Background New atrial pacing techniques and overdrive pacing algorithms have been introduced to prevent atrial fibrillation. This study was designed to test the hypotheses that (1) interatrial septum pacing (IASP) at the triangle of Koch would be more effective than right atrial appendage pacing (RAAP) in preventing paroxysmal atrial fibrillation (PAF) in patients with sinus bradycardia and (2) an algorithm (CAP) designed to achieve constant atrial capture would increase the efficacy of rate-responsive atrial pacing.

Methods We studied 46 patients with PAF and sinus bradycardia implanted with a DDD(R) (Medtronic Thera) pacemaker. Twenty-four patients (6.0 ± 10.1 PAF episodes/month within 3 months before study) were randomized to RAAP and 22 patients (5.4 ± 7.1, not significant) to IASP. Within each arm 2 randomized crossover periods of CAP-OFF and CAP-ON function were programmed.

Results The PAF episodes per month significantly decreased in the RAAP (CAP-OFF: 2.1 ± 4.2, P < .05; CAP-ON: 1.9 ± 3.8, P < .05) and in the IASP group (CAP-OFF: 0.2 ± 0.5, P < .05; CAP-ON: 0.2 ± 0.5, P < .05). Values were significantly lower in the IASP group than in the RAAP group in both CAP-OFF (0.2 ± 0.5 vs 2.1 ± 4.2, P < .05) and CAP-ON (0.2 ± 0.5 vs 1.9 ± 3.8, P < .05) conditions. PAF burden was significantly lower in the IASP than in the RAAP group in CAP-OFF (47 ± 84 min/d vs 140 ± 217, P < .05) and in CAP-ON (41 ± 72 vs 193 ± 266, P < .05) conditions. No differences were observed within each arm in PAF burden between the 2 crossover CAP programing periods.

Conclusions Rate-adaptive IASP at the triangle of Koch is more effective than RAAP in preventing PAF in patients with sinus bradycardia. In our sample of patients no additional clinical benefit is furnished by the CAP algorithm. (Am Heart J 2001;142:1047-55.)

Atrial pacing has been documented to prevent atrial fibrillation (AF) in patients in whom the onset of the arrhythmia is associated with bradycardia or long pauses (Coumel’s syndrome). Clinical studies indicate that atrial pacing may be associated with a lower risk of AF than ventricular pacing in patients with sick sinus syndrome. To obtain additional benefits, new algorithms have been developed that, ensuring almost constant atrial pacing, reduce gross irregularity in heart rate and avoid pauses that follow premature atrial complexes (short-long cycle sequences).

Recently, new methods such as biatrial pacing, dual-site right atrial pacing, and single-lead interatrial pacing at the Bachmann’s bundle or at the triangle of Koch have been proposed to obtain incremental benefits relative to right atrial appendage pacing (RAAP).

The current study was designed to test the hypotheses that (1) interatrial septum pacing (IASP) at the triangle of
Koch would be more effective than RAAP in preventing paroxysmal AF (PAF) in patients with sinus bradycardia and (2) an algorithm, named consistent atrial pacing (CAP), designed to achieve a continuous overdrive suppression of spontaneous atrial activity would increase the efficacy of rate-adaptive atrial pacing.

Methods

Study population
Forty-six patients (18 male, 28 female, mean age 74 ± 12 years) with a history of sinus bradycardia and PAF who had had at least 2 episodes per month of symptomatic PAF within 3 months before study were enrolled. At least one of these episodes was documented electrocardiographically. No patients had atrial linear or atrioventricular node ablation before or during the trial. The study was approved by the institutional review board, and witnessed informed consent was obtained from each patient.

Study protocol
The study design is outlined in Figure 1. To verify the real efficacy of pacing in the prevention of AF and to be sure that results were not confused by the use of previously used antiarrhythmic drugs, the pharmacologic treatment adopted before the implant procedure remained stable throughout the follow-up study.

All the enrolled patients underwent the implantation of a DDD(R) pacemaker (Medtronic Thera D[R]). This device has an automatic mode switch (AMS) mechanism that changes from an atrial tracking to a nonatrial tracking mode (DDI-R mode) on the basis of atrial tachycardia detection criteria. The programming parameters for PAF detection were selected to reduce the likelihood that nonsustained PAF would fill the diagnostic counters and to ensure that intermittent sense failure of atrial events would not be inappropriately classified as PAF.12

In particular, an AF detection threshold equal to 180 beats/min, number of beats for AF detection equal to 200, and number of beats for AF termination equal to 10 were set. The postventricular atrial blanking period was set at 150 milliseconds. No PAF episodes shorter than 1 minute were detected.

After implant a lead stabilization period of 2 weeks was programmed. At the first follow-up visit validation of appropriate detection of PAF was carried out looking at atrial electrograms to exclude false-positive detection resulting from R-wave far-field oversensing. Before study randomization and data collection, atrial sensitivity, whose default value was set at 0.5 milliseconds, was optimized to avoid R-wave far-field oversensing.

CAP algorithm functioning
The algorithm monitors beat-by-beat spontaneous atrial activity and continuously updates the atrial escape interval to overdrive suppress it. After every sensed atrial event outside the postventricular atrial refractory period, resulting from pre-

Figure 1

Study protocol. At implant, patients were randomized to RAAP or IASP and to a CAP-OFF or CAP-ON condition. After 3 months patients were assessed, diagnostic data were retrieved by telemetry, and diagnostic counters were cleared. At this point patients in the CAP-ON condition were switched to CAP-OFF and vice versa. On the completion of the following 3-month follow-up patients were reassessed and diagnostic data were retrieved by telemetry.
mature atrial complexes or breakthrough of sinus rhythm, the atrial escape interval is shortened by a programmable value (delta deceleration). After a programmable number of paced atrial events (plateau beats), the atrial escape interval is lengthened by a programmable value (ARS delta). The atrial escape interval shortening is limited by the programmed upper rate value. The atrial escape interval lengthening is limited by the programmed lower rate value. When rate responsiveness is activated by physical activity, the atrial escape interval determined by the sensor and the atrial escape interval calculated by the algorithm is applied. If spontaneous sinus rhythm is faster than sensor-induced pacing rate, the CAP algorithm paces the atrium at a cycle shorter than sinus rhythm cycle until the upper rate limit is reached (Figure 2). When PAF occurs and AMS is activated, the CAP algorithm is switched off and starts working again at the end of atrial tachyarrhythmia. The software can be placed into the pacemaker by telemetry with use of a custom research telemetry device. It includes a diagnostic, which can be interpreted by a special Microsoft Excel spreadsheet. Retrieved diagnostic data include atrial pacing percentage, CAP algorithm intervention number, premature atrial and ventricular complex number, and AMS number and duration. Short-lasting and early recurrent AMS episodes can be analyzed separately. Diagnostic data are available also when the algorithm is switched off. In our study programmed values were delta deceleration 50 milliseconds, plateau beats 5, ARS delta 20 milliseconds, lower rate 70 beats/min, upper rate 120 beats/min.

Methods of measuring clinical effectiveness for AF prevention
The study has been designed to measure the number of symptomatic episodes per month, the percentage of asymptomatic patients during follow-up, the AF burden, the time to first AF recurrence, the number of premature atrial contractions (PACs), and the atrial pacing percentage.

Symptomatic episodes were assessed during follow-up visits by submitting a simple questionnaire to patients and by

![Figure 2](image)

**Table I.** Characteristics of study population

<table>
<thead>
<tr>
<th></th>
<th>IASP (n = 22)</th>
<th>RAAP (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>76 ± 6</td>
<td>74 ± 10</td>
</tr>
<tr>
<td>Female (%)</td>
<td>11 (50)</td>
<td>17 (71)</td>
</tr>
<tr>
<td>Symptomatic PAF episodes/mo</td>
<td>5.4 ± 7.1</td>
<td>6.0 ± 10.1</td>
</tr>
<tr>
<td>Heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>5 (23)</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (41)</td>
<td>6 (25)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>10 (45)</td>
<td>12 (50)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>2 (9)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Primary cardiomyopathy</td>
<td>–</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>1 (5)</td>
<td>–</td>
</tr>
<tr>
<td>Digitalis</td>
<td>3 (14)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>1 (5)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>None</td>
<td>3 (14)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Class IA</td>
<td>4 (18)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Class IC</td>
<td>9 (41)</td>
<td>8 (33)</td>
</tr>
<tr>
<td>Type III</td>
<td>3 (14)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>7 (32)</td>
<td>9 (38)</td>
</tr>
</tbody>
</table>

Values in parentheses are percent. Percentages do not add up to 100% because some patients were taking more than one drug or had more than one disease. Therefore they have been counted more than once.
checking correspondence between patients symptoms and the presence of high-rate tachycardia episodes in the Thera D(R) memory.

AF burden, calculated as the total duration of atrial arrhythmias during the time of evaluation and expressed in minutes for day and time to first AF recurrence were measured by the Thera D(R) high-rate atrial tachycardia detection feature, which has been reported to have a high sensitivity and specificity for the detection of atrial tachyarrhythmias. In this way both symptomatic and asymptomatic episodes were considered.

The same high-rate tachycardia detection feature allowed measurement of PACs during the time of evaluation. This parameter was normalized as a function of time and expressed as PAC number for day.

The percentage of atrial pacing was measured by the Holter monitor of the device, which counts each atrioventricular (AV) sequence (atrial sense-ventricular sense, atrial pace-ventricular sense, atrial sense-ventricular pace, and atrial pace-ventricular pace). In standard Thera devices the number of AV sequences is influenced by atrial arrhythmias because counters are not frozen during mode switch periods. In our study we downloaded the CAP software into the pacemaker by telemetry. With this software, either when CAP algorithm is enabled or when it is suspended, AV sequences are counted only outside of mode switch; therefore atrial pacing percentage estimation is not influenced by the occurrence of atrial arrhythmia.

Data analysis

Primary study objectives were to compare the previous quantities between 2 pacing sites (ie, IASP vs RAAP) and to compare the previous quantities according to 2 different pacing modalities (ie, CAP-ON vs CAP-OFF). In the first comparison unpaired statistical tests were used and in the second comparison paired statistical tests were used.

To the statistical significance in the difference of percentage of patients with symptomatic episodes the Pearson χ² test was used.

The times of occurrence of the first episode of PAF constitute measurements that may form neither a random nor a normal distribution; therefore, we have presented data as geometric means, after log transformation, and 95% CI. Comparison between CAP-OFF and CAP-ON, in the different pacing sites, is presented by showing Kaplan-Meier curves. Differences in the curves were compared by the log rank test.

Results

Study population

Twenty-two patients (11 male, 11 female, 76 ± 6 years old) were randomized to the IASP group and 24 (7 male, 17 female, 74 ± 10 years old) to the RAAP group. The clinical characteristics of the 2 groups were similar and are shown in Table I. The mean episodes per month of PAF in the 3-month period before implantation was 5.4 ± 7.1 in the IASP group and 6.0 ± 10.1 in the RAAP group (not significant [NS]). All patients completed the study.

RAAP group

During CAP-OFF the atrium was paced 79% ± 27% of the time. PACs per day were 2743 ± 4381. A significant decrease of symptomatic PAF was observed (2.1 ± 4.2 episodes/mo, P < .05) (Figure 3). PAC burden was 425 ± 586 minutes per day (Figure 4). The time to the first episode of PAF was characterized by a geometric mean of 6.8 days and a 95% CI between 3 and 28 days (Figure 5). Twenty patients (83%) did not have recurrences of PAF (Table II).

During CAP-ON the atrium was paced 96% ± 8% of the time (P < .001 vs CAP-OFF). PACs per day were 425 ± 586 (P < .02 vs CAP-OFF). The mean symptomatic episodes per month were similar to those of CAP-OFF (1.9 ± 3.8) and were significantly lower than those of the preimplantation period (P < .05) (Figure 3). The

Table II. Results in RAAP patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CAP-OFF</th>
<th>CAP-ON</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent atrial pacing</td>
<td>79 ± 27</td>
<td>96 ± 8</td>
<td>.001</td>
</tr>
<tr>
<td>PACs/d</td>
<td>2743 ± 4381</td>
<td>425 ± 586</td>
<td>.02</td>
</tr>
<tr>
<td>Symptomatic PAF episodes/mo</td>
<td>2.1 ± 4.2*</td>
<td>1.9 ± 3.8*</td>
<td>NS</td>
</tr>
<tr>
<td>PAF burden (min/d)</td>
<td>140 ± 217</td>
<td>193 ± 266</td>
<td>NS</td>
</tr>
<tr>
<td>Time to first PAF (d)</td>
<td>6.8 [3-28]</td>
<td>6.7 [1-28]</td>
<td>NS</td>
</tr>
<tr>
<td>Asymptomatic patients</td>
<td>20 [83%]</td>
<td>18 [75%]</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are geometric mean with 95% CIs in parentheses or mean ± SD. *P < .05 versus before implant.

Table III. Results in IASP patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CAP-OFF</th>
<th>CAP-ON</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent atrial pacing</td>
<td>83 ± 16</td>
<td>97 ± 3</td>
<td>.001</td>
</tr>
<tr>
<td>PACs/d</td>
<td>2005 ± 3184</td>
<td>1103 ± 2745</td>
<td>.01</td>
</tr>
<tr>
<td>Symptomatic PAF episodes/mo</td>
<td>0.2 ± 0.5*</td>
<td>0.2 ± 0.5*</td>
<td>NS</td>
</tr>
<tr>
<td>PAF burden (min/d)</td>
<td>47 ± 84</td>
<td>41 ± 72</td>
<td>NS</td>
</tr>
<tr>
<td>Time to first PAF (d)</td>
<td>9.6 [1-78]</td>
<td>6.7 [1-84]</td>
<td>NS</td>
</tr>
<tr>
<td>Asymptomatic patients</td>
<td>20 [91%]</td>
<td>21 [95%]</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are geometric mean with 95% CIs in parentheses or mean ± SD. *P < .05 versus before implant.
PAF burden was 193 ± 266 minutes per day (Figure 4) (NS vs CAP-OFF). The time to the first episode of PAF was characterized by a geometric mean of 6.7 days and a 95% CI between 1 and 28 days (NS vs CAP-OFF) (Figure 5). Eighteen patients (75%) did not have recurrences of PAF. Four patients (17%) had recurrences of PAF during both CAP-ON and CAP-OFF; 2 patients (85%) had recurrences of PAF only during CAP-ON (NS vs CAP-OFF) (Table II).

**IASP group**

During CAP-OFF the atrium was paced 83% ± 16% of the time. PACs per day were 2005 ± 3164. A significant decrease of symptomatic PAF was observed (0.2 ± 0.5 episodes/mo, \(P < .005\)) (Figure 3). The PAF burden was 47 ± 84 minutes per day (Figure 4). The time to the first episode of PAF was characterized by a geometric mean of 9.6 days and a 95% CI between 1 and 78 days (median value 9.6 days) (Figure 5). Twenty patients (91%) did not have recurrences of PAF (Table III).

During CAP-ON the atrium was paced 97% ± 3% of the time (\(P < .001\) vs CAP-OFF). PACs per day was 1103 ± 2745 (\(P < .01\) vs CAP-OFF). The mean symptomatic episodes per month were similar to those of CAP-OFF (0.2 ± 0.5) and significantly lower than those of the preimplantation period (\(P < .05\)) (Figure 3). The PAF burden was 41 ± 72 minutes per day (NS vs CAP-OFF) (Figure 4). The time to the first episode of PAF was characterized by a geometric mean of 6.7 days and a 95% CI between 1 and 84 days (NS vs CAP-OFF) (Figure 5). Twenty-one patients (95.5%) did not have recurrences of PAF (NS vs CAP-OFF). The only patient who had PAF during CAP-ON was 1 of 2 who had PAF during CAP-OFF. One patient had symptomatic recurrences during both CAP-ON and CAP-OFF. No differences were observed within each group between the CAP-ON and CAP-OFF conditions.

**Comparison between the 2 groups**

During CAP-OFF there was no difference in the percentage of atrial pacing, the number of PACs per day, the time to the first episode of PAF (Figure 6) and the percentage of asymptomatic patients between both pacing techniques. The symptomatic episodes per month and the PAF burden were significantly lower in the IASP group (\(P < .05\) and \(P < .05\), respectively) (Figures 3 and 4).

During CAP-ON there was no difference in the per-
centage of atrial pacing, the number of PACs per day, and the time to first PAF (Figure 6) and the percentage of asymptomatic patients between both pacing techniques.

The symptomatic episodes per month and the PAF burden were significantly lower in the IASP group (\(P < .05\) and \(P < .05\), respectively) (Figures 3 and 4).

**Discussion**

**Pacing and prevention of AF**

Becker et al\(^{16}\) studied the effects of single-, dual-, triple-, and quadruple-site atrial pacing on atrial activation and refactoriness in normal canine hearts. Single-site septal, triple-site (2 in the right atrium and 1 in the left atrium) and quadruple-site (2 in the right atrium and 2 in the left atrium) pacing was similar and was more efficient than biatrial and dual-site right atrial pacing in minimizing activation times and local recovery intervals.

Yu et al\(^{17}\) showed that in patients with PAF single-site pacing at either Bachmann’s bundle and right posterior interatrial septum near the coronary ostium and distal coronary sinus is similar and more effective than biatrial and dual-site right atrial pacing in minimizing activation times and local recovery intervals.

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interval in the site where re-entry is initiated may reduce the probability of initiating AF. This has been evidenced by electrophysiologic studies in which the driving train pre-excites the triangle of Koch and prolongs the coupling interval of the premature beats induced by the extrastimuli delivered in the high right atrium. In most patients with spontaneous paroxysmal AF, the premature beats triggering the arrhythmia originate in the high or superior region of the atria. When the triangle of Koch is permanently paced a condition similar to that observed in short-term studies would occur: if the critical site of anisotropic conduction and re-entry is excited by the premature atrial beats in the antidromic direction, their coupling interval is prolonged, with a lessened probability of inducing AF.

Dispersion of refractory periods is considered one of the main factors that underlie the inducibility and the persistence of AF. IASP induces a very short interatrial conduction delay and significantly decreases P-wave duration. Consequently, a reduction in dispersion of atrial refractoriness and a more homogeneous recovery of excitability leading to a reduced propensity for development of AF can be expected.

Clinical effectiveness of RAAP and IASP

Several methods have been used to measure the effects of pharmacologic or pacing treatment on prevention of PAF. The number of patients with no detected recurrences of AF during the follow-up period has been used to test the efficacy of drug therapy. In our study patients free from symptomatic recurrences were 20 of 22 (91%) and 21 of 22 (95.5%) when paced at IAS in DDDR and in DDDR + CAP modes, respectively. In the patients paced at the RAA, asymptomatic patients were 20 of 24 (83%) in DDDR and 18 of 24 (75%) in DDDR + CAP. Although results show a trend toward a benefit from IASP, no significant differences were observed because of the small number of patients. We can exclude the fact that the reduction of the symptomatic episodes may be due to a ventricular rate control by ventricular pacing because our patients had rapid rate responses associated with AF and we did not use a ventricular rate stabilization algorithm after AMS started. Moreover, no subjective improvement in patient symptoms has been described when such an algorithm was used.
A common method for comparing treatment arms is based on measuring the time to first recurrence of an AF episode documented by electrocardiogram. In patients with an implanted pacemaker the time of recurrence of an attack is documented by the Holter function of the device. In our study, no statistical difference was observed between the 2 pacing techniques and within each arm according to the pacemaker programs.

In patients with an implantable pacemaker the frequency and total duration of PAF recurrences (PAF burden) can be recorded with adequate sensitivity and specificity, which may be a reasonable method of comparison of treatment arms.

Appropriate detection of all episodes of symptomatic PAF was observed in the symptomatic patients who were referred for PAF attacks after implantation. IASP was significantly more effective than RAAP in reducing the number of symptomatic episodes per month of PAF recurrences and PAF burden in both arms of pacemaker program.

**Overdrive pacing algorithms**

Pacing algorithms have been developed to increase the pacing rate after a sensed atrial event and to reduce the pacing rate after a period of no sensed events. In spite of a high atrial pacing percentage and significant reductions of PACs, no significant reduction in the frequency of PAF has been reported in 2 short-lasting studies.

In our study population during a 3-month CAP-ON programed period, both RAAP and IASP induced a significantly higher pacing percentage and significantly suppressed PAC frequency but had no effect on time to first episode of PAF (Figure 6) and did not reduce the frequency (Figure 3) of symptomatic episodes of PAF (Figure 4) and PAF burden compared with the CAP-OFF condition. Thus in patients with sinus bradycardia the percentage of atrial pacing obtained by the rate-responsive modality had the same clinical effectiveness as the almost-total overdrive atrial suppression obtained by the CAP algorithm.

In conclusion, in patients with sinus bradycardia and PAF, rate-responsive RAAP and IASP were both effective in preventing PAF. Recurrences of PAF and PAF burden were significantly lower in IASP than RAAP. No additional benefit was observed when an algorithm designed to obtain continuous atrial pacing was used.
References


