Comparison of permanent left ventricular and biventricular pacing in patients with heart failure and chronic atrial fibrillation: prospective haemodynamic study

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Objective: To compare clinical and haemodynamic variables between left ventricular and biventricular pacing in patients with severe heart failure, and to analyse haemodynamic changes during daily life and maximum exercise during chronic left ventricular and biventricular pacing.

Design: Prospective single blinded randomised study with crossover.

Setting: University hospital (tertiary referral centre).

Patients and methods: 13 patients (mean (SD) age, 62 (6) years) with chronic atrial fibrillation, severe heart failure (mean ejection fraction 24 (8)%), and QRS prolongation of > 140 ms had His bundle ablation and installation of a pacemaker providing left ventricular and biventricular pacing. The pacemaker was equipped with a peak endocardial acceleration (PEA) sensor. The PEA pattern was used as a haemodynamic marker during exercise as it is highly correlated with left ventricular dP/dt.

Results: PEA values were higher with left ventricular pacing (0.58 (0.38) m/s) and biventricular pacing (0.62 (0.24) m/s) than at baseline (0.49 (0.18) m/s) (p < 0.05). The six minute walk test showed similar performance in both pacing modes, but patients had more symptoms with left ventricular pacing (125 (18) W; p = 0.03). On cardiopulmonary exercise testing, there was a greater increase in mean percentage variation of PEA with biventricular pacing than with left ventricular pacing (125 (18)% vs 97 (36)%, respectively; p = 0.048) and better performance figures (92 (34) W vs 77 (23) W; p = 0.03).

Conclusions: During symptom limited and daily life exercise tests, chronic biventricular pacing provides better haemodynamic performance than left ventricular pacing. In heart failure patients with wide QRS complexes, the interventricular dyssynchronisation induced by left ventricular pacing may impair myocardial function during exercise.

New non-invasive tools for the mid and long term assessment of cardiac function are needed to clarify which patients can benefit from multisite ventricular pacing. One such tool is an implantable intracardiac accelerometer (connected to a pacemaker), which is suitable for non-invasive monitoring of myocardial contractility. This sensor provides intracavity recordings of the maximum amplitude of the vibrations produced by the first heart sound (peak endocardial acceleration (PEA)), using an implantable micromass tip-mounted accelerometer. The recorded changes in PEA are highly correlated with changes in left ventricular dP/dt in humans.

Our first aim in this study was to compare clinical and haemodynamic variables during LVP and BVP at mid term follow up in patients with severe heart failure. Our second objective was to analyse haemodynamic changes during daily life and maximum exercise with the two pacing modes, using the PEA data provided by the pacemaker sensor.

Abbreviations: BVP, biventricular pacing; LVP, left ventricular pacing; NYHA, New York Heart Association; PEA, peak endocardial acceleration

Biventricular pacing (BVP) is a novel and promising form of treatment for patients with severe chronic heart failure. This type of pacing has been shown to reduce pulmonary capillary wedge pressure and to increase cardiac output. Left ventricular pacing (LVP) alone has also been shown to improve cardiac function in patients with heart failure, but results in a longer QRS duration than BVP, or even than spontaneous rhythm. These studies reported that left ventricular free wall pacing acutely enhanced femoral systolic pressure while lowering pulmonary wedge pressure, and the responses from single left ventricular sites were similar to BVP. LVP tended to result in a greater increase in stroke work than BVP, along with lower end systolic volumes. Several studies have also emphasised that the improvement in cardiac function in heart failure is not dependent upon QRS narrowing in patients with baseline intraventricular conduction delay.

There has been no assessment of chronic LVP compared with chronic BVP. An ideal chronic assessment would consist of repeated invasive catheterisation procedures and measurement of the first derivative of left ventricular pressure (left ventricular dP/dt) during follow up, with the aim of correlating variations in dP/dt with the clinical status of the patient.
METHODS

Patients were considered for inclusion in the study if they presented with the following:

- Functional class III or IV (New York Heart Association, NYHA) congestive heart failure despite treatment with diuretics, angiotensin converting enzyme inhibitors, and β blockers at the maximum tolerated doses
- A left ventricular ejection fraction of < 40% assessed by radionuclide angiography
- A left ventricular end diastolic diameter of ≥ 60 mm
- QRS duration of > 140 ms (recorded at 50 mm/s)
- Chronic atrial fibrillation

Patients were also required to have a suitable acoustic window for reliable echocardiographic analysis. All patients received a pacemaker providing both IVP and BVP after providing written informed consent. The study was approved by our local ethics committee. Patients were excluded if they were less than 18 or more than 80 years of age, if they had unstable angina pectoris within two months of the start of the study, if they had acute myocardial infarction within six months of the study, or if they had had percutaneous coronary angioplasty or coronary artery bypass grafts within the preceding year.

The study population consisted of 13 men (mean (SD) age, 64 (12) years) with severe chronic heart failure and chronic atrial fibrillation with a long QRS (168 (15) ms). Eight patients had left bundle branch block and five had a non-specific intraventricular conduction block. The mean left ventricular ejection fraction was 24 (8)%. Ten patients were in New York Heart Association class III or IV at the time of randomisation. The mean left ventricular ejection fraction was 24 (8)%. Ten patients were in New York Heart Association class III or IV at the time of randomisation.

The 13 patients presented with an intermittent symptomatic rapid ventricular rate despite the maximum tolerated treatment with amiodarone, calcium channel blockers, β blockers, or combinations of these. All patients underwent His bundle ablation followed by DDDR pacemaker implantation (Living Plus, Sorin Biomedica, Saluggia, Italy). This pacemaker is equipped with an intracardiac accelerometer sensor recording the PEA variations and thus provides the facility for continuous monitoring of myocardial contractility.

A specific lead configuration was designed to provide left ventricular pacing, right ventricular pacing, and simultaneous left and right ventricular pacing. The left ventricular lead was successfully implanted transvenously in all patients. The left ventricle was paced with a specially designed lead for pacing through the coronary sinus (model 2188, Medtronic, Minneapolis, Minnesota, USA). The lead was positioned at the base/anterolateral left ventricular wall through the great cardiac vein (at its proximal part) in all patients to allow reproducible interpretation of the effects of left ventricular pacing. A bipolar pacing lead was then positioned at the right ventricular apex, and both leads were connected to the atrial port using a Y adapter. Programming the pacemaker to unipolar AAI mode resulted in left ventricular pacing, while a bipolar AAI pacing mode provided biventricular pacing.

A second bipolar pacing lead was positioned at the right ventricular apex and connected to the ventricular port to provide back up right ventricular pacing alone. The latter was a specific lead with an accelerometer incorporated at its tip allowing continuous measurement of PEA variations.

Study protocol

Baseline measurements (table 1) were obtained after one month of right ventricular apical pacing following the His bundle ablation. After this there were two randomised phases with crossover: two months of BVP (phase 1) and two months of LVP (phase 2). Seven patients underwent LVP during the first phase, while six underwent BVP. Radionuclide left ventricular ejection fraction, QRS duration, echocardiographic measurements (aortic ejection duration, aortic pre-ejection time interval, and aortic velocity–time integral), and PEA measurements (averaged over a 10 minute period during each phase) were recorded at the end of each phase (including the baseline) at a fixed pacing rate of 70 impulses/min. In addition, all patients underwent a six minute walking test and a symptom limited bicycle ergometer test with peak oxygen uptake (V̇O₂) calculation. The two exercise tests were performed at a fixed heart rate (70 impulses/min), and the memory function of the pacemaker recorded the number of premature ventricular complexes.

Statistical analysis

The sample size (n = 13) was determined as the following: a statistical power reaching 80% with an α risk of 0.05 when the difference between the two pacing modes reaches 25% (that is, a difference of 25% in PEA variation measurements between BVP and LVP at rest and/or on exercise). Results are expressed as mean (SD). Multivariate analysis of variance with repeated measurements was performed to

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Table 1: Clinical, echocardiographic, and haemodynamic variables at baseline in the study population

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Cardiac disease</th>
<th>PEA (G)</th>
<th>QRS duration* (ms)</th>
<th>Aortic TVI (mm)</th>
<th>Aortic pre-ejection time interval (ms)</th>
<th>Aortic ejection duration (ms)</th>
<th>Left ventricular ejection fraction (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>M</td>
<td>Ischaemic</td>
<td>0.49</td>
<td>220</td>
<td>133</td>
<td>203</td>
<td>221</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>M</td>
<td>Idiopathic</td>
<td>0.74</td>
<td>230</td>
<td>81</td>
<td>261</td>
<td>178</td>
<td>21</td>
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<tr>
<td>3</td>
<td>64</td>
<td>M</td>
<td>Idiopathic</td>
<td>0.80</td>
<td>225</td>
<td>106</td>
<td>240</td>
<td>215</td>
<td>21</td>
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<tr>
<td>4</td>
<td>76</td>
<td>M</td>
<td>Ischaemic</td>
<td>0.35</td>
<td>210</td>
<td>109</td>
<td>248</td>
<td>232</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>M</td>
<td>Idiopathic</td>
<td>0.33</td>
<td>220</td>
<td>82</td>
<td>240</td>
<td>247</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
<td>M</td>
<td>Idiopathic</td>
<td>0.52</td>
<td>220</td>
<td>180</td>
<td>235</td>
<td>272</td>
<td>18</td>
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<tr>
<td>7</td>
<td>78</td>
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<td>Ischaemic</td>
<td>0.46</td>
<td>210</td>
<td>102</td>
<td>198</td>
<td>228</td>
<td>17</td>
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<tr>
<td>8</td>
<td>58</td>
<td>M</td>
<td>Ischaemic</td>
<td>0.55</td>
<td>210</td>
<td>124</td>
<td>206</td>
<td>204</td>
<td>33</td>
</tr>
<tr>
<td>9</td>
<td>79</td>
<td>M</td>
<td>Ischaemic</td>
<td>0.18</td>
<td>200</td>
<td>130</td>
<td>213</td>
<td>223</td>
<td>24</td>
</tr>
<tr>
<td>10</td>
<td>46</td>
<td>M</td>
<td>Idiopathic</td>
<td>0.38</td>
<td>195</td>
<td>109</td>
<td>221</td>
<td>198</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>76</td>
<td>M</td>
<td>Idiopathic</td>
<td>0.70</td>
<td>190</td>
<td>125</td>
<td>186</td>
<td>203</td>
<td>24</td>
</tr>
<tr>
<td>12</td>
<td>64</td>
<td>M</td>
<td>Idiopathic</td>
<td>0.31</td>
<td>185</td>
<td>155</td>
<td>228</td>
<td>330</td>
<td>38</td>
</tr>
<tr>
<td>13</td>
<td>63</td>
<td>M</td>
<td>Ischaemic</td>
<td>0.60</td>
<td>190</td>
<td>90</td>
<td>283</td>
<td>255</td>
<td>18</td>
</tr>
</tbody>
</table>

Mean (SD) 64 (12) 0.49 (0.18) 208 (15) 117 (28) 228 (27) 231 (39) 25 (08)

*QRS duration during right ventricular pacing alone.

M, male; PEA, peak endocardial acceleration, TVI, time–velocity integral.
RESULTS
Rest
After two months of LVP, QRS duration was similar to the value at baseline (205 (23) ms vs 208 (15) ms, respectively; NS), while after two months of BVP QRS duration was significantly shorter than at baseline (153 (21) ms; p < 0.01) (fig 1). PEA measurements gave higher values with both LVP and BVP than at baseline (0.49 (0.18) m/s at baseline vs 0.58 (0.38) m/s with LVP vs 0.62 (0.24) m/s with BVP; p < 0.05) (fig 1). Similar results were observed for the aortic time–velocity integral (fig 1). The aortic pre-ejection time interval and ejection duration shortened significantly only with BVP (fig 1). The left ventricular ejection fraction increased from 25 (8)% at baseline to 29 (10)% after two months of LVP (p < 0.05) and to 30 (11) after two months of BVP (p < 0.05).

Ten patients improved both clinically (by NYHA functional class) and haemodynamically (as shown by an increased left ventricular ejection fraction and aortic time–velocity integral and by the PEA measurements) (fig 2A). Four patients had higher PEA values with LV than BVP pacing. Two of these were not clinically improved (shown in grey) by LV or BVP pacing. The absence of clinical improvement was associated with absence of haemodynamic improvement, as PEA values were decreased with both LV and BVP pacing compared with baseline. (B) Seven patients had higher PEA measurements with BV than LV pacing. One patient did not improve either clinically or haemodynamically (shown in grey). This patient had a decrease in the PEA values during LV pacing as well as during BVP pacing compared with baseline. Three patients (dashed lines) were not clinically or haemodynamically improved by LV pacing, while BVP pacing resulted in significantly higher PEA values associated with clinical improvement compared with baseline.
Figure 3 Correlation between the percentage variations in left ventricular ejection fraction and peak endocardial acceleration (PEA) values after two months of biventricular (BV) or left ventricular (LV) pacing compared with baseline.

Figure 4 Correlation between the percentage variations in the aortic time–velocity integral and peak endocardial acceleration (PEA) values after two months of biventricular (BV) or left ventricular (LV) pacing compared with baseline.

Exercise
The walking test
Eleven patients underwent this protocol. The remaining two were in NYHA functional class IV despite cardiac resynchronisation and were unable to accomplish this part of the protocol. Performance in the six minute walk test was similar with LVP (table 2). However, more patients with LVP were symptomatic at the end of the test (p = 0.035; table 2). During and BVP (table 2). However, more patients with LVP were in NYHA functional class IV despite cardiac resynchronisation and were unable to accomplish this part of the protocol.

DISCUSSION
Multisite ventricular pacing to treat severe heart failure was first investigated haemodynamically using invasive catheterisation protocols. The initial acute studies also used temporary leads. We were interested to discover whether PEA recordings might be useful in the long term non-invasive monitoring of patients during chronic multisite ventricular pacing.

In our patients, all of whom had His bundle ablation and so no atrioventricular delay that might influence haemodynamic measurements, we placed the left ventricular pacing lead at the base of the anterolateral left ventricular wall. In our experience, this site can be reached in all patients and our main goal was to study a population with standardised pacing lead location. Choosing the mid lateral left ventricular wall would have been more difficult, as four patients had small calibre lateral branches of the coronary sinus. Although results from short term studies suggest that the lateral left ventricular wall—midway between base and apex—is optimal, this remains to be confirmed in mid and long term follow up. In addition, a recent study showed that pacing the left ventricle at the base/anterior wall provided the highest dP/dt and cardiac output when compared with the mid lateral wall and the mid posterior wall; this haemodynamic study was further supported by electrophysiological experiments showing that the shortest left ventricular activation time was observed when pacing the left ventricle at the base/anterior wall rather than at the posterior or the lateral wall.

Table 2 Comparison of effects of left ventricular pacing and biventricular pacing on exercise

<table>
<thead>
<tr>
<th>Variable</th>
<th>After 2 months of LVP</th>
<th>After 2 months of BVP</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Six minute walk test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance [m]</td>
<td>428 (68)</td>
<td>437 (59)</td>
<td>0.88</td>
</tr>
<tr>
<td>Patients with heart failure symptoms after the test (%)</td>
<td>64</td>
<td>18</td>
<td>0.035</td>
</tr>
<tr>
<td>Number of PVCs during the test</td>
<td>49 (71)</td>
<td>10 (23)</td>
<td>0.04</td>
</tr>
<tr>
<td>Symptom limited cardiopulmonary exercise test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance (W)</td>
<td>77 (23)</td>
<td>92 (34)</td>
<td>0.03</td>
</tr>
<tr>
<td>Peak V\textsubscript{O} \textsubscript{2} (mL/kg/min)</td>
<td>16.5 (3.6)</td>
<td>18.5 (4.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>Number of PVCs during the test</td>
<td>64 (74)</td>
<td>25 (29)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Data are mean (SD). BVP, biventricular pacing; LVP, left ventricular pacing; PVCs, premature ventricular complexes; V\textsubscript{O} \textsubscript{2}, oxygen consumption.
Although Edner and colleagues suggested that His bundle ablation can influence left ventricular ejection fraction for at least three months, our protocol started only one month after His ablation. The pacing mode randomisation used in our study controlled for the influence of postablation time interval on the results, as seven patients had initial left ventricular pacing while six had initial biventricular pacing. Irrespective of the initial pacing mode, every patient had a lower percentage increase in PEA with biventricular pacing compared with baseline, even with early activation. However, this slowing of conduction could worsen on exercise owing to the emergence of regional ischaemic areas. In that case biventricular pacing would provide better right and left electromechanical synchrony than LV pacing. In fig 6 it can be seen that the difference in percentage variation in the PEA pattern between LV and biventricular pacing appears to be similar in all the patients during exercise. We performed a separate analysis for patients with ischaemic cardiomyopathy (n = 6) and idiopathic cardiomyopathy (n = 7) to try to characterise a
specific category of patients benefiting to a greater extent from BVP than from LVP. Patients with ischaemic heart failure showed a somewhat greater difference in the measurements of PEA variation between LVP and BVP than patients with idiopathic heart failure (62 (16) % vs 54 (18) %, respectively), but this did not reach significance. Our study was only designed to investigate whether or not BVP was better than LVP; splitting the 13 patients into smaller groups is unlikely to provide sufficient statistical power for further analyses.

The fact that during exercise there were more premature ventricular complexes with LVP than with BVP suggests an increased catecholamine release resulting from a temporary, more pronounced disturbance of myocardial function. Whether the haemodynamic difference between LVP and BVP on exercise will influence long term mortality remains to be determined. In the present study, there was a tendency toward an increase in peak VO₂ with BVP compared with LVP. However, it is likely that the sample size was too small for the difference in peak VO₂ (+2 ml/kg/min for biventricular pacing) to reach significance. On the other hand, we cannot exclude the possibility that biventricular pacing increases exercise duration but not specifically the peak VO₂. Our patients all had very disturbed cardiac function and it is possible to increase the anaerobic performance with only a slight improvement in aerobic performance, as shown in larger randomised prospective studies. 20, 21

Conclusions
These data, along with results of other recent studies, 12 support the view that chronic BVP can provide similar haemodynamic and clinical improvement as BVP at rest. However, during activities of daily living and during symptom limited exercise, BVP allowed better performance than LVP, along with improved haemodynamic measurements and significantly fewer ventricular arrhythmias. It seems that the right bundle branch block induced by LVP may have a detrimental effect on daily living activities in patients with heart failure.

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