Background—Late recurrence of atrial fibrillation (AF) after radiofrequency ablation remains significant. Asymptomatic recurrence poses a difficult clinical problem as it is associated with an equally increased risk of stroke and death compared with symptomatic AF events. Meta-analyses reveal that no single preablation patient characteristic efficiently predicts these AF recurrences. This study aimed to evaluate the prognostic value of premature atrial complex (PAC) occurrence with regard to the risk of late AF recurrence after radiofrequency ablation.

Methods and Results—The study cohort consisted of 124 patients with 7-day Holter recordings at 6 months post radiofrequency ablation for AF. No patients had AF recurrence before this time. Patients were followed-up every 6 months. Holter-detected PACs were defined as any supraventricular complexes occurring >30% earlier than expected. During a median follow-up of 4.2 years (first quartile to third quartile [Q1–Q3]=1.6–4.5), 32 patients (26%) had late recurrences of AF at a median of 462 days (Q1–Q3=319–1026) post radiofrequency ablation. The number of PACs per 24 hours was 248 (Q1–Q3=62–1026) in patients with and 77 (Q1–Q3=24–448) in patients without recurrence of AF (P=0.02). Multivariate analysis of the risk of late AF recurrence found ≥142 PACs per 24 hours to have a hazard ratio 2.84 (confidence interval, 1.26–6.43), P=0.01.

Conclusions—This study showed that occurrence of ≥142 PACs per day at 6 months after PVI was independently associated with a significantly increased risk of late AF recurrence. These results could have important clinical implications for the design of post-PVI follow-up.
Methods

Patients

The patients included in this study were enrolled in a randomized clinical trial comparing the efficacy of 2 different technical approaches for attaining PVI in highly symptomatic patients with drug-refractory AF. Patients were reviewed at 3, 6, and 12 months and then every 6 months thereafter. At 6 months, follow-up patients had a 7-day Holter monitor recording as a mean of documenting recurrent arrhythmias. The primary end point was defined as recurrence of any atrial arrhythmia >30 s documented by ECG or Holter. A 3-month postprocedure blanking period was used.

In 142 of the 220 study patients, a 7-day Holter recording was performed in conjunction with their 6-month follow-up. Recordings were omitted per protocol in patients who had either documented recurrence of AF (n=29), documented other atrial tachycardia (n=24), or if reblation procedure for symptomatic recurrence of either AF (n=10), other atrial tachycardia (n=3), or both (n=4) had been performed. Eight patients refused or were unable to participate in the recordings.

Of the 142 patients with Holter recordings, 124 were included in this study. These patients were all without recurrence of AF before the end of the 7-day Holter recording at 6 months after the primary procedure. In 17 of the excluded patients, AF recurrence occurred on the 7-day Holter (n=13) or before the Holter recording (n=4). In 1 excluded patient, the Holter recording was corrupted before analysis.

A flowchart of the patient selection process is displayed in Figure 1.

End Points and Means of Recording

All 7-day Holter recordings were performed using DMS Holter ECG recorder model 300-3A and CardioScan Premier 11 (DMS, Stateline, NV) for analyses. Analyses were done by experienced cardiac technicians and reviewed by the responsible investigating cardiologist. PACs were defined as supraventricular complexes occurring >30% earlier than expected compared with the previous RR interval. Any recurrence of ECG or Holter (later than 6 months post procedure) documented sustained AF >30 s duration was considered a primary end point in this study.

Statistics

Characteristics of patients with and without late recurrence of AF were compared statistically. Categorical variables were compared by χ² or Fisher exact test where appropriate. Continuous variables were compared using Kruskal–Wallis or Student t test. Skewed distributions were normalized by logarithmic transformation if necessary. Univariate hazard ratios and 95% confidence intervals were determined by fitting Cox proportional hazard regression models for all patient characteristics and Holter variables. All univariate predictive covariates were selected for multivariate modeling. Where clinically relevant, continuous variables were dichotomized using optimum Youden index (J) derived from receiver operating characteristics curve analysis for cut-point determination. Cox model validity was confirmed by checking of assumptions. The time to AF development from 6-month Holter monitoring was illustrated by the Kaplan–Meier method and significance of stratified analyses estimated by Log-rank test. Patients were censored at the end of follow-up, death, lost to follow-up, or at the time of a second ablation procedure because of

Figure 1. Flowchart of the patient selection process. Details are provided in the methods section. AF indicates atrial fibrillation; and PVI, pulmonary vein isolation.
other atrial tachyarrhythmia. Two-sided \( P \) values of \(<0.05\) were considered statistically significant. SAS version 9.3 (SAS Institute, Cary, NC) was used for all analyses.

**Ethics**

The study was conducted with appropriate approvals of and under the supervision of Sydney West Area Health Service Human Research Ethics Committee and was registered in the Australian New Zealand Clinical Trial Registry. The study complied with the declaration of Helsinki and supplements thereof.

**Results**

**Patients**

Late recurrent events of sustained AF were documented in 32 patients (26%) during a median follow-up of 4.2 years (first quartile to third quartile \([Q1–Q3]=1.6–4.5\)) after 6-month Holter recording. The median time to event was 271 days \((Q1–Q3=121–815)\) after Holter recording. AF occurred in the blanking period of 3 months post ablation in 9 (27%) and 15 (16%) patients with and without later end point of AF recurrence, respectively \((P=0.17)\). The median time to the 6-month Holter recordings from the PVI was overall 190 days \((Q1–Q3=183–207)\), and the median recorded period was 7 days \((Q1–Q3=6–7)\). Five patients died during follow-up, and 3 patients were lost to follow-up at a median of 1109 days \((Q1–Q3=1006–1725)\) and 1058 days \((Q1–Q3=923–1321)\) after the RFA procedure, respectively.

Patient characteristics are displayed in Table 1. The patient groups were similar in comorbidity, medication, echocardiography parameters, and sex. The group who had late AF recurrence was however significantly older \((63±11\) versus \(58±10\) years; \(P=0.02)\), more frequently had the wide antral isolation procedure \((72\%\) versus \(47\%;\ P=0.01)\), and had significantly more PACs \((248 [Q1–Q3=62–1026] versus 77 [Q1–Q3=24–448]; \ P=0.02)\) on their 6-month Holter recording. Among patients who underwent single-ring isolation procedure, the median number of PACs per day was 75 \((Q1–Q3=20–320)\), whereas it was 151 \((Q1–Q3=48–759)\) in patients who had the wide antral isolation procedure \((P=0.10)\). There was a higher proportion of patients with nonparoxysmal AF in the group who later had recurrence but this difference was insignificant \((45\%\) versus \(34\%;\ P=0.25)\).

**PAC Cut Point**

The maximum number of PAC recorded in a 24-hour period during the 7-day Holter recording in each patient was used. To derive a clinically meaningful cut point for the severely left-skewed distribution of PAC, we chose to dichotomize the variable at its diagnostic optimum corresponding to 142 PACs per day. The cut point was found to have the highest Youden index \((J=0.35)\) by receiver operating characteristics curve analysis. The sensitivity and specificity were 72\% and 63\%, respectively. The cut point corresponds to the 54th percentile and is thus close to the median. Twenty-three \((72\%)\) of the patients with later AF recurrence were correctly identified, whereas 34 \((37\%)\) patients without recurrence were falsely found to be at an increased risk.

**Predictive Value**

Patient characteristic associated with the risk of recurrent AF was modeled by univariate Cox proportional hazards regression. Results are shown in Table 2. Age, procedure type, and PAC per day were all significantly associated with a higher risk of AF recurrence. PAC was also tested univariately as a continuous variable after logarithmic transformation \((\text{hazard ratio}, 2.84 [\text{confidence interval}, 1.26–6.43]; \ P=0.04)\). A multivariate model including these variables was fitted. The results showed that \(\geq142\) PACs per day \((\text{hazard ratio}, 2.84 [\text{confidence interval}, 1.26–6.43]; \ P=0.04)\) was the only variable independently associated with an increased risk of late AF recurrence. Both procedure type and age were in this model found to be without predictive value with regard to AF recurrence when adjusted for PAC \(\geq142\) per day.

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Atrial Fibrillation, n=32</th>
<th>No Atrial Fibrillation, n=92</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics at inclusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y(^*)</td>
<td>63±11</td>
<td>59±10</td>
<td>0.024</td>
</tr>
<tr>
<td>Male, sex</td>
<td>25 (78)</td>
<td>73 (79)</td>
<td>0.88</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>4 (13)</td>
<td>12 (13)</td>
<td>0.94</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (41)</td>
<td>40 (43)</td>
<td>0.78</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (6)</td>
<td>5 (5)</td>
<td>0.86</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0)</td>
<td>3 (3)</td>
<td>0.30</td>
</tr>
<tr>
<td>CHADS(_2\geq2)</td>
<td>6 (19)</td>
<td>15 (16)</td>
<td>0.75</td>
</tr>
<tr>
<td>Temporal class of atrial fibrillation at inclusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>18 (56)</td>
<td>60 (65)</td>
<td>0.39</td>
</tr>
<tr>
<td>Persistent</td>
<td>10 (31)</td>
<td>18 (20)</td>
<td></td>
</tr>
<tr>
<td>Long-standing persistent</td>
<td>4 (13)</td>
<td>14 (15)</td>
<td></td>
</tr>
<tr>
<td>Antiarrhythmic medication at 6-mo follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>3 (1)</td>
<td>1 (1)</td>
<td>0.43</td>
</tr>
<tr>
<td>Class II</td>
<td>4 (13)</td>
<td>11 (12)</td>
<td>0.94</td>
</tr>
<tr>
<td>Class III</td>
<td>3 (9)</td>
<td>7 (8)</td>
<td>0.75</td>
</tr>
<tr>
<td>Class IV</td>
<td>2 (6)</td>
<td>5 (5)</td>
<td>0.86</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0.55</td>
</tr>
<tr>
<td>Echocardiography at 6-mo follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction biplane, %</td>
<td>56±8</td>
<td>57±7</td>
<td>0.39</td>
</tr>
<tr>
<td>Left atrial end-systolic volume biplane, mL</td>
<td>60±18</td>
<td>57±18</td>
<td>0.47</td>
</tr>
<tr>
<td>Pulmonary vein isolation ablation procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-ring isolation*</td>
<td>9 (28)</td>
<td>49 (53)</td>
<td>0.014</td>
</tr>
<tr>
<td>Supplementary mitral isthmus line</td>
<td>18 (56)</td>
<td>49 (53)</td>
<td>0.77</td>
</tr>
<tr>
<td>Supraventricular ectopy on 7 day-Holter at 6-mo follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum number of PAC per day*</td>
<td>248 (62–1026)</td>
<td>77 (24–448)</td>
<td>0.021</td>
</tr>
<tr>
<td>Maximum no. of PAC per day, (\geq142) (%)*</td>
<td>23 (72)</td>
<td>34 (37)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(^*\) indicates 2-sided \( P \) values of \(<0.05\).
Arrhythmia-free survival for patients with and without ≥142 PACs per day is displayed in Figure 2. The Log-rank test for significance of difference between strata was highly significant (P=0.0005).

Fifteen of the patients who had late recurrent AF went on to have reablation procedures. Breaches of earlier created isolation lines were found in 11 (73%) patients, whereas 4 (27%) had no detectable breaches. The median time to AF recurrence from primary procedure was 396 days (Q1–Q3=245–715) in patients with PV reconnections and 609 days (Q1–Q3=466–747) in those without evident reconnection (P=0.30). The median number of PAC was 391 (Q1–Q3=18–768) and 95 (Q1–Q3=36–381) for patients with and without PV reconnection, respectively (P=0.51).

### Discussion

The main finding of this study is that ≥142 PACs per day detected by 7-day Holter recordings at 6 months after PVI in drug-refractory and highly symptomatic AF patients are independently associated with a significantly increased risk of late recurrence of AF. As a significant proportion of post-PVI patients have asymptomatic recurrences of AF, this predictive value of PAC has clear clinical implications as a potential tool for determining the intensity of post-PVI follow-up.14–16

Contradictory reports have been published on incidence rates and characteristics of PAC in patients with symptomatic AF without previous ablative therapy compared with healthy subjects.17–19 However, in population-based studies, excessive atrial ectopy has been shown to predict occurrence of new-onset AF, stroke, and death.1 In a single study, the occurrence of PAC before and after RFA for AF was evaluated.12 These results showed a generally high frequency of PAC before ablation procedure (12.8±10.7% of recorded heart beats during 24 hours) and a significant reduction after successful treatment. The reduction was shown to be progressive in the first 6 months after which time it stabilized. On the other hand, patients with recurrence of AF showed an initial decrease in PAC post RFA, but at 6 months, frequency was increased to levels similar to preablation. These phenomena are consistent with the findings from our cohort.

The increased number of PAC in patients with late recurrence of AF after PVI may result from breaches in the isolation lines surrounding the PV. In fact, PV reconnection is reported to be the most frequent electrophysiological mechanism (>95%) of recurrent AF after RFA with PVI.6,20–23 Other evidence indicates that the underlying mechanism might be different in late AF recurrence involving non-PV foci.24 For patients in this study who had reablation procedures after AF recurrence, there was no clear difference in pattern of time to AF recurrence or PAC incidence with regard to PV reconnection. The median number of PAC was higher among patients who underwent wide antral isolation procedures, and the risk of AF recurrence was also higher in this group. A positive correlation between extent of isolated atrial area and lower risk of AF recurrence has previously been reported.25 The difference between procedural approaches could therefore be explained by the difference in the area isolated.

### Table 2. Risk of Late AF Recurrence

<table>
<thead>
<tr>
<th>Effect</th>
<th>Hazard Ratio of Late AF Recurrence</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAC, ≥142/d</td>
<td>3.64 (1.68–7.88)</td>
<td>0.001</td>
</tr>
<tr>
<td>Wide antral isolation procedure</td>
<td>2.57 (1.18–5.61)</td>
<td>0.018</td>
</tr>
<tr>
<td>Age per 5-y increase</td>
<td>1.26 (1.05–1.53)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

No other variables were found to have significant association to the risk of late AF recurrence. AF indicates atrial fibrillation; CI, confidence interval; HR, hazard ratio; and PAC, premature atrial complex.

### Figure 2.

Kaplan–Meier curves of survival time free of recurrence of atrial fibrillation (AF). Kaplan–Meier curve of arrhythmia-free survival stratified by premature atrial complexes (PACs) ≥142 per day. The Log-rank test of difference between strata was highly significant with P=0.0005. PVI indicates pulmonary vein isolation.
Besides PACs, there were no patient characteristics found to be independently associated with late AF recurrence. This is consistent with recent meta-analyses.8,10 Survival rates after stroke associated with AF are increasing, but the subsequent disability and morbidity remain a major concern and reason for systematic follow-up in post-PVI patients.26 Evidence is insufficient and conflicting as to the effect of oral anticoagulant therapy on risk reduction of stroke in post-PVI care, but current guidelines recommend continued oral anticoagulant be CHADS2 (risk score of congestive heart failure, hypertension, age >75 years, diabetes, prior stroke or transient ischemic attack) guided.3,27,28 PAC has been indicated as a possible surrogate marker of AF in studies of stroke of undetermined cause.29 Whether PAC could be used to guide oral anticoagulant therapy remains unknown.

In unselected series of post-PVI patients seen in follow-up clinics, a significant proportion of patients have asymptomatic recurrence of AF.14–16 Current guidelines recommend that post-PVI patients in general be followed-up at a minimum of 3 months after the ablation procedure and then every 6 months for at least 2 years with ECG performed on each occasion.30 A possible additional approach derived from this study could be to use the 6-month Holter data in asymptomatic patients to adjust the frequency and intensity of follow-up. More frequent and extended follow-up might be warranted in patients with a PAC incidence above a certain number. The present results do not allow recommendation of any specific cut point for the critical number of PAC. However, as the optimum diagnostic cut point was relatively low, the study indicates that attention to patient follow-up should be increased in the event of even limited PAC occurrences.

The sensitivity and specificity of PAC found in this study compared with other diagnostic tools used in clinical decision making but leave room for improvement in the search for an optimal predictive tool for late AF after PVI.31 However, no other parameter had equal predictive capabilities or added to its diagnostic value. Future studies are required to confirm the value of these findings and establish a robust cut point for clinical application.

Limitations

This study was performed as a post hoc analysis of a previous clinical trial with all the statistical limitations implied therein.

The included patients were all free of recurrent arrhythmia at 6 months after a single PVI procedure. Our results of PAC as a predictive measure derived from 6-month Holter monitoring are thus limited to similar patient populations and may not be directly extrapolated to those who have undergone multiple ablation procedures.

The resolution of our Holter recordings does not allow for detailed analyses of P wave morphology and thus limits us from further investigations of the possible focal origin of recorded postablation PAC.

Conclusions

This study shows that occurrence of ≥142 PACs per day at 6 months after PVI is independently associated with significantly increased risk of late AF recurrence. These results could have important clinical implications in the design of post-PVI follow-up.

Sources of Funding

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Disclosures

None.

References


Atrial Ectopy Predicts Late Recurrence of Atrial Fibrillation After Pulmonary Vein Isolation

Uffe J.O. Gang, Chrishan J. Nalliah, Toon Wei Lim, Aravinda Thiagalingam, Pramesh Kovoor, David L. Ross and Stuart P. Thomas

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