Direct His bundle pacing preserves coronary perfusion compared with right ventricular apical pacing: a prospective, cross-over mid-term study

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Aims The His bundle is regarded as the most physiological site for ventricular pacing, in that it avoids the adverse effects of right ventricular apical pacing (RVAP). However, very few studies have compared the effects of direct His bundle pacing (DHBP) and RVAP. The aim of our study was the intra-patient comparison of myocardial perfusion corresponding to these two different pacing techniques, as perfusion expresses local workload and is related to long-term outcome.

Methods and results Twelve consecutive patients with standard pacemaker indication (9 male, 74 ± 9 years) entered the study. Pacing leads were implanted in the right ventricular apex and directly in the His bundle, and were connected to different ports of the pacemaker. All patients first underwent 3 months of DHBP, followed by 3 months of RVAP. At the end of each 3-month period, myocardial perfusion was measured at rest using scintigraphy with Tc99m-SestaMIBI. The average values of perfusion were evaluated on a 20-segment basis. All patients also underwent clinical evaluation, echocardiography, and tissue Doppler imaging (TDI), to measure dyssynchrony, and a blood sample was taken for brain natriuretic peptide (BNP) assay. The perfusion score during DHBP pacing was significantly better than during RVAP (0.44 ± 0.5 vs. 0.71 ± 0.53, respectively; P = 0.011). None of the patients showed lower perfusion during DHBP than during RVAP. We found no significant difference in NYHA class, ventricular volumes, ejection fraction, or plasmatic BNP between DHBP and RVAP. However, mitral regurgitation (0.26 ± 0.21 vs. 0.37 ± 0.25; P < 0.001) and dyssynchrony (13.75 ± 4.28 vs. 22.02 ± 8.44; P = 0.008) were significantly less during DHBP than during RVAP.

Conclusion Direct His bundle pacing is superior to RVAP in preserving the physiologic distribution of myocardial blood flow and reducing mitral regurgitation and left ventricular dyssynchrony.

Introduction

Permanent intravenous pacing is traditionally performed by means of leads placed in the right ventricular (RV) apex. This choice is almost entirely based on the simplicity of reaching this site, the stability of the final position of the leads and the reliability of pacing performance. However, several studies on animals and humans have revealed that propagation of the pacing pulse from the right to the left ventricle can cause an asynchronous contraction similar to that observed during left bundle branch block.1 This asynchronous contraction leads to regionally different oxygen requirements and, consequently, regional differences in perfusion. Long-term consequences of asynchronous activation are ventricular hypertrophy and dilatation, decreased cardiac pump function, and structural myocellular remodelling, ultimately leading to deteriorating heart function.2 Right ventricular apical pacing (RVAP) has been shown to increase morbidity and mortality in patients receiving a high percentage of cumulative pacing3 and in patients with already low ejection fraction.4 Several studies have explored pacing sites that allow more physiological stimulation. RV septal pacing is the most frequently studied technique, as it can be achieved with
standard screw-in leads; however, no unanimous results have
been reported on short- or long-term follow-up.5–8 Direct His
bundle pacing (DHPB) most likely yields optimal, completely
normal, activation of the ventricles, as demonstrated by the
duration and morphology of the paced QRS complex, which
mimics the intrinsic QRS perfectly.9 However, only one study
has directly compared para-His bundle pacing with RV apical
stimulation.10 Using a novel implantation technique,11 we
were able to establish permanent DHPB.

The aim of our study was to compare myocardial perfusion
during DHPB and during RVAP. The distribution of myocardial
perfusion was chosen because it expresses the distribution
of myocardial workload.

Methods

Study protocol

Patients with standard indication for permanent pacemaker (PM)
implantation and preserved His bundle conduction were eligible
for the study. Exclusion criteria were: (i) history of coronary
artery disease, including angina pectoris, myocardial infarction, or
previous revascularization procedure (PTCA or coronary by-pass);
(ii) history of vascular arterial disease including stroke; (iii) dia-
betes; (iv) previous episodes of heart failure; (v) uncontrolled
hypertension; (vi) valve disease. Moreover, patients were excluded
if any coronary or vascular event occurred during the study.

The DHPB technique followed by our group has been described
previously.11 Briefly, we mapped the His potential by means of a
standard diagnostic electrophysiology catheter with 2 mm
intra-electrode spacing, inserted via the subclavian vein. Once the
His potential had been located, permanent DHPB was attempted
by means of a lead-delivery system (Select Secure, Medtronic Inc.,
Minneapolis, MN, USA) composed of a steerable catheter and a
4.1 Fr bipolar fixed-screw lead. The steerable catheter was inserted
into the RV through the left subclavian vein and advanced close to
the distal dipole of the quadripolar diagnostic catheter. It was
then gently rotated counter-clockwise towards the His bundle and
positioned exactly on the distal dipole of the quadripolar diagnostic
catheter; the lead was then screwed-in by applying four or five
clockwise rotations. The steerable catheter was subsequently
retracted 3 or 4 cm in order to allow electrical measurements to
be taken and to assess lead performance. Successful DHPB criteria
were considered: (i) recording of His bundle potential through the
screw-in pacing lead; (ii) pace-ventricular interval equal to His-
ventricular interval ± 15 ms; (iii) paced QRS morphology and dur-
ation equal to those of the Intrinsic QRS in all 12-lead ECGs; (iv)
His bundle capture in an all-or-none fashion, as demonstrated by
the absence of QRS widening at a lower pacing output; (v) at high
output, possible capture of the septal muscle with widening of
the QRS complex; (vi) pacing from the screw-in lead up to
150 bpm to achieve 1:1 conduction from stimulus artifact to QRS,
in order to test His bundle conduction. If any of the above-
mentioned criteria were not met the lead was un-screwed and a
new position was chosen until satisfactory values were obtained.
We used standard bipolar tined leads to pace the right atrium (RA)
and RV apex. All patients in sinus rhythm were implanted with a
triple-chamber PM: the atrial channel was connected to a standard
atrial lead implanted in the RA and the ventricular channels were
connected to: (i) the His bundle pacing lead in the RV port and (ii)
the RV apical pacing lead in the LV port. Ventricular sensing was
always enabled by the RV apical lead, while the pacing site was
changed according to the protocol phase, as explained below.
Patients with chronic atrial fibrillation (AF) were implanted with a
dual-chamber PM with the His pacing lead connected to the atrial
port and the ventricular apical lead to the RV port. The PM was
then programmed to the DVI mode so that the RV apical lead was
used as a back-up electrode; indeed, when this pacing configuration
is used, the RV pacing spike is inhibited if the His bundle is captured,
while a loss of His bundle capture results in pacing from RV apical
lead. On the basis of our previous experience11 and in accordance
with the results reported by Deshmukh et al.,9 the RV back-up
lead was also used as a sensing lead to overcome low ventricular
sensing issues.

After hospital discharge, all patients received DHPB for 30 ± 5
days. At this time, all patients who satisfied the following criteria
were enrolled in the study: (i) stable ventricular pacing arbitrarily
defined as percentage of DHPB rhythm >90%; (ii) stable clinical
status, without any adverse event (hospitalization, dyspnea,
fatigue, etc.) reported since the date of implantation; (iii) stable
PM electrical parameters; (iv) the absence of contraindications for
myocardial scintigraphy. All patients received only DHPB for the fol-
lowing 3 months. At the end of this 3-month period, they underwent
at-rest myocardial scintigraphy with Tc99m-SestaMIBI in order
to evaluate myocardial perfusion. They also underwent clinical eval-
uation including medical history, physical examination, quality of life
(QoL) evaluation, PM check, echocardiography, and first time blood
sample analysis for brain natriuretic peptide (BNP) assessment.
The PM was then reprogrammed to the RV apical pacing mode. After 3
months of RV apical pacing, all patients again underwent at-rest myo-
cardial scintigraphy and the same clinical examinations described
above. The percentage of ventricular paced beats was assessed

![Figure 1 Study flow chart.](https://academic.oup.com/europace/article-abstract/10/5/580/597211)
during the PM check. At the end of the study, all PMs were reprogrammed to DHBP. The study flow chart is shown in Figure 1. Each patient was blinded on his programmed pacing mode. The protocol was approved by the local Ethics Committee and all patients gave their informed consent before entering the study. The investigation conformed to the principles outlined in the Declaration of Helsinki.

Patient population
From January 2006 to August 2006, a total of 12 consecutive patients who fulfilled the inclusion criteria were admitted to our institution for PM implantation and enrolled in the study (Table 1). Indications for permanent pacing were: AF with slow ventricular rate (four patients, 33%), second-degree AV block (six patients, 50%), third-degree AV block (two patients, 16%) with narrow QRS due to a preserved His-Purkinje conduction. Indications for pacing in the AF subgroup were: heart rate <40 and <80 bpm at rest and during effort, respectively, and intact His-ventricular conduction.

Clinical evaluation
Clinical status was evaluated by means of the SF-36 questionnaire, a multipurpose, short-form health survey composed of 36 questions. This yields an 8-scale profile of functional health and well-being scores, as well as psychometrically based physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Each scale is graduated from 0 to 100, a higher score indicating a better condition of the patient with regard to the specific parameter evaluated.

Scintigraphic imaging methods and single photon emission computerized tomography acquisition protocol
Myocardial perfusion was assessed through single photon emission computerized tomography (SPECT) imaging with Tc99m-SestaMIBI in accordance with a standard protocol used in our laboratory: with the patient at rest, 800 MBq of Tc99m-SestaMIBI was injected intravenously; imaging began 60 minutes after injection. Single photon emission computerized tomography imaging was performed by means of a Siemens-E.cam dual detector gamma camera equipped with low-energy, high-resolution collimators. Thirty-two images, each of 40 s, were acquired over a 90° anterior orbit. Images were acquired using a 64 × 64 image matrix. A 15% window centred on the 140 keV peak was used. Single photon emission computerized tomography acquisition was repeated when insufficient hepatobiliary clearance or a motion artifact was present on the raw images. Oblique reconstruction was performed by means of filtered back-projection with re-orientation into short axis and horizontal and vertical long axes. Filtering was performed by using a Butterworth filter applying a 0.50 Nyquist cut-off frequency with an order of 9.

Image interpretation
Images were visually interpreted by using short-axis, vertical and horizontal long-axis tomograms, which were displayed on a paper film at 2 pixel thickness with staggered summation. The intensity of each image was normalized to the highest pixel value in that image. The short-axis and vertical long-axis myocardial tomograms were divided into 20 segments for each study, as previously described. These segments were assigned to six evenly spaced regions in the apical, mid-ventricular, and basal slices of the short-axis views and two apical segments on the mid-ventricular long-axis slice. Segments were scored by consensus of two skilled nuclear medicine physicians using a 5-point scoring system (0, normal; 1, slightly reduced; 2, moderately reduced; 3, severely reduced; 4, absent uptake); in the event of discrepancy, a final diagnosis was reached by consensus. According to standard practice, five myocardial perfusion SPECT studies without perfusion defects, recorded in patient without a PM, were used as controls. The observers were unaware of the patient’s clinical history and pacing modality.

Echocardiographic data
Before implantation, all patients included in the study underwent full M-mode, two-dimensional, and colour-Doppler examinations. Echocardiographic evaluation was performed by means of a commercially available imaging system (VIVID Five, GE Medical System, Milwaukee, WI, USA) equipped with a 2.5–3.6 MHz transducer. Echo recordings were obtained through the apical 2-chamber and apical 4-chamber views, with the patient lying down in the left lateral position. All measurements were taken for five consecutives cycles and the mean values were calculated. Two-dimensional echocardiograms were obtained in accordance with the American Society of Echocardiography guidelines. Global LV function was assessed from two-dimensional apical views by measuring LV end-diastolic volume (EDV), LV end-systolic volume (ESV), and ejection fraction (EF), using the modified biplane Simpson rule (inter-observer and intra-observer correlation for LV volume: 0.93 and 0.95, respectively). Echocardiograms were deemed of acceptable quality if 80% or more of the endocardium was visible. Colour-Doppler echocardiography was used to detect and quantify mitral regurgitation by means of the Vena Contracta method, since this is a simple and efficacious quantitative method of identifying mild or severe mitral valve regurgitation. We considered mitral valve insufficiency as mild (<0.3), moderate (0.3–0.69), and severe (>0.70). Parameters of ventricular dyssynchrony
Tissue Doppler imaging was performed by means of pulsed-wave Doppler from the three apical views (four-chamber, two-chamber, and long-axis) to assess longitudinal myocardial regional function of the LV. Tissue Doppler Imaging was applied by placing the sample volume in the middle of the basal and mid-segmental portions of the lateral, inferior, anterior, antero-septal, and posteroseptal walls in the apical four-chamber view. Gain and filters were adjusted, as required, to eliminate background noise and to obtain a clear tissue signal. Tissue Doppler imaging signals were recorded at a sweep of 100 mm/s. From the Doppler spectrum,
we evaluated: (i) the electromechanical delay (EMD) for each segment, defined as the delay between the onset of the QRS complex on the surface ECG and the onset of the systolic TDI wave; (ii) mechanical dysynchrony, calculated as the standard deviation (SD) of the EMD of all the segments. Each parameter was measured on the average of five consecutive beats. Intra-observer and inter-observer correlations for LV basal segment measurements were assessed in 29 patients and reached 0.97 and 0.96, respectively. Reproducibility of lateral left- right wall activation measurements was also tested in 20 patients (intra-observer and inter-observer correlations were 0.92 and 0.90). We characterized the cut-off range of intra-LV values as follows: the statistical a risk was fixed at 0.05, so that the physiologic range of the parameter would be included in the ‘mean ± 2 SD’ range, which represents 95% of the control group distribution. Abnormal intra-LV was defined as a SD > 22 ms.

**BNP**

The plasma levels of BNP were measured by means of a solid-phase sandwich immunoradiometric assay utilizing two monoclonal antibodies against sterically remote sites, the first being coated on the solid-phase of the beads and the second radiolabelled with iodine 125 as a tracer (analysis performed with ADVIA CENTAUR Bayer). Upper normal value: 100 pg/mL.

**Statistical analysis**

Data distribution in our population was considered normal by the test of Kolmogorov-Smirnov. Descriptive statistics for continuous variables were computed as mean ± standard deviation if normally distributed and compared by means of paired two-tailed T-test. Non-parametric Wilcoxon’s test was applied to quantitative variables. Statistical analysis was performed by means of SPSS 9.0 (SPSS Inc., Chicago, IL, USA) software. Each patient was considered as its own control during the two different pacing modalities, in a prospective, non-randomized cross-over study. A value of P < 0.05 was considered statistically significant.

**Results**

Twelve consecutive patients (9 male, 74 ± 9 years) were implanted. Baseline NYHA class was 1.6 ± 0.7 and EF, assessed through echocardiography, was 59.8 ± 7. All patients in chronic AF were programmed at a lower rate of 70 bpm. Patients in sinus rhythm and AV block were programmed at a lower rate of 70 bpm and an AV interval of 150 ± 20 ms in accordance with the Ritter formula. Pacemaker recordings documented a percentage of paced beats >97% in the AF group and >90% in the sinus rhythm group. No complications or complaints by patients were reported during the study period. No patient was excluded from the study owing to the occurrence of an adverse event. The perfusion results are summarized in Tables 2–4. The perfusion score (evaluated as mean perfusion value of all ventricular segments) was significantly better during DHBP than during RVAP (0.44 ± 0.5 vs. 0.71 ± 0.53, respectively, P = 0.011). None of the patients showed lower perfusion during DHBP than during RVAP. An example is represented in Figure 2. The greatest differences in perfusion were localized in the infero-septal region—mid (−0.75) and apical (−0.91) segments—and in the apical (−0.75) region (Table 4; Figure 3). In all but one segment, perfusion during DHBP was either better than or equal to that seen during RVAP (Table 2 and 3).

**Clinical evaluation**

Clinical evaluation by means of the SF-36 questionnaire is reported in Table 5. All patients considered their physical and mental status to be better during DHBP than during RVAP. In particular, the 8-scale profile of functional health and well-being showed DHBP to have a better outcome than RVAP with regard to the job/physical sphere (P = 0.038). Though still marked, differences in perceptions of general well-being (P = 0.060) and vitality (P = 0.065) were less significant. NYHA class did not change significantly during the two pacing modes.

The echocardiographic data showed that the mean EF was 0.63 ± 0.12 after 3 months of DHBP vs. 0.61 ± 0.10 after 3 months of RVAP (P = NS). After DHBP, left ventricular volumes during the systolic and diastolic phases were 25.5 ± 12.9 and 68.2 ± 15.6 mL/m², respectively, whereas after RAVP, left ventricular systolic volume was 27.3 ± 18.9 mL/m² and left ventricular diastolic volume was 67.3 ± 23.2 mL/m². Mitral regurgitation was 0.25 ± 0.10 mm on DHBP vs. 0.45 ± 0.16 mm on RVAP (P < 0.001) (Table 6).

Mechanical dysynchrony was significantly less during DHBP than during RAVP (13.75 ± 4.2 vs. 22.01 ± 8.4; P = 0.008). Assuming a SD of EMD as the threshold for dysynchrony, half of the patients showed dyssynchrony during RVAP, whereas none did during DHBP (Figure 4).

**BNP**

The difference in plasmatic BNP between RVAP and DHBP did not reach statistical significance. The mean BNP value was 69.3 ± 57.2 pg/mL on DHBP vs. 74.1 ± 62.58 pg/mL on RVAP (P = 0.60 NS).

**Discussion**

Our study shows that perfusion defects are associated with RVAP. In patients with bradycardia and preserved His conduction, chronic His pacing is not only feasible, but is also...
associated with a more physiological distribution of myocardial perfusion than RVAP.

Several reports have indicated perfusion defects of the left ventricular myocardial wall after exercise and after pharmacologic stress in paced patients, despite the absence of coronary artery disease. These defects occur mainly in the apical and inferior walls, but reduced perfusion is also described in other left ventricular regions. Animal and human studies have shown that regional differences in myocardial blood flow and oxygen consumption start immediately at the onset of RV apical pacing. Animal studies have shown a close correlation between regional flow, oxygen consumption, and mechanical work, with early-activated regions, such as the apex and septum, receiving ~30% lower perfusion than regions with normal electrical activation. According to these animal studies, the reduced perfusion in early-activated regions is primarily due to a reduced workload, thus providing an explanation for our observations of lower perfusion in apical and inferior segments during RVAP.

However, impairment of myocardial perfusion may also be due to abnormal contraction patterns. Evidence for this idea was provided by Helmer et al. who found that in animals fast pacing induced cardiomyopathy and caused perfusion defects after only 1 week. Similarly, Ono et al. showed increasing perfusion defects with increasing heart rate. These authors also found that perfusion abnormalities occur before significant ventricular remodelling. In the only clinical study in this field, Tse and Lau found that during RVAP the number of perfusion defects increased between 6 and 18 months of pacing and that these defects were related to deterioration in cardiac function. In the group of patients on right ventricular outflow-tract pacing, fewer perfusion defects were found and this pacing modality was associated with better preservation of pump function and less heart failure. These results could be explained by assuming regular under-perfusion during increasing heart rate, leading to cumulative hibernation or stunning.

The fact that we observed differences in perfusion defects within as little as 3 months may be explained by the direct mechano-energetic effects of ventricular pacing and the cross-over design of the present study, allowing to use each patient as its own control. Because DHBP uses normal conduction pathways, dyssynchrony is absent and regional differences in energy demand and/or flow impairment are avoided. Also, our echocardiographic data also suggest a role for the lack of stunning during DHBP.

In agreement with Helmer et al., our study evidenced that 3 months of right apical pacing was not enough to cause significant ventricular remodelling. Similarly, it was not anticipated that the short period of RVAP in relatively healthy subjects would lead to heart failure. Comparing the various clinical studies, RVAP only lead to deleterious
effects in the DAVID trial,4 which examined ICD patients with low EF. In contrast, in patients with preserved LV function, the negative effect of RV apical pacing needs more time to show effects on heart failure.3,32

Also, longer term studies on the effect of DHBP by Deshmukh et al.9 showed in nine patients an improvement in functional class and a significant increase in EF, with a significant reduction in left ventricular diameters and a reduction in cardiothoracic ratio. Similar results were also reported by Vazquez et al.33 in 8 of 12 patients in whom DHBP was attempted.

Interestingly, although patients were blinded, QoL questionnaires results reveal a statistically significant improvement in the job-physical sphere during DHBP in comparison with RVAP.

Limitations

In the present study, we did not investigate the pre-implantation coronary condition through coronary angiography because most of the enrolled patients had an urgent indication for permanent pacing. However, any possible coronary disease was excluded on the basis of medical history, objective examination, electrocardiogram, and negative ischaemic biochemical markers. Moreover, as we investigated coronary perfusion only at rest, we cannot extrapolate our results to dynamic conditions, such as physical exercise. The choice of selecting only patients without ischaemic disease or heart failure was made in order to exclude the presence of poor perfusion or ventricular remodelling at enrollment. It is likely that the perfusion abnormalities observed in this study are equal or even more pronounced in ischaemic or heart failure patients. It should be emphasized that a 3-month period may be too short to show the entire impact of DHBP vs. RVAP. A much

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**Table 3 Segment perfusion score**

<table>
<thead>
<tr>
<th></th>
<th>DHBP</th>
<th>RVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base</td>
<td>Mid</td>
</tr>
<tr>
<td>Antero-basal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Antero-septal</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Infero-septal</td>
<td>0.91</td>
<td>0.25</td>
</tr>
<tr>
<td>Infero-lateral</td>
<td>1.25</td>
<td>1</td>
</tr>
<tr>
<td>Antero-lateral</td>
<td>0.67</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Mean perfusion rate per segment expressed as the average of all the patients. On the left are reported the perfusion score after DHBP, while on the right after RVA.

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**Table 4 Perfusion difference for each segment**

<table>
<thead>
<tr>
<th></th>
<th>Base</th>
<th>Mid</th>
<th>Apical</th>
<th>Apex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antero-basal</td>
<td>0</td>
<td>0</td>
<td>−0.166</td>
<td>−0.41</td>
</tr>
<tr>
<td>Antero-septal</td>
<td>0.16</td>
<td>0</td>
<td>−0.25</td>
<td>−0.75</td>
</tr>
<tr>
<td>Infero-septal</td>
<td>−0.16</td>
<td>−0.75</td>
<td>−0.91</td>
<td></td>
</tr>
<tr>
<td>Infero-lateral</td>
<td>−0.16</td>
<td>−0.5</td>
<td>−0.5</td>
<td></td>
</tr>
<tr>
<td>Antero-lateral</td>
<td>−0.25</td>
<td>−0.08</td>
<td>−0.16</td>
<td></td>
</tr>
</tbody>
</table>

For each ventricular segment the difference in perfusion is expressed as mean of all the differences in perfusion related to that segment.

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**Table 5 Quality of life questionnaire significant correlations**

<table>
<thead>
<tr>
<th></th>
<th>T-score</th>
<th>Z-score</th>
<th>P-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHYSICAL FUNCTIONING INDEX_HIS VS DX</td>
<td>0.561</td>
<td>0.586</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROLE-PHYSICAL INDEX_HIS VS DX</td>
<td></td>
<td>−2.070</td>
<td>0.038</td>
<td></td>
</tr>
<tr>
<td>PAIN INDEX_HIS VS DX</td>
<td>1.707</td>
<td>0.116</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GENERAL HEALTH PERCEPTIONS INDEX_HIS VS DX</td>
<td>2.101</td>
<td>0.060</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VITALITY INDEX_HIS VS DX</td>
<td>2.052</td>
<td>0.065</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOCIAL FUNCTIONING INDEX_HIS VS DX</td>
<td></td>
<td>−1.604</td>
<td>0.109</td>
<td></td>
</tr>
<tr>
<td>ROLE-EMOTIONAL INDEX_HIS VS DX</td>
<td></td>
<td>−1.633</td>
<td>0.102</td>
<td></td>
</tr>
<tr>
<td>MENTAL HEALTH INDEX_HIS VS DX</td>
<td>1.185</td>
<td>0.261</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Table 6 Clinical summary**

<table>
<thead>
<tr>
<th></th>
<th>DHBP</th>
<th>RVAP</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class</td>
<td>2.0</td>
<td>2.0</td>
<td>0.7</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>69.3</td>
<td>74.1</td>
<td>0.068</td>
</tr>
<tr>
<td>EF</td>
<td>0.63</td>
<td>0.61</td>
<td>0.10</td>
</tr>
<tr>
<td>EDV (mL/mq)</td>
<td>68.7</td>
<td>67.4</td>
<td>0.23</td>
</tr>
<tr>
<td>ESV (mL/mq)</td>
<td>26.3</td>
<td>27.4</td>
<td>0.16</td>
</tr>
<tr>
<td>MRVC</td>
<td>0.26</td>
<td>0.37</td>
<td>0.25</td>
</tr>
<tr>
<td>Dyssynchrony (ms)</td>
<td>14.65</td>
<td>21.64</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Clinical, echocardiographic data, and brain natriuretic peptide (BNP) determination in both pacing modalities. EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; MRVC, mitral regurgitation calculated as Vena Contracta; EMD, electromechanical delay; Dyssynchrony: SD, standard deviation of EMD of all segments (modified Yu-index).
longer pacing period could further increase the differences in perfusion and remodelling between DHBP and RVAP.

Our study population was small. However, the cross-over design reduced inter-individual variation, thereby enabling the reproducible effects of RVAP on flow distribution to be demonstrated even with a limited number of subjects.

Possible clinical implications

Evidence that RV apical pacing can impair LV function is reported in the scientific literature. The medical community should take into account alternatives to RV stimulation. DHBP in patients with preserved His conduction, or para-Hisian pacing in patients with conduction disturbances, could become a new standard for chronic RV stimulation in the near future. Meanwhile, the technology of His pacing and sensing should be improved, in order to guarantee the maximum level of safety and reliability of the implanted system.

Conclusions

Pacing the His bundle is superior to RVAP in preserving the physiologic distribution of myocardial blood flow and reducing mitral regurgitation and ventricular dyssynchrony.

Normal blood flow distribution during His bundle pacing appears to be an important prerequisite in preventing the development of heart failure in patients requiring a high percentage of ventricular pacing. This relatively short-lasting study is a good starting point for larger studies inquiring into the long-term implications of the benefit of a more physiologic pacing site in anti-bradycardia pacing.

Acknowledgements

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Conflict of interest: none declared.

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