Atrioventricular Conduction During Long-Term Follow-Up of Patients With Sick Sinus Syndrome

Henning Rud Andersen, MD, DMSc; Jens Cosedis Nielsen, MD; Poul Erik Bloch Thomsen, MD, DMSc; Leif Thuesen, MD, DMSc; Thomas Vesterlund, MD; Anders Kirstein Pedersen, MD, DMSc; Peter Thomas Mortensen, MD

Background—It has been claimed that patients with sick sinus syndrome have an increased risk of developing AV block, but this has never been assessed prospectively. The aim of the present study was to evaluate in a prospective trial AV conduction during the long-term follow-up of patients with sick sinus syndrome.

Methods—Two hundred twenty-five consecutive patients with sick sinus syndrome and intact AV conduction were randomized to undergo single-chamber atrial pacing (110 patients) or single-chamber ventricular pacing (115 patients). Follow-up after 3 months and then yearly included measurement of the PQ interval and, in patients with atrial pacemakers, determination of the atrial stimulus–Q intervals at pacing rates of 100 and 120 bpm. The occurrence of AV block in the atrial group was recorded. During follow-up (mean, 5.5±2.4 years), there was no change in PQ interval in either group and no change in atrial stimulus–Q intervals or Wenckebach block point in the atrial group. Four of 110 patients in the atrial group developed grade 2 to 3 AV block that required upgrading of the pacemaker (0.6% per year). Two of these 4 patients had right bundle-branch block at pacemaker implantation.

Conclusions—AV conduction, estimated as PQ interval and atrial stimulus–Q interval at atrial pacing rates of 100 and 120 bpm and the Wenckebach block point, remains stable during long-term follow-up. Thus, treatment with single-chamber atrial pacing is safe and can be recommended to patients with sick sinus syndrome without bundle-branch block.

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Key Words: sick sinus syndrome • pacing • atrioventricular block • follow-up studies

In prospective randomized evaluation, single-chamber atrial pacing is superior to single-chamber ventricular pacing in patients with sick sinus syndrome due to lower overall and cardiovascular mortality rates, less atrial fibrillation, less arterial thromboembolism, and less heart failure. Therefore, it has been recommended that such patients be treated with single-chamber atrial pacing. In retrospective analyses, it has been claimed that patients with sick sinus syndrome have an increased risk of developing AV block after the implantation of an atrial pacemaker, but until now this risk has never been assessed prospectively. Based on the claimed risk reported in retrospective analyses, it is frequently recommended in the literature that a ventricular pacemaker lead also be implanted into these patients. Therefore, when a physiological pacemaker system is selected for patients with sick sinus syndrome, a dual-chamber pacing system is most often implanted instead of a single-chamber atrial pacing system. This strategy is chosen despite the lack of prospective data to document the risk of AV block and despite the lack of prospective trials to document the superiority of dual-chamber pacing over single-chamber atrial or ventricular pacing. The aim of the present prospective study was to evaluate the AV conduction and the risk of developing AV block during long-term follow-up of patients with sick sinus syndrome.

Methods

The study design has been described in detail previously. The trial was conducted as a single-center study at Skejby University Hospital. All patients who were referred to receive treatment with their first pacemaker during the recruitment period of May 15, 1988, through December 31, 1991, were evaluated for randomization. The patients were asked to participate in the trial if the inclusion criteria (symptomatic bradycardia of <50 bpm or symptomatic QRS pauses of >2 seconds) and none of the exclusion criteria were met. After giving informed consent, patients were randomized before implantation to receive treatment with single-chamber atrial or ventricular pacing stratified in blocks of 10-year age groups. Medical history, physical examination, 12-lead standard ECG, and echocardiography were done before implantation. Patients were excluded from randomization who had grade 1 AV block defined as a PQ interval of >0.22 second in patients ≤70 years old and >0.26 second in patients >70 years old, grade 2 or 3 AV block, or bifascicular or complete left bundle-branch block. Right bundle-branch block or fascicular block was not considered a contraindication for inclusion in the study. Patients underwent an atrial pacing test during pacemaker implantation at 100 and 120 bpm; 1:1 atrioventricular conduction at 100 bpm was required for an atrial pacemaker to be implanted. If second-degree AV block occurred at a pacing rate of <100 bpm, the lead was implanted in the right ventricle. PQ interval...
during sinus rhythm and atrial stimulus–Q interval at atrial pacing rates of 100 bpm (Stim-Q100) and 120 bpm (Stim-Q120) were determined at pacemaker implantation in all patients. Medical treatment was not discontinued before implantation.

Follow-up visits occurred after 3 and 12 months and subsequently once a year. At each follow-up visit, PQ interval at sinus rhythm, Stim-Q100, and Stim-Q120 were measured as parameters of AV conduction in patients with atrial pacemakers (and without atrial fibrillation). In patients with ventricular pacemakers, PQ interval was measured during sinus rhythm. Furthermore, the follow-up visits included physical examination, 12-lead ECG, and pacemaker check-up. Follow-up evaluation was not blinded.

Termination of Study
In 1995, it was decided that the last patient included should be followed up for 5 years before final data analysis, which was determined to be performed on December 31, 1996.

Ethics
The study was approved by the National Danish Ethical Committee and was conducted in accordance with the rules of the Helsinki Declaration.

Analysis
Power calculations were done before start of the study and have been reported previously. All statistical analyses were done according on an intention-to-treat basis. Continuous variables are expressed as mean (SD) values. Treatment groups were compared with the use of χ² test (2-tailed) for discrete variables and of 2-tailed Student’s t test or paired t test for continuous variables. Changes in parameters of AV conduction 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) with the use of a paired t test. Changes between groups were evaluated by comparing mean values at the time of implantation, mean values at the time of last follow-up, and mean change from pacemaker implantation to last follow-up with the use of a Student’s t test. To reduce the number of statistical tests, intergroup comparisons were not done repeatedly at several time points after implantation—only at the last follow-up or on change from implantation to last follow-up. A P value of <0.05 was deemed significant. SPSS for Windows was used for statistical analysis.

Results
A total of 225 patients (142 women and 83 men; mean age, 76 years; age range, 50 to 92 years) were randomized to undergo atrial pacing (110 patients) or ventricular pacing (115 patients), respectively. Baseline parameters in the 2 groups have been reported previously and were equal between groups. Baseline parameters of AV conduction are shown in Table 1. A total of 1294 ambulatory visits were performed during the study period, and no patients were lost to follow-up. One patient, who emigrated after the 1-year follow-up visit, underwent subsequent follow-up by telephone interview, but no ECG recordings were accessible for this patient. Mean follow-up until death or end of study was 5.5 (2.4) years for the total study population and equal in the atrial (5.7 [2.3] years) and ventricular (5.3 [2.5] years) groups.

Ninety-four patients (85%) randomized to undergo atrial pacing were treated as randomized during follow-up. Of the remaining 16 patients randomized to undergo atrial pacing, ventricular leads were initially implanted in 6 patients; the reasons were Wenckebach block at <100 bpm on the atrial pacing test (1 patient), atrial fibrillation during implantation (2 patients), intra-atrial electrogram of <2.5 mV (2 patients), and high stimulation threshold (1 patient). After implantation, 1 patient developed a high stimulation threshold on the first postoperative day and instead had the lead implanted in the right ventricle. During follow-up, 4 patients had ventricular leads implanted because of infection after 3 months (1 patient), lead fracture after 1 year (1 patient), isolation defect of a bipolar lead after 3 years (1 patient), and loss of atrial sensing after 6 years (1 patient). The physicians in charge of the repeat operations chose to implant ventricular leads instead of new atrial leads in these 4 patients, although no AV block was documented. In 1 patient with bradychyndrome, it was necessary to replace a defective pacemaker after 6 years. During pacemaker replacement, the patient had paroxysmal atrial fibrillation, and although the atrial lead was intact, the physician in charge of the operation chose to implant an additional ventricular lead and a new dual-chamber pacemaker. The pacemaker system was upgraded to a dual-chamber system in 4 patients because of AV block.

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

PQ Interval During Follow-Up
A total of 1515 investigational 12-lead ECGs were evaluated during the study (767 in the atrial group and 748 in the ventricular group). PQ intervals in the atrial and ventricular groups are shown in Figure 1. At inclusion in the study, there was no difference in PQ interval between the 2 groups (Table 1). Mean follow-up time of PQ interval was significantly longer in the atrial group (4.7 [2.3] years) than in the ventricular group (3.9 [2.2] years) (P=0.006, t test) because more patients in the ventricular group developed atrial fibrillation. In the ventricular group, PQ interval increased during follow-up from 185 (32) ms at implantation to 199 (37) ms at last follow-up in patients with sinus rhythm (109 patients) (P<0.001, paired t test). In the atrial group, PQ interval changed from 190 (30) to 191(33) ms (105 patients) (P=0.65,
Atrial Stimulus–Q Intervals and Wenckebach Block Point During Follow-Up

Stim-Q100 and Stim-Q120 during follow-up in the atrial group are shown in Figure 2. The mean follow-up time of Stim-Q100 was 4.5 (2.4) years, and the mean follow-up time of Stim-Q120 was 4.4 (2.4) years. Stim-Q100 increased a mean of 1 (42) ms ($P=0.82$, paired $t$ test) to 245 (48) ms (100 patients) from implantation to last follow-up, and Stim-Q120 increased a mean of 9 (50) ms ($P=0.10$, paired $t$ test) to 267 (54) ms (93 patients) from implantation to last follow-up.

Development of AV Block in the Atrial Group

The pacemaker system was upgraded to a dual-chamber system in 4 patients because of AV block (Table 2). One patient developed third-degree AV block with Syncope 7 months after implantation during acute pneumonia and was upgraded, but there was a normal PQ interval during the remaining 5 years of follow-up (Stim-Q100 and Stim-Q120 were not measured during follow-up after upgrading in this case), and the patient was alive at the end of the study. In 1 patient, the Wenckebach block point decreased asymptotically from the interval 100 to 119 bpm to 80 bpm at 1.5 years after implantation because of treatment with increasing doses of $\beta$-blocker and calcium antagonist that were necessitated by progression of angina pectoris, and therefore the pacemaker was upgraded to a dual-chamber system. This patient died 7 years after primary pacemaker implantation from noncardiac causes with a well-functioning dual-chamber pacemaker. One patient developed second-degree AV block accompanied by dyspnea during treatment with a tetracyclic antidepressive drug (maprotiline) 3 years after implantation and died from abdominal cancer 1.5 months after upgrade of the pacemaker. The last patient developed second-degree AV block with syncope after 5.8 years. This patient was still alive at the end of the study. Two of the 4 patients who developed AV block had right bundle-branch block on their ECG at
the time of randomization. The development of AV block could not have been predicted by a decrease in the Wenckebach block point or prolongation of PQ interval or atrial stimulus–Q intervals during follow-up in any of the 4 patients (Table 2). The incidence of AV block could not be assessed in the ventricular group.

Influence of Medication During Follow-Up

The number of patients in the atrial group who were treated with drugs that could influence AV conduction are reported in Table 3. At the time of implantation, 32 of 110 patients were treated with ≥1 of these drugs, whereas at the last follow-up, 46 of 109 patients (1 patient in the atrial group died before the first follow-up visit) were receiving ≥1 of these drugs (χ² test=4.1, df=1, P=0.046). Eight of 16 patients in whom the Wenckebach block point was lower at the last follow-up than at inclusion were treated with drugs that could influence AV conduction.

Among the 34 patients in the atrial group in whom the Wenckebach block point changed during follow-up (Figure 3), the change was associated with an alteration in medication in 16 patients. In 12 of these patients, the change in the Wenckebach block point from ≥120 bpm to the interval 110 to 119 bpm was associated with the patient starting to receive a β-blocker (4 patients), a calcium channel blocker (3 patients), digoxin (3 patients), or an antiarrhythmic drug (2 patients). In 2 patients, the Wenckebach block point increased from the interval 110 to 119 bpm to ≥120 bpm at the same time as the patient stopped receiving digoxin and a β-blocker plus an antiarrhythmic drug, respectively. In 2 patients, the Wenckebach block point increased from the interval 100 to

**Table 2. AV Conduction in Patients Developing AV Block**

<table>
<thead>
<tr>
<th>No.</th>
<th>Age, y</th>
<th>Sex, M/F</th>
<th>PQ, ms</th>
<th>Stim-Q100, ms</th>
<th>Stim-Q120, ms</th>
<th>BBB</th>
<th>Time</th>
<th>PQ, ms</th>
<th>Stim-Q100, ms</th>
<th>Stim-Q120, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>M</td>
<td>180</td>
<td>210</td>
<td>220</td>
<td>RBBB</td>
<td>3 mo</td>
<td>180</td>
<td>210</td>
<td>260</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>M</td>
<td>240</td>
<td>340</td>
<td>…</td>
<td>…</td>
<td>1 y</td>
<td>N</td>
<td>320</td>
<td>…</td>
</tr>
<tr>
<td>3</td>
<td>79</td>
<td>F</td>
<td>200</td>
<td>230</td>
<td>240</td>
<td>RBBB</td>
<td>2 y</td>
<td>200</td>
<td>230</td>
<td>280</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>M</td>
<td>160</td>
<td>220</td>
<td>230</td>
<td>…</td>
<td>5 y</td>
<td>190</td>
<td>180</td>
<td>190</td>
</tr>
</tbody>
</table>

Age indicates age at time of inclusion in the study; PQ, PQ interval; BBB, bundle-branch block; RBBB, right bundle-branch block; and N, no spontaneous sinus rhythm.

*In patient 1, Stim-Q100 and Stim-Q120 were not measured during follow-up after upgrading of the pacemaker to a dual-chamber system.*

†Patient 4 developed AV block after 5.8 years, and later he was seen at only 1 ambulatory follow-up visit, 7 years after pacemaker implantation.
119 bpm to ≥120 bpm at the same time as the patient started receiving calcium channel blocker and digoxin, respectively.

Discussion

The present study documents that in patients with sick sinus syndrome, AV conduction estimated as PQ interval and atrial stimulus–Q interval at atrial pacing rates of 100 and 120 bpm remains stable during long-term follow-up and AV block occurs at a rate of only 0.6% per year.

The 0.6% annual incidence rate of AV block requiring upgrade of the pacemaker system found in the present prospective study confirms observational findings; most studies have reported an annual incidence rate of significant AV block of <1%. In a literature survey of 28 studies of atrial pacing, Rosenqvist and Obel reported an annual incidence rate of second- and third-degree AV block of 0.6% per year. Similarly, in an observational study performed by Bernstein et al of 187 patients, an 0.9% annual incidence rate of second- and third-degree AV block was reported, and Witte et al reported first- to third-degree AV block or fascicular block in 11 of 261 patients (0.8% per year). However, a higher incidence of high-degree AV block (1.8% per year) was reported by Brandt et al, probably because more patients with bundle-branch block and bifascicular block were included in their study.

As indicated by the results of the present study and several observational studies, the presence of bundle-branch block at the time of implantation is associated with an increased risk of the development of AV block, whereas isolated fascicular block is not associated with such a risk. Thus, the present study confirms that single-chamber atrial pacing should be avoided in patients with right bundle-branch block, as is the case in patients with left bundle-branch block, whereas it can still be used in patients with isolated fascicular block. Patients with right or left bundle-branch block should be treated with a dual-chamber pacemaker.

The present trial is the first prospective study to document that PQ interval and atrial stimulus–Q interval at atrial pacing rates of 100 and 120 bpm remain stable during long-term follow-up in patients with sick sinus syndrome. Criteria used for the selection of patients for inclusion in the present study were PQ interval of ≤0.22 second in patients ≤70 years old and PQ interval of ≤0.26 second in patients >70 years old; in addition, 1:1 AV conduction at an atrial pacing rate of 100 bpm at implantation was required for the implantation of an atrial pacemaker. Thus, the present trial also documents that these criteria could be used safely in the selection of patients for single-chamber atrial pacing among those with sick sinus syndrome. Most previous studies have used a Wenckebach point of <120 bpm or <130 bpm as a contraindication for single-chamber atrial pacing. However, as indicated by the present trial and by other studies, a Wenckebach block point of <120 or <130 bpm has a poor predictive value in identifying patients at risk for the development of high-degree AV block. Therefore, a Wenckebach block point of ≥100 bpm, as used in the present trial, is sufficient to select patients for single-chamber atrial pacing.

In several patients in the present study, the Wenckebach block point changed 2, 3, or even 4 times during follow-up, with or without changes in medication. That demonstrates that the atrial stimulus–Q interval and Wenckebach block point undergo large spontaneous variations over time, probably influenced by physiological variables such as autonomous tone. This further illustrates that the Wenckebach block point measured at the time of implantation is a poor predictor for late deterioration of AV conduction.

In the present study, PQ interval increased slightly in the ventricular group but not in the atrial group during follow-up. The cause of prolongation of the PQ interval in the ventricularly paced patients is not known, but it might be associated with the increased left atrial dilatation seen in this group. The enlarged atrium might result in a prolonged intra-atrial conduction time, which is reflected in the 12-lead ECG as a prolonged PQ interval.

In the atrial group, more patients were treated with antiarrhythmic agents by the last follow-up than at the time of pacemaker implantation. This probably reflects that many antiarrhythmic drugs which caused bradycardia were withdrawn prior to pacemaker implantation and introduced again after pacemaker implantation. However, despite the increase in the use of antiarrhythmic medication, AV conduction remained stable during follow-up.

Why should single-chamber atrial pacing be used instead of dual-chamber pacing? Dual-chamber pacing protects the patients in case of AV block or atrial fibrillation with bradycardia, whereas patients with atrial pacemakers require repeat operation with upgrade of the pacemaker if 1 of these situations occurs. However, very few patients with sick sinus syndrome and atrial pacemakers develop ventricular bradycardia and must be exposed to the risk of repeat operation. Some observational studies indicate that dual-chamber pacing is superior to single-chamber ventricular pacing in patients with sick sinus syndrome. On the contrary, the largest observational study that compared the use of dual-chamber pacing with ventricular pacing failed to demonstrate any differences in the rates of congestive heart failure or death between the 2 groups, which may indicate that ventricular stimulation caused by

---

TABLE 2. Continued

<table>
<thead>
<tr>
<th>Time</th>
<th>Type</th>
<th>Symptoms</th>
<th>Time</th>
<th>Stim-Q100, ms</th>
<th>Stim-Q120, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 mo</td>
<td>Grade 3</td>
<td>Syncope</td>
<td>5 y</td>
<td>180</td>
<td>...*</td>
</tr>
<tr>
<td>1.5 y</td>
<td>Grade 2</td>
<td>None</td>
<td>5 y</td>
<td>180</td>
<td>320</td>
</tr>
<tr>
<td>3 y</td>
<td>Grade 2</td>
<td>Dypsnea</td>
<td></td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>5.8 y</td>
<td>Grade 2</td>
<td>Syncope</td>
<td>7 y†</td>
<td>160</td>
<td>200</td>
</tr>
</tbody>
</table>
dual-chamber pacing has the same harmful effect on the heart as ventricular stimulation caused by single-lead ventricular pacing. In the prospective randomized PASE trial that compared dual-chamber pacing with single-chamber ventricular pacing, the 1-year incidence rates of death and stroke were less in the group treated with dual-chamber pacing, but the differences between groups were not significant. Thus, the beneficial effect of dual-chamber pacing versus ventricular pacing has not yet been documented in prospective trials, whereas it has been demonstrated that single-chamber atrial pacing is superior to single-chamber ventricular pacing. Therefore, based on prospective data, single-chamber atrial pacing should be considered the treatment of choice in patients with sick sinus syndrome and normal AV conduction.

Conclusions
AV conduction estimated as PQ interval and atrial stimulus–Q interval at atrial pacing rates of 100 and 120 bpm remains stable during long-term follow-up. Thus, treatment with single-chamber atrial pacing is safe and can be recommended for patients with sick sinus syndrome without bundle-branch block.

Acknowledgments
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