DDD(R)-pacing, but not AAI(R)-pacing induces left ventricular desynchronization in patients with sick sinus syndrome: tissue-Doppler and 3D echocardiographic evaluation in a randomized controlled comparison

Andi Eie Albertsen*, Jens Cosedis Nielsen, Steen Hvitfeldt Poulsen, Peter Thomas Mortensen, Anders Kirstein Pedersen, Peter Steen Hansen, Henrik Kjæerulf Jensen, and Henrik Egeblad

Department of Cardiology, Aarhus University Hospital, Skejby, Brendstrupgaardsvej 100, 8200 Aarhus N, Denmark

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Aims Increasing evidence from randomized trials and experimental studies indicates that right ventricular (RV) pacing may induce congestive heart failure. We studied regional left ventricular (LV) dyssynchrony and global LV function in 50 consecutive patients with sick sinus syndrome (SSS) randomized to either atrial pacing [AAI(R)] or dual chamber RV-pacing [DDD(R)].

Methods and results Fifty consecutive patients were randomized to AAI(R) or DDD(R)-pacing. Tissue-Doppler imaging was used to quantify LV dyssynchrony in terms of number of segments with delayed longitudinal contraction (DLC). Left ventricular ejection fraction (LVEF) was measured using three-dimensional echocardiography. Dyssynchrony was more pronounced in the DDD(R)-group than in the AAI(R)-group at the 12 months follow-up (P, 0.05). This reflected a significant increase of dyssynchrony in the DDD(R)-group from baseline to the 12 months follow-up (1.3 ± 1 to 2.1 ± 1 segments displaying DLC per patient), P < 0.05. No change was observed in the AAI(R)-group (1.6 ± 2 to 1.3 ± 2 segments displaying DLC per patient, NS). No difference in LVEF, NYHA or NT-proBNP was observed between AAI(R)- and DDD(R)-mode after 12 months of pacing although LVEF decreased significantly in the DDD(R)-group from baseline (63.1 ± 8%) to the 12 months follow-up (59.3 ± 8%, P < 0.05), while LVEF remained unchanged in the AAI(R)-group (61.5 ± 11% at baseline vs. 62.3 ± 7% after 12 months, NS.

Conclusion In patients with SSS, DDD(R)-pacing but not AAI(R)-pacing induces significant LV desynchronization and reduction of LVEF.

**KEYWORDS**
Right ventricular pacing; Dyssynchrony; 3D-echocardiography; Heart failure

Background
Randomized trials indicate that single site right ventricular (RV) pacing may be harmful.1–4 In patients with sick sinus syndrome (SSS), single site RV-pacing increases the risk of atrial fibrillation and thromboembolism.1–3 Impairment of left ventricular (LV) fractional shortening and increasing left atrial dimension measured by M-mode echocardiography may also occur after RV-pacing.1,3 In addition, RV-pacing seems to increase the risk of congestive heart failure in patients who receive a conventional pacemaker or an implantable cardioverter defibrillator.1–4 Experimental studies in animal models have demonstrated altered myocardial contraction pattern and structural changes in LV geometry during single site RV-pacing.5–7

The optimal pacing mode in patients with SSS is not yet clarified. Most patients with SSS have normal atrioventricular (AV)-conduction and in these patients single site right atrial pacing [AAI(R)] may seem adequate.

Tissue-Doppler imaging was recently introduced to quantify mechanical dyssynchrony of the LV in patients receiving cardiac resynchronization therapy8 and it has been shown that mechanical dyssynchrony does not always correlate with electrical dyssynchrony indicated by electrocardiograms.9

Knowledge of the LV response to permanent single site RV-pacing in a clinical setting is limited. In this study LV dysynchrony and LV ejection fraction (LVEF) were measured by means of echocardiographic techniques in patients with SSS randomized to AAI(R)- or dual chamber [DDD(R)]-pacing.
We hypothesized that DDD(R)-pacing causes increased LV dyssynchrony and impairment of LVEF as compared with AAI(R)-pacing.

Methods

Study population

All patients referred to our institution for their first pacemaker implantation during the period from August 2003 to March 2005 were screened for inclusion in the study. Patients with SSS were asked to participate in the study if they met the clinical inclusion criteria (syncope, dizzy spells or heart failure) in combination with the electrocardiographic criteria (sinus arrest > 2 s, tachy-brady syndrome with sinus pauses > 2 s or sinus bradycardia [<40 beats/min (bpm) in awake hours]. Reasons for exclusions are listed in Figure 1 and demographics of the study population are shown in Table 1.

Ethical considerations

The study was approved by the local ethical committee and conducted in accordance with the Helsinki Declaration. The study was notified to the GCP-unit (Good Clinical Practice) at the Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark and registered on www.clinicaltrials.gov (identification number: NCT00228241). Patients volunteered to participate in the study and were included after spoken and written informed consent.

Pacemaker implantation and pacemaker programming

All patients received active fixation bipolar atrial leads inserted transvenously in the right atrial appendage. Patients randomized to dual chamber pacing had an additional active fixation lead inserted transvenously in the RV apex. Single chamber or dual chamber pacemakers from several different companies were used (Medtronic®, Sct. Jude Medical®, Guidant®, ELA®). All pacemakers were programmed with a basal rate of 60 bpm and with rate modulation active to maximum 120–140 bpm. The paced AV-delay in dual chamber pacemakers was programmed to a maximum of 220–225 ms and rate adaptive. The sensed AV-delay was programmed 20 ms shorter than the paced AV-delay. Mode-switch was active.

Echocardiographic techniques

Echocardiography was performed using a Vingmed Vivid Five apparatus (GE Medical, Horten, Norway) with a multi-frequency transducer using 1.7 MHz and second harmonic mode. The left atrial and LV dimensions were measured by conventional M-mode echocardiography. Three-dimensional (3D) echocardiography was performed during one breath hold using ECG-triggered coaxial rotation from the apical position with 30° interval between scanning planes. The resulting six loops were analysed off-line by manually drawing of the endocardial borders in end-diastole and end-systole. Left ventricular ejection fraction was calculated from the end-diastolic and end-systolic volumes. EchoPAC-3D version 1.0.1 (GE Medical, Horten, Norway) was used for analyses. The observer was blinded during the echocardiographic analyses with respect to pacing mode of the patients.

Digital tissue-Doppler loops of the LV were recorded in the three standard apical views and were used to analyse regional systolic and diastolic function.

Table 1 Baseline characteristics of the study population. No statistically significant difference between the groups except *P < 0.05 (ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AAI(R)-group (n = 24)</th>
<th>DDD(R)-group (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean ± SD)</td>
<td>72 ± 10</td>
<td>73 ± 13</td>
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<tr>
<td>Female (n)</td>
<td>14</td>
<td>18</td>
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<tr>
<td>Body mass index (kg/m²)</td>
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<td>25 ± 4</td>
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<tr>
<td>Blood pressure (mmHg)</td>
<td>143/78</td>
<td>141/78</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>66 ± 14</td>
<td>66 ± 12</td>
</tr>
<tr>
<td>Sinus arrest/sinus-atrial block (n)</td>
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<td>16</td>
</tr>
<tr>
<td>Brady-tachy syndrome (n)</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Sinus bradycardia (n)</td>
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<td>8</td>
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<td>7</td>
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<td>Beta-blockers (n)</td>
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<td>11*</td>
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<tr>
<td>Calcium channel blockers (n)</td>
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<td>5</td>
</tr>
<tr>
<td>ACE inhibitors/ARBs (n)</td>
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<tr>
<td>Diuretics (n)</td>
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</tr>
<tr>
<td>Aspirin (n)</td>
<td>20</td>
<td>14</td>
</tr>
</tbody>
</table>

Figure 1 Study flowchart including reasons for exclusion.
post-systolic motion towards the apex. To avoid aliasing, the colour-coded area and the settings of the echocardiographic equipment were adjusted to obtain the highest possible frame rate (≥130 frames/s).

Analysis was carried out in each of the 16 segments of the model of The American Society of Echocardiography. If present in a given segment, the peak velocity of post-systolic motion after aortic valve closure was recorded. Delayed longitudinal contraction (DLC) was considered to be present if a segment with post-systolic motion of more than 1 cm/s exhibited negative strain rate reflecting shortening. Thus, DLC was considered as marker of LV dyssynchrony.

The intra-observer variability of LVEF and DLC was determined in 14 randomly selected patients. The mean difference and the 95% limits of agreement (LOA) were calculated according to Bland and Altman. Left ventricular ejection fraction: mean difference 0.4% ± 1.1 (SD), 95% LOA –1.8–2.6; DLC mean difference –0.3 ± 0.9 (SD), 95% LOA –2.1–1.5.

Endpoints and follow-up

The primary end points in the study were changes in LV dyssynchrony from baseline to 12 months of follow-up recorded by tissue-Doppler echocardiography and LVEF measured with 3D echocardiography. Secondary endpoints were NT-proBNP and 6-min walk test. Patient demographics and ECG characteristics were obtained at baseline. All data were collected at baseline within 12 h before pacemaker implantation and again at 3 and 12 months of follow-up.

Statistical considerations

Power calculation was done on the basis of LVEF. Calculation was performed before including patients in the study. The risk of type 1 error was set to 5% and the statistical power to 80%. With a minimal relevant difference of 5% (absolute percent) between LVEF in the AAI(R)- and DDD(R)-group, a total of 44 patients were needed in the study. With an expected dropout rate of 10%, the total number of patients included was decided to be 50. Statistical calculations were done using STATA 8.1 software (Stata Corporation, Texas, USA).

All data were analysed according to the intention-to-treat principle. 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 Wilcoxon or Mann-Whitney’s test for non-parametric data. Natural logarithm was used for normalisation for skew data to the normal distribution. Normally distributed data were reported as mean ± SD, otherwise as median (first and third quartile). P-values below 5% were considered statistically significant. No corrections were done for multiple testing.

Results

Fifty consecutive patients were randomized to AAI(R)-pacing (n = 24) or DDD(R)-pacing (n = 26) (Figure 1). Baseline demographics of the study population are shown in Table 1.

Implantation success was 100%. However, two patients in the AAI(R)-group had a ventricular lead inserted due to Wenkebach block at atrial pacing 100 bpm during the implantation procedure. Another patient from the AAI(R)-group refused further participation in the study at the 3-months follow-up visit.

Mean proportion of pacing in the atrium during follow-up was 53% in the AAI(R)-group and 62% in the DDD(R)-group (non-significant, NS). Ventricular pacing was observed 66% of time in the DDD(R)-group. The two patients from the AAI(R)-group who received RV leads were paced in the ventricle 3 and 99% of the time, respectively.

Left ventricular desynchronization

The percentage of segments with LV dyssynchrony (segments with DLC) differed significantly between groups at the 12 months follow-up where significantly more segments displayed DLC in the DDD(R)-group (2.1 ± 1.5 segments displaying DLC per patient) as compared with the AAI(R)-group (1.3 ± 1.9 segments displaying DLC per patient), P < 0.05 (Figure 2). This reflected a significant increase of dyssynchrony in the DDD(R)-group from baseline (1.3 ± 1.3 segments displaying DLC per patient) to the 12-months follow-up (2.1 ± 1.5 segments displaying DLC per patient), P < 0.05. In contrast there was no significant change during follow-up in the AAI(R)-group (1.6 ± 2.1 segments per patient at baseline and 1.3 ± 1.9 segments after 12 month) (NS). Comparing these changes in the two groups from baseline to the 12 months of follow-up...
[DDD(R) 0.8 ± 1 vs. AAI(R) −0.3 ± 1] there was a significant difference (P < 0.05).

**Left ventricular systolic function**

At baseline LVEF was 63.1 ± 8% in the DDD(R)-group and 61.5 ± 11% in the AAI(R)-group (NS) (Figure 3). Despite a significantly decrease of LVEF during 12 months of ventricular pacing in the DDD(R)-group (to 59.3 ± 8%, P < 0.05), and insignificant increase in the AAI-group (62.3 ± 7%, NS), the LVEF remained with no significant difference between groups at the 12 months follow-up, NS (Figures 3 and 4). Furthermore, the changes within groups between baseline and the 12 months follow-up did not differ significantly between the DDD(R)-group (−3.8 ± 9%) and AAI(R)-group (0.8 ± 11%), NS.

**Six-minutes walk test**

Walking distance increased in both groups [DDD(R)-group: from 415 ± 76 m at baseline to 446 ± 96 m at 12 months (7.5%), NS and AAI(R)-group: from 444 ± 105 m at baseline to 500 ± 89 m at 12 months (12.6%), P < 0.05]. Walking distance was similar in the two groups at baseline (NS) whereas a significant difference was found after 12 months of follow-up (P < 0.05).

**N-terminal pro brain natriuretic peptide (NT-ProBNP)**

NT-proBNP did not change in the DDD(R)-group (78 ± 85 pmol/L at baseline and 86 ± 125 pmol/L at the 12 months follow-up, NS). In contrast, a significant decrease was found in the AAI(R)-group (from 120 ± 178 pmol/L at baseline to 57 ± 79 pmol/L after 12 months, P < 0.05). However there was no difference between groups neither at baseline nor at the 12 months follow-up (both NS).

**New York Heart Association functional class (NYHA)**

NYHA functional class (I/II/III/IV) did not change significantly in either group. DDD(R)-group (18/8/0/0) at baseline and (14/10/1/1) after 12 months; AAI(R)-group (19/3/2/0) at baseline and (18/5/0/0) at the 12-month follow-up.

**Medication**

Baseline medical treatments are shown in Table 1. At subsequent follow-up after three and 12 months there were no differences between numbers of patients using beta-blockers in the two groups [3 months: AAI(R) = 12, DDD(R) = 14; 12 months: n = 14 in both groups]. Neither ACE-inhibitors nor angiotensin receptor blockers differed between groups at subsequent follow-up visits.

**Implantation and complications**

Surgery time of 39 ± 16 min. in the DDD(R)-group was significantly longer than the 26 ± 6 min used in the AAI(R)-group (P < 0.05). X-ray time was also longer in the DDD(R)-group [5.9 ± 6.5 min. vs. 3.4 ± 2.1 in the AAI(R)-group] although this difference was insignificant, NS. No lead displacements, infections or haematomas were observed in any of the two groups.

**Discussion**

The study demonstrates that 12 months of DDD(R)-pacing induces statistically significant LV desynchronization and reduction of walking distance in patients with SSS as
compared with AAI(R)-pacing. No difference between groups was found for LVEF, NYHA or NT-proBNP (Figure 3).

Animal studies have demonstrated obvious changes in LV electrical activation and mechanical dyssynchrony induced by RV apical pacing.5–7,14–17 In the clinical setting LV dyssynchrony is associated with poor haemodynamic outcome and major cardiac events.9,18 An observational study in patients with congenital heart block paced for 10 years in mean demonstrated that RV-pacing was associated with increased LV dyssynchrony, adverse LV remodelling and decreased cardiac output as compared with matched controls.19 In patients with atrial fibrillation who had AV-node ablation and RV apical pacing LV dyssynchrony developed in 49% during a 3–4 year period.20 A significant reduction in LVEF was observed in this fraction of patients who developed dysynchrony whereas no change in LVEF occurred in those who did not develop dyssynchrony.20

In our prospective randomized study we attempted to quantify LV dyssynchrony by means of tissue-Doppler echocardiographic identification of segments with post-systolic contraction, i.e. DLC (Figure 2). Recording of DLC for localization and quantification of dyssynchrony has earlier proved useful in the context of cardiac resynchronization therapy.21 Our hypothesis was that DDD(R)-pacing causes increased LV dyssynchrony as compared with AAI(R)-pacing and that this difference would be reflected in a corresponding difference regarding LVEF. Post-systolic LV contraction with predilection of the septum and anterior wall may be seen in young healthy individuals.22 In patients with heart failure and left bundle branch block DLC may be seen in up to 50% of myocardial segments. Cardiac resynchronization therapy may reduce the dyssynchrony to include <25% of segments. In our elderly patients DLC was present in 8–10% of segments before pacemaker implantation. At the 1-year follow-up the extent of dyssynchrony was statistically unchanged in the AAI(R)-group while a significant increase of segments with dyssynchrony was observed in the DDD(R)-group (Figure 2). In these patients the dyssynchrony increased from 8 to 13% of the segments or considerably less than in an average patient with left bundle branch block, heart failure and low LVEF.21

The increased dyssynchrony observed in DDD(R)-patients after 1 year was accompanied by a small but statistically significant decrease of LVEF (Figure 4). No change took place in the AAI(R)-paced patients. An acute decrease of LVEF of 6–13% after initiation of DDD-pacing has been reported previously.23,24 In our patients we recorded a decrease of LVEF from 63 to 59% even after 1 year of DDD(R)-pacing. Yet, our patients were paced only 66% of the time in the ventricles due to the programmed AV-delay. A substantial proportion of the ventricular beats may also have been fusion or pseudo-fusion beats rather than beats with full capture from the pacing site. In contrast to pathophysiological experiments with 100% ventricular capture our study was a comparison of two clinically relevant pacing modes in consecutive patients referred for their first pacemaker implantation.21,24 The finding of a modest decline of LV systolic performance in our study supports previous studies of DDD(R)-paced patients with SSS.1,3 It may also seem in accordance with the relatively small increase in dyssynchrony observed (from 8 to 13% of segments). It is questionable whether the small but statistically significant increase in dyssynchrony and accompanying reduction of LVEF in the DDD(R)-group was of clinical significance.

The DDD(R)-paced patients in our study did very well during 12 months of follow-up supporting the general impression from daily clinical practice. Interestingly, patients from the DDD(R)-group with low LVEF at baseline also did very well (Figure 4). This finding indicates the existence of some as yet unidentified characteristics that protects some patients from desynchronization and promotes dyssynchrony in others. Such characteristics are not necessarily related to pacing mode.

We have no definite explanation of the predilection for DLC in septal segments in our patients paced in the RV. However other investigators have suggested a paradoxical contraction in late systole in the septum in these patients.25,26

Compared with baseline the patients of both groups had increased their 6-min walking distance at the 12 months follow-up visit although the difference was not significant in the DDD(R)-group. This supports that both pacing modes are suitable for treatment of bradycardia and chronotrope incompetence a possible obstacle for the patients at baseline. After 12 months the improvement of the 6-min walking distance was significantly greater in the AAI(R)-group than in the DDD(R)-group, a potential result of unpaired LVEF in the former group.

Based on currently available data, it is advisable to avoid ventricular pacing in patients who do not need it. However, the optimal pacing mode and pacing site in patients who require ventricular pacing has yet to be clarified. In acute and midterm studies RV outflow tract pacing has been shown to have more beneficial LV haemodynamics than RV apical pacing used in the present study.27–29 Alternative RV pacing sites such as His- and para-Hisian pacing are currently investigated. Biventricular pacing might be an alternative especially in patients with depressed LV function and bradycardia.30 New pacemaker software algorithms have also been developed to minimize unnecessary RV-pacing, but persuasive clinical data from large scale randomized trials are so far missing.31

It is generally accepted that AAI(R)-pacing is associated with shorter implantation time, quicker pacemaker follow-up visits and lower economic costs as compared with DDD(R)-pacing. The risk of later AV-block in patients with SSS implanted with AAI(R)-pacemakers is lower (1.7% per year).32 As AAI(R)-pacing seemed to be superior to DDD(R)-pacing in the present study we suggest AAI(R)-pacing to be considered as a possible first choice in patients with SSS and no AV-block. Patients with SSS and varying degree of AV-block may benefit from pacemakers automatically switching from AAI(R)- to DDD(R)-pacing mode in the future.

An ongoing trial in Denmark (DANPACE) aims to elucidate possible differences between atrial pacing and AV synchronous RV-pacing regarding mortality and other important clinical endpoints in patients with SSS.33

Our study is the first randomized clinical trial showing the occurrence of significant dyssynchrony during DDD(R)-pacing despite a programmed AV-delay of maximum 220–225 ms to minimize ventricular pacing in patients with SSS.

**Study limitations**

Knowledge of the pacing mode during collection of data at follow-up visits might have lead to bias particular regarding 6-min walk test and NYHA classification. However, echocardiograms and plasma NT-proBNP were analysed with no
knowledge of the pacing mode. There was a large variation of the NT-proBNP measurements, and we cannot rule out, that the present findings may have occurred by chance. However, the significant decrease of NT-proBNP in the AAI(R)-group supports the findings of less dyssynchrony and improved walking distance at 12 months in contrast to no changes observed in the DDDR-group.

All echocardiographic analyses were done by one investigator, reducing the variability of the measurements. In a clinical setting with different investigators, the variability is expected to be higher. However, in the setting of a randomized trial with a relatively small sample size, the lower variability also could be considered as an advantage.

We only measured dyssynchrony in the longitudinal direction of the LV. Other investigators have identified dyssynchrony in radial direction by standard M-mode echocardiography or tissue-Doppler radial strain. Therefore, we cannot rule out that more dyssynchrony was present in our patients that could not be detected using DLC.

Patients were treated with different medications as clinically indicated, and at baseline the use of beta-blockers differed between groups. Therefore we cannot rule out, that differences in medication between groups may have had influence on the results. However, at follow-up visits no difference was observed between groups concerning beta-blockers or ACE-inhibitors/angiotensin receptor blockers.

The study results should be interpreted in the context of a relatively small study population. However, the size of the population was predetermined by adequate power calculation.

Conclusion
The present study demonstrates that 1 year of DDD(R)-pacing but not AAI(R)-pacing is associated with a mild but true LV desynchronization and accompanying reduction of LVEF in patients with SSS. These changes were small and hardly of immediate clinical importance. No difference in LVEF, NYHA or NT-proBNP was observed between AAI(R)- and DDDR(R)-mode after 12 months of pacing. More long-term studies are awaited to see if there will be any clinical significance to these findings.

Conflict of interest: none declared.

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Reference


