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Predictive value of premature atrial complex characteristics in pulmonary vein isolation for patients with paroxysmal atrial fibrillation

Abbreviated title: PAC characteristics for predicting PVI success in paroxysmal AF

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Summary

Background. – Premature atrial complexes from pulmonary veins are the main triggers for atrial fibrillation in the early stages. Thus, pulmonary vein isolation is the cornerstone of catheter ablation for paroxysmal atrial fibrillation. However, the success rate remains perfectible.

Aim. – To assess whether premature atrial complex characteristics before catheter ablation can predict pulmonary vein isolation success in paroxysmal atrial fibrillation.

Methods. – We investigated consecutive patients who underwent catheter ablation for paroxysmal atrial fibrillation from January 2013 to April 2017 in two French centres. Patients were included if they were treated with pulmonary vein isolation alone, and had 24-hour Holter electrocardiogram data before catheter ablation available and a follow-up of ≥ 6 months. Catheter ablation success was defined as freedom from any sustained atrial arrhythmia recurrence after a 3-month blanking period following catheter ablation.

Results. – One hundred and three patients were included; all had an acute successful pulmonary vein isolation procedure, and 34 (33%) had atrial arrhythmia recurrences during a mean follow-up of 30 ± 15 months (Group 1). Patients in Group 1 presented a longer history of atrial fibrillation (71.9 ± 65.8 vs 42.9 ± 48.4 months; $P = 0.008$) compared with those who were “free from arrhythmia” (Group 2). Importantly, the daily number of premature atrial complexes before catheter ablation was significantly lower in Group 1 (498 ± 1413 vs 1493 ± 3366 in Group 2; $P = 0.028$). A daily premature atrial complex cut-off number of < 670 predicted recurrences after pulmonary vein isolation (41.1% vs 13.3%; sensitivity 88.2%; specificity 37.7%; area under the curve 0.635; $P = 0.017$), and was the only independent predictive criterion in the multivariable analysis (4-fold increased risk).

Conclusion. – Preprocedural premature atrial complex analysis on 24-hour Holter electrocardiogram in paroxysmal atrial fibrillation may improve patient selection for pulmonary vein isolation.

Résumé

Contexte. – L'isolation des veines pulmonaires (IVP) est la pierre angulaire du traitement invasif de la fibrillation atriale paroxystique (FAP). Cependant le taux de succès de cette procédure reste perfectible.

Objectif. – Identifier si certaines caractéristiques des extrasystoles atriales (ESA) enregistrées sur le Holter électrocardiogramme de 24 heures précédant l’ablation constituent un facteur prédictif de succès de procédure.

Méthodes. – Tous les patients ayant eu une IVP seule pour une FAP ont été analysés entre janvier 2013 et avril 2017 au sein de deux centres français. Les critères d’inclusion étaient : les patients adressés pour une primo-ablation de FAP, disposant d’un Holter électrocardiogramme avant l’ablation, dont le suivi post-ablation était ≥ 6 mois. Le critère de jugement principal était la récurrence d’une arythmie atriale après une période de blanking de 3 mois post-ablation.

Résultats. – Cent trois patients ont été inclus, et 34 (33 %) ont récidivé après un suivi moyen de 30 ± 15 mois. Ces patients présentaient une histoire de FA plus ancienne ($71,9 \pm 65,8$ mois vs $42,9 \pm 48,4$ mois ; $P = 0,008$). Le nombre d’ESA total sur 24 heures pré-ablation était significativement plus important dans le groupe « non récurrence » que dans le groupe « récurrence » (1493 ± 3366 vs 498 ± 1413 respectivement ; $P = 0,028$). Un seuil d’ESA $< 670/24$ heures prédisait la récurrence post-IVP (sensibilité 88,2 % ; spécificité 37,7 % ; AUC 0,635 ; $P = 0,017$).

Conclusion. – L’étude des ESA en pré-ablation peut potentiellement améliorer la sélection des patients pour l’ablation de FAP par IVP seule.

KEYWORDS

Premature atrial complexes;
Holter electrocardiogram monitoring;
Paroxysmal atrial fibrillation;
Catheter ablation

MOTS CLÉS

Extrasystoles atriales ;
Holter électrocardiogramme;
Fibrillation atriale paroxystique ;
Ablation par cathéter

Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; AUC, area under the curve; CA, catheter ablation; CFAE, complex fractionated atrial electrogram; CHA₂DS₂-VASc, Congestive heart failure, Hypertension, Age ≥ 75 years (Doubled), Diabetes, Stroke/transient ischaemic attack/thromboembolism (Doubled) – Vascular disease, Age 65–74 years and Sex category (Female); CI, confidence interval; F-HR-PAC, fast heart rate-dependent premature atrial complex; HR, heart rate; I-HR-PAC, independent heart rate premature atrial complex; PV, pulmonary vein; PVI, pulmonary vein isolation; S-HR-PAC, slow heart rate-dependent premature atrial complex.

Background

Atrial fibrillation (AF) is the most common arrhythmia, and will affect nearly 18 million people in Europe by 2060 [1]. Pulmonary vein (PV) isolation (PVI) is the cornerstone of catheter ablation (CA) in paroxysmal atrial fibrillation (AF), targeting the area of origin of most premature atrial complexes (PACs) leading to paroxysmal AF [2, 3]. However, freedom from arrhythmia after this standardized CA is only achieved in 60–80% of patients [4-6]. Tailored approaches that target the AF substrate have been proposed (mainly for persistent AF), such as complex fractionated atrial electrogram (CFAE) [7], left atrial additional linear ablation or spatiotemporal electrogram dispersion [8, 9] in the absence of PVI, without improving long-term clinical outcomes. Therefore, efforts should be made to improve patient selection for CA. The characterization of PACs during 24-hour Holter electrocardiogram monitoring has not been investigated for predicting arrhythmia recurrence after CA using PVI alone in patients with paroxysmal AF. We hypothesized that patients presenting predominantly trigger activation from the PVs, with a high rate of PACs, would have a higher success rate following PVI alone.

Methods

Study population

From January 2013 to April 2017, we retrospectively included all consecutive patients who underwent PVI alone (with additional cavotricuspid isthmus ablation when typical atrial flutter was documented) for paroxysmal AF in two French centres (CHU Henri Mondor, AP-HP, Creteil, and CHU Bichat, AP-HP, Paris, France), with detailed Holter monitoring before CA. When multiple Holter electrocardiograms were found, only the closest to the procedure was analysed. A minimal follow-up of 6 months had to be available. Patients with unavailable recent 24-hour Holter electrocardiogram monitoring, those who had undergone CA before the period of analysis and those who had extensive ablation lesions (CFAE ablation strategy, left atrial linear ablation lesions) were excluded from this analysis.

Baseline data collection

Patient characteristics, such as cardiovascular risk factors, CHA₂DS₂-VASc (Congestive heart failure, Hypertension, Age ≥ 75 years [Doubled], Diabetes, Stroke/transient ischaemic

attack/thromboembolism [Doubled] – Vascular disease, Age 65–74 years and Sex category [Female]) score, co-morbidities and clinical and therapeutic AF history, were collected.

Two-dimensional transthoracic echocardiography was performed with commercially available echocardiographic systems (GE Vivid 7 or GE Vingmed System V; GE Vingmed Ultrasound AS, Horten, Norway) using a 2 MHz or 2.5 MHz phased array transducer. Echocardiographic images were obtained in standard parasternal and apical views, and were stored digitally. Echocardiographic measurements were collected according to the American Society of Echocardiography guidelines [10]. Left ventricular ejection fraction was evaluated by Simpson's biplane in the apical view, and semi-quantitative left atrial enlargement was assessed by area and volume, measured in the four-chamber view, defined as follows: normal = $\leq 20 \text{ cm}^2$ and/or $22 \pm 6 \text{ mL/m}^2$; mild = $20\text{--}30 \text{ cm}^2$ and/or $29\text{--}33 \text{ mL/m}^2$; moderate = $30\text{--}40 \text{ cm}^2$ and/or $34\text{--}39 \text{ mL/m}^2$; severe = $> 40 \text{ cm}^2$ and/or $\geq 40 \text{ mL/m}^2$.

24-hour Holter electrocardiogram analysis

Holter monitoring was performed either by the hospital of inclusion or during an outpatient cardiologist visit, and subsequent data were collected: after manual classification, mean, maximum and minimum heart rate (HR); the total numbers of PACs and of single, doublet and runs of PACs (< 30 seconds) per 24 hours were automatically counted by software and then subsequently validated by trained electrophysiologists; further, sustained atrial arrhythmias lasting > 30 seconds were classified as atrial tachycardia, atrial flutter or AF as appropriate by two independent trained electrophysiologists. All data were normalized for a 24-hour duration to ensure comparability between groups.

PAC circadian distribution was performed during the night (from 11 p.m. to 6 a.m.) and during the day (from 8 a.m. to 9 p.m.). The hourly PAC relationship to the corresponding mean HR during preprocedural Holter monitoring was evaluated. If the hourly PAC number had a positive correlation with mean HR (Pearson, $P < 0.05$), patients were defined as fast HR-dependent PAC (F-HR-PAC) type. Conversely, negative correlation was defined as slow HR-dependent PAC (S-HR-PAC) type. Patients with no statistical link between PAC number and mean HR were defined as independent HR PAC (I-HR-PAC) type. Patients with permanent atrial arrhythmia during Holter monitoring were excluded from the circadian analysis.

Ablation procedure

Ablation was performed either by radiofrequency catheter ablation or cryoballoon ablation. An electroanatomical navigation system was used at the operator's discretion. All patients received effective anticoagulation therapy (target international normalized ratio of 2–3) for at least 1 month before AF ablation. All antiarrhythmic drugs (AADs), with the exception of amiodarone, were discontinued five half-lives before the procedure. Oral anticoagulation was stopped the day before the procedure. The electrophysiological study was performed under conscious sedation using remifentanyl or general anaesthesia.

Transseptal puncture was performed with the guidance of fluoroscopy or transoesophageal echocardiography. Following transseptal access, a single bolus of 100 IU/kg body weight of heparin was administered, and repeated only if the activated clotting time was < 300 ms.

Surface electrocardiograms and bipolar endocardial electrograms were continuously monitored and recorded on a computer-based digital amplifier/recorder system for off-line analysis (Bard Electrophysiology, Lowell, MA, USA). Intracardiac electrograms were filtered from 30 to 500 Hz and measured at a sweep speed of 100 mm/s.

For the procedure with radiofrequency, the following catheters were introduced via the right femoral vein for electrophysiological study: (1) a steerable quadripolar or decapolar catheter (Xtrem; ELA Medical, Le Plessis-Robinson, France) was positioned within the coronary sinus at 4–5 o'clock along the mitral annulus in a left anterior oblique projection; (2) a circumferential mapping catheter (Lasso; Biosense Webster, Diamond Bar, CA, USA) was introduced following transseptal access and stabilized using a long sheath (SL0 sheath; St. Jude Medical, Saint Paul, MN, USA) continuously perfused with heparinized saline solution; and (3) a 3.5 mm externally irrigated-tip ablation catheter using contact force (SmartTouch SF ThermoCool; Biosense Webster, Diamond Bar, CA, USA) was used for mapping and ablation.

Radiofrequency energy was delivered with power up to 25–30 W using irrigation rates of 7 mL/min (0.9% saline via Cool Flow; Biosense Webster, Diamond Bar, CA, USA) or more to achieve the desired power delivery. Temperature was limited to 45 °C. The procedure was considered successful when all the PVs were isolated electrically.

Using cryoballoon ablation, a 23 or 28 mm Arctic Front cryoablation balloon catheter (Medtronic, Minneapolis, MN, USA) was advanced over a guidewire to the orifice of the PV. Balloon selection was based on PV size as established by preprocedure computed tomography. Cryoablation was performed

in 240-second deliveries, with assessment of entrance and/or exit blockage using pacing and a circular mapping catheter after a 30-minute waiting period. A 15-F steerable sheath (FlexCath; Medtronic, Minneapolis, MN, USA) was used to introduce the cryoballoon catheter system into the left atrium. A cryoballoon catheter (Arctic Front Advance; Medtronic, Minneapolis, MN, USA) was then advanced through the FlexCath sheath, and positioned at the antrum of each PV, guided by the circular mapping catheter (Achieve; Medtronic, Minneapolis, MN, USA). To minimize the risk of phrenic nerve injury, right phrenic nerve pacing was performed by an electrode catheter in the superior vena cava, and capture was confirmed by palpation and intermittent fluoroscopy. Application of cryoenergy was terminated immediately upon attenuation or loss of phrenic nerve capture. PVI was confirmed using the Achieve™ mapping catheter. Whenever possible, the electrodes of the circular mapping catheter were positioned as close as possible to the PV antrum to monitor for real-time PVI.

Likewise, cavotricuspid isthmus ablation was performed in patients with previous documented typical atrial flutter.

Follow-up

Follow-up data were collected from hospitalization reports, hospital or outpatient cardiologist visits and patient telephone interviews. Treatments at hospital discharge, including all AADs, were collected and compared with those preceding the PVI procedure. Atrial arrhythmia recurrence (including AF, atrial flutter or atrial tachycardia) was defined as any atrial arrhythmia exceeding 30 seconds, and was documented by any form of monitoring, regardless of symptoms, after a 3-month postprocedural blanking period. Based on our hospital's routine practice, the recommended Holter electrocardiogram follow-up was at 6 ± 3 months with the patient's cardiologist, at 12 ± 3 months during a hospital outpatient visit with the electrophysiologist who performed the procedure, and subsequently with the patient's cardiologist, at their own discretion. It is noteworthy that, because most patients were symptomatic, some of AF recurrences could also be documented on an electrocardiogram during an emergency visit or with new remote monitoring tools, such as connected watches or temporary patches purchased by patients.

If the report was available, Holter monitoring data in the year after CA were collected and analysed.

Statistical analysis

Continuous variables are expressed as means \pm standard deviations, and were compared using the Mann-Whitney test or Wilcoxon's test (for paired samples). Categorical variables are expressed as counts and percentages, and were compared using Fisher's exact test or the χ^2 test, as appropriate. Relevant variables that were associated with atrial arrhythmia recurrences after PVI with a P value < 0.1 in the univariate analysis were entered into multiple logistic regression analysis to assess whether they displayed an independent association. Odds ratios were estimated on the basis of this model as measures of the strength of the association between potential predictors.

Receiver operating characteristic curves were constructed for continuous variables, computing area under the curve (AUC) to quantify the discriminative performance of each individual variable to predict recurrences after PVI. Optimal cut-off values were determined on the basis of the maximal Youden's index, using bootstrapping based on 1000 replications to provide more robust estimations. The performance of the optimal cut-offs was described by using sensitivity and specificity. Internal validation of optimal cut-offs also relied on bootstrapping with 1000 replications to provide optimism-corrected estimates.

To test whether there was a linear correlation between the 24-hour Holter hourly mean HR and the corresponding PAC frequencies, the Pearson correlation test was used to assess the strength of this relationship, and to classify patients into the F-HR-PAC, S-HR-PAC or I-HR-PAC groups if a positive correlation ($P < 0.05$), negative correlation ($P < 0.05$) or no correlation (P not significant) was found, respectively. $P < 0.05$ was considered significant. Statistical analyses were performed using SPSS for Windows, version 16.0, released 2007 (SPSS Inc., Chicago, IL, USA) and R, version 3.6.0 (R Foundation, Vienna, Austria; package "cutpointr").

Results

One hundred and ninety-three consecutive patients who underwent CA for paroxysmal AF were screened, and 103 patients were included. Reasons for exclusion were: unavailable 24-hour Holter electrocardiogram monitoring ($n = 61$); and additional ablation lesions ($n = 29$).

Ten patients had structural heart disease, including four hypertrophic cardiomyopathies, three arrhythmia-induced cardiomyopathies, two dilated cardiomyopathies and one patient with previous Bentall surgery.

Bidirectional block of all PVs was achieved in all patients during the index procedure. Complications were three cases of vascular complications (two arteriovenous fistulae, one retroperitoneal haematoma), three cases of cardiac tamponade (one percutaneous drainage and two treated surgically), one case of right diaphragmatic paralysis and one case of periprocedural stroke. There was no death immediately associated with the procedure.

Thirty-four (33%) patients (Group 1) had atrial arrhythmia recurrences after the 3-month blanking period, including 29 (85.3%) AF, four (11.8%) atrial tachycardia and one (2.9%) left atrial flutter, whereas 69 patients (67%) remained free from arrhythmia (Group 2) after a mean follow-up of 30 ± 15 months. Recurrences occurred at 9.3 ± 9.2 months. Clinical baseline characteristics are summarized in [Table 1](#). In Group 1, six (17.6%) patients had arrhythmia recurrences managed with AAD use, and 19 (55.9%) underwent a second ablation, including 17 (89.5%) patients with at least one PV reconnection and one (5.3%) patient who underwent complementary CFAE ablation. One patient had a redo procedure in another centre.

Group 1 patients presented a longer AF history duration (71.9 ± 65.8 vs 42.9 ± 48.4 months; $P = 0.008$) and had their AAD interrupted immediately after CA (versus 3 months after the blanking period) more frequently (82.4% vs 60.9%; $P = 0.042$) compared with Group 2 patients. Importantly, an AF history duration exceeding 33 months predicted recurrences after PVI (sensitivity 70%; specificity 60%; $AUC_{AFduration} 0.670$; 95% confidence interval [CI] 0.566–0.763; $P = 0.006$).

Preablation Holter monitoring analysis

The total number of PACs/24 hours before CA was significantly lower in Group 1 (498 ± 1413 vs 1493 ± 3366 in Group 2; $P = 0.028$). No differences were found between groups for duration of AF episodes and number of AF episodes/24 hours ([Table 2](#)). A daily PAC cut-off number of < 670 predicted recurrences after PVI alone (sensitivity 88.2%; specificity 37.7%; $AUC_{PAC} 0.635$; 95% CI 0.533–0.727; $P = 0.017$) (bootstrapped optimism-corrected sensitivity 76.9%; specificity 31.9%; $AUC_{PAC} 0.633$) ([Fig. 1](#)). The recurrence rate among patients with a daily PAC cut-off number of < 670 was 41.1% (of whom 60% experienced an early recurrence within 6 months), whereas it was 13.3% when the daily PAC cut-off was > 658 (with only one early recurrence).

Predictors of atrial arrhythmia recurrence after CA

Logistic multivariable regression analysis of clinical and Holter variables associated with recurrence in the univariate analysis identified total daily number of PACs < 670 as the only independent predictor of atrial arrhythmia recurrence after CA (odds ratio 4.26, 95% CI 1.28–14.20; $P = 0.018$) (Table 3).

Importantly, AAD management preceding or following (weaning delay) the ablation procedure had no significant impact on this analysis.

Postablation Holter monitoring analysis

A Holter monitoring full report in the year following CA (ranging from 3 to 12 months after CA), before any redo procedure, was available in 82 (79.6%) of included patients (30 and 52 patients in Groups 1 and 2, respectively). The total number of PACs/24 hours was higher in Group 1 (1713 ± 3789 vs 405 ± 1051 in Group 2; $P = 0.003$). There was a trend towards higher numbers of doublet PACs/24 hours and runs of PACs/24 hours in Group 1 compared with Group 2 (105 ± 317 vs 18 ± 68 [$P = 0.09$] and 44 ± 42 vs 14 ± 58 [$P = 0.11$], respectively) (Table 4).

Comparison between pre- and postablation Holter monitoring

Twenty-two and 37 patients in Groups 1 and 2, respectively, were found to have both pre- and postablation Holter monitoring available.

In Group 1, the total numbers of PACs/24 hours and single PACs/24 hours increased significantly after PVI (from 310 ± 695 to 1713 ± 3798 [$P = 0.008$] and from 249 ± 634 to 1071 ± 2645 [$P = 0.006$], respectively).

Conversely, in Group 2, the total number of PACs/24 hours decreased after CA from 1256 ± 2641 to 405 ± 1051 ($P = 0.017$).

PAC circadian distribution and hourly PAC relationship to the corresponding mean HR

Seventy-seven patients had a detailed hourly PAC distribution available before CA. No differences were found between minimum, mean and maximum HR between the two groups before PVI. Eleven (14%) patients had a positive correlation (F-HR-PAC), and nine (12%) had a negative correlation (S-HR-PAC). The proportions of patients with a positive, negative or independent correlation did not differ between groups (Table 5).

Twenty-two patients in Group 1 and 37 in Group 2 had an hourly PAC distribution available both before and after CA. In both groups, diurnal and nocturnal minimum and mean HR were significantly lower during the period after CA. Further, the nocturnal PAC count/hour was lower after CA in Group 2 (58 ± 119 vs 13 ± 40 ; $P = 0.031$).

Discussion

To our knowledge, this is the first study assessing PAC analysis before CA as a predictive factor for atrial arrhythmia recurrences after PVI alone in paroxysmal AF.

The main findings of this study were as follows: a total daily PAC number before CA of < 670 was the only independent predictor of atrial arrhythmia recurrences following CA, associated with a 4-fold increased risk; and the total number of PACs/24 hours and the number of single PACs/24 hours increased significantly after PVI in patients with atrial arrhythmia recurrences.

PACs originating from PVs are the main trigger in AF. The trigger tends to be predominant in paroxysmal AF, whereas the substrate tends to be dominant in the persistent AF form [11]. In our study, the daily PAC number before CA was significantly higher in patients free from arrhythmia following PVI. Likewise, a daily PAC cut-off number of < 670 predicted arrhythmia recurrences after PVI after a mean follow-up of 30 ± 15 months. One could hypothesize that PV foci play a more important role in some patients (with a minor role for extra-PV foci), whereas the occurrence and perpetuation of paroxysmal AF rely more on substrate than in other patients. The fact that 60% of recurrences in the low PAC before CA group (versus one recurrence in the high PAC before CA group) occurred early (< 6 months) after PVI, strengthens this hypothesis. Consequently, better patient selection for PVI, as well as a tailored ablative strategy according to the main supposed AF mechanism, could potentially be proposed to improve results [12].

It is noteworthy that we identified AAD management and weaning delay (at the time of CA versus at 3 months) imbalances between groups. However, they may not be relevant considering the follow-up duration (30 ± 15 months), and were not associated with recurrence in the multivariable model. In our study, AF history duration > 33 months predicted atrial arrhythmia recurrences after a 3-month blanking period after PVI. The formation of substrate is correlated with AF duration, suggesting that patients with a longer AF duration history (patients with “long-standing paroxysmal AF”), had substantially greater anatomical and structural atrial remodelling, and could potentially benefit from

additional ablative strategies. The fact that substantial (moderate-to-severe) left atrial enlargement tended to be more common in the recurrence group (26% versus 12%) strengthens this hypothesis. Misclassification of AF in paroxysmal AF could potentially contribute to this result. Charitos et al. demonstrated that 6% of patients with paroxysmal AF classified by physicians were in a persistent form according to device memories [13].

Currently, ablative strategies are only based on the length of AF episodes [2]. However, this AF classification has several limitations, in terms of Holter monitoring duration to document AF and preablative treatment strategies (electrical or pharmacological cardioversion). The pathophysiology of AF may not always correlate with the length of episodes, which usually acts as the main determinant of the electrophysiologist's modus operandi. Delayed enhancement magnetic resonance imaging to identify the degree of left atrial fibrosis [14] or dominant frequency changes [15] have been proposed to help to classify AF forms, and may be applied in practice to guide CA in a more tailored approach. Yet, none of these criteria has been integrated, given difficulties with evaluation and lack of reproducibility.

Postablation Holter monitoring analysis was performed in 82 (79.6%) of included patients, with an average Holter monitoring delay after CA of 69 ± 87 days. In patients free from recurrence, the total number of PACs/24 hours after CA was significantly lower than in patients with atrial recurrences. PVI has been shown to significantly reduce the PAC burden. Haïssaguerre et al. described a decrease in the number of PACs/24 hours from 4377 ± 3629 to 98 ± 91 after PVI alone in their cohort [3]. Yamane et al. studied Holter monitoring after PVI in patients with or without recurrences; they reported that, immediately after CA, all patients had a rapidly decreasing number of PACs, and a longer coupling interval compared with at baseline. They subsequently described a PAC reincrease at 1 month, with a shorter coupling interval in the recurrence group as a result of early PV reconnection, confirmed by an electrophysiology study [16]. Gang et al. proposed a cut-off of ≥ 142 PACs/24 hours at 6 months after PVI, which was independently associated with an increased risk of AF recurrence [17].

We finally investigated in this study whether circadian PAC distribution would predict arrhythmia recurrence, and we could not identify any association. We hypothesized that I-HR-PAC would suggest a PAC pathogenesis that was probably independent of autonomic variation, whereas F-HR-PAC and S-HR-PAC types would be evoked by sympathetic and vagal triggers, respectively. However, unlike PVC analysis [18], PAC family cluster analysis is currently not possible in routine practice, and the

failure of our analysis may be explained by heterogeneous PAC families being analysed together. However, we noticed an increase in minimum HR and mean nocturnal HR in both groups after PVI compared with Holter monitoring before CA, which could be explained by ganglionated plexi inadvertent ablation during PVI or postprocedural weaning of AADs.

Study limitations

This retrospective study with a small sample size had several limitations. First, data collection was heterogeneous, involving medical inclusion reports, ambulatory physicians' reports, telephone calls or patient telephone interviews. Atrial arrhythmia recurrences were reported on available electrocardiogram or Holter monitoring or if mentioned on medical reports (including cardiac device interrogation). Therefore, some asymptomatic recurrences may have been underestimated. Further, given the retrospective non-interventional approach, no pathophysiological data linking the PAC Holter description with its genesis from PVs during CA could be established in this study. It should also be highlighted that raw Holter data were no longer available at the time of analysis. Thus, short coupling interval PV-originated non-conducted PACs may not have been counted by automatic Holter monitoring analysis, leading to an underestimate of the total daily PAC number. Although interesting, these data would have been difficult to translate into clinical practice.

Second, Holter data was not adjusted upon AAD use during Holter monitoring before CA, which is likely to have influenced PAC characteristics and burden.

Third, while there is a possible inter-Holter PAC burden variability, analysis was based on a single Holter monitoring before PVI. Yet, Meyer et al. demonstrated that the 38-day average repeatability of PAC assessment in a non-AF population was excellent for recording lengths ranging from 6 to 24 hours [19].

Finally, it is admitted that not only does PVI exclude PV foci, it also damages several adjacent structures, such as extra-PV foci, anatomical or functional left atrial substrate or ganglionated plexi, which play a significant role in the occurrence and maintenance of AF.

Conclusions

PVI is the most common ablative strategy in paroxysmal AF. Our study suggests that a daily PAC number before CA of < 670, independent of a history of AF > 33 months or any other criterion, predicts

atrial arrhythmia recurrence (with a 4-fold increase) after PVI alone. These results should pave the way for better assessment of patients, including not only the duration of the AF episode, but also additional criteria, such as PAC characteristics, AF history and imaging characterisation of atrial tissue, before referring them for PVI. This could improve patient selection, and help to develop a mechanism-tailored ablative strategy, to improve outcomes. Further prospective studies are needed to confirm these preliminary results.

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Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Figure legends

Figure 1. Kaplan-Meier arrhythmia-free survival curve by premature atrial complex (PAC) burden before pulmonary vein isolation (PVI) on 24-hour Holter monitoring.

Table 1 Baseline characteristics.

	Total (<i>n</i> = 103)	Group 1 (arrhythmia recurrences) (<i>n</i> = 34)	Group 2 (no arrhythmia recurrences) (<i>n</i> = 69)	<i>P</i>
Epidemiological characteristics				
Patient age (years)	60.3 ± 9.4	60.3 ± 9.4	60.2 ± 9.4	0.69
Male sex	71 (68.9)	23 (67.6)	48 (69.6)	1.00
Hypertension	50 (48.5)	16 (47.1)	34 (49.3)	0.84
Diabetes mellitus	8 (7.7)	4 (11.8)	4 (5.8)	0.43
Active smoking	15 (17.0)	7 (21.8)	8 (14.3)	0.39
Dyslipidaemia	39 (37.9)	12 (35.3)	27 (39.1)	0.83
Ischaemic heart disease	15 (14.6)	5 (14.7)	10 (14.5)	1.00
Other structural heart disease	10 (9.7)	3 (8.8)	7 (10.1)	1.00
Obstructive sleep apnoea	12 (11.7)	6 (17.6)	6 (8.7)	0.20
Previous TIA or stroke	9 (8.7)	1 (2.9)	8 (11.6)	0.27
History of typical atrial flutter ablation	18 (17.5)	3 (8.8)	15 (21.7)	0.17
History of AF				
CHA ₂ DS ₂ -VASc score	1.6 ± 1.3	1.5 ± 1.2	1.7 ± 1.3	0.75
Duration of AF history (months)	52.1 ± 55.8	71.9 ± 65.8	42.9 ± 48.4	0.008
Palpitations	77 (77.8)	24 (75.0)	53 (79.1)	0.80
Dyspnoea	29 (29.3)	6 (18.8)	23 (34.3)	0.16
Angina	7 (7.1)	2 (6.3)	5 (7.5)	1.00
Lipothymia or syncope	8 (8.1)	5 (15.6)	3 (4.5)	0.11
Asthaenia	16 (15.8)	3 (8.8)	13 (19.4)	0.25
Treatments before CA				
Anticoagulant therapy	96 (93.2)	32 (94.1)	64 (92.7)	1.00
Class IC AAD	28 (27.2)	10 (29.4)	18 (26.1)	0.82
Beta-blockers	52 (51.0)	18 (52.9)	34 (50.0)	0.84

Sotalol	9 (8.8)	2 (5.9)	7 (10.3)	0.71
Dronedarone	1 (0.9)	1 (2.9)	0 (0)	0.33
Amiodarone	37 (36.3)	9 (26.5)	28 (41.2)	0.19
Non-dihydropyridine calcium channel blockers	3 (2.9)	2 (5.9)	1 (1.5)	0.26
Echocardiography				
LVEF (%)	59 ± 6	59 ± 5	59 ± 7	0.75
LA surface (cm ²)	23 ± 5	24 ± 5	23 ± 5	0.24
LA volume (ml/m ²)	44 ± 12	48 ± 14	42 ± 11	0.35
Normal LA	29 (37.7)	8 (29.6)	21 (42.0)	0.29
Mild LA enlargement	35 (45.5)	12 (44.5)	23 (46.0)	
Moderate LA enlargement	12 (15.6)	6 (22.2)	6 (12.0)	
Severe LA enlargement	1 (1.2)	1 (3.7)	0 (0)	
Ablation data				
RFA procedure	81 (78.6)	29 (85.3)	52 (75.4)	0.31
Procedural RFA time (minutes)	48.4 ± 14.6	48.1 ± 16.2	48.5 ± 13.9	0.74
Cryoballoon procedure	22 (21.4)	5 (12.8)	17 (24.6)	0.31
Cryoballoon procedural time (minutes)	21.2 ± 6.8	23.1 ± 13.2	20.6 ± 4.1	0.53
Fluoroscopy time (minutes)	17.2 ± 11.1	16.2 ± 12.4	17.6 ± 10.4	0.27
Fluoroscopy dose (cGy/cm ²)	3324 ± 3834	2511 ± 2999	3718 ± 4143	0.07
CTI ablation per procedure	25 (24.3)	9 (26.5)	16 (23.2)	0.81
AAD at hospital discharge				
Postprocedural decrease in AAD dosage	41 (39.8)	16 (47.1)	25 (36.2)	0.39
Class I or III AAD interrupted	69 (67.0)	28 (82.4)	42 (60.9)	0.042
Postprocedural class I or III AAD time (minutes)	5.5 ± 11.5	5.5 ± 14.5	5.5 ± 9.8	0.14
Class I AAD	14 (13.7)	4 (11.8)	10 (14.7)	0.77
Beta-blockers	54 (52.9)	19 (55.9)	35 (51.5)	0.83
Sotalol	6 (5.8)	0 (0)	6 (8.6)	0.17
Amiodarone	13 (12.6)	2 (5.9)	11 (15.9)	0.21
Non-dihydropyridine calcium channel blockers	3 (2.9)	2 (5.9)	1 (1.4)	0.25

Data are expressed as mean ± standard deviation or number (%). AAD: antiarrhythmic drugs; AF: atrial

fibrillation; CA: catheter ablation; CHA₂DS₂-VAsc: Congestive heart failure, Hypertension, Age ≥ 75 years (Doubled), Diabetes, Stroke/transient ischaemic attack/thromboembolism (Doubled) – Vascular disease, Age 65–74 years and Sex category (Female); CTI: cavotricuspid isthmus; LA: left atrial; LVEF: left ventricular ejection fraction; RFA: radiofrequency catheter ablation; TIA: transient ischaemic attack.

Table 2 Preprocedural Holter monitoring analysis.

	Total (<i>n</i> = 103)	Group 1 (arrhythmia recurrences) (<i>n</i> = 34)	Group 2 (no arrhythmia recurrences) (<i>n</i> = 69)	<i>P</i>
Minimum HR	40 ± 8	39 ± 8	41 ± 8	0.12
Mean HR	66 ± 15	67 ± 17	65 ± 15	0.97
Maximum HR	133 ± 46	138 ± 53	130 ± 43	0.63
Duration of analysis/24 hours (hours)	22.1 ± 3.1	20.9 ± 3.9	22.7 ± 2.4	0.010
Total number of PACs/24 hours	1164 ± 2902	498 ± 1413	1493 ± 3366	0.028
Number of single PACs/24 hours	594 ± 1702	333 ± 853	738 ± 2014	0.08
Number of doublet PACs/24 hours	68 ± 287	12 ± 37	96 ± 348	0.13
Number of runs of PACs/24 hours	57 ± 179	30 ± 143	70 ± 195	0.17
Nocturnal PACs/hour	43 ± 108	21 ± 76	53 ± 120	0.19
Diurnal PACs/hour	24 ± 62	9 ± 12	31 ± 74	0.54
Duration of AF/24 hours (minutes)	170 ± 393	222 ± 458	144 ± 357	0.66
Number of AF episodes/24 hours	4 ± 19	7 ± 30	3 ± 9	0.72

Data are expressed as mean ± standard deviation. AF: atrial fibrillation; HR: heart rate; PAC: premature atrial complex.

Table 3 Logistic multivariable analysis to predict atrial arrhythmia recurrences.

	Odds ratio	95% CI	<i>P</i>
Preprocedural amiodarone use	0.50	0.19–1.35	0.17
History of AF	1.01	0.99–1.02	0.08
History of CTI ablation	0.30	0.08–1.20	0.09
Number of daily PACs < 670	4.26	1.28–14.20	0.018

AF: atrial fibrillation; CI: confidence interval; CTI: cavotricuspid isthmus; PAC: premature atrial complex.

Table 4 Postprocedural Holter monitoring analysis.

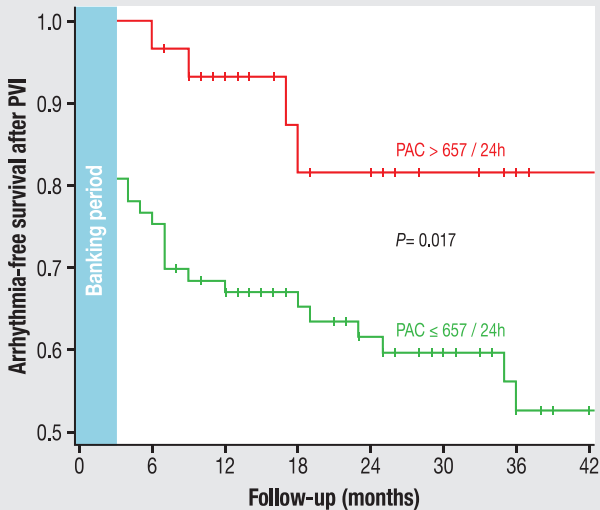
	Total (<i>n</i> = 82)	Group 1 (arrhythmia recurrences) (<i>n</i> = 30)	Group 2 (no arrhythmia recurrences) (<i>n</i> = 52)	<i>P</i>
Duration of postprocedural Holter monitoring (days)	69 ± 87	40 ± 61	85 ± 95	0.017
Minimum HR	49 ± 10	48 ± 10	50 ± 10	0.52
Mean HR	70 ± 12	69 ± 13	70 ± 11	0.87
Maximum HR	116 ± 27	123 ± 37	112 ± 19	0.43
Duration of analysis/24 hours (hours)	23.3 ± 1.3	23.6 ± 0.6	22.3 ± 4.6	0.041
Total number of PACs/24 hours	867 ± 2416	1713 ± 3789	405 ± 1051	0.003
Number of single PACs/24 hours	548 ± 1729	1071 ± 2645	263 ± 811	0.004
Number of doublet PACs/24 hours	48 ± 197	105 ± 317	18 ± 68	0.09
Number of runs of PACs/24 hours	25 ± 81	44 ± 111	14 ± 58	0.11
Nocturnal PACs/hour	42 ± 185	92 ± 300	13 ± 37	0.06
Diurnal PACs/hour	44 ± 130	83 ± 195	21 ± 59	0.036
Diurnal minimum HR	53 ± 10	51 ± 9	55 ± 11	0.12
Diurnal mean HR	72 ± 12	71 ± 12	73 ± 11	0.45
Diurnal maximum HR	113 ± 27	119 ± 35	109 ± 21	0.37
Nocturnal minimum HR	51 ± 9	50 ± 9	52 ± 10	0.60
Nocturnal mean HR	65 ± 11	67 ± 13	64 ± 10	0.33
Nocturnal maximum HR	97 ± 21	105 ± 28	92 ± 14	0.030

Data are expressed as mean ± standard deviation. HR: heart rate; PAC: premature atrial complex.

Table 5 Preprocedural premature atrial complex circadian distribution and hourly premature atrial complex relationship to the corresponding mean heart rate analysis.

	Total (<i>n</i> = 77)	Group 1 (arrhythmia recurrences) (<i>n</i> = 26)	Group 2 (no arrhythmia recurrences) (<i>n</i> = 51)	<i>P</i>
Diurnal minimum HR	43 ± 8	43 ± 9	44 ± 8	0.30
Diurnal mean HR	69 ± 16	71 ± 20	68 ± 14	0.86
Diurnal maximum HR	129 ± 48	132 ± 9	128 ± 46	0.89
Nocturnal minimum HR	42 ± 9	40 ± 9	43 ± 9	0.21
Nocturnal mean HR	61 ± 13	62 ± 14	60 ± 12	0.46
Nocturnal maximum HR	109 ± 35	114 ± 43	106 ± 30	0.78
Correlation coefficient between hourly PACs and corresponding mean HR	0.001 ± 0.348	0.023 ± 0.317	-0.010 ± 0.344	0.80
F-HR-PAC patients	11 (14.3)	3 (11.5)	8 (15.7)	0.74
S-HR-PAC patients	9 (11.7)	1 (3.8)	8 (15.7)	0.26
I-HR-PAC patients	57 (74.0)	22 (84.6)	35 (68.6)	0.18

Data are expressed as mean ± standard deviation or number (%). F-HR-PAC: fast heart rate-dependent premature atrial complex; HR: heart rate; I-HR-PAC: independent heart rate premature atrial complex; PAC: premature atrial complex; S-HR-PAC: slow heart rate-dependent premature atrial complex.



Number of patients at risk

	PAC > 657 / 24h							
	30	29	20	14	12	8	4	3
	PAC ≤ 657 / 24h							
	73	55	46	37	32	24	13	8