Pulmonary Veins to Left Atrium Cycle Length Gradient Predicts Procedural and Clinical Outcomes of Persistent Atrial Fibrillation Ablation

Running title: Pascale et al.; Venoatrial cycle length gradient in persistent AF

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Journal Subject Codes: [106] Electrophysiology, [5] Arrhythmias, clinical electrophysiology, drugs
Abstract

Background - Rapid pulmonary vein (PV) activity has been shown to maintain paroxysmal AF. We evaluated in persistent AF (PsAF) the cycle length (CL) gradient between PVs and the left atrium (LA) in an attempt to identify the subset of patients where PVs play an important role.

Methods and Results - 97 consecutive patients undergoing first ablation for PsAF were studied. For each PV, the CL of the fastest activation was assessed over 1 min (PV_fast) using Lasso recordings. The PV to LA CL gradient was quantified by the ratio of PV_fast to LA appendage (LAA) AFCL. Stepwise ablation terminated AF in 73 patients (75%). In the AF Termination group, the PV_fast CL was much shorter than the LAA CL resulting in lower PV_fast/LAA ratios compared to the Non-termination group (71±10% vs 92±7%, p<0.001). Within the Termination group, PV_fast/LAA ratios were notably lower if AF terminated after PVI or limited adjunctive substrate ablation compared to patients who required moderate or extensive ablation (63±6% vs 75±8%, p<0.001). PV_fast/LAA ratio <69% predicted AF termination after PVI or limited substrate ablation with 74% positive predictive value and 95% negative predictive value. After a mean follow-up of 29±17 months, freedom from arrhythmia recurrence off-antiarrhythmic drugs was achieved in most patients with PV_fast/LAA ratios <69% as opposed to the remaining population (80% vs 43%, p<0.001).

Conclusions - The PV to LA CL gradient may identify the subset of patients in whom PsAF is likely to terminate after PVI or limited substrate ablation and better long-term outcomes are achieved.

Key words: ablation, atrial fibrillation arrhythmia, pulmonary vein isolation, pulmonary vein, cardiac electrophysiology, cycle length, persistent atrial fibrillation
Introduction

Pulmonary vein (PV) triggers play a major role in the initiation of atrial fibrillation (AF) and PV isolation (PVI) is the cornerstone of catheter ablation for AF. While this strategy is effective in patients with paroxysmal AF, the success rate is limited in nonparoxysmal forms of AF. It is generally thought that early in the course of AF, triggers predominate. As the arrhythmia becomes more established, the sustained high rates in the atrium and/or the presence of underlying heart disease induce alterations in the underlying substrate that promote AF perpetuation (“AF begets AF”)¹. This has led to the development of adjunctive substrate modification strategies to improve persistent AF ablation²,³. However, the mechanisms underlying AF persistence are not uniform. A trigger-based mechanism may be operative in a subset of patients as demonstrated by the impact of strategies targeting triggers reinitiating AF immediately after cardioversion⁴,⁵. The challenge however still remains to identify such patients to allow individual-specific tailoring of the ablation strategy.

Prior clinical studies have demonstrated that intermittent rapid rhythms arising in the PVs are commonly observed during sustained episodes of paroxysmal AF. These rapid activities were identified when the cycle length (CL) recorded inside the PV was shorter than the AF CL recorded in the adjacent left atrium (LA)⁶ or when a clustering of shorter CL was observed on the plotted frequency histogram of the PV activity⁷. These studies demonstrated that intermittent rapid PV rhythms represent an active phenomenon that may have a critical role in the maintenance of AF by providing a continued refueling of the fibrillatory process⁶-⁹. Whether the identification of such PV activities can help characterize the contribution of PVs in the maintenance of persistent AF has not been addressed. We hypothesized that a high gradient between the CL of PV activity and the left atrial AF CL would identify patients where PVs play
an important role whereas the absence of such a gradient would point towards passive PV activity. We therefore aimed to evaluate if this CL gradient would predict 1) procedural AF termination 2) AF termination with PVI only and 3) post-ablation clinical success.

Methods

Study population

The study population consisted of consecutive patients who underwent first-time catheter ablation for symptomatic drug-refractory persistent AF. AF was defined as persistent (sustained beyond 7 days or lasting less than 7 days but necessitating cardioversion) or long-lasting persistent (continuous AF of greater than 1 year duration). All patients were in AF spontaneously at the beginning of the procedure and had PV mapping with a circumferential catheter prior to ablation. To evaluate the contribution of PV activity to the maintenance of AF, only patients in whom isolation of all PVs was completed before starting substrate-based ablation were included. All patients provided written informed consent.

Electrophysiological study

Antiarrhythmic medication was discontinued \( \geq 5 \) half-lives before ablation, with the exception of amiodarone. Before the procedure, all patients were receiving oral anticoagulation therapy for at least one month, and transesophageal echocardiography was performed within 48 hours before the procedure to exclude atrial thrombi.

Surface electrocardiograms and bipolar intracardiac electrograms (EGM) were monitored continuously and stored on a computer-based digital amplifier/recorder system (Labsystem Pro, Bard Electrophysiology, Lowell, MA, USA). Signals were band-pass filtered as follows: ECGs from 0.1 to 50 Hz; PV electrograms from 100 to 250 Hz; other intracardiac electrograms from 30 to 250 Hz.
The following catheters were introduced through the right femoral vein: 1) a steerable decapolar catheter was positioned within the coronary sinus; 2) a 10-pole circumferential catheter (Lasso, Biosense Webster, Diamond Bar, CA, USA) was used for PV mapping; 3) a 3.5-mm externally irrigated-tip ablation catheter (Biosense-Webster, Diamond Bar, CA, USA). The Lasso was stabilized with a long sheath (SLO, St. Jude Medical, St Paul, MN, USA) perfused continuously with heparinized DW solution. A single bolus of 50 IU/kg heparin was administered immediately after transseptal puncture. The activated clotting time was maintained thereafter within a range of 250 to 300 seconds.

**Ablation procedure for persistent AF**

In all patients, sequential stepwise ablation was performed as previously described. In brief, as the first step, PVI was performed using contiguous circumferential lesions around ipsilateral PVs. EGM-guided LA ablation was then performed and targeted sites displaying complex EGM features: continuous electrical activity, complex fractionated EGMs, locally short AF CL and sites with a gradient of activation. When ablation of the inferior LA did not result in organization of the coronary sinus, additional ablation within the coronary sinus was performed. Linear LA ablation was performed if AF persisted and targeted the LA roof followed by the mitral isthmus, with the end point of significant reduction or abolition of local EGMs. In the presence of shorter AF CL in the right atrium, EGM-guided ablation was performed in that chamber using the same criteria as in the LA. Cavotricuspid isthmus ablation was performed in most patients. After restoration of sinus rhythm, PVI and conduction across all the deployed linear lesions were checked. Additional RF applications to achieve PVI and complete linear conduction block were undertaken, if required.
Procedural endpoint

The procedural end point was termination of AF by catheter ablation to either a sustained atrial tachycardia (AT) or directly to sinus rhythm (AF Termination group). If AF converted into AT, ablation was performed until the restoration of sinus rhythm. If termination was not achieved by the stepwise ablation approach, electrical cardioversion was performed to restore sinus rhythm and the patient was assigned to the AF Non-termination group (procedural failure).

PV activity and AF cycle length measurement

PV activity during AF was analyzed with respect to the LA AF CL assessed from the intracardiac recording of the LA appendage (LAA) immediately following transseptal access \(^{10}\). The mean LAA AF CL was first measured manually with online calipers by averaging 100 consecutive cycles to ensure accurate and reproducible measurements.

The CL of PV activity was then assessed from the recordings obtained with the 10-pole circumferential mapping catheter (Lasso) before ablation. Sequential recordings were made from each of the four PVs. Analysis was made by a cardiologist blinded to the clinical and procedural information. For each PV, both the mean CL and the CL of the fastest recorded PV activation were assessed. The mean CL was obtained by averaging 100 consecutive cycles measured manually with online calipers from a preablation sample. Regarding the recording of the shortest PV CL, an observation window of 1 min was chosen considering the previously reported periodicity of the intermittent burst of fast PV activity \(^{7,8}\). The time interval between each PV signal was measured at a sweep speed of 100 mm/sec using electronic calipers. In the event of beat to beat changes in the PV activation, double potentials or when the interpotential delays were not uniform along the Lasso bipoles, the PV CL was defined as the delay between the earliest potentials of two successive PV breakthroughs (Fig. 1 A). When depolarizations of more
than one overlapping muscle fascicle were simultaneously recorded at some segments of the PV ostia, care was taken to identify each fascicle activity by comparing the activation patterns recorded at adjacent sites (Fig. 1 B). In such cases, the shortest CL of each fascicle was considered for analysis. In order to derive the maximum difference in CL between PVs and the LA AF CL, the lowest value of the four PVs was considered for analysis for both the mean CL and the CL of the fastest PV activation (PV\textsubscript{mean} and PV\textsubscript{fast}, respectively). The CL gradient between the PV and the LA was quantified by the computing the ratio of the PV CL divided by the LAA CL.

**Follow-up**

All patients were monitored in hospital for 3–5 days post-procedure. Antiarrhythmic drugs (AADs) were discontinued 3 months after the index procedure in the absence of a continued indication. Patients were reevaluated at 1, 3, 6, 9, and 12 months, and in the absence of AF or symptoms, followed up with their referring physician. At each visit, ambulatory 24–48 hour monitoring was performed to detect asymptomatic arrhythmias. One year from the last procedure, patients were seen every 6 months by their referring cardiologist. All patients underwent 24-h Holter monitoring within the last 3 months of follow-up. In the event of arrhythmia recurrence, patients were offered a trial of drug therapy and then additional ablation. As for the index procedure, the sequential stepwise ablation was performed with the end point of AF termination.

**Clinical outcome**

Success after first procedure was defined as maintenance of sinus rhythm (absence of symptomatic and asymptomatic AF or AT) during follow-up after the index ablation, with a post-procedural blanking period of 3 months. Success after the last procedure was defined as maintenance of sinus rhythm after the last ablation with or without AADs with a post-procedural
blanking period of 3 months.

**Statistical analysis**

Continuous variables are presented as arithmetic means ± SD or median with interquartile range (IQR) where indicated. Categorical variables are expressed as absolute numbers and percentages. Categorical variables were compared with the Chi-square test or the Fisher exact test and continuous variables with the unpaired Student t-test or the Mann-Whitney test, as appropriate. One-way ANOVA test was used to compare values between groups categorized according to the extent of substrate-based ablation needed to terminate AF. Diagnostic performance of predictors of AF termination was evaluated by receiver-operator characteristic (ROC) analysis. The optimal cut point was chosen as the combination with the highest sensitivity and specificity. To analyze independent predictive factors of termination of AF during ablation, and independent factors of clinical success, univariate factors presenting a p value < 0.1 were analyzed using logistic regression (multivariate analysis). Candidate covariates for adjustment were: age, duration of continuous AF, LA dimensions, structural heart disease, ejection fraction, hypertension and amiodarone use. Cumulative event rates (recurrence of arrhythmia) were calculated according to the Kaplan- Meier method and the log-rank test was used to detect significant differences between groups. All tests were 2-tailed, and statistical significance was assumed for p values < 0.05. Statistical analysis was performed using the software SPSS, 17.0 (SPSS, Inc, Chicago, IL, USA).

**Results**

A total of 97 consecutive patients were studied. The baseline characteristics of the patient population are presented in Table 1. The mean age was 58 ± 11 years and 81% were male. The mean duration of continuous AF was 19 ± 21 months (median 12 months, IQR 6 to 24 months).
**Procedural termination of AF**

AF was terminated by catheter ablation in 73 of 97 patients (75%), while in the remaining 24 patients (25%), AF could not be terminated and required electrical cardioversion. Baseline LAA CL was comparable between the Termination and Non-termination group (156 ± 29 versus 161 ± 24, respectively; p = 0.34).

**PV activity CL and procedural termination of AF**

At baseline, the lowest mean CL of the four PVS (PV_{mean}) did not significantly differ between patients with AF termination compared to patients without termination (157 ± 27 versus 166 ± 34 ms, p = 0.186) (Fig. 2 A). On the other hand, the fastest recorded PV CL (PV_{fast}) was significantly shorter in patients with AF Termination compared to those in whom AF could not be terminated (114 ± 23 ms versus 143 ± 31 ms, p < 0.001). There was, however, a notable overlap of values between the two groups (Fig. 2 B). Nonetheless, fast PV activities were rarely observed in patients whom AF could not be terminated by ablation. A cutoff value, PV_{fast} ≤ 110 ms, predicted AF termination with 95% positive predictive value (PPV) (sensitivity 53%, specificity 92%, negative predictive value (NPV) 39%). The fastest PV CL was recorded in the left superior PV in 39% of patients, the left inferior PV in 24%, the right superior PV in 21% and the right inferior PV in 15%. Figure 3 displays an example of the baseline LAA and PV recordings from a 45-year-old man with continuous AF duration of 8 months.

**PV to LA CL gradient and procedural AF termination**

The gradient between the fastest PV activity and the LA AF CL (PV_{fast}/LAA ratio) showed a limited overlap of values between the AF Termination and the Non-Termination group (Fig. 3 C). In the Non-Termination group, the PV_{fast} CLs were similar to the LAA CLs resulting in a mean PV_{fast}/LAA ratio of 92 ± 7%. On the other hand, the PV_{fast} CLs were much shorter than the LAA
CLs resulting in a significantly lower PV_{fast}/LAA ratio (ie higher gradient) of 71 \pm 10\% (p < 0.001) in the AF Termination group. The ROC curve analysis of the PV_{fast}/LAA ratio yielded an optimal cutoff value of \leq 85\% to predict AF termination with an area under the curve (AUC) of 0.968 (95\% confidence interval (CI): 0.922 to 1.000, p < 0.001) (Fig. 4 A). PV_{fast}/LAA ratio \leq 85\% provided a 96\% PPV, 91\% NPV, 97\% sensitivity and 88\% specificity for AF termination.

**Predictors of procedural AF termination**

The pre-procedural clinical variables were compared in patients in whom AF terminated by catheter ablation versus those in whom AF could not be terminated. AF termination was associated with a younger age (56 \pm 10 versus 64 \pm 9 years old, p = 0.001), a shorter duration of continuous AF (16 \pm 17 versus 28 \pm 28 months, p = 0.025), and a non-significant trend towards smaller LA dimensions (46 \pm 7 versus 48 \pm 7 mm, p = 0.13). Using a stepwise logistical regression technique incorporating pre-ablation clinical and procedural variables, only the PV_{fast}/LAA ratio independently predicted AF termination (adjusted odds ratio (OR) 0.691; 95\% confidence interval (CI) 0.580 to 0.823; p < 0.001).

**PV to LA CL gradient: ablation time to AF termination and mode of termination**

AF terminated during PVI in 11 patients (11\%) while in the remaining 62 patients (64\%), AF terminated during the EGM-guided or linear ablation steps. In the latter group, the additional (after PVI) procedural and ablation times were 64 \pm 43 min (median 54, IQR 30 to 90) and 34 \pm 21 min (median 30, IQR 19 to 45), respectively.

In the AF Termination group, the PV_{fast}/LAA ratio was compared between patients in whom AF terminated during PVI (PVI Term) versus those who required adjunctive substrate-based ablation to terminate AF. The extent of substrate-based ablation was further categorized according to the quartiles of ablation time needed to terminate AF after completion of PVI.
Limited or extensive substrate-based ablation was defined as the lowest and highest quartiles while moderate ablation was defined as the interquartile range of ablation time. In patients with AF termination during PVI, the PV\textsubscript{fast} CLs were much shorter than the LA AF CL with a mean PV\textsubscript{fast}/LAA ratio of 63% ± 6% (Fig. 5). A similar PV to LA CL gradient was found in the group of patients with AF termination after limited substrate ablation (PV\textsubscript{fast}/LAA ratio: 63% ± 6%, p = 0.995). In both groups, the PV\textsubscript{fast}/LAA ratios were notably lower compared to that in the patients where moderate or extensive substrate ablation was required. The mean PV\textsubscript{fast}/LAA ratio was 74% ± 8% in patients with AF Termination after moderate substrate ablation (p = 0.001 versus PVI Term and < 0.001 versus limited substrate ablation), and 79% ± 7% in those with AF Termination after extensive substrate ablation (p < 0.001 versus each of PVI Term and limited substrate ablation). The ROC curve analysis to discriminate patients with AF termination after PVI or limited substrate ablation from those who required more substantial ablation yielded an optimal cutoff value of < 69% with an AUC of 0.921 (95% CI: 0.867 to 0.975, p < 0.001) (Fig. 4B). A PV\textsubscript{fast}/LAA ratio < 69% provided a 74% PPV, 95% NPV, 88% sensitivity and 89% specificity for AF termination after PVI or limited additional substrate ablation.

The PV to LA CL gradient was also evaluated with respect to the mode of AF termination. AF terminated via an intermediate step of AT in 52 patients (71%) and directly into sinus rhythm in the remaining 21 (29%). Termination into sinus rhythm was associated with significantly lower PV\textsubscript{fast}/LAA ratios when compared to termination into an AT (66% ± 10% versus 73% ± 9%, p = 0.005).

**Predictors of AF termination after PVI or limited substrate ablation**

The pre-procedural clinical variables were compared between patients in whom AF terminated after PVI or limited additional substrate ablation and those who required more than limited...
substrate ablation to terminate AF. AF termination with no or limited substrate ablation was associated with younger age (53 ± 9 versus 60 ± 11 years old, p = 0.014), shorter duration of continuous AF (10 ± 8 versus 22 ± 23 months, p = 0.016), and lower prevalence of structural heart disease (19% versus 48%, p = 0.014). In the multivariate analysis incorporating pre-ablation clinical and procedural variables, both the PV_fast/LAA ratio (adjusted OR 0.772; 95% CI 0.688 to 0.866; p < 0.001) and the presence of structural heart disease (adjusted OR 0.071; 95% CI 0.012 to 0.438; p = 0.004) independently predicted termination of AF with PVI only or limited additional substrate ablation.

Follow-up and clinical outcome

Two patients were lost to follow-up after the initial procedure. After a mean follow-up of 36 ± 18 months, freedom from atrial arrhythmia was achieved in 34 patients (36%) after a single-ablation procedure with or without AADs. Among the patients who presented with recurrent arrhythmia, 38% were in persistent AF, 12% in paroxysmal AF and the remaining 50% were in AT (persistent or paroxysmal). Recurrence in persistent AF was more often observed in the Non-termination group compared to the Termination group (52% versus 18%, p = 0.001).

A repeat ablation procedure was performed in 41 out of the 61 patients with arrhythmia recurrence. Ten patients underwent more than 2 procedures. After 1.6 ± 0.7 procedures and a mean follow-up of 29 ± 17 months from the last procedure, the overall success rate was 71% (including 21% on AADs, n = 20). Long-term clinical success was higher in patients with AF Termination during the index procedure (81%, 28% taking AADs) compared to the Non-Termination group (39%, p < 0.001, 44% taking AADs).

PV activity to LA CL gradient and long-term clinical outcome

In patients with a PV_fast/LAA ratio > 85%, freedom from atrial arrhythmias after the last
procedure was achieved only in 41% of cases (44% taking AADs) against 80% (29% taking AADs) in patients with a ratio \( \leq 85\% \) \( p < 0.001 \).

With regard to the subgroup of patients with \( \text{PV}_{\text{fast}}/\text{LAA} \) ratio \(< 69\% \), the arrhythmia-free survival after the last procedure with or without AADs was superior when compared with the remaining population (84% versus 64%, \( p = 0.049 \)). A ratio below 69% provided additional outcome stratification over an 85% cutoff as, among the patients without arrhythmia recurrence, only 8% were on AAD compared to 44% in the subgroup with a 69 to 85% \( \text{PV}_{\text{fast}}/\text{LAA} \) ratio \( p = 0.002 \). Therefore, even among the patients with a more favorable outcome (ie with \( \text{PV}_{\text{fast}}/\text{LAA} \) ratio \( \leq 85\% \)), a higher clinical success rate off-AADs was observed in patients with a ratio \(< 69\% \) compared to those with a 69-85% ratio (80% versus 55%, \( p = 0.032 \)). Also, among the patients with arrhythmia recurrence, paroxysmal forms of AF were more often observed in the subgroup with \( \text{PV}_{\text{fast}}/\text{LAA} \) ratio \(< 69\% \) than in the rest of the study population (25% versus 6%, \( p = 0.032 \)) (Fig.6). Figure 7 displays Kaplan-Meier arrhythmia-free survival curves stratified according to \( \text{PV}_{\text{fast}}/\text{LAA} \) cutoff values.

**Predictors of success after the last ablation procedure**

In comparison with the patients with recurrent arrhythmias, patients who remained in stable sinus rhythm after the last procedure were younger (56 \( \pm \) 10 versus 63 \( \pm \) 9 years old, \( p = 0.002 \)), had lower LA dimension (45 \( \pm \) 6 versus 50 \( \pm \) 7 mm, \( p = 0.003 \)) and a trend towards shorter duration of continuous AF (16 \( \pm \) 17 versus 26 \( \pm \) 28 months, \( p = 0.056 \)). In the multivariate analysis incorporating pre-ablation clinical and procedural variables, both the \( \text{PV}_{\text{fast}}/\text{LAA} \) ratio (adjusted OR 0.939; 95% CI 0.899 to 0.981; \( p = 0.004 \)) and the LA dimension (adjusted OR 0.905; 95% CI 0.840 to 0.974; \( p = 0.008 \)) independently predicted long-term freedom from recurrent arrhythmia.
Discussion

Main findings

The present study evaluated whether the analysis of the PV activity in relation to the atrial AF CL could help stratify the procedural and long-term outcome of patients undergoing persistent AF ablation. The major findings of this study are: (i) the occurrence of intermittent rapid activity within the PVs, but not their mean CL, helps characterize the contribution of PVs to the maintenance of persistent AF. (ii) A high CL gradient between the fastest recorded PV activity and the AF CL (PV_{fast}/LAA ratio < 69%) identifies patients in whom AF is likely to terminate after PVI or limited additional substrate ablation (iii) The absence of substantial gradient between the fastest PV activity and the AF CL (PV_{fast}/LAA ratio > 85%) identifies patients in whom AF is unlikely to terminate by ablation and the long-term success is limited.

Markers and role of PV activity in persistent AF

There has been an accumulating body of evidence demonstrating that PVs play an important role in a subset of patients with persistent AF. Our group previously showed that the PVs were the dominant triggers reinitiating chronic AF after cardioversion (94%) and their ablation resulted in sinus rhythm maintenance in a significant proportion of patients. More recently, Inoue et al observed reproducible immediate recurrences of AF after cardioversion in 27% of 263 persistent AF patients. The triggers reinitiating AF originated mostly from the PVs (81%). The role of the reinitiating triggers in the persistence of AF was demonstrated by the strong influence of their successful elimination on clinical outcome. These findings support the hypothesis that PV activity may be elevated enough to trigger repetitive “paroxysmal” AF episodes before the preceding one terminates leading to persistent AF. The role of PV is further supported by the evidence that a substantial proportion of patients can achieve stable long-term sinus rhythm off-
AAD after PVI only even in longstanding persistent AF \(^{11,12}\). The challenge however remains to identify during ongoing AF that subgroup of persistent AF patients where PVs play a major role. Previous studies including mostly paroxysmal AF patients have shown that intermittent rapid PV activities during sustained AF were recorded from the same PVs that exhibited arrhythmogenic foci that triggered AF during sinus rhythm \(^7\). The likelihood of inducing persistent AF by rapid pacing was markedly diminished after the elimination of the intermittent bursts of PV tachycardia. Moreover, the probability of AF termination during isolation of a PV was directly related to the extent of tachycardia recorded in that vein \(^6,8\). These observations suggest that the PVs are not only a source of the triggers that initiate AF but may also have a role in the maintenance of AF. This has been further corroborated by the observation that isolation of each PV in patients with sustained paroxysmal AF episodes was associated with a gradual slowing of the fibrillatory process that culminated in the termination of AF \(^13\). Intermittent bursts of PV tachycardia may maintain AF in the same way as intermittent bursts of rapid pacing do prevent the tendency towards spontaneous conversion of experimental pacing induced AF \(^14\).

**PV activity to LA AF CL gradient provides mechanistic insights into the mechanism of persistent AF**

Our study shows that the observations made previously during sustained paroxysmal AF can also be extended to persistent AF. We could demonstrate that the recording of a significant CL gradient between PV activity and the LA AF CL allowed to discriminate patients whose AF was likely to terminate with PVI only or limited additional substrate ablation. Moreover, long-term freedom from arrhythmia recurrence was achieved in most of these patients as opposed to the rest of the study population. Also, both termination of AF directly to sinus rhythm and recurrences in paroxysmal AF were more often observed. Both findings further suggest a trigger-
dependent mechanism of AF persistence as opposed to one based on advanced changes in the substrate.

On the other hand, the absence of a significant gradient between the fastest PV and the AF CL pointed towards passive PV activity. Indeed, we observed that procedural AF termination could not be achieved in most of these patients or required extensive substrate modification. A passive role of PVs was further suggested by the limited long-term success rate achieved despite PVI. In these patients, the mechanism underlying AF persistence was likely attributable to advanced atrial substrate changes.

**Role of PV in patients with AF termination after limited additional substrate ablation**

It is usually considered that termination of AF after limited additional defragmentation is a direct effect of the early identification of critical AF targets located outside the PVs. However, these patients could be specifically discriminated form the rest of the study population based on the identification of rapid PV rhythms in the same way as those with AF termination during PVI. Therefore, our findings reinforce the major role of PVs in these patients even though limited substrate-based modification could still be required to achieve AF termination.

It has been shown experimentally that the longer AF has been present for, the longer artificially induced AF paroxysms last. Therefore, one can reasonably assume that in persistent forms of AF, a certain period of latency is likely before AF terminates once critical targets have been ablated. This may also explain why AF failed to terminate during PVI in some of the patients with a high PV to LA CL gradient. Consistent with the latency assumption is the observation that sinus rhythm restoration occurred well after the cessation of radiofrequency application rather than during ongoing ablation in more than one third of the study population (37%). These considerations raise the question whether adjunctive substrate-based ablation was
indeed warranted to achieve similar long-term outcome in patients demonstrating high PV to LA CL gradients.

**Importance of sampling time during PV activity evaluation**

Studies performing spectral analysis and frequency mapping during AF have demonstrated the ability to localize the sites of rapid and periodic activity closely linked to the sources that maintain AF\textsuperscript{15-18}. These studies consistently demonstrated that these dominant frequency sources of activity often emanated from the PV region in paroxysmal AF\textsuperscript{15,19-21}. On the other hand, in patients with persistent AF, the PVs were less likely to harbor sites of high frequency. However, these studies were based on recordings of a few seconds or averaged in sliding windows over 20 to 30 seconds. The assumed temporal stability of the AF activity underlying this methodology is challenged by our findings. Our data indicate that the occurrence of intermittent rapid activity within the PVs, but not their average CL, could help characterize their contribution to AF persistence. The assessment of the fastest recorded PV activity over a 1-minute observation window allowed to detect these episodic burst phenomena that would have otherwise been missed with shorter or averaged recording intervals. The periodicity of these rapid repetitive activities may be as low as one per minute and they may occur in temporal clusters of less than few seconds\textsuperscript{7,8}. It is plausible that longer recording intervals may be required in remodeled atria with persistent AF where less frequent rapid PV activity may suffice to sustain AF as opposed to paroxysmal AF episodes where more constant refueling of the fibrillatory process is required.

**Study limitations**

This study primarily makes a novel observation and infers a causal link between intermittent rapid PV activities and AF maintenance based on the ablation outcome. However, the assumption that these rapid PV activities actually represented an active phenomenon was not
systematically demonstrated by the simultaneous recording of a slower AF CL in the adjacent LA. It is possible that these rapid rhythms were sometimes caused by fractionation of wavefronts entering the PV from the LA instead of by paroxysmal burst of tachycardia generated within the vein.

Moreover, although a relationship between rapid PV rhythms and ablation outcome was demonstrated, their role has not been established by this observational study. Whether these repetitive activities act as triggers of AF or contribute to sustain episodes triggered outside PVs remains to be determined.

Conclusions
An attentive monitoring of the PV activity in relation to the atrial AF CL may discriminate patients in whom AF is likely to terminate after PVI or limited substrate ablation from those in whom AF is unlikely to terminate by ablation and long-term success is limited. By providing the tool to identify the subset of patients where PVs still play an important role in AF persistence, these findings may be a step towards more tailored ablation strategies.

Acknowledgments: We are grateful to Valérie Aurillac for statistical assistance.

Funding Sources: Patrizio Pascale acknowledges financial support from the Swiss National Science Foundation and the SICPA Foundation

Conflict of Interest Disclosures: None.

References:


### Table 1. Clinical characteristics of the study population

<table>
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<tr>
<th></th>
<th>Total (n = 97)</th>
<th>AF Termination group (n = 73)</th>
<th>AF Non-Termination group (n = 24)</th>
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<td>Age (years)</td>
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<td>56 ± 10</td>
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<td>Male sex (%)</td>
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<td>History of AF (months)</td>
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<td>75 ± 66</td>
<td>70 ± 51</td>
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<td>Duration of continuous AF (months)</td>
<td>19 ± 21</td>
<td>16 ± 17</td>
<td>28 ± 28</td>
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<td>Long-lasting persistent AF (%)</td>
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<td>53</td>
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<td>LVEF (%)</td>
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<td>LA diameter (mm)</td>
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<td>Number of failed AAD</td>
<td>1.9 ± 0.9</td>
<td>2.0 ± 0.9</td>
<td>1.9 ± 1.2</td>
<td>0.755</td>
</tr>
<tr>
<td>Administration of amiodarone (%)</td>
<td>45</td>
<td>41</td>
<td>58</td>
<td>0.141</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; LVEF = left ventricular ejection fraction; LA = left atrial; AAD = antiarrhythmic drugs.
Figure Legends:

Figure 1: Measurement of the PV activity CL in changing (A) or complex (B) activation patterns. A. Tracing of a change in the activation pattern between the second and the third beat recorded by the Lasso catheter positioned in left inferior PV. The PV CL is defined as the delay between the earliest activation of the two successive PV breakthroughs (arrows, 140 ms). B. Simultaneous recording of more than one PV muscle fascicle on the Lasso catheter positioned in the right inferior PV. The shortest delay between two successive PV breakthroughs in this tracing would be 60 ms (between the second and the third beat). However, when comparing the timing and the activation patterns of each PV breakthroughs, the activity of two distinct overlapping PV fascicles becomes apparent. The first (asterisks) has a stable activation pattern (bipole PV 1-2 activated first) with a fairly regular CL of 130 ms while the breakthrough of the second fascicle (dashed circles) occurs at bipole PV 5-6 with a CL of 230 ms. Of note, if a conventional quadripolar catheter is used to measure electrograms within the PV or if the activation patterns recorded on the Lasso are not compared, it is likely that the PV activity CL would have been erroneously measured to be 70 ms shorter than the true shortest CL measured on this tracing (ie 130 ms). PV = pulmonary vein; CL = cycle length.

Figure 2: Scatterplot showing the individual values of (A) the mean PV CL (PV_{mean}), (B) the fastest PV CL (PV_{fast}) and (C) the PV_{fast} to left atrial AF CL gradient (PV_{fast}/LAA ratio) in patients with and without procedural AF termination. Horizontal line indicates optimal diagnostic cutoff values to predict AF termination. LAA = left atrial appendage; other abbreviations as in Figure 1.
**Figure 3:** Baseline tracings of the LAA and four PVs from a 45-year-old man with continuous AF for 8 months. **(left)** The fastest recorded PV activities observed over a 1 minute observation window are illustrated for each vein. Far-field LAA activity is apparent in the left superior PV (asterisks). Rapid PV activities are observed in all four PVs, the fastest being recorded in the left inferior PV (PV$_{fast}$ 82 ms). Of note, these fast activities occur as intermittent bursts that are separated by slow PV rhythm (slower than the LAA AF CL). The mean PV CLs (averaged on 100 beats) are lowest in the right superior PV (PV$_{mean}$ 154 ms). While no gradient of CL is observed between the PV$_{mean}$ and the LAA CL, the PV$_{fast}$ CL is much lower than the LAA CL (PV$_{fast}$/LAA ratio 57%). The high PV to LAA CL gradient alternating with periods of slow PV rhythm (gradient “inversion”) both suggested intermittent active PV firing. **(right)** Catheter ablation terminated AF after PV isolation, during the second min. of radiofrequency application for adjunctive substrate-based ablation. Same abbreviations as in Figure 1 and 2.

**Figure 4:** Procedural outcome according to the PV$_{fast}$ to left atrial AF CL gradient. Receiver operating characteristic curve analysis of the PV$_{fast}$/LAA ratio to predict **(A)** AF termination during stepwise ablation and **(B)** AF termination with only PV isolation or limited substrate-based ablation (first quartile of ablation time). Arrows show optimal cutoff point for sensitivity and specificity. CI = confidence interval; other abbreviations as in Figure 1 and 2.

**Figure 5:** Boxplot showing the values of the PV$_{fast}$ to left atrial AF CL gradient (PV$_{fast}$/LAA ratio) in patients with AF termination achieved during PV isolation versus substrate-based ablation. The extent of substrate ablation is categorized as limited, moderate and extensive.
according to the quartiles of ablation time needed to terminate AF after completion of PV isolation. Same abbreviations as in Figure 1 and 2.

**Figure 6:** Tracings from a 40-year-old man with continuous AF for 12 months recorded during (left) the index procedure and (right) the repeat procedure three years later for paroxysmal AF recurrence. (left) At baseline, fast PV activities are recorded in all four PVs with a high gradient between the fastest PV activity and the LA AF CL (PVfast/LAA ratio 68%). AF terminated after PV isolation and 21 min. of additional radiofrequency application for substrate-based ablation. At the repeat procedure, reisolation of three reconnected PVs was performed in sinus rhythm. (right) Subsequently, intermittent burst of fast PV activities with exit block were observed in two of them. Isoproterenol and rapid burst pacing failed to induce AF afterwards. The mode of recurrence and the demonstration of active PV firing provided a late confirmation that a trigger-based mechanism was contributing to AF persistence as initially suspected based on the low PV$_{fast}$/LAA ratio. Same abbreviations as in Figure 1 and 2.

**Figure 7:** Kaplan-Meier curves of the arrhythmia free survival after the last procedure for (A) the entire population and (B) the population off-antiarrhythmic drugs. Patients are stratified according to the baseline PV$_{fast}$/LAA ratio. AADs = antiarrhythmic drug; other abbreviations as in Figure 1 and 2.
PV_{mean} = 154 ms
PV_{fast} = 82 ms
PV_{fast}/LAA ratio = 57%

RSPV mean CL 154 ms, shortest CL 112 ms

RIPV mean CL 160 ms, shortest CL 105 ms

LSPV mean CL 156 ms, shortest CL 94 ms

LIPV mean CL 172 ms, shortest CL 82 ms

AF Termination after PVI and 2 min. of substrate ablation time
AF Termination during stepwise ablation

PV_{fast}/LAA ratio \leq 85\%

Area under the ROC curve = 0.968
Standard error = 0.019
95\% CI = 0.922-1.000
P < 0.001

AF Termination with PVI only or limited additional substrate ablation

PV_{fast}/LAA ratio < 69\%

Area under the ROC curve = 0.921
Standard error = 0.027
95\% CI = 0.867-0.975
P < 0.001
PVfast/LAA CL ratio (%)

Termination with PVI only
Limited ablation
Moderate ablation
Extensive ablation

Extent of substrate ablation to AF Termination

p < 0.001
p = 0.001
p = 0.995
Shortest CL 116 ms

$PV_{fast} = 100$ ms

$PV_{fast}/LAA$ ratio = 68%

Shortest CL 100 ms

Paroxysmal AF recurrence

Shortest CL 108 ms

Shortest CL 106 ms

After PV reisolation

RIPV

LIPV

LAA mean CL 146 ms
Outcomes of Persistent Atrial Fibrillation Ablation

Pulmonary Veins to Left Atrium Cycle Length Gradient Predicts Procedural and Clinical

Patrizio Pascale, Ashok J. Shah, Laurent Roten, Daniel Scherr, Yuki Komatsu, Khaled Ramoul,
Matthew Daly, Arnaud Denis, Nicolas Derval, Frédéric Sacher, Mélèze Hocini, Pierre Jais and Michel
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Circ Arrhythm Electrophysiol. published online May 14, 2014;

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