Heart Failure and Echocardiographic Changes During Long-term Follow-up of Patients With Sick Sinus Syndrome Randomized to Single-Chamber Atrial or Ventricular Pacing

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Background—In patients with sick sinus syndrome, choice of pacing mode has been implicated in the development of congestive heart failure.

Methods and Results—A total of 225 consecutive patients with sick sinus syndrome and intact atrioventricular conduction were randomized to either single-chamber atrial pacing (n = 110) or single-chamber ventricular pacing (n = 115). Clinical assessment included New York Heart Association classification, medication, and M-mode echocardiography before pacemaker implantation, after 3 months, and subsequently once every year. At long-term follow-up (mean, 5.5 ± 2.4 years), NYHA class was higher in the ventricular group than in the atrial group (NYHA class I/II/III/IV: 65/44/4/0 versus 84/22/2/1 patients, P = .010). Increase in NYHA class during follow-up was observed in 35 of 113 patients in the ventricular group versus 10 of 109 in the atrial group (P < .0005). Increase in dose of diuretics from randomization to last follow-up was significantly higher in the ventricular group than in the atrial group (21 ± 649 versus 8 ± 42 mg furosemide/d, P = .033). The left ventricular fractional shortening decreased significantly in the ventricular group (from 0.36 ± 0.12 to 0.31 ± 0.08, P < .0005) but not in the atrial group (from 0.35 ± 0.13 to 0.33 ± 0.09, P = .087). The left atrial diameter increased significantly in both treatment groups (ventricular group: from 34 ± 7 to 41 ± 7 mm, P < .0005; atrial group: from 34 ± 6 to 37 ± 7 mm, P = .002), but the increase was significantly higher in the ventricular group than in the atrial group (P < .0005).

Conclusions—During long-term follow-up, ventricular pacing is associated with a higher incidence of congestive heart failure and consumption of diuretics than atrial pacing. This is accompanied by a decrease in left ventricular fractional shortening and an increased dilatation of the left atrium in the ventricular paced patients. (Circulation. 1998;97:987-995.)

Key Words: sick sinus syndrome ■ pacing ■ echocardiography ■ heart failure ■ ventricles

In several observational studies of patients with sick sinus syndrome, single-chamber ventricular pacing has been associated with a higher incidence of congestive heart failure than single-chamber atrial pacing.1–5 Furthermore, experimental studies have demonstrated that long-term ventricular pacing is associated with both structural and functional changes in the ventricular myocardium, which could lead to congestive heart failure.6–9 However, echocardiographic studies in ventricular paced patients have failed to demonstrate significant changes in left ventricular systolic dimensions and function,10,11 whereas left ventricular diastolic dimensions have been found to increase in one study11 and to decrease in two other studies.10,12 In the first prospective, randomized trial comparing atrial and ventricular pacing in patients with sick sinus syndrome, the left atrial diameter increased significantly in the ventricular paced patients, whereas the trial did not show any significant difference in heart failure between the two groups after short-term follow-up.13 Thus conflicting results exist about development of heart failure and echocardiographic parameters in ventricular paced patients with sick sinus syndrome, possibly due to lack of long-term randomized trials including sequential echocardiographic evaluation during follow-up.

Therefore, a long-term prospective trial with sequential echocardiographic evaluation was performed to study the evolution in congestive heart failure and elucidate the left atrial and left ventricular dimensions and the left ventricular function (left ventricular fractional shortening) in patients with sick sinus syndrome randomized to atrial or ventricular pacing.

Methods

Protocol

The trial was conducted as a one-center study at Skejby University Hospital. All patients who were referred to treatment with their first
Mortality as the result of congestive heart failure did not include patients dying suddenly.

### Atrial Fibrillation

Atrial fibrillation was diagnosed by 12-lead ECG at the follow-up visits (not from ECGs taken at any other time). Atrial fibrillation was categorized as chronic if recorded at two consecutive follow-up visits and no sinus rhythm was observed subsequently.

### Echocardiography

Left atrial diameter and left ventricular end-systolic (LVEDD) and end-diastolic diameters (LVESD) were determined by M-mode echocardiography in accordance with the recommendations of the American Society of Echocardiography. Left ventricular dimensions were obtained at the level of the chordae. Measurements were done by the leading edge methodology. Left ventricular fractional shortening (LVFS) was calculated as (LVESD – LVEDD)/LVEDD.

### Study Population

During the recruitment period, 1052 patients (568 men, age 71 ± 17 years) had their first pacemaker implanted; 827 were excluded from randomization (Table 1).15

### Pacemaker Implantation

Patients had an atrial pacing test during implantation at 100 and 120 bpm. Atrioventricular conduction (1:1) at 100 bpm was required for an atrial pacemaker to be implanted; otherwise, the lead was implanted in the right ventricle. Patients randomized to ventricular pacing always had a ventricular lead implanted whatever the result of the atrial pacing test. Whether to use a pacemaker with rate-adaptive modality was decided by the physician in charge of the implantation from clinical criteria. The programmed pacing rate after implantation and during follow-up was set from clinical criteria.

Retrograde atrioventricular conduction was assessed only in patients randomized to ventricular pacing, as previously described in detail.15

### Ethics

The study was approved by the National Danish Ethical Committee and was conducted in accordance with the rules of the Helsinki Declaration. Informed consent was obtained from all patients before inclusion in the study.

### Analysis

Power calculations were done before start of the study and have been published previously.13 All statistical analyses were done according to the intention-to-treat principle. Continuous variables are expressed as mean ± SD in text and tables and as mean ± SEM in the figures. Treatment groups were compared by $\chi^2$ test or Fisher’s exact test (two-tailed) for discrete variables and by two-tailed Student’s $t$ test for continuous variables. Changes in echocardiographic parameters within treatment groups were analyzed by comparing mean values before pacemaker implantation with mean values at last follow-up (last ambulatory visit before end of study or death of patient), using the paired $t$ test. Intergroup statistics were done by comparing mean change from pacemaker implantation to last follow-up between treatment groups, using the Student’s $t$ test. To reduce the number of statistical tests, intergroup comparisons were not done repeatedly at several time points after implantation but only at last follow-up or on change from implantation to last follow-up. Kaplan-Meier plots were calculated for mortality as the result of congestive heart failure and compared by log-rank test. Relative risk and 95% confidence interval were calculated by univariate Cox proportional hazards method. A value of $P<.05$ was deemed significant. Unadjusted probability values are presented.

### Results

**Patients**

A total of 225 patients (142 women, 83 men; age 76 ± 8 years; range, 50 to 92 years) were randomized to atrial pacing.

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**TABLE 1. Study Population**

<table>
<thead>
<tr>
<th>Excluded from randomization</th>
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<tbody>
<tr>
<td>Referred for first pacemaker implantation</td>
<td>1052</td>
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<tr>
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<tr>
<td>Grade 1, 2, 3 atrioventricular block*</td>
<td>552</td>
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<tr>
<td>Chronic atrial fibrillation</td>
<td>75</td>
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<tr>
<td>Bifascicular bundle branch block</td>
<td>37</td>
</tr>
<tr>
<td>Blood pressure &gt; 250/120 mm Hg</td>
<td>37</td>
</tr>
<tr>
<td>Atrial fibrillation &gt; 50% of time</td>
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<tr>
<td>Age &lt; 50 years</td>
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<td>Atrial fibrillation with RR interval &gt; 3 seconds</td>
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<tr>
<td>Cardiac surgery planned</td>
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<tr>
<td>Cancer</td>
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<tr>
<td>Cerebral disease</td>
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<tr>
<td>Atrial fibrillation with QRS rate &lt; 40 bpm</td>
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<tr>
<td>Stroke within the last 3 months</td>
<td>5</td>
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<tr>
<td>Follow-up not possible</td>
<td>2</td>
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<tr>
<td>Major surgery, noncardiac</td>
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<tr>
<td>Wenckebach block &lt; 100 bpm</td>
<td>1</td>
</tr>
<tr>
<td>Refusal</td>
<td>8</td>
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<tr>
<td>Other reasons</td>
<td>16</td>
</tr>
<tr>
<td>Total excluded</td>
<td>827</td>
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</table>

*Grade 1 atrioventricular block: Patients ≤ 70 years were excluded if the PQ interval was > 0.22 seconds and patients > 70 years if the PQ interval was > 0.26 seconds.**

...
(n=110) and ventricular pacing (n=115), respectively. No patients were lost to follow-up. One patient, who emigrated after the 1-year follow-up visit, had subsequent follow-up by telephone interview, but no echocardiographic measurements were accessible in this patient. Mean follow-up was 5.5±2.4 years for the total study population with similar follow-up in the atrial (5.7±2.3 years) and ventricular (5.3±2.5 years) group. Baseline characteristics of the two groups were similar except that more patients in the atrial group were treated with digoxin (Table 2).

Of the 110 patients randomized to atrial pacing, 6 had ventricular leads at primary implantation. Thirty-five patients (32%) had rate-adaptive pacemakers. During follow-up, another 5 patients had ventricular leads, and in 5 patients the pacemaker was upgraded to a dual-chamber system (in 4 cases due to AV block). Ninety-four patients (85%) of the 110 patients randomized to atrial pacing were treated as randomized during follow-up.

All patients randomized to ventricular pacing were discharged from the hospital with ventricular pacing. Sixteen (14%) patients had rate-adaptive pacemakers. During follow-up, 1 patient had the pacing system changed to atrial pacing; in another 3 patients, upgrading to a dual-chamber system was necessary, and 2 patients had the pacemaker system explanted. One hundred nine patients (95%) were treated as randomized during follow-up.

During follow-up, the mean programmed pacemaker-rate varied between 66 and 70 bpm in the atrial group and between 62 and 63 bpm in the ventricular group (except at 7 and 8 years follow-up, in which the mean rate in the ventricular group was 67 and 69 bpm, respectively). Medical treatment, including digoxin, was similar during follow-up in the two groups. The only exception was dosage of diuretics, which changed significantly (see below).

**Heart Failure**

At randomization, there was no difference in the NYHA classification and no difference in the use of diuretics between the two groups (Table 2). NYHA class at last follow-up (3 patients died before their first follow-up visit, leaving 222 patients) was significantly higher in the ventricular group than in the atrial group (NYHA class I/II/III/IV: 65/44/4/0 versus 84/22/2/1 patients, P=.010, \(\chi^2\) test). Increase in NYHA class during follow-up was observed in 10 of 109 patients in the atrial group versus 35 of 113 patients in the ventricular group (P<.0005, \(\chi^2\) test). Use of diuretics increased in the ventricular group but not in the atrial group during follow-up (Fig 1). The increase in dose of diuretics from randomization to last follow-up was significantly higher in the ventricular group than in the atrial group (21±49 versus 8±42 mg furosemide/d, P=.033). At the 3- and 5-year follow-up visits, information about use of diuretics was missing in 1 patient.

During follow-up, the proportion of patients suffering from dyspnea increased from 20% to 36% in the ventricular group, whereas it was always lower than 20% in the atrial group (Fig 2). There was no statistically significant difference in occurrence of dyspnea at last follow-up between the atrial group and the ventricular group (18% versus 24%, P=.31, \(\chi^2\) test). The occurrence of crural edema during follow-up was higher in the

<table>
<thead>
<tr>
<th>TABLE 2. Baseline Characteristics</th>
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<tbody>
<tr>
<td><strong>Atrial Group</strong></td>
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<td>No. of patients</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Sex</td>
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<td>Women</td>
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<td>Symptoms indicating pacemaker treatment</td>
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<tr>
<td>Syncope</td>
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<td>Dizzy spells</td>
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<tr>
<td>Heart failure</td>
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<tr>
<td>Arrhythmia indicating pacemaker treatment</td>
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<tr>
<td>Sinus bradycardia</td>
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<td>Sino atrial block</td>
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<td>Brady-tachy syndrome</td>
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<td>Clinical events before randomization</td>
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<td>Angina pectoris</td>
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<tr>
<td>Myocardial infarction</td>
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<td>Stroke</td>
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<td>Transitory cerebral ischemia</td>
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<td>Pulmonary embolus</td>
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<td>Left atrial diameter, mm</td>
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<td>LVEDD, mm</td>
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<tr>
<td>LVESD, mm</td>
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<td>Wenckebach point†</td>
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<td>&lt; 100 bpm</td>
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<td>100-119 bpm</td>
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<td>Antiarrhythmic drugs</td>
</tr>
<tr>
<td>Furosemide, mg/d</td>
</tr>
<tr>
<td>Aspirin</td>
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<tr>
<td>Warfarin</td>
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</table>

*NYHA class, New York Heart Association heart failure classification; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVFS, left ventricular fractional shortening.
†Measurements represent data from 215 patients because of an inadequate echocardiographic window in 4 patients.
ventricular group than in the atrial group, most markedly after long-term follow-up (Fig 3), but there was no statistically significant difference in occurrence of crural edema at last follow-up between the atrial group and the ventricular group (14% versus 19%, P=.33, χ² test).

A total of 7 patients died from congestive heart failure in the ventricular group versus 3 in the atrial group. Kaplan-Meier plots are shown in Fig 4. The mortality as the result of congestive heart failure was not significantly different between the two groups (relative risk for atrial group, 0.41 [95% CI, 0.11 to 1.59], P=.18).

Atrial Fibrillation
All patients had sinus rhythm at the time of randomization. In the ventricular group, 40 patients (35%) had atrial fibrillation at one or more follow-up visits versus 26 patients (24%) in the atrial group (P=.066, χ² test). Twenty-one patients died before the 1-year follow-up visit, leaving 204 patients (102 in each group) at risk of developing chronic atrial fibrillation. In the ventricular group, 22 patients (22%) developed chronic atrial fibrillation versus 9 patients (9%) in the atrial group (P=.011, χ² test).

Echocardiographic Findings
All patients had echocardiographic examination before implantation as a part of the trial. Initially, echocardiography at follow-up was not done routinely in all patients, but from February 1990 to December 1996, all patients had echocardiographic examination at each follow-up visit as a part of the trial. A total of 625 echocardiographic examinations were done in the atrial group and 630 in the ventricular group. Only a low number of cases were echocardiographic measurements not possible because of poor image quality. In some patients, left atrial diameter but not left ventricular dimensions could be assessed, and sometimes vice versa. Consequently, the number of patients with measurements of atrial and ventricular dimensions is not always the same. The numbers of patients investigated are reported in Table 3 and below abscissa in Figs 5 to 8.

Left Atrial Diameter
During follow-up, there was an increase in the left atrial diameter in both treatment groups, most markedly in the ventricular group (Fig 5). Statistically, the increase was significant in both the atrial group (P=.002) and the ventricular group (P<.0005), and the increase was significantly higher in the ventricular group than in the atrial group (P<.0005) (Table 3). Because atrial enlargement may be a consequence of atrial fibrillation, subgroup analyses were performed in (1) patients who were without atrial fibrillation at any follow-up visit, (2) patients without atrial fibrillation at the time of the last echocardiographic examination, (3) patients without chronic atrial fibrillation, and (4) patients with chronic atrial fibrillation (Table 3). In all these subgroups the left atrial diameter increased more in the ventricular group than in the atrial group, but in the small group of patients with chronic atrial fibrillation, the difference was not statistically significant (Table 3). In subgroup 1 (patients without atrial fibrillation at any follow-up visit) and subgroup 2 (patients without atrial fibrillation at the time of the last echocardiographic examination), follow-up time was slightly longer in the atrial group than in the ventricular group (subgroup 1: 5.5±2.3 versus 4.6±2.5 years, P=.013, t test; and subgroup 2: 5.5±2.3 versus 4.8±2.4 years, P=.035, t test), whereas there was no difference in follow-up time in subgroups 3 and 4.

Left Ventricular End-systolic Diameter
Graphically, the LVESD appeared to increase more in the ventricular group than in the atrial group (Fig 6). Compared with preoperative values, the increase was significant in the ventricular group (P=.005) but not in the atrial group (P=.40). The increase in LVESD in the ventricular group was highest in the group of patients with chronic atrial fibrillation (Table 3). In patients without atrial fibrillation at last echocardiographic measurement and in patients without chronic atrial fibrillation, there was no statistically significant increase in LVESD in the ventricular group (Table 3).

Left Ventricular End-diastolic Diameter
Graphically, the LVEDD appeared to be higher in the ventricular group than in the atrial group (Fig 7), but statistically, there was no significant change in LVEDD from pacemaker implantation to last follow-up in either the atrial group or the ventricular group (Table 3).

Left Ventricular Fractional Shortening
In the plot of the LVFS during follow-up, the LVFS apparently decreased more in the ventricular group than in the atrial group (Fig 8). Comparing the mean values before pacemaker implantation with the mean values at last follow-up, we found that the LVFS decreased significantly in the ventricular group (P<.0005) but not in the atrial group (P=.087). There was no statistically significant difference in the decrease in LVFS between the two groups (P=.097). In all subgroup analyses, the LVFS decreased significantly in the ventricular group but not in the atrial group except in the group of patients without atrial fibrillation at last follow-up, in which a minor decrease was seen also in the atrial group (Table 3).

Blood Pressure
At the time of randomization there was no difference in either systolic or diastolic blood pressure between the atrial and the ventricular group (Table 2). Blood pressure during follow-up

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**Figure 1.** Mean dose of diuretics (converted to milligrams of furosemide per day) during follow-up of patients randomized to atrial (AAI) (n=110) or ventricular (VVI) (n=115) pacing. Numbers below abscissa indicate number of patients in the two treatment groups. See text for statistical comparison between groups.
is shown in Fig 9. At last follow-up, there was no difference in systolic or diastolic blood pressure between the atrial and ventricular groups (151±26 mm Hg in the ventricular group versus 151±23 mm Hg in the atrial group, P=.93, and 83±14 mm Hg in the ventricular group versus 84±12 mm Hg in the atrial group, P=.92).

Retrograde Conduction
Retrograde conduction was present in 63 patients in the ventricular group. Left atrial diameter increased both in the group with retrograde conduction (from 35±7 to 41±7 mm, P<.0005) and in the group without retrograde conduction (from 34±7 to 40±7 mm, P<.0005), but there was no difference comparing the two groups (P=.94). LVESD increased significantly in the group with retrograde conduction (from 31±8 to 40±7 mm, P=.012), whereas the increase was insignificant in the group without retrograde conduction (from 31.6±9 to 32.3±7 mm, P=.15), but there was no significant difference when comparing the two groups (P=.53). There was no change in LVEDD in either group. The diastolic blood pressure at last follow-up was significantly higher in the group with retrograde conduction than in the group without retrograde conduction (86±15 versus 80±11 mm Hg, P=.026), whereas there was no difference in systolic blood pressure (151±29 versus 150±21 mm Hg, P=.74). There was no difference in NYHA class at last follow-up between the patients with retrograde conduction (NYHA I/II/III/IV: 37/23/1/0) and the patients without retrograde conduction (NYHA I/II/III/IV: 28/21/3/0), P=.44, χ² test. The proportion of patients with dyspnea at last follow-up was slightly higher in the group with retrograde conduction (28%) than in the group without retrograde conduction (19%), but the difference was not statistically significant (P=.28). There was no difference in proportion of patients with crural edema at last follow-up between the groups with and without retrograde conduction (18% versus 19%, P=.65).

Discussion
The present study shows that after long-term follow-up of patients with sick sinus syndrome treated with either ventric-
retrospective studies. In our previous short-term follow-up study (mean follow-up, 3.3 years), there was no significant difference in degree of heart failure between the two groups. This indicates that although ventricular pacing is tolerated for some years, long-term ventricular pacing is associated with an increased risk of heart failure. In the present study, ventricular pacing was associated with a decrease in LVFS, which reflects deterioration of the left ventricular diastolic function could also be involved as found in

<table>
<thead>
<tr>
<th>TABLE 3. Echocardiographic Changes During Follow-up</th>
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<tbody>
<tr>
<td>No. of Patients Examined</td>
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<tr>
<td>--------------------------</td>
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<tr>
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<tr>
<td><strong>Left atrial diameter, mm</strong></td>
</tr>
<tr>
<td>All patients</td>
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<tr>
<td>Patients without AF during follow-up</td>
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<tr>
<td>Patients without AF at last follow-up</td>
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<td>Patients without chronic AF</td>
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<tr>
<td>Patients with chronic AF</td>
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<td><strong>Left ventricular end-systolic diameter, mm</strong></td>
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<td>Patients without AF during follow-up</td>
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<td><strong>Left ventricular end-diastolic diameter, mm</strong></td>
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<td>Patients with chronic AF</td>
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</tbody>
</table>

AAI indicates atrial pacing; VVI, ventricular pacing; and AF, atrial fibrillation.

Comparing values "before" with values at "last follow-up" within the AAI or the VVI group: *P<.05, †P<.01, ‡P<.001. The last column—AAI vs VVI—shows probability values comparing differences from "before" to "last follow-up" between the AAI group and the VVI group.

Figure 5. Left atrial diameter measured by M-mode echocardiography during follow-up of patients randomized to atrial (AAI) (n=110) or ventricular (VVI) (n=115) pacing. Numbers below abscissa indicate number of patients examined in the two treatment groups. See text for statistical comparison between groups.

Figure 6. Left ventricular end-systolic diameter (LVESD) measured by M-mode echocardiography during follow-up of patients randomized to atrial (AAI) (n=110) or ventricular (VVI) (n=115) pacing. Numbers below abscissa indicate number of patients examined in the two treatment groups. See text for statistical comparison between groups.
other studies\textsuperscript{5,15–17} but left ventricular diastolic function has not been assessed in the current study. In a large, retrospective study performed by Sgarbossa et al\textsuperscript{18} ventricular pacing was not found to be associated with an increased risk of congestive heart failure compared with physiological pacing. However, in the study by Sgarbossa et al, ventricular pacing (112 patients) was not compared with atrial pacing but with physiological pacing (374 patients with dual-chamber pacemakers and only 19 patients with atrial pacemakers). Thus in that study, most of the patients in the physiological group were implanted with a ventricular lead and stimulated very frequently in the right ventricle.\textsuperscript{19,20} The ventricular stimulation per se is potentially harmful to cardiac function,\textsuperscript{6–9} and even dual-chamber pacing might be associated with a similar risk of congestive heart failure as observed in the current study for ventricular pacing due to stimulation of the ventricular myocardium in both pacing modes.\textsuperscript{6,9} Only single-chamber atrial pacing is without any artificial stimulation of the ventricles. Therefore, the conclusion reached in the retrospective study by Sgarbossa et al\textsuperscript{18} that there is no difference in incidence of congestive heart failure between ventricular and physiological pacing (dual-chamber pacemakers) may very well be correct. However, this conclusion regarding physiological dual-chamber pacing cannot automatically be extended to be valid also for atrial pacing.

The mechanisms leading to heart failure during ventricular pacing are not known, but changes in myocardial blood flow causing functional ischemia,\textsuperscript{6,9} altered left myocardial thickness,\textsuperscript{8} and myocardial cellular changes\textsuperscript{7,21} have been demonstrated during chronic pacing in the right ventricular apex.

In the current study, mortality as the result of congestive heart failure was higher in the ventricular than in the atrial group, but the number of congestive heart failure deaths was low, and the difference was not statistically significant. This is in accordance with observational findings.\textsuperscript{2,3}

**Left Atrial Diameter**

The left atrial diameter increased in both treatment groups during long-term follow-up, but the increase was significantly higher in the ventricular group compared with the atrial group. This confirms findings in our short-term follow-up study\textsuperscript{13} and in two minor observational studies.\textsuperscript{11,22} Atrial enlargement was not only a consequence of atrial fibrillation, as has been reported in patients without a pacemaker,\textsuperscript{23,24} because atrial dilatation was seen also in patients without atrial fibrillation. The cause of the marked additional left atrial dilatation during ventricular pacing is not known. Stimulation of the right ventricular apex during ventricular pacing results in an altered activation sequence of the ventricles and consequently a change in the ventricular mechanical contraction pattern.\textsuperscript{6,17,25,26} This has been found to be associated with a decrease in the left ventricular systolic function\textsuperscript{17,25} and diastolic function\textsuperscript{17} and an increase in both the right atrial pressure and the pulmonary capillary wedge pressure,\textsuperscript{25,27} which might be involved in the left atrial dilatation.\textsuperscript{26} The lack of atrioventricular synchrony in single-chamber ventricular pacing could be associated with an increased risk of mitral regurgitation,\textsuperscript{12,29} which also leads to left atrial dilatation. In the current study we found no evidence that the presence of retrograde atrioventricular conduction was involved in the pathogenesis of left atrial dilatation during ventricular pacing. The increase in the left atrial diameter observed in both the atrial and the ventric-
ular group might be explained partly by increasing age but could also represent a feature in the natural evolution of the sick sinus syndrome disease, which, in part, could explain the increased risk of arterial thromboembolism and atrial fibrillation observed in this disease.

Left Ventricular Dimensions and LVFS
During long-term follow-up, we observed a decrease in LVFS in the ventricular group, whereas there was no significant change in the atrial group. The changes were associated with an increase in mean LVESD in the ventricular group without simultaneous changes in mean LVEDD. A decrease in LVFS during ventricular pacing was also described in a prospective study of 13 patients followed for 6 months and is in accordance with the acute decrease in left ventricular systolic function observed during ventricular (VVI) pacing in several experimental studies. The decrease in mean LVFS could be explained by the asynchronous ventricular contraction caused by the altered activation sequence of the ventricles due to stimulation of the right ventricular apex. The decrease in LVFS is probably the major cause of the increased risk of heart failure observed in the ventricular group in the present study.

In one previous observational study, no difference in LVESD was found after 5.3 years VVI pacing as compared with AAI/DDD pacing. Similarly, in two prospective short-term follow-up studies, no difference in LVESD was found during (1) 3 weeks of VVI pacing as compared with VDD pacing and (2) 6 months of VVIR pacing comparing preoperative and follow-up values. These findings are in contrast with the present results.

In the observational study by Mohan et al, LVEDD was higher after 5.3 years VVI pacing than after AAI/DDD pacing, whereas in the two prospective short-term follow-up studies, LVEDD decreased during 3 weeks of VVI pacing as compared with VDD pacing and during 6 months of VVIR pacing, respectively. These conflicting results are all in contrast to the present findings and are probably caused by the small number of patients and echocardiographic examinations included in these studies as compared with the current study.

Blood Pressure
In the current study, there was no difference in systolic or diastolic blood pressure between the two groups during long-term follow-up. Thus blood pressure during long-term follow-up of patients with sick sinus syndrome is unaffected by mode of pacing.

Retrograde Conduction
The presence of perioperative retrograde conduction in the patients treated with ventricular pacing was not associated with an increase in left atrial diameter or left ventricular diameters, or a decrease in LVFS as compared with the absence of retrograde conduction. Nor was retrograde conduction associated with a lower blood pressure, occurrence of dyspnea, or higher degree of heart failure, which could be indicative for presence of the pacemaker syndrome. Previously, retrograde conduction during ventricular pacing was believed to be associated with the pacemaker syndrome and with the development of congestive heart failure, but in the current study we found no such associations. In accordance with our results, one previous prospective, long-term follow-up study found no difference in the incidence of congestive heart failure during VVI pacing with and without retrograde conduction, respectively. Therefore, no clear evidence exists that retrograde conduction causes heart failure. It might instead be the ventricular stimulation per se that is most important.

Study Limitations
The physical examination, NYHA classification, and M-mode echocardiography at ambulatory follow-up was not done blinded with regard to the randomization. This introduces a possible observer bias in these parameters. The NYHA class was difficult to define precisely in some of our patients, many of whom were very old and immobile, but the significant higher dose of diuretics in the ventricular group during long-term follow-up indicates that ventricular pacing was really associated with a higher incidence of heart failure.

The echocardiographic measurements were done by many different physicians otherwise not involved in the study. Although the physicians were all experienced in echocardiography, the many investigators might increase the dispersion of these measurements due to a larger interobserver variation. On the other hand, no single physician (biased or unbiased) had sufficient influence to change the overall results in any direction. Only M-mode echocardiography was performed. Two-dimensional echocardiography would probably have added more information regarding left atrial and left ventricular volumes and function. The subgroup analyses performed were not anticipated at the time of design of the study but were decided post hoc and therefore the study was not necessarily powered to do these subgroup analyses. This should be taken into account when the results of the subgroup analyses are interpreted.

In the current study, the pacemaker event counters were not checked regularly. Thus it was not possible to correlate number of ventricular or atrial stimulated beats versus sensed beats to the changes in left atrial and left ventricular dimensions, LVFS, or occurrence of heart failure.

Conclusions
During long-term follow-up, ventricular pacing is associated with a higher incidence of congestive heart failure and consumption of diuretics than atrial pacing. This is accompanied by a decrease in left ventricular fractional shortening and an increased dilatation of the left atrium in the ventricular paced patients. Consequently, patients with sick sinus syndrome and intact atrioventricular conduction should be treated with atrial pacing instead of ventricular pacing to avoid development or worsening of congestive heart failure, decrease in left ventricular fractional shortening, and increase in left atrial diameter.

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References


Heart Failure and Echocardiographic Changes During Long-term Follow-up of Patients With Sick Sinus Syndrome Randomized to Single-Chamber Atrial or Ventricular Pacing

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