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Permanent His-bundle pacing maintains long-term ventricular synchrony and left ventricular performance, unlike conventional right ventricular apical pacing

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Aims Right ventricular apical pacing (RVAP) may be deleterious, determining abnormal left ventricular (LV) electrical activation and progressive LV dysfunction. Permanent His-bundle pacing (HBP) has been proposed to prevent this detrimental effect. The aim of our study was to compare the long-term effects of HBP on LV synchrony and systolic performance with those of RVAP in the same group of patients.

Methods Our analysis included 26 patients who received both an HBP lead and an RVAP lead, as backup, in our electrophysiology laboratory between 2004 and 2007. After implantation, all devices were programmed to obtain HBP. An intra-patient comparison of the effects of HBP and RVAP on LV dyssynchrony and function was performed at the last available follow-up examination.

Results After a mean of 34.6 $\pm$ 11 months, the pacing modality was temporarily switched to RVAP. During RVAP, LV ejection fraction significantly decreased (50.1 $\pm$ 8.8% vs. 57.3 $\pm$ 8.5%, $P < 0.001$), mitral regurgitation significantly increased (22.5 $\pm$ 10.9% vs.16.3 $\pm$ 12.4%; $P = 0.018$), and *inter-ventricular delay* significantly worsened (33.4 $\pm$ 19.5 ms vs. 7.1 $\pm$ 4.7 ms, $P = 0.003$) in comparison with HBP. However, the *myocardial performance index* was not statistically different between the two pacing modalities ($P = 0.779$). No asynchrony was revealed by *tissue Doppler imaging* during HBP, while during RVAP the asynchrony index was significantly higher in both the four-chamber (125.8 $\pm$ 63.9 ms; $P = 0.035$ vs. HBP) and two-chamber (126 $\pm$ 86.5 ms; $P = 0.037$ vs. HBP) apical views.

Conclusion His-bundle pacing has long-term positive effects on inter- and intra-ventricular synchrony and ventricular contractile performance in comparison with RVAP. It prevents asynchronous pacing-induced LV ejection fraction depression and mitral regurgitation.

Keywords His-bundle pacing • His bundle • Preserved infra-Hisian conduction • Cardiac pacing • Ventricular dyssynchrony

Introduction

Right ventricular apical pacing (RVAP) induces dyssynchronous activation of the left ventricle,[1] reduces left ventricular (LV) ejection fraction,[2,3] and may be associated with an adverse clinical outcome.[4–11] Permanent His-bundle pacing (HBP) has been proposed to maintain physiological electrical activation, and has been shown to prevent detrimental pacing-induced effects due to abnormal LV electrical activation in the acute phase and on short-term follow-up.[12–29] However, few data are available on the long-term prognosis of patients undergoing HBP.

The aim of our study was to compare the long-term effects of HBP with those of RVAP on ventricular synchrony and LV systolic performance in the same group of patients.

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What's New?

- Long-term effect of His-bundle pacing (HBP) on ventricular synchrony in patients with preserved left ventricular systolic function, indicated permanent ventricular pacing.
- Echocardiographic comparison between HBP and right ventricular apical pacing at long-term follow-up.

Methods

Patients

Our analysis involved patients with a standard indication for permanent pacing according to American College of Cardiology/American Heart Association/Heart Rhythm Society Guidelines[30] and preserved infra-Hisian conduction who had undergone successful HBP and concomitant implantation of an additional permanent lead in the right ventricular apex between 2004 and 2007 in our electrophysiology laboratory, and who had been followed up in our centre for at least 2 years. Patients without an implanted apical right ventricular lead, those with major comorbidities, and those who did not attend follow-up visits in our centre were excluded from the analysis.

All patients provided written informed consent before implantation. The study complied with the Declaration of Helsinki, and the Institutional Ethics Committee approved the study protocol.

Between May and July 2009, all patients underwent a long-term follow-up examination, which consisted of clinical assessment, New York Heart Association functional class evaluation, 12-lead surface electrocardiogram, telemetric check of the implanted device, and echocardiographic assessment.

Implantation technique

A detailed description of the permanent HBP implantation procedure has been reported elsewhere.[14] Briefly, a 4.1 Fr bipolar active-fixation lead (SelectSecure®, mod.3830, Medtronic) was positioned in the Hisian region by means of a steerable sheath and was screwed into the apical part of Koch's triangle, where HBP was obtained. Direct HBP was defined as the paced rhythm characterized by QRS-T wave morphology identical to the sinus rhythm and an isoelectric tract between the pacing stimulus artefact and the beginning of the QRS complex similar to the H–V interval. At higher pacing outputs a slight widening and an early slurred 'delta wave-like' segment of the QRS complex could be observed, owing to the capture of the adjacent RV septum (*Figure 1*).

Permanent para-hisian pacing (PHP) was defined when, at higher pacing output, a narrow QRS complex with ventricular fused beats and shortening of concomitant retrograde atrial conduction was obtained, owing to the indirect capture of the His bundle, while at lower output, a wider morphology of QRS complex was observed, owing to the capture of the muscle tissue alone[12,16] (*Figure 2*).

Patients with sinus rhythm and associated permanent atrioventricular block (AVB) received an Insync III pacemaker (model 8042, Medtronic Inc.), with the His-bundle lead connected to the 'LV port' of the device and the back-up RVAP lead connected to the 'RV port'. The HBP channel was programmed as the first pacing site, while the RVAP stimulus was set after a delay of 80 ms. In patients with permanent atrial fibrillation and low ventricular response (due to associated AV nodal conduction

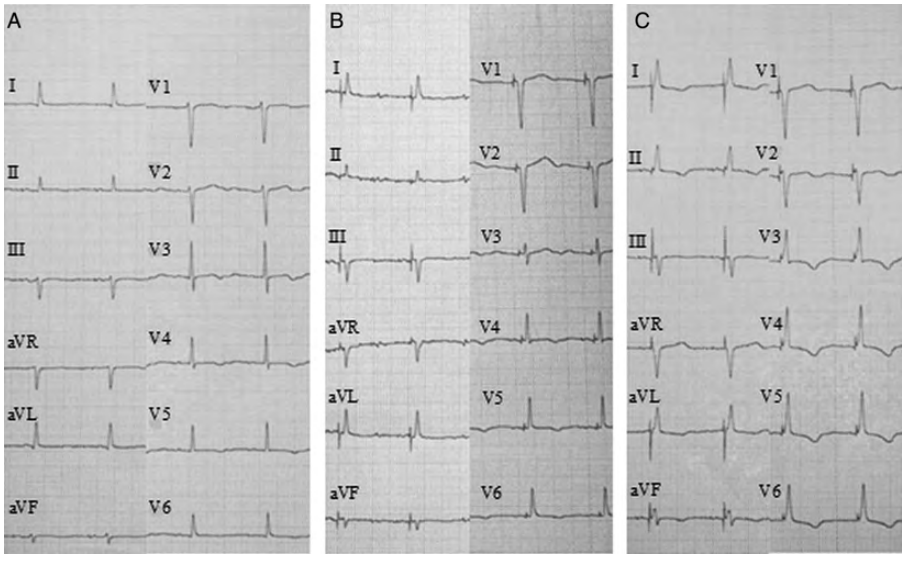

Figure 1 The 12-lead surface ECG recordings in the same patient during sinus rhythm (*A*), during direct HBP (*B*), and during HBP and adjacent right ventricular septum pacing (*C*). In this patient, the pacemaker output of the His-bundle lead was programmed in order to obtain ECG type B. HBP, His-bundle pacing; ECG, electrocardiogram.

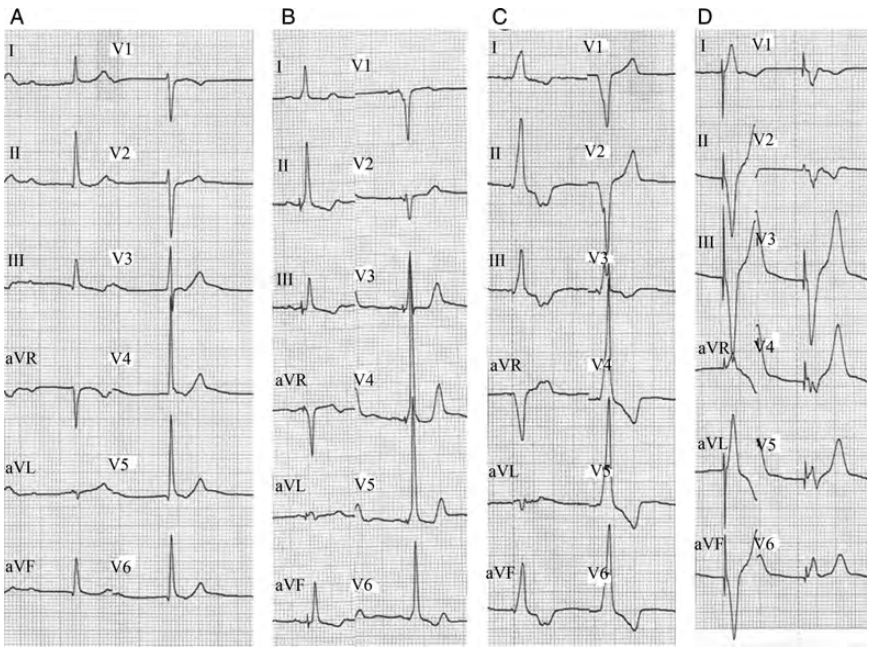

Figure 2 The 12-lead surface ECG recordings in the same patient during sinus rhythm (*A*), during PHP at higher pacing output (*B*), during RV septum pacing from the same lead but at lower pacing output (*C*), and during RVAP (*D*). In this patient, the pacemaker output of the His-bundle lead was programmed in order to obtain ECG type B. PHP, para-hisian pacing; RV, right ventricle; RVAP, right ventricular apical pacing; ECG, electrocardiogram.

defect), a dual-chamber pacemaker (Kappa DR, Enpulse DR, Adapta DR, Medtronic Inc.) was implanted, with the His-bundle lead connected to the 'atrial port' of the device and with the shortest programmable interval (i.e. 80 ms) between the HBP and the RVAP channels (*Figure 3*).

In each patient, the pacing output was programmed in order to obtain His-bundle capture with the shortest QRS complex duration.

Echocardiographic evaluation

Echocardiographic examination was performed sequentially by the same sonographer during HBP and RVAP at the same follow-up visit. In order to compare site-specific effects, each echocardiographic assessment was performed after 5 min of each pacing modality (HBP or RVAP). His-bundle pacing and RVAP were performed at the same fixed rate, ranging from 60 to 80 b.p.m: in the DDD mode with optimized AV delay in each patient in sinus rhythm, and in the VVI mode in patients with permanent atrial fibrillation. Two-dimensional images of the LV chamber were acquired in the parasternal short-axis view and apical four-, three-, and two-chamber views, as recommended by the American Society of Echocardiography Committee.[31]

M-mode, pulsed-wave Doppler echocardiography, and tissue Doppler imaging (TDI) were recorded at a paper speed of 100 mm/s on a videotape for off-line analysis performed by a different sonographer blinded to the pacing modality. For all echocardiographic measurements, the values reported are the means of measurements taken from three cardiac cycles.

Aortic and pulmonary systolic flows were sampled just below the valve from the apical three-chamber view and parasternal short-axis view, respectively, to assess the inter-ventricular activation delay.

Left ventricular *(or RV) electromechanical delay* was defined as the time from the beginning of the QRS interval to the onset of aortic (or pulmonary) outflow.

Inter-ventricular delay (IVD) was assessed as the difference between the LV electromechanical delay and the RV electromechanical delay. Inter-ventricular delay values >40 ms were considered pathological.

Myocardial performance index (MPI), an integrated index of diastolic and systolic function, was calculated as the ratio between the sum of isovolumetric contraction and relaxation times (ICT and IRT), divided by the LV ejection time (LVET), according to the standard formula: $\text{MPI} = (\text{ICT} + \text{IRT}/\text{LVET})$.[32,33] Values <0.45 were considered normal.

Mitral regurgitation (MR) was assessed semi-quantitatively as the ratio between the area of the regurgitant flow and the left atrium area in the apical four-chamber view, or, as a second choice, in the long-axis parasternal view.

Tissue Doppler imaging waveforms were recorded to assess left intra-ventricular activation delay. Left intra-ventricular activation delay was evaluated by mapping the regional myocardial contraction velocities of 12 LV basal segments in both four- and two-chamber views[34–39] using off-line colour tissue Doppler-derived tissue velocity imaging. The advantage of this technique is that it enables the dyssynchrony of opposite LV walls (or different

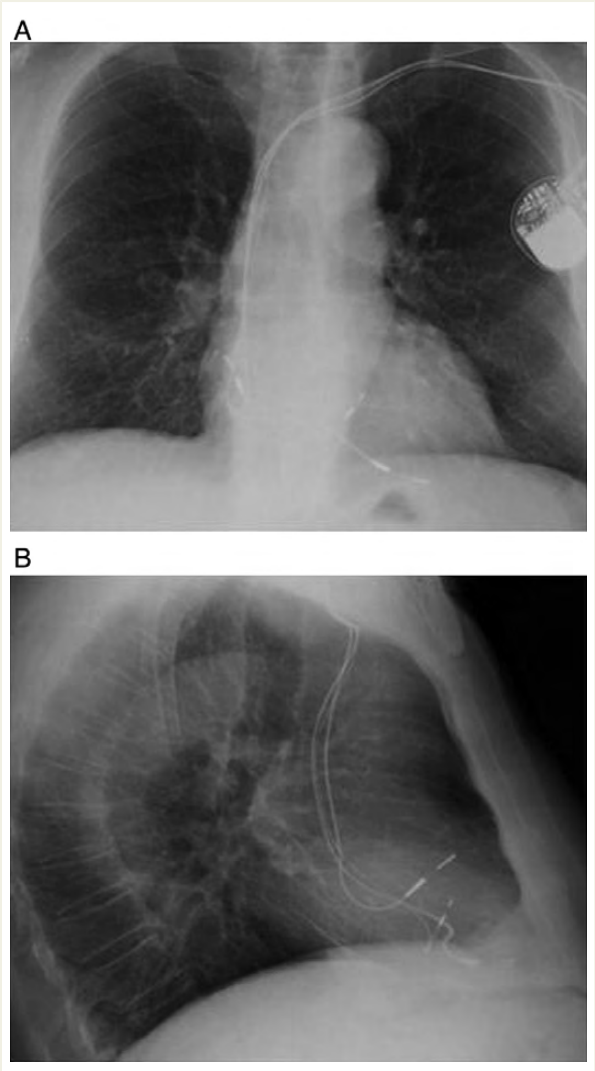

Figure 3 Chest X-ray AP (*A*) and LL (*B*) of a pacemaker with atrial, His-bundle and RVAP leads. AP, antero-posterior; LL, latero-lateral; RVAP, right ventricular apical pacing.

segments of the same LV wall) to be measured in the same echocardiographic view and cardiac cycle. Specifically, an *asynchrony index* was defined as the maximum time difference (MD) between TDI systolic contraction velocity peaks of two of the 12 LV basal segments in the same echocardiographic view. A value of MD >100 ms identified asynchrony.[40]

Telemetric device check

During follow-up visits, the appropriate functioning of the implanted system was checked by means of a programmer (model 2090, Medtronic, Minneapolis, MN, USA). Battery voltage, P- and R-wave amplitudes, pacing thresholds, and impedances of the atrial, ventricular, and Hisian leads were measured. In addition, the presence of possible arrhythmic events was assessed.

Table 1 Demographics, baseline clinical parameters, and pharmacological treatment

Parameter	*n* = 26
Male, *n* (%)	16 (61.5)
Age, years mean ± SD	71.6 ± 8.8
Cardiopathy, *n* (%)	16 (62)
Ischaemic, *n* (%)	6 (37)
Hypertensive, *n* (%)	2 (13)
Other, *n* (%)	8 (50)
Comorbidities, *n* (%)	18 (69)
Hypertension	10 (38)
Dyslipidaemia	5 (19)
TIA	2 (8)
TEA	3 (12)
Other	10 (38)
LVEF, %	57.2 ± 7.4
Baseline QRS duration, ms	97.7 ± 11.8
Pharmacological therapy use, *n* (%)	26 (100)
ASA	12 (46)
Diuretics	19 (73)
Calcium antagonists	10 (39)
Nitrates	5 (19)
β-Blockers	18 (69)
Statins	7 (27)
Amiodarone	2 (8)
ACE inhibitors	13 (50)
Oral anticoagulants	8 (31)
α-Blockers	2 (8)
Digitalis	2 (8)

TIA, transient ischaemic attack; TEA, thromboendarterectomy; LVEF, left ventricular ejection fraction; ASA, acetil salicylate acid; ACE, angiotensin-converting enzyme.

Statistical analysis

Continuous data are expressed as mean ± standard deviation.

Differences between continuous variables were assessed by using a Student's *t*-test or Wilcoxon non-parametric test. The statistical significance level was defined as a *P* value <0.05. Analyses were performed with SPSS 12.0 software for Windows.

Results

Population characteristics

Twenty-six patients who underwent effective HBP implantation with a back-up RVA lead were included in our analysis. Among these 26 patients, direct HBP was obtained in 20 and PHP in 6.

Baseline clinical characteristics and pharmacological treatment of study patients are summarized in *Table 1*. The indication for permanent pacing was: atrial fibrillation with low ventricular response in 10 patients (38%); second- or third-degree AVB in 10 patients (38%); and sick sinus syndrome in 6 patients (24%). Mean LV ejection fraction (LVEF) was 57.8 ± 7.1% and mean duration of the

Table 2 Electrical parameters

Variable	Implant	Long-term follow-up	P[a]
Impedance, Ohm (Average ± SD)			
Atrial lead	529 ± 116	499 ± 156	>0.05[a]
RVA lead	552 ± 70	569 ± 66	>0.05[a]
His bundle lead	482 ± 54	476 ± 51	>0.05[a]
Sensing, mV (mean ± SD)			
Atrial lead	2.7 ± 0.8	2.9 ± 0.7	>0.05[a]
RVA lead	13 ± 5	11 ± 5	>0.05[a]
His bundle lead	2.8 ± 1.3	2.4 ± 1.4	>0.05[a]
Pacing threshold, V @ 0.5 ms (mean ± SD)			
Atrial lead	0.5 ± 0.4	0.7 ± 0.6	>0.05[a]
RVA lead	0.7 ± 0.2	0.6 ± 0.2	>0.05[a]
His bundle lead	1.9 ± 0.6	1.8 ± 0.7	>0.05[a]

SD, standard deviation.
[a]Paired *t*-test.

Table 3 Two-dimensional and M-mode echocardiographic data

Parameter (mean ± SD)	HIS	RVA	P value
LVEF, %	57.3 ± 8.5	50.1 ± 8.8	**<0.001**[a]
LVEDD, mm	50.3 ± 4.0	53.0 ± 6.2	0.089[a]
LVESD, mm	34.2 ± 7.0	32.1 ± 8.2	0.213[a]
IS (diastole), mm	13.7 ± 1.9	13.0 ± 2.8	0.310[a]
IS (systole), mm	18.1 ± 4.2	18.8 ± 3.9	0.506[a]
Posterior wall, diastole (mm)	11.3 ± 1.8	11.4 ± 1.4	0.872[a]
Posterior wall, systole (mm),	18.0 ± 2.9	17.9 ± 2.3	0.916[a]

SD, standard deviation; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; IS, inter-ventricular septum.
[a]Paired *t*-test.
Bold value indicates $P < 0.05$.

Table 4 Doppler and tissue Doppler imaging data

Parameter (mean ± SD)	HIS	RVA	P value
MR (%)	16.3 ± 12.4	22.5 ± 10.9	**0.018**[a]
Aortic pre-ejection time interval	117.6 ± 62.1	110.1 ± 51.7	0.745[a]
Pulmonary pre-ejection time interval	116.0 ± 58.6	83.5 ± 46.0	0.096[a]
IVD	7.1 ± 4.7	33.4 ± 19.5	**0.003**[b]
MPI	0.6 ± 0.04	0.6 ± 0.3	0.779[b]
Asynchrony index—4C	81.7 ± 49.0	125.8 ± 63.9	**0.035**[a]
Asynchrony index—2C	56.0 ± 43.9	126.0 ± 86.5	**0.037**[a]

SD, standard deviation; MR, mitral regurgitation; IVD, inter-ventricular delay; MPI, myocardial performance index; 4C, four chambers; 2C, two chambers.
[a]Paired *t*-test.
[b]Non-parametric Wilcoxcon test.
Bold value indicates $P < 0.05$.

QRS complex was 97.7 ± 11.8 ms before implantation. During HBP, QRS duration did not significantly differ from the intrinsic QRS duration (102.4 ± 15.4 ms; $P > 0.05$ vs. baseline). Fourteen patients received a three-chamber pacemaker and 12 patients a dual-chamber device.

Mean follow-up was 34.6 ± 11 months (range: 22–59 months). During the follow-up period, no arrhythmic events occurred, as confirmed by device memory recordings. Moreover, no patients died or developed an exit block.

At the last follow-up examination, the mean paced QRS complex duration during HBP was not statistically different from that recorded on implantation ($P > 0.05$ vs. implantation).

Device performance

During the observation period, the elective replacement indicator prompted device replacement in three patients: 30, 33, and 38 months after implantation. In these patients, a high pacing output had to be programmed on implantation in order to obtain His-bundle capture. No lead dislodgments, episodes of loss of capture, or sensing issues were observed during follow-up.

Table 2 summarizes the electrical performance of implanted leads on both implantation and long-term follow-up examination. The electrical parameters of atrial, right ventricular apical, and Hisian leads displayed no statistically significant differences between implantation and long-term follow-up.

Echocardiographic data

Echocardiographic parameters were evaluated in all patients both during HBP and, thereafter during the same visit, after 5 min of continuous RVAP.

Tables 3 and *4* summarize echocardiographic parameters during pacing from the two different pacing sites. Mean LVEF was greater during HBP (57.3% ± 8.5) than RVAP (50.1% ± 8.8, $P < 0.001$). No significant differences were found between HBP and RVAP in all M-mode parameters, though a trend ($P = 0.089$) towards a smaller end-diastolic diameter was found during HBP.

Mitral regurgitation was observed in14 patients, and was significantly greater during RVAP than during HBP: 22.5% ± 10.9 and 16.3% ± 12.4, respectively ($P = 0.018$) (*Table 4*).

The mean value of IVD was 7.1 ± 4.7 ms during HBP, vs. 33.4 ± 19.5 ms during RVAP ($P = 0.003$).

The MPI did not differ significantly between HBP and RVAP (0.6 ± 0.04 vs. 0.6 ± 0.3, $P = 0.779$, respectively) (*Table 4*).

Tissue Doppler imaging evaluation showed an absence of asynchrony during HBP. Moreover, the asynchrony index was significantly lower during HBP than during RVAP, in both the four-chamber (81.7 ± 49 vs. 125.8 ± 63.9 ms; $P = 0.035$) and two-chamber (56 ± 42.9 vs. 126 ± 86.5 ms; $P = 0.037$) apical views (*Table 4*).

Discussion

Right ventricular apical pacing may have a detrimental effect on LV function due to anomalous electrical activation of the left ventricle. Indeed, it alters the sequence of regional myocardial shortening and reduces the efficiency of mechanical work by inducing temporal asynchrony and energy dispersion due to early activation of septal regions during isometric contraction and late activation of lateral segments during early diastolic relaxation.[41]

Mitral regurgitation is a common finding during RVAP, owing to the reduced transvalvular pressure gradient and asynchronous papillary muscle contraction induced by the altered sequence of intraventricular contraction.[42]

In order to avoid the detrimental effect of RVAP in patients in whom a permanent dual-chamber pacemaker has been implanted, two strategies can be adopted: minimizing the percentage of pacing by using dedicated algorithms, or implanting the permanent RV lead in selected ventricular sites other than the right ventricular apex.

The Hisian region has been proposed as an alternative pacing site in patients with disorders of AV nodal/supra-Hisian conduction. Positioning an active-fixation small-tipped lead in this site by means of a deflectable sheath has proved feasible in the vast majority of patients. However, optimal lead positioning in the Hisian region can require a longer procedural time than conventional RV apical lead positioning, higher pacemaker outputs and the implantation of an additional back-up lead in the RV apex.[12–14] His-bundle pacing, as it does not alter the physiological impulse conduction, might maintain rapid and synchronous LV activation, thus favourably affecting contractile performance.

Although case reports[23,24] and acute studies on the feasibility and efficacy of direct HBP[20] or PHP[25] have been performed, only few papers have evaluated the long-term effects and benefits of these strategies.[13] Moreover, no data have been reported on the effect of HBP in comparison with RVAP on long-term follow-up.

The results of the present study confirm, in a long-term perspective, the assumption that HBP, by allowing physiological electrical activation of the left ventricle, do not induce interventricular or intra-ventricular mechanical dyssynchrony. In addition, in our observation HBP preserved LV systolic function and limited the MR induced by right ventricular pacing, thus confirming, on long-term follow-up, the acute results previously published by our group.[20]

Inter-ventricular delay, which is an index of dyssynchrony between the two ventricles, was preserved during HBP (7.1 ± 4.7 ms) owing to rapid conduction in both ventricles along the specialized conduction system, as documented by the narrow paced QRS complex. In contrast, RVAP, by inducing a left bundle-branch block-like activation pattern, prolonged total activation time owing to the slowed conduction through the septum and to the Purkinje network; this resulted in a long IVD of 33.4 ± 19.5 ms, which was statistically greater than that recorded during HBP ($P = 0.003$).

As already observed during acute studies,[20,25] HBP avoids the pacing-induced MR elicited by RVAP; indeed, it is correlated with the synchronism of mechanical forces straining the papillary muscles, optimal coaptation of valve leaflets and the consequent haemodynamic improvement of the patient. It is noteworthy that in our experience MR induced by RVAP began just a few beats after the initiation of apical pacing; this suggests the induction of acute haemodynamic effects, apart from long-term unfavourable ventricular remodelling, which requires many months to develop. In contrast, HBP preserved valvular function in the long term (even some years after implantation), maintaining significantly lower values of MR than RVAP ($P = 0.018$).

Our results showed a statistical trend towards a smaller end-diastolic diameter during HBP than during RVAP on follow-up examination after a mean of 34 months. In addition, HBP seemed to maintain a better LV systolic function ($57.3 \pm 8.5\%$) than RVAP ($50.1 \pm 8.8\%$; $P < 0.001$ vs. HBP). These data confirmed, in the long term, the published acute effects of HBP on LVEF in comparison with RVAP,[12] as well as the recently documented positive effects of HBP on 3-month follow-up examination in patients who required permanent cardiac pacing in the presence of AV or bundle-branch blocks with either a narrow or a wide QRS complex.[29]

In our series, the negative effect on LV synchrony induced by RVAP, which had already been observed in our acute study[20] and which is one of the main causes of acute LV dysfunction in pacemaker patients, was confirmed on long-term follow-up. Intraventricular contraction of LV segments was found to be synchronous after more than 2 years of HBP; in contrast, when the pacemaker was switched to RVAP, the asynchrony index (MD) increased significantly to 125.8 ± 63.9 ms in the four-chamber apical view ($P = 0.035$ vs. HBP) and to 126.0 ± 86.5 ms in the two-chamber view ($P = 0.037$ vs. HBP). This phenomenon is analogous to what occurs in patients with left bundle-branch block and dilated cardiomyopathy.

Telemetric device checks during follow-up confirmed that the technique we used to obtain permanent HBP is safe in the long term. Indeed, a mean of 34 months after implantation, the electrical performance of the lead implanted in the His bundle was stable. Neither lead dislodgments nor exit blocks were observed in the study. However, as already shown in the acute phase,[20] mean His-bundle lead pacing thresholds were also higher than those of the right ventricular apical lead on long-term follow-up. This may be due to fibrotic wrapping and electrical insulation of the specific conduction system within the membranous septum. Despite its protective role, this wrapping could increase the distance between the electrode catheter tip and the target tissue, thereby increasing HBP thresholds. Probably for the same reasons, R-wave sensing by the His-bundle lead remained stable but lower than by the conventional right ventricular apical lead, confirming the necessity of implanting an additional back-up lead for RVAP and sensing in all patients. Using this safer approach, we might consider HBP as a valuable alternative to RVAP in order to preserve ventricular synchrony and LV contractile performance in all patients with preserved infra-Hisian conduction, with or without LV systolic dysfunction, who need a high percentage of ventricular pacing.

Impedance pacing values were in line with published values for the lead model implanted[14,21] and remained stable in comparison with the baseline, indicating the integrity of the electrode and of the electrode–tissue electrical interface.

Conclusions

In the long term, HBP has favourable effects on inter- and intra-ventricular synchronism and ventricular systolic function in comparison with RVAP. It prevents asynchronous pacing-induced LV ejection fraction depression and MR.

Larger studies are needed to confirm the benefits of this pacing modality in comparison with RVAP and to evaluate its clinical role in patients with AV nodal conduction disturbances and reduced ejection fraction.

Conflict of interest:

A.V. is an employee of Medtronic, Inc. No other conflict of interest exists.

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Unusual complication after permanent pacemaker insertion

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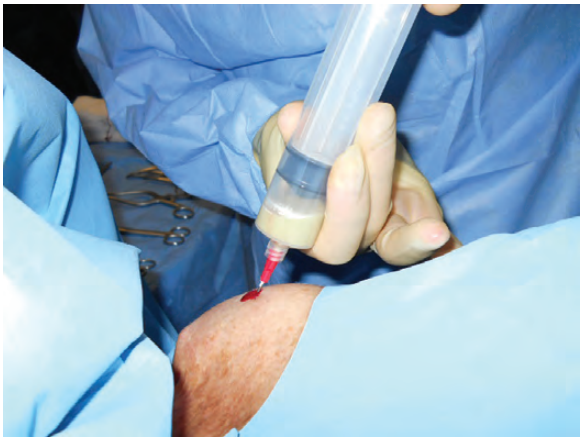
Summary

This 83-year-old woman had a left sided AAI pacemaker inserted via subclavian puncture in 2007 for sinus node disease. It was complicated by a chylous effusion of the left pacemaker site, which was initially managed with aspiration and pressure dressing. Four years later, she developed recurrent swelling, aspirated in the local A/E and primary care practice and also treated with antibiotics. Our initial management included aspiration of milky green pus (*Figure 1*). She was referred urgently as an outpatient for pacemaker extraction and replacement. A new pacemaker system was inserted via a right subclavian puncture and the old generator was removed, leaving the left sided leads in place.

Chylous effusion of the pacemaker site could occur as a complication of transvenous pacemaker insertion due to puncture of the thoracic duct. The thoracic duct may insert directly into the left internal left sublcavian vein. In a surgical series, trauma to the thoracic duct resulting in chylothorax does not respond to conservative therapy. All cases required surgical exploration in order to obliterate the cause of the chylous leak. Recurrence of the chylous effusion in this patient may indicate lead extraction and surgical exploration of the thoracic duct.



Conflict of interest: none declared.

The full-length version of this report can be viewed at: http://www.escardio.org/communities/EHRA/publications/ep-case-reports/Documents/complication-permanent-pacemaker-insertion.pdf