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ORIGINAL ARTICLE

His bundle pacing and left bundle branch area pacing: Feasibility and safety

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Abstract
Introduction and objectives: There has been increasing interest in pacing methods that provide physiological stimulation, such as His bundle pacing (HBP) or left bundle branch area pacing (LBBAP). Our goal was to assess the feasibility and safety of these techniques.
Methods: Prospective observational single-center study evaluating 46 patients with indication for a pacemaker that attempted HBP or LBBAP from July 2020 to November 2021. Procedural endpoints and pacing parameters were assessed and compared at implantation and three-month follow-up.
Results: Overall acute procedural success was achieved in 96% of the cases. Successful HBP was achieved in 91% of the patients and all patients for LBBAP. During implantation, HBP patients presented a higher capture threshold (0.80 [0.55–1.53] V vs. 0.70 [0.40–0.90] V, p=0.08) and lower R-wave amplitude (4.0 [2.9–6.2] mV vs. 7.8 [5.5–10.5] mV, p=0.001) compared to LBBAP patients. There was no difference between groups, either acutely or at 3-months, regarding paced QRS duration (125±22 ms vs. 133±16 ms, p=0.08; 118±16 ms vs. 124±14 ms, p=0.19). Although procedural time was similar with both techniques (95 [75–139] min vs. 95 [74–116] min, p=0.79), fluoroscopy time was significantly reduced during LBBAP (8.1 [5.3–13.4] min vs. 4.1 [3.1–11.3] min, p=0.05). At 3 months of follow-up, the pacing threshold remained with a stable profile in HBP as in LBBAP (1.25 [0.75–2.00] V, p=0.09 and 0.60 [0.50–0.80] V, p=0.78), respectively. The need for re-intervention occurred in 3 (6.5%) HBP cases during follow-up.
Conclusion: This first national study demonstrates the feasibility and safety of the HBP and LBBAP in patients with pacemaker indication.

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PALAVRAS-CHAVE
Pacing do feixe His;
Pacing da área do ramo esquerdo;
Pacing fisiológico

Pacing do Feixe de His e _pacing_ da área do ramo esquerdo: viabilidade e segurança

Resumo
Introdução e objetivos: Tem havido um interesse crescente em métodos de *pacing* que promovem uma estimulação fisiológica, como o *pacing* do feixe de His (HBP) ou da área do ramo esquerdo (LBBAP). O nosso objetivo foi avaliar a viabilidade e segurança destas técnicas.
Métodos: Estudo prospetivo, de um único centro, avaliando 46 doentes submetidos a implantação de HBP ou LBBAP de julho/2020 a novembro/2021. *Endpoints* relacionados com o procedimento e parâmetros de *pacing* foram comparados na implantação e aos três meses.
Resultados: Sucesso na implantação ocorreu em 96% dos casos. No implante, o grupo HBP apresentou limiares superiores (0,80 [0,55-1,53] V *versus* 0,70 [0,40-0,90] V, p=0,08) e amplitude de onda R menor (4,0 [2,9-6,2] ms *versus* 7,8 [5,5-10,5] ms, p=0,001) comparativamente com o grupo LBBAP. Apesar de o tempo de procedimento ter sido semelhante (95 [75-139] min *versus* 95 [74-116] min, p=0,79), o tempo de fluoroscopia foi significativamente menor no grupo LBBAP (8,1 [5,3-13,4] min *versus* 4,1 [3,1-11,3] min, p=0,05). Não houve diferença na duração do QRS depois de *pacing* na implantação (125±22 *versus* 133±16 ms, p=0,08) ou aos três meses (118±16 ms *versus* 124±14 ms, p=0,19). Aos três meses, o limiar permaneceu estável, quer no grupo de HBP quer no de LBBAP (1,25 [0,75-2,00] V, p=0,09 and 0,60 [0,50-0,80] V, p=0,78, respetivamente). Em três casos (6,5%), houve necessidade de reintervenção (deslocamento de eletrodos ou elevação dos limiares) durante o *follow-up*.
Conclusão: Este primeiro estudo nacional demonstra a viabilidade e segurança do HBP e LBBAP em doentes com indicação para *pacemaker*.

Introduction

Cardiac pacing is an effective therapy for patients with conduction tissue disease.[1] Right ventricular apical pacing (RVAP) has been widely used for decades for the management of bradyarrhythmias. However, it causes electric and mechanical desynchrony, and is associated with an increased risk for heart failure and atrial fibrillation (AF).[2,3]

Recently, His bundle pacing (HBP) has been performed as a strategy to prevent the deleterious effect of RVAP. By stimulating the His-Purkinje system, HBP secures a more physiologic electrical activation of both ventricles and may avoid marked desynchrony. However, several challenges remain when performing HBP, like the difficulty to identify the His location in some patients, a high and unstable pacing threshold, a low R-wave amplitude, large atrial signals, and heart block distal to pacing site.[4] Therefore, a more stable physiological pacing approach has been assessed – left bundle branch area pacing (LBBAP).[5] However, there is a lack of national data concerning these physiologic pacing strategies.

The purpose of this study was to report the initial experience of a national center in HBP and LBBAP.

Methods

Study design and setting

Prospective single-center, observational study of patients referred for pacemaker or cardiac resynchronization therapy (CRT) implantation from July 2020 to November 2021. HBP was attempted from July 2020 to April 2021 and LBBAP from May 2021 to November 2021. Patient baseline demographic data and procedural characteristics (procedural success, lead/delivery equipment, fluoroscopy time and dosage, pacing thresholds, sensing, impedance, and programmed stimulation energy) were recorded.

All patients provided written informed consent. The study complied with the Declaration of Helsinki and the study protocol was approved by the institutional ethics committee.

Patient eligibility criteria

Patients with indication for *de novo* permanent pacemaker implantation according to the current guidelines were eligible for inclusion in the study.[1] Clinical indications for HBP/LBBAP were classified into four categories: (a) intermittent/permanent AV block (including Mobitz type II second-degree AV block and complete heart block); (b) sinus node dysfunction (SND, including tachy-brady syndrome); (c) slowly conducted AF; and (d) CRT. Exclusion criteria included: age <18 years, patients with previous cardiac devices, patients with indication for implantable cardioverter-defibrillator (ICD), and patients with less than three months of follow-up.

Procedural details

All procedures were performed under local anesthesia. In patients under vitamin K antagonists (VKA), anticoagulation was continued in the peri-procedural period with an

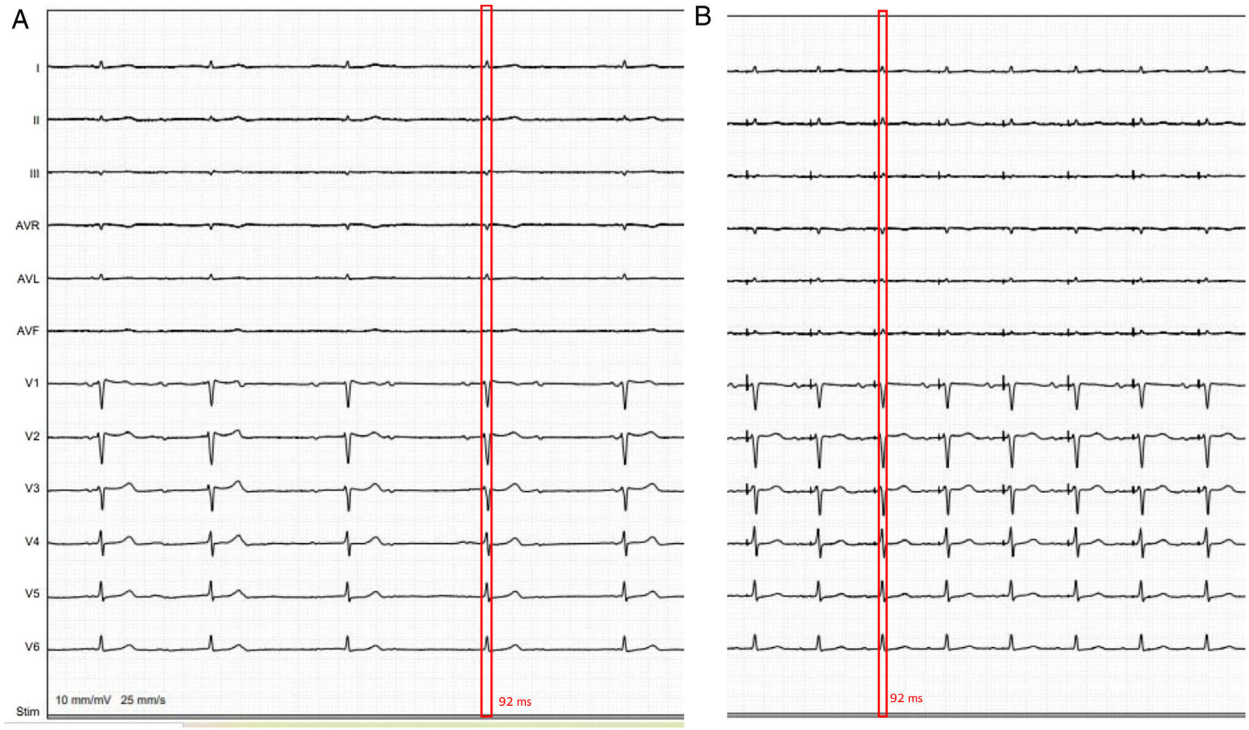

Figure 1 Selective His bundle pacing. (A) The 12-lead basal electrocardiogram at 25 mm/s demonstrating complete atrioventricular block, with a QRS 92 ms (inside red bars) and (B) after selective His bundle pacing, showing a paced QRS of 92 ms with the same morphology of native QRS (inside red bars).

international normalized ratio within 2.0–2.5 range. In patients taking non-VKA, the last drug dose was omitted.

All electrograms were displayed on an Electrophysiology recording system (EP-TRACER 2 Portable, Schwarzer Cardiotek). An experienced operator was present during all cases.

His bundle pacing procedure

His bundle pacing was performed using the Select Secure model 3830 (Medtronic Inc., Minneapolis) pacing lead delivered through a fixed (C315HIS) or steerable (C304-HIS) (Medtronic Inc., Minneapolis) dedicated delivery sheath as previously described.[6,7] Briefly, the delivery sheath was inserted into the right ventricle near the tricuspid annulus over a guidewire through the subclavian vein. The pacing lead was then advanced until the screw was beyond the tip of the catheter. The His bundle electrogram was identified by mapping the atrioventricular septum and subsequently the lead was screwed with clockwise rotations. No backup lead was used. Pacing response was categorized as selective or non-selective HBP according to previously defined criteria.[6,7] Selective HBP was considered if: (a) the pacing stimulus to QRS (S-QRS) onset interval was equal to the native His-QRS onset interval (H-QRS); (b) the local ventricular electrogram was not captured by the pacing stimulus, with the stimulus to local ventricular (S-V) activation time on the pacing lead being equal to the His to local ventricular (H-V) activation time (S-V≅H-V) or the difference between the two intervals was less than 10 ms; and (c) the paced QRS morphology was the same as the native QRS morphology (except in cases with correction of the His-Purkinje conduction disease, where the paced QRS is smaller than the native QRS) (Figure 1).[6,7] Non-selective HBP was recognized if: (a) S-QRS interval was equal to zero, due to the presence of a pseudo-delta wave, and the stimulus to the end of QRS (S-QRS end) is ≤H-QRS end; (b) the local ventricular electrogram was directly captured by the pacing stimulus; (c) the paced QRS duration was longer than the native QRS duration by the H-QRS interval[6,7] (Figure 2).

Left bundle branch area pacing procedure

Left bundle branch area pacing was performed using the Select Secure model 3830 (Medtronic Inc., Minneapolis) pacing lead delivered through the C304-HIS steerable sheath (Medtronic Inc., Minneapolis). The delivery sheath was inserted into the right ventricle near the tricuspid annulus over a guidewire through the subclavian vein. The pacing lead was then advanced until the screw was beyond the tip of the catheter. The His bundle electrogram was first mapped and recorded, and subsequently, the tip of the pacing lead was moved 1.5 cm towards the apex of the right ventricle. In the right anterior oblique 30° position, while pace-mapping at 5 V at 1.0 ms at unipolar pacing, the ideal pacing site was searched according to the presence in lead V1 of a ''W'' morphology with a mid-notch.[8] While screwing in clockwise rotation, the notch migrated towards the end of the QRS wave and the stimulus-to-peak LV activation time (S-LVAT), defined as the duration between the spike and peak of ventricular activation in lead V6, started to decrease their duration. The following criteria were used to confirm capture of the left bundle branch: a paced QRS of right bundle branch conduction delay pattern, and at least one of the

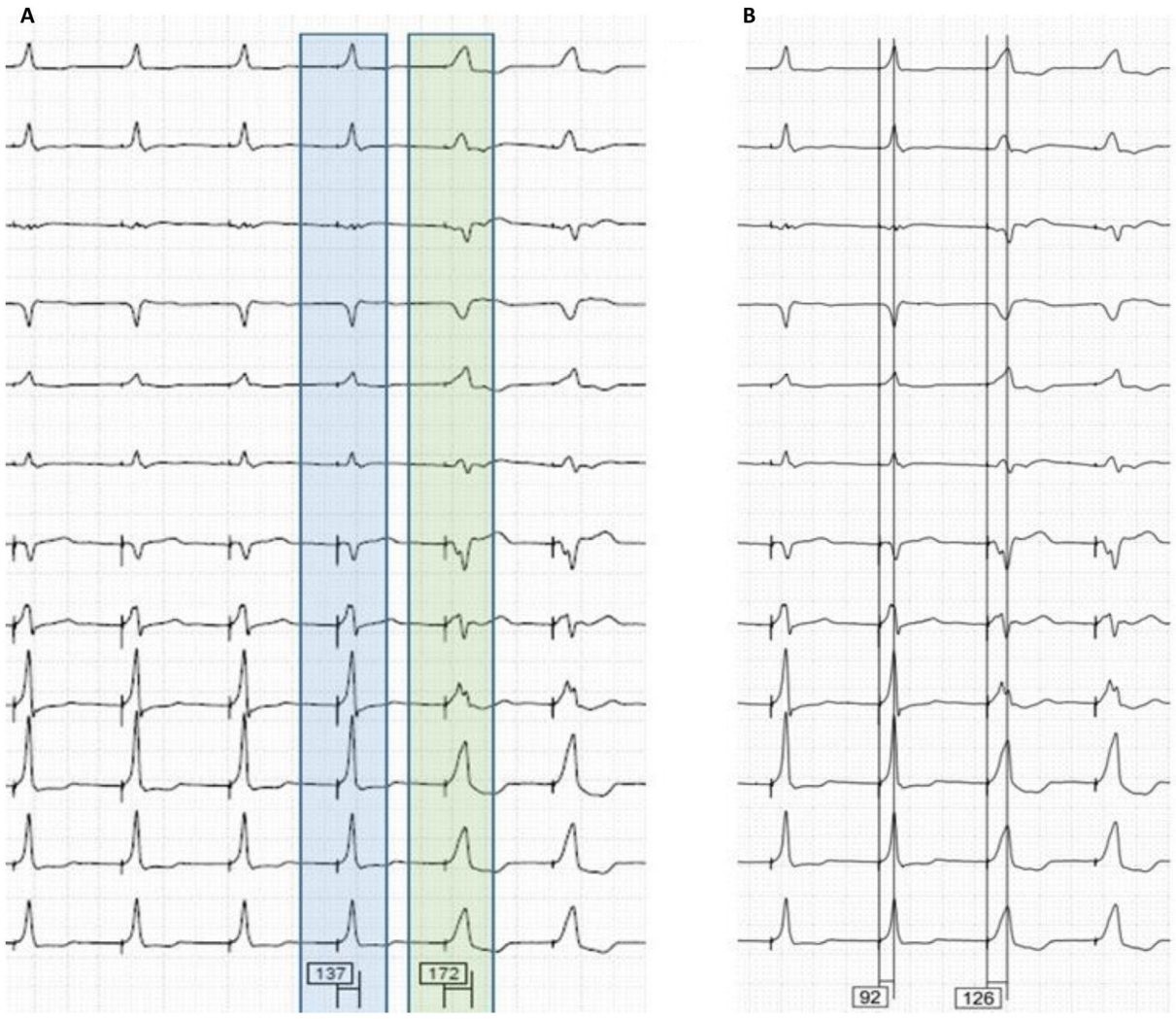

Figure 2 Non-selective His bundle pacing. (A) The 12-lead electrocardiogram at 25 mm/s demonstrating the passage from non-selective His bundle pacing (blue) to myocardial capture (green). The pacing stimulus to QRS interval is equal to zero given the presence of a pseudo-delta wave (blue arrow) and paced QRS is wider than native QRS. (B) Demonstration of non-selective His-bundle pacing with a R wave peak time in V6 <100 ms.

next: (a) demonstration of left bundle potential with left bundle-local ventricular electrogram interval of 20–35 ms; (b) demonstration of transition in QRS morphology from non-selective to selective left bundle capture or nonselective to LV septal capture with decrementing output; (c) S-LVAT measured in leads V5–V6 <80 ms; (d) programmed deep septal stimulation to demonstrate refractory period of left bundle[9] (Figure 3**).** If an acceptable His bundle/left bundle capture could not be achieved after 30 minutes, the lead was placed in the mid-septum as confirmed by fluoroscopic views. Programmed stimulation was 5.0 V at 1 ms for HBP and 3.5 V at 0.4 ms for LBBP for safety reasons. After the first month, programmed stimulation was modified according to pacing thresholds.

Study endpoints

The primary endpoint focused on the feasibility and safety of the physiologic pacing approach. Feasibility was defined as acute success implantation according to the above-described criteria.[6–9] Device-related complications were defined as the composite outcome of infection, procedural complications (pneumothorax, pericardial effusion with need for pericardiocentesis, cardiac tamponade, hematoma requiring interventions and thrombotic events), and lead-related complications (repositioning of the lead due to displacement, unsatisfactory threshold rise).

Pacing parameters and clinical outcomes differences between HBP and LBBAP techniques were evaluated perioperatively and at 3-month follow-up.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics version 20 (IBM, Armonk, New York). Categorical variables are expressed as in frequencies and percentages and continuous variables are expressed as mean ± standard

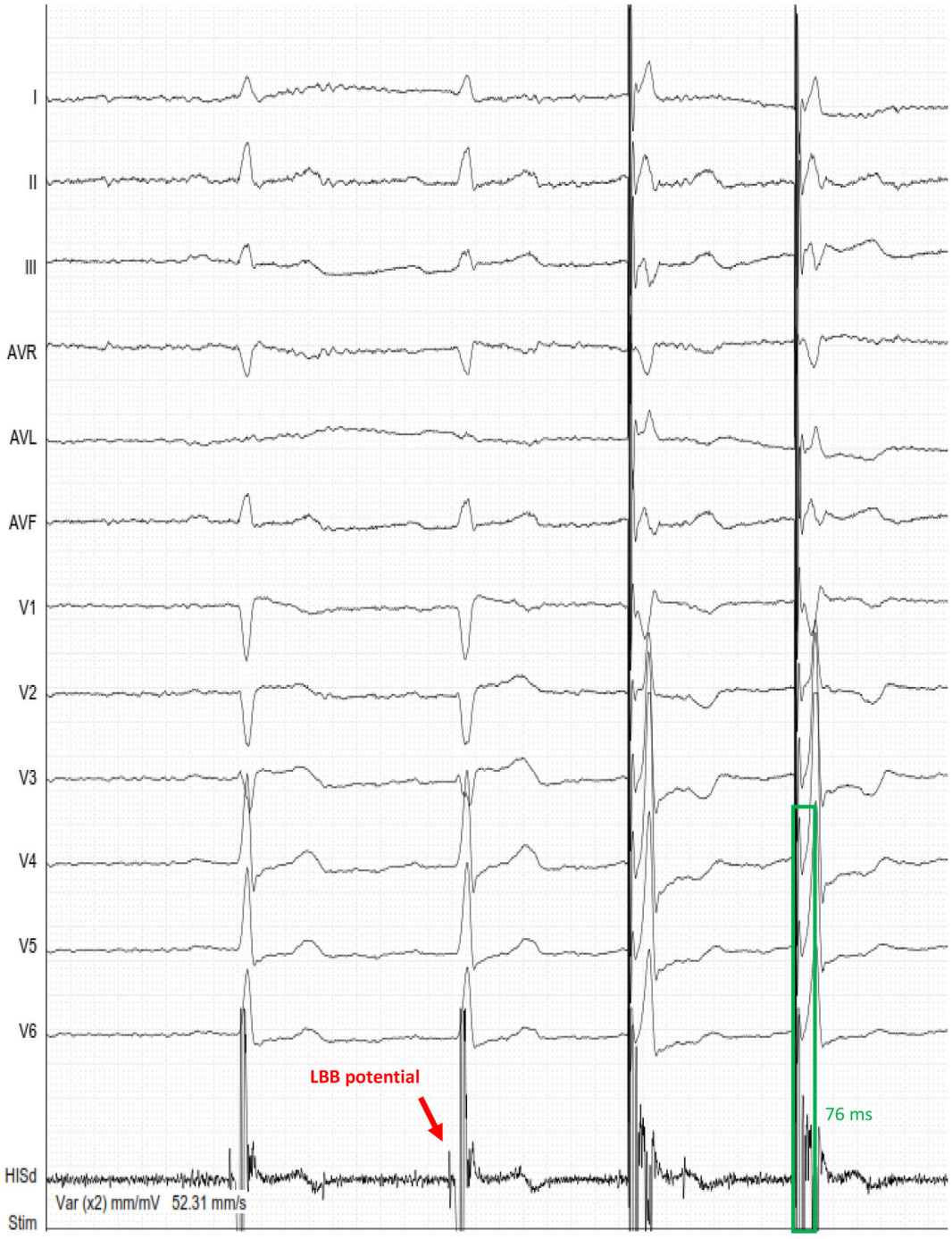

Figure 3 Left bundle brunch area pacing with a paced QRS morphology of right bundle branch block pattern and terminal R wave in lead V1, a stimulus-to-peak LV activation time is 76 ms in lead V6. Left bundle branch potential was also visible in the tip of the pacing lead (red arrow).

deviation or median and interquartile range for variables with and without a normal distribution, respectively. The χ^2 test was used to assess for differences between categorical variables and the Student t-test or the Wilcoxon test was used to compare continuous variables with or without normal distribution, respectively. For within-patient changes in parameters, paired t-tests were performed. Statistical significance was accepted for $p<0.05$.

Results

Baseline characteristics and procedure details

During the enrolment period, a total of 46 patients fulfilled the inclusion criteria and were included in this study (62% male, mean age of 75±9 years). The main baseline characteristics are described in Table 1. Intraventricular

Table 1 Baseline population demographics.

	Overall (n=46)	His bundle pacing (n=21)	Left bundle area branch pacing (n=23)	p
Age, years	76±9	75±8	79±9	0.17
Male, n (%)	27 (61%)	13 (62%)	14 (61%)	0.94
Hypertension, n (%)	28 (67%)	12 (63%)	15 (75%)	0.43
Diabetes mellitus, n (%)	9 (22%)	3 (16%)	6 (32%)	0.25
Body mass index, kg/m²	28.7±5.9	27.6±5.3	30.2±6.4	0.24
Mean LV ejection fraction, %	57±9	58±8	57±11	0.56
NYHA functional class				0.10
II, n (%)	8 (21%)	2 (11%)	5 (28%)	
III, n (%)	4 (10%)	0 (0%)	3 (17%)	
IV, n (%)	1 (3%)	1 (6%)	0 (0%)	
Baseline heart disease				0.67
Ischemic, n (%)	5 (14%)	1 (6%)	3 (17%)	
Valvular, n (%)	3 (8%)	1 (6%)	2 (11%)	
Idiopathic dilated, n (%)	4 (11%)	2 (13%)	1 (6%)	
Alcoholic dilated, n (%)	1 (3%)	0 (0%)	0 (0%)	
Atrial fibrillation				0.54
Paroxistic, n (%)	9 (21%)	4 (21%)	5 (25%)	
Permanent, n (%)	4 (10%)	1 (5%)	3 (15%)	
LBBB, n (%)	6 (13%)	3 (14%)	2 (9%)	0.56
RBBB, n (%)	4 (9%)	2 (9%)	2 (9%)	0.94
Non-specific IVCD, n (%)	3 (6%)	0 (0%)	3 (13%)	0.86
Pacing indication				0.45
High degree AV block, n (%)	20 (44%)	11 (52%)	8 (38%)	
SND, n (%)	15 (33%)	8 (38%)	7 (33%)	
Slowly conducting AF, n (%)	5 (11%)	1 (5%)	4 (19%)	
CRT	3 (7%)	2 (10%)	1 (5%)	
QRS duration, ms	114±26	116±25	112±29	0.64

AF: atrial fibrillation; AV: atrioventricular; CRT: cardiac resynchronization therapy; IVCD: intraventricular conduction disturbance; LBBB: left bundle branch block; LV: left ventricular; NHYA: New York Heart Association; RBBB: right bundle branch block; SND: sinus node disfunction.

conduction disturbance was present in 27% (n=13) of the patients. Most of the patients (65%) implanted a dual-chamber pacemaker, while 7% (n=3) received a CRT device (all of them had an electrode in the coronary sinus in addition to HBP or LBBAP).

Procedural characteristics are depicted in Table 2. During the HBP procedure, the median HV interval was 50 [43–60] ms, while the median S-LVAT was 80 [76–95] ms for LBBAP.

HBP and LBBAP pacing thresholds, R-wave amplitude and paced QRS duration are depicted in Table 3. In patients with intraventricular conduction delay, there was a reduction in QRS duration after pacing (138±16 ms to 128±20 ms).

Feasibility and safety

Overall, physiologic pacing was attempted in 46 patients. Acute procedural success was achieved in 96% of the cases (44/46 procedures: 21/23 for HBP and 23/23 for LBBAP). Effective HBP was achieved in 91% of the cases (seven patients with selective HBP and 14 patients with non-selective HBP) and in all cases where LBBP was attempted.

No acute complication related to the procedure was reported.

Pacing thresholds remained stable compared to acute thresholds within each group, with exception to R-wave amplitude in the LBBAP that increased significantly at three-months (Table 3). There was no difference between groups concerning paced QRS duration, either at implantation or during follow-up (p=0.54 and p=0.06, respectively).

During the follow-up, need for re-intervention occurred in three patients (6.5%), (due to lead displacement [n=1] or unsatisfactory threshold rise [n=2]). All re-interventions occurred in patients that performed HBP and successful lead repositioning in the His bundle was achieved in all of them.

Differences between His bundle pacing procedure and left bundle branch area pacing procedure

Patients that performed HBP presented lower R-wave amplitude and higher threshold voltage than patients subjected to LBBAP, both acutely and at 3-month follow-up (Table 4).

Fluoroscopy time was almost halved in LBBAP compared to HBP (8.1 [5.3–13.4] min vs. 4.1 [3.1–11.3] min, p=0.05).

Table 2 Procedural characteristics.

	Overall (n=44)	His bundle pacing (n=21)	Left bundle area branch pacing (n=23)	p
Median procedure time, minutes	95 [75–126]	95 [75–139]	95 [74–116]	0.79
Fluoroscopy time, minutes	6.5 [3.3–11.2]	8.1 [5.3–13.4]	4.1 [3.1–11.3]	0.05
Lead number				
Single, n (%)	9 (22%)	2 (10%)	7 (33%)	
Dual, n (%)	28 (68%)	16 (80%)	12 (57%)	
Triple, n (%)	3 (7%)	2 (10%)	1 (4%)	

Table 3 Comparison of pacing parameters at implantation and at three-month follow-up for His bundle pacing and left bundle branch area pacing.

	Acute	Three-months	p
His bundle pacing			
Pacing parameters			
Sensing amplitude, mV	4.0 [2.9–6.2]	3.0 [2.1–5.4]	0.90
Pacing threshold, V @ ms	0.8 [0.55–1.53] @ 1	1.25 [0.75–2.00] @ 1	0.09[a]
Paced QRS duration, ms	125±22	118±16	0.05
Left bundle branch area pacing			
Pacing parameters			
Sensing amplitude, mV	7.8 [5.5–10.5]	15.0 [9.4–20]	0.001
Pacing threshold, V @ ms	0.70 [0.40–0.90] @ 0.4	0.60 [0.50–0.80] @ 0.4	0.78[a]
Paced QRS duration, ms	133±16	124±14	0.06

PW: pulse width.
[a] Refers to difference in voltage.

Table 4 Pacing parameters at implantation and at three-months follow-up for His bundle pacing and left bundle branch area pacing (comparison between groups).

	His bundle pacing (n=21)	Left bundle branch area pacing (n=23)	p
Acute pacing parameters			
Pacing parameters			
Sensing amplitude, mV	4.0 [2.9–6.2]	7.8 [5.5–10.5]	0.001
Pacing threshold, V @ ms	0.8 [0.55–1.53] @ 1	0.70 [0.40–0.90] @ 0.4	0.08[a]
Pacing impedance, Ω	475 [385–589]	741 [666–855]	<0.001
Paced QRS duration, ms	125±22	133±16	0.08
3 month pacing parameters			
Pacing parameters			
Sensing amplitude, mV	3.0 [2.1–5.4]	15.0 [9.4–20]	0.001
Pacing threshold, V @ ms	1.25 [0.75–2.00] @ 1	0.60 [0.50–0.80] @ 0.4	<0.001[a]
Pacing impedance, Ω	437 [399–532]	532 [437–626]	0.03
Paced QRS duration, ms	118±16	124±14	0.19

PW: pulse width.
[a] Refers to difference in voltage.

No difference between groups was noted regarding procedure time (see Table 2).

In a sensitivity analysis, excluding patients that had received a CRT device (n=2 for HBP group and n=1 in the LBBAP group), procedure and fluoroscopy times remained similar between groups (90 [75–132] vs. 95 [70–105] min, p=0.74; 8.1 [5.1–11.1] vs. 4.1 [3.2–11.6] min, p=0.71, respectively).

Discussion

To our knowledge, this is the first national study evaluating physiologic pacing. The main findings of this study are (1) HBP and LBBAP are both feasible and safe with an overall acute procedural success of 96% and a 6.5% complication rate observed during the initial follow-up; (2) LBBAP

presented a significantly lower threshold voltage and a higher R wave amplitude, compared to HBP.

Our overall success implantation rate was in line with previous reports[10–16] demonstrating the feasibility of the physiologic pacing and strengthening that similar results can be expected in procedures performed by experienced operators. The need for re-intervention was 6.5%, which is also in concordance with previous data, where reported rates of His pacing requiring either a repeat intervention or deactivation ranged from 5 to 11%.[13,16–18] It is of note that all the re-interventions occurred in the HBP group, confirming the safety profile associated with the LBBAP.[8,14] Therefore, the need for a backup lead can be waived in LBBAP procedures which can prevent some complications associated with adding another lead.[13]

Performing physiologic pacing required more than the usual time required in RVAP.[10,19] However, as the experience grows a reduction in the procedure time is expected, given the learning curve associated with these procedures.[13,16] Although, in LBBAP pacing there is a large anatomic area suitable for pacing, and therefore implantation could be simpler and faster,[20,21] this did not translate, in our study, into faster procedures with LBBAP. This probably was the result of the learning curve associated with this technique. However, fluoroscopy time was almost halved compared to HBP. Physiologic pacing, either HBP or LBBAP, resulted in paced QRS duration <130 ms, which is shorter than the one obtained during RV pacing.[14] Moreover, there was a reduction in QRS duration in patients with intraventricular conduction disturbance, which also has been reported.[9,13,22–25] However, our study included few patients with intraventricular conduction disorders and therefore our results should be interpreted with caution.

Our data corroborate that LBBAP appears to be a more stable approach than HBP, providing a lower capture threshold and higher R-wave amplitude[15,20,14,22] while maintaining a similar paced QRS duration. This is logical since the pacing site occurs in the septal tissue.[14,22] Thresholds at three months remained stable and are comparable to those reported in the literature.[14,20,22]

In summary, physiologic pacing is a feasible and safe approach for patients with an indication for a permanent pacemaker. Our preliminary observational study also suggests that LBBAP is more stable than HBP, with a lower voltage threshold and higher R-wave amplitude. Further randomized studies with larger samples may help to clarify the data obtained in our study.

Limitations

We acknowledge several limitations in our work. First, this was a nonrandomized, observational study designed to assess the feasibility and safety of physiologic pacing. Second, an experienced operator was present during all cases and therefore our results cannot be extrapolated to other centers. Third, the sample included a relatively small number of patients and therefore the comparison between groups may be underpowered. Clinical outcomes of LBBAP compared to HBP are needed in the future in large randomized clinical trials. Fourth, longer-term follow-up is necessary for the evaluation of clinical outcomes and adverse events. The long-term electrical performance of the lead and potential risks associated with lead extraction are unknown and should be carefully studied.

Conclusion

This study demonstrates that physiologic pacing is feasible and safe in patients with a pacemaker indication. Left bundle branch area pacing appears to overcome some of the HBP disadvantages providing a better R-wave amplitude and lower pacing threshold.

Conflicts of interest

P.A.S has received speaker fees from Abbott, Biosense Webster, Boston Scientific and Medtronic. All other authors declare that there are no proprietary, financial, professional or other personal interests of any nature or kind in any product, service and/or company that could be construed as influencing the content of the manuscript.

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