CHAPTER 5

RIGHT ATRIAL PREVENTIVE AND ANTITACHYCARDIA PACING FOR PREVENTION OF PAROXYSMAL ATRIAL FIBRILLATION IN PATIENTS WITHOUT BRADYCARDIA – A RANDOMIZED STUDY


Provisionally accepted: Europace
ABSTRACT

Aims
To investigate the efficacy of preventive and antitachycardia pacing (ATP) in patients with symptomatic paroxysmal atrial fibrillation (AF) without bradyarrhythmias.

Methods
In this randomized, crossover pilot study, we randomized 38 symptomatic paroxysmal AF patients without bradyarrhythmias to atrial pacing lower rate 70 pulses per minute (ppm) and prevention and ATP therapies ON or to atrial pacing lower rate 34 ppm and prevention and ATP therapies OFF during 12 weeks with a 4 week wash-out period in between. The atrial lead was preferably placed in the interatrial septum. Antiarrhythmic drugs were continued during the study. Primary endpoint was AF burden.

Results
Mean age was 62±9 years and 27 (71%) patients had lone AF. Septal lead placement was accomplished in 26 (68%) patients. During treatment ON, there was a trend for AF burden reduction [from median 3.3% (1.0-15.2) to 2.4% (0.2-12.2), p=0.06, reduction 27%]. If septal lead placement was accomplished, AF burden reduction was statistically significant [44% reduction, from median 2.5% (1.0-8.0) to 1.4% (0.2-8.4), p=0.03]. Quality of life and symptoms did not change, also not in the septal group.

Conclusion
A hybrid therapy of preventive and ATP pacing and antiarrhythmic drugs may significantly reduce but not abolish AF burden if septal pacing is realized.
INTRODUCTION

Rate control is an accepted primary treatment strategy in atrial fibrillation (AF), especially in the presence of underlying heart disease. Rhythm control, however, remains therapy of choice in patients suffering from symptomatic AF. The cornerstone for rhythm-control therapy is serial antiarrhythmic drug treatment with or without cardioversions. This strategy often fails. Transvenous catheter ablation of the left atrium is nowadays the first choice in therapy if antiarrhythmic drug therapy fails. Success, i.e. long term maintenance of sinus rhythm can be accomplished in up to 70-90% of patients, but severe complications occur. Recurrent AF, thereafter, may happen asymptotically overestimating the success rate. The role that pacing therapies play in the prevention of AF remains unclear. Multiple randomized trials have demonstrated that atrial single- or dual-chamber pacing may prevent AF in patients with symptomatic bradycardia as primary pacing indication, especially in patients with sinus node dysfunction. The efficacy of atrial preventive pacing therapies in patients without symptomatic bradycardia is still uncertain, as is the influence of specific atrial pacing sites. The AT500™, a DDDR-P-pacemaker (Medtronic Inc.), has additional preventive and termination pacing therapies that may reduce AF burden and improve quality of life in patients with symptomatic AF. The primary objective of the present randomized pilot study was to investigate to what extent atrial prevention and termination pacing therapies of AT500™ compared to no active treatment (AAI 34 pulses per minute [ppm] backup pacing) can reduce AF burden in patients with symptomatic AF without bradyarrhythmias. Secondary objectives were to investigate the patients’ quality of life and symptoms.

METHODS

Study design

Seven centers in the Netherlands participated in this randomized, single blind, cross-over pilot study (see appendix). All patients gave their written informed consent. The institutional review boards of all hospitals approved the protocol. The study started in June 2004. Total follow-up was 36 weeks in all patients. The study ended in November 2005.

Patients between 18 and 70 years of age with documented paroxysmal AF, who had at least three symptomatic episodes of 30 minutes during the previous three months, and who failed on at least two different antiarrhythmic drugs (of which at least one belonged to class IC or III) were included in the study. Exclusion criteria were bradyarrhythmias necessitating
pacing (sick sinus node or atrioventricular node disease), presence of clinically significant valve disease, unstable angina pectoris, untreated coronary artery disease or hypertension (systolic tension >160 mmHg and/or diastolic tension >95 mmHg), advanced chronic heart failure NYHA III or IV, thyroid disorders, malignancy, and alcohol or drug abuse.

**Pacemaker features – AT/ AF prevention and termination algorithms**

Patients received a AT500™ (DDDR-pacemaker, Medtronic Inc.) with two bipolar leads. The atrial lead, with a tip-ring distance of a maximum of 12 mm, was preferably positioned in the interatrial septum. In the case of significant far-field R-wave oversensing (i.e. detected by the device) or in the case that no adequate position could be obtained in the interatrial septum, the atrial lead was positioned in the right atrial lateral wall or right atrial appendage. The ventricular lead was positioned in the right ventricular apex, but ventricular pacing was never performed during the study.

The device distinguishes between AF and atrial tachycardia (AT) using a) the P-P interval length (see below) and b) the dual chamber rhythm pattern information which can discriminate between far-field R wave oversensing and sinus tachycardia from atrial arrhythmias. During the entire study period, the AF detection zone was programmed between 100 ms and 200 ms (600 beats per minute [bpm] – 300 bpm) and the AT detection zone between 160 ms and 350 ms (375 bpm – 171 bpm). To ensure accurate atrial arrhythmia detection, an atrial threshold 25% of the telemetered P-wave >0.2mV was provided, resulting in a sensitivity of ≥ 0.45 mV. Both, AF and AT episodes, contribute to the AF burden. The latest 35 episodes were stored in the episode storage log, but the AF burden was calculated from all AT and AF episodes during a study period. The DDDRP-device offers the following preventive and termination pacing therapies, as has been previously described: 

1. **Atrial preference pacing (APP),** an atrial overdrive algorithm which dynamically sets the pacing rate just above the intrinsic rate. In the present study, after an intrinsic atrial event the pacing interval was decreased with 50 ms up to a minimum of 600 ms. After each 10 consecutive paced beats, the interval was increased again with 20 ms; 
2. **Atrial rate stabilization (ARS),** an atrial pacing therapy designed to inhibit the onset of atrial arrhythmias by eliminating the long pause that typically follows a premature atrial contraction. It is a programmable feature that resets each atrial escape interval by multiplying the last PP interval by an increment of, in the present study, 25%. In this way after a premature atrial complex, the atrial rate gradually returns to the intrinsic or programmed rate; and 
3. **Post mode switch overdrive pacing (PMOP) to prevent immediate recurrences of AF after an AF episode has stopped by transiently pacing at a higher rate, e.g. 90 bpm for 10 minutes.** Since all our patients were
paced in the AAI mode and in this setting the device does not switch mode, the PMOP feature was not be enabled in this study. In addition, the anti-tachycardia pacing (ATP) termination algorithm was used, which can detect and terminate a fast atrial rhythm, which not rarely is the onset of AF. ATP is analogous to the pacing techniques used to terminate ventricular tachycardias by pacing. There are two automatic pacing strategies, Ramp and Burst+, which aim to capture the atrium during a tachyarrhythmia and are able to terminate the abnormal rhythm. ATP was programmed as follows in the present study: a) 10 Ramp sequences starting at 88% of the AT cycle length (the average of the last four P-P intervals prior to detection) for a total of 10 pulses with a decrement of the cycle length of each pulse with 10 ms; b) if unsuccessful 10 Burst+ sequences, starting at 84% of the AT cycle length, second sequence with an interval of 75% of the AT cycle length, for a total of 10 pulses with a decrement of cycle length of each pulse with 10 ms, and finally c) 10 Ramp sequences starting at 81% of the AT cycle length for a total of 10 pulses with a decrement of cycle length of each pulse with 10 ms. ATP will only occur when the device defines the atrial arrhythmia as AT, not when it recognizes AF. ATP is considered successful if sinus rhythm has been restored for at least 5 consecutive sinus beats.

Study protocol
Figure 1 shows the study flow-chart. During the four weeks run-in period, echocardiography was used to assess underlying heart disease, exercise testing to exclude coronary artery disease and 24 hour Holter monitoring was performed to exclude persistent or permanent AF. Antiarrhythmic drugs were allowed but patients had to be on stable antiarrhythmic therapy for at least 8 weeks before they were randomized. Daily record card data was collected from the run-in period in order to assess the proper recording of AF related symptoms (see below). Patients were not randomized if no proper recording of symptoms on the diary cards was confirmed. After this run-in period, an AT500™ pacemaker was implanted. During the first four weeks after implantation and in between the two treatment periods, i.e. from 12 to 16 weeks after randomization, all AT/AF prevention and termination features were programmed to “OFF” in both groups. The purpose of the first period is to allow lead fixation and stabilization of the patient’s atrial tachyarrhythmia since these might be induced by the implant procedure. The purpose of the second period, i.e. from 12 to 16 weeks after randomization, is to prevent a carry-over effect from the first study period to the second study period. One month after implantation, all patients meeting the randomization criteria were randomized to either group A or group B. In group A APP, ARS, and ATP were programmed to “ON” and the lower rate was set at 70 ppm from 0 to 12 weeks after randomization. In
group B these features were programmed “ON” from 16 to 28 weeks after randomization. During the remaining time, APP and ARS were programmed “OFF” and the lower rate was set at 34 ppm (figure 1). During the “OFF” period a “dummy-programming” was done. This means that an ineffective (fake) ATP (1 pulse at 1 Volt during 0.03 ms at 97% of the current AA interval) was programmed in order to obtain similar episode information in both groups. In order to prevent bradycardia induced AF we choose a lower rate of 70 ppm during the ON period. To avoid pacing as much as possible the lowest possible pacing rate (34 ppm) was programmed during the OFF period.

Figure 1. Study flow chart.

Quality of life and symptoms
The quality of life was assessed using the Medical Outcomes Study Short-Form health survey (SF-36).28 The SF-36 is a standardized, validated, generic health survey that has been frequently used in arrhythmia studies. The SF-36 has been translated and validated in the Netherlands.29 It contains items to assess physical health (general health perception, physical functioning, role limitations due to physical problems and bodily pain) and mental health (social functioning, role limitations due to emotional problems, mental health and vitality). In addition, a healthy, age-matched control group was selected from Dutch subjects who served to validate the Dutch version of the SF-36. Symptoms related to
AF were assessed by means of diary cards and by the Symptom Checklist—Frequency and Severity Scale. The latter was developed as disease-specific instrument intended to measure the patient’s perception of the frequency and severity of arrhythmia-related symptoms.\textsuperscript{30} The instrument has been demonstrated to be valid for use in patients with persistent or paroxysmal AF. For each of 16 symptoms, patients assigned numerical scores (0-4 for frequency and 0-3 for severity). The overall possible scores are 0-64 (0= never, 64= always) for frequency and 0-48 for severity. Symptoms were also assessed on a daily basis using diary cards. Every day patients assessed to what extent he or she suffered from fatigue, palpitations, dyspnea, dizziness and chest pain (1= none, 2= a little/mild, 3= moderate 4= severe, 5= extreme). Severity of fatigue was measured at the same moments as quality of life with the multidimensional fatigue index (MFI-20).\textsuperscript{31} Patients were asked to fill in all questionnaires at home within three days after the screening visit and all other study visits. Daily record card data was collected from the run-in period to assess the proper recording of AF related symptoms. Patients were not randomized if no proper recording of symptoms on the diary cards was confirmed.

**Definitions**
AF burden was defined as the time the patient was in AT/AF divided by the total treatment time. The AF burden was calculated from all AT and AF episodes during a study period (e.g. run in phase, ON period, as measured by the device).

**Statistical analysis**
For this pilot study, no formal sample size calculations were performed. The primary outcome parameter was the reduction of AF burden. To evaluate the efficacy of atrial pacing (AAI 70 ppm, ARS and APP) and ATP using the AT500\textsuperscript{TM} on the AF burden we used a Wilcoxon test for paired samples, as the AF burden was not normally distributed. In addition, the AF burden was dichotomized and conditional logistic regression was used to evaluate the presence of an AF burden below and above the median AF burden (41 minutes). In this analysis treatment as well as the sequence, period and patients within the sequence were included, to account for carry-over effect and treatment by period interaction. The same methods were used for the secondary outcome parameters. A two way crossover analysis of variance was used for continuous data. Baseline and results descriptive statistics are given as the mean ± standard deviation (SD) or median (interquartile range) for continuous variables and counts with percentages for categorical variables. Commercially available computer software (Statistical Analysis System version 9.1, SAS Institute, Cary, North Carolina) was used for all analyses.
Table 1. Baseline characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Randomized patients (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age – years</td>
<td>62±9</td>
</tr>
<tr>
<td>Male gender - number of patients (%)</td>
<td>20 (53)</td>
</tr>
<tr>
<td>History of paroxysmal AF – years</td>
<td>7.1±5.4</td>
</tr>
<tr>
<td>Number symptomatic PAF episodes (last 3 months)</td>
<td>24 (9-90)</td>
</tr>
<tr>
<td>Duration symptomatic PAF episodes (last 3 months, hrs per episode)</td>
<td>2.5 (1.0-10.8)</td>
</tr>
<tr>
<td>History of hypertension - number of patients (%)</td>
<td>10 (26)</td>
</tr>
<tr>
<td>Old myocardial infarction - number of patients (%)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>No apparent heart disease - number of patients (%)</td>
<td>27 (71)</td>
</tr>
<tr>
<td>Heart failure - number of patients (%)</td>
<td></td>
</tr>
<tr>
<td>NYHA I</td>
<td>35 (92)</td>
</tr>
<tr>
<td>NYHA II</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Blood pressure – mmHg</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>137±19</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79±8</td>
</tr>
<tr>
<td>Echocardiographic findings – mm</td>
<td></td>
</tr>
<tr>
<td>Left atrium, long axis</td>
<td>41±4</td>
</tr>
<tr>
<td>LVEDD</td>
<td>50±16</td>
</tr>
<tr>
<td>LVESD</td>
<td>32±5</td>
</tr>
<tr>
<td>Septal-wall thickness</td>
<td>10±2</td>
</tr>
<tr>
<td>Posterior-wall thickness</td>
<td>9±2</td>
</tr>
<tr>
<td>Medication use – No. (% of patients)</td>
<td></td>
</tr>
<tr>
<td>Acenocoumaron/ phenprocoumon</td>
<td>26 (68)</td>
</tr>
<tr>
<td>Flecainide / propafenon</td>
<td>14 (37)*</td>
</tr>
<tr>
<td>Sotalol</td>
<td>10 (26)*</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>8 (21)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>13 (34)</td>
</tr>
<tr>
<td>Verapamil/ Diltiazem</td>
<td>10 (26)</td>
</tr>
<tr>
<td>ACE-inhibitor</td>
<td>9 (34)</td>
</tr>
<tr>
<td>ARB</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Statin</td>
<td>8 (21)</td>
</tr>
</tbody>
</table>

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic diameter; NYHA = New York Heart Association class for heart failure; * Two patients used flecainide in combination with sotalol.
RESULTS

Characteristics of patients
A total of 52 patients were enrolled in the study. Pacemakers were not implanted in two patients because one of them developed persistent AF and the other improved on amiodarone. One patient was withdrawn from the study prior to the planned implantation due to clinically significant atrioventricular nodal conduction disturbances necessitating pacemaker implantation. After successful implantation, 11 other patients were not randomized because of the development of persistent AF (n=5), bradycardia necessitating pacing (n=4), and refusal to participate further (n=2). The remaining 38 patients were randomized and treated according to the protocol (figure 1). Baseline characteristics are depicted in table 1. Median number of AF episodes during the last 3 months before inclusion was 24 (range 9-90), median duration 2.5 hours (1.0-10.8). 30 patients (79%) were on class I and/or class III antiarrhythmic drugs and continued these drugs throughout the study. Septal lead placement was accomplished in 26 patients and failed in 12 patients (no stable septal positioning, n=6, and significant far-field R-wave sensing, n=6). Accordingly, the atrial lead was placed in the free lateral wall (6 patients) or right atrial appendage (6 patients). There were no differences in baseline characteristics between the patients with septal and non-septal lead placement.

Atrial pacing and AF burden
During the OFF periods atrial pacing was 0%, during the ON periods 98 (93-99)% both for the total and septal group. The median AF burden during the run-in phase was 2.8 (0.5-28.7)% in the total group. The median daily AF burden fell from 3.3 (1.0-15.2)% to 2.4 (0.2-12.2)%, p=0.06 (figure 2A), a reduction of 27% during active treatment (ON phases). This means a reduction from a median of 48 (14-219) minutes per day to 35 minutes (3-176) per day. During the run-in phase in 6 patients (16%) no AF occurred, and during the ON and OFF period, 7 (18%) and 4 patients (11%) were free from AF episodes, respectively (p=NS). One patient developed persistent AF during the first study period (OFF period) and discontinued the study after this period. In the subgroup of 26 patients with septal lead placement, the AF burden fell during pacing therapy from a daily median AF burden from 2.5 (1.0-8.0)% to 1.4 (0.2-8.4)%, p=0.03 (figure 2B), a reduction of 44%, i.e. from 36 (14-115) minutes to 20 (3-121) minutes per day. During the run-in, ON and OFF period, respectively, 5 (19%), 6 (23%) and 2 patients (8%) were free from AF episodes, p=NS. Conditional logistic regression analysis, after dichotomization of the AF burden during the run-in phase (median AF burden 2.8%, i.e. 41 minutes), showed a comparable result without evidence of carry-over effect.


Figure 2. Difference in median AF burden between no treatment (OFF period) and active treatment (ON period), in all patients (n=38, panel A) and in the septally paced patients (n=26, panel B).

However, there was a trend for a period effect (p=0.06): therapy ON during the first period was borderline significantly more effective as compared to therapy ON during the last period (figure 3A and B). Time to first recurrence was not different between the groups: a median of 1 (1-5) days versus 3 (1-12) days in the ON versus OFF group respectively, also not in the patients with septal lead placement. During follow up 6 and 5 patients in the ON and OFF group, respectively, did not have any recurrence of AF. The individual responses are depicted in figures 4A and B. Mean efficacy of ATP during active treatment was 57±30% and during the OFF period (dummy) ATP was effective in 24±19%, p<0.05.
Figure 3. AF burden during each study phase (monitor and washout phase [white], ON period [gray], and OFF period [black]) according to randomization groups in all patients (group A [n=19] and group B [n=19], panel A) and in the septal paced patients (group A [n=12] and group B [n=14], panel B). Note that in group A the ON period (grey) was during the first study period after the monitor phase versus the last study period after the washout phase in group B.
Figure 4. Individual AF burden during the OFF and ON period in the total (panel A) and septal (panel B) group.

Quality of life, symptoms and fatigue index
The quality of life at study entry was lower for our patients compared to a healthy age- and sex-matched control group for physical role limitations, social functioning and vitality (figure 5). Comparing quality of life during the ON and OFF period, only mental health was
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significantly higher during the ON period, indicating a better quality of life on this subscale (data not shown). Comparable data was found in patients with septal lead placement.

Figure 5. Differences in quality of life subscales between the total group at baseline versus age- and sex-matched healthy controls. *p<0.05.

Analysis of the symptom checklist revealed no changes, neither in symptom frequency and symptom severity nor in number of symptoms during the OFF and ON periods (table 2). Also daily complaints were comparable. Fatigue and palpitations were the most frequently recorded symptoms during the study (figure 6). Whereas palpitations predominantly occurred during days of AF, fatigue was also present at the first days after an AF episode (figure 7). Comparison of the daily symptoms scores with the days on which AT or AF occurred (device data) revealed that 23% of the AT/AF episodes were completely asymptomatic, 45% of AT/AF periods slightly symptomatic, and 32% of AT/AF periods moderate to severely symptomatic. The multidimensional fatigue index also showed no significant changes comparing the OFF and ON periods (table 3).

Table 2. Symptom checklist scores (mean ± SD) during the OFF versus ON period.

<table>
<thead>
<tr>
<th></th>
<th>OFF period</th>
<th>ON period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom frequency score</td>
<td>17±10</td>
<td>16±8</td>
</tr>
<tr>
<td>Symptom severity score</td>
<td>12±7</td>
<td>12±8</td>
</tr>
<tr>
<td>Number of symptoms</td>
<td>10±4</td>
<td>10±4</td>
</tr>
</tbody>
</table>
Figure 6. AF related daily symptom scores during the OFF versus ON phase. Percentage of days with symptoms is presented.

Table 3. Multidimensional Fatigue Index (MFI-20) scores during the OFF versus the ON period.

<table>
<thead>
<tr>
<th>MFI- Scales</th>
<th>OFF period</th>
<th>ON period</th>
</tr>
</thead>
<tbody>
<tr>
<td>General fatigue</td>
<td>11±4</td>
<td>12±4</td>
</tr>
<tr>
<td>Physical fatigue</td>
<td>10±4</td>
<td>10±4</td>
</tr>
<tr>
<td>Reduced activity</td>
<td>10±4</td>
<td>10±4</td>
</tr>
<tr>
<td>Reduced motivation</td>
<td>9±3</td>
<td>9±4</td>
</tr>
<tr>
<td>Mental fatigue</td>
<td>9±4</td>
<td>8±4</td>
</tr>
</tbody>
</table>

Cardioversions and antiarrhythmic drugs
During the ON and OFF period, 1 and 4 electrical cardioversions were performed, respectively, in a total of 3 patients. No chemical cardioversions were performed. There were no changes in antiarrhythmic drugs during active treatment, while during the OFF period the amiodarone dose was increased (from 200 mg to 400 mg daily for 4 weeks) in two patients and metoprolol was started in one patient for rate control.
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**Figure 7.** Percentage of patients with palpitations (panel A) and fatigue (panel B) in the total group the day before AF, at the day of (an) AF episode(s) and the days after that AF episode(s). *p<0.05 in comparison with the day before and the days after.

**Figure 7A**

**Figure 7B**
DISCUSSION

This pilot study shows that a hybrid therapy of preventive and ATP pacing and antiarrhythmic drugs in patients with severely symptomatic AF without bradycardia may reduce but not abolish AF burden if septal pacing is realized. However, the patients’ quality of life and symptoms do not improve.

Rhythm control remains indicated in patients suffering from symptomatic AF. Antiarrhythmic drug therapy with or without cardioversion is only moderately effective. Atrial catheter ablation is nowadays first choice therapy for refractory symptomatic patients. Even before the widespread use of atrial ablation, pacing with or without preventive and antitachycardia features was studied for its value to prevent AF. Previous studies with atrial pacing alone instead of ventricular-based pacing have supported the idea that atrial pacing may prevent or reduce AF. Prevention of AF by atrial pacing, especially in the presence of sick sinus syndrome has been demonstrated to be beneficial. The magnitude of its benefit, however, is only modest. Other pacing methods have therefore been evaluated. These include alternate site pacing, multisite pacing, overdrive pacing, and various preventive and termination pacing algorithms. Up to now, studies on the additional value of preventive and termination pacing therapies have not been conclusive, and only a limited number of studies have investigated this issue in patients without a bradycardia indication for pacing. The present study shows a trend for AF burden reduction during active treatment, that was significant in the subgroup of patients with septal lead placement. However, the patients’ quality of life and symptoms did not significantly change.

Importantly, septal pacing seems more effective than pacing at more conventional sites. Previous studies demonstrated that septal pacing, and also dual site right atrial and biatrial pacing shorten total atrial activation time and reduce overall dispersion of atrial refractoriness. In addition, clinical studies suggest that atrial septal lead placement is superior in preventing AF. Therefore, in this study, atrial septal lead placement was chosen as the preferred pacing site. This was accomplished in 68% of patients. In accordance with these data, our study also demonstrates a better outcome for these patients. Although AF burden reduction was significant, this was not accompanied by improvement in quality of life and symptom scores. This may be explained by the fact that the AF burden reduction reached statistical significance, but was not clinically relevant: AF burden was reduced but not abolished. Despite therapy, in more than half of the patients, AF still occurred during approximately 2.5% of the time, which was obviously noticed by the patients. Unfortunately, in only 32% of septal lead placement failed either because no stable septal positioning could
be reached or significant far-field R-wave sensing was present. This low success rate may, on one hand, relate to insufficient investigators’ experience, on the other hand to the well known problem of far field R-wave oversensing if this lead position is attempted.47,48

Why may atrial preventive pacing be effective? Firstly, it may prevent triggers, i.e. atrial premature complexes, bradycardia and atrial tachycardias.49 Secondly, it may alter the substrate, i.e. prevent dispersion in conduction velocity and atrial effective refractory periods. Additionally, the presently used device offers ATP that was effective in 57% of episodes. However, also during the OFF period ATP was effective in 24±19% of the episodes. This suggests that part of the ATP-efficacy relates to spontaneous termination of AF during ATP. As septal pacing was most effective, shortening of total atrial activation time and reduction of dispersion of atrial refractoriness and conduction velocity, i.e. modification of the substrate, seems essential.

At baseline, quality of life was importantly reduced compared to age and sex-matched healthy controls. Nevertheless, despite a reduction in the AF burden, we observed no change in the quality of life, nor in the severity and frequency of symptoms, nor in fatigue. On one hand, this may be explained by the fact that the observed reduction in the AF burden, also in the septal lead placement group, was too small to improve quality of life. On the other hand, pacing with a lower rate of 70 ppm in combination with preventive and termination pacing therapies may have offset the beneficial effects of the AF burden reduction.

Finally, one of our findings may be of clinical significance. Whereas palpitations were only present on the day of a symptomatic AF episode, fatigue was also present during the first two days thereafter. Indeed, AF patients always complain about fatigue outlasting the AF episode, which their social environment does not always understand. The present data may add to the understanding that AF may also severely impair physical and social activities beyond an AF paroxysm.

Limitations

A limited number of patients has been included in this pilot study. This precludes definite conclusions, but it may be used to generate hypotheses. Possibly, if more patients were randomized and septal lead position was achieved in a higher percentage of patients, the outcome might have been different, also for the quality of life results. In addition, in studies like ours, AF burden is not normally distributed and usually shows a high spontaneous inter- and intra-patient variability, which has a negative impact on statistical power and impairs the ability to identify patients as responders or nonresponders.50,51 Even patients with a very low AF burden were included, which may have further affected the outcome negatively. We
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used a one month washout period between treatment periods in this crossover study design in order to combat the possible effects of ongoing atrial remodeling impairing the outcome of the patients who were first randomized to have the therapy 'OFF'. Nevertheless, we observed a trend for a period effect.

Conclusions

The present pilot study, albeit small, suggests that pacing in AF may significantly reduce the AF burden. However, it did not reveal a clinically relevant effect on the patients' quality of life and the reduction of symptoms. Although it requires further study, it seems to be most effective if septal pacing is realized. This may have future significance, probably also in heart failure patients treated with cardiac resynchronization as compensation for the long interatrial conduction delay. Whether additional preventive pacing and termination therapies offer additional value is currently being investigated in the Study of Atrial Fibrillation Reduction (SAFARI).52

ACKNOWLEDGMENT

This study was supported by Medtronic Inc. We thank Hindrik W.J. Robbe, PhD, and Rogier Kessels, PhD, for their valuable contributions to the study.

APPENDIX

The following people participated in 'The Features in AT500™ study; Chances for patients with Episodes of atrial Tachyarrhythmia without bradycardia indication for pacing': Medical Center Alkmaar, Alkmaar - J.H. Ruiter; Medisch Spectrum Twente, Enschede - G.P. Molhoek; Antonius Hospital, Sneek - D. De Waard; Cathernia Hospital, Eindhoven - A. Meijer; Sint Franciscus Hospital, Rotterdam - R. Van Mechelen; Medical Center Haaglanden, Den Haag - L.H. Savalle; University Medical Center Groningen, Groningen - M.E.W. Hemels, A.C.P. Wiesfeld, I.C. Van Gelder.
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