of AF progression in pts with pacing burden ≥40%
Teigeler (39)	2021	295	69± 15	SSS 41% AVB 36% CRT 7% AF 15%	Single center prospecti ve observati onal cohort	23± 20	274/295 (93)	At implant 1.1±0.9V at 0.8± 0.2ms  At FU 1.7±1.1V at 0.8±0.3ms		Threshold ≥2.5V in 24%; ≥1V in 28%. Loss of HBP capture in 17%. Total 11% lead revision, primarily for high thresholds

AF - atrial fibrillation, AVB - atrioventricular block, AVN - atrioventricular node, CRT - cardiac resynchronization therapy, FU – follow-up, HBP - His bundle pacing, HR - hazard ratio, mo – months, NS - non-selective, NR - not reported, pts – patients, RVP - right ventricular pacing, SSS - sick sinus syndrome, yrs -years

His bundle pacing was associated with a decrease in combined endpoint of death from any cause, HF hospitalizations or upgrade to BiVP compared with RVP (25% vs 32%; hazard ratio (HR) 0.71, 95% CI 0.534-0.944;  $p=0.02$ ).

The primary outcome was predominantly driven by significant reduction in HF hospitalizations (12.4% vs. 17.6%; HR: 0.63; 95% CI: 0.430 to 0.931;  $p = 0.02$ ). There was a trend towards reduced mortality in the HBP group (17.2% vs. 21.4%, respectively;  $p=0.06$ ). Patients with >20% ventricular pacing burden benefited most from HBP. Pastore et al. (32) performed HBP in 148 patients with complete or advanced AVB. His bundle pacing was associated with lower risk of AF (16.9% vs right ventricular septal pacing - 25.7% vs right ventricular apical pacing - 28.0%,  $p=0.049$ ). Ravi et al. (38) compared the effect of HBP ( $n=105$ ) with RVP ( $N=120$ ) on the risk of new onset AF and AF progression. In patients with no history of AF, HBP was associated with lower risk of new onset AF (adjusted HR 0.53; 95% CI 0.28-0.99;  $p=0.046$ ) compared with RVP, especially in patients with RVP burden >20%. In patients with prior history of AF, there was no difference in the risk of AF progression between the 2 groups. In patients with pacing burden  $\geq 40\%$ , HBP showed a trend towards lower risk of AF progression versus RVP (HR 0.19; 95% CI 0.03-1.16;  $p=0.072$ ).

Sharma et al. (44) studied 94 pacemaker recipients without HF, HBP significantly reduced HF hospitalization (2% vs 15% in RVP patients,  $p=0.02$ ) in those requiring >40% ventricular pacing (in >60% of patients), during a mean follow-up period of  $25.5 \pm 8.6$  months. There was no difference in mortality between HBP and RVP patients.

#### ***Randomized control trials (RCT) on HBP in non-heart failure patients with pacing indications (Table 4)***

Occhetta et al. conducted two small RCTs on HBP. In the first study (41), 16 patients with chronic AF requiring AVN ablation were implanted with a RVA pacing lead and a para-Hisian pacing lead. Patients were randomized and received crossover to two 6-month periods of para-Hisian pacing and conventional RVA pacing. Para-Hisian pacing resulted in improvement of interventricular electromechanical delay, NYHA class, QoL score, 6MWT, mitral and tricuspid regurgitation. Another RCT by Occhetta et al. (42) randomized 17 patients with chronic AF requiring AVN ablation or sinus rhythm with AVB and narrow QRS to HBP and RVA pacing. At 21 months follow-up, HBP was associated with improved NYHA, exercise tolerance, QoL, interventricular mechanical delay, mitral and tricuspid regurgitation. Left ventricular ejection fraction was preserved versus baseline. Kronborg et al. (43) randomized 38 patients with high grade AVB, narrow QRS and preserved LVEF >40% to HBP and right ventricular septal pacing. At follow-up of 24 months, there was no difference in NYHA class, 6MWT, QoL and device-related complications. The mean threshold was higher in HBP. His bundle pacing was associated with better preserved LVEF than right ventricular septal pacing ( $55 \pm 10\%$  vs  $50 \pm 11\%$ ,  $p=0.005$ ).

#### ***Systematic review and meta-analysis of His Bundle Pacing Studies***

Six meta-analysis were reviewed. Zanon et al (45) performed the first systematic review and meta-analysis of 1438 patients who received permanent HBP over a period of nearly 20 years, in 16 centers around the world. The average implant success rate was 84.8%. The LVEF of HBP patients improved from 42.8% at baseline to 49.5% at 16.9 months' follow-up.

**Table 4. Randomized controlled trials (RCT) on HBP in non-heart failure patients with pacing indications**

Study	Year	Pts n = 222	Age, yrs	Patient selection	Study Design	FU, mo	Success Rate, n(%)	Pacing threshol d	QRS duration	Long-term outcome
Occhetta (41)	2006	16	71± 5	Chronic AF narrow QRS post AVN ablation	Cross over blinded RCT	12	16/16 (100)	0.92±0.7 V at 0.5 ms	Intrinsic 88.3±7 HBP 121 ± 10, p<0.05	Improved QoL, NYHA, 6MWT, interventricular EMD
Occhetta (42)	2007	68	79± 6	AVN ablation for chronic AF, narrow QRS; sinus rhythm with AVB and narrow QRS	RCT (first 17 patients) Cross-over HBP vs RV apical pacing	21	NR	At implant 0.7±0.5V  At FU 0.9±0.7V  p = 0.08	Intrinsic 91±13.5 HBP 123±14 RVP 164.5±18, p<0.05	Improved NYHA, exercise tolerance, QoL, MR, TR and ICVD; preserved LVEF vs baseline
Kronborg (43)	2014	38	67± 10	High grade AVB, narrow QRS LVEF >40%	Crossover double blinded RCT (His bundle vs RV septal pacing)	24	17/19 (89)	At implant 1V  At FU 1.5V	Intrinsic 93±16  HBP 111±19  RVP 153±12	No difference in NYHA class, 6MWT, QOL HBP was associated with better preserved LVEF and mechanical synchrony vs RV septal pacing

6MWT - six-minute walk test, AF - atrial fibrillation, AVB - atrioventricular block, AVN - atrioventricular node, EMD- electromechanical delay, FU – follow-up, HBP - His bundle pacing, ICVD - interventricular conduction delay, LVEF - left ventricular ejection fraction, mo – months, MR- mitral regurgitation, NYHA - New York Heart Association, pts - patients, QoL- quality of life, RV = right ventricular, TR - tricuspid regurgitation, yrs -years

Among the 907 patients in the 17 studies, which reported safety information, implant complication rate was 4.7%.

There were 26 lead revisions due to lead dislodgement (n = 6) and elevated threshold (n=20). Early device replacement due to battery depletion was uncommon (0.66%).

Qian et al. (46) systematically reviewed 11 HBP studies including 494 patients with HF. The mean follow-up duration was 23.7 months. In CRT candidates who received HBP, the paced QRS duration decreased from 165.4 ± 8.7 ms at baseline to 116.9 ± 15.8 ms after HBP

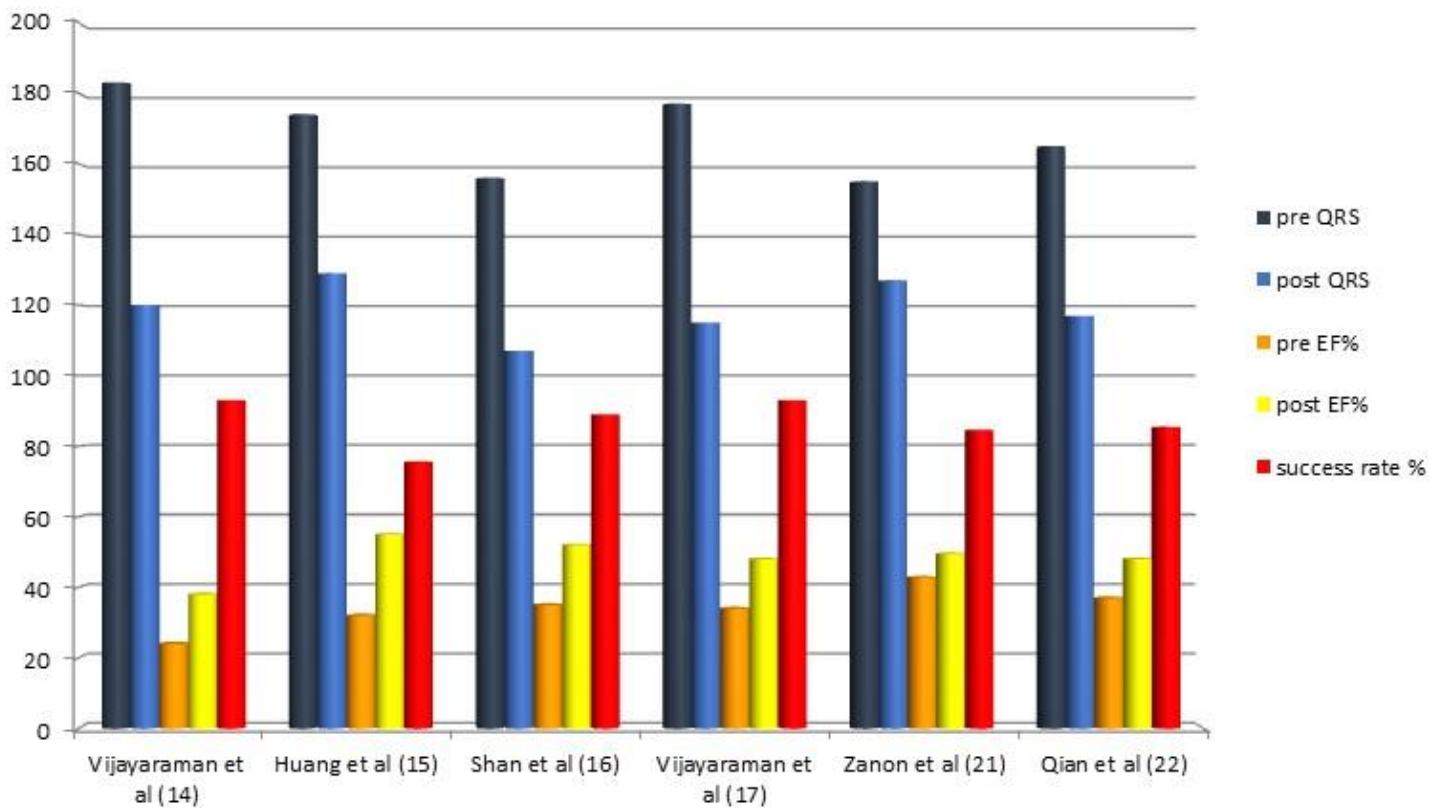
(p<0.0001). Left ventricular ejection fraction significantly improved from 36.9±3.3% at baseline to 48.1 ± 3.0% at follow-up (p <0.0001). Left ventricular end-diastolic volume decreased from 58.2±1.7 mm at baseline to 52.8 ± 1.7 mm (p<0.0001). His bundle pacing also improved LVEF in patients with AF who had received AVN ablation.

Slotwiner et al. (47) performed a systematic review on physiologic pacing versus RVP among patients with LVEF > 35%. The review included 679 patients in 8 HBP studies.

HBP was associated with higher LVEF compared with RVP (mean difference [MD] 4.33% 95% CI: 0.85-7.81%;  $p < 0.01$ ) at 8.36 months follow-up. However, the HBP did not demonstrate consistent benefit in QoL and 6MWT distance.

Pooled analysis of BiVP and HBP recipients showed that physiologic pacing improved left ventricular reverse remodelling as shown in Figure 2 (left ventricular end-systolic volume and left ventricular end-diastolic volume reduced by  $-7.09$  ml,  $p = 0.0009$ ;  $I^2 = 12.98\%$ ; and  $-2.77$  mL;  $p = 0.001$ ;  $I^2 = 0\%$  respectively) and LVEF (LVEF

improved by 5.328%; 95% CI: 2.86–7.8;  $p < 0.0001$ ;  $I^2 = 39.11\%$ ) compared with RVP at mean follow-up of 1.64 years. His bundle pacing did not demonstrate consistent benefit over RVP in terms of functional status, quality of life and survival. Patients with LVEF between 36% and 52% were more likely to derive cardiovascular benefit from physiologic pacing. Patients with chronic AF who underwent AVN ablation derived improvement of LVEF from physiologic pacing versus RVP.



**Figure 2. QRS duration, ejection fraction before and after His-bundle pacing along with success rate in reported in various studies**

Sun et al. (48) performed a systematic review and meta-analysis of 13 HBP studies (comprising 2348 patients) reporting long-term clinical outcome. His bundle pacing had improved LVEF (MD, 5.65; 95% confidence interval [CI], 4.38-6.92), shorter paced QRS width (MD, -39.29; 95% CI, -41.90 to -36.68), higher pacing threshold (MD, 0.8; 95% CI, 0.71-0.89) and lower rate of heart failure hospitalization (odds ratio [OR], 0.65; 95% CI, 0.44-0.96) compared with RVP. There were no statistically significant differences in left ventricular volume and all-cause mortality between the two groups.

Qi et al. (49) reviewed 13 studies (involving 503 patients) on the effect of HBP in CRT candidates. His bundle pacing resulted in narrowing of QRS duration from  $165.5 \pm 8.7$  to  $122.9 \pm 12.0$  ms (MD = 43.5, 95%CI: 36.34 ~ 50.56,  $p < 0.001$ ), improvement in NYHA class (MD = 1.2, 95% CI: 1.09 ~ 1.31,  $p < 0.001$ ), LVEF (MD = -12.60, 95% CI: -14.32 ~ -10.87,  $p < 0.001$ ), and left ventricular end-diastolic dimension (MD = 4.30, 95% CI: 3.05 ~ 5.55,  $p < 0.001$ ) at >3 months follow-up compared with that at baseline ( $p < 0.001$ ). The most commonly reported complication was HBP capture threshold rise.

Fernandes et al. (50) compared the effect of HBP with BiVP and RVP in patients with normal or mildly reduced LVEF. Six studies comparing 704 BiVP patients with 614 RVP patients. Vijayaraman et al. (52) reported that His-bundle capture threshold at 5-year follow-up was significantly higher than that in RVP patients ( $1.62 \pm 1.0$  V vs.  $0.84 \pm 0.4$  V at 0.5 ms,  $p < 0.05$ ). Moreover, 5-year lead revisions rate (6.7% vs 3%) and generator replacement rate (9% vs 1%) were higher in HBP patients compared with RVP patients.

Thirdly, the concern of lead instability/ dislodgement often requires an additional backup pacing lead in some patients. The early lead revision rate was higher in HBP patients (4.2% versus 0.5% in RVP) (34). In a latest

RVP patients and four studies comparing 463 HBP patients with 568 RVP patients were included. Both HBP and BiVP increased LVEF and decreased QRS duration (MD, 5.27 [3.86-6.69],  $p < 0.001$ ; MD -42.2 [-51.2 to -33.3],  $p < 0.001$ , respectively). In HBP or BiVP patients, mortality and HF hospitalization rate was lower compared with RVP patients (odds ratio [OR], 0.66, [0.51-0.85],  $p = 0.002$ ; OR, 0.61 [0.45-0.82],  $p < 0.001$ , respectively). No significant clinical outcome difference was demonstrated between BiVP and HBP.

### Guideline recommendations

Latest guideline has given HBP a class IIa recommendation in patients with reduced LV ejection fraction (LVEF) between 36% and 50% who require chronic ventricular pacing (51).

### Limitations of HBP

There are certain limitations for HBP. Firstly, the implant success varies considerably in early studies, ranging from 56% to 95%. The success rate in later studies (1, 19, 20, 31, 41) improved with accumulation of operator experience. Secondly, HBP patients have higher pacing threshold compared with conventional RVP. Some patients encountered chronic threshold elevation at follow-up.

A study of 295 HBP patients, Teigeler et al. (39) has shown that loss of HBP capture and lead revision occurred in 17% and 11% of patients respectively at long term follow-up (~23 months). Finally, the progression of infra-Hisian His / Purkinje system conduction disease distal to the site of HBP might result in unpredictable ventricular non-capture at follow-up. The advent of left bundle branch pacing might potentially alleviate some of the above limitations of HBP.

### Ongoing HBP studies

The His-bundle pacing vs RVA pacing in patients with reduced ejection fraction (HIS-PrEF) study (ClinicalTrials.gov Identifier: NCT04529577) is a double-blinded, RCT with crossover design. It aims to compare the effect of HBP with RVA pacing in patients with slightly or moderately reduced ejection fraction and AVB with pacing indication. The primary outcome is LVEF at 6 months.

The His bundle pacing in bradycardia and HF study (ClinicalTrials.gov Identifier: NCT03008291) by the Mayo Clinic group is a prospective cohort study. It aims to study the effect of HBP on normalization of atrioventricular conduction in heart failure, CRT candidates with conduction disease. The mapping and pacing of the His bundle for HF patients with LBBB (MAP HIS HF) study (ClinicalTrials.gov Identifier: NCT03803995) is a prospective, single-arm, non-randomized study to assess the locations of HBP that results in correction of electrical dyssynchrony using electroanatomical mapping system.

### What our paper adds?

Our paper has reviewed the latest and most large-scale observational studies of HBP, RCTs and meta-analysis on HBP over the 2 decades. It has systematically summarized the major HBP trials, study sample sizes, study design, patient characteristics, follow-up duration, pacing thresholds, QRS duration at implant and follow-up, long term clinical outcome and complication rates. It has also summarized conclusion from major meta-analysis regarding the benefit and limitations of HBP.

### Knowledge gap and future research directions – what is still unknown

Most of the published HBP studies are observational cohort studies and small-scale randomized trials. The patient populations in these studies were heterogeneous. The long-term beneficial effect of HBP over RVP or CRT, in terms of heart failure hospitalization and mortality remains to be demonstrated by future large-scale randomized control trials. The long-term durability and stability of HBP leads and the effect of high pacing threshold on current drain and device longevity requires long-term follow-up evaluation.

### Conclusion

His bundle pacing restores physiological electrical conduction and mechanical synchrony in patients with pacemaker indications and/or heart failure with CRT indications.

In pacing-dependent patients without heart failure, HBP improves electrical synchrony and reduces the risk of pacing induced left ventricular dysfunction. In heart failure patients with CRT indications, HBP as an adjunct or alternative therapy improves left ventricular systolic function, reduces left ventricular remodelling, heart failure hospitalization and mortality.

It is a viable alternative for CRT eligible patients who have failed left ventricular lead implantation or who are CRT non-responders. The current evidence and clinical guideline support the use of HBP in patients with impaired LVEF (between 36-50%) and high pacing dependence. Future randomized studies are warranted to assess the long-term clinical benefit and safety of HBP in pacing dependent and heart failure population.



**Peer-review:** Internal and external

**Conflict of interest:** None to declare

**Authorship:** J.K.C., S.M., N.K. are equally contributed to study and preparation of article

**Acknowledgement and funding:** None to declare

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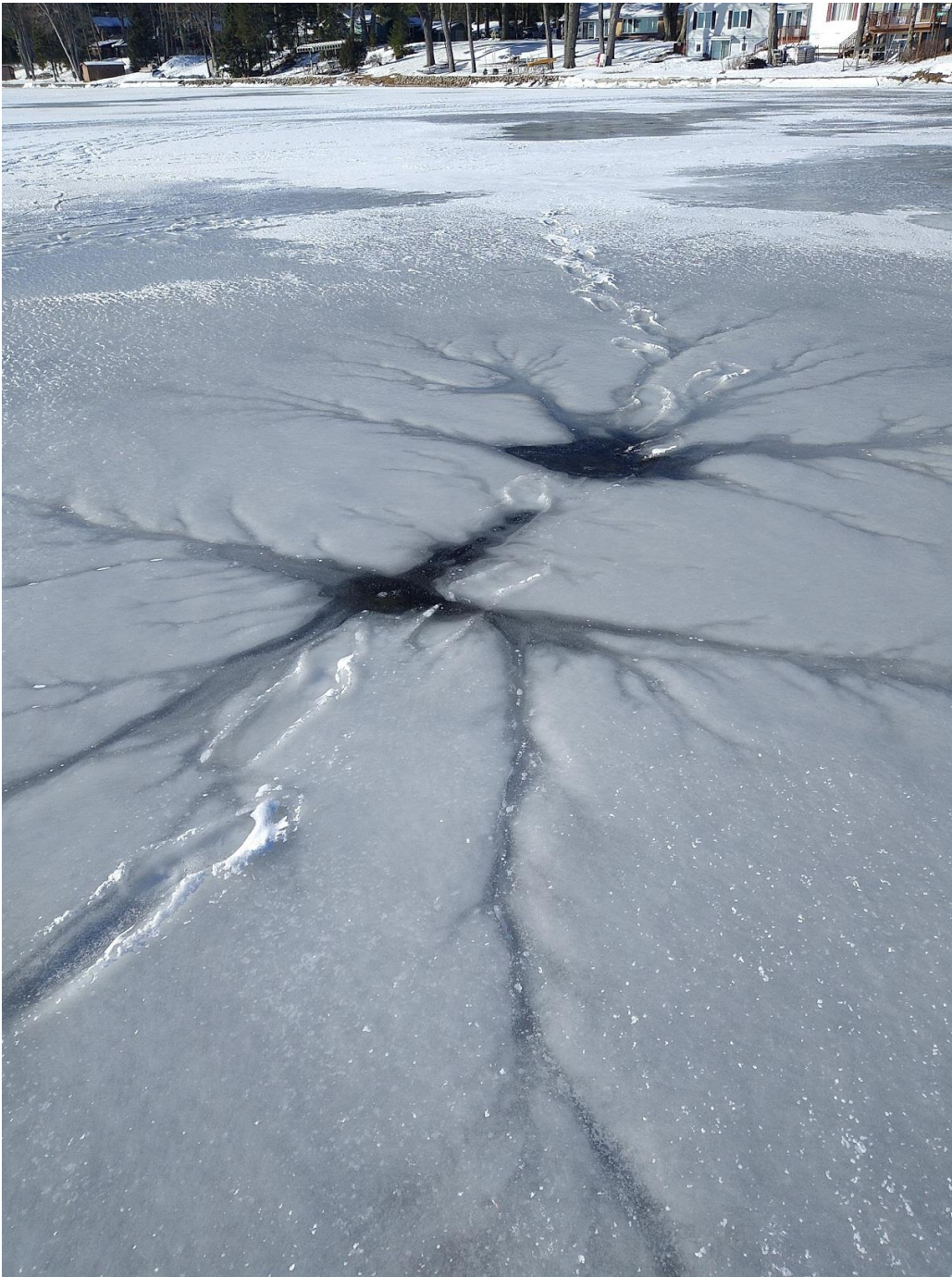
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**Lake Higgins in Northern Michigan, USA. National Geographic rated it as the sixth most beautiful lake in the world. It is a glacier formed lake, and is spring fed, and is incredibly clear with an underwater visibility of 42 feet. It has an average depth of 35 feet and is 135 feet deep at most. It freezes sufficiently in winter that one can walk and snowmobile and ice fish on it. Dan Hermes, Rossomon, Michigan, USA.**