Adverse effect of right ventricular pacing prevented by biventricular pacing during long-term follow-up: a randomized comparison

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Aims
To investigate whether biventricular (BIV) pacing preserves left ventricular ejection fraction (LVEF) and reduces LV dyssynchrony when compared with standard dual-chamber right ventricular (RV) pacing in consecutive patients with high-grade atrioventricular block during 3 years of pacing.

Methods and results
Fifty patients were randomized to RV pacing or BIV pacing. LVEF was measured using three-dimensional echocardiography. Tissue Doppler imaging was used to quantify LV dyssynchrony in terms of the standard deviation of the time-to-peak velocity (Ts-SD). LVEF differed significantly between the two groups during 3 years of pacing (ANOVA: \( P = 0.003 \)). LVEF in the RV group decreased from \( 59 \pm 5\% \) at baseline to \( 53 \pm 11\% \) (\( P = 0.01 \)), while LVEF remained unchanged in the BIV group (\( 57 \pm 7\% \) at baseline vs. \( 58 \pm 10\% \) (\( P = 0.40 \)). After 3 years of follow-up, we observed no difference in LV dyssynchrony, LV remodelling or measurements of clinical heart failure (N-terminal pro-brain natriuretic peptide, walking test, and New York Heart Association functional class) between the two groups. However, in the RV group, but not in the BIV group, dyssynchrony increased significantly (\( P = 0.005 \)) during follow-up. Furthermore, adverse LV remodelling was observed in the RV group with increased systolic volume and thinning of the LV septum.

Conclusion
BIV pacing preserves LVEF and minimizes LV dyssynchrony during long-term follow-up. Adverse remodelling observed during 3 years of RV pacing was prevented by BIV pacing. However, the adverse impact of RV pacing on LV function was not reflected in measures of clinical heart failure.

Clinical trial registration: www.clinicaltrials.gov (identification number: NCT00228241).

Keywords
3D echocardiography • Tissue Doppler imaging • Dyssynchrony • Right ventricular pacing • Biventricular pacing

Introduction
Although conventional single-site right ventricular (RV) pacing has been used for more than 50 years, recent data suggest that it may have a detrimental effects in some patients leading to heart failure.1–3 In contrast, biventricular (BIV) pacing has showed the possibility of reverting heart failure symptoms and reducing mortality in patients with low ejection fraction, left bundle branch block, and New York Heart Association functional class (NYHA) III or IV.4 Even patients with mild heart failure symptoms seem to benefit from BIV pacing.5–8

We published a randomized trial comparing BIV pacing and dual-chamber RV pacing in patients with atrioventricular (AV) block and normal left ventricular ejection fraction (LVEF) in 2008.9 We showed that implantation of BIV pacemakers was feasible and safe in patients with AV block. Furthermore, BIV pacing minimized LV dyssynchrony, preserved LV function, and reduced N-terminal pro-brain natriuretic peptide (NT-proBNP) when compared with RV pacing during 1 year of follow-up. A recent large study from Yu et al.10 confirmed the positive findings of BIV pacing in patients with AV block and normal LVEF during an 1-year follow-up.
This paper focuses on 3-year echocardiographic results of BIV pacing in patients with AV block and normal baseline LVEF. We hypothesized that BIV pacing preserves LV function, reduces LV dyssynchrony, and prevents adverse LV remodelling during long-term follow-up.

Methods
Consecutive patients referred for their first pacemaker implantation during the period from September 2003 to June 2005 underwent screening for inclusion in the study.9 Fifty patients with permanent or paroxysmal high-grade AV block were included and randomized to either atrial sequential RV outflow tract pacing or BIV pacing. Randomization in the present study was done without stratification for pre-implant intrinsic QRS duration.

The study was approved by the local Ethics Committee and followed the Helsinki declaration. The study was notified to the Good Clinical Practice unit at the Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark, and reported to www.clinicaltrials.gov (identification number: NCT00228241). Patients volunteered for participation in the study and inclusion was done after informed consent.

The methods used in the present study have been described in detail earlier but will be summarized briefly here.9

Pacemaker implantation and pacemaker settings
All patients received a BIV pacemaker (Insync III 8042, Medtronic Inc., Minneapolis, MN, USA). Both patient groups had active fixation leads implanted in the right atrial appendage and in the RV outflow tract. Patients in the BIV group had a third LV lead implanted transvenously through the coronary sinus to a lateral or posterolateral branch of the coronary sinus tributary.

Echocardiographic techniques
Echocardiography was recorded as digital loops using Vingmed Vivid Five and data were analysed off-line using EchoPAC version 6.4.2 and EchoPAC-3D version 1.0.1, GE Medical, Horten, Norway. M-mode, two-dimensional, three-dimensional, and tissue Doppler echocardiograms were performed. Dyssynchrony was measured using tissue Doppler recordings of the longitudinal velocity of the LV myocardium in the three standard apical views of the 16-segment model of The American Society of Echocardiography.11 Thus, time from the beginning of the QRS complex to the peak longitudinal systolic velocity was measured in each segment. The ‘dyssynchrony-index’ (Ts-SD) was defined as the standard deviation of the time-to-peak measurement from the 12 mid- and basal segments.12

LVEF was measured from three-dimensional echocardiography.13 All echocardiographic measurements were performed without knowledge of clinical status and pacing mode.

The baseline echocardiographic and clinical assessment was performed within 12 h after pacemaker implantation and repeated after 3, 12, and 36 months. All echocardiographic measurements were done with the pacemaker programmed to 80 b.p.m. to ensure standardized heart rate during subsequent examinations during follow-up.

Clinical and laboratory tests
Blood samples for p-Nt-proBNP (terminal piece of brain natriuretic peptide) measurement from baseline and the 1-year follow-up were frozen and analysed after completion of the 1-year follow-up using the same test-kit. Blood samples from the 3-year follow-up were analysed after completion of the study. The Elecsys 1010 (La Roche Ltd, Basel, Switzerland) was used for the analyses.

A 6-min walk test was performed as the last test at every follow-up.

Endpoints
The primary endpoint was LVEF measured by three-dimensional echocardiography. Secondary endpoints were the extension of LV dyssynchrony (Ts-SD), LV volumes, plasma NT-proBNP, 6-min walk test, and NYHA.

Statistical analysis
Power calculations based on changes in LVEF were performed before including patients in the study.9 Data analysis was performed according to the intention-to-treat principle. ANOVA analysis was used for repeated measurements. Paired analysis was used for comparison within groups and non-paired analysis for comparison between groups, all as two-sided tests. Student’s t-test was used for parametric data and $\chi^2$ test, Wilcoxon’s or Mann–Whitney’s test for non-parametric data. Natural logarithm was used if appropriate for shaping data to the normal distribution. Normally distributed data were reported as mean ± SD. Error bars on figures represent the standard error of the mean (SEM). P-values below 5% were considered statistically significant.

Results
All patients received the pacing treatment as randomly assigned to RV pacing (n = 25) or BIV pacing (n = 25). Implantation success was 100% in both groups. The median time period of ventricular pacing was 100 (99–100)% in both groups after 3 years of follow-up. Baseline characteristics are shown in Table 1.

Ten patients (mean age 86.6 years and five patients from each group) died during the 3-year follow-up period leaving 40 patients to analysis.

Left ventricular structure and function
There was no difference in LVEF between the RV and the BIV groups at baseline nor at the 3-year follow-up ($P = 0.15$ and 0.19, respectively). The time-dependent changes of LVEF differed significantly between the two groups during the 3-year follow-up period (ANOVA: $P = 0.003$) (Figure 1).

In the RV group, there was a significant decrease in LVEF from $59 \pm 5$% at baseline to $53 \pm 11$% at the 3-year follow-up ($P = 0.01$). LVEF did not change in the BIV group ($57 \pm 7$% at baseline vs. $58 \pm 10$% at the 3-year follow-up, $P = 0.40$) (Figure 1).

In contrast to the BIV group, the LV end-systolic volume increased significantly during follow-up in the RV group (baseline $39 \pm 10$ to $49 \pm 17$ ml at 3 years, $P = 0.03$) (Figure 2 and Table 2). The diastolic thickness of the LV septum decreased in the RV group from baseline to the 3-year follow-up ($1.3 \pm 0.4$ to $1.0 \pm 0.2$ cm, $P = 0.02$) and was unchanged in the BIV group ($1.1 \pm 0.2$ to $1.1 \pm 0.2$ cm, $P = 0.61$) (Table 2). The left atrial dimension decreased significantly in the BIV group ($4.1 \pm 0.6$ to $3.9 \pm 0.5$ cm at 3 years, $P = 0.008$) and remained unchanged in the RV group (Table 2).

Statistical analysis
Power calculations based on changes in LVEF were performed before including patients in the study.9 Data analysis was performed according to the intention-to-treat principle. ANOVA analysis was used for repeated measurements. Paired analysis was used for comparison within groups and non-paired analysis for comparison between groups, all as two-sided tests. Student’s t-test was used for parametric data and $\chi^2$ test, Wilcoxon’s or Mann–Whitney’s test for non-parametric data. Natural logarithm was used if appropriate for shaping data to the normal distribution. Normally distributed data were reported as mean ± SD. Error bars on figures represent the standard error of the mean (SEM). P-values below 5% were considered statistically significant.
There was no significant difference in dyssynchrony index (Ts-SD) between groups at baseline or after 3 years of pacing (P = 0.49 and 0.12; respectively). The dyssynchrony index increased significantly in the RV group from baseline to 3 years of follow-up (18.4 ± 14 to 32.0 ± 17 ms, P = 0.006) and remained unchanged in the BIV group (16.8 ± 12 to 22.7 ± 17 ms, P = 0.26) (Figure 3).

The latest activated areas in the RV group were the lateral and septal segments, whereas in the BIV group, the latest activated areas were the posterior segments (Figure 4).

Patients in the BIV group had wider QRS than patients in the DDD(R) group, 144 ± 38 and 117 ± 33 ms (P = 0.01) before pacemaker implantation (Table 1). The width of the QRS complex increased significantly in the DDD(R) group after pacemaker implantation to 155 ± 28 ms (P < 0.001) and decreased in the BIV group to 137 ± 23 ms (P = 0.30). No significant changes were observed in either group during follow-up in this parameter.

### Table 1 Baseline characteristics

<table>
<thead>
<tr>
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<th>RV group (n = 25)</th>
<th>BIV group (n = 25)</th>
<th>P-value</th>
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<tr>
<td><strong>Age (years) (median, quartiles)</strong></td>
<td>76 (67–81)</td>
<td>76 (71–81)</td>
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<td><strong>Female patients, n (%)</strong></td>
<td>8 (32%)</td>
<td>8 (32%)</td>
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<td><strong>Body mass index (kg/m²) (mean ± SD)</strong></td>
<td>26 ± 6</td>
<td>25 ± 3</td>
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<td><strong>Mean blood pressure (mmHg)</strong></td>
<td>155/83</td>
<td>146/79</td>
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<td><strong>Syncope, n (%)</strong></td>
<td>11 (44%)</td>
<td>7 (28%)</td>
<td>0.24</td>
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<tr>
<td><strong>Dizzy spells, n (%)</strong></td>
<td>15 (60%)</td>
<td>18 (72%)</td>
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<td><strong>NYHA (I/II/III/IV), n</strong></td>
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<td>12/9/3/1</td>
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<tr>
<td><strong>Intrinsic QRS-width (ms)</strong></td>
<td>117 ± 33</td>
<td>143 ± 38</td>
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<td><strong>LBBB, n</strong></td>
<td>1</td>
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<td>24 (96%)</td>
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<td><strong>Heart valve disease, n (%)</strong></td>
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<td><strong>Previous stroke, n (%)</strong></td>
<td>0 (0%)</td>
<td>3 (12%)</td>
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<td><strong>Diabetes, n (%)</strong></td>
<td>5 (20%)</td>
<td>3 (12%)</td>
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<table>
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<th><strong>Cardiovascular medication</strong></th>
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<tbody>
<tr>
<td><strong>β-Blockers, n (%)</strong></td>
<td>4 (16%)</td>
<td>4 (16%)</td>
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<td><strong>Calcium channel blockers, n (%)</strong></td>
<td>5 (20%)</td>
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<td><strong>ACE-inhibitors/ARBs, n (%)</strong></td>
<td>15 (60%)</td>
<td>12 (48%)</td>
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<td><strong>Diuretics, n (%)</strong></td>
<td>17 (68%)</td>
<td>12 (48%)</td>
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<td><strong>Aspirin, n (%)</strong></td>
<td>13 (52%)</td>
<td>15 (60%)</td>
<td>0.57</td>
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</tbody>
</table>

**LBBB**, left bundle branch block; **ACE**, angiotensin-converting enzyme; **ARB**, angiotensin receptor blocker.

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**Left ventricular dyssynchrony**

There was no significant difference in dyssynchrony index (Ts-SD) between groups at baseline or after 3 years of pacing (P = 0.49 and 0.12; respectively). The dyssynchrony index increased significantly in the RV group from baseline to 3 years of follow-up (18.4 ± 14 to 32.0 ± 17 ms, P = 0.006) and remained unchanged in the BIV group (16.8 ± 12 to 22.7 ± 17 ms, P = 0.26) (Figure 3).

The latest activated areas in the RV group were the lateral and septal segments, whereas in the BIV group, the latest activated areas were the posterior segments (Figure 4).

**QRS duration**

Patients in the BIV group had wider QRS than patients in the DDD(R) group, 144 ± 38 and 117 ± 33 ms (P = 0.01) before pacemaker implantation (Table 1). The width of the QRS complex increased significantly in the DDD(R) group after pacemaker implantation to 155 ± 28 ms (P < 0.001) and decreased in the BIV group to 137 ± 23 ms (P = 0.30). No significant changes were observed in either group during follow-up in this parameter.
There was no difference between the walking distance in two treatment groups at baseline or at the 3-year follow-up ($P = 0.42$ and $0.35$; respectively).

Both pacing groups had an increase in walking distance, although only patients in the BIV group went statistically longer at the end of follow-up ($509 + 66$ m) compared with baseline ($469 + 70$ m, $P = 0.001$) (Figure 5).

N-terminal pro-brain natriuretic peptide (p-NT-proBNP) did not differ between the two groups, neither at baseline nor after 3 years of constant pacing ($P = 0.47$ and 0.81; respectively) (Figure 6).

Six-minute walk test

There was no difference between the walking distance in two treatment groups at baseline or at the 3-year follow-up ($P = 0.42$ and 0.35; respectively).

Both pacing groups had an increase in walking distance, although only patients in the BIV group went statistically longer at the end of follow-up ($509 + 66$ m) compared with baseline ($469 + 70$ m, $P = 0.001$) (Figure 5).

N-terminal pro-brain natriuretic peptide (p-NT-proBNP) did not differ between the two groups, neither at baseline nor after 3 years of constant pacing ($P = 0.47$ and 0.81; respectively) (Figure 6).

New York Heart Association classification I–IV

There was no difference in NYHA class between the two groups at baseline (NYHA class I/II/III/IV; RV group 12/12/1/0 and BIV group 12/9/3/1; $P = 0.49$) nor at the 3-year follow-up (RV 12/8/0/0 and BIV 13/3/0/0; $P = 0.17$). And there was no significant changes within the groups during follow-up (RV group: $P = 0.44$ and BIV group: $P = 0.08$).

Discussion

This study shows that the potential harmful effect of RV pacing may be prevented by BIV pacing in patients with AV block and no heart failure at the time of pacemaker implantation. We showed that BIV pacing minimized pace-induced LV dyssynchrony, preserved LV systolic performance, and prevented LV remodelling during 3 years of permanent pacing.

The present randomized study was designed to measure difference over time between two different pacemaker treatments during a 3-year follow-up period. At the pre-implant stage, patient haemodynamics were influenced by various degrees of AV block. Many of the patients had severe bradycardia because of second- or third-degree AV block with ventricular escape rhythm and we did not find that measurement of LVEF or clinical parameters were reliable or representative in this situation. Pacemakers were programmed with a fixed rate of 80 b.p.m. at the post-implant baseline evaluation and at clinical visits to ensure standardized heart rates during measurements. As we ignored the difference in clinical presentation at admission and did the measurements after pacemaker implantation, we are able to study time-dependent changes in pacemaker treatment between the two groups during a period of 3 years.

We have previously demonstrated promising results of BIV pacing in patients with AV block with 1 year of follow-up. The present study confirms these findings in a long-term perspective. In spite of the fact that the RV lead was placed in the outflow tract, patients in the RV group had a significant decrease in LVEF from 59 to 53% during 3 years of follow-up.

The decrease in LVEF observed in the RV-paced group during long-term follow-up in our study is modest. Patients in the BIV group exhibited no change in LVEF during 3 years of constantly pacing and protection from future pace-induced heart failure seems to be likely. We have no evidence of any clinically important
The detrimental effect of RV pacing in patients with normal LVEF at the time of pacemaker implantation; walking distance, NT-proBNP, and NYHA did not differ between the two treatment groups during follow-up. In the post hoc analysis of data from the MOST trial, more than 15% of the patients were in NYHA functional class III or IV before pacemaker implantation and hospitalization for heart failure observed in 9.6% of the patients during a median follow-up of almost 3 years is therefore not unexpected.

In patients with poor LVEF at the time of implantation, the harmful effect of RV pacing is much more important as indicated in the DAVID trial. Heart failure hospitalization and mortality increased during dual-chamber RV pacing compared with no pacing in the single-chamber RV-paced group. As demonstrated in an animal model, the myocardium adapts its mass and structure to altered workload. In the setting of asynchronous electrical activation induced by RV pacing, regional differences in workload resulted in lower workload in early- than in late-activated regions. Our study showed significant thinning of the early-activated myocardial septum in the RV-paced group and no significant change in the BIV group (Table 2). This remodeling of the LV was not present at 1-year follow-up. This finding indicates that BIV pacing offers some protection against RV pacing-induced LV remodelling.

The LV dyssynchrony increased significantly during 3 years of constant RV pacing in the present study, although no significant difference was observed between the two groups at the last follow-up. The latest activated segments in the RV group were located in the septal and lateral areas of the LV (Figure 4). The late activation of the lateral part of the LV in the RV group can...
be explained by the travelling route of the activation sequence from the RV lead in the outflow tract to the remote part of the LV which is comparable to findings in other studies. In contrast, the activation sequence was more homogenous in the BIV group where the segments of latest activation were located in the posterior part of the LV.

Randomization in the present study was done regardless of the pre-implant intrinsic QRS duration which might be an uncertain measurement in patients with ventricular escape rhythms due to high-degree AV block. However, the randomization resulted in a significant difference in QRS duration between the two groups at the pre-implant stage. We cannot rule out that this imbalance in randomization may have influenced the results, despite the fact that dyssynchrony measurements were not significantly different between the groups in the baseline echocardiography done up to 12 h after implantation. This has to be considered a limitation in interpreting the present results. The randomization of patients within mean wider QRS complexes to the BIV group may have lead to an underestimation of the true difference between the treatment groups, as wider QRS is a marker of more diffuse conduction tissue involvement, often associated with myocardial dyssynchrony.

Other studies have compared RV pacing and BIV pacing in patients with conventional indication for permanent pacing. Recently, Yu et al. published a study of 177 patients with normal LVEF and 1 year of follow-up. The RV lead was placed in the apical region in contrast to our placement in the RV outflow tract. However, the data of Yu et al. confirms our findings of a significant decrease in LVEF during RV pacing and preserved LVEF during BIV stimulation.

No solid baseline predictors of pacing-induced heart failure during RV pacing in patients with normal baseline LVEF can be specified at present time. However, if new onset heart failure, dyssynchrony, and decreasing LVEF develop in a pacemaker patient, it seems advisable to upgrade to a BIV pacing system at an early stage.

Limitation
Using modern echocardiography, it is possible to measure LV dyssynchrony in a three-dimensional modus and this would add some more accurate measure of dyssynchrony. The present study, however, was initiated in 2003 using Vingmed Vivid Five (GE Medical) which did not allow measurement of three-dimensional tissue Doppler imaging. Furthermore, three-dimensional estimation of left atrial volume would have been a more accurate measure when compared with the two-dimensional recordings used in the study.

Conclusion
In this 3-year follow-up of patients with permanent AV block, BIV pacing preserved LVEF better than conventional RV pacing. At the end of follow-up, no significant difference was observed with respect to LV dyssynchrony, LV remodelling, or clinical heart failure (6-min walk test, NT-proBNP, and NYHA) between the two treatment groups.

Conflict of interest: none declared.

Funding
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References