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

Running title: Gang et al.; Atrial ectopy predict late AF recurrence after PVI

Uffe J.O. Gang, MD, PhD1; Chrishan J. Nalliah, MBBS, FRACP2; Toon W. Lim, MBBS, FRACP, PhD2; Aravinda Thiagalingam, MBBS, FRACP, PhD2; Pramesh Kovoor, MBBS, FRACP, PhD2; David L. Ross, MBBS, FRACP, PhD2; Stuart P. Thomas, BMed, FRACP, PhD2

1Gentofte University Hospital, Department of Cardiology, Copenhagen, Denmark; 2Department of Cardiology and University of Sydney, Westmead Hospital, Sydney, Australia

Correspondence:
Uffe Jakob Ortved Gang, MD, PhD
Gentofte University Hospital
Department of Cardiology
Niels Andersens Vej 65
2900 Hellerup, Denmark
Tel: +4539772280 / Cell: +4526716467
Fax: +4543233783
E-mail: dr.gang@dadlnet.dk

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Key words: atrial fibrillation, ablation, pulmonary vein isolation, recurrent event
Abstract:

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

Methods and Results – The study cohort consisted of 124 patients with 7-day Holter recordings at 6 months post-RFA for AF. No patients had AF recurrence prior to this time. Patients were followed-up every 6 months. Holter detected PAC were defined as any supraventricular complex occurring > 30% earlier than expected. During a median follow-up of 4.2 years (1st-Quartile – 3rd-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-RFA. The number of PAC 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 PAC ≥ 142 per 24 hours to have a hazard ratio of HR=2.84 (CI 1.26-6.43), p=0.01.

Conclusions - This study showed that occurrence of ≥ 142 premature atrial complexes per day at 6 months after PV1 was independently associated with a significantly increased risk of late AF recurrence. These results could have important clinical implications for the design of post-PV1 follow-up.

Clinical Trial Registration - http://www.anzctr.org.au ; ACRTN12606000467538

Key words – atrial fibrillation, ablation, pulmonary vein isolation, recurrent event
Introduction

The pathogenesis and initiation of atrial fibrillation (AF) is associated with premature atrial complexes (PAC)–particularly atrial ectopic activity coming from areas near the ostia of the pulmonary veins.\textsuperscript{1,2} The treatment of AF with radiofrequency ablation (RFA) to attain pulmonary vein isolation (PVI) has been increasing worldwide since the pivotal findings of Michel Haissaguerre and colleagues and are now considered an appropriate first-line strategy in carefully selected cases.\textsuperscript{3-5} Reports on the long-term results describe steadily increasing numbers of patients who benefit from this procedure.\textsuperscript{6} However, a significant number of patients require more than one procedure to achieve freedom of arrhythmia.\textsuperscript{7,8} As the number of patients who undergo procedures increases, the practical task of following these patients in the clinic afterwards becomes more challenging and burdensome. The importance of early recognition of recurrence of AF is nevertheless of the utmost importance to reduce the risk of stroke and subsequent disability or death. Thus, there is a need for predictive tools for recurrence of AF following PVI to facilitate evidence based prioritizing and structuring of post-PVI follow up. Several pre-procedure patient characteristics have been shown to worsen the prognosis for PVI success. These included age, left atrial (LA) size, non-paroxysmal AF, valvular AF, non-ischemic cardiomyopathy and early post-procedure recurrence.\textsuperscript{9-11} However, meta-analyses conclude that no individual or group of pre-procedural patient characteristics consistently and independently predict recurrence of AF after RFA.\textsuperscript{8,10} The value of Holter documented PAC during the follow up of post-PVI procedure patients has been only sparsely investigated. Some evidence suggests that successful PVI reduces the number of PAC.\textsuperscript{12} The aim of this study was to assess the long-term prognostic significance of PAC documented by 7-day Holter recording in regards to the risk of late recurrence of AF following PVI.
Methods

Patients

The patients included in this study were enrolled in a randomized clinical trial comparing the efficacy of two different technical approaches for attaining PVI in highly symptomatic patients with drug-refractory atrial fibrillation.\(^1\)\(^3\) Patients were reviewed at 3, 6 and 12 months and then every 6 months thereafter. At 6 month follow-up patients had a 7-day Holter monitor recording as a means of documenting recurrent arrhythmias. The primary endpoint was defined as recurrence of any atrial arrhythmia >30 s documented by ECG or Holter. A 3-month post-procedure 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 redo-ablation 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 the present study. These patients were all without recurrence of AF prior to 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 prior to the Holter recording (n=4). In one excluded patient the Holter recording was corrupted prior to analysis.

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

Endpoints 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, USA) for analyses. Analyses were done by experienced cardiac technicians and reviewed by the responsible investigating cardiologist. PAC was defined as supraventricular complexes occurring >30% earlier than expected compared to the previous R-R interval. Any recurrence of ECG or Holter (later than 6 months post-procedure) documented sustained AF >30 seconds duration was considered a primary endpoint in this study.

**Statistics**

Characteristics of patients with and without late recurrence of atrial fibrillation were compared statistically. Categorical variables were compared by $\chi^2$- or Fishers exact test where appropriate. Continuous variables were compared using Kruskal-Wallis- or Students’ t-test. Skewed distributions were normalized by logarithmic transformation if necessary. Univariate hazard ratios (HR) and 95% confidence intervals (CI) 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 Youdens’ index ($J$) derived from receiver operator 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 end of follow-up, death, lost-to-follow-up or at the time of a second ablation procedure due to other atrial tachyarrhythmia. Two-sided p-values of <0.05 were considered statistically significant. SAS 9.3 (SAS Institute, Cary NC, US) 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 (1st Quartile – 3rd Quartile (Q1-Q3) = 1.6-4.5) following the 6 months 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 endpoint 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 = 183-267) and the median recorded period was 7 days (Q1-Q3 = 6-7). Five patients died during follow-up and three 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 very similar in co-morbidity, medication, echocardiography parameters and gender. The group who had late AF recurrence was however significantly older (63 ± 11 vs. 58 ± 10 years, p=0.02), more frequently had the wide antral isolation (WAI) procedure (72% vs. 47%, p=0.01) and had significantly more PAC (248 (Q1-Q3 = 62-1026) vs. 77 (Q1-Q3 = 24-448), p=0.02) on their 6 months Holter recording. Among patients who underwent single-ring isolation (SRI) procedure the median number of PACs per day were 75 (Q1-Q3 = 20-320) while it was 151 (Q1-Q3 = 48-759) in patients who had the WAI procedure (p=0.10). There was a higher proportion of patients with
non-paroxysmal AF in the group who later had recurrence but this difference was insignificant (45% vs. 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. In order 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 PAC per day. The cut-point was found to have the highest Youden index ($J=0.35$) by receiver operator characteristics curve analysis. The sensitivity and specificity were 72% and 63% respectively. The cut-point corresponds to the 54th-percentile and are thus very close to the median. Twenty-three (72%) of the patients with later AF recurrence were correctly identified while 34 (37%) of 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 to a higher risk of AF recurrence. PAC was also tested univariately as a continuous variable after logarithmic transformation (HR=1.12 (CI 1.00-1.25, p=0.04). A multivariate model including these variables was fitted. The results showed that $\geq 142$ PAC per day (HR=2.84 (CI 1.26-6.43), p=0.01) 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 in regards to AF recurrence when adjusted for PAC $\geq 142$ per day.

Arrhythmia-free survival for patients with and without $\geq 142$ PAC 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 re-ablation procedures. Breaches of earlier created isolation lines were found in 11 (73%) patients while 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 PAC/day detected by 7-day Holter recordings at 6 months after PVI in drug-refractory and highly symptomatic AF patients is 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 to 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 prior to ablation procedure (12.8% ± 10.7% of recorded hearts beats over 24 hours) and a significant reduction following 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 pre-ablation. 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. Other evidence indicates that the underlying mechanism might be different in very late AF recurrence involving non-PV foci. For patients in this study who had re-ablative procedures after AF recurrence there was no clear difference in pattern of time to AF recurrence or PAC incidence in regards 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. The difference between procedural approaches could therefore be explained by the difference in the area isolated.

Besides PAC there were no patient characteristics found to be independently associated with late AF recurrence. This is consistent with recent meta-analyses.

Survival rates following 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. Evidence is insufficient and conflicting as to the effect of oral anticoagulant (OAC) therapy on risk reduction of stroke in post-PVI care but current guidelines recommend continued OAC be CHADS2 guided. PAC has been indicated as a possible surrogate marker of AF in studies of stroke of undetermined etiology. Whether PAC could be used to guide OAC 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. Current guidelines recommend that post-
PVI patients in general be followed up at a minimum of three months following the ablation
procedure and then every six months for at least two years with ECG performed on each
occasion. 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 compare to 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. 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

The present 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 months 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 post-ablation PAC.

Conclusion

This study shows that occurrence of ≥ 142 premature atrial complexes 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.

Funding Sources: The original clinical trial was funded by a grant from the national health and medical research council, Australia.

Conflict of Interest Disclosures: None.

References:


15. Wokhlu A, Hodge DO, Monahan KH, Asirvatham SJ, Friedman PA, Munger TM, Cha YM, Shen WK, Brady PA, Bluhm CM, Haroldson JM, Hammill SC, Packer DL. Long-term outcome


Table 1: Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Atrial fibrillation N=32</th>
<th>No atrial Fibrillation N=92</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics at inclusion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)†</td>
<td>63± 11</td>
<td>59 ± 10</td>
<td>0.024</td>
</tr>
<tr>
<td>Male gender</td>
<td>25 (78)</td>
<td>73 (79)</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Comorbidity</strong></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</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>CHADS2 ≥ 2</td>
<td>6 (19)</td>
<td>15 (16)</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>Temporal class of atrial fibrillation at inclusion</strong></td>
<td></td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>18 (56)</td>
<td>60 (65)</td>
<td></td>
</tr>
<tr>
<td>Persistent</td>
<td>10 (31)</td>
<td>18 (20)</td>
<td></td>
</tr>
<tr>
<td>Longstanding persistent</td>
<td>4 (13)</td>
<td>14 (15)</td>
<td></td>
</tr>
<tr>
<td><strong>Antiarrhythmic medication at 6 months follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>1 (3)</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><strong>Echocardiography at 6 months follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction bi-plane (%)</td>
<td>56 ± 8</td>
<td>57 ± 7</td>
<td>0.39</td>
</tr>
<tr>
<td>Left atrial end-systolic volume bi-plane (ml)</td>
<td>60 ± 18</td>
<td>57 ± 18</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Pulmonary vein isolation ablation procedure</strong></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><strong>Supraventricular ectopy on 7 day-Holter at 6 months follow-up</strong></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 number of PAC per day ≥ 142 (%) *</td>
<td>23 (72)</td>
<td>34 (37)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Categorical variables are displayed as absolute number and percentages of subgroup. Continuous variables are displayed as mean ± standard deviation or median (Q1-Q3). *Indicates two-sided p-values <0.05.
Table 2: Risk of late AF recurrence

<table>
<thead>
<tr>
<th>Effect</th>
<th>HR (CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAC ≥ 142 /day</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 years 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.

Figure Legends:

Figure 1: Flowchart of the patient selection process. For details see methods section.

Figure 2: Kaplan-Meier curves of survival time free of recurrence of atrial fibrillation.

Kaplan-Meyer curve of arrhythmia-free survival stratified by PAC ≥ 142 per day.

The log-rank test of difference between strata was highly significant with p = 0.0005.
220 Patients included in randomized trial of PVI

53 Documented recurrent arrhythmia prior to 6 months post-PVI
17 Re-ablation procedures prior to 6 months post-PVI
8 Refused or were unable to have Holter recording

142 patients with 6 month Holter recordings post-PVI

13 Recurrence of AF on 6 months 7-day Holter
4 Documented recurrent AF prior to Holter at 6 months post-PVI
1 Corrupted 7-day Holter recording

124 patients without documented recurrence of AF at 6 months post-PVI
Kaplan-Meier plot of late AF recurrence

With Number of Subjects at Risk

Years from Holter recording 6 months after PVI

<table>
<thead>
<tr>
<th>PAC &lt; 142 /day</th>
<th>67</th>
<th>60</th>
<th>55</th>
<th>53</th>
<th>48</th>
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</thead>
<tbody>
<tr>
<td>PAC &gt;= 142 /day</td>
<td>57</td>
<td>40</td>
<td>37</td>
<td>30</td>
<td>28</td>
</tr>
</tbody>
</table>
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