Atrial Pacing Periablation for Prevention of Paroxysmal Atrial Fibrillation

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for the Atrial Pacing Periablation for Paroxysmal Atrial Fibrillation (PA3) Study Investigators

Background—This study tested the hypothesis that rate-adaptive atrial pacing would prevent paroxysmal atrial fibrillation (PAF) in patients with frequent PAF in the absence of symptomatic bradycardia.

Methods and Results—Patients (n=97) with antiarrhythmic drug-refractory PAF received a Medtronic Thera DR pacemaker 3 months before planned AV node ablation. Patients were randomized to no pacing (n=48) or to atrial rate-adaptive pacing (n=49). After a 2-week stabilization period, patients were followed up for an additional 10 weeks. The time to first recurrence of sustained PAF, the interval between successive episodes of PAF, and the frequency of PAF were compared between the 2 groups in intention-to-treat analysis. Time to first episode of sustained PAF was similar in the no-pacing (4.2 days; 95% CI, 1.8 to 9.5) and the atrial-pacing (1.9 days; 95% CI, 0.8 to 4.6; P=NS) groups. PAF burden was lower in the no-pacing (0.24 h/d; 95% CI, 0.10 to 0.56) than in the atrial-pacing (0.67 h/d; 95% CI, 0.30 to 1.52; P=0.08) group. Paired crossover analysis in 11 patients revealed that time to first PAF was shorter during atrial pacing (1.6 days; 95% CI, 0.6 to 4.9) than with no pacing (6.0 days; 95% CI, 2.4 to 15.0; P=0.13), and PAF burden was greater during atrial pacing (1.00 h/d; 95% CI, 0.35 to 2.91) than with no pacing (0.32 h/d; 95% CI, 0.09 to 1.13; P<0.016).

Conclusions—Atrial rate-adaptive pacing does not prevent PAF over the short term in patients with antiarrhythmic drug-resistant PAF without symptomatic bradycardia. (Circulation. 1999;99:2553-2558.)

Key Words: fibrillation ■ pacemakers ■ tachyarrhythmias

S omething clinical data suggest that atrial pacing might prevent paroxysmal atrial fibrillation (PAF). Atrial pacing could prevent PAF by preventing bradycardia-induced dispersion of repolarization. Overdrive atrial pacing might also reduce at least 1 potential trigger for PAF, frequent supraventricular premature beats (SVPBs). Finally, atrial pacing preserves atrioventricular (AV) synchrony, which might prevent stretch-induced changes in atrial repolarization predisposing to PAF. This last mechanism might explain the many retrospective studies and 1 prospective study reporting that atrial pacing reduces the incidence of chronic atrial fibrillation compared with ventricular pacing in patients with sinus node disease. Atrial pacing as a primary therapy for the prevention of PAF has not been evaluated previously in patients without an indication for cardiac pacing.

The present study was designed to test the hypotheses that (1) atrial-based pacing reduces the time to first recurrence of sustained PAF and (2) atrial-based pacing reduces the frequency and duration of PAF.

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Atrial Pacing for PAF

Figure 1. Study protocol. Patients were randomized to receive a dual-chamber rate-adaptive pulse generator with ability to store information on time, date, and duration of up to 15 consecutive episodes of a high-rate atrial event. Patients were randomized to no pacing or to atrial pacing, and their devices were programmed to DDI rate 30 bpm mode or DDIR lower-rate 70 bpm mode, respectively. After a 2-week stabilization period to allow lead maturation, diagnostic data were retrieved by telemetry and diagnostic counters were cleared. Some patients crossed over early to atrial pacing because of recurrence of highly symptomatic PAF. Patients were reassessed 3 months after pacemaker implantation, and diagnostic data used for analysis of study outcome events were retrieved by telemetry. At this point, untreated patients could cross over to atrial pacing and be followed up for an additional 3 months, including a 2-week stabilization period. AV node ablation was considered after completion of study protocol.

TABLE 1. Programming Parameters

<table>
<thead>
<tr>
<th></th>
<th>No Pacing</th>
<th>Atrial Pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacing mode</td>
<td>DDI</td>
<td>DDIR</td>
</tr>
<tr>
<td>Lower rate, bpm</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>Upper rate, bpm</td>
<td>NA</td>
<td>Age maximum HR×0.8</td>
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<tr>
<td>AV interval</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pace, ms</td>
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<td>200</td>
</tr>
<tr>
<td>Sense, ms</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>PVARP, ms</td>
<td>310</td>
<td>Sensor varied (range, 150–350)</td>
</tr>
<tr>
<td>Atrial sensitivity, mV</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>PVAB, ms</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>Activity threshold</td>
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<td>Low-medium</td>
</tr>
<tr>
<td>Activity rate response</td>
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<td>8</td>
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<tr>
<td>Acceleration, min</td>
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<tr>
<td>Deceleration, min</td>
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<td>5</td>
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<tr>
<td>AF diagnostic parameter counters</td>
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<td>Frozen</td>
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<tr>
<td>AF detection, bpm</td>
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<td>180</td>
</tr>
<tr>
<td>AF detection number, beats</td>
<td>200</td>
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</tr>
<tr>
<td>AF termination number, beats</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

PVARP indicates postventricular atrial refractory period; PVAB, postventricular atrial blanking period; AF, atrial fibrillation; and Age maximum HR×0.8, 80% of maximum heart rate predicted for age.

episode data were retrieved. These data were used to determine the primary outcome event. Patients in the no-pacing group could cross over to a trial of atrial pacing after the 3-month follow-up period or earlier if they experienced intolerable recurrent symptomatic PAF. On completion of the 3-month follow-up, patients either proceeded to AV node ablation or could defer the procedure. Ambulatory ECGs were obtained at baseline and at 3 months.

Study Outcome Events

The primary study outcome was the time to first recurrence of PAF lasting ≥5 minutes occurring ≥2 weeks after randomization. Because the time course of recurrence may not be completely random, the interval between the first and second episodes of PAF was also determined.19 Other outcome measures included intervals between successive episodes of PAF, frequency of PAF, and proportion of patients who chose to defer ablation.

PAF Detection

The Thera DR high-rate atrial tachycardia detection feature was used for PAF detection in this study. This feature has been reported to have a high sensitivity and specificity for the detection of atrial tachyarrhythmias.19 The programming parameters for PAF detection (Table 1) were selected to reduce the likelihood that nonsustained PAF would fill the diagnostic counters and to ensure that intermittent sense failure of atrial events during PAF would not be inappropriately classified as PAF.19 No PAF episodes <1 minute long were detected as an episode of PAF. To maximize collection of sequential episodes of PAF, the atrial electrogram storage feature was not used. Validation of appropriate detection of PAF was carried out in 28 patients by use of an enhanced marker channel feature of the device combined with ambulatory ECG. One channel of the ambulatory ECG and downloaded marker signals representing what the device interpreted as atrial and ventricular electrograms were recorded simultaneously. Appropriate detection of all episodes of PAF was observed in 10 patients who experienced PAF during ambulatory ECG monitoring.

False-positive detection of PAF by the Thera DR could occur because of oversensing of near-field P waves or far-field R waves or competitive atrial pacing when the atrial rate is high and the postventricular atrial refractory period is long.20–22 To exclude false-positive detections of PAF, all episodes of PAF detected by the pulse generator were reviewed by 2 observers who were blinded to the programmed pacing modality.22 Episodes designated as oversensing or competitive atrial pacing were then reviewed by an additional 2 observers for a final classification. Of 1636 episodes of PAF detected in the study population, 48 (2.9%) were inappropriately detected as PAF.19 No PAF episodes >1 minute long were detected as an episode of PAF. To maximize collection of sequential episodes of PAF, the atrial electrogram storage feature was not used. Validation of appropriate detection of PAF was carried out in 28 patients by use of an enhanced marker channel feature of the device combined with ambulatory ECG. One channel of the ambulatory ECG and downloaded marker signals representing what the device interpreted as atrial and ventricular electrograms were recorded simultaneously. Appropriate detection of all episodes of PAF was observed in 10 patients who experienced PAF during ambulatory ECG monitoring.

Data Analysis

Analysis was performed according to the intention-to-treat principle. The times to occurrence of the first and second episodes of PAF were determined by the Kaplan-Meier method.23 Differences in the curves were compared by the log-rank test.24 Differences between curves for paired data were compared by a Cox proportional hazards model incorporating the cluster term. PAF burden was calculated as the total duration of atrial fibrillation during the follow-up period. When the event counters were filled, PAF burden was calculated as the total duration of atrial fibrillation during the time available for analysis. Geometric mean data were calculated after log transformation, and differences were compared by a nonpaired t test. Differences in proportions were compared with a χ2 analysis. Data are presented as mean±SD or geometric mean and 95% CIs when log transformation was used. A value of P<0.05 for 2-sided comparisons was considered significant.
Results

Study Population
Forty-eight patients were randomized to the no-pacing group and 49 to the atrial-pacing group. The characteristics of the 2 groups were similar and are shown in Table 2. At the 3-month follow-up visit, pacing had not occurred in either chamber in the no-pacing group, whereas the atrium was paced 67.634% of the time and the ventricle was paced 64.631% of the time in the atrial-pacing group. Ambulatory ECG recordings indicated that 67% of pacing in the ventricle was competitive.

Early Crossovers to Atrial Pacing or AV Node Ablation
Twelve patients randomized to no pacing crossed over to atrial pacing before completion of the 2-week stabilization period. AV node ablation was performed before completion of the 3-month follow-up period in 12 patients (25%) randomized to no pacing and in 17 patients (35%) randomized to atrial pacing. Eleven patients completed trials of no pacing and subsequent atrial pacing. AV node ablation was deferred in 14 patients (29%) in each group.

Intention-to-Treat Analysis
Survival free of recurrent PAF after the 2-week stabilization period is shown in Figure 2. No significant differences were observed between the 2 groups (P=0.26). Event-free survival of the interval between the first and second episodes of sustained AF was also compared and was similar between the 2 groups (Figure 3).

The characteristics of PAF are shown in Table 3. The majority of patients (84%) experienced PAF, and most patients experienced multiple episodes. No significant differences in the time to first episode of PAF, the interval between first and second episodes of PAF, the number of episodes of PAF, or the rate of PAF were observed. The total PAF burden tended to be lower in the no-pacing group than in the atrial-pacing group (P=0.08). The interval between the first and second episodes of PAF was significantly shorter than the time to first episode of PAF in both groups (P<0.05).

Analysis of PAF recurrence immediately after pacemaker implantation was also performed. The time to first episode of PAF occurring during the 2-week stabilization period before the occurrence of any patient crossovers to atrial pacing was similar in the no-pacing (4.6 days; 95% CI, 2.4 to 7.1) and the atrial-pacing (2.4 days; 95% CI, 1.7 to 3.0; P=0.16) groups. The interval between first and second episodes of PAF occurring during the 2-week stabilization period was also similar in the 2 groups.

Ambulatory ECG monitoring demonstrated that atrial pacing reduced the frequency of SVPBs (3.8/h; 95% CI, 1.4 to 10.9 at baseline, to 0.5/h; 95% CI, 0.2 to 1.1 at 3-month follow-up; P<0.01), whereas SVPB frequency was unchanged in the no-pacing group over time (3.2 SVPB/h; 95% CI, 0.9 to 11.9 at baseline and 3.2 SVPB/h; 95% CI, 0.8 to 12.6 at 3-month follow-up; P=NS).

Table 2. Characteristics of Study Population

<table>
<thead>
<tr>
<th></th>
<th>No Pacing (n=48)</th>
<th>Atrial Pacing (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62±12</td>
<td>61±11</td>
</tr>
<tr>
<td>Female, %</td>
<td>26 (54)</td>
<td>21 (43)</td>
</tr>
<tr>
<td>Duration of PAF, y</td>
<td>6±8</td>
<td>5±6</td>
</tr>
<tr>
<td>Heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>25 (52)</td>
<td>21 (43)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (29)</td>
<td>12 (24)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>8 (17)</td>
<td>13 (27)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>11 (23)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>0</td>
<td>1 (2)</td>
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<tr>
<td>Reason for AV node ablation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs ineffective at maintaining sinus rhythm</td>
<td>45 (94)</td>
<td>40 (82)</td>
</tr>
<tr>
<td>Drugs ineffective at controlling heart rate</td>
<td>18 (38)</td>
<td>16 (33)</td>
</tr>
<tr>
<td>Intolerable adverse effects of drugs</td>
<td>21 (44)</td>
<td>25 (51)</td>
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<tr>
<td>Antiarrhythmic drugs</td>
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<tr>
<td>β-Blockers</td>
<td>5 (10)</td>
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<tr>
<td>Digitalis</td>
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<td>Ca²⁺ channel blockers</td>
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</tr>
<tr>
<td>Type III</td>
<td>6 (13)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>15 (31)</td>
<td>16 (33)</td>
</tr>
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</table>

Values in parentheses are percent. Percentages do not add to 100% because some patients were taking more than 1 drug. Data are mean±SD.
Paired Crossover Data

Eleven patients completed the 3-month follow-up in the no-pacing limb and then crossed over to a 3-month trial of atrial pacing. Event-free survival to the first episode of PAF and between the first and second episodes of PAF is shown in Figure 4. PAF tended to recur earlier during atrial pacing than with no atrial pacing. The characteristics of PAF during follow-up in the 2 treatment modes are shown in Table 4. The time to first PAF tended to be shorter during atrial pacing than with no pacing (P=0.13). The total PAF burden was significantly greater during atrial pacing than with no pacing (P=0.016).

Discussion

Present therapeutic strategies for the management of PAF are unsatisfactory for many patients. Recently, atrial-pacing modalities have been proposed for the prevention of PAF.3–5 To the best of our knowledge, the present study is the first to test the hypothesis that atrial pacing might prevent or reduce the burden of PAF in patients without symptomatic bradycardia. The results show that atrial rate-adaptive pacing does not prevent PAF recurrence, nor does atrial pacing reduce the frequency or duration of PAF over the short term after implantation of a DDDR pacemaker in patients without symptomatic bradycardia.

Coumel et al1 reported that atrial pacing prevented vagally mediated PAF in 4 of 6 patients as long as a sufficient pacing rate was maintained. Attuel et al2 reported that DDD pacing with the lower rate programmed to exceed the diurnal mean heart rate prevented PAF in 10 patients with sinus node disease in whom PAF was associated with bradycardia or atrial pauses. Other such data have been reviewed.3 Saksena et al4 reported that single- and dual-site right atrial pacing prolonged the PAF-free interval compared with the preimplant interval in patients with sinus node disease and PAF. Some of these studies were not prospective, drug therapy before and after pacing was not carefully controlled, and therapy was not randomly assigned. Moreover, all patients had bradycardia as an indication for pacing. In the present study, a no-pacing treatment group was possible because the study population did not require pacing for bradycardia and patients were stabilized on antiarrhythmic drug therapy during the 2-week run-in phase.

Mechanisms for Pacing Prevention of PAF

Atrium-based pacing might prevent PAF by preventing bradycardia-dependent episodes of PAF. Bradycardia-induced increased dispersion of atrial repolarization may provide a substrate for PAF.3,6,7,25 We hypothesized that atrial pacing might prevent PAF by preventing “relative” bradycardia-induced changes in atrial electrophysiology. In our study population randomized to atrial pacing, the atrium was paced 67% of the time. If consistent atrial activation is important, selection of a higher lower rate for pacing would have increased the proportion of time the atrium was paced and might have altered the time course of PAF recurrence. However, other investigators evaluating an algorithm that ensures almost constant atrial pacing have not shown a significant reduction in the frequency of PAF.26 Furthermore,
episodes of PAF documented during ambulatory ECG monitoring were frequently observed during atrial pacing in our patients. 27

Atrial overdrive suppression of SVPBs has also been postulated to be a mechanism for prevention of PAF. 3,5,8 A pacing algorithm to suppress SVPBs in patients with PAF has been reported to prevent PAF in some patients but to increase PAF recurrence in other patients. 5 In our study population, atrial pacing did suppress SVPB frequency, but this did not correlate with a reduction in PAF. 27

More rapid atrial pacing might provoke atrial arrhythmias, as has been suggested by the paired crossover data analysis in the present study. It is possible that an aggressive rate-response algorithm could initiate episodes of rapid atrial pacing, leading to atrial fibrillation. During ambulatory ECG monitoring, we never observed episodes of atrial pacing at the upper sensor rate provoking atrial fibrillation. 27 Competitive atrial pacing resulting in short atrial-pacing intervals due to programming a long postventricular atrial refractory period might initiate PAF. However, we saw no evidence of this during ambulatory ECG monitoring. It may be that atrial pacing per se has no direct antiarrhythmic effects. Atrioventricular pacing may allow more aggressive antiarrhythmic therapy, because symptomatic sinus bradycardia or high-grade AV block is no longer a concern. Furthermore, it is possible that ventricular pacing may be proarhythmic by virtue of the deleterious effects of ventricular pacing on cardiac hemodynamics, which might cause asynchronous ventricular activation, 28 valvular regurgitation, 11,12 and stretch-induced changes in atrial repolarization that might predispose to PAF. 7,9,10

Possible Limitations
The high proportion of early crossovers to atrial-pacing therapy reduces the power of this study. Thus, it is possible that a modest treatment effect of atrial pacing would not be detected. However, because patients in the atrial-pacing group were experiencing PAF earlier than the no-treatment group, such an outcome is unlikely.

The majority of atrial leads were positioned in the right atrial appendage. It is possible that stimulation in this site results in delayed activation of some areas in the atria that are important in the initiation of PAF. Site-specific atrial pacing, eg, Bachmann’s bundle, 29,30 left atrial, or dual-site atrial pacing, 3,21 might be more efficacious by virtue of shortening total atrial activation times. These modalities are currently being tested. As discussed, it is possible that more continuous atrial pacing might prevent PAF, because the patients in the present study were not paced in the atrium 33% of the time. Other studies are currently testing algorithms to promote more continuous pacing. The present study compared no pacing with atrial pacing in the DDIR mode. In the DDIR mode, ventricular rate acceleration is not dependent on the atrium. Hence, the present study results cannot necessarily be extrapolated to other pacing modalities. The primary study outcome depended on reliable detection of PAF by the device. It is possible that undersensing of PAF occurred in some patients; however, the frequency should have been similar in both groups. The study design did not discriminate between symptomatic and asymptomatic episodes of PAF.

Conclusions
Atrial rate-adaptive pacing does not prevent recurrence of PAF over the short term, nor does it reduce PAF frequency or duration in patients with PAF in the absence of symptomatic bradycardia.

Appendix
The following institutions and individuals participated in this study (listed in descending order of number of patients randomized).


Acknowledgments
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References


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