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A Randomized Comparison of Atrial and Dual-Chamber Pacing in 177 Consecutive Patients With Sick Sinus Syndrome

Echocardiographic and Clinical Outcome

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OBJECTIVES A randomized trial was done to compare single-chamber atrial (AAI) and dual-chamber (DDD) pacing in patients with sick sinus syndrome (SSS). Primary end points were changes in left atrial (LA) size and left ventricular (LV) size and function as measured by M-mode echocardiography.

BACKGROUND In patients with SSS and normal atrioventricular conduction, it is still not clear whether the optimal pacing mode is AAI or DDD pacing.

METHODS A total of 177 consecutive patients (mean age 74 ± 9 years, 73 men) were randomized to treatment with one of three rate-adaptive (R) pacemakers: AAIR (n = 54), DDDR with a short atrioventricular delay (n = 60) (DDDR-s), or DDDR with a fixed long atrioventricular delay (n = 63) (DDDR-l). Before pacemaker implantation and at each follow-up, M-mode echocardiography was done to measure LA and LV diameters. Left ventricular fractional shortening (LVFS) was calculated. Analysis was on an intention-to-treat basis.

RESULTS Mean follow-up was 2.9 ± 1.1 years. In the AAIR group, no significant changes were observed in LA or LV diameters or LVFS from baseline to last follow-up. In both DDDR groups, LA diameter increased significantly ($p < 0.05$), and in the DDDR-s group, LVFS decreased significantly ($p < 0.01$). Atrial fibrillation was significantly less common in the AAIR group, 7.4% versus 23.3% in the DDDR-s group versus 17.5% in the DDDR-l group ($p = 0.03$, log-rank test). Mortality, thromboembolism, and congestive heart failure did not differ between groups.

CONCLUSIONS During a mean follow-up of 2.9 ± 1.1 years, DDDR pacing causes increased LA diameter, and DDDR pacing with a short atrioventricular delay also causes decreased LVFS. No changes occur in LA or LV diameters or LVFS during AAIR pacing. Atrial fibrillation is significantly less common during AAIR pacing. (J Am Coll Cardiol 2003;42:614–23)

In patients with sick sinus syndrome (SSS), normal atrioventricular (AV) conduction, and no bundle branch block, the bradycardia-related symptoms can be treated successfully with a single-chamber atrial pacemaker (AAI), a single-chamber ventricular pacemaker (VVI), or a dual-chamber pacemaker (DDD). In a previous randomized trial

See page 624

of 225 patients with SSS (1,2), AAI pacing was superior to VVI pacing due to lower mortality, less atrial fibrillation (AF), less arterial thromboembolism, and less heart failure (HF). In that study, VVI pacing caused an increased dilation of the left atrial (LA) diameter and a decreased left ventricular (LV) fractional shortening (LVFS) as documented by serial M-mode echocardiograms. It is likely that the atrial dilation and reduced LV function caused by right ventricular (RV) pacing was associated with a worse clinical outcome in the VVI group. It is, however, not known whether the disturbance of AV synchrony or the abnormal ventricular contraction induced by RV pacing is the most important harmful factor in VVI pacing. Whether AAI or DDD pacing is the optimal pacing mode in SSS is still not clear. Both pacing modes preserve AV synchrony. Additionally, AAI pacing preserves the normal ventricular activation pattern; however, if AV block occurs, a re-operation with implantation of a ventricular lead is needed. In contrast, DDD pacing protects against bradycardia if AV block occurs, but the ventricular pacing causes an abnormal ventricular activation pattern similar to that caused by VVI pacing (3,4).

The primary aim of the present randomized study was to compare the echocardiographic changes in LA size and LV size and function during rate-adaptive AAI and DDD pacing in patients with SSS and relatively normal AV conduction.

METHODS

Protocol. The trial of AAIR versus DDDR pacing enrolled patients during the period from December 1994 to March 1999, and follow-up was completed in March 2000.

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Abbreviations and Acronyms

AAI(R) = single-chamber atrial pacemaker (R indicates rate-adaptive pacing)
AF = atrial fibrillation
AV = atrioventricular
DDD = dual-chamber pacemaker
DDDR-l = dual-chamber pacemaker programmed with a conventional fixed long AV delay of 300 ms
DDDR-s = dual-chamber pacemaker programmed with a conventional short rate-adaptive AV delay of ≤150 ms
HF = heart failure
LA = left atrial
LV = left ventricular
LVED = left ventricular end-diastolic
LVES = left ventricular end-systolic
LVEF = left ventricular ejection fraction
LVFS = left ventricular fractional shortening
NYHA = New York Heart Association
RV = right ventricular
SSS = sick sinus syndrome
VVI(R) = single-chamber ventricular pacemaker (R indicates rate-adaptive pacing)

Table 1. Reasons for Exclusion in the AAIR Versus DDDR Trial

Reasons for Exclusion	Number of Patients
AV block grade 1,* 2, or 3	455
Chronic AF	98
Bundle branch block	43
AF >50% of time	22
AF with QRS rate <40 beats/min	22
Cerebral disease including dementia	17
Cardiac surgery planned	13
Follow-up not possible	11
Cancer	10
Pacing for HOCM	10
Age <18 yrs	9
Prior heart transplant	7
Major surgery, non-cardiac	5
Bradycardia and ventricular tachycardia	4
Wenckebach block <100 beats/min, known before implantation	3
Carotid sinus syndrome	3
AF with RR intervals >3 s	2
Refusal	23
Other reasons	18
Total	775

*Grade 1 atrioventricular (AV) block was defined as: PQ interval >0.22 s in patients ≤70 years and PQ interval >0.26 s in patients >70 years.

AAIR = rate adaptive single chamber atrial pacemaker; AF = atrial fibrillation; HOCM = hypertrophic obstructive cardiomyopathy; DDDR = rate adaptive dual chamber pacemaker.

The primary end points were changes in LA size and LV size and function during follow-up measured by M-mode echocardiography. Secondary echocardiographic end points were changes in LA volume and LV volume and left ventricular ejection fraction (LVEF) measured by two-dimensional echocardiography. Secondary clinical end points were AF, thromboembolism, all-cause and cardiovascular mortality, and congestive HF. The trial included consecutive patients with SSS, normal AV conduction, and no bundle branch block referred to Skejby University Hospital, Aarhus, Denmark, for their first pacemaker implantation. The patients were asked to participate in the trial if the inclusion criteria (symptomatic bradycardia <40 beats/min or symptomatic QRS pauses of more than 2 s) and none of the exclusion criteria (Table 1) were met. A normal AV conduction was arbitrarily defined as PQ interval ≤220 ms for patients ≤70 years and PQ interval ≤260 ms for patients >70 years, as used in a prior study (the AAI vs. VVI trial) (2,5). In a one-year period, patients were furthermore enrolled at the neighboring Viborg County Hospital.

After giving written informed consent, patients were randomized to three arms: AAIR pacemaker, DDDR pacemaker programmed with a conventional short rate-adaptive AV delay (≤150 ms) (DDDR-s), and DDDR pacemaker programmed with a fixed long AV delay (300 ms) (DDDR-l).

Medical history and physical examination were done before implantation. Echocardiography was done before, and again within 24 h after, pacemaker implantation. Follow-up visits were after three months, 12 months, and then once a year. The follow-up visits included physical examination, electrocardiogram (ECG) recordings, pacemaker check-up, and echocardiography. Physical examination and echocardiography were done unblinded regarding randomization and pacing mode. Echocardiography was done blinded regarding prior echocardiographic examinations.

Echocardiography. A Vingmed CFM 750 echocardiograph (Vingmed, Horten, Norway) with a 3.25 MHz transducer was used for echocardiograms.

M-mode echocardiography was done to measure LA, LV end-systolic (LVES) and end-diastolic (LVED) diameters, and LVFS was calculated by the formula LVFS = (LVED diameter − LVES diameter)/LVED diameter. M-mode echocardiography was done in accordance with the recommendations of the American Society of Echocardiography, using the leading-edge methodology (6).

Two-dimensional echocardiography was used to measure LA, LVED, and LVES volumes, allowing calculation of the LVEF. Echocardiographic images were digitally stored on optic disc and analyzed off-line using Echopac 6.0 (VINGMEDsound, Horten, Norway) software. The bi-plane disc summation method was used for calculation of ventricular volumes (7,8). Each LV volume was averaged from three beats. If only one of the two apical standard views could be obtained, the single plane disc summation method was used. At follow-up of patients in the DDDR-s group, echocardiographic parameters were initially obtained in that pacing mode the patient presented—typically with ventricular pacing. If ventricular pacing was present at that

first echocardiogram, another echocardiogram was done 5 min after programming the pacemaker in AAI mode, same rate (DDDR-s-AAI). Echocardiographic parameters at the end of follow-up were defined as the measurements obtained at the last follow-up of each patient, which could be in the range from three months to five years. All echocardiograms were obtained and analyzed by one of three experienced echocardiographers.

Variability. Thirty consecutive patients underwent independent and separate M-mode echocardiographies by two observers on the same day. Left atrial diameter and LVED and LVES diameters were measured, and LVFS was calculated. The bias (the mean intra-individual difference) was low in all four parameters, whereas the limits of agreement (the mean intra-individual difference ± twice the SD of the differences) were quite wide: −6.6 to 6.4 mm (LA diameter), −9.5 to 8.7 mm (LVES diameter), −9.1 to 8.3 mm (LVED diameter), −0.19 to 0.20 (LVFS) (9). Two-dimensional echocardiography was performed and analyzed by the same examiner in 10 consecutive patients, in whom paired standard apical two- and four-chamber views were available, on two separate days. For these two-dimensional parameters, the bias was acceptable, and the limits of agreement were quite wide: −6.9 to 11.7 ml (LVES volume), −19.5 to 34.3 ml (LVED volume), −0.09 to 0.11 (LVEF).

During follow-up, good quality paired standard apical two- and four-chamber views were available in only 50% to 60% of the patients. At the three-month follow-up, they were available in 53% of the patients. In most of the remaining patients, only one of the two apical views was available and could be used to calculate the LV volumes.

Clinical end points. Atrial fibrillation was diagnosed only by standard 12-lead ECG at planned follow-up visits. Stroke was diagnosed when neurological symptoms of presumably cerebral ischemic origin persisted for more than 24 h or if patients died within 24 h from an acute cerebrovascular event. Peripheral embolus was diagnosed if verified at embolectomy or necropsy. Cause of death was obtained by interviewing the doctors who had care of the patient and by review of hospital and necropsy reports. Cardiovascular death included sudden death, death due to congestive HF, arterial thromboembolism, or a pulmonary embolus. Heart failure was classified according to New York Heart Association (NYHA) criteria and quantitated by the daily dose of diuretics.

Pacemaker telemetry data. Numbers of sensed and paced events were retrieved from the pacemaker event counters at every follow-up, and mean proportions of paced events in the atrium and in the ventricle during the entire follow-up period were calculated for each patient.

Pacemaker implantation. Standard rate-adaptive single-chamber pacemakers and dual-chamber pacemakers (Cardiac Pacemakers Inc. [St. Paul, Minnesota], Pacesetter [St. Paul, Minnesota], Medtronic [Minneapolis, Minnesota]) were used, all fulfilling the study requirements for reporting cumulative numbers of paced and sensed events for a 12-month period.

All atrial leads were implanted in the upper parts of the right atrial wall. Among patients randomized to AAIR pacing, 19 patients had unipolar leads, and 35 patients had bipolar leads. Among patients randomized to DDDR pacing, 37 patients had unipolar leads, and 86 patients had bipolar leads in the right atrium. All patients randomized to DDDR pacing had unipolar leads with passive fixation implanted in the RV apex. Atrial fibrillation at the time of pacemaker implantation was not a reason for implanting another pacemaker rather than according to the randomized mode.

During implantation, an atrial pacing test at 100 beats/min was performed; 1:1 AV conduction was required for an atrial pacemaker to be implanted. If Wenckebach block occurred at a rate of 100 beats/min, the patient received a DDDR pacemaker.

The rate response function was active in all but two patients. Lower and upper rates were programmed individually. Mode-switch function was active in all patients implanted with DDD pacemakers.

In patients randomized to DDDR-l pacing, the AV delay was fixed at 300 ms. In four patients a shorter AV delay had to be programmed to avoid induction of endless loop tachycardia during initial pacemaker testing. In patients randomized to DDDR-s pacing, the AV delay was 150 ms and rate adaptive but even shorter if necessary to obtain ventricular pacing with full capture.

Analysis. Power calculations were based on M-mode echocardiographic data from the AAI versus VVI study (2). With a statistical power of 80% and a 0.05 level of significance, a total of 450 patients were to be included in the study to detect a 10% difference between the AAIR group and the DDDR group in LA diameter. No differences between the DDDR-s and the DDDR-l groups were expected. However, inclusion was stopped after randomization of 177 patients, because at that time a national multi-center trial of AAIR versus DDDR pacing in patients with SSS was initiated and started in Denmark (the Randomized comparison of AAIR and DDDR pacing in 1,900 patients with SSS [DANPACE] trial) (10). Patients included in the present study were not rolled over into the DANPACE study.

The last patient included was to be followed up for at least one year before data were analyzed, which was March 2000. Analysis was on an intention-to-treat basis. Continuous variables were expressed as mean ± SD. Treatment groups were compared by the chi-square test for discrete variables. Paired two-tailed *t* test was used for within-group comparisons. One-way analysis of variance (ANOVA) was used to compare continuous variables between groups. Correlation analysis between proportion of pacing and changes in echocardiographic parameters was done. Kaplan-Meier survival curves were compared by log-rank test. A Cox regression analysis was done to calculate the relative

Table 2. Baseline Characteristics at the Time of Pacemaker Implantation

Patients' Characteristics	AAIR	DDDR-s	DDDR-l
Number of patients	54	60	63
Age (yrs)	74 ± 9	74 ± 9	74 ± 9
Female (n)	31	34	39
Mean follow-up (yrs)	3.1 ± 1.3	2.8 ± 1.5	2.8 ± 1.4
Blood pressure (mm Hg)			
Systolic	145 ± 24	139 ± 22	144 ± 22
Diastolic	80 ± 13	75 ± 12	80 ± 10
Arrhythmia indicating pacemaker treatment			
Sinus bradycardia (n)	8	5	11
Sino-atrial block (n)	19	17	16
BTS (n)	27	38	36
Symptoms indicating pacemaker treatment			
Syncope (n)	19	26	24
Dizzy spells (n)	34	32	34
Heart failure (n)	1	2	5
CAD (n)	21	25	22
DM (n)	6	6	7
NYHA class (n)			
I	32	38	46
II	18	22	14
III	2		3
IV	1		
Electrocardiographic parameters			
PQ interval (ms)	186 ± 27	183 ± 28	184 ± 27
Wenckebach block point (n)*			
<100/min	2	5	3
≥100/min	50	52	57
Medication (n)			
Beta-blocker	4	5	7
Ca-blocker	14	7	11
Digoxin	11	9	11
Sotalol	7	8	10
Aspirin	35	40	36
Warfarin	5	5	11

Continuous data are mean ± SD, other variables reported as number of patients. *The Wenckebach block point could not be tested in patients having atrial fibrillation during implantation.

AAIR = rate adaptive single chamber atrial pacemaker; BTS = brady-tachy syndrome; CAD = coronary artery disease; DDDR-l = dual-chamber pacemaker programmed with a conventional fixed long AV delay of ≥250 ms; DDDR-s = dual-chamber pacemaker programmed with a conventional short rate-adaptive AV delay of 110 to 150 ms; DM = diabetes; NYHA = New York Heart Association.

risk proportion of AF adjusted for brady-tachy syndrome. A p value <0.05 (two-sided) was considered statistically significant. No correction was done for multiple comparisons. SPSS 10.0 was used for statistical analysis. The Institutional Scientific Ethical Committee approved the study.

RESULTS

Patients. A total of 952 consecutive patients were implanted with their first pacemaker during the recruitment period. Of these, 775 patients were excluded (Table 1), and 177 patients were included, 166 patients at Skejby Hospital (20% of the population screened) and 11 patients at Viborg County Hospital (11% of the population screened).

The 177 consecutive patients were randomized to AAIR (n = 54), DDDR-s (n = 60), or DDDR-l (n = 63) pacing. Mean follow-up was 2.9 ± 1.1 years (range, 6 days to 5.3 years) and similar in the three groups. No patients were lost to follow-up. Baseline characteristics of the three groups were similar (Table 2). The programmed minimum rate was 63 ± 8 (range, 40 to 80) versus 60 ± 4 (range, 50 to 70) versus 61 ± 5 (range, 50 to 70) beats/min, in the AAIR, DDDR-s, and DDDR-l groups, respectively ($p = 0.04$, ANOVA). The programmed maximum rate was 120 ± 8 (range, 100 to 130) versus 120 ± 5 (range, 100 to 130) versus 108 ± 8 (range, 90 to 120), respectively ($p < 0.01$, ANOVA).

Pacing mode at implantation and at the end of follow-up or death is shown in Figure 1. All patients randomized to DDDR pacing were discharged from hospital with DDDR pacing. Three patients randomized to AAIR pacing were implanted with a DDDR pacemaker at primary implantation. In two patients the reason was Wenckebach block below 100 beats/min at implantation; in one patient it was impossible to obtain an acceptable atrial sensing value during AF, and a ventricular lead was implanted for safety reasons.

During follow-up, three patients randomized to AAIR pacing had ventricular leads implanted because of develop-

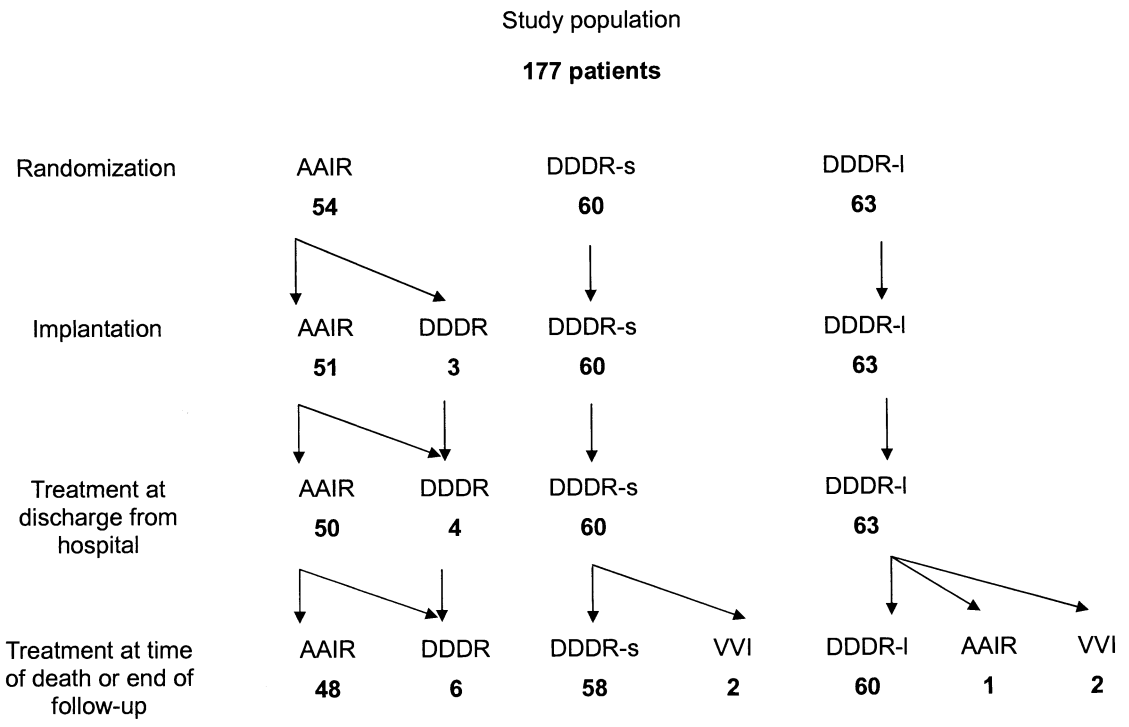


Figure 1. Pacing mode at implantation and at the end of follow-up or death. VVI = single chamber ventricular pacemaker; other abbreviations as in Tables 1 and 2.

ment of high-degree AV block (1.9% per year). The symptoms associated with AV block were dizzy spells in two patients and syncope in one patient. The PQ interval at baseline for each of these three patients was 200 ms, 180 ms, and 160 ms, respectively. In these patients, AAIR mode was changed to DDDR-l mode. Four patients in the DDDR group had their pacing mode changed to VVI pacing because of development of persistent AF. One patient was changed from DDDR mode to AAIR mode after 13 months because of malfunction of the ventricular lead. Re-operation was not done in this patient, because of lung cancer.

Echocardiographic changes. M-MODE. The within-group comparisons of the M-mode parameters obtained before pacemaker implantation and at the end of follow-up are listed in Table 3. The within-group differences (delta values) did not differ between groups for any of the parameters.

LA diameter. Mean LA diameter at implantation and during follow-up is shown in Figure 2. Before pacemaker implantation there was no difference in LA diameter between groups ($p = 0.98$, ANOVA), nor was there any difference between groups at last follow-up ($p = 0.23$, ANOVA). Graphically, LA diameter seemed to increase during follow-up, especially in the DDDR-s group (Fig. 2). Statistically, LA diameter increased significantly during follow-up in the two DDDR groups and in the DDDR-s-AAI group, but not in the AAIR group (Table 3).

LV diameters and LVFS. Left ventricular diameters and LVFS did not differ between groups at baseline or at last follow-up. A significant increase in LVES diameters in both the DDDR-s group and the DDDR-l group was observed during follow-up (Table 3). In the DDDR-l group, a significant increase was seen also in the LVED diameter. In the DDDR-s-AAI group, both LVES and LVED diameters increased significantly during follow-up. In the DDDR-s group and in the DDDR-s-AAI group, LVFS decreased significantly from baseline to last follow-up.

The changes observed in the LA and LV diameters during follow-up were similar after exclusion of the patients who had AF at echocardiography before pacemaker implantation or at one or more of the follow-up visits (Table 3).

Two-dimensional parameters. The within-group comparisons of the two-dimensional echocardiographic parameters obtained before pacemaker implantation and at the end of follow-up are listed in Table 4. The within-group differences did not differ between groups for any of the parameters. Left atrial, LVED, and LVES volumes did not differ between groups at baseline or at last follow-up, nor did LVEF differ between groups at baseline or at last follow-up.

Comparing LA volume before pacemaker implantation and at last follow-up within groups, no significant changes were found in the three randomization groups nor in the DDDR-s-AAI group (Table 4).

In the AAIR group and in the DDDR-s group, LVES volume increased, and LVEF decreased significantly during follow-up (Table 4).

Pacemaker telemetry data. Mean proportion of pacing during follow-up was, in the atrium: 69% in the AAIR

Table 3. M-Mode Echocardiographic Measurements

	AAIR (n = 54)			DDDR-l (n = 63)			DDDR-s (n = 60)			DDDR-S-AAI (n = 60)		
	PRE	LAST-FU	n	PRE	LAST-FU	n	PRE	LAST-FU	n	PRE	LAST-FU	n
LA-D												
All patients	39 ± 8	41 ± 7	52	39 ± 5	41 ± 7†	57	39 ± 6	43 ± 8§	52	39 ± 6	42 ± 8‡	51
No AF*	39 ± 7	41 ± 7	45	39 ± 5	40 ± 6	44	39 ± 6	42 ± 7‡	36	39 ± 6	41 ± 7†	36
LVES-D												
All patients	31 ± 6	32 ± 8	49	30 ± 8	32 ± 7†	57	30 ± 7	33 ± 10†	52	30 ± 7	33 ± 10‡	50
No AF*	31 ± 6	33 ± 8	43	30 ± 8	31 ± 6	44	30 ± 7	32 ± 7	36	30 ± 7	33 ± 8†	35
LVED-D												
All patients	50 ± 7	50 ± 6	49	47 ± 8	49 ± 8‡	57	49 ± 7	51 ± 9	52	49 ± 7	51 ± 9†	50
No AF*	51 ± 7	51 ± 6	43	46 ± 8	50 ± 8‡	44	50 ± 7	50 ± 8	36	50 ± 7	51 ± 7	35
LVFS												
All patients	0.39 ± 0.07	0.36 ± 0.1	49	0.37 ± 0.09	0.36 ± 0.09	57	0.39 ± 0.08	0.36 ± 0.09‡	52	0.39 ± 0.08	0.36 ± 0.1‡	50
No AF*	0.39 ± 0.06	0.37 ± 0.1	43	0.36 ± 0.09	0.37 ± 0.08	44	0.40 ± 0.08	0.37 ± 0.09‡	36	0.40 ± 0.08	0.35 ± 0.09‡	35

Data are mean ± SD. *Patients without atrial fibrillation at echocardiography before pacemaker implantation or at any follow-up; †$p < 0.05$; ‡$p < 0.01$; §$p < 0.001$.
AF = atrial fibrillation; LA-D = left atrial diameter; LAST-FU = last follow-up; LVED-D = left ventricular end-diastolic diameter; LVES-D = left ventricular end-systolic diameter; LVFS = left ventricular fractional shortening; n = number of patients in the paired samples tests; PRE = before pacemaker implantation; Other abbreviations as in Tables 1 and 2.

Figure 2. Mean left atrial diameter from M-mode echocardiographic measurements at implantation and during follow-up. Pre = the day before pacemaker implantation; 1 day = the day after pacemaker implantation. Numbers below x-axis indicate numbers of patients who had M-mode echocardiography at each follow-up in each group. **Solid diamonds** = AAIR; **solid squares** = DDDR-s; **solid triangles** = DDDR-l; **stars** = DDDR-s-AAI. Abbreviations as in Tables 1 and 2.

group, 57% in the DDDR-s group, and 67% in the DDDR-l group (p = 0.08, ANOVA); in the ventricle: 90% in the DDDR-s group and 17% in the DDDR-l group ($p < 0.001$, ANOVA). Correlation between mean proportion of pacing in the ventricle during follow-up and the relative changes in LA diameter, LVES and LVED diameters, and LVFS from before implantation until end of follow-up was done for the DDDR-s and the DDDR-l groups. Correlation between mean proportion of pacing in the atrium during follow-up and the relative change in LA diameter was done for all three randomization groups. No significant linear correlation was observed.

Clinical end points. During follow-up, AF at one or more ambulatory visits was significantly less common in the AAIR group, 7.4% (n = 4) versus 23.3% (n = 14) in the DDDR-s group versus 17.5% (n = 11) in the DDDR-l group (p = 0.03, log-rank test). Kaplan-Meier plots of the proportions of patients in the three groups without AF during follow-up are shown in Figure 3. Brady-tachy syndrome at pacemaker implantation was strongly associated with AF during follow-up (relative risk 3.3 [95% confidence interval 1.3 to 8.1], p = 0.01). The risk of developing AF in the AAIR group compared with the DDDR-s group was still significantly decreased after adjusting for brady-tachy syndrome (relative risk 0.27 [95% confidence interval 0.09 to 0.83], p = 0.02). Programmed lower rate was not different among patients with and without AF during follow-up (61.3 beats/min vs. 61.7 beats/min, p = 0.74).

A total of 16 strokes occurred during follow-up in 14

Table 4. Two-dimensional Echocardiographic Measurements

	AAIR (n = 54)			DDDR-1 (n = 63)			DDDR-s (n = 60)			DDDR-S-AAI (n = 60)		
	PRE	LAST-FU	n	PRE	LAST-FU	n	PRE	LAST-FU	n	PRE	LAST-FU	n
LAVOL												
All patients	66 ± 28	68 ± 33	46	69 ± 24	66 ± 30	54	76 ± 32	75 ± 36	51	76 ± 32	73 ± 33	49
No AF*	65 ± 23	66 ± 30	41	65 ± 23	64 ± 29	42	77 ± 35	75 ± 39	34	72 ± 26	70 ± 33	32
LVSVOL												
All patients	29 ± 13	38 ± 25†	38	32 ± 18	35 ± 19	49	32 ± 18	43 ± 48†	47	31 ± 17	42 ± 50	42
No AF*	30 ± 14	39 ± 25†	32	31 ± 18	35 ± 20	41	29 ± 8	38 ± 22†	30	29 ± 9	36 ± 20†	27
LVDVOL												
All patients	71 ± 26	83 ± 37	38	77 ± 28	78 ± 30	49	78 ± 29	87 ± 57	47	78 ± 29	92 ± 67	42
No AF*	73 ± 27	86 ± 38	32	77 ± 29	78 ± 30	41	75 ± 20	81 ± 32	30	75 ± 20	85 ± 32†	27
LVEF												
All patients	0.60 ± 0.07	0.56 ± 0.1†	38	0.60 ± 0.08	0.57 ± 0.09	49	0.61 ± 0.08	0.56 ± 0.1†	47	0.6 ± 0.08	0.6 ± 0.09	42
No AF*	0.60 ± 0.07	0.56 ± 0.1†	24	0.61 ± 0.08	0.58 ± 0.09	39	0.61 ± 0.07	0.56 ± 0.09	32	0.62 ± 0.07	0.59 ± 0.08	27

Data are mean ± SD. *Patients without atrial fibrillation at echocardiography before pacemaker implantation or at any follow-up; †$p < 0.05$.
LAST-FU = last follow-up; LAVOL = left atrial volume; LVDVOL = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVSVOL = left ventricular end-systolic volume; n = number of patients in the paired samples tests; PRE = before pacemaker implantation; Other abbreviations as in Tables 1 and 2.

patients, 3 patients from the AAIR group (5.6%), 7 patients from the DDDR-s group (11.7%), and 4 patients from the DDDR-l group (6.3%) ($p = 0.32$, log-rank test). Peripheral emboli were not observed.

A total of 37 patients died during follow-up, nine patients (16.7%) in the AAIR group, 14 patients (23.3%) in the DDDR-s group, and 14 patients (22.2%) in the DDDR-l group ($p = 0.51$, log-rank test). Annual rate of mortality was 5.4%, 8.4%, and 8.0%, respectively. Cardiovascular mortality was 7.4% versus 11.7% versus 14.3% ($p = 0.43$, log-rank test).

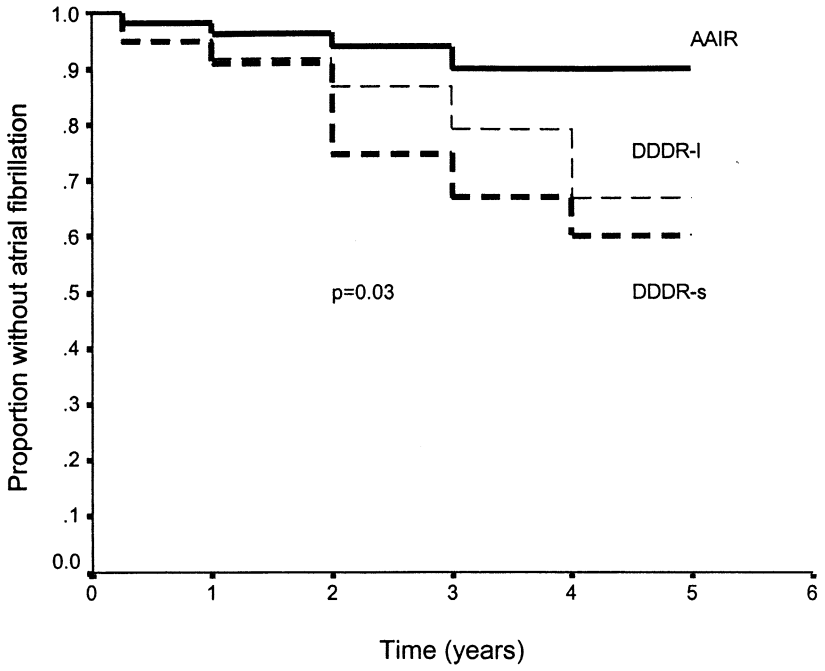
Before pacemaker implantation, there were no differences in NYHA functional class or consumption of diuretics between the AAIR, DDDR-s, and DDDR-l groups. During follow-up, 31% versus 30% versus 46% of patients in the three groups increased at least one NYHA class ($p = 0.17$, chi-square test), and increase in consumption of diuretics was observed in 28% versus 32% versus 21% of patients in the three groups ($p = 0.34$, chi-square test).

DISCUSSION

Our study is the first randomized trial comparing AAIR and DDDR pacing in patients with SSS and normal AV conduction. The study indicates that long-term DDDR pacing induces LA dilation and, in the case of a high proportion of RV pacing, also reduces LV function. Furthermore, AF is significantly less common during AAIR pacing. These findings support AAIR pacing as the preferred pacing mode in this group of patients.

In the present trial, DDDR pacing with 90% RV pacing induced changes identical to the changes observed in the VVI group in the AAI versus VVI trial (1,2), with a decrease in LVFS and an increase in LA dilation, and DDDR-l pacing (with a mean 17% of RV pacing) caused only an increase in LA diameter, with no change in LVFS. These findings support that a high proportion of RV pacing causes a decrease in LV function. This is in accordance with recent findings from the randomized MOST (The Mode Selection Trial in Sinus-Node Dysfunction) (11) trial, where increasing proportions of pacing in the RV was associated with increase in the risk of hospitalization for HF (12).

The persistent LA dilation and LVFS decrease in the DDDR-s group after programming to AAI mode (DDDR-s-AAI) indicate that the effects of long-term RV pacing on LV function and LA size also persist after cessation of pacing. The echocardiographic study in AAI mode was, however, done only 5 min after programming to AAI mode, and it is not known whether the LA dilation and LVFS decrease would revert, given a longer period without RV pacing. In dogs, long-term AV synchronous LV pacing has been reported to induce ventricular remodeling with asymmetrical hypertrophy of the LV wall, thinning of the earliest activated free wall, and thickening of the late-activated septum (13,14). The present results do not answer whether



Number of patients at risk during follow-up:

AAIR	54	52	38	22	14	1
DDDR-s	60	48	33	18	9	3
DDDR-I	63	55	35	22	12	3

Figure 3. Kaplan-Meier plots of freedom from atrial fibrillation during follow-up. Atrial fibrillation was diagnosed only by standard 12-lead electrocardiogram at planned follow-up visits, not in-between these visits. AAIR = single lead atrial pacing; DDDR-l = dual-chamber pacing with the pacemaker programmed with a fixed atrioventricular (AV) delay of 300 ms; DDDR-s = dual-chamber pacing with the pacemaker programmed with a rate-adaptive AV delay ≤150 ms and ventricular capture.

a similar remodeling occurs during long-term RV pacing in humans.

In the present study, LA diameter increased significantly in both DDDR groups but not in the AAIR group. The LA dilation is possibly caused by the abnormal activation sequence and mechanical contraction pattern of the ventricles induced by RV pacing (3,4,15,16) associated with a decrease in the LV systolic (3,4) and diastolic function (15) and an increase in the right atrial pressure and the pulmonary capillary wedge pressure (3,17,18). The LA dilation was more marked in the DDDR-s group with 90% RV pacing than in the DDDR-l group with 17% RV pacing, supporting an association between these two parameters. The non-significant increase in LA diameter observed in the AAIR group could represent a feature in the natural evolution of the SSS and/or be related to increasing age (19). In the present study, the ventricular lead was implanted in the RV apex. Using RV septal pacing might have influenced the present results (20,21).

Patients with DDDR pacemakers were programmed with either a short rate-adaptive AV delay or a long fixed AV delay. Optimizing the AV delay individually might have influenced the present results (22). However, the study was designed to evaluate effects of different proportions of ventricular pacing rather than DDDR pacing with an optimized AV delay. Despite programming of a fixed long AV interval, pacing in the RV was reduced to a mean of only 17%. The explanation of this finding probably is RV fusion beats, RV pacing during AF, and RV pacing during different forms of pacemaker tachycardias, as previously documented (22).

When the present study was designed in the early 1990s, two-dimensional echocardiography was expected to yield more precise information of the changes over time in LA and LV dimensions than M-mode echocardiography. The results of our two-dimensional echocardiographic studies do not support the findings done by M-mode echocardiography. The changes observed in left chamber volumes and LVEF during follow-up were all small in size and within the 95% confidence intervals of repeated two-dimensional echocardiographic studies (23,24). Measuring the LA volume by two-dimensional echocardiography has never found any place in clinical or scientific echocardiography. Furthermore, in contrast with LA diameter measured by M-mode

echocardiography (25), LA volume has never been found predictive of later cardiovascular events.

The correlations between mean proportion of RV pacing and the changes in LA and LV diameters during follow-up and the correlations between mean proportion of pacing in the atrium and changes in LA diameter were all non-significant, most likely because of the insufficient accuracy of echocardiography (23,26).

In the present trial, AF was significantly more common in the two DDDR groups, indicating that RV pacing may promote AF, most likely because it causes LA dilation. Similar changes in the echocardiographic parameters were observed after excluding patients who had AF at their echocardiographic examinations, indicating that AF was not the cause of the echocardiographic changes observed. We observed no differences in occurrence of thromboembolism, congestive HF, or death between pacing modes during follow-up, indicating that AAIR and DDDR pacing is similar regarding these outcomes. The limited sample size must, however, be kept in mind when interpreting these data. The incidence of high-degree AV block in the AAIR group was comparable to the annual rate of 1.7% observed in a recent retrospective study of 399 consecutive patients treated with AAI(R) pacing in our institution (27).

At present time, AAI(R) pacing mode seems to be the optimal treatment for isolated SSS. In the future, new mode switching abilities between DDD and AAI pacing may enable AAI pacing the majority of the time and, in addition, protect the patients from severe bradycardia due to AV block. The currently ongoing DANPACE trial (10) is expected to answer whether the risks associated with AAI(R) pacing and AV block are less than the risks associated with RV pacing in DDD(R) mode.

Study limitations. In our previous study, the differences between pacing modes increased markedly during long-term follow-up (2,28). In the present study the mean follow-up was just below three years. The present results cannot be extrapolated beyond this period after pacemaker implantation. Our study was initially designed to include 450 patients, but inclusion was stopped prematurely after randomizing 177 patients, reducing the statistical power.

The echocardiographic measurements were done unblinded with regard to pacing mode and randomization group. Furthermore, at the ambulatory follow-up visits, echocardiography was done in the AAI mode 5 min after echocardiography in the DDD mode when ventricular pacing had been present in that mode. These factors may have introduced an observer bias. However, results from prior echocardiographic studies of any particular patient in the study were not known at the time of later echocardiographic studies or analyses of echocardiographic data in that patient.

For evaluating the proportions of pacing and sensing in the chambers, we had to rely on telemetered data. Far-field over-sensing of R waves in the atrium and of T waves in the ventricle as well as under-sensing of small atrial electrograms during AF may have influenced these data. To reduce these sense problems, bipolar atrial leads were used in the majority of patients. It is unlikely that the reliability of telemetered data should be different between randomization groups.

Conclusions. Our study is the first randomized trial comparing AAIR and DDDR pacing in patients with SSS and normal AV conduction. The study indicates that long-term DDDR pacing induces LA dilation and, in the case of a high proportion of LV pacing, also reduces LV function. Furthermore, AF is significantly less common during AAIR pacing. These findings support AAIR pacing as the preferred pacing mode in this group of patients.

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REFERENCES

1. Andersen HR, Thuesen L, Bagger JP, Vesterlund T, Thomsen PE. Prospective randomised trial of atrial versus ventricular pacing in sick-sinus syndrome. Lancet 1994;344:1523–8.
2. Andersen HR, Nielsen JC, Thomsen PE, et al. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick sinus syndrome. Lancet 1997;350:1210–6.
3. Leclercq C, Gras D, Le Helloco A, Nicol L, Mabo P, Daubert C. Hemodynamic importance of preserving the normal sequence of ventricular activation in permanent cardiac pacing. Am Heart J 1995;129:1133–41.
4. Rosenqvist M, Bergfeldt L, Haga Y, Ryden J, Ryden L, Öwall A. The effect of ventricular activation sequence on cardiac performance during pacing. Pacing Clin Electrophysiol 1996;19:1279–86.
5. Andersen HR, Nielsen JC, Thomsen PE, et al. Atrioventricular conduction during long-term follow-up of patients with sick sinus syndrome. Circulation 1998;98:1315–21.
6. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978;58: 1072–83.
7. Schiller NB. Two-dimensional echocardiographic determination of left ventricular volume, systolic function, and mass: summary and discussion of the 1989 recommendations of the American Society of Echocardiography. Circulation 1991;84 Suppl:I280–7.
8. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358–67.
9. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307–10.
10. Andersen HR, Nielsen JC. Pacing in sick sinus syndrome—need for a prospective, randomized trial comparing atrial with dual chamber pacing. Pacing Clin Electrophysiol 1998;21:1175–9.
11. Lamas GA, Lee KL, Sweeney M, Silverman R. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. N Engl J Med 2002;346:1854–62.
12. Sweeney M. Effect of pacing mode and cumulative percent time ventricular paced on heart failure in patients with sick sinus syndrome and baseline QRS duration <120 milliseconds in MOST (abstr). Pacing Clin Electrophysiol 2002;24:561.
13. Prinzen FW, Cheriex EC, Delhaas T, et al. Asymmetric thickness of the left ventricular wall resulting from asynchronous electric activation: a study in dogs with ventricular pacing and in patients with left bundle branch block. Am Heart J 1995;130:1045–53.

14. Van Oosterhout MFM, Prinzen FW, Arts T, et al. Asynchronous electrical activation induces asymmetrical hypertrophy of the left ventricular wall. Circulation 1998;98:588–95.
15. Lee MA, Dae MW, Langberg JJ, et al. Effects of long-term right ventricular apical pacing on left ventricular perfusion, innervation, function and histology. J Am Coll Cardiol 1994;24:225–32.
16. Rosenqvist M, Isaaz K, Botvinick EH, et al. Relative importance of activation sequence compared to atrioventricular synchrony in left ventricular function. Am J Cardiol 1991;67:148–56.
17. Boucher CA, Pohost GM, Okada RD, Levine FH, Strauss HW, Harthorne JW. Effect of ventricular pacing on left ventricular function assessed by radionuclide angiography. Am Heart J 1983;106:1105–11.
18. Ishikawa T, Kimura K, Yoshimura H, et al. Acute changes in left atrial and left ventricular diameters after physiological pacing. Pacing Clin Electrophysiol 1996;19:143–9.
19. Henry WL, Gardin JM, Ware JH. Echocardiographic measurements in normal subjects from infancy to old age. Circulation 1980;62:1054–61.
20. Schwaab B, Frohlig G, Alexander C, et al. Influence of right ventricular stimulation site on left ventricular function in atrial synchronous ventricular pacing. J Am Coll Cardiol 1999;33:317–23.
21. Victor F, Leclercq C, Mabo P, et al. Optimal right ventricular pacing site in chronically implanted patients: a prospective randomized crossover comparison of apical and outflow tract pacing. J Am Coll Cardiol 1999;33:311–6.
22. Nielsen JC, Pedersen AK, Mortensen PT, Andersen HR. Programming a fixed long atrioventricular delay is not effective in preventing ventricular pacing in patients with sick sinus syndrome. Europace 1999;1:113–20.
23. Kim WY, Sogaard P, Egeblad H, Andersen NT, Kristensen B. Three-dimensional echocardiography with tissue harmonic imaging shows excellent reproducibility in assessment of left ventricular volumes. J Am Soc Echocardiogr 2001;14:612–7.
24. Goerge G, Erbel R, Brennicke R, Rupprecht H, Todt M, Meyer J. High-resolution two-dimensional echocardiography improves the quantification of left ventricular function. J Am Soc Echocardiogr 1992;5:125.
25. Gardin JM, McClelland R, Kitzman D, et al. M-mode echocardiographic predictors of six- to seven-year incidence of coronary heart disease, stroke, congestive heart failure, and mortality in an elderly cohort (the Cardiovascular Health study). Am J Cardiol 2001;87:1051–7.
26. Nielsen JC. Optimal pacing mode in patients with sick sinus syndrome: on the consequences of implanting a ventricular lead. Denmark: Aarhus University; 2000. Thesis.
27. Kristensen L, Nielsen JC, Pedersen AK, Mortensen PT, Andersen HR. AV block and changes in pacing mode during long-term of 399 consecutive patients with sick sinus syndrome treated with an AAI/AAIR pacemaker. Pacing Clin Electrophysiol 2001;24:358–65.
28. Nielsen JC, Andersen HR, Thomsen PE, et al. Heart failure and echocardiographic changes during long-term follow-up of patients with sick sinus syndrome randomized to single chamber atrial or ventricular pacing. Circulation 1998;97:987–95.