New Insights Into the Initiation of Atrial Fibrillation
A Detailed Intraindividual and Interindividual Analysis of the Spontaneous Onset of Atrial Fibrillation Using New Diagnostic Pacemaker Features

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Background—This study investigated onset scenarios of atrial fibrillation (AF), the first phase of the Atrial Fibrillation Therapy (AFT) trial, to determine potential arrhythmogenic triggers as targets for atrial pacing algorithms that have been proposed for prevention of AF.

Methods and Results—Ninety-eight patients (58 men; age 65 ± 11 years) with recurrent, symptomatic, drug-refractory AF and a conventional pacemaker indication in 31 of 98 received a dual-chamber pacemaker. Using novel diagnostic pacemaker features AF onset scenarios were prospectively evaluated in 612 AF episodes during a 2-month monitoring period, with atrial pacing limited to 40 bpm. The most common onset scenario was premature atrial complexes (PACs) before AF (48% onsets per patient), followed by bradycardia (33%), sudden onset (17%), and tachycardia (0%). Combinations of onset scenarios were frequent (median 2 different scenarios per patient). A main study finding was the significance of repetitive AF, with 33% of onsets per patient being initiated within 5 minutes of a previous AF episode. Sudden onsets were more frequent among patients with than without repetitive AF (24% versus 0% onsets per patient, \( P = 0.011 \)), whereas the proportion of PACs before AF was not statistically different (50% versus 37%, \( P = 0.52 \)); however, patients with repetitive AF had more PACs per hour (72 versus 29, \( P = 0.023 \)) and a higher number of AF episodes per day (17 versus 0, \( P = 0.001 \)) and were more likely to have at least 1 PAC-related onset (90% versus 53%, \( P < 0.0001 \)).

Conclusions—Novel diagnostic pacemaker features allowed a detailed individual analysis of rate and rhythm changes before AF and thus uncovered a substantial intraindividual and interindividual variability of AF onset scenarios. (Circulation. 2006;113:1933-1941.)

Key Words: arrhythmia ■ pacing ■ atrial fibrillation ■ onset mechanism

Atrial-based pacing has emerged as a new concept for prevention of atrial fibrillation (AF) over the past 10 years. Prospective randomized pacing trials reported significantly lower incidences of AF with physiological pacing than with ventricular pacing in patients with symptomatic bradycardia.1–3 In patients with a history of AF, novel pacing strategies including sophisticated pacing algorithms were evaluated; however, their efficacy for AF suppression remains unclear.4–10

Clinical Perspective p 1941

Future applications of pacing for prevention of AF will depend on the successful elimination of triggers that initiate AF. Our current knowledge of the complex nature of AF initiation is very limited. From anecdotes and small clinical studies, AF initiation has been linked to the occurrence of bradycardia and premature atrial complexes (PACs).11–14 Recent electrophysiological studies suggested that pacing may render atrial activation and repolarization more homogeneous by eliminating bradycardia, suppressing PACs, and lengthening the coupling interval of PACs, thereby preventing the initiation of AF.15

The Atrial Fibrillation Therapy (AFT) study investigated the safety and efficacy of conventional pacing and specific trigger-based pacing algorithms for AF suppression. The aim of the present study was to analyze the type and frequency of heart rate and rhythm changes that preceded the onset of AF during the monitoring period of AFT.
The AFT trial was a prospective, randomized, multicenter study conducted in 12 countries in Europe and Canada at 35 study centers. The study protocol consisted of 4 consecutive study periods: (1) monitoring, (2) conventional pacing versus no pacing, (3) all preventive algorithms versus conventional pacing, and (4) single preventive algorithm versus conventional pacing. By protocol, all patients completed all study periods. The study protocol was approved by the ethics committee at all participating centers, and all patients gave their informed written consent before inclusion in the study. The present study reports the results of the monitoring period of AFT.

**Methods**

The onset of an AF episode was detected when an atrial rate \( \geq 200 \text{ bpm} \) was sensed during 6 consecutive ventricular beats. AF termination was defined as an atrial rate \( \leq 100 \text{ bpm} \) during 10 ventricular beats. Thus, the shortest detection of AF consisted of 6 ventricular beats with an atrial rate \( \geq 200 \text{ bpm} \). The presence of AF was confirmed by manual inspection of the stored marker ECGs and rate-profile diagrams at the onset of AF with the following criteria: (1) presence of irregular interatrial intervals, (2) interatrial intervals of 250 ms and shorter, and (3) irregular atrio-ventricular conduction. A minimum of 12 onset recordings per patient comprising the first 3 and last 9 AF detections during monitoring were available for analysis. A PAC was defined as an atrial sensed beat with a rate \( > 100 \text{ bpm} \) and at least 15 bpm faster than the mean rate in AF. AF onsets were characterized according to 11 predefined onset triggers condensed to 4 onset categories: PAC-related, bradycardia-related, tachycardia-related, and sudden onset. Detailed definitions for each onset trigger and category are given in Table 1. The reliability of counter data depends on correct AF detection by the pacemaker, counter data analysis was restricted to patients with appropriate AF onset recordings only. As a clinical AF severity measure, the number of symptomatic AF episodes before study inclusion was documented for all patients and categorized into 3 groups: 3 to 10, 11 to 100, or \( > 100 \) AF episodes in 3 months. AF onset analysis was based on the atrial rate and PAC frequency histograms of the 5 minutes before AF and rate-profile diagrams with marker ECGs of the preceding 10 seconds of a maximum of 12 AF episodes per patient. Inappropriately detected AF onset recordings (n=357 of 969 AF detections) due to far-field sensing, 2:1 block (n=50) or the spontaneous AV conduction time and the atrial blanking period (50 ms [first quartile 50; third quartile 100]).

**AF Detection**

AF detection was performed with the pacemaker-implemented Selection AF 1.0 diagnostic software (Vitatron BV). This allowed the recording of AF irrespective of other operational pacemaker settings. In the present study, the onset of an AF episode was detected when an atrial rate \( \geq 200 \text{ bpm} \) was sensed during 6 consecutive ventricular beats and AF termination when the atrial rate was sensed at \( < 200 \text{ bpm} \) during 10 ventricular beats.

### TABLE 1. Definition of 11 Onset Trigger and 4 Onset Categories

<table>
<thead>
<tr>
<th>Onset Category and Trigger</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAC-related</td>
<td></td>
</tr>
<tr>
<td>Short run</td>
<td>( \geq 2 ) PACs or TS beats in a row with either intervening AS or intervening AP occurring within 20 beats before onset</td>
</tr>
<tr>
<td>Multiple preceding PACs</td>
<td>( \geq 2 ) Isolated PACs within last 20 beats</td>
</tr>
<tr>
<td>Short-long</td>
<td>PAC—post-PAC pause—onset</td>
</tr>
<tr>
<td>PAC trend increase</td>
<td>( \geq 3 \times [\text{PACs/min count during storage period}] ) within 5 minutes before onset</td>
</tr>
<tr>
<td>Bradyarrhythm-related</td>
<td></td>
</tr>
<tr>
<td>Sudden rate drop</td>
<td>Rate decrement ( &gt; 15 \text{ bpm} ) within last 4 beats</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Rate ( &lt; 60 \text{ bpm} ) during last 10 AS beats</td>
</tr>
<tr>
<td>Rate decline</td>
<td>Rate decrement ( &gt; 30 \text{ bpm} ) within last 5 minutes</td>
</tr>
<tr>
<td>Bradyarrhythm-tachycardia</td>
<td>Rate variations ( &gt; 30 \text{ bpm} ) during last 20 beats</td>
</tr>
<tr>
<td>Tachycardia-related</td>
<td></td>
</tr>
<tr>
<td>Sudden rate increase</td>
<td>Rate increment ( &gt; 15 \text{ bpm} ) within last 4 beats</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Rate ( &gt; 100 \text{ bpm} ) during last 10 AS beats</td>
</tr>
<tr>
<td>Rate increase</td>
<td>Rate increment ( &gt; 30 \text{ bpm} ) within last 5 minutes</td>
</tr>
<tr>
<td>Sudden onset</td>
<td>None of the above</td>
</tr>
</tbody>
</table>

TS indicates tachy sensed beat; AS, atrial sensed beat; and AP, atrial paced beat.

**Study Sample and Protocol**

Patients who had experienced drug-refractory (\( \geq 2 \) ineffective antiarrhythmic drugs) paroxysms of AF for at least 1 year with \( \geq 3 \) recurrences (1 ECG-documented) in the 3 months before study inclusion were asked to participate in the AFT trial. An indication for pacemaker implantation according to current guidelines was not required for study inclusion. Patients with severe heart failure, unstable angina, recent myocardial infarction, and treatable causes of AF were excluded from the trial. Physicians were asked to consecutively enroll all patients at their study centers who complied with the inclusion and exclusion criteria of the trial.

After the implantation of a Vitatron Selection DDDR pacemaker (Vitatron BV, Arnhem, the Netherlands) and a 2- to 4-week period of lead maturation, all patients entered the 2-month monitoring period with atrial pacing limited to \( 40 \text{ bpm} \). Study data were obtained from the extended pacemaker memory at the end of the monitoring period. All patients who completed the monitoring period and presented with pacemaker-stored diagnostic data were enrolled in the present analysis if they had experienced at least 1 appropriately device-detected recurrence of AF and had been able to tolerate \( 40 \text{ bpm} \) pacing during monitoring.

**Data Acquisition and Analysis**

AF severity data retrieved from the pacemaker counter included the number of AF episodes per day; AF burden (%), defined as the total time in AF/follow-up period; and the total number of PACs per hour. Because the reliability of counter data depends on correct AF detection by the pacemaker, counter data analysis was restricted to patients with appropriate AF onset recordings only. As a clinical AF severity measure, the number of symptomatic AF episodes before study inclusion was documented for all patients and categorized into 3 groups: 3 to 10, 11 to 100, or \( > 100 \) AF episodes in 3 months. AF onset analysis was based on heart rate and PAC frequency histograms of the 5 minutes before AF and rate-profile diagrams with marker ECGs of the preceding 10 seconds of a maximum of 12 AF episodes per patient. Inappropriately detected AF onset recordings (n=357 of 969 AF detections) due to far-field sensing, 2:1 block pattern, or undersensing were excluded from the onset analysis. AF onset scenarios were characterized according to 11 predefined triggers condensed to 4 onset categories: PAC related, bradycardia related, tachycardia related, and sudden onset. Detailed definitions for each onset trigger and category are given in Table 1. The circadian distribution of AF onsets (night, 6 PM to 6 AM) was evaluated and the duration of AF episodes categorized into seconds, minutes, hours, or days. If 2 AF episodes were separated by \( < 5 \) minutes of sinus rhythm, the succeeding episode was called repeti-
tive AF (early < 1 minute, late 1 to 5 minutes). Each AF onset was analyzed by 2 independent observers.

Statistical Analysis

Variables are reported as median (first quartile; third quartile), except age. For analysis of the relationship between the number of AF episodes per day, AF burden (%), and PACs per hour, the Spearman rho coefficient was calculated. A Kruskal-Wallis test was used to compare the number of pacemaker-documented versus clinical AF episodes. Onset analysis was performed on a maximum of 12 AF onset recordings per patient (comprising the first 3 and last 9 recordings during monitoring). To account for the within-patient clustering of AF episodes, a cluster level analysis was performed by calculating the median number of triggers/total number of episodes per patient, as well as the median number of trigger episodes in daytime/total number of trigger episodes per patient. A Mann-Whitney U test was used to compare values between patients with and without repetitive AF and patients with and without a conventional pacemaker indication. Two-sided probability values of < 0.05 were considered statistically significant.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Study Sample

Of 132 patients enrolled in the AFT trial and completing the monitoring period, 98 (mean age 65 ± 11 years, 58 males) were eligible for the present analysis. A total of 34 patients were excluded, 10 owing to intolerability to DDD 40-bpm pacing and 24 because of missing onset data.

Among the 98 patients analyzed, coronary artery disease was present in 12, cardiomyopathy in 5, valvular heart disease in 9, other heart disease in 2, and hypertension in 28. Left atrial diameter on echocardiography was > 40 mm in 26 of 48 patients. Before study enrollment, 26 patients were taking class I antiarrhythmic drugs and 53 were taking class III antiarrhythmic drugs. The conventional indication for pacing was sick sinus syndrome in 26 patients and conduction system disease in 5. All patients had frequent recurrent symptomatic AF: In the 3 months before inclusion, 12 patients had an estimated 3 to 10 AF episodes, 12 patients had 11 to 100, and 76 had > 100 AF episodes.

Pacemaker-Documented AF

The device classified 969 episodes in 98 patients as AF. The investigators confirmed 612 episodes as correctly detected onsets of AF on the basis of detailed analysis of rate-profile diagrams. Examples of recordings illustrating the different onset scenarios of AF are shown in Figure 1. All 357 incorrectly detected AF onsets (37%) were excluded from the final analysis of AF onset scenarios (46 onsets due to far-field sensing, 80 due to undersensing, and 167 due to 2:1 block). In 64 recordings, an AF onset was not definable owing to multiple atrial salvos. An example
of AF overdetection and of AF underdetection is given in Figures 2A and 2B.

At least 1 inappropriately detected AF onset was recorded in 45 of 98 patients. Because the reliability of counter data essentially relies on the appropriate detection of AF, counter data analysis, eg, AF frequency and burden, was performed in the remaining 53 patients who presented with appropriate AF onset recordings only. The median number of AF episodes per day was 8 (1; 51), and the median AF burden amounted to 6% (2%; 22%), with wide variation among the study sample, as shown in Figure 3. The number of AF episodes per day correlated weakly with AF burden ($r_s=0.30, P=0.024$). The median number of PACs per hour was 48 (18; 258), with a significant correlation with the number of AF episodes per day ($r_s=0.586, P<0.0001$) but not with AF burden ($r_s=-0.001, P=0.10$). The number of pacemaker-documented AF episodes per month was not significantly different between patients with few (3 to 10), frequent (11 to 100), and very frequent (>100) symptomatic AF episodes in the 3 months before study enrollment (267 versus 322 versus 244 pacemaker-documented AF episodes per month; $P=0.74$).

**Onset and Duration of AF**

The subsequent analyses are based on 612 rate-profile diagrams from 98 patients, with a median of 6 (2; 10) AF onsets.

**Figure 2.** Device recordings of incorrectly detected AF onsets. A, Oversensing of far-field R waves in the atrial channel. The atrial blanking period after ventricular depolarization was programmed to 50 ms. Intermittently, the ventricular depolarization was sensed in the atrial channel at a fixed ventriculoatrial interval of 51 to 60 ms (-----). B, Intermittent underdetection of an atrial tachyarrhythmia due to a 2:1 atrial sensing block pattern. Intermittently, the recording appears to show a sinus tachycardia (-----) at an atrial cycle length (CL) of 422 to 455 ms; however, the CL is about twice the CL of AF at the end of the recording (AA CL 217 to 244 ms; ----). This is due to the nondetection of every other atrial event, concealed by the atrial blanking period during high ventricular rates. • indicates atrial sensed beat (AS); ◯, atrial tachy sensed beat (TAS); ▼, PAC; ▼, ventricular sensed beat (VS); and ■, ventricular paced beat (VP).
The median AF episode duration per patient was 127 seconds (29.5 seconds; 160 minutes). There were 276 of 612 episodes that lasted for seconds, 173 for minutes, 128 for hours, and only 35 for >1 day. An almost equal number of episodes started at night (295 of 612) and in the daytime (317 of 612). AF onsets occurred during night and day in 52 (53%) of 98, at night only in 26 (27%) of 98, and only during the day in 20 patients (20%).

Type and Frequency of Rate and Rhythm Changes Before the Onset of AF

Overall Distribution of Onset Categories

Analysis of 612 AF onset scenarios identified 441 (72%) AF episodes with and 171 (28%) without rate or rhythm changes before AF (Table 2). PACs were seen before AF in 48% of onsets per patient (11%; 67%), bradycardia in 33% (0%; 91%), tachycardia in 0% (0%; 8%), and sudden onsets in 17% (0%; 49%). Most patients (79%) had at least 1 PAC-related onset. Seventy percent of patients had at least 1 bradycardia-related and 27% at least 1 tachycardia-related onset. Initiation of AF without preceding rate or rhythm changes was found in 67% of all patients.

Combinations of onset categories were frequent, occurring in 21% of all AF episodes in 54% of all patients. The most common combination was PACs and bradycardia (110/612, 18%) in 47% of all patients, whereas the combination of PACs and tachycardia, bradycardia and tachycardia, and PACs, bradycardia, and tachycardia was present in only 3%, 1%, and 0.5% of episodes and in 11%, 5%, and 2% of patients, respectively.

Intraindividual Onset Patterns

A per-patient analysis revealed a great intraindividual variability of onset triggers, with a median of 3 (2; 5) different triggers per patient (range 0 to 7) and 2 (2; 3) different onset categories per patient (range 1 to 4). Despite this considerable variation of AF onset scenarios, a characterization of patient-specific patterns was attempted.

Figures 4A and 4B illustrate the number of patients and the proportion of PAC- and bradycardia-related AF onsets to the total number of AF episodes per patient. This frequency distribution indicates a peak at 0% for both onset categories. Thus, a substantial number of patients showed neither PAC-related (21%) nor bradycardia-related (30%) triggers in any of their AF onsets. Conversely, only a few patients had 1 specific onset category that preceded all their AF episodes. No rate or rhythm changes at all before AF were detected in only 8% of patients.

Circadian Distribution of Onset Categories

The preceding heart rate of AF was different during night and day: Bradycardia-related onsets were seen more often at night (80% of onsets per patient [0%; 100%]), whereas tachycardia-related onsets were more common during daytime (80% of onsets per patient [0%; 100%]). PAC-related onsets were found equally frequently during day and night (50% of

<table>
<thead>
<tr>
<th>Onset Category and Trigger</th>
<th>Onsets (n=612), (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAC-related</td>
<td>289 (47)</td>
</tr>
<tr>
<td>Short run</td>
<td>28</td>
</tr>
<tr>
<td>Multiple preceding PACs</td>
<td>20</td>
</tr>
<tr>
<td>Short-long</td>
<td>9</td>
</tr>
<tr>
<td>PAC trend increase</td>
<td>90</td>
</tr>
<tr>
<td>Multiple PAC-related triggers</td>
<td>142</td>
</tr>
<tr>
<td>Bradycardia-related</td>
<td>241 (39)</td>
</tr>
<tr>
<td>Sudden rate drop</td>
<td>26</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>203</td>
</tr>
<tr>
<td>Rate decline</td>
<td>2</td>
</tr>
<tr>
<td>Bradycardia-tachycardia</td>
<td>4</td>
</tr>
<tr>
<td>Multiple bradycardia-related triggers</td>
<td>6</td>
</tr>
<tr>
<td>Tachycardia-related</td>
<td>43 (7)</td>
</tr>
<tr>
<td>Sudden rate increase</td>
<td>24</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>16</td>
</tr>
<tr>
<td>Rate increase</td>
<td>2</td>
</tr>
<tr>
<td>Multiple tachycardia-related triggers</td>
<td>1</td>
</tr>
<tr>
<td>Sudden onset</td>
<td>171 (28)</td>
</tr>
</tbody>
</table>

Figure 3. Individual AF burden (%) (A) and number of AF episodes per day (B). The horizontal bar indicates median values.
onsets per patient (0%; 100%). No rate and rhythm changes before AF were seen in 70% of onsets per patient (0%; 100%) during daytime.

Repetitive AF

Initiation of AF within 5 minutes was observed in 50% of all episodes (305/612) and 69% of all patients (68/98). Repetitive AF initiated early in 225 of 305 onsets and occurred during daytime in 134 of 225 episodes. Figure 5A shows the distribution of onset categories in repetitive and nonrepetitive AF. In a per-patient analysis, repetitive AF was found in 33% (0%; 67%) of onsets, initiating early in 17% (0%; 50%) of onsets. Figure 5B shows the number of patients and the proportion of repetitive AF to the total number of episodes per patient.

Patients with as compared to those without repetitive AF had a significantly higher proportion of sudden onsets among their AF episodes (median [number of sudden onsets/total number of episodes] per patient 0.24 [0.09; 0.49] versus 0.00 [0.00; 0.50], *P* = 0.011) and showed a trend toward fewer bradycardia-related onsets (0.25 [0.00; 0.72] versus 0.50 [0.00; 1.00], *P* = 0.092), whereas the proportion of PACs that preceded AF was not different between patient groups (0.50 [0.23; 0.67] versus 0.37 [0.00; 1.0], *P* = 0.52). Nevertheless, patients with repetitive AF were more likely to have at least 1 PAC-related onset (90% versus 53%, *P* < 0.0001) and at least 1 sudden onset (82% versus 33%, *P* < 0.0001). Bradycardia- and tachycardia-related AF onsets were not statistically different between patient groups (74% versus 63%, *P* = 0.31 and 29% versus 20%, *P* = 0.33, respectively). With respect to AF severity, assessed only in the 53 patients without a single false AF onset detection, patients with repetitive AF (n = 39/53; 74%) compared with patients without repetitive AF (n = 14/53; 26%) had more AF episodes per day (17 [5; 96] versus 0 [0; 2.5] *P* = 0.001) and more PACs per hour (72 [30; 329] versus 29 [5; 61] *P* = 0.023). However, AF burden was not different (7.0% [3.0%; 22.0%] versus 5.5% [0.0%; 27.0%], *P* = 0.52).

AF Onset and Pacemaker Indication

A standard indication for pacemaker implantation was present in 31 of 98 patients; 67 patients had “AF only.” Patients with a pacemaker indication were more likely to have had at least 1 bradycardia-related onset (84% versus 64%, *P* = 0.048) and showed a trend toward more PACs preceding AF (90% versus 73%; *P* = 0.055). The proportion of at least 1 sudden-onset episode between patients with and without a pacemaker indication was not statistically different (67% versus 68%, *P* = 0.96). Repetitive AF was found in patients with a pacemaker indication.

Figure 5. A, Frequency of AF episodes according to onset categories. Data are shown for AF episodes without preceding AF (hatched bars) and for repetitive AF episodes (solid bars). B, Frequency of patients according to their proportion of repetitive AF to the number of onsets, categorized in groups of 5%.

Figure 6. Proportion of onset categories to all onsets per patient in patients with (n = 31) vs without (n = 67) a standard pacemaker indication.
maker indication and in patients with “AF only” (81% versus 64% of patients, \(P=0.10\)). Analysis of the proportion of onset categories to all onsets per patient revealed a significantly higher proportion of sudden onsets in patients with “AF only” (0.33 [0.00; 0.58] versus 0.10 [0.00; 0.22], \(P=0.044\)) and a trend toward fewer PACs (0.40 [0.00; 0.67] versus 0.58 [0.25; 0.80], \(P=0.07\)), as shown in Figure 6. AF severity was not statistically different between patient groups (17 of 53 patients with pacemaker indication [32%]; 36 of 53 patients with “AF only” [68%]), with a median AF frequency of 16 (1; 42) versus 8 (1; 68) episodes per day (\(P=0.74\)), 50 (21; 311) versus 48 (16; 222) PACs per hour (\(P=0.73\)), and 6% (1%; 23%) versus 8% (2%; 22%) AF burden (\(P=0.75\)).

Discussion

Atrial-based continuous or triggered overdrive pacing has been proposed as a new technique to prevent AF by eliminating bradycardia and suppressing atrial ectopy, both considered potential AF triggers. However, the exact number, duration, and timing of symptomatic and asymptomatic AF episodes, as well as the frequency and type of onset triggers, are unknown. The identification of patient-specific AF patterns and onset scenarios may be of importance for selecting pacing responders and an efficient AF pacing strategy. The present investigation showed that continuous diagnostic monitoring capabilities of implanted devices can be used for the detailed analysis of AF onsets, thereby improving the understanding of AF initiation and allowing a comparison of pacing efficacy and patient-specific AF onset scenarios in the AFT trial.

AF Characteristics

In the present analysis, the number of pacemaker-documented AF episodes did not differ between patients with few or frequent symptomatic AF episodes before study inclusion. This finding supports results from Holter studies that showed that most AF is asymptomatic\(^16,17\) and suggests that clinical and pacemaker-derived AF study end points may provide complementary information in pacing trials. The latter hypothesis is supported by recent findings of a subgroup analysis in the ASPECT trial (The Atrial Septal Pacing Efficacy Clinical Trial), which reported a reduction of symptomatic AF frequency during septal pacing without a corresponding change in pacemaker-documented AF burden.\(^9\) The short median duration of AF episodes of seconds or minutes in the majority of patients in the present study (72%) is comparable to the frequent detection of short AF episodes in other pacing trials.\(^5,10\) This finding may explain the occurrence of asymptomatic AF episodes and may lead to an underestimation of the actual presence of AF; however, the clinical relevance of asymptomatic or short-lived AF and its influence on mortality and morbidity is as yet unknown.

AF Onset Characteristics

The present study is the first to provide extensive information on the type and frequency of rate and rhythm changes before spontaneous AF. There is a striking overall variability of AF onset scenarios and a great intraindividual variability, with a median of 2 different onset categories per patient, which emphasizes the complex nature of AF initiation. These results confirm observations from Holter studies by Hnatkova et al.,\(^18\) who had previously described an inconsistent initiation of AF, both across a patient population and within individual patients. The most common onset scenario was an increase in PAC frequency in 48% of AF onsets per patient, followed by bradycardia in 33% of AF onsets per patient. Because of the nonuniform initiation of AF, all attempts to characterize patients’ AF initiation solely by the presence of specific triggers failed; however, a major proportion of patients revealed either no PAC-related (21%) or no bradycardia-related (30%) AF onset scenario. A minority of patients presented with sudden onsets (8%) or preceding tachycardia (1%) only; in these patients, the concept of atrial pacing for AF prevention is most likely to fail.

PAC-Related AF Onset

The present study is the first to analyze PAC density in the seconds before AF. In contrast, previous pacing trials reported overall counts of PACs in pacemaker patients.\(^8,9,19\) The majority of patients in the present study (79%) showed at least 1 AF episode anticipated by an increase in PAC frequency, with this being more frequent in patients with repetitive AF. Changes in PAC frequency and the occurrence of repetitive AF may reflect an increased atrial vulnerability that facilitates AF initiation. The latter is supported by the finding that the overall PAC density counts correlated positively with the number of AF episodes but not with AF burden. Previous pacing trials investigating the efficacy of preventive overdrive pacing demonstrated significant reductions in overall PAC counts but not in the number of AF episodes or burden.\(^8,9,19\) However, those studies did not take PAC density immediately preceding AF onset into consideration. PAC suppression algorithms may be effective in patients with frequent PACs before AF. The overall relevance of PACs as a predictor for preventive pacing efficacy remains to be determined.

Bradycardia

Previous pacing trials have shown a lower incidence of chronic AF in sick sinus syndrome patients with AAI/DDD versus VVI pacing, which suggests bradycardia as an important factor for the development of AF in these patients.\(^1–3\) Limited information from Holter studies has been available to show only an 8% to 10% incidence of AF with preceding bradycardia in a general AF population.\(^18,20\) The present study is the first to extend the knowledge on rate and rhythm changes before AF that included patients without a pacemaker indication in the analysis. Patients with “AF only” showed a considerable amount of onsets without any rate or rhythm changes before AF (33% of onsets per patient). Intriguingly, however, a heart rate <60 bpm preceding AF was seen in patients with as well as without sick sinus syndrome (42% and 25% of onsets per patient, respectively). This finding supports the idea that bradycardia is a universal phenomenon before AF irrespective of the presence of sick sinus syndrome and that it may play a role during AF initiation. From Holter studies, it has been hypothesized that bradycardia-associated AF is vagally induced in patients...
without sick sinus syndrome.11 Coumel et al21 described a subset of patients without structural heart disease who were unresponsive to β-blocker therapy in whom the elimination of bradycardia by pacing resulted in the prevention of AF recurrences. In the present analysis, bradycardia preceding AF was seen primarily during the night; conversely, tachycardia and sudden onsets were observed during the day. Moreover, a temporal clustering of AF initiations was identified in 27% of patients with AF that began at night and in 20% during daytime only. Thus, autonomic tone may have played a role in AF initiation in some of the patients studied.

Repetitive AF

The issue of early initiations of AF after AF termination has been addressed in only a few clinical postcardioversion studies.22–25 Previous pacemaker trials used the number and duration of mode-switch episodes as a surrogate parameter for AF; they were unable to validate AF onset detections by the pacemaker except by conventional Holter recordings and neglected to make a detailed exploration of temporal AF patterns. The present study is the first to reliably describe the temporal clustering of AF episodes using extensive data-logging capabilities and an implemented AF diagnostic software that allows AF recordings to be made independent of operational pacemaker settings. A main study finding was the high prevalence of repetitive AF, eg, recurrences of AF within 5 minutes after termination of the preceding episode, seen in 50% of AF episodes and 69% of all patients. These frequencies compare with pacemaker data reported by Israel et al26 of immediate AF recurrences of within 1 minute in 66% of patients and 39% of episodes. Electrophysiological studies have attributed the phenomenon of early AF recurrences to a vulnerable state of the atrium immediately after AF termination that favors AF initiation.27 This goes along with the observation that the overall PAC count and the AF episode frequency but not burden was higher in patients with repetitive AF.

The common appearance of repetitive AF both in patients with (25/31, 81%) and without (43/67, 64%) a conventional pacemaker indication described for the first time in the present study will provide a challenging task for preventive pacing strategies. The efficacy of overdrive atrial pacing after AF termination in suppressing early repetitive AF episodes has been explored in only a few studies.28–30 The frequent observation of sudden onsets in patients with repetitive AF (33% of onsets per patient versus 10% in patients without repetitive AF) may in part explain the failure of these trials to successfully prevent AF recurrences.

Study Limitations

The present analysis is based on marker ECGs, not on intracardiac electrograms, which limits the validity of atrial signal interpretation. Second, the storage capacity of the pacemaker was limited to 12 AF onset recordings per patient and follow-up. Although most patients experienced more AF episodes during follow-up, the onset analysis represents a sample of onsets per patient, comprising the first 3 and the last 9 recordings during monitoring. Thus, the study is unable to determine the extent to which bradycardia or PACs that are associated with AF occur at times when AF is not initiated. We are therefore unable to determine the sensitivity and specificity of AF onset scenarios in the present analysis. Furthermore, the study provided observations on rate and rhythm changes rather than definite insights into the substrate and the electrophysiological mechanisms underlying the initiation of AF. We cannot exclude the possibility that the patients participating in the present study are a biased sample, favoring those with frequent attacks of symptomatic AF recurrences and refractory to antiarrhythmic drug treatment while excluding patients with severe symptomatic bradycardia that requires sufficient pacing support. Finally, false-negative or false-positive onset detections by the pacemaker accounted for 37% of onset recordings and had to be excluded from the analysis. Because the reliability of counter data, eg, AF episode frequency and burden, depends on the correct detection of AF, the analyses of counter data were confined to patients presenting with valid AF onset recordings only. Technical improvements are required for significant reduction of AF misdetections.

Conclusions

The present study is the first to provide a detailed analysis of spontaneous AF, including severity, episode duration, night and day distributions, and rate and rhythm changes before the onset of AF. The results emphasize the importance of PAC-related and bradycardia-related onset scenarios in an unselected patient population with and without a pacemaker indication and drug-refractory AF. Repetitive AF has been defined as a major phenomenon in the complex nature of AF initiation. The data collected showed not only a great inter-individual variability of onset scenarios but also, for the first time, nonuniform rhythm patterns preceding AF in individual patients. AF onset characterization sets the basis for a better understanding of the effects of newly designed atrial pacing algorithms.

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Disclosures

Professor Hoffmann and Professor Edvardsson have received research funding and honoraria from Vitatron BV. Professor Camm served on the Speakers’ Bureau of and/or received honoraria from Vitatron BV. The other authors report no conflicts.

References


**CLINICAL PERSPECTIVE**

Atrial-based pacing has emerged as an additional treatment modality aimed at the elimination of potentially arrhythmogenic triggers of atrial fibrillation, eg, bradycardia, pauses, or premature atrial beats, in patients with a conventional class I or II pacemaker indication. The present study investigated onset scenarios of spontaneous atrial fibrillation using extensive data-logging capabilities of implanted pacemakers that analyzed rate and rhythm changes on a beat-to-beat basis before the onset of atrial fibrillation independently of operational pacemaker settings. The data collected showed not only a great interindividual variability of onset scenarios but also, for the first time, nonuniform rhythm patterns preceding atrial fibrillation in individual patients, which emphasizes the complex nature of atrial fibrillation initiation. The most common onset scenario was an increase in premature atrial complexes before atrial fibrillation. Intriguingly, a heart rate of less than 60 bpm preceding atrial fibrillation was seen in onsets of patients with and without sick sinus syndrome and supports the hypothesis that bradycardia is a universal phenomenon in the initiation of atrial fibrillation. Moreover, the present study is the first to reliably describe the temporal clustering of atrial fibrillation episodes. Repetitive atrial fibrillation, ie, recurrences of atrial fibrillation within 5 minutes after termination of the preceding episode, is a common phenomenon in patients with and without a conventional pacemaker indication and will be a challenging task for any preventive pacing strategy.
New Insights Into the Initiation of Atrial Fibrillation: A Detailed Intraindividual and Interindividual Analysis of the Spontaneous Onset of Atrial Fibrillation Using New Diagnostic Pacemaker Features

Ellen Hoffmann, Neil Sulke, Nils Edvardsson, Jacob Ruiter, Thorsten Lewalter, Alessandro Capucci, Andreas Schuchert, Sabine Janko and John Camm
on behalf of the Atrial Fibrillation Therapy (AFT) Trial Investigators

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