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REVIEW TOPIC OF THE WEEK

The Continued Search for Physiological Pacing

Where Are We Now?

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ABSTRACT

Cardiac pacing is an effective treatment for patients with bradycardia due to sinus node dysfunction or atrioventricular block. Despite decades of technological advances, the optimal ventricular pacing site to mimic normal human ventricular physiology and best hemodynamic response remains elusive. Beginning with atrial synchronous right ventricular (RV) apical pacing, the search has continued through alternate RV pacing sites, minimizing RV pacing, biventricular pacing, left ventricular (LV) pacing, and His-bundle pacing. Understanding the deleterious effects of long-term RV apical pacing in vulnerable populations has created tremendous interest in alternate pacing options. This paper reviews the current status of available pacing options, with particular focus on His-bundle pacing. Permanent His-bundle pacing has emerged as the leading candidate for physiological pacing because it provides nearly normal electrical activation of both ventricles and thereby avoids ventricular dyssynchrony. Synchronized LV pacing, multisite LV pacing, and LV endocardial pacing offer promise as novel pacing options in select patients. (J Am Coll Cardiol 2017;69:3099–114) © 2017 by the American College of Cardiology Foundation.

The incidence and prevalence of cardiac conduction disease continues to increase worldwide with the aging of the population. The number of patients receiving permanent pacemakers and their mean age have increased over the last several decades. The only effective treatment for bradyarrhythmias is cardiac pacing. Despite decades of technological advances, the optimal pacing site and pacing modes are still being debated. Although the early single-chamber ventricular pacemaker provided adequate bradycardia support, its nonphysiological nature was quickly recognized due to its adverse hemodynamic effects. The goal of physiological pacing is to provide a pacing strategy that mimics or provides a full return to normal atrioventricular (AV) activation, which should guarantee an optimal clinical outcome.

Despite maintenance of AV synchrony, dual-chamber pacing (DDD/DDDR) with a right ventricular (RV) lead positioned at the apex can be considered physiological in terms of timing between right atrial and RV activation, but it is clearly nonphysiological in terms of ventricular activation, with the creation of a left bundle branch block (LBBB)-like activation sequence. Large randomized controlled trials failed to show superiority of DDD/R pacing over single-chamber right ventricular apical (RVA) pacing with respect to death, progression of heart failure (HF), and atrial fibrillation (AF). The failure of AV sequential pacing to show benefit is multifactorial, but

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ABBREVIATIONS AND ACRONYMS

AV = atrioventricular

BVP = biventricular pacing

CRT = cardiac resynchronization therapy

HBP = His-bundle pacing

HF = heart failure

LBBB = left bundle branch block

LV = left ventricle/ventricular

LVEF = left ventricular ejection fraction

RVA = right ventricular apical

VP = ventricular pacing

largely due to ventricular dyssynchrony induced by RVA pacing. Retrospective analysis of MOST (MOde Selection Trial) showed that the risk of HF hospitalization and AF significantly increased with the cumulative ventricular pacing (VP) percent burden (1). This risk persisted, irrespective of the pacing mode (DDDR vs. VVIR) and was attributed to ventricular desynchronization induced by RVA pacing. A meta-analysis comparing atrial- and ventricular-based pacing in patients with bradycardia did not show a significant reduction in mortality or HF in more than 8,200 patients (2). There was a significant reduction in AF and a borderline reduction in stroke. The DAVID (Dual Chamber and VVI Implantable Defibrillator) trial (3) reported a composite endpoint (time to death or first HF hospitalization) hazard ratio (HR) of 1.61 in favor of single-chamber implantable cardioverter-defibrillators (ICDs) (VVI) compared with dual-chamber ICDs (DDD) in patients with left ventricular ejection fraction (LVEF) <40%. In this trial, the DDD group was ventricularly paced 60% of the time, compared with 1% in the VVI group. This study highlighted the negative consequences of ventricular desynchronization attributable to RVA pacing in patients with reduced LV systolic function. The lowest risks of HF worsening and death were observed in patients randomized to DDD/R mode, but with a low cumulative VP percent.

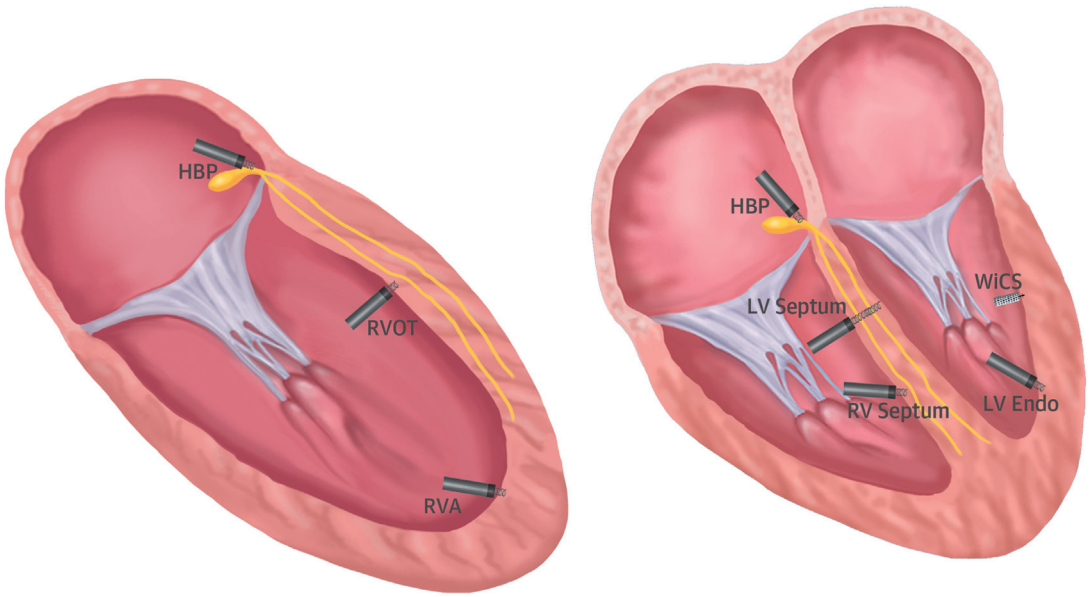
The potential mechanisms by which RV pacing increases the risk for HF and AF are not completely understood. Notably, not all patients with RV pacing experience adverse outcomes; these detrimental effects seem to be dependent on a high cumulative percentage of RV pacing. The increased risk of HF has been more frequently observed in patients with pre-existing left ventricular (LV) systolic dysfunction. In published studies of congenital complete AV block diagnosed in utero or at birth, the prevalence of dilated cardiomyopathy (DCM) ranges between 5% and ~30% after long-term permanent RV pacing (4–7). Pacing-induced dyssynchrony has been proposed as a potentially important cause of DCM in this patient group. However, doubts persist with respect to the exclusive relationship between RV pacing and the development of DCM. Indeed, in young patients paced for inherited AV block with the same high percentage of VP, but without immunological disorder, the prevalence of DCM is significantly less. The deposition of immunoglobulin G throughout the myocardium observed in postmortem immunofluorescent studies in patients with congenital AV block suggests a strong relationship between SSA/Ro and SSB/La antibodies and the development of DCM (7). It is likely that the 2 different putative mechanisms (immunopathological detrimental role played by the SSA/Ro and SSB/La antibodies + myocardial dystrophic changes and adverse remodeling caused by pacing-induced ventricular desynchronization) may interact and add up to favor the development of DCM. In the following paragraphs, we discuss strategies of physiological pacing.

CONSERVATIVE PHYSIOLOGICAL PACING STRATEGY: VP REDUCTION

There are extensive published reports on pacing reduction, and we will briefly summarize the main results and their clinical implications. Current clinical practice guidelines strongly recommend the reduction of RV pacing for patients with pacemakers implanted for sinus node dysfunction and in patients with preserved AV conduction undergoing ICD implantation (8).

In the majority of patients with sinus dysfunction (50% of the total indications for cardiac pacing), AV conduction is preserved and the ventricular activation sequence can be considered “physiological.” Thus, the strategy for “physiological” pacing in these patients is theoretically straightforward: respect the intrinsic activation to spare the pulse generator battery and avoid the potential detrimental effect of apical RV pacing. Therefore, the industry has developed dedicated algorithms with positive results, in terms of a decrease in the percentage of VP, and also with initially very promising results: a first positive study with a reduction of the incidence of AF in the group with managed ventricular pacing (Medtronic, Minneapolis, Minnesota). Subsequent results were summarized in a recent meta-analysis of 7 randomized controlled trials, which compared standard DDD programming with ventricular pacing reduction algorithms and showed no significant difference in the incidence of persistent AF, all-cause hospitalization, or all-cause mortality (9). Although VP reduction algorithms improve device longevity, one of the problems is that these algorithms can result in nonphysiological AV delays, and can potentially be proarrhythmic. Prolonged PR intervals have been shown to increase risk for AF and all-cause mortality. The managed ventricular pacing algorithm has been shown to be associated with more HF and an increased incidence of persistent AF (10). Prolonged PR intervals lead to adverse hemodynamic effects, such as shortening and impairment of LV filling, elevated left atrial pressure, reduction in atrial

CENTRAL ILLUSTRATION **Alternative Pacing Sites to Mimic Physiological Pacing**



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Various pacing sites have been evaluated in the past to reduce ventricular dyssynchrony induced by right ventricular apical pacing. Newer pacing options, such as His-bundle pacing, LV septal pacing, and LV endocardial pacing require further evaluation. Endo = endocardial; HBP = His-bundle pacing; LV = left ventricular; RV = right ventricular; RVA = right ventricular apical; RVOT = right ventricular outflow tract; WiCS = Wireless cardiac stimulation.

contribution to LV filling, and diastolic mitral regurgitation, and may trigger autonomic reflexes leading to increased sympathetic tone and symptoms of pacemaker syndrome. We conclude that the search for preserving intrinsic activation in patients with completely normal AV conduction seems logical and appropriate, but that intermediate situations (long PR intervals, intermittent AV block) may be more problematic, and there is room in these patients for permanent "physiological" VP.

ALTERNATIVE STRATEGIES FOR RVA PACING

ALTERNATIVE RV PACING SITES. Although unnecessary RV pacing can be avoided in patients with sinus node dysfunction, the need for VP led to the search for alternate pacing sites in the hope of avoiding the detrimental effects of RVA pacing. Acute hemodynamic studies have shown that individual optimization of RV pacing sites in patients with normal LV function may preserve cardiac performance (11). It had also been postulated that pacing closer to the conduction system can result in relative narrowing of the QRS interval and may be associated with reduced LV dyssynchrony (**Central Illustration**). RV septal and outflow regions have been studied in multiple small, randomized studies with conflicting results. A meta-analysis of more than 14 studies involving 754 patients comparing RV apical versus nonapical pacing suggested a higher ejection fraction in patients with RV nonapical pacing (12). This effect was primarily in studies with >12 months of follow-up and reduced LV function (ejection fraction <40% to 45%) at baseline. In the most recent, largest randomized study of RVA versus RV high septal pacing, including 240 patients with normal LV function and high-grade AV block, there were similar reductions in LVEF in both groups at 2 years of follow-up (13). There were no significant differences in HF hospitalizations, mortality, the burden of AF, or plasma B-type natriuretic peptide levels. The study also showed that septal positioning of the pacing lead is challenging, with successful placement in only 66% of patients, despite the use of a steerable delivery system.

BIVENTRICULAR PACING

Cardiac resynchronization therapy (CRT) in the form of biventricular pacing (BVP) was primarily introduced to correct pre-existing interventricular and

intraventricular conduction delays in patients with severe LV systolic dysfunction, thereby improving ventricular function. CRT was proposed to counteract the detrimental effect of LBBB and to restore a more "physiological" activation. Further studies have demonstrated differential hemodynamic and clinical effects of BVP, depending on the underlying baseline electrical substrate. It is now accepted that sufficient LV electrical conduction delay needs to be present for CRT to produce improvements in cardiac pump function. Subgroup analysis of MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) showed that only patients with LBBB derived substantial clinical benefit from CRT, and reports have shown that in patients with non-LBBB (narrow QRS interval, right bundle branch block [RBBB], nonspecific intraventricular conduction delay [NICD]), BVP can be inefficient or even harmful. Patients with narrow QRS duration demonstrate relatively uniform patterns of ventricular activation. The onset of LV activation is rapid and is mediated by Purkinje fibers, as evidenced by the consistent presence of Purkinje potentials at breakthrough sites. As a result, LV activation has a rapid, multifocal onset and reduced duration. In LBBB patients, the RV is activated early by the right Purkinje system, with a rapid and centrifugal spread of activation across the RV free wall (14). The LV is delayed and entirely activated from single breakthrough points located in the midseptal area, not preceded by Purkinje potentials, and is dependent upon cell-to-cell slow conduction with lines of slow conduction oriented in the base to apex direction. In contrast, conduction patterns are highly variable in patients with nonspecific intraventricular conduction delay with onset of LV activation mediated by Purkinje fibers, but late components of ventricular activation are distributed depending on the underlying areas of LV scar or slow conduction (15).

The electrical activation sequence observed during BVP is not dependent on baseline conduction characteristics, and BVP produces similar levels of electrical dyssynchrony, regardless of the underlying electrical substrate (16). Improvement or worsening in LV function is mostly determined by the severity of ventricular conduction impairment during baseline conduction. CRT responders show significantly higher baseline electrical dyssynchrony parameters than nonresponders, but a similar degree of electrical dyssynchrony during BVP. The mean amount of BVP-induced dyssynchrony is somewhere in between the baseline dyssynchrony values for patients with narrow QRS duration and those with LBBB.

In patients with intrinsic narrow QRS duration and little or no electrical dyssynchrony, BVP causes an iatrogenic electropathy, producing a prolongation in ventricular activation time, which worsens cardiac function and results in altered clinical outcomes. In patients with LBBB, BVP significantly reduces the different levels of dyssynchrony, but does not fully reverse the conduction impairment and does not allow a full return to "physiological" ventricular activation. Therefore, if the search for the optimal pacing site and configuration is to obtain the most "physiological" activation as possible, there appears to be significant potential for improving resynchronization therapy and developing techniques to improve the delivery of ventricular resynchronization to produce additional improvements in cardiac function.

Current guidelines indicate that CRT may be useful for patients with symptomatic HF and LVEF ≤35% who are expected to require frequent VP (>40%) after device implantation. This subject is summarized in a recent review in the *Journal* (17). However, the role of BVP in patients with AV block and a normal LVEF or only modest depression of LV function remains unsettled. The results of several studies comparing BVP and RV pacing are summarized in **Table 1** (18–25). Although the BLOCK HF (Biventricular versus RV Pacing in Heart Failure Patients with Atrioventricular Block) study reported a significant reduction in the primary outcome favoring BVP over RV pacing (19), the difference was driven primarily by an increase in LV end-systolic volume index. A limitation to this 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 reported a similar rate of the composite endpoint, which included time-to-death or first hospitalization due to HF, with a nonsignificant trend in favor of BVP (HR: 0.87; $p = 0.08$) (21). This trend persisted, still without reaching statistical significance, when patients were stratified according to their LVEF. At present, it is unclear which subgroup of patients with AV block might benefit from BVP.

Based on these 2 large randomized trials, we are left with inconclusive data on which patient populations benefit from BVP. Although BVP prevents adverse LV remodeling in patients with preserved or mildly reduced LV function compared with RVA pacing, to date there is no documented mortality benefit despite more than 5 years of follow-up.

TABLE 1 Right Ventricular Pacing Versus Biventricular Pacing in Patients With AV Block

Study (Ref. #)	Patients	Design	Endpoints	Outcomes
AV block				
PACE (18)	n = 177 LVEF >45% Bradycardia (SND, AVB)	Prospective, randomized, double-blind, multicenter CRT vs. RV 1- to 2-yr follow-up	LVEF LVESV	1-yr: 62.2% ± 7.0% vs. 54.8% ± 9.1%; p < 0.001 2-yr: 62.9% ± 8.8% vs. 53.0% ± 10.1%; p < 0.001 1-yr: 27.6 ± 10.4 ml vs. 35.7 ± 16.3 ml; p < 0.001 2-yr: 25.3 ± 10.2 ml vs. 38.3 ± 20.3 ml; p < 0.001
PREVENT HF (20)	n = 108 LVEF 54 ± 12% AV block, VP >80% NYHA functional class I, II	Prospective, 1:1 randomized, multicenter BVP vs. RVP (pacer/ICD) 12-month follow-up	Primary: change in LVEDV at 12 months Secondary: LVESV, EF, HF hospitalization, mortality	No significant differences in volumes, EF, mortality, or HF
Block-HF (19)	n = 691 LVEF <50% AV block NYHA functional class I, II, III	Prospective, randomized, multicenter BVP vs. RVP (pacer/ICD) Mean follow-up of 37 months	Primary: composite of death, urgent care visit for HF, 15% increase in LVESVI	45.8% vs. 55.6% (HR: 0.74; 95% CI: 0.60 to 0.90)
BioPace (21)	n = 1,810 Any LVEF AV block	Prospective, randomized, multicenter BVP vs. RVP Mean follow-up of 5.6 yrs	Primary: composite of time to death, HF hospitalization	HR: 0.87; 95% CI: 0.75 to 1.01; p = 0.08 Nonstatistically significant trend toward BVP
AV node ablation				
PAVE (22)	n = 184 Permanent AF AV node ablation	Prospective, randomized, multicenter, BVP vs. RVP 6-month follow-up	6-min walk QOL LVEF %	82.9 ± 94.7 m vs. 61.2 ± 90.0 m; p = 0.04 No difference 0.46 ± 0.13 vs. 0.41 ± 0.13; p = 0.03
AVAIL CLS/CRT (24)	n = 108 Refractory AF AV node ablation	Prospective, 2:2:1 randomized, BVP with CLS vs. BVP vs. RVP 6-month follow-up	LVEF, 6-min walk, QOL, mortality	LVEF improved significantly with BVP compared with baseline (56.1 ± 9.4% to 59.3 ± 7.7%; p < 0.05). No change in RV. No difference in 6-min walk, QOL, mortality
Ablate and Pace in AF (25)	n = 186 Permanent AF AV node	Prospective, randomized, multicenter, echocardiography-guided CRT vs. RVP Median follow-up of 20 months	Primary: composite of HF death, HF hospitalization	11% vs. 26%; HR: 0.37; p = 0.005 No difference in total mortality

AF = atrial fibrillation; AV = atrioventricular; AVAIL CLS/CRT = AV Node Ablation With CLS and CRT Pacing Therapies for Treatment of AF trial; AVB = AV block; BioPace = Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization; BLOCK-HF = Biventricular versus RV Pacing in Heart Failure Patients with Atrioventricular Block; BVP = biventricular pacing; CI = credible interval; CLS = closed loop stimulation; CRT = cardiac resynchronization therapy; EF = ejection fraction; HF = heart failure; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVESVI = left ventricular end-systolic volume index; NYHA = New York Heart Association; PACE = Pacing to Avoid Cardiac enlargement trial; PAVE = left ventricular-based cardiac stimulation Post AV nodal ablation Evaluation; PREVENT HF = Prevent Heart Failure; QOL = quality of life; RV = right ventricle; RVP = right ventricular pacing; SND = sinus node dysfunction; VP = ventricular pacing.

HIS-BUNDLE PACING

Electrical activation from the sinus node reaches the AV node through nonspecialized atrial tissue. The penetrating bundle of His originates from the distal AV node, runs through the inferior portion of the membranous interventricular septum, and then, in most cases, continues along the left side of the crest of the muscular interventricular septum. The proximal part of the His-bundle rests on the RA-LV part of the membranous septum and the more distal part travels along the RV-LV part of the membranous septum, immediately below the aortic root. Both the atrial and ventricular portion of the His-bundle can be accessed for permanent VP. The His-bundle is an ideal site for physiological pacing from an electrical and hemodynamic standpoint. However, the technical challenge of permanent His-bundle pacing (HBP) had been an obstacle to its reliable application in routine clinical practice. By preserving normal electrical activation of the ventricles, HBP prevents ventricular dyssynchrony and its long-term consequences. In 2000, Deshmukh et al. (26) first described permanent HBP in patients with AF and LV systolic dysfunction undergoing AV node ablation. The results of several studies using HBP, including procedural success and implant characteristics, are summarized in **Table 2** (26–34).

IMPLANT SUCCESS AND PROCEDURAL DURATION. Early investigators primarily utilized traditional stylet-driven, active fixation leads to achieve permanent HBP. The implant procedure was challenging and took a long time, even in the hands of skilled

TABLE 2 Permanent HBP Implant Characteristics

First Author, Year (Ref. #)	Patients	AV Nodal Block (Success %)	Infranodal Block	Lead Type	Delivery Sheath
Deshmukh et al. 2000 (26) (N = 18)	Chronic AF, AV node ablation, DCM	12 of 18 (66%)	0	Stylet-driven	0
Occhetta et al., 2006 (27) (N = 18)	Chronic AF, AV node ablation	16 of 18 (89%) DHBP: 25% PHP: 75%	0	Stylet-driven	0
Occhetta et al., 2007 (28) (N = 68)	AF, AV node ablation (n = 52) AV block (n = 16)	63 of 68 DHBP: 21% PHP: 79%	0	Stylet-38 SS 25	C304
Barba-Pichardo 2010 (29) (N = 182)	HBP attempted in 91 (AVB with HB recruitment with temporary pacing)	44 of 65 (68%)	15 of 26 (57%)	Stylet-driven	0
Kronborg et al., 2014 (30) (N = 38)	AV node block QRS duration <120 ms LVEF >40% Crossover, randomized	32 of 36 (85%) DHBP: 4 PHP: 28	0	SS	C304
Zanon et al., 2011 (31) (N = 307)	SSS: 126 AVB: 181	95% DHBP: 28% PHP: 72%	0	SS	C304
Vijayaraman et al., 2015 (32) (N = 67)	SSS: 40%, AVB: 60% HB IC positive: 37% HB IC negative: 63%	60 of 67 (90%) S-HBP: 45% NS-HBP: 55%		SS	C315His
Sharma et al., 2015 (33) (N = 95)	SSS: 41% AVB: 59%	75 of 95 (80%) S-HBP: 45% NS-HBP: 55%	21 of 26	SS	C315HIs
Vijayaraman et al., 2015 (34) (N = 100)	Advanced AVB AVN: 46, infranodal: 54	43 of 46 (93%) S-HBP: 44% NS-HBP: 56%	41 of 54 (76%) S-HBP 7%	SS	C315His

AVB = atrioventricular block; DCM = dilated cardiomyopathy; DHBP = direct His-bundle pacing; F = fluoroscopy duration; HB IC = His-bundle injury current; HBP = His-bundle pacing; HR = hazard ratio; NS = nonselective; P = procedure duration; PHP = para-Hisian pacing; RVSP = right ventricular septal pacing; S = selective; SS = SelectSecure; SSS = sick sinus syndrome; other abbreviations as in Table 1.

operators. However, the advent of dedicated pacing lead and delivery sheaths (SelectSecure, SelectSite C304, C315His, Medtronic) resulted in a decreased procedural duration and improved success. Several operators have demonstrated procedural and fluoroscopy duration only slightly longer than for conventional pacemakers. Some investigators had routinely used an electrophysiology mapping catheter via femoral or axillary venous access to identify the His location, which added to the perceived procedural complexity (26–31). However, it has been shown that the location of the His-bundle can be easily identified in 95% of patients without the need for a mapping catheter (32–34).

PACING CHARACTERISTICS. A major concern with HBP had been the high capture thresholds reported during the early experience. However, the use of newer delivery sheaths has resulted in improved pacing thresholds. Acute His-bundle injury current demonstrated at the time of HBP lead implant (~40% of patients) is associated with better acute and chronic His-bundle capture thresholds (32). His capture thresholds reported in recent series are comparable to LV capture thresholds obtained in CRT trials. Frank dislodgement of the HBP lead is uncommon. A significant increase in capture thresholds requiring lead revisions has been reported in up to 5% of patients (27,31,34).

DEFINITIONS. There have been several different descriptions of His-bundle capture. To provide uniformity, we proposed the following definitions on the basis of the original descriptions published by Williams et al. (35) and Deshmukh et al. (26).

Selective His-bundle pacing (S-HBP) is defined by ventricular activation occurring solely over the His-Purkinje system. S-HBP is recognized by the following criteria: 1) His-Purkinje–mediated cardiac activation and repolarization, as evidenced by electrocardiographic concordance of QRS and T-wave complexes, similar to baseline; 2) the paced-ventricular interval is almost identical to the His-ventricular interval; and 3) the local ventricular electrogram will be separate from the pacing artifact (**Figure 1**) (36). S-HBP has variably been described in published reports as direct HBP (26), pure-His pacing (27), and selective-direct HBP (37). S-HBP may result in normalization of pre-existing right or left bundle branch block with T-wave memory changes (38,39).

Nonselective His-bundle pacing (NS-HBP) was previously defined on the basis of capture of basal ventricular septum in addition to His-bundle capture (40) as: 1) no isoelectric interval between pacing stimulus

TABLE 2 Continued

Backup RV Lead	Fluoroscopy Times (Procedure)	Pacing Threshold (Implant)	Lead Failure	Clinical Outcomes
Yes	3.5 ± 1.5 h (P)	DHBP: 2.4 ± 0.9 V at 0.5 ms	2 of 12	Improved LVEF, decreased LV dimension, improved NYHA functional class
16	18 ± 9 min (F)	DHBP: 3.7 V at 0.5 ms PHP: 0.9 ± 0.7 V at 0.5 ms	1 of 16	Improved NYHA functional class, QOL, 6-min walk, electromechanical delay compared with RVA pacing
17	15 ± 8 min (F)	DHBP: 3.7 V PHP: 0.6 ± 0.3 V at 0.5 ms	3 of 68	Improved NYHA functional class, QOL, 6-min walk
15	NA	Nodal: 1.4 ± 0.6 V at 1 ms Infranodal: 1.9 ± 1.2 V at 1 ms	3 of 59	
32	23 ± 13 min (F) 85 ± 31 min (P)	DHBP: 2.3 ± 1 V at 0.5 ms PHP: 1.7 ± 1.5 V at 0.5 ms	3 of 32	LVEF 55% vs. 50% with RVSP ($p = 0.005$) at 1 yr
126 of 307 41%	S: 15 ± 9 min NS: 18 ± 13 min	DHBP: 2.5 ± 2.3 V at 0.5 ms PHP: 1.3 ± 1.3 V at 0.5 ms	4%	
0	IC+ 8.9 ± 4.0 m (F) 64 ± 10 m (P) IC− 9.5 ± 3.0 m (F) 67 ± 13 m (P)	1.16 ± 0.40 V at 0.5 ms 1.75 ± 0.70 V at 0.5 ms	1	HB IC associated with significantly lower pacing thresholds ($p < 0.05$)
0	12 ± 8 min (F) 79 ± 25 min (P)	1.35 ± 0.9 V at 0.5 ms	3%	Improved HF hospitalizations compared with RVP (2% vs. 15%; $p = 0.02$) No difference in mortality (13% vs. 18%; $p = 0.45$)
BVP 6	11 ± 6 min (F) 71 ± 21 min (P)	1.4 ± 1.0 V at 0.5 ms	5%	

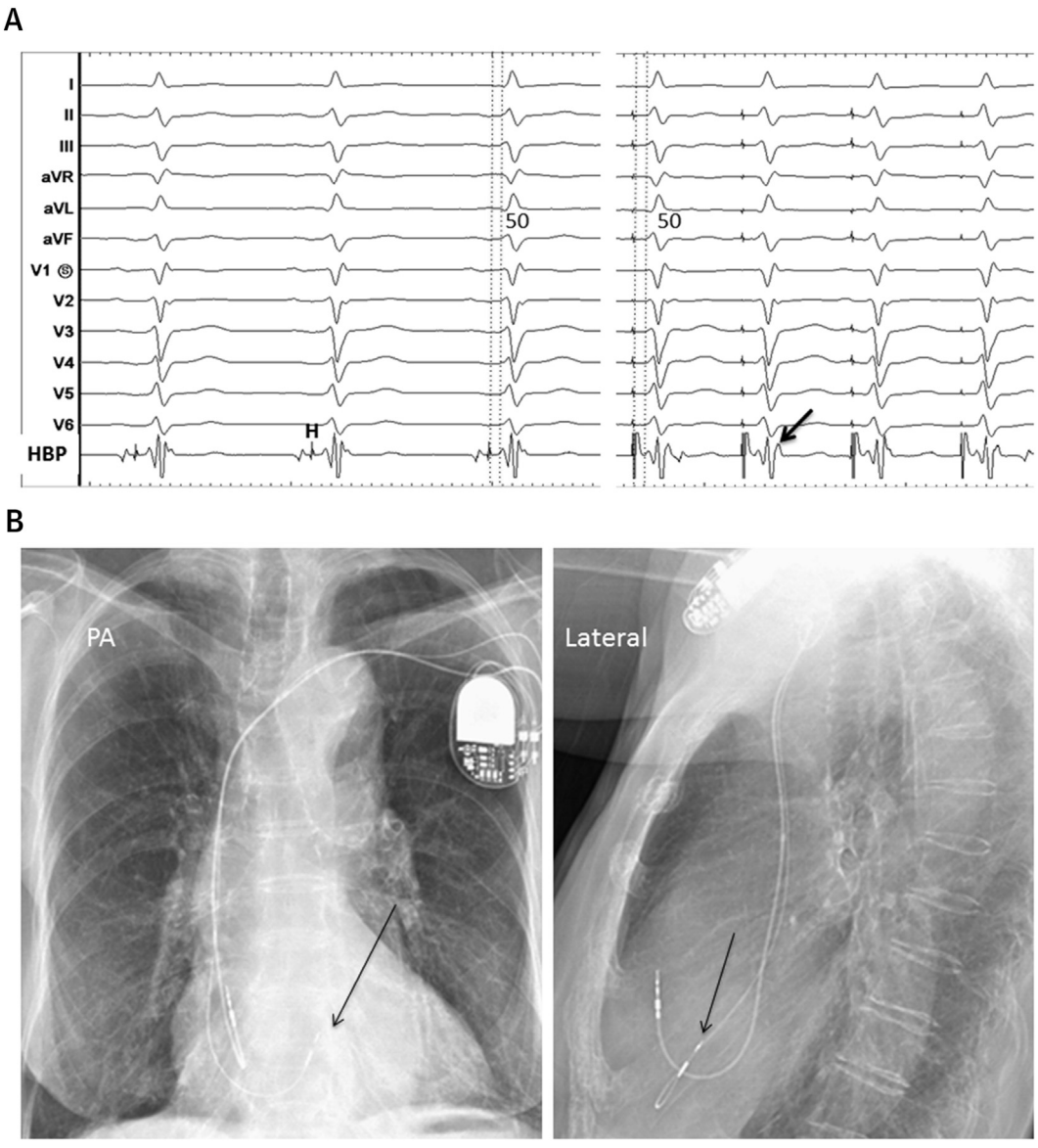
and QRS complex; 2) recording His-bundle electrograms on the pacing lead; 3) the electrical axis of the paced QRS complex must be concordant with the electrical axis of the spontaneous QRS (if known); 4) narrowing of the QRS complex at higher output due to fusion between the RV and His-bundle capture and widening of the QRS complex at lower output due to loss of His-bundle capture or vice versa; and 5) the local ventricular electrogram is pulled close to the pacing stimulus due to local myocardial capture (36). Paced QRS complexes may be narrower than the baseline rhythm (e.g., possibly due to latent capture of fascicles or ventricular fusion) in the setting of preexisting bundle-branch block (BBB) or infranodal AV block. NS-HBP has variably been described in the published data as para-Hisian pacing (26), pure para-Hisian pacing (27), and nonselective-direct HBP (37). Significant confusion still exists regarding para-Hisian pacing, as several investigators do not report actual HBP thresholds (the lowest pacing output at which QRS narrowing occurs) that may be higher than the RV capture threshold. To avoid confusion, when His-bundle capture is present with fusion, it should be referred to as nonselective HBP and both HB and RV capture thresholds specified (**Figures 2 and 3**).

AV BLOCK. Early studies of HBP focused on patients undergoing AV nodal ablation. Subsequent investigators have attempted permanent HBP in patients with spontaneous nodal and infranodal AV block with varying success. Kronborg et al. (30) achieved successful permanent HBP in 85% of patients with high-grade AV nodal block and narrow QRS complex. In a recent series of 100 patients with advanced AV block (34), HBP was successful in 84% of patients (93% of AV nodal block and 76% of infranodal block). A high percentage of patients with infranodal (HV) block were noted to have intra-Hisian block.

BUNDLE BRANCH BLOCK. The concept of functional longitudinal dissociation of the His-bundle was first proposed by Kaufman and Rothberger in 1919 (41). They suggested that normal conduction in the HPS was mediated by specific pathways starting in the AV junction that connected to specific right or left ventricular Purkinje-muscle junctions. Narula (42) reported that BBB pattern or axis deviation may result from a lesion within the bundle of His itself. He also demonstrated the LBBB pattern could be corrected in a series of 25 patients with temporary pacing at a slightly distal site in the His-bundle. Vijayaraman et al. (43) reported that permanent HBP corrected underlying BBB in 82% of patients undergoing permanent pacemaker implantation for standard indications (RBBB in 29 of 31; LBBB in 11 of 14; IVCD in 1 of 5) (**Figures 4 and 5**). In a recent study, Lustgarten et al. (44) reported that in 21 of 29 patients (72%) with cardiomyopathy (ischemic 13, nonischemic 16) and BBB (LBBB 28, atypical RBBB 1), HBP significantly narrowed the QRS at implant.

HEMODYNAMICS. Although the deleterious effects of RV apical pacing are well-established, insufficient data exist supporting the beneficial effects of permanent HBP. Because of the early report of HBP

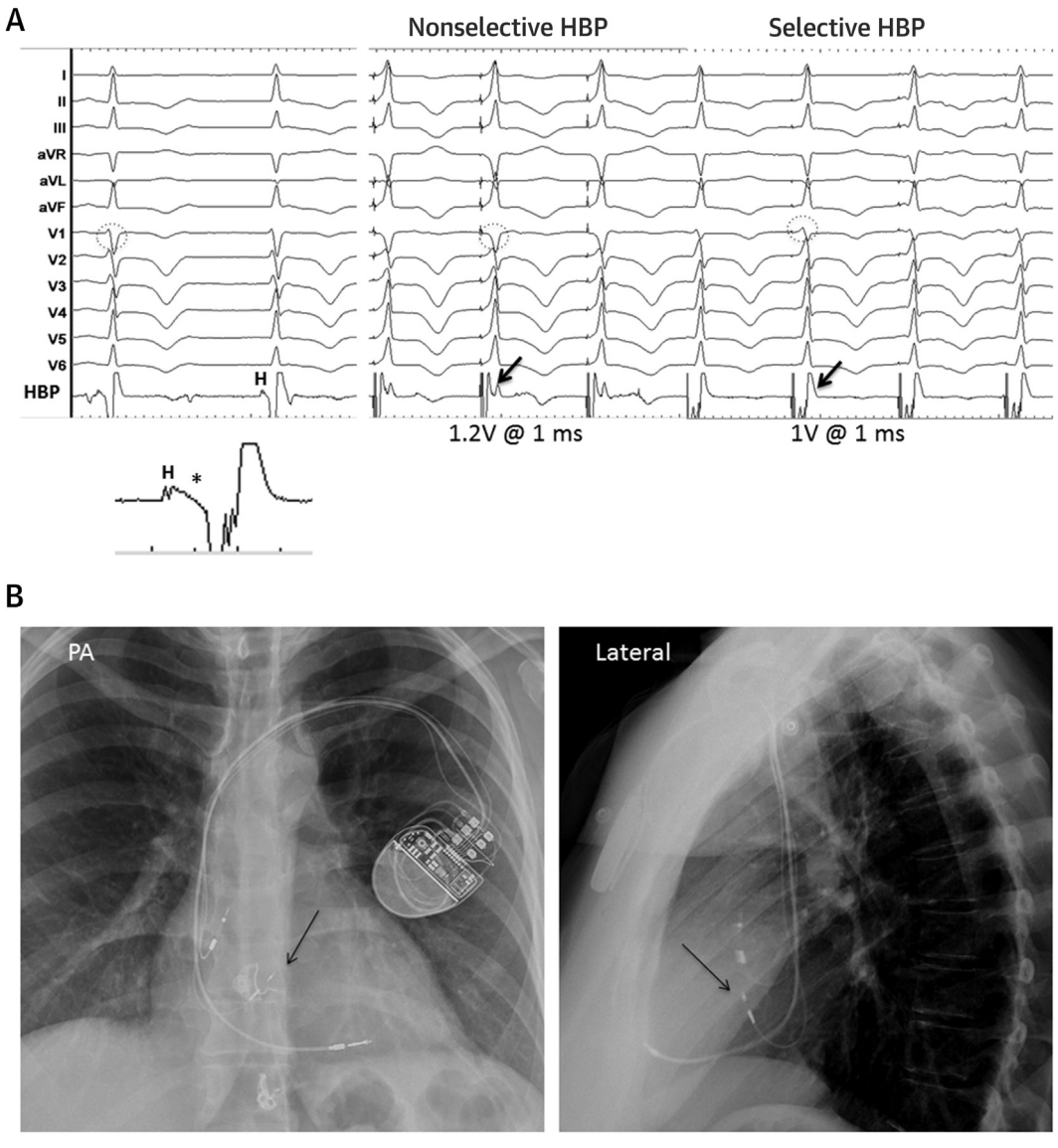
FIGURE 1 Selective HBP



(A) The 12-lead electrocardiogram and intracardiac electrogram from HBP lead (Medtronic 3830) after fixation is shown. Pacing from HBP lead results in QRS complexes identical to the intrinsic rhythm with stimulus to QRS interval of 50 ms, similar to the baseline HV interval. Note the separation of the ventricular electrogram from the pacing stimulus in the HBP electrogram **(arrow)**. **(B)** Chest x-ray of HBP lead. PA and lateral chest x-ray images of the HBP lead **(arrows)** from the same patient. H = His; HBP = His-bundle pacing; PA = posteroanterior.

resulting in improvement in LVEF, other studies have shown increases in oxygen uptake, exercise duration, and anaerobic threshold compared with RV apical pacing (19,20). HBP has been shown in small studies to significantly improve exercise tolerance, New York Heart Association (NYHA) functional class, LVEF, and mitral and tricuspid regurgitation compared with RVA pacing (27,30). In a recent case-control study, Sharma et al. (33) reported that HBP was associated with a significant reduction in HF hospitalizations compared with RV pacing in patients with >40% ventricular pacing (2% vs. 15%; $p = 0.02$) over a 2-year follow-up. There are no long-term, randomized controlled studies currently evaluating clinical outcomes and mortality that compare HBP and RV pacing in patients with pacemakers.

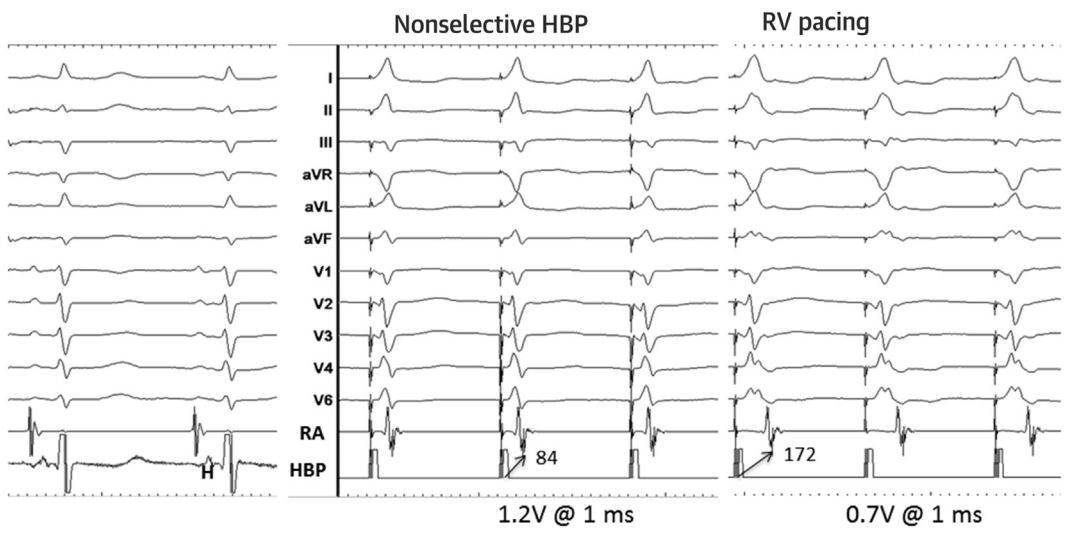
FIGURE 2 **Nonselective HBP**



(A) The **left panel** shows the baseline 12-lead electrocardiogram of a patient with congenital complete AV block and narrow QRS rhythm. The **middle panel** shows nonselective HBP with minimal RV fusion **(dotted circle)** during pacing at 1.2 V. As the pacing output is decreased to 1 V, there is loss of RV capture but persistent selective His-bundle capture and QRS morphology identical to the escape rhythm **(right)**. **(*)** A magnified view of the His-bundle electrogram with current of injury. During nonselective HBP, the **arrow** shows the local ventricular electrogram pulled close to the stimulus in HBP lead, suggesting local myocardial capture compared with the separation observed during selective HBP. **(B)** PA and lateral chest x-ray images of the RA, RV, and H **(arrows)** leads from the same patient. AV = atrioventricular; RA = right atrial; RV = right ventricular; other abbreviations as in Figure 1.

CARDIAC RESYNCHRONIZATION THERAPY. Although BVP is effective in 60% to 70% of patients with severe LV dysfunction and QRS prolongation, it has not been shown to improve outcomes in 30% to 40% of patients (nonresponders). Functional dissociation in the diseased His-Purkinje tissue and the ability of HBP to narrow QRS duration in patients with chronic bundle branch block has allowed several investigators to study the effect of HBP in this population. In a group of patients with refractory HF and QRS duration >120 ms in whom LV lead placement was unsuccessful, Barba-Pichardo et al. (45) were

FIGURE 3 Nonselective HBP



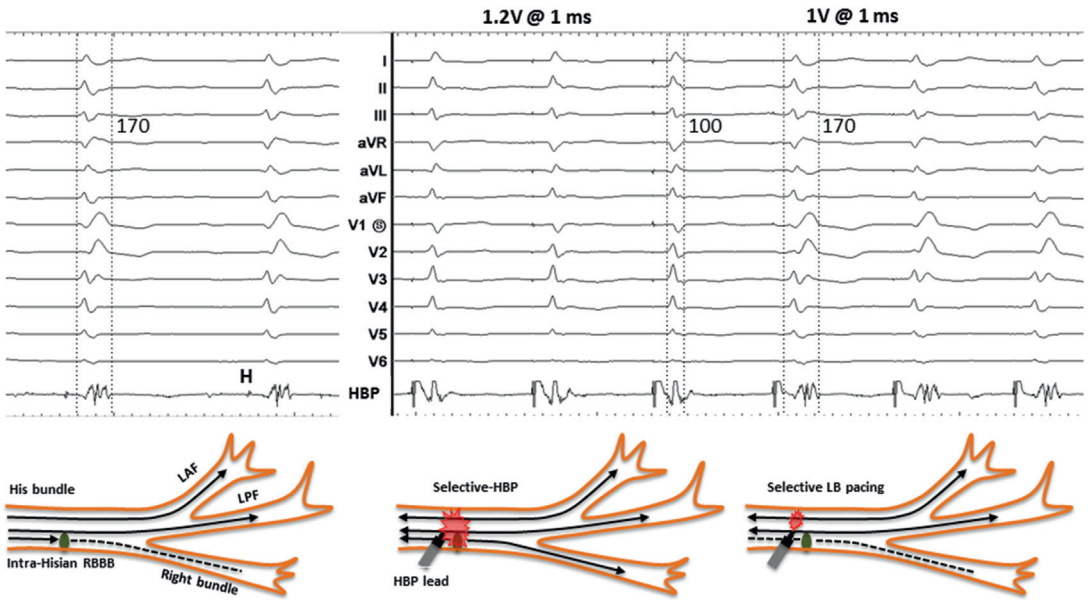
The 12-lead electrocardiograms, intracardiac electrograms from the RA and HBP lead at baseline **(left)**, during pacing at an output of 1.2 V at 1 ms **(middle)**, and at 0.7 V at 1 ms **(right)** are shown. Note that the electrical axis of the paced QRS complex is concordant with the baseline QRS complex **(middle)**. There is no isoelectric interval between the pacing stimulus and QRS complex. The resultant QRS complex is due to fusion between conduction through the His-bundle and basal RV myocardial capture. The His-bundle capture threshold was 1.2 V at 1 ms. The **right panel** shows only myocardial capture without conduction through the His-bundle. The RV capture threshold was 0.6 V at 1 ms. During nonselective HBP, the stimulus to atrial interval is 84 ms **(arrows)**, and with the loss of His-bundle capture, the stimulus-atrial interval is prolonged to 172 ms. Abbreviations as in Figures 1 and 2.

successful in resynchronizing the LV by S-HBP in 9 of 13 patients, with resultant improvement in LV function and NHYA functional class. Lustgarten et al. (44) evaluated the role of permanent HBP in 29 patients with severe LV dysfunction and LBBB in a 6-month crossover study of HBP and BVP. A total of 12 patients completed this crossover comparison study. At 1 year, HBP showed improvement in NYHA functional class, quality of life, 6-min walk distance, and LVEF compared with baseline and was equivalent to BVP. Su et al. (46) recently reported the feasibility of permanent HBP in a group of 38 patients with severe LV dysfunction (25 patients with LBBB and failed LV lead implantation, 13 patients with AF and AV node ablation). They reported a significantly lower capture threshold for correcting LBBB with the His tip-RV coil configuration compared with the bipolar His tip-ring configuration (1.99 ± 0.85 V vs. 2.85 ± 1.11 V at 0.5 ms; $p < 0.0001$).

HBP has the potential to improve outcomes in patients with advanced HF in whom traditional BVP has not been shown to be beneficial (Figure 6). In patients with a non-LBBB, BVP may not be effective. The amount of LV dyssynchrony invoked by non-physiological pacing is offset by any potential benefit from narrowing the QRS complex. However, in a subgroup of these patients with a prolonged PR interval (>230 ms), CRT was associated with a 73% reduction in the cumulative risk of HF and/or death (47). In patients with narrow QRS intervals (<130 ms) and cardiomyopathy, CRT did not result in improvement in exercise capacity, quality of life, NYHA functional class, or LV indexes (48). Recently, Sohaib et al. (49) presented acute hemodynamic data in 16 patients with LV dysfunction (narrow QRS complexes 13, RBBB 3) and prolonged PR interval (>200 ms) during AV synchronous HBP. They demonstrated a mean increment of 4.1 ± 3.8 mm Hg in systolic blood pressure (BP) with HBP, comparable to a 4.3 ± 4.2 mm Hg increment in systolic BP with BVP. There was no change in systolic BP during RV pacing. HBP has the potential to improve clinical outcomes in this subgroup of patients by correcting underlying RBBB and optimizing AV delay without causing new ventricular dyssynchrony.

FUTURE OF HBP. Despite recent advances in HBP, many questions and concerns remain. Permanent HBP is a reasonable option for physiological pacing in several groups of patients listed in Table 3. Although HBP is feasible in patients with infranodal and

FIGURE 4 HBP in a Patient With Chronic RBBB



The 12-lead and HBP electrograms are shown at baseline **(left)**. **(Right)** During pacing at 1.2 V at 1 ms, there is selective HBP with complete normalization of the baseline RBBB, with a decrease in QRS duration from 170 to 100 ms. At 1 V, there is loss of right bundle capture, with resultant QRS morphology identical to baseline, with conduction only through the left bundle. A schematic representation of BBB and selective capture of His-bundle is shown at the **bottom**. BBB = bundle branch block; HBP = His-bundle pacing; LAF = left anterior fascicle; LB = left bundle; LPF = left posterior fascicle; RBBB = right bundle branch block.

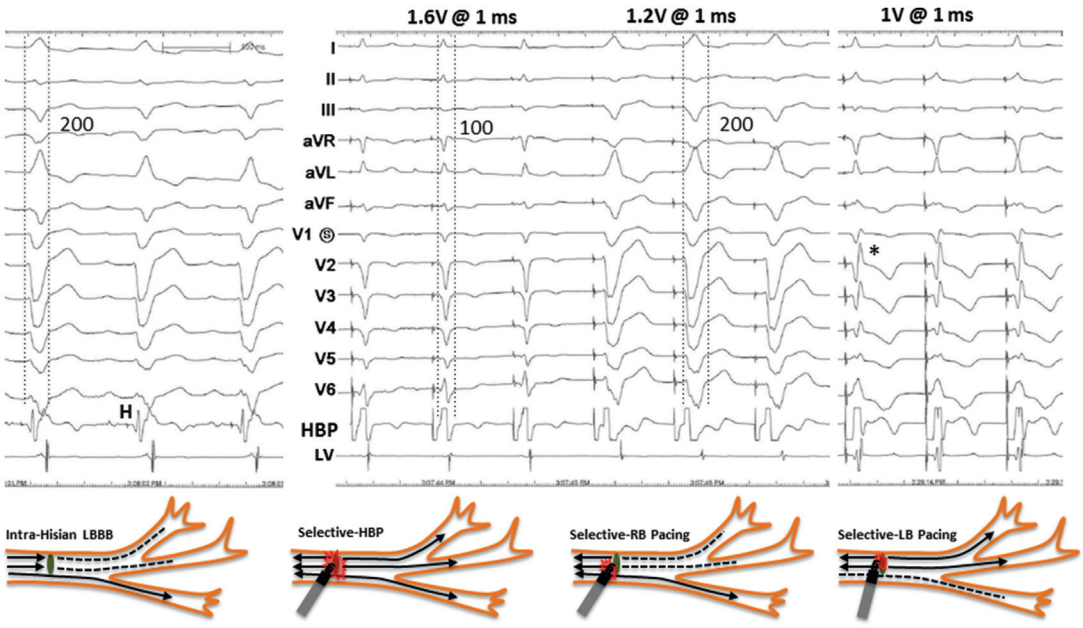
intra-Hisian AV block, the long-term safety of this approach has not been well studied. Do patients with infranodal AV block and HBP require a backup RV lead? Although S-HBP is aesthetically more appealing, our experience suggests that it is often constrained by difficult to predict/characterize anatomic variation (50,51). Preliminary evidence from small studies suggests that NS-HBP is also associated with acute hemodynamic benefits similar to S-HBP. However, larger, longer-term clinical studies are necessary to prove improved clinical outcomes (LV function, HF, mortality, among others) compared with RV pacing or BVP. Given higher pacing thresholds in the His-bundle region, further improvements in delivery systems, leads, and devices must be engineered to make HBP the physiological pacing of choice. The long-term performance of HBP in patients with traditional CRT indications needs to be further studied.

NOVEL ALTERNATE PACING OPTIONS

BVP PROGRAMMING. AV delay optimization is an important concept, and attempts to optimize the timing between left atrial and LV activation to obtain the best hemodynamic results. Algorithms to optimize AV intervals have been developed by different manufacturers, although no clinical trials show a benefit over empiric AV interval programming (52). A new idea about programming of the AV delay has been proposed: most patients with LBBB demonstrate a "normal and physiological" activation of the RV, and late and dyssynchronous LV activation. The concept of the Adaptiv CRT (aCRT, Medtronic) is not to optimize AV delay to obtain optimal filling, but to adjust the AV delay to respect the physiological activation of the RV and obtain fusion between a spontaneous RV activation and a paced LV. This is another demonstration of the quest for physiological pacing: respect as much as possible of what can be considered physiological (RV activation) (53). In a study of 478 patients, the risk of death or HF hospitalization was significantly reduced in patients with >50% synchronized LV pacing compared with patients with <50% synchronized LV pacing (HR: 0.49; 95% CI: 0.28 to 0.85; p = 0.012).

Multipolar LV leads have recently become available for clinical use to provide BVP. The availability of multiple electrodes in the coronary sinus branch greatly increases the options for lowering the LV

FIGURE 5 HBP in a Patient With Chronic LBBB



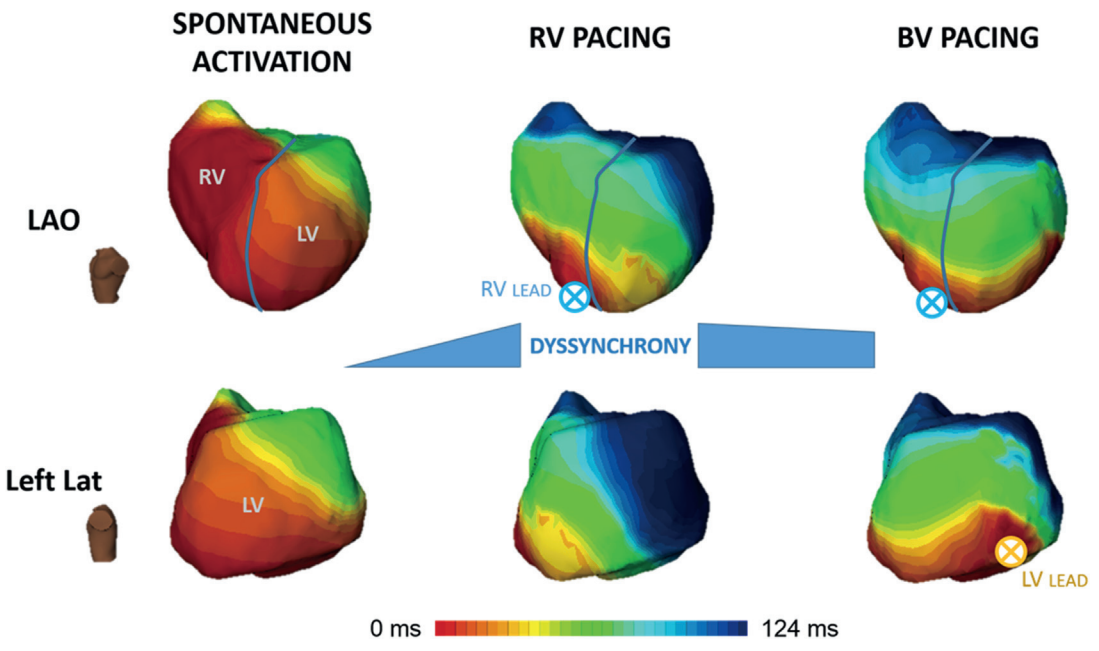
(Left) The 12-lead electrocardiogram in a patient with chronic LBBB and QRS duration of 200 ms, along with electrograms from the HBP lead and LV lead. During pacing at 1.6 V at 1 ms, there is selective HBP with output-dependent recruitment of the left bundle and QRS duration of 100 ms. QS complexes in V_1 to V_4 suggest underlying old anteroseptal myocardial infarction. At a pacing output of 1.2 V, there is loss of left bundle capture, with resultant LBBB identical to native QRS complexes. **(Right)** Several min later, during threshold testing, selective left bundle capture with RBBB morphology is shown **(*)**, likely due to resolution of local edema and/or change in orientation of the lead. A schematic representation of BBB and selective capture of the His-bundle are shown at the **bottom**. LB = left bundle; LBBB = left bundle branch block; RB = right bundle; other abbreviations as in Figure 4.

pacing threshold, avoiding phrenic stimulation, and stimulating a large area of the latest activated LV. In addition, studies show acute hemodynamic benefit associated with multisite pacing compared with standard BVP, with multiple LV stimulation sites along a single quadripolar lead to capture a larger region of excitable myocardium (54). Recent non-randomized studies have shown better clinical response compared with optimal single-site LV lead pacing (55). In addition, multipoint pacing was associated with greater LVEF at 6 months compared with standard BVP (56). Further prospective, large studies of multipolar pacing are in progress.

LV SEPTAL PACING. Studies in animals have shown that pacing at the LV septum (LVS) yields LV pump function closely approximating that during normal ventricular conduction and significantly better than that during right ventricular septum (RVS) pacing, suggesting recruitment of the normal specialized conduction system. Mafi-Rad et al. (57) recently published a study of the acute hemodynamic effects of RVA (A), RVS (S), and LVS pacing by invasive rate of LV pressure rise ($LVdP/dt_{max}$) measurements in 10 patients undergoing pacemaker implantation for sinus node dysfunction. A custom pacing lead with an extended helix (4 mm) was introduced via the left subclavian vein, and after positioning against the RVS using a pre-shaped guiding catheter, it was driven through the interventricular septum to the LVS. The QRS duration was shorter during LVS pacing (144 ± 20 ms) than during RVA (172 ± 33 ms; $p = 0.02$ vs. LVS) and RVS pacing (165 ± 17 ms; $p = 0.004$ vs. LVS). RVA and RVS pacing reduced $LVdP/dt_{max}$ compared with baseline atrial pacing (−7.1 ± 4.1% and −6.9 ± 4.3%, respectively), whereas LVS pacing maintained $LVdP/dt_{max}$ at baseline levels (1.0 ± 4.3%; $p = 0.001$ vs. RVA and RVS). The findings from this study require confirmation in large prospective studies.

LV ENDOCARDIAL PACING. Endocardial LV pacing appears to provide a more physiological electrical activation of the LV, with the activation spreading from the endocardium to the epicardium, and might be less arrhythmogenic than epicardial stimulation. Indeed, in some patients, the onset of LV

FIGURE 6 Mapping of Ventricular Electrical Activation



Electrocardiographic maps (CardioInsight Technologies Inc, Cleveland, Ohio) of a single heart failure patient presenting with a narrow QRS duration (115 ms) during spontaneous conduction **(left)**, RV pacing **(middle)**, and BVP **(right)**. He was resynchronized (+ His ablation) because he demonstrated episodes of rapidly conducted atrial fibrillation. For comparison purposes, all maps referred to the same relative scale of 124 ms. The spontaneous activation is driven by the His-Purkinje system and results in short LV and total ventricular activation times (55 and 60 ms, respectively). VDD (80 ms AVD) and RV apical pacing results in major alteration of the ventricular activation, with lengthening of both the LV and total ventricular activation times (104 ms). The addition of a LV posterolateral pacing site to apply BVP reduces the LV activation time (88 ms), but not the total activation time (103 ms) compared with RV pacing. Comparison with spontaneous activation shows that BVP does not fully reverse the conduction impairment induced by RV pacing. This figure demonstrates the detrimental effect of apical RV pacing on different levels of ventricular dyssynchrony and the beneficial, but incomplete, effect of BVP, causing an intermediate level of dyssynchrony between the narrow QRS interval and RV pacing. AVD = AV delay; BVP = biventricular pacing; LAO = left anterior oblique view; Left Lat = left lateral view; LV = left ventricular; RV = right ventricular.

TABLE 3 Current Candidates for Consideration of Permanent HBP

AV nodal block: second- and third-degree block
Infranodal, intra-Hisian AV block
Atrial fibrillation and slow ventricular response
Sinus node dysfunction and marked first-degree AV block (PR interval >240 ms)
AV nodal ablation (especially if EF <40%)
Any patient with anticipated need for high burden of RV pacing, especially if EF <40%-50%
ICD-eligible patients with previously-listed indications and high RV pacing burden (>40%)
CRT-eligible patients with LBBB who failed LV lead placement
CRT nonresponder: especially RBBB

LBBB = left bundle branch block; RBBB = right bundle branch block; other abbreviations as in Tables 1 and 2.

epicardial stimulation causes the development of polymorphous ventricular arrhythmias, as it reverses the LV transmural activation sequence. Furthermore, a transseptal LV endocardial approach allows a free choice of stimulation site, as opposed to being constrained by the anatomy of the coronary sinus, with the possibility of screening different pacing locations in an attempt to determine the position that results in the greatest improvement in cardiac function. Hemodynamic acute studies in animals and in patients with heart failure are promising (58-60).

ALSYNC (ALternate Site Cardiac ResYNChronization) was an international, multicenter, prospective study to evaluate the clinical feasibility and safety of LV endocardial pacing using a single-incision, pectoral, atrial transseptal approach to lead delivery in CRT-indicated patients for whom conventional CRT

had failed or was unsuitable (61). The ALSYNC study showed promising results, but a high rate of complications related to stroke and transient ischemic attack argues strongly against this being a widely-used clinical strategy.

PHYSIOLOGICAL ATRIAL PACING

During sinus rhythm, the right and left atria are activated nearly simultaneously, with spread of activation occurring over preferential pathways, such as Bachman's bundle, limbus fossa ovalis, and coronary sinus musculature. Atrial conduction disorders in the form of intra-atrial or interatrial conduction delays are well-known predisposing factors for the development and maintenance of AF (62). Right atrial appendage pacing can result in significant left atrial conduction delay and lead to left AV dyssynchrony. This may play a major role in CRT patients with atrial conduction delay, resulting in suboptimal AV timing and nonresponse to CRT. Acute hemodynamic studies have shown favorable atrial hemodynamics and improved left AV synchrony during biatrial pacing (63). Bachman's-bundle pacing may be effective in attenuating the progression of AF (64), especially in patients with underlying atrial conduction delays, but have not been found to be effective in prevention of AF (65). Optimal physiological atrial pacing site(s) have not been fully evaluated in large, randomized controlled clinical trials.

CONCLUSIONS

Findings from several clinical studies have confirmed the need to avoid unnecessary RVA pacing, especially in patients with normal intrinsic AV conduction or intermittent AV block. However, in patients requiring ventricular pacing, especially those at risk for HF, alternate pacing options should be pursued. Although HBP is the most physiological form of pacing, its long-term safety, efficacy, and clinical superiority over traditional RV pacing needs to be fully established with large, randomized clinical trials. Similarly, in patients requiring CRT, the role of novel LV pacing options, such as multisite pacing and LV endocardial pacing, needs to be further established by carefully designed studies. Optimal atrial pacing site(s), especially in patients with underlying atrial conduction delays and requiring CRT, need further evaluation.

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