Chronic Atrial Fibrillation and Stroke in Paced Patients With Sick Sinus Syndrome

Relevance of Clinical Characteristics and Pacing Modalities

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Background. The goal of the report was to study the long-term incidence and the independent predictors for chronic atrial fibrillation and stroke in 507 paced patients with sick sinus syndrome, adjusting for differences in baseline clinical variables with multivariate analysis.

Methods and Results. From 1980 to 1989, we implanted 376 dual-chamber, 19 atrial, and 112 ventricular pacemakers to treat patients with sick sinus syndrome. After a maximum follow-up of 134 months (mean: 59±38 months for chronic atrial fibrillation, 65±37 months for stroke), actuarial incidence of chronic atrial fibrillation was 7% at 1 year, 16% at 5 years, and 28% at 10 years. Independent predictors for this event, from Cox’s proportional hazards model, were history of paroxysmal atrial fibrillation (P<.001; hazard ratio [HR]=16.84), use of antiarrhythmic drugs before pacemaker implant (P<.001; HR=2.25), ventricular pacing mode (P=.003; HR=1.98), age (P=.005; HR=1.03), and valvular heart disease (P=.008; HR=2.05). For patients with preimplant history of paroxysmal atrial fibrillation, independent predictors were prolonged episodes of paroxysmal atrial fibrillation (P<.001; HR=2.56), long history of paroxysmal atrial fibrillation (P=.004; HR=2.05), ventricular pacing mode (P=.025; HR=1.69), use of antiarrhythmic drugs before pacemaker implant (P=.024; HR=1.71), and age (P=.04; HR=1.02). Actuarial incidence of stroke was 3% at 1 year, 5% at 5 years, and 13% at 10 years. Independent predictors for stroke were history of cerebrovascular disease (P<.001; HR=5.22), ventricular pacing mode (P=.008; HR=2.61), and history of paroxysmal atrial fibrillation (P=.037; HR=2.81).

Conclusions. Development of chronic atrial fibrillation and stroke in paced patients with sick sinus syndrome are strongly determined by clinical variables and secondarily by the pacing modality. Ventricular pacing mode predicts chronic atrial fibrillation in patients with preimplant paroxysmal atrial fibrillation but not in those without it. (Circulation. 1993;88:1045-1053.)

KEY WORDS • atrial fibrillation • morbidity • pacing • sick sinus syndrome

Atrial fibrillation and embolic stroke are frequent and potentially grave complications of the sick sinus syndrome.1 Single-chamber ventricular pacing is efficacious in preventing bradycardia-related symptoms in patients with sick sinus syndrome,2 but it may not decrease morbidity from atrial fibrillation and stroke.4 Although no differences in long-term survival between ventricular pacing and physiological pacing have been demonstrated,5 atrial and dual-chamber pacemakers may be more efficient than ventricular pacemakers in improving quality of life and exercise tolerance6 and in reducing morbid event rates.7 However, no randomized study or multivariate analysis of a large retrospective cohort has addressed this issue. As sick sinus syndrome is the most frequent indication for permanent pacing, the investigation of the optimal pacing mode for these patients is important both clinically and economically.5

To address the impact of different pacing modalities on the incidence of chronic atrial fibrillation and stroke, we studied 507 consecutive patients who had an initial pacemaker implant for sick sinus syndrome.

Methods

Study Patients

We retrospectively analyzed all 507 adult patients (age of more than 18 years) with isolated sick sinus syndrome who received an initial pacemaker between January 1, 1980, and December 31, 1989. Sick sinus syndrome was defined by the presence of inappropriate, persistent sinus bradycardia (rate of less than 50 beats per minute), sinus pauses longer than 3 seconds, or sinoatrial block. Patients with established atrial fibrillation or with concomitant complete atrioventricular block or type II second-degree atrioventricular block at time of implant were excluded from the study. All patients were symptomatic, required bradycardia-producing drugs for treatment of tachyarrhythmias, or both. Baseline variables describing cardiac disease, concomitant diseases, and ECG and echocardiographic findings were analyzed (Table 1). History of cerebrovascular disease was defined as prior stroke, carotid endarterectomy, transient ischemic attack, or asymptomatic...
Table 1. Clinical Characteristics of Patients With Pacemakers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients</th>
<th>Physiological pacemakers</th>
<th>Ventricular pacemakers</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>66±12</td>
<td>65.5±11</td>
<td>67.4±12</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Male (n, %)</strong></td>
<td>308 (61)</td>
<td>248 (63)</td>
<td>60 (54)</td>
<td>NS</td>
</tr>
<tr>
<td><em><em>Structural heart disease</em> (n, %)</em>*</td>
<td>293 (58)</td>
<td>234 (59)</td>
<td>59 (53)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Coronary artery disease</strong></td>
<td>217 (43)</td>
<td>173 (44)</td>
<td>44 (39)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Valvular heart disease</strong></td>
<td>61 (12)</td>
<td>45 (11)</td>
<td>16 (14)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Cardiomyopathy</strong></td>
<td>35 (7)</td>
<td>29 (7)</td>
<td>6 (5)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Other†</strong></td>
<td>46 (9)</td>
<td>40 (10)</td>
<td>6 (5)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Concomitant diseases (n, %)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>217 (43)</td>
<td>161 (41)</td>
<td>56 (50)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>72 (14)</td>
<td>54 (14)</td>
<td>18 (16)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Cerebrovascular disease</strong></td>
<td>101 (20)</td>
<td>69 (17)</td>
<td>32 (29)</td>
<td>.01</td>
</tr>
<tr>
<td><strong>Peripheral vascular disease</strong></td>
<td>45 (9)</td>
<td>29 (7)</td>
<td>16 (14)</td>
<td>.03</td>
</tr>
<tr>
<td><strong>Electrocardiographic findings (n, %)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bundle branch block</strong></td>
<td>77 (15)</td>
<td>59 (15)</td>
<td>18 (17)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Paroxysmal atrial tachyarrhythmia</strong></td>
<td>375 (74)</td>
<td>298 (74)</td>
<td>77 (69)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Long history of PAF (&gt;5 y)</strong></td>
<td>61 (12)</td>
<td>46 (12)</td>
<td>15 (13)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Prolonged episodes of PAF (&gt;1 h)</strong></td>
<td>120 (24)</td>
<td>92 (24)</td>
<td>28 (25)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Complex ventricular arrhythmia</strong></td>
<td>162 (32)</td>
<td>136 (34)</td>
<td>26 (23)</td>
<td>.03</td>
</tr>
<tr>
<td><strong>Medication (n, %)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Preimplant antiarrhythmic drugs</strong></td>
<td>89 (18)</td>
<td>69 (17)</td>
<td>20 (18)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Preimplant warfarin</strong></td>
<td>42 (8)</td>
<td>31 (8)</td>
<td>11 (10)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Antiarrhythmic drugs at discharge</strong></td>
<td>152 (30)</td>
<td>125 (32)</td>
<td>27 (24)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Warfarin at discharge</strong></td>
<td>43 (8)</td>
<td>33 (8)</td>
<td>10 (9)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Left ventricular dysfunction† (n, %)</strong></td>
<td>137 (27)</td>
<td>112 (28)</td>
<td>25 (22)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Mild impairment</strong></td>
<td>65 (17)</td>
<td>53 (13)</td>
<td>12 (11)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Moderate impairment</strong></td>
<td>45 (12)</td>
<td>34 (9)</td>
<td>11 (10)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Severe impairment</strong></td>
<td>27 (7)</td>
<td>25 (6)</td>
<td>2 (2)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Left atrial enlargement (&gt;42 mm)‡</strong></td>
<td>117 (48)</td>
<td>92 (23)</td>
<td>25 (22)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Preimplant DC cardioversion (n, %)</strong></td>
<td>24 (5)</td>
<td>18 (5)</td>
<td>6 (5)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Mean lower rate limit at discharge</strong></td>
<td>64±9</td>
<td>64.3±9</td>
<td>63.8±8</td>
<td>NS</td>
</tr>
</tbody>
</table>

PAF indicates paroxysmal atrial fibrillation.
*Some patients had more than one cardiac disease.
†Mitral valve prolapse and congenital heart disease.
‡n=383.
§n=245.

Carotid stenosis (more than 50%) documented by Doppler or angiography. The history and clinical characteristics of preimplant paroxysmal atrial fibrillation were scrutinized intensively. Duration (in months) from onset of attacks of documented paroxysmal atrial fibrillation was assessed carefully for each patient. The range varied widely from 1 to 485 months. Analysis was performed by dichotomizing the population with a history of paroxysmal atrial fibrillation of less than or more than 5 years. From the information available on Holter recordings, taped telemetry strips, and self-assessment by symptomatic patients, the duration of the longest episode of atrial fibrillation was further quantified as lasting less or more than 1 hour. The eventual need for electrical cardioversion and chronic treatment with antiarrhythmic drugs also was considered (Table 1).

In a subgroup of patients with echocardiogram (n=245; 48%), left atrial size was analyzed; similarly, left ventricular function was available from contrast ventriculography (60%), radionuclide ventriculogram (5%), or echocardiogram (34%) in 383 patients (75.5%). In this subgroup, left ventricular function was analyzed as ejection fraction, fractional shortening, or qualitative assessment as mild, moderate, or severe dysfunction.

Selection of the pacing mode was not randomized but based on the attending physician's judgment. Units implanted were ventricular in 112 patients (22%; VVI and VVIR), atrial in 19 patients (4%; AAIR and AAI), and dual-chamber in 376 (74%; DVI, DDI, DDIR, DDR, and DDD). Atrial and dual-chamber pacemakers were defined as "physiological pacing" and compared with ventricular pacemakers. Due to technological improvements during the time frame of the study, year of implantation was the strongest determinant of type of pacemaker, with a progressive increase in the number of dual-chamber pacemakers. Patients with physiological and ventricular pacemakers were similar regarding most of the variables analyzed, except for cerebrovascular and peripheral vascular disease (more prevalent in patients with ventricular pacemakers) and complex ventricular arrhythmia (more prevalent in pa-
patients with physiological pacemakers) (Table 1). Only 31 of the devices (6%) had sensors to provide rate responsiveness, too few to justify a separate statistical analysis.

**Follow-up**

Two end points—"chronic atrial fibrillation" and "stroke"—were independently analyzed in this study. Because our patients had periodic assessment of their cardiac rhythm during pacemaker clinic visits, Holter monitoring sessions, and routine transtelephonic ECG transmissions, we chose a rather tight definition of "chronic atrial fibrillation." Chronic atrial fibrillation was defined as atrial fibrillation present in two ECGs or Holter strips obtained in a period of 3 to 4 months, with no interim documented sinus rhythm or further evidence of sinus rhythm until the end of the study or the patient's death. Stroke was defined as sudden development of permanent focal neurological deficit after which a clinical evaluation and/or a brain computed tomography (CT) scan established a cerebrovascular accident as the most probable cause. For both end points, follow-up began on the date of pacemaker implant and ended at time of death, occurrence of the end point (ie, chronic atrial fibrillation, stroke), or the end of the study (December 31, 1990). Survival status, underlying cardiac rhythm, generator or lead replacement, and eventual reprogramming of the initial pacing mode were ascertained through review of medical records, questionnaires completed by the patient's private physician, and telephone interviews with the patients or their families. Follow-up was complete in 499 patients (98.5%). The other eight patients were lost to follow-up after a mean of 56 months and had their follow-up censored at time of last contact.

**Statistical Analysis**

Continuous variables are presented as mean±1 SD. Actuarial curves for the incidence of chronic atrial fibrillation and stroke were calculated with the method of Kaplan and Meier. In both analyses, patients were censored at the time of death, development of the end point, or the end of the study.

Baseline variables were screened by the log-rank test to identify those associated with the end points. Multivariate regression analysis, performed with the Cox proportional-hazards model, was applied to all variables that had at least marginal univariate predictive value (P<.10). Variables with significant independent predictive value (P<.05) were identified. Hazard ratio is defined as the relative likelihood for developing a particular end point during the time frame of the study. As a history of preimplant atrial fibrillation was almost universal in patients who developed chronic atrial fibrillation, a second multivariate analysis was performed for patients with this variable. All statistical analyses were performed with an interactive statistical package.

To avoid cross-over-induced bias, pacemaker reprogramming during the follow-up was not considered, by performing an intention-to-treat analysis. Similarly, the effects of pacemaker lower rate limit, as well as effects of antiarrhythmic drugs and warfarin, were analyzed only regarding the discharge treatment. Frequent pacemaker reprogramming during follow-up in the first case and changes in treatment as well as patient non-compliance for drug therapy would limit the postdischarge predictive value of these variables.

**Results**

**Chronic Atrial Fibrillation**

For the end point "chronic atrial fibrillation," patients were followed for a maximum of 134 months (mean: 59±38 months), and 88 patients (17%) developed chronic atrial fibrillation. Actuarial incidence of chronic atrial fibrillation was 7% at 1 year, 16% at 5 years, and 28% at 10 years (Fig 1). Univariate predictors for atrial fibrillation were a prior history of paroxysmal atrial fibrillation (P<.001) (Fig 2), history of paroxysmal atrial fibrillation for more than 5 years (P<.001) (Fig 3), prolonged episodes of paroxysmal atrial fibrillation (more than 1 hour) (P<.001) (Fig 4), valvular heart disease (P<.001), use of preimplant antiarrhythmic drugs (P<.001), left atrial enlargement (P<.001), discharge on antiarrhythmic drugs (P<.005), DC cardioversion (P=.005), age (P=.002), and ventricular pacing mode (P=.01) (Fig 5). The variable "left ventricular dysfunction" did not reach statistical significance in the subgroup of patients for whom this information was available. Interestingly, the incidence of chronic atrial fibrillation was 0% during the first 5 years of follow-up for patients without a history of paroxysmal atrial fibrillation, for both pacing modalities (Fig 2).

**FIG 1.** Plot of incidence of chronic atrial fibrillation (CAF) and stroke (n=507). Fib indicates fibrillation.

**FIG 2.** Plot of comparative incidence of chronic atrial fibrillation (CAF) according to history of preimplant atrial fibrillation (n=507). PAF indicates paroxysmal atrial fibrillation.
Independent predictors for chronic atrial fibrillation are listed in Table 2. Patients without history of paroxysmal atrial fibrillation were not at particular risk for chronic atrial fibrillation (one patient in the physiological pacing group, after 51 months of follow-up; and another patient in the ventricular pacing group, at 99 months of follow-up) (Fig 6). Left atrial enlargement, a risk factor from univariate analysis, was not an independent predictor for chronic atrial fibrillation in the 245 patients with atrial size assessment.

Our incidence of preimplant paroxysmal atrial fibrillation (74%) was higher than in previously reported series, probably due to the high number of 24-hour monitoring sessions (Holter monitors and inpatient telemetry) available in our population. A multivariate analysis in the subgroup of patients with paroxysmal atrial fibrillation allowed us to identify the duration of both the history of paroxysmal atrial fibrillation and the longest clinical episode (Figs 3 and 4) as arrhythmia characteristics with independent prognostic value (Table 3).

During follow-up, only 9 patients (8%) who received a ventricular pacemaker were upgraded to a dual-chamber mode. At the same time, 63 patients (16.7%) with physiological pacemakers were reprogrammed to ventricular pacing because of loss of atrial capture (6 patients) or development of chronic atrial fibrillation (57 patients). Because all 57 patients with physiological pacemakers were reprogrammed as soon as the diagnosis of chronic atrial fibrillation was made, a statistical analysis censoring patients at the time of cross-over would not have resulted in different incidences of the arrhythmia.

Stroke
For this end point, maximum follow-up was 134 months (mean: 65±37 months), and 32 patients (6.3%) developed stroke. Actuarial incidence of stroke was 3% at 1 year, 5% at 5 years, and 13% at 10 years (Fig 1). Depending on their clinical repercussion, strokes were characterized as minor (10 patients; 2%), disabling (16 patients; 3%), and fatal (6 patients; 1%). In addition, transient ischemic attack was diagnosed in 16 patients (3%) but was not considered an end point. Stroke could not be precisely classified as “ischemic” versus “hemorrhagic” or “thrombotic” versus “embolic” (not all patients had a head CT scan, and detailed medical records were unavailable for some patients followed at other institutions). At the time of the stroke, 2 of 32 patients had developed chronic atrial fibrillation (6%); one patient established chronic atrial fibrillation on the same day, and 19 other patients only had history of preimplant paroxysmal atrial fibrillation. However, 7 of these patients developed chronic atrial fibrillation months or years after the stroke. Nine patients with stroke did not have documented preimplant paroxysmal atrial fibrillation and did not develop chronic atrial fibrillation.

<table>
<thead>
<tr>
<th>Variables</th>
<th>P</th>
<th>Hazard ratio</th>
<th>95% Confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of PAF</td>
<td>&lt; .001</td>
<td>16.84</td>
<td>4.10-68.7</td>
</tr>
<tr>
<td>Preimplant AD</td>
<td>&lt; .001</td>
<td>2.25</td>
<td>1.43-3.55</td>
</tr>
<tr>
<td>Ventricular pacing</td>
<td>.003</td>
<td>1.98</td>
<td>1.26-3.09</td>
</tr>
<tr>
<td>Age</td>
<td>.005</td>
<td>1.03</td>
<td>1.00-1.05</td>
</tr>
<tr>
<td>Valvular HD</td>
<td>.008</td>
<td>2.05</td>
<td>1.20-3.47</td>
</tr>
</tbody>
</table>

PAF indicates paroxysmal atrial fibrillation; AD, antiarrhythmic drugs; and HD, heart disease.
TABLE 3. Independent Predictors of Chronic Atrial Fibrillation in Patients with History of PAF

<table>
<thead>
<tr>
<th>Variables</th>
<th>P</th>
<th>Hazard ratio 95% Confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged episodes of PAF</td>
<td>&lt;.001</td>
<td>2.56 [1.65-3.97]</td>
</tr>
<tr>
<td>Long history of PAF</td>
<td>.004</td>
<td>2.05 [1.25-3.34]</td>
</tr>
<tr>
<td>Ventricular pacing</td>
<td>.025</td>
<td>1.69 [1.06-2.67]</td>
</tr>
<tr>
<td>Preimplant AD</td>
<td>.024</td>
<td>1.71 [1.07-2.73]</td>
</tr>
<tr>
<td>Age</td>
<td>.04</td>
<td>1.02 [1.00-1.04]</td>
</tr>
</tbody>
</table>

PAF indicates paroxysmal atrial fibrillation; and AD, antiarrhythmic drugs.

fibrillation during follow-up; 2 of them died because of stroke, and another 3 presented with episodes of paroxysmal atrial fibrillation during follow-up that could have been related to their strokes.

Stroke was associated with the following univariate factors: history of cerebrovascular disease (P<.001), ventricular pacing mode (P=.002), warfarin at discharge (P=.007), history of paroxysmal atrial fibrillation (P=.08), and valvular heart disease (P=.09). By multivariate analysis, history of cerebrovascular disease was the strongest predictor for stroke after pacemaker implant (P<.001; hazard ratio [HR]=5.22, 95% confidence intervals [CI], 2.57-10.58). Other independent predictors were ventricular pacing mode (P=.008; HR=2.61; 95% CI, 1.29-5.29) and history of paroxysmal atrial fibrillation (P=.037; HR=2.81; 95% CI, 1.06-7.42).

One patient had his pacemaker upgraded to DDD mode and two other patients crossed-over to VVI mode before having a stroke. Analysis performed by censoring follow-up at the time of cross-over showed results similar to the analysis using the intention-to-treat approach.

Discussion

Chronic Atrial Fibrillation

Chronic atrial fibrillation is part of the natural history of sick sinus syndrome. An age-related process of sinus node fibrosis results in the loss of functioning pacemaker cells and in inability to maintain sinus rhythm, with subsequent escape of subsidiary atrial pacemakers. Concomitant ultrastructural alterations in the atrium (not depending on the associated bradycardia) may favor reentry. Macroeentry has been confirmed as the mechanism for atrial fibrillation in humans by computerized intraoperative mapping. Thus, the transition between "paroxysmal" and "chronic" atrial fibrillation may reflect only a quantitative imbalance between the remaining healthy sinus cells (capable of electric automatic control of the atrium) and sick atrial myocardial cells. In our study, a prior history of paroxysmal atrial fibrillation was the strongest independent predictor of postimplant chronic atrial fibrillation; the risk was increased almost 17-fold. Furthermore, characteristics quantifying preimplant paroxysmal atrial fibrillation (long duration of episodes, long prior history) were important risk factors. Similarly, for unpaced populations undergoing cardioversion, the likelihood of converting to or maintaining sinus rhythm decreases inversely with the number of months of ongoing atrial fibrillation. After cardioversion, the best predictors of intractability with antiarrhythmic drugs are "number of previous episodes of atrial fibrillation" and "total arrhythmia duration." To our knowledge, however, the confounding influence of temporal features of pre-existent atrial fibrillation has not been analyzed by other investigators who reported on the effects of pacing modalities on atrial tachyarrhythmias.

Pacing Mode Effects on Atrial Fibrillation: Comparison With Previous Studies

In the absence of randomized trials, the impact of different pacing modalities on the development of chronic atrial fibrillation in patients with the sick sinus syndrome is difficult to determine. Previous studies have suggested that single-chamber ventricular pacing has a strong influence on the incidence of chronic atrial fibrillation and stroke. However, most of those studies lack methodological rigor and thus are subject to bias, such as may occur with incomplete follow-up mainly restricted to patients who regularly check their pacemakers at a particular hospital. Non-contemporary cohorts are another source of bias, as when ventricularly paced patients enter years earlier into retrospective studies and thus undergo longer follow-up periods than physiologically paced patients. When differences in baseline risk factors are not adjusted with multivariate techniques, a long-term survival similar to or better than that of the general population in patients with atrial pacing suggests selection bias. The same problem can be suspected when a higher noncardiac mortality in VVI-paced patients is reported, as well as in cases where ventricular pacemakers are mostly reserved for elderly patients, patients with more severe general diseases, or patients with a higher prevalence of paroxysmal atrial fibrillation. In one study, for example, a preimplant history of atrial fibrillation was present in 15% of AAI patients versus 36% of VVI patients (P<.01). Even in series in which the overall prevalence of preimplant atrial fibrillation is reported as similar for patients with ventricular and physiological pacemakers, it seems likely that paroxysmal atrial fibrillation was significantly more severe (in terms of years of history or duration of each paroxysm) in patients who received ventricular pace-

FIG 6. Plot of comparative incidence of chronic atrial fibrillation (CAF) according to preimplant history of paroxysmal atrial fibrillation (PAF) for each pacing modality (n=507).
Role of Antiarrhythmic Drugs

"Discharge on antiarrhythmic drugs" after pacemaker implant was a risk factor for chronic atrial fibrillation by univariate analysis. Despite this paradoxical association, a role of antiarrhythmic drug therapy in preventing or delaying the onset of atrial fibrillation in patients with sick sinus syndrome cannot be discarded; such effect has been demonstrated through controlled studies in other populations. Most likely, "discharge on antiarrhythmic drugs" acted as a marker for more severe, more prolonged, or more symptomatic episodes of atrial fibrillation. In fact, when the variable "discharge on antiarrhythmic drugs" was included into the multivariate model, it was displaced by the risk factors quantifying paroxysmal atrial fibrillation. Furthermore, "use of antiarrhythmic drugs" is an imprecise variable in many patients; actual patient compliance, eventual changes in dosages, interaction with other drugs, and addition or deletion of particular drugs cannot be measured in a retrospective study.

Role of Pacing Mode in the Development of Atrial Fibrillation

The exact mechanisms associating VVI pacing and the development of chronic atrial fibrillation in sick sinus syndrome are far from being understood. Single-chamber ventricular pacing may predispose to chronic atrial fibrillation, or, as an alternative, pacing in the atrium may prevent or delay the natural evolution of sick sinus syndrome to chronic atrial fibrillation. It has been suggested that loss of atrioventricular synchrony perpetuated by ventriculoatrial conduction—observed in ventricularly paced patients—leads to progressive increases in left atrial pressure and consequently to left atrial enlargement, thus predisposing to atrial fibrillation. However, prospective studies in patients with baseline normal atria have showed that atrial enlargement is a consequence of atrial fibrillation rather than its predisposing factor. Furthermore, if the adverse hemodynamic effects associated with atrioventricular asynchrony were the cause for chronic atrial fibrillation, it is not clear why our patients with ventricular pacemakers and without preimplant paroxysmal atrial fibrillation did not develop chronic atrial fibrillation as well. Another theory is that ventriculoatrial conduction predisposes to atrial fibrillation by modifying atrial refractoriness. However, in patients without structural heart disease, the atrial refractory periods do not appear to change with extreme alterations in the atrioventricular interval, nor is inducibility of atrial fibrillation different. Although these findings need to be confirmed in larger populations, they are helpful in explaining why ventricular pacing did not predispose our patients without preimplant paroxysmal atrial fibrillation to chronic atrial fibrillation. It seems that ventricular pacing may allow progression of paroxysmal atrial fibrillation into the chronic arrhythmia, rather than creating a new milieu leading to atrial fibrillation. Precise understanding of the mechanisms involved in the association between atrial fibrillation and ventricular pacing (if such an association is confirmed in a randomized study) may require complex computer-simulated models of sinoatrial nodal and atrial networks capable of reliably reproducing the true interactions between chronic ventricular pacing and the human sick sinus node.

It has been hypothesized that atrial pacing prevents paroxysmal atrial fibrillation from evolving to chronicity by eliminating sinus bradycardia with concomitant homogenization of atrial refractory periods. However, Luck and Engel found that patients with sick sinus syndrome vulnerable to atrial fibrillation did not consistently show increased dispersion of refractoriness and that abnormal refractoriness did not improve by eliminating bradycardia with atrial pacing, suggesting that in humans the role of heart rate as a determinant of dispersion of atrial refractoriness is negligible. Thus, it is more likely that the beneficial effect of atrial pacing resides in preventing reinitiation of the arrhythmia (once sinus rhythm is restored) by maintaining a high degree of exit block from all natural subsidiary atrial pacemakers. However, this antiarrhythmic effect should also be provided by retrograde ventriculoatrial conduction during VVI pacing. Nonetheless, only a "proarrhythmic" effect has been classically attributed to ventriculoatrial conduction in VVI pacing. Clearcut electrophysiological information simply is not available to completely explain the clinical benefit of atrial pacing in avoiding chronic atrial fibrillation, and further studies are needed.

Stroke

As in unpaced populations, stroke was predicted by history of cerebrovascular disease and history of paroxysmal atrial fibrillation. It is noteworthy that ventricular pacing mode remained an independent predictor for stroke after adjusting for paroxysmal atrial fibrillation. A statistically significant higher proportion of patients in the VVI group had history of cerebrovascular disease. Therefore, although ventricular pacing remained an independent predictor for stroke in the multivariate analysis, it cannot be ruled out that it may have acted as a surrogate for an unmeasured variable associated with stroke.

Role of Pacing Mode on Development of Stroke

In addition to the presence of atrial fibrillation as the mechanism linking ventricular pacing with embolic stroke, other factors must be involved in this association, because stroke was predicted by VVI pacing independent of atrial fibrillation. Alternative mechanisms may include the existence of ventriculoatrial conduction in the absence of atrial fibrillation, sublin-
tical "atrial hypervulnerability,"47 and short-lived, occult episodes of paroxysmal atrial fibrillation.48 Left ventricular dysfunction was not a risk factor for stroke in our population; left ventricular ejection fraction has been reported to remain stable with VVI pacing.49 It is unlikely that undocumented reductions in cardiac output resulting from VVI pacing can decrease carotid flow to the point of ischemia and thrombotic stroke. It should be noted that the relation between pacing mode and stroke will be less clinically relevant in the future; a widespread use of aspirin and warfarin in patients with paroxysmal atrial fibrillation is likely to markedly decrease the number of thrombotic and embolic events, regardless of the pacing modality.

Study Limitations

The possibility that ventricular pacing mode is only a surrogate for undetected confounding variables cannot be excluded. Although multivariate analysis is the best tool to analyze retrospective studies, it can be used only to adjust for the known imbalances between patient groups50; the potential effects of hidden variables remain possible.

Comparison with “chronic” atrial fibrillation rates reported in other studies should be cautious. No standard definition of “chronic” atrial fibrillation exists; there is tacit agreement that atrial fibrillation is “chronic” when no further return to sinus rhythm takes place. However, that is a “retrospective” diagnosis. The actual presence or absence of the arrhythmia is not always apparent from symptoms, and vice versa, some symptoms may be falsely ascribed to atrial fibrillation.51 In patients who are not aware of their episodes, “paroxysmal” atrial fibrillation may be undiagnosed, or the diagnosis of “chronic” atrial fibrillation may be delayed. Likewise, eventual unrecorded return to sinus rhythm after prolonged episodes of paroxysmal atrial fibrillation may lead to overdagnosis of “chronic” atrial fibrillation. When sinus rhythm is restored and maintained after cardioversion for several months after sustained atrial fibrillation, a confusing status from the semiotic point of view arises. The ECG manifestation of a paced rhythm may add further limitations to the identification of the underlying rhythm during the follow-up, particularly in pacemaker-dependent patients. These problems have led to the use of arbitrary definitions,7,21,52-54 which contributes to the wide interstudy variations regarding incidence of “chronic” atrial fibrillation in paced patients with sick sinus syndrome.7,25,55 The definition for “paroxysmal” atrial fibrillation, instead, is more uniform. Yet, paroxysmal atrial fibrillation may be an unrecognized portion of a patient’s past history. Thus, the number of hours of ambulatory and telemetry ECG recordings plays an essential role in characterizing the population a priori and in eliciting conclusions about the true incidence of “chronic” atrial fibrillation.

The relation between left atrial size and the development of chronic atrial fibrillation remains controversial.37,38,56-57 In our subgroup of patients with echocardiograms, left atrial enlargement was only an univariate predictor for chronic atrial fibrillation. However, it is possible that if atrial size had been available for all patients, left atrial enlargement may have been an independent risk factor.

Finally, the lack of precise information on the characteristics of the stroke events in our population raises the possibility of erroneously ascribing some of the cerebrovascular accidents to atrial fibrillation. At the same time, the low number of patients discharged on oral anticoagulation (mainly patients with previous stroke or mechanical valvular prosthesis) makes it difficult to extrapolate our data to current paced populations with sick sinus syndrome. An expected increased use of anticoagulants and antiplatelet agents in patients with paroxysmal atrial fibrillation will change the natural history in these populations, considerably limiting the stroke rates.

Need for a Randomized Study

Based on this and previous reports, the deleterious role of ventricular pacing modalities in development of atrial fibrillation is still not conclusive. It is noteworthy that dual-chamber pacing might not prevent the development of chronic atrial fibrillation in patients at greater risk (ie, with prolonged episodes or many years of paroxysmal atrial fibrillation). Hummel and colleagues58 and Gross and colleagues59 reported a relatively high incidence of loss of DDD pacing mode (15% and 18%, respectively) after much shorter follow-up periods than ours (mean: 30 and 33 months, respectively). An incomplete follow-up in the first study (only 61% patient records were available) raises the question of a higher true incidence of loss of atrial pacing in that population. Although these statistics include a few instances of reprogramming to VVI(R) mode because of atrial lead problems, their incidence of chronic atrial fibrillation was higher than ours. This is especially surprising because sick sinus syndrome was the less prevalent disease in their populations (45% and 38%), and all patients had dual-chamber pacemakers. Moreover, the existence of selection bias had been admitted by Gross and colleagues in a previous report60 as patients perceived as “inevitably” developing atrial fibrillation received a VVI pacemaker, eliminating the subgroup at the highest risk from the analysis.

A large, randomized study appears to be necessary to confirm the role of pacing modalities in the development of chronic atrial fibrillation.61 In our study, the incidence of this arrhythmia was extremely low for patients with no history of paroxysmal atrial fibrillation and did not appear to be influenced by the pacing modality during the first 10 years after implant. Thus, a randomized study probably should focus only on patients with preimplant paroxysmal atrial fibrillation. To increase the power of the study, a particular effort to enroll patients with “high-risk” paroxysmal atrial fibrillation (ie, with episodes lasting more than 1 hour or with a history of the arrhythmia for more than 5 years) should be made.62 This will allow the performance of a rigorous analysis of the cost-effectiveness and quality of life of dual-chamber versus single-chamber ventricular pacing modalities as physiologically paced patients with more persistent preimplant paroxysmal atrial fibrillation are the most likely to require reprogramming to a ventricular pacing mode.63

Conclusions and Clinical Implications

From the present retrospective study, it appears that morbid events in paced patients with sick sinus syn-
drome are strongly predicted by clinical variables. Pacing mode appears to play a significant but less important role as a risk factor for chronic atrial fibrillation and stroke. Development of chronic atrial fibrillation is relatively frequent; almost 50% of total incidence occurs within the first 2 years after implant. However, patients without a history of paroxysmal atrial fibrillation are expected to remain free of chronic atrial fibrillation during the first 4 years after pacemaker implantation and to have a negligible incidence of this complication afterward regardless of pacing modality. Chronic atrial fibrillation is strongly predicted not only by history of paroxysmal atrial fibrillation but also by the characteristics quantifying its persistence; such variables have not been previously analyzed and could have acted as important confounding factors in previous reports. Ventricular pacing mode, age, and valvular heart disease are additional independent risk factors for chronic atrial fibrillation. Stroke is a less frequent complication, but it can be fatal. Unlike chronic atrial fibrillation, it is not an early event; most of the episodes occur after the fifth year of pacemaker implantation. Independent risk factors for stroke are history of cerebrovascular disease, ventricular pacing mode, and history of paroxysmal atrial fibrillation; consequently, it would be appropriate to chronically anticoagulate patients with any of these risk factors. Ventricular pacing remains the most frequently selected modality in the United States. Considering the higher costs of dual-chamber devices, ventricular pacing should not be precluded in selected patients with sick sinus syndrome without paroxysmal atrial fibrillation because for these patients, the risk of chronic atrial fibrillation and stroke probably is negligible.

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