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Clinical Outcomes of His Bundle Pacing Compared to Right Ventricular Pacing

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ABSTRACT

BACKGROUND Right ventricular pacing (RVP) is associated with heart failure and increased mortality. His bundle pacing (HBP) is a physiological alternative to RVP.

OBJECTIVES This study sought to evaluate clinical outcomes of HBP compared to RVP.

METHODS All patients requiring initial pacemaker implantation between October 1, 2013, and December 31, 2016, were included in the study. Permanent HBP was attempted in consecutive patients at 1 hospital and RVP at a sister hospital. Implant characteristics, all-cause mortality, heart failure hospitalization (HFH), and upgrades to biventricular pacing (BiVP) were tracked. Primary outcome was the combined endpoint of death, HFH, or upgrade to BiVP. Secondary endpoints were mortality and HFH.

RESULTS HBP was successful in 304 of 332 consecutive patients (92%), whereas 433 patients underwent RVP. The primary endpoint of death, HFH, or upgrade to BiVP was significantly reduced in the HBP group (83 of 332 patients [25%]) compared to RVP (137 of 433 patients [32%]; hazard ratio [HR]: 0.71; 95% confidence interval [CI]: 0.534 to 0.944; $p = 0.02$). This difference was observed primarily in patients with ventricular pacing >20% (25% in HBP vs. 36% in RVP; HR: 0.65; 95% CI: 0.456 to 0.927; $p = 0.02$). The incidence of HFH was significantly reduced in HBP (12.4% vs. 17.6%; HR: 0.63; 95% CI: 0.430 to 0.931; $p = 0.02$). There was a trend toward reduced mortality in HBP (17.2% vs. 21.4%, respectively; $p = 0.06$).

CONCLUSIONS Permanent HBP was feasible and safe in a large real-world population requiring permanent pacemakers. His bundle pacing was associated with reduction in the combined endpoint of death, HFH, or upgrade to BiVP compared to RVP in patients requiring permanent pacemakers. (J Am Coll Cardiol 2018;71:2319–30)
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Right ventricular pacing (RVP) is known to cause electrical and mechanical dyssynchrony (1,2). Over the long term, RVP is associated with a higher incidence of atrial fibrillation (AF), heart failure, and mortality (3–5). Results from the MOST (MOde Selection Trial) showed that, in patients with a normal baseline QRS duration, ventricular pacing >40% of the time conferred a 2.6-fold increased risk of heart failure hospitalization (HFH) (3). The DAVID (Dual Chamber and VVI Implantable Defibrillator) trial also demonstrated increased risk for death or HFH in patients with left ventricular systolic dysfunction and >40% ventricular pacing (6). Furthermore, recent studies suggest that the ventricular pacing threshold for HFH is as low as 20% (7,8).

Recognition of the deleterious effects of RVP has led to a continued search for alternate pacing sites (9). Permanent His bundle pacing (HBP) was first described by Deshmukh et al. (10) in 2000 in a small series of patients with AF and dilated

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BiVP = biventricular pacing

EF = ejection fraction

HBP = His bundle pacing

HFH = heart failure hospitalization

LV = left ventricle

LVEF = left ventricular ejection fraction

RV = right ventricle

RVP = right ventricular pacing

cardiomyopathy. The feasibility and safety of permanent HBP has subsequently been demonstrated by several investigations (11-14). Permanent HBP is a physiological alternative to RVP. Depolarization of the ventricles through the His-Purkinje system induces normal synchronous ventricular activation and, therefore, avoids the dyssynchrony induced by RVP.

The aim of the present study was to: 1) determine the feasibility and safety of permanent HBP in a large real-world population requiring permanent pacemakers; and 2) evaluate the clinical outcomes of HBP compared to RVP.

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METHODS

STUDY DESIGN. We studied consecutive patients referred to Geisinger Wyoming Valley Medical Center, Wilkes-Barre, Pennsylvania, and Geisinger Medical Center, Danville, Pennsylvania, from October 2013 to December 2016 for permanent pacemaker implantation for standard indications (15). All consecutive patients at the Geisinger Wyoming Valley Medical Center underwent an attempt at permanent HBP, whereas all the patients at the Danville Geisinger Medical Center underwent conventional right ventricular (RV) lead implantation (RV apex or septum) according to the clinical practice at that institution. The 2 centers are highly integrated institutions, 60 miles apart, and part of the Geisinger Health System, using a single electronic medical record system. The institutional review board approved the study protocol. Patients were >18 years of age and met the requirement for de novo permanent pacemaker implantation for bradycardia indications (15). Patients were excluded if they were younger than 18 years of age, had undergone cardiac resynchronization therapy, or had an existing cardiac implantable electronic device. All patients provided written, informed consent.

PROCEDURE. His bundle pacing. HBP was performed using the Select Secure (model 3830, 69 cm, Medtronic, Dublin, Ireland) pacing lead delivered through a fixed curve or a deflectable sheath (C315HIS and C304; Medtronic) as previously described (16). The delivery sheath was inserted into the right ventricle near the tricuspid annulus over a guide wire through the cephalic, axillary, or subclavian vein. Subsequently, the pacing lead was advanced through the sheath such that the distal electrode/screw was beyond the tip of the catheter. A unipolar electrogram was recorded from the lead tip at a gain setting of 0.05 mV/mm and displayed on an Electrophysiology recording system (Bard/Boston Scientific, Lowell, Massachusetts; or Prucka Cardiolab, GE Healthcare, Waukesha, Wisconsin) and a pacing system analyzer (model 2290, Medtronic) at a sweep speed of 50 mm/s. A His bundle electrogram was identified by mapping the atrioventricular septum, and the lead was then screwed into this position by means of 4 to 5 clockwise rotations. If an acceptable His bundle capture could not be achieved after 5 attempts at lead positioning or fluoroscopy duration exceeded 20 min, the lead was then placed in a nonapical location (presumed RV mid-septum as confirmed by fluoroscopy views). When a His bundle electrocardiogram was not recordable during mapping, pace mapping was performed in a unipolar fashion to identify the successful site. Pacing response was categorized as selective on nonselective HBP on the basis of previously defined criteria (17).

Right ventricular pacing. RV leads were implanted in a standard fashion at the RV apex or nonapical location.

Follow-up. Patient demographics, medical history, current medications, and electrocardiographic and echocardiographic findings were collected. His bundle and RV capture thresholds, pacing impedances, and R-wave amplitudes were obtained at implantation and during device follow-up examinations. Patients were followed in the device clinic at 2 weeks and 2 months and yearly thereafter. Patients were also followed by using remote devices when feasible. Patients with high-grade and complete atrioventricular (AV) block were programmed to DDD pacing mode with nominal AV delays. In patients with HBP, the AV delay was shortened by 40 to 50 ms to accommodate the His-ventricular conduction delay. In patients with sinus node dysfunction and intermittent AV block, ventricular pacing avoidance algorithms were used to minimize ventricular pacing. Ventricular pacing burden was routinely documented in all patients. Pacing percentage was recorded at the end of follow-up, censored to an earlier date if the primary outcome was reached. Procedure- and lead-related complications, device infections, and generator changes were documented.

The primary outcome measured was death from any cause, first episode of HFH, or the need for upgrading to biventricular pacing (BiVP). HFH was defined as an unplanned outpatient or emergency department visit or inpatient hospitalization in which the patient presented with signs and symptoms consistent with heart failure and required

intravenous therapy. Information regarding mortality was obtained from hospital records and/or social security death index. Primary outcome was analyzed on an intention-to-treat basis. Secondary outcomes included separate outcomes of death from any cause and HFH.

STATISTICAL ANALYSIS. All data were summarized using frequencies and percentages for categorical data and mean ± SD or median (interquartile range) for continuous data (distribution dependent). Descriptive statistics were reported for the full sample and stratified by HBP and RVP groups. Comparison between the groups was accomplished by using the chi-square or Fisher exact test, and 2-sample *t*-test or Wilcoxon rank sum test, as appropriate. Kaplan-Meier curves and univariate and multivariate Cox proportional hazard models were used to estimate survival probability, HFH, or upgrade to BiVP by HBP and RVP groups. Initially, univariate analysis was carried out using variables previously determined to be clinically significant. Multivariate regression models were then performed using statistically significant hazard ratios and were subsequently repeated until significance was evident for all variables. For survival probability and HFH models, univariate and multivariate regression models were performed as described previously. Competing risk analysis was performed for HFH and mortality to estimate the marginal probability of a certain event as a function of its cause-specific probability and overall survival probability. Patients' last follow-up dates were determined by the last time they were seen in the Geisinger Health system or until the time of death, whichever occurred first. All data and follow-up dates were censored after December 31, 2017. For the Kaplan-Meier curves and Cox and competing risk analyses, time censoring was determined by time to event (primary or secondary) or time to last follow-up in the Geisinger Health System, whichever came first. Statistical analysis was performed using SAS software (version 9.4, SAS Institute, Cary, North Carolina). A p value of <0.05 was considered significant.

RESULTS

BASELINE CHARACTERISTICS. During the study period, 765 patients underwent permanent pacemaker implantation and met inclusion criteria. HBP was attempted in 332 consecutive patients, whereas 433 patients underwent RVP. The mean age was 75.7 ± 11 years of age, with males accounting for 55.8% of the study cohort. History of heart failure and atrial fibrillation were present in 28.8% and 50%, respectively, of patients. Mean baseline left ventricular ejection fraction (LVEF) of the entire cohort was 54.5 ± 9.5%, and mean QRS duration was 108 ± 27 ms. Indication for pacemaker implantation was sinus node dysfunction and AV conduction disease (35% vs. 65% of patients, respectively). Patients were considered lost to follow-up if they did not have an event and were not seen in the Geisinger Health System between January 1, 2017, and December 31, 2017. In the HBP group 16 patients (4.8%) were lost to follow-up compared to 15 patients (3.5%) in the RVP group. The mean follow-up duration for the entire cohort was 725 ± 423 days. The median follow-up in the RVP group was 648 days compared to 754 days in

TABLE 1 Baseline Clinical and Demographic Characteristics of Patients Who Underwent Pacemaker Implantation

	His Bundle Pacing (n = 332)	RV Pacing (n = 433)	p Value
Age	74.8 ± 11.0	76.4 ± 11.3	0.053
White	326 (98.2)	430 (99.3)	0.19
Males	200 (60.2)	227 (52.4)	**0.03**
Active smokers	22 (6.6)	20 (4.6)	0.23
Medical history			
Hypertension	283 (85.2)	358 (82.7)	0.34
Diabetes	106 (31.9)	151 (35.0)	0.39
Hyperlipidemia	238 (71.7)	315 (72.7)	0.75
Coronary artery disease requiring intervention	71 (21.4)	77 (17.8)	0.21
Percutaneous coronary artery intervention	40 (12.1)	40 (9.2)	0.21
Coronary artery bypass surgery	46 (13.9)	52 (12.0)	0.45
Chronic kidney disease	120 (36.1)	128 (29.6)	0.056
Ischemic stroke	43 (13.0)	49 (11.3)	0.49
Heart failure	85 (25.6)	135 (31.2)	0.09
NYHA functional class II	60 (18.1)	82 (18.9)	0.68
NYHA functional class III	23 (6.9)	44 (10.2)	0.12
NYHA functional class IV	2 (0.6)	9 (2.0)	0.09
Atrial fibrillation	189 (56.9)	193 (44.6)	**<0.01**
Permanent atrial fibrillation	50 (15.1)	60 (13.9)	0.91
Baseline medical regimen			
ACE or ARB	243 (73.2)	317 (73.2)	0.99
Beta-blockers	262 (78.9)	315 (72.8)	**0.049**
Loop diuretics	179 (53.9)	258 (59.6)	0.12
Spironolactone	24 (7.2)	29 (6.7)	0.78
Antiarrhythmics usage (including amiodarone)	125 (37.6)	137 (31.6)	0.08
Amiodarone	84 (25.3)	122 (28.2)	0.37
Baseline ejection fraction, %	54.9 ± 8.5	54.2 ± 10.2	0.28
Baseline QRS duration, ms	104.5 ± 24.5	110.5 ± 28.4	**<0.01**
Ventricular pacing burden	54.5 ± 45.2	58.3 ± 43.8	0.24
Sinus node dysfunction	118 (36.0)	152 (35.0)	0.90
AV conduction disease	214 (64.0)	283 (65.0)	0.80
Dual-chamber PPM	270 (81.3)	369 (85.2)	0.15
Single-chamber PPM	51 (15.4)	64 (14.8)	0.82

Values are mean ± SD or n (%). p values <0.05 **(bold)** were considered statistically significant.
ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; AV = atrioventricular; NYHA = New York Heart Association; PPM = permanent pacemaker.

TABLE 2 Procedures and Pacing Characteristics

	His Bundle Pacing (n = 304)	RV Pacing (n = 433)	p Value
Procedure duration, min	70.21 ± 34	55.02 ± 25	**<0.01**
Fluoroscopy duration, min	10.27 ± 6.5	7.40 ± 5.1	**<0.01**
Measurements at implantation			
QRS duration, ms	104.5 ± 24.5	110.5 ± 28.4	**<0.01**
Capture threshold, V @ ms	1.30 ± 0.85 @ 0.79 ± 0.26	0.59 ± 0.42 @ 0.5 ± 0.03	**<0.01**
R wave amplitude, mV	4.93 ± 3.46	11.24 ± 6.37	**<0.01**
Ventricular impedance, Ohms	550 ± 126	723 ± 162	**<0.01**
Measurements at last follow-up			
QRS duration, ms	128 ± 27.7	166 ± 21.8	**<0.01**
Capture Threshold, V @ ms	1.56 ± 0.95 @ 0.78 ± 0.30	0.76 ± 0.29 @ 0.46 ± 0.09	**<0.01**
R wave amplitude, mV	5.54 ± 5.0	11.7 ± 5.5	**<0.01**
Ventricular impedance, Ohms	456 ± 68	517 ± 116	**<0.01**
Change in threshold, V	0.28 ± 1.1	0.16 ± 0.5	0.09

Values are mean ± SD. p values <0.05 **(bold)** were considered statistically significant.
RV = right ventricle.

the HBP group (p = 0.01). Table 1 shows patient baseline characteristics, preimplantation medical history, medications, LVEF, and QRS width. Demographics in the HBP group were similar to those in the RVP group, except for higher prevalence of males (60% vs. 52%, respectively; p < 0.05) and incidence of atrial fibrillation (57% vs. 45%, respectively; p < 0.05) in the HBP group. Mean baseline QRS duration was slightly longer in the RVP group than in the HBP group (105 ± 25 ms vs. 110 ± 28 ms, respectively; p <0.01).

IMPLANTATION OUTCOMES. Permanent HBP was successful in 304 of 332 patients (91.6%). Selective His bundle capture was achieved in 115 patients (37.8%), whereas nonselective His bundle capture occurred in 189 patients (62.2%). In 28 patients in whom HBP was unsuccessful, the lead was placed in a nonapical RV location. Reasons for failure were inability to map the His bundle (8 patients) or successfully fix the lead in 3 patients (3% of the total HBP cohort); 17 patients had infranodal (His-ventricular) block, with inability to recruit distal His-Purkinje conduction in 11 patients and high thresholds to correct in 6 patients (5% of the total HBP cohort). In the RVP group, RV apical pacing was obtained in 176 of 433 patients (40.6%) and nonapical pacing in 257 patients (59.4%).

The mean procedure (70 ± 34 min vs. 55 ± 25 min, respectively; p <0.01) and fluoroscopy duration (10 ± 7 min vs. 7 ± 5 min, respectively; p <0.01) were significantly longer in the HBP group than in the RVP group. His Bundle capture threshold was significantly higher than the right ventricular pacing threshold at implantation (1.30 ± 0.85 V vs. 0.59 ± 0.42 V, respectively; p < 0.01). The His bundle capture threshold increased slightly during a mean follow-up of 24 months to 1.56 ± 0.95 V compared to 0.76 ± 0.29 V in the RVP group (p < 0.01). In the HBP group, at 12 months' follow-up, 43 patients (14%) had His capture thresholds >2.5 V. The His capture threshold in that group increased from 1.6 ± 0.9 V at implantation to 3.27 ± 0.6 V at 12 months. Twenty-six patients in that group had nonselective HBP (61%), and right ventricular capture threshold increased from 1.2 ± 0.6 V at implantation to 1.9 ± 0.8 V at 12 months. R-wave amplitudes and lead impedances were significantly lower in the HBP group than in the RVP group at implantation, and these differences persisted during follow-up. Paced QRS duration was significantly narrower in the HBP group than in the RVP group (128 ± 27 ms vs. 166 ± 22 ms, respectively; p < 0.01). Procedural and pacing characteristics are shown in Table 2.

COMPLICATIONS. In the HBP group, ventricular lead revision was required in 14 patients (4.2%). Failure to capture or unacceptably high capture thresholds occurred in 6 patients within the first 30 days after implantation, and progressive increases in His capture threshold occurred in 8 patients at more than 30 days after implantation. In these 8 patients, there were progressive increases in His capture threshold from 0.8 ± 0.39 V at implantation to 4.5 ± 0.8 V at a median follow-up of 118 days. Two of these patients (who had underlying sinus node dysfunction) had no His capture at the time of lead revision. In the RVP group, 2 patients (0.5%) underwent ventricular lead revisions in the first 30 days post-procedure. Pericardial effusion requiring pericardiocentesis occurred in 3 patients (0.7%) in the RVP group and none in the HBP group. Infection necessitating device or lead removal occurred in 1 patient in each group. Premature battery depletion resulted in pacemaker generator change in 1 patient in the HBP group, 3.5 years after the initial implant compared to none in the RVP group.

OUTCOMES. The primary outcome (combined endpoint of death from any cause or HFH or upgrade to BiVP) occurred in 25% of patients in the HBP group versus 31.6% of patients in the RVP group (hazard ratio [HR]: 0.71; p = 0.02) (Central Illustration, Table 3). Patients were further stratified and analyzed on the basis of their ventricular pacing burden as recorded at the end of follow-up and were censored to an earlier date if the primary outcome was reached. Sixteen patients were removed from this analysis (13 in the HBP group and 3 in the RVP group) because there was no documented ventricular pacing burden. In patients with ventricular pacing burden >20%, the

CENTRAL ILLUSTRATION **His Bundle Pacing and Outcomes: Kaplan-Meier Survival Curves and Analysis of the Primary Endpoint in All Patients**

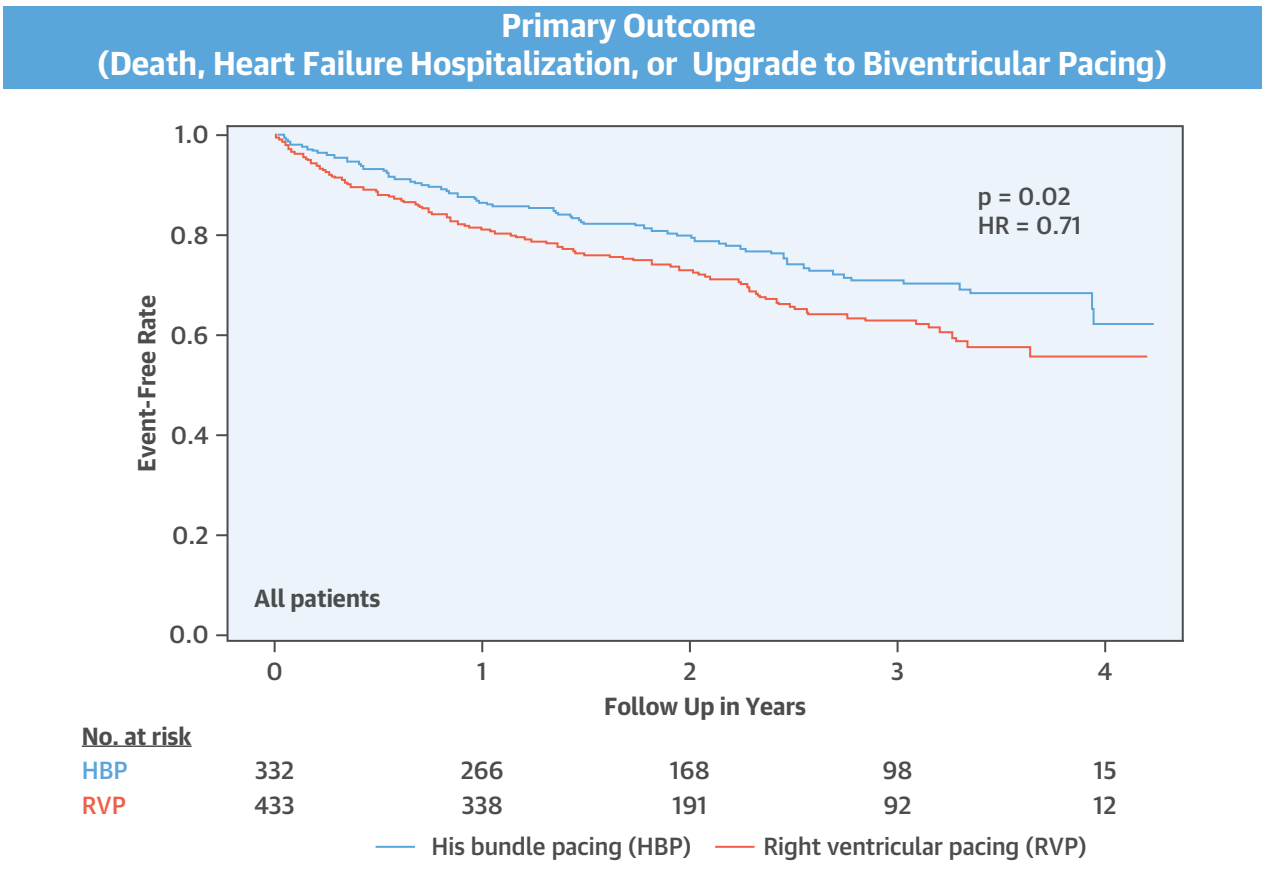

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Figure and analysis shows a statistically significant reduction in the primary endpoint (composite endpoint of all cause death, heart failure hospitalization, or upgrade to biventricular pacing) associated with HBP compared to RVP. HBP = His bundle pacing; HR = hazard ratio; RVP = Right ventricular pacing.

primary outcome was reached in 25.3% of patients (49 of 194) in the HBP group compared to 35.6% of patients (99 of 278) in the RVP group (HR: 0.650; p = 0.02) (Figure 1). In those patients with ventricular pacing burden of ≤20%, the primary outcome in the HBP group was similar to that in the RVP group (22% vs. 23.7%, respectively; p = 0.34) (Table 4).

During the study period, there were 117 HFH events of which 104 were inpatient hospitalizations lasting >24 h (89%), and in 96 patients (82%) the HFH lasted longer than 48 h. There was a significant decrease in HFH in all patients with HBP (41 of 332 [12.4%]) compared to those with RVP (76 of 433 [17.6%]; HR: 0.633; p = 0.02) (Figure 2). This difference was seen primarily in patients with ventricular pacing burden of >20% (Figure 3). There were no differences in HFH in patients with ventricular pacing ≤20%. Competing risk analysis for HFH with mortality as a competing risk was performed and confirmed the significant reduction in HFH associated with HBP in all patients (HR: 0.675; p = 0.045) and in patients with ventricular pacing burden >20% (HR: 0.574; p = 0.03). There was a trend toward longer survival in the HBP group than in the RVP group, but it did not reach statistical significance (Figure 2). This trend was noticed in all patients as well as in those with a ventricular pacing burden of >20% (Table 4).

Furthermore, there were no significant differences in HFH within the HBP group, regardless of the ventricular pacing burden. In HBP patients with ventricular pacing >20%, 24 patients (12.4%) had HFH versus 16 patients (13%) in those with ventricular pacing burden ≤20% (HR: 1.045; p = 0.89); these HFH rates were similar to those in the RVP group with

TABLE 3 Univariate and Multivariate Hazard Ratio for Composite Outcome of All-Cause Death, HFH, or Upgrade to Biventricular Pacing*

	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p Value	HR	95% CI	p Value
HBP vs. RVP	0.708	0.538–0.933	0.01	0.71	0.534–0.944	0.02
Age	1.035	1.020–1.049	<0.01	1.022	1.007–1.037	<0.01
Male	0.922	0.706–1.204	0.55	-	-	-
Hypertension	1.728	1.102–2.711	0.02	-	-	-
Diabetes	1.555	1.190–2.033	<0.01	-	-	-
Hyperlipidemia	1.142	0.831–1.571	0.67	-	-	-
Coronary artery disease requiring intervention	1.145	0.835–1.571	0.71	-	-	-
Chronic kidney disease	2.238	1.714–2.921	<0.01	1.747	1.317–2.317	<0.01
Ischemic stroke	1.702	1.203–2.409	<0.01	-	-	-
Heart failure	2.944	2.255–3.844	<0.01	2.087	1.57–2.763	<0.01
Atrial fibrillation	1.739	1.319–2.293	<0.01	-	-	-
ACE or ARB	1.338	0.979–1.828	0.07	-	-	-
Beta-blockers	1.569	1.097–2.244	0.01	-	-	-
Antiarrhythmic usage	1.554	1.189–2.032	<0.01	-	-	-
Baseline QRS duration	1.002	0.998–1.007	0.32	-	-	-
Paced QRS duration	1.009	1.004–1.014	<0.01	-	-	-
Baseline ejection fraction	0.973	0.961–0.985	<0.01	0.982	0.970–0.994	<0.01
Ventricular pacing percentage	1.003	1.000–1.006	0.05	-	-	-

*Univariate and multivariate Cox proportional hazards models were used.

CI = confidence interval; HBP = His bundle pacing; HFH = heart failure hospitalization; HR = hazard ratio; RVP = right ventricular pacing; other abbreviations as in Table 1.

ventricular pacing ≤20%. Both of the HBP groups had significantly fewer HFH events than the RVP patients with ventricular pacing >20% (Figure 3).

In the subgroup of patients with VP >80%, the primary outcome was reached in 25% of patients (39 of 156) in the HBP group compared to 34.2% of patients (76 of 222) in the RVP group (HR: 0.669; 95% CI: 0.449 to 0.999; p = 0.049). The secondary outcome of HFH was significantly reduced in the HBP group than in the RVP group (12.2% vs. 19.8%, respectively; HR: 0.526; 95% CI: 0.303 to 0.911; p = 0.022). There were no differences in mortality (17.9% in HBP vs. 22.5% in RVP; HR: 0.732; p = 0.186).

PATIENTS WITH REDUCED LVEF. There were 99 patients with baseline LVEF <50% in the study (Table 5). Baseline characteristics were similar in both groups, except for a higher incidence of AF in the HBP group (81% vs. 58%, respectively; p = 0.02) and a slightly lower EF in the RVP group (36 ± 8% vs. 38 ± 7%, respectively; p = 0.001). In this subgroup of patients with reduced LV function, there was a trend toward reduction in the primary outcome among patients with HBP compared to those with RVP without reaching statistical significance (38% vs. 53%, respectively; HR: 0.384; 95% CI: 0.146 to 1.013;

FIGURE 1 Kaplan-Meier Survival Curves and Analysis of the Primary Endpoint With VP Burden >20%

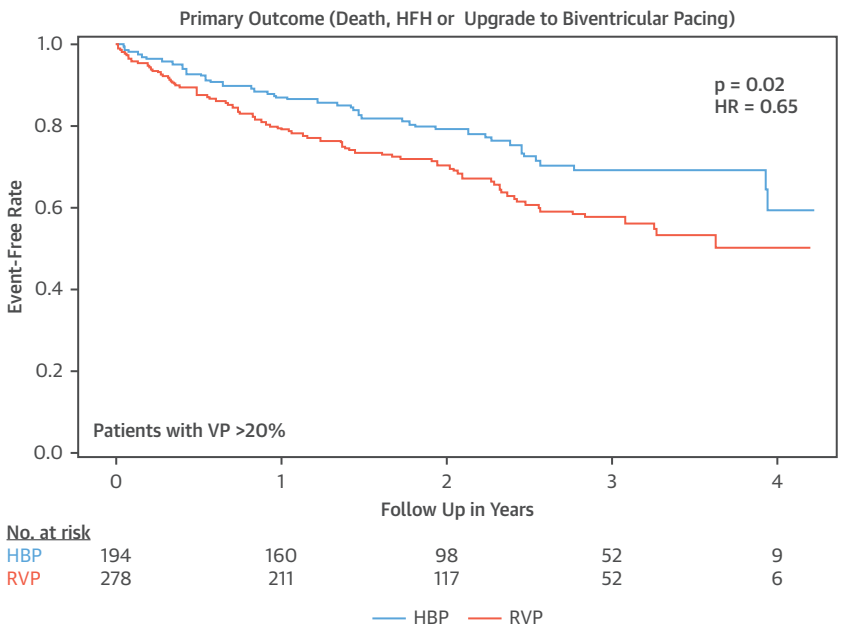


Figure and analysis shows a statistically significant reduction in the primary endpoint (composite endpoint of all cause death, HFH, or upgrade to BiVP) associated with HBP compared to RVP. BiVP = biventricular pacing; HBP = His bundle pacing; HFH = heart failure hospitalization; HR = hazard ratio; RVP = right ventricular pacing; VP = ventricular pacing burden.

TABLE 4 Comparison of Primary and Secondary Outcomes (All-Cause Mortality, HFH, and Upgrade to Biventricular Pacing) Between HBP and RVP in All Patients, Patients With Ventricular Pacing Burden of >20% and Those With ≤20%

			Univariate Analysis			Multivariate Analysis		
	HBP	RVP	HR	95% CI	p Value	HR	95% CI	p Value
All patients	332	433	-	-	-	-	-	-
All-cause mortality, heart failure hospitalization and upgrade to biventricular pacing	**83 (25)**	**137 (31.6)**	**0.708**	**0.538–0.933**	**0.01**	**0.710**	**0.534–0.944**	**0.02**
All-cause mortality	57 (17.2)	93 (21.4)	0.728	0.523–1.014	0.06	-	-	-
Heart failure hospitalizations	**41 (12.4)**	**76 (17.6)**	**0.642**	**0.439–0.939**	**0.02**	**0.633**	**0.430–0.931**	**0.02**
Competing risk analysis for HFH (mortality as competing risk)			**0.644**	**0.441–0.940**	**0.02**	**0.675**	**0.460–0.992**	**0.045**
Upgrade to biventricular pacing	1 (0.3)	6 (1.4)	0.211	0.025–1.752	0.15	-	-	-
Ventricular pacing >20%	194	278	-	-	-	-	-	-
All-cause mortality, heart failure hospitalization and upgrade to biventricular pacing	**49 (25.3)**	**99 (35.6)**	**0.625**	**0.443–0.882**	**<0.01**	**0.650**	**0.456–0.927**	**0.02**
All-cause mortality	35 (18.0)	66 (23.7)	0.687	0.455–1.035	0.07	-	-	-
Heart failure hospitalizations	**24 (12.4)**	**56 (20.1)**	**0.548**	**0.340–0.866**	**0.01**	**0.543**	**0.334–0.882**	**0.01**
Competing risk analysis for HFH (mortality as competing risk)			**0.551**	**0.341–0.890**	**0.01**	**0.574**	**0.351–0.939**	**0.03**
Upgrade to biventricular pacing	1 (0.5)	6 (2.2)	0.229	0.468–1.299	0.34	-	-	-
Ventricular pacing ≤20%	125	152	-	-	-	-	-	-
All-cause mortality, heart failure hospitalization and upgrade to biventricular pacing	27 (22)	36 (23.7)	0.780	0.468–1.299	0.34	-	-	-
All-cause mortality	15 (12)	25 (16)	0.640	0.337–1.216	0.17	-	-	-
Heart failure hospitalizations	16 (13)	20 (13.2)	0.876	0.453–1.692	0.69	-	-	-
Competing risk analysis for HFH (mortality as competing risk)			0.876	0.458–1.675	0.69	-	-	-
Upgrade to biventricular pacing	0	0	-	-	-	-	-	-

Values are n or n (%), unless otherwise indicated. Comparison between univariate and multivariate Cox proportional hazards models are shown. Values in **bold** indicate significant hazard ratios and p values. Abbreviations as in Table 3.

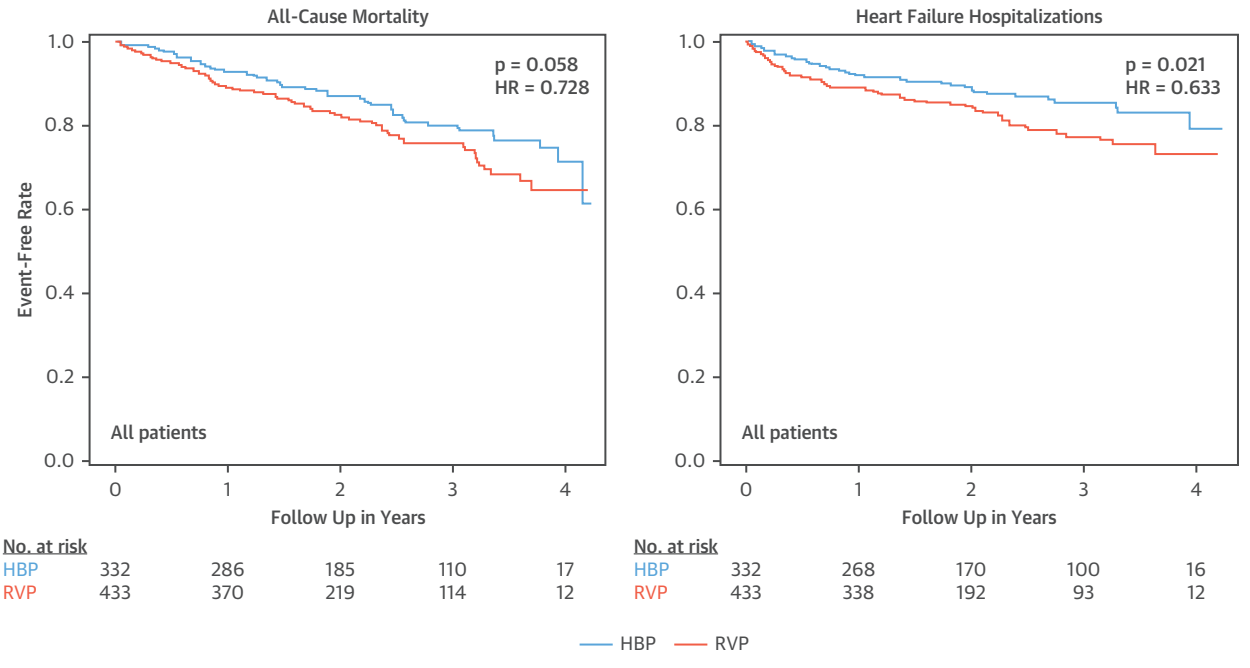
p = 0.053). In the RVP group, LVEF <50% was associated with significantly increased risk for reaching the primary endpoint (HR: 1.785; 95% CI: 1.054 to 3.023; p = 0.031) compared to patients with LVEF >50%. However, this did not reach statistical significance in the HBP group (Table 6).

In the RVP group, 6 patients underwent an upgrade to BiVP compared to 1 patient in the HBP group. In patients with HFH or who were upgraded to BiVP, echocardiograms were available for 34 of 41 patients in the HBP group and 71 of 78 patients in the RVP group. Mean age (79 ± 8 years vs. 78 ± 9 years, respectively; p = 0.72) and baseline EF in HBP were similar to those in the RVP group (53 ± 10% vs. 51 ± 12%, respectively; p = 0.22) (Table 7). During follow-up, LVEF significantly dropped in the RVP group to 44.2% ± 15% compared to 51.3 ± 10.4% in the HBP group (p = 0.01). In this subset of patients, pacing induced cardiomyopathy (decrease in LVEF by >10% and >20% ventricular pacing burden) was noted in 3 of 41 patients in the HBP group compared to 24 of 78 patients in the RVP group (7.3% vs. 30.8%, respectively; p < 0.01). Of the 24 patients in the RVP group, only 6 underwent an upgrade to BiVP. In 8 of those patients, BiVP was not considered due to associated co-morbidities (old age, renal failure, malignancy). In 3 patients ventricular pacing burden was <40%, and in 7 patients no clear reason for failure to upgrade could be identified.

DISCUSSION

Results of our study showed that permanent HBP was associated with a significant reduction in the primary endpoint of all-cause mortality or heart failure hospitalization or upgrade to BiVP compared to conventional RV pacing in patients undergoing permanent pacemaker implantation for bradycardia. Our primary outcome was driven predominantly by a significant reduction in the incidence of HFH associated with HBP. Additionally, the significant reduction in the primary endpoint was entirely due to differences in outcomes for patients with ≥20% ventricular pacing burden. These findings addressed the clinical need to determine the best possible ventricular pacing site in patients requiring permanent pacemakers for bradycardia therapy. This study supports the concept that HBP can prevent ventricular dyssynchrony by

FIGURE 2 Secondary Outcomes



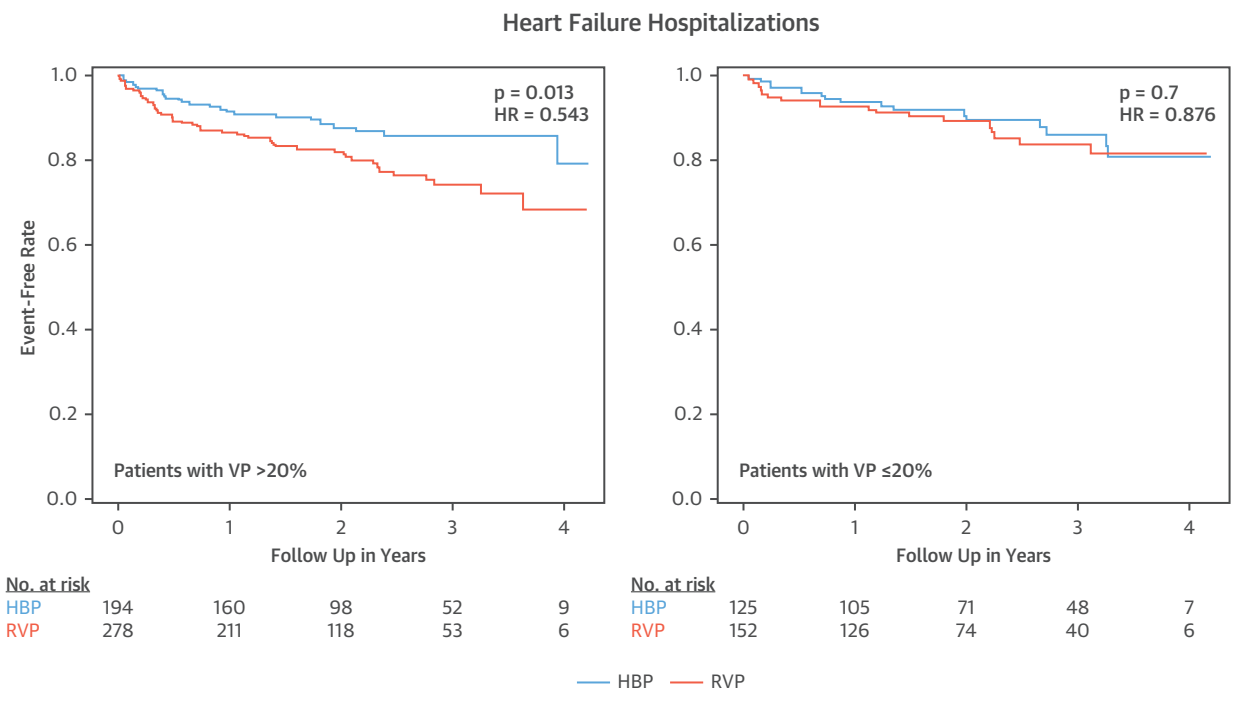
Kaplan-Meier survival curves and analysis of all-cause mortality (left) and HFH (right) in all patients. Figures and analysis show a statistically significant reduction in HFH associated with HBP compared to RVP. There was a trend for longer survival in HBP patients, but it did not reach statistical significance. Abbreviations as in Figure 1.

facilitating conduction through the native His-Purkinje system.

Chronic RVP induces interventricular and intraventricular dyssynchrony, which is detrimental to left ventricular function and is associated with heart failure and increased mortality (1-4). The MOST study of sinus node dysfunction demonstrated that patients with ventricular pacing >40% had 2.5 times higher risk of HFH than patients with <40% ventricular pacing (3). Recent studies suggest that the ventricular pacing threshold for HFH can be as low as 20% (7,8). In a study by Kiehl et al. (8) involving 823 patients with complete heart block, the incidence of pacing-induced cardiomyopathy was 12.3% during a mean follow-up of 4.3 ± 3.9 years. RV pacing burden >20% as a categorical variable was strongly associated with increased risk for pacing-induced cardiomyopathy (HR: 6.95; p = 0.002). Consistent with these previous studies, we noted a significant difference in HFH between patients with right ventricular pacing burden of >20% and those with <20% ventricular pacing. However, there was no association between ventricular pacing burden and HFH in the HBP group. Despite higher incidence of coronary artery disease and AF in the HBP group, the reduction in HFH could partly be attributed to higher use of beta-blocker drugs (78.9% vs. 72.8%, respectively; p = 0.049).

Recently, BiVP has been proposed as an alternative to RVP to prevent heart failure. Although the BLOCK HF (Biventricular versus RV Pacing in Heart Failure Patients with Atrioventricular Block) study (19) reported a significant reduction in the primary outcome favoring BVP over RV pacing, the difference was driven primarily by an increase in LV end-systolic volume index. A limitation of that trial was the inclusion of patients with LVEF ≤35%, comprising 30% of the study population and forced ventricular pacing in 20% who had first-degree AV block. However, the larger BioPace (Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization) trial (20) reported a similar rate of composite endpoint that included time-to-death or first hospitalization due to heart failure with a nonsignificant trend in favor of BiVP (HR: 0.87; p = 0.08). This trend persisted, still without reaching statistical significance, when patients were stratified according to their LVEF.

FIGURE 3 Kaplan-Meier Survival Curves and Analysis Comparing HFH Outcomes Among Patients With VP >20% and VP ≤20%



There was a significant reduction in HFH in patients with HBP and VP >20% **(left)**. There were no differences among RVP and HBP patients with VP ≤20% **(right)**. Abbreviations as in Figure 1.

TABLE 5 Baseline Clinical and Demographic Characteristics of Patients Who Underwent Pacemaker Implantation and had a Baseline LVEF <50%

	His Bundle Pacing (n = 37)	RV Pacing (n = 62)	p Value
Age, yrs	77.3 ± 8	77.7 ± 12	0.50
Males	23 (62)	38 (61)	0.93
Medical history			
Hypertension	31 (84)	50 (81)	0.70
Diabetes	14 (38)	26 (42)	0.69
Coronary artery disease requiring intervention	10 (27)	18 (29)	0.83
Chronic kidney disease	16 (43)	30 (48)	0.62
Atrial fibrillation	30 (81)	36 (58)	**0.02**
Baseline ejection fraction, %	38 ± 7	36 ± 8	**<0.01**
Ventricular pacing burden	55 ± 44	55 ± 43	0.67
Sinus node dysfunction	10 (27)	25 (40)	0.18
AV conduction disease	27 (73)	37 (60)	0.18

Values are mean ± SD or n (%). p values <0.05 **(bold)** were considered statistically significant.

AV = atrioventricular; LVEF = left ventricular ejection fraction; RV = right ventricular.

Presently, it is unclear which subgroup of patients with AV block may benefit from BiVP. Our current study suggests that HBP may be effective in reducing HFH and may reduce mortality in patients requiring ventricular pacing.

In 2012, Catanzariti et al. (21) published data from 26 patients with His bundle lead and backup RV lead, comparing echocardiographic data during pacing at both sites. HBP was associated with lower interventricular dyssynchrony, intraventricular dyssynchrony, and mitral regurgitation, with better myocardial performance indices. Zhang et al. (22) assessed LV mechanical synchrony parameters by using single-photon emission computed tomography myocardial perfusion imaging in 23 patients with HBP and backup RV septal pacing. Mechanical synchrony parameters were significantly better during HBP compared to RV septal pacing (22). It is likely that the mechanism for preventing HFH in our study was due to the maintenance of ventricular synchrony during HBP. This study also demonstrated a trend toward longer survival with HBP compared to RVP. Longer follow-up duration and a larger patient cohort may be

TABLE 6 Comparison of Primary Outcomes (All-Cause Mortality, HFH, and Upgrade to Biventricular Pacing) Among Patients With LVEF <50% and Patients With LVEF ≥50%

		HBP (n = 37)	RVP (n = 62)	Univariate Analysis			Multivariate Analysis		
				HR	95% CI	p Value	HR	95% CI	p Value
Patients with LVEF <50% (n = 99)	All-cause mortality, heart failure hospitalization and upgrade to biventricular pacing	14 (37.8)	33 (53.2)	0.349	0.138–0.883	0.03	0.384	0.146–1.013	0.053
		Baseline LVEF <50% (n = 37)	**Baseline LVEF ≥50% (n = 295)**						
His bundle pacing (n = 332)	All-cause mortality, heart failure hospitalization and upgrade to biventricular pacing	14 (37.8)	69 (23.3)	2.92	1.429–5.965	<0.01	1.966	0.928–4.168	0.08
		Baseline LVEF <50% (n = 62)	**Baseline LVEF ≥50% (n = 371)**						
Right ventricular pacing (n = 433)	All-cause mortality, heart failure hospitalization and upgrade to biventricular pacing	33 (53.2)	104 (28.0)	**2.699**	**1.631–4.467**	**<0.01**	**1.785**	**1.054–3.023**	**0.03**

Values are n (%) unless otherwise indicated. Comparisons are shown as univariate and multivariate Cox proportional hazards models. Values in **bold** indicate significant hazard ratios and p values.
Abbreviations as in Tables 3 and 5.

required to definitely assess the effect of HBP on mortality.

Despite a high number of patients with pacing-induced cardiomyopathy (24 of 78 patients with HFH) in the RVP group, only 6 patients (25%) underwent an upgrade to BiVP, which is similar to 28% reported in previous studies (7,8). It likely reflects the reluctance to refer or consider upgrade to BiVP in this elderly population.

TABLE 7 Baseline Clinical and Demographic Characteristics of Patients Who Had HFH or Were Upgraded to Biventricular Pacing

	His Bundle Pacing (n = 41)	RV pacing (n = 78)	p Value
Age, yrs	79 ± 8	78 ± 9	0.72
Male	23 (56)	40 (51)	0.62
Medical history			
Hypertension	40 (98)	70 (90)	0.13
Diabetes	22 (54)	36 (46)	0.44
Coronary artery disease requiring intervention	11 (27)	20 (26)	0.89
Chronic kidney disease	27 (66)	36 (46)	**0.04**
Heart failure	22 (54)	49 (63)	0.33
Atrial fibrillation	31 (76)	50 (64)	0.20
Baseline medical regimen			
ACE or ARB	33 (80)	63 (81)	0.97
Beta blockers	36 (88)	65 (83)	0.52
Spironolactone	3 (7)	7 (9)	0.76
Baseline ejection fraction, %	53 ± 10	51 ± 12	0.22
Baseline QRS duration, ms	106 ± 21	110 ± 29	0.34
Ventricular pacing burden	55 ± 44	65 ± 41	0.25
Sinus node dysfunction	15 (37)	28 (36)	0.94
AV conduction disease	26 (63)	50 (64)	0.94

Values are mean ± SD or n (%). p values <0.05 **(bold)** were considered statistically significant.
Abbreviations as in Tables 1, 3, and 5.

Although HBP is a physiological alternative to RVP, it has not become mainstream therapy owing to technical challenges and higher pacing thresholds. We previously reported the safety and feasibility of permanent HBP in a cohort of 94 patients with a success rate of 80% (13). Our current study has confirmed the safety and feasibility of permanent HBP in a larger cohort of patients with a success rate of 92%. It should be emphasized that most of the His bundle pacing leads were implanted by experienced operators (P.V., 60%; G.D., 25%). The operators' experience at the beginning of the study ranged from 7 years for P.V. and 4 years for G.D. The newest implanter with no experience (F.A.S.) also contributed to a significant number of implantations (15%) with high success rates, under expert guidance. There were no significant differences among the 3 operators with regard to procedural outcomes. The procedural and fluoroscopy times were only slightly longer with HBP compared with conventional RVP leads. It should again be emphasized that this was achieved due to the significant expertise accumulated over the years. Although a novice implanter may not be able to achieve similar results (procedural times and pacing thresholds), it is our belief that 20 to 25 implants would be adequate to complete the necessary learning curve and achieve consistent results. We also demonstrated the relative stability of the His bundle capture threshold with an average increase of 0.28 ± 1.1 V during a mean follow-up of 2 years. The need for

His bundle pacing lead revision was 4.2% in this series, similar to that in prior reports (12-14,18). Although significantly higher than RV pacing, lead-related complications were comparable to those seen with cardiac resynchronization therapy devices (19).

STUDY LIMITATIONS. This was an observational study using consecutive patients in the Geisinger HBP registry, comparing a cohort of consecutive RVP patients who underwent implantation in a nearby sister hospital of the Geisinger Health System during the same period. Patients underwent HBP or RVP on the basis of location and clinical practice of the treating hospital. Due to the nonrandomized nature, this study does not ensure homogeneity between the study groups, and the results should be interpreted with caution. Operators with significant experience performed HBP in this study. The high success rates and low implantation times may not be achievable in centers where this procedure has been recently initiated. Large, prospective, randomized trials comparing HBP to RVP are necessary to prove heart failure benefits and reduction of mortality attributable to HBP.

CONCLUSIONS

Permanent HBP was feasible and safe in a large real-world population requiring permanent pacemakers. His bundle pacing thresholds remained stable in most patients, although lead revisions were required in a higher number of patients compared to traditional RVP. During a mean follow-up duration of approximately 2 years, HBP was associated with significant reduction in the composite outcome of all-cause mortality, HFH, or upgrade to BiVP compared to conventional RVP. These differences in clinical outcomes were primarily realized in patients who required >20% ventricular pacing.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with bradycardia requiring pacemakers, right ventricular pacing is associated with an increased risk of heart failure hospitalization and mortality, and permanent His bundle pacing may lower these risks.

TRANSLATIONAL OUTLOOK: Randomized studies with long-term follow-up are necessary to evaluate the advantages and limitations of His bundle pacing compared to right ventricular pacing.

REFERENCES

1. Tops LF, Schalij MJ, Bax JJ. The effects of right ventricular apical pacing on ventricular function and dys-synchrony implications for therapy. J Am Coll Cardiol 2009;54:764–76.

2. Tse HF, Lau CP. Long-term effect of right ventricular pacing on myocardial perfusion and function. J Am Coll Cardiol 1997;29:744–9.

3. Sweeney MO, Hellkamp AS, Ellenbogen KA, et al., for the MOde Selection Trial Investigators. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 2003;107:2932–7.

4. Wilkoff BL, Cook JR, Epstein AE, et al. Dual chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial. JAMA 2002;288:3115–23.

5. Nielsen JC, Kristensen L, Andersen HR, Mortensen PT, Pedersen OL, Pedersen AK. A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome: echocardiographic and clinical outcome. J Am Coll Cardiol 2003;42:614–23.

6. Sharma AD, Rizo-Patron C, Hallstrom AP, et al. Percent right ventricular pacing predicts outcomes in the DAVID trial. Heart Rhythm 2005;2:830–4.

7. Khurshid S, Epstein AE, Verdino RJ, et al. Incidence and predictors of right ventricular pacing-induced cardiomyopathy. Heart Rhythm 2014;11:1619–25.

8. Kiehl EL, Makki T, Kumar R, et al. Incidence and predictors of right ventricular pacing-induced cardiomyopathy in patients with complete atrioventricular block and preserved left ventricular systolic function. Heart Rhythm 2016;13(12):2272–8.

9. Vijayaraman P, Bordachar P, Ellenbogen KA. The continued search for physiological pacing: where are we now? J Am Coll Cardiol 2017;69:3099–114.

10. Deshmukh P, Casavant D, Romanyshyn M, Anderson K. Permanent direct His bundle pacing: a novel approach to cardiac pacing in patients with normal His-Purkinje activation. Circulation 2000;101:869–77.

11. Occhetta E, Bortnik M, Magnani A, et al. Prevention of ventricular desynchronization by permanent para-hisian pacing after atrioventricular node ablation in chronic atrial fibrillation: a crossover, blinded randomized study versus right ventricular pacing. J Am Coll Cardiol 2006;47:1938–45.

12. Zanon F, Svetlich C, Occhetta E, et al. Safety and performance of a system specifically designed for selective site pacing. Pacing Clin Electrophysiol 2011;34:339–47.

13. Sharma P, Dandamudi G, Naperkowski A, et al. Permanent His bundle pacing is feasible, safe and superior to right ventricular pacing in routine clinical practice. Heart Rhythm 2015;12:305–12.

14. Vijayaraman P, Naperkowski A, Ellenbogen KA, Dandamudi G. Permanent His bundle pacing in advanced AV block. Electrophysiological insights into site of AV block. J Am Coll Cardiol EP 2015;1:571–81.

15. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. J Am Coll Cardiol 2013;61:e6–75.

16. Vijayaraman P, Dandamudi G. How to perform His bundle pacing: tips and tricks. PACE 2016;39:1298–304.

17. Vijayaraman P, Dandamudi G, Zanon F, et al. Permanent His bundle pacing (HBP): recommendations from international HBP collaborative group for standardization of definitions, implant measurements and follow-up. Heart Rhythm 2018;15:460–8.

18. Vijayaraman P, Naperkowski A, Subzposh F, et al. Permanent His bundle pacing: long-term performance and clinical outcomes. Heart Rhythm 2017 Dec 20 [E-pub ahead of print].

19. Curtis AB, Worley SJ, Adamson PB, et al. Biventricular pacing for atrioventricular block and systolic dysfunction. N Engl J Med 2013;368:1585–93.

20. Blanc JJ et al., for Biopace trial investigators. Biventricular pacing for atrioventricular block to prevent cardiac desynchronization. Results presented at European Society of Cardiology Congress, Barcelona, Spain, September 2014.

21. Catanzariti D, Maines M, Manica A, Angheben C, Varbaro A, Vergara G. Permanent His-bundle pacing maintains long-term ventricular synchrony and left ventricular performance, unlike conventional right ventricular apical pacing. Europace 2013;15:546–53.

22. Zhang J, Guo J, Hou X, et al. Comparison of the effects of selective and non-selective His bundle pacing on cardiac electrical and mechanical synchrony. Europace 2017 May 31 [E-pub ahead of print].

KEY WORDS **biventricular pacing, heart failure hospitalization, His bundle pacing, mortality, right ventricular pacing**