Upgrade to biventricular pacing in patients with conventional pacemakers and heart failure: a double-blind, randomized crossover study

Carl J. Höijer*, Carl Meurling, and Johan Brandt

Department of Cardiology, Heart and Lung Division, Lund University Hospital, S-221 85 Lund, Sweden

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Aims To investigate whether patients with previously implanted conventional pacemakers and severe heart failure benefit from an upgrade to a biventricular system.

Methods and results Study inclusion criteria were New York Heart Association (NYHA) classes III and IV, dominant paced rhythm, and no left bundle branch block in the pre-pacing ECG. Ten patients with pacemakers (four VVIR due to slow atrial fibrillation and six DDDR, of which four were due to high-degree atrioventricular block and two to sinus node disease) were upgraded to a biventricular pacing (BVP) system. The median duration of pacing before the upgrade was 5.7 years. Assessments of 6-min walk test, symptom score, brain natriuretic peptide (pro-BNP), and echocardiography were made pre-operatively. After a run-in period of 1 month in BVP following the upgrade, the patients were randomized to a 2-month period in either BVP or right ventricular pacing (RVP), followed by 2 months in the other mode, in a double-blind crossover fashion. After each period, the pre-operative measurements were repeated. After study completion, patients were asked to select their preferred period. The median 6-min walking distance was significantly longer in BVP (400 m) vs. RVP (315 m), \( P = 0.02 \). The symptom score was also significantly better in BVP (\( P = 0.005 \)). Median pro-BNP was significantly lower in BVP than in RVP, 3030 vs. 5064 ng/L (\( P = 0.005 \)). Six patients demanded an early crossover in RVP but none in BVP (\( P = 0.015 \)), and all patients except one expressed a preference for BVP. However, echo parameters did not show any significant differences between BVP and RVP.

Conclusion Pacemaker patients with heart failure and dominant paced heart rhythm benefit substantially from an upgrade to BVP, in terms of physical performance and symptoms. The upgrade resulted in significantly improved cardiac function as reflected by reduced levels of pro-BNP.

KEYWORDS
Biventricular pacing; Heart failure; Upgrade; Cardiac function

Introduction
Biventricular pacing (BVP) is currently indicated in patients with severe heart failure, depressed left ventricular (LV) function with dilatation, and ventricular dyssynchrony indicated by a prolonged QRS interval most commonly due to left bundle branch block (LBBB).\(^1\) Several studies have shown improvements in myocardial performance, exercise tolerance, and in quality-of-life by cardiac resynchronization with BVP.\(^2\text{-}^6\) Conventional right ventricular pacing (RVP) creates an ECG pattern similar to LBBB, and there is growing evidence of negative effects of this pacing-induced ventricular dyssynchrony.\(^7\text{-}^8\) Theoretically, there is therefore reason to suspect that patients with right ventricular (RV) pacemakers implanted for bradyarrhythmia and who develop severe heart failure might benefit from cardiac resynchronization by an upgrade to BVP.

Methods
Patients
Study inclusion criteria were severe heart failure (New York Heart Association (NYHA) classes III and IV) and no LBBB in the pre-pacing ECG. Furthermore, patients included had to have dominant paced heart rhythm, implying pacing-induced ventricular dyssynchrony.

Table 1 summarizes the baseline characteristics of the study group. Four patients had received a standard RV DDDR pacing system for high-degree atrioventricular (AV) block and four patients for sinus node disease (two patients had a DDDR-implantable cardioverter defibrillator). Two patients had VVIR
systems implanted because of chronic AF and bradycardia. The median time in RVP before upgrading was 68 months (5.7 years). Five patients had signs of heart failure (NYHA classes I and II) at the time of implantation of their original pacing system. At the time of enrolment, four patients were in permanent atrial fibrillation and six in sinus rhythm. The median 6-min walk distance before upgrading was 315 m, and brain natriuretic peptide (pro-BNP) was 4651 ng/L. The median left ventricular diastolic diameter (LVIDd) was 69 mm. All patients had a left ventricular ejection fraction (LVEF) of ≤25%.

Study design
This study was designed as a randomized, double-blind crossover study (Figure 1). After enrolment and baseline evaluation, patients were upgraded to a biventricular system with the addition of a transvenous LV lead via the coronary sinus (nine cases) or via sternotomy (one case with superior caval vein occlusion). Post-operatively, optimal AV delays were determined for the patients in sinus rhythm according to the Ritter method,\textsuperscript{9} both for RVP and for BVP. The optimal ventriculo-ventricular (VV) interval in BVP was also determined by Doppler echocardiographic measurements of the LV velocity–time integrals (VTI). Other pacing parameters such as rest rate and rate response settings were also optimized and left unchanged during the course of the study. To ensure correct biventricular pacemaker function, the patients then had a run-in period of 1 month before randomization, with the pacemakers programmed to BVP. Thereafter, patients were randomized to a 2-month period in either RVP (n = 5) or BVP (n = 5) with optimal pacemaker settings, after which they crossed over to the other mode. Patients were allowed to crossover before the end of the 2-month period upon request. A new evaluation was performed at the time of crossover and at the end of the study. After completing the study, the patients were asked to choose their preferred pacing period. The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Medical Faculty, Lund University Hospital.

Patient evaluation
At baseline, at crossover, and at the end of the study, patients were evaluated with a 6-min walk test, blood samples were taken for assessment of pro-BNP, an echocardiographic study was performed, and a simplified symptom score was recorded. This consisted of a linear scale where patients were asked to state their perceived fitness in activities of daily living, the quality of their sleep, and their general state of well-being. The score was measured from 0 to 100 mm, with a higher score denoting a better health status.

The 6-min walk tests were supervised by one of the staff who was unaware of the patients’ randomization. Likewise, echocardiographic measurements and evaluations were performed by a separate investigator blinded to the programmed pacing mode. Measurements were taken with a Philips/HP SONOS 5500 machine using standard projections. The evaluated parameters included left ventricular end-diastolic diameter (LVIDd) and end-systolic diameter (LVIDs), left atrial (LA) size, the time–velocity integral at the level of the aorta (Ao–VTI) and the outflow tract (LVOT–VTI), the rate-pressure product (RPP) over the mitral valve, and the pressure gradient over the tricuspid valve (RA/RV). Blinded assays of pro-BNP were analysed at our local laboratory with an immunometric assay from Roche (Basel, Switzerland), on a Hitachi Modular E unit.

Endpoints
The endpoints of the study were the 6-min walking distance, the pro-BNP levels, the results of the symptom score, the echocardiographic measurements, and the patients’ preferred period at the end of the study.

Statistics
The investigation was designed as a crossover study, with the patients thus acting as their own controls. Dichotomous variables were assessed with Fisher’s exact test and continuous variables with the Wilcoxon signed rank test. Consequently, median values are given instead of mean values. Results are illustrated graphically with box plots, where the central line indicates the median value.

Results
Study progress and early crossovers
Ten patients were included between September 2002 and August 2003. All gave their informed consent to participate in the study. All patients completed the study, but six patients requested early crossover while in RVP vs. none in the BVP period (P = 0.015). The median time to crossover was 11 days.

Six-minute walk test
The median 6-min walked distance increased from 315 m at baseline to 400 m in BVP (P = 0.02). The walked distance in BVP was also significantly longer than that in RVP (240 m, 250 m, 260 m, 272 m, 12,002 m, 5439 m, 10,268 m, 12,78 m, 11,842 m, 13,811 m, 3398 m, 3926 m, 4923 m, 4651 m, 6224 m, 70 m, 71 m, 64 m, 62 m, 68 m, 69 m, 70 m, 71 m, 64 m, 62 m, 68 m).
The latter distance did not differ significantly from the baseline value ($P = 0.64$).

**Brain natriuretic peptide**

Pro-BNP levels were significantly reduced in BVP, with a median value of 3030 ng/L when compared with 4651 ng/L before the upgrade ($P = 0.03$) and 5064 ng/L in RVP ($P = 0.005$). The levels of pro-BNP in RVP were not significantly different from baseline ($P = 0.28$) (Figure 2).

**Symptom score**

Quality-of-life, as assessed by the symptom score, improved significantly in BVP when compared with baseline concerning fitness during daily activities ($P < 0.05$) and general well-being ($P < 0.05$), but not in quality-of-sleep ($P = 0.06$). When compared with RVP, the median symptom score was significantly higher in BVP with a higher sense of general well-being: 83 vs. 35 ($P = 0.01$) but not in terms of perceived fitness: 75 vs. 29 ($P = 0.06$) and quality-of-sleep: 82 vs. 61 ($P = 0.07$). Symptom score in RVP, in contrast, did not differ significantly from baseline in any of the modalities. The median sums of the three symptom scores were significantly better in BVP (221) when compared with both baseline (154), $P = 0.005$ and RVP (126), $P = 0.005$. There was no significant difference between RVP and baseline ($P = 0.99$).

**Echocardiography**

There were no significant differences between baseline, BVP, or RVP in any of the observed parameters, as shown in Table 2.

**Patient preference**

Nine of the 10 patients in the study preferred the BVP period to the RVP ($P = 0.015$), and one patient was undecided.

**Discussion**

Cardiac resynchronization therapy (CRT) by means of BVP has been shown to increase both myocardial performance and quality-of-life in patients with severely depressed LV function and assumed ventricular dyssynchrony, manifested as a wide QRS complex. However, there is currently no consensus on the optimal way of evaluating lack of ventricular synchrony. The studies to date have used endpoints such as 6-min walk test, quality-of-life questionnaires, and echocardiographic indices of myocardial performance such as EF, LVIDd, and others. A wide QRS usually due to LBBB has been one of the inclusion criteria in these studies, although the cut-off value has varied between the studies, with $\geq 120$ ms in the COMPANION trial, $\geq 130$ ms in the MIRACLE study, and $\geq 150$ ms in the InSync and MUSTIC studies.

Conventional RVP often produces a very wide QRS complex with an ECG pattern similar to LBBB. Previous studies have indicated that RVP has adverse effects on cardiac function, such as deterioration of LV function following AV-nodal ablation and RVP in patients with permanent atrial fibrillation, and impaired LV diastolic and systolic function in paediatric patients with long-term RVP.
Table 2 Echocardiographic measurements

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>RVP</th>
<th>BVP</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVIDd (mm)</td>
<td>69</td>
<td>69</td>
<td>72</td>
<td>ns</td>
</tr>
<tr>
<td>LVIDs (mm)</td>
<td>59</td>
<td>61</td>
<td>60</td>
<td>ns</td>
</tr>
<tr>
<td>LA (mm)</td>
<td>54</td>
<td>54</td>
<td>54</td>
<td>ns</td>
</tr>
<tr>
<td>Ao-VTI (m)</td>
<td>19.7</td>
<td>22.8</td>
<td>27.8</td>
<td>ns</td>
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<tr>
<td>LVOT-VTI (m)</td>
<td>11.0</td>
<td>12.9</td>
<td>11.0</td>
<td>ns</td>
</tr>
<tr>
<td>RPP (mmHg/s²)</td>
<td>441.9</td>
<td>457.0</td>
<td>533.0</td>
<td>ns</td>
</tr>
<tr>
<td>RA/RV (mmHg)</td>
<td>42.5</td>
<td>34</td>
<td>28.5</td>
<td>ns</td>
</tr>
</tbody>
</table>

Median values are presented.

Indications that RVP might cause heart failure were seen in the DAVID study, where 506 patients with an ICD but no indication for pacing were randomized to either backup VVI at 40/min or DDDR at 70/min. After 1 year follow-up, the DDDR-paced patients did significantly worsen concerning the combined endpoint of death and hospitalization for heart failure. Sweeney et al. could show that in patients with sinus node disease and normal baseline QRS duration randomized to either DDDR or VVIR, ventricular pacing in the DDDR mode \(\geq 40\%\) of the time conferred a 2.6-fold increased risk of hospitalization for heart failure. Furthermore, the risk for atrial fibrillation increased linearly with the cumulative percentage of ventricular pacing both in DDDR and in VVIR.

It therefore seems reasonable to assume that patients with conventional RV pacemakers who develop severe heart failure would benefit from an upgrade to BVP, but this has not been extensively studied. The upgrading of heart failure patients with prior AV-nodal ablation for atrial fibrillation and VVIR pacing was reported in a non-randomized study by Leon et al. They studied 20 patients in NYHA classes III and IV, LVEF <35%, and RV pacing for at least 6 months, who were upgraded to a biventricular system. They found an increase in LVEF from 21.5 to 30.9%, a decrease in LVIDd, an improvement in NYHA functional class, a decreased number of hospitalizations, and an improved quality-of-life score after 6 months.

The feasibility and safety of the upgrade procedure have been reported by Baker et al. in a non-randomized observational study. They reported a low complication rate of one lead dislodgement, one pocket haematoma, and three wound infections in 60 patients scheduled for an upgrade from RVP to BVP. In six patients, the upgrade was not successful. At a 3-month follow-up, they found an increase in quality-of-life scores, improved LVEF from 23 to 29%, and significant improvement in NYHA class.

The present study is, to our knowledge, the first study of patients with long-term RVP (median 5.7 years) and representing the everyday spectrum of pacemaker patients, including patients with AV block and sinus node disease, with either AF or sinus rhythm. Patients were in NYHA class III or IV and their median baseline 6-min walk distance of 315 m is comparable with that in the MUSTIC study. We did not use changes in NYHA class as an endpoint, partly because of the small size of the study group and partly because such changes are hard to measure objectively. The use of a double-blind crossover design was chosen to eliminate any placebo effect of the upgrading procedure.

An obvious limitation of this single-centre study is the relatively small number of patients. However, using a crossover design, we were able to use the patients as their own controls and increase the likelihood of detecting true differences. We chose to use a simplified symptom score instead of a more comprehensive form like the Minnesota Living-With-Heart-Failure questionnaire, as quality-of-life measurements of that kind are not well suited to small sample sizes. The evaluation of many parameters in a limited number of subjects tends to yield mainly non-significant results.

The echocardiographic evaluation failed to show any significant differences between the two pacing modalities. This might partly be due to the limited number of patients. In contrast, a large randomized study such as the MIRACLE ICD trial failed to detect any changes in LV size or function. This was also the case in the AF subgroup of the MUSTIC study. It may also be that the standard measurements of LV size and function are not the most suitable for evaluation of cardiac resynchronization. Newer techniques such as tissue Doppler imaging or 3D-echo may prove more rewarding in this regard.

Pro-BNP is widely used for diagnostic and prognostic purposes in heart failure. In this study, we found a significantly lower level of this marker in BVP when compared with both baseline and RVP, and the latter did not differ significantly from baseline. This implies a haemodynamic benefit that is reflected by BVP, despite the lack of significant echocardiographic changes.

In conclusion, patients with severe heart failure (NYHA classes III and IV) and conventional RV pacemakers benefit from an upgrade to BVP, with an improvement in patient symptoms, an increase in physical performance in the 6-min walk test, and a decrease in a parameter of neuro-endocrine activation.

References


