Original Article

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

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Background—Rapid pulmonary vein (PV) activity has been shown to maintain paroxysmal atrial fibrillation (AF). We evaluated in persistent AF 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—Ninety-seven consecutive patients undergoing first ablation for persistent AF were studied. For each PV, the CL of the fastest activation was assessed over 1 minute (PV_{fast}) using Lasso recordings. The PV to LA CL gradient was quantified by the ratio of PV_{fast} to LA appendage (LAA) AF CL. 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 with the nontermination group (71±10% versus 92±7%; $P<0.001$). Within the termination group, PV_{fast}/LAA ratios were notably lower if AF terminated after PV isolation or limited adjunctive substrate ablation compared with patients who required moderate or extensive ablation (63±6% versus 75±8%; $P<0.001$). PV_{fast}/LAA ratio <69% predicted AF termination after PV isolation 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% versus 43%; $P<0.001$).

Conclusions—The PV to LA CL gradient may identify the subset of patients in whom persistent AF is likely to terminate after PV isolation or limited substrate ablation and better long-term outcomes are achieved. **(*Circ Arrhythm Electrophysiol*. 2014;7:473-482.)**

Key Words: atrial fibrillation ■ cardiac electrophysiology ■ pulmonary veins

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. Although 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 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 ablation.[2,3] 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 cardioversion.[4,5] The challenge, however, still remains to identify such patients to allow individual-specific tailoring of the ablation strategy.

Clinical Perspective on p 482

Previous 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 activity.[7] 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 process.[6–9] 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 LA AF CL would identify patients where PVs play an important role, whereas the absence of

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such a gradient would point toward 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) postablation 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 >7 days or lasting <7 days but necessitating cardioversion) or long-lasting persistent (continuous AF of >1 year duration). All patients were in AF spontaneously at the beginning of the procedure and had PV mapping with a circumferential catheter before 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 ≥5 half-lives before ablation, with the exception of amiodarone. Before the procedure, all patients were receiving oral anticoagulation therapy for ≥1 month, and transesophageal echocardiography was performed <48 hours before the procedure to exclude atrial thrombi.

Surface electrocardiograms and bipolar intracardiac electrograms were monitored continuously and stored on a computer-based digital amplifier/recorder system (Labsystem Pro; Bard Electrophysiology, Lowell, MA). 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) was used for PV mapping; and (3) a 3.5-mm externally irrigated tip ablation catheter (Biosense Webster). The Lasso was stabilized with a long sheath (SLO; St Jude Medical, St Paul, MN) perfused continuously with heparinized 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.[2] In brief, as the first step, PVI was performed using contiguous circumferential lesions around ipsilateral PVs. Electrogram-guided LA ablation was then performed and targeted sites displaying complex electrogram features: continuous electric activity, complex fractionated electrograms, 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 electrograms. In the presence of shorter AF CL in the right atrium, electrogram-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 radiofrequency applications to achieve PVI and complete linear conduction block were undertaken, if required.

Procedural End Point

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, electric cardioversion was performed to restore sinus rhythm, and the patient was assigned to the AF nontermination group (procedural failure).

PV Activity and AF CL 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 after 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 4 PVs. Analysis was made by a cardiologist blinded to the clinical and procedural information. For each PV, both the mean CL and 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 minute 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 per second 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 2 successive PV breakthroughs (Figure 1A). When depolarizations of >1 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 (Figure 1B). In such cases, the shortest CL of each fascicle was considered for analysis. To derive the maximum difference in CL between PVs and the LA AF CL, the lowest value of the 4 PVs was considered for analysis for both the mean CL and the CL of the fastest PV activation (PV_{mean} and PV_{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 to 5 days postprocedure. Antiarrhythmic drugs (AADs) were discontinued 3 months after the index procedure in the absence of a continued indication. Patients were re-evaluated 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- to 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-hour 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 postprocedural 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 postprocedural blanking period of 3 months.

Statistical Analysis

Continuous variables are presented as arithmetic means±SD or median with interquartile range where indicated. Categorical variables are expressed as absolute numbers and percentages. Categorical variables were compared with the χ^2 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

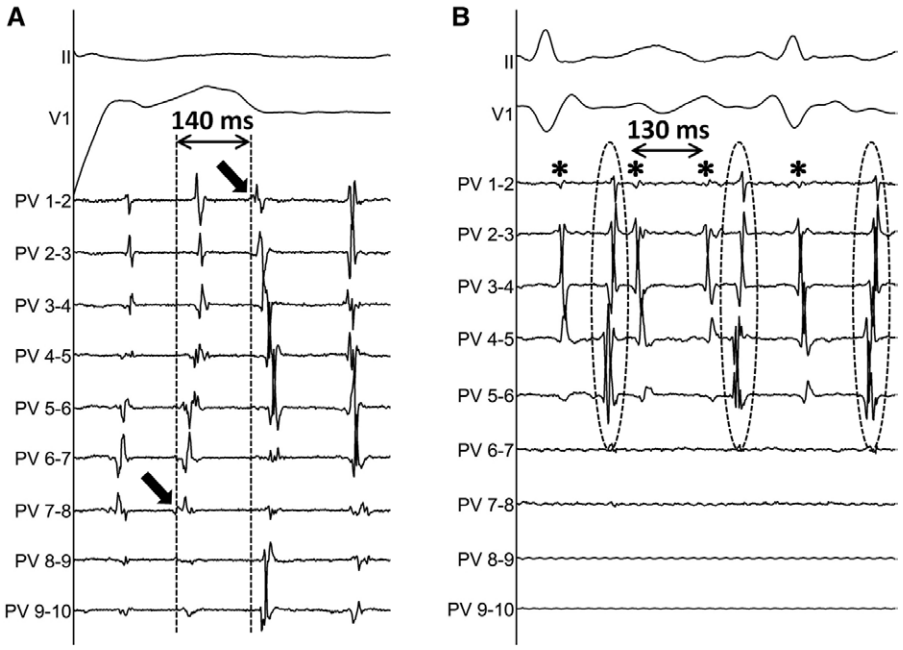

Figure 1. Measurement of the PV activity CL in changing (**A**) or complex (**B**) activation patterns. **A**, Tracing of a change in the activation pattern between the second and the third beat recorded by the Lasso catheter positioned in left inferior PV. The PV CL is defined as the delay between the earliest activation of the 2 successive PV breakthroughs (arrows; 140 ms). **B**, Simultaneous recording of >1 PV muscle fascicle on the Lasso catheter positioned in the right inferior PV. The shortest delay between 2 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 2 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, whereas the breakthrough of the second fascicle (dashed circles) occurs at bipole PV 5 to 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). CL indicates cycle length; and PV, pulmonary vein.

of AF termination was evaluated by receiver-operator characteristic analysis. The optimal cutpoint was chosen as the combination with the highest sensitivity and specificity. To analyze independent predictive factors of AF termination 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).

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 men.

Table. Clinical Characteristics of the Study Population

	Total (n=97)	AF Termination Group (n=73)	AF Nontermination Group (n=24)	*P* Value
Age, y	58±11	56±10	64±9	0.001
Male sex, %	81	85	71	0.123
History of AF, mo	74±63	75±66	70±51	0.726
Duration of continuous AF, mo	19±21	16±17	28±28	0.025
Long-lasting persistent AF, %	58	53	71	0.134
LVEF, %	56±14	56±13	53±15	0.363
LV dysfunction (LVEF <50%), %	26	25	29	0.661
LA diameter, mm	46±7	46±7	48±7	0.128
Hypertension, %	41	37	54	0.138
Structural heart disease, %	40	37	50	0.259
Number of failed AAD	1.9±0.9	2.0±0.9	1.9±1.2	0.755
Administration of amiodarone, %	45	41	58	0.141

AAD indicates antiarrhythmic drugs; AF, atrial fibrillation; LA, left atrial; and LVEF, left ventricular ejection fraction.

The mean duration of continuous AF was 19±21 months (median, 12 months; interquartile range, 6–24 months).

Procedural Termination of AF

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

PV Activity of CL and Procedural Termination of AF

At baseline, the lowest mean CL of the 4 PVs (PV_{mean}) did not significantly differ between patients with AF termination compared with patients without termination (157±27 versus 166±34 ms; P=0.186; Figure 2A). On the contrary, the fastest recorded PV CL (PV_{fast}) was significantly shorter in patients with AF termination compared with those in whom AF could not be terminated (114±23 versus 143±31 ms; P<0.001). There was, however, a notable overlap of values between the 2 groups (Figure 2B). Nonetheless, fast PV activities were rarely observed in patients in whom AF could not be terminated by ablation. A cut-off value, PV_{fast} ≤110 ms, predicted AF termination with 95% positive predictive value (sensitivity 53%, specificity 92%, negative predictive value 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 nontermination group (Figure 3C). In the nontermination group, the PV_{fast} CLs were similar to the LAA CLs resulting in a mean PV_{fast}/LAA ratio of 92±7%. On the contrary, 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±10% (P<0.001) in the AF termination group. The receiver-operator characteristic curve analysis of the PV_{fast}/LAA ratio yielded an optimal cut-off value ≤85% to predict AF termination with an area under the curve of 0.968 (95% confidence interval [CI], 0.922–1.000; P<0.001; Figure 4A). PV_{fast}/LAA ratio ≤85% provided a 96% positive predictive value, 91% negative predictive value, 97% sensitivity, and 88% specificity for AF termination.

Predictors of Procedural AF Termination

The preprocedural 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±10 versus 64±9 years; P=0.001), a shorter duration of continuous AF (16±17 versus 28±28 months; P=0.025), and a nonsignificant trend toward smaller LA dimensions (46±7 versus 48±7 mm; P=0.13). Using a stepwise logistical regression technique incorporating preablation clinical and procedural variables, only the PV_{fast}/LAA ratio independently predicted AF termination (adjusted odds ratio [OR], 0.691; 95% CI, 0.580–0.823; 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%), whereas in the remaining 62 patients (64%), AF terminated during the electrogram-guided or linear ablation steps. In the latter group, the additional (after PVI) procedural and ablation times were 64±43 minutes (median, 54; interquartile range, 30–90) and 34±21 minutes (median, 30; interquartile range, 19–45), 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, whereas moderate ablation was defined as the interquartile range of ablation time. In patients with AF termination during PVI, the PV_{fast} CLs were much shorter than the LA AF CL with a mean PV_{fast}/LAA ratio of 63±6% (Figure 5). A similar PV to LA CL gradient was found in the group of patients with AF termination after limited substrate ablation (PV_{fast}/LAA ratio, 63±6%; P=0.995). In both groups, the PV_{fast}/LAA ratios were notably lower compared with that in the patients where moderate or extensive substrate ablation was required. The mean PV_{fast}/LAA ratio was 74±8% in patients with AF termination after moderate substrate ablation (P=0.001 versus PVI term and P<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 receiver-operator characteristic curve analysis to discriminate patients with AF termination after PVI or limited substrate ablation from those who required more substantial ablation yielded an optimal cut-off value <69% with an area under the curve of 0.921 (95% CI, 0.867–0.975; P<0.001; Figure 4B). A PV_{fast}/LAA ratio <69% provided a 74% positive predictive value, 95% negative predictive value, 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_{fast}/LAA ratios when compared with termination into an AT (66±10% versus 73±9%; P=0.005).

Predictors of AF Termination After PVI or Limited Substrate Ablation

The preprocedural clinical variables were compared between patients in whom AF terminated after PVI or limited additional

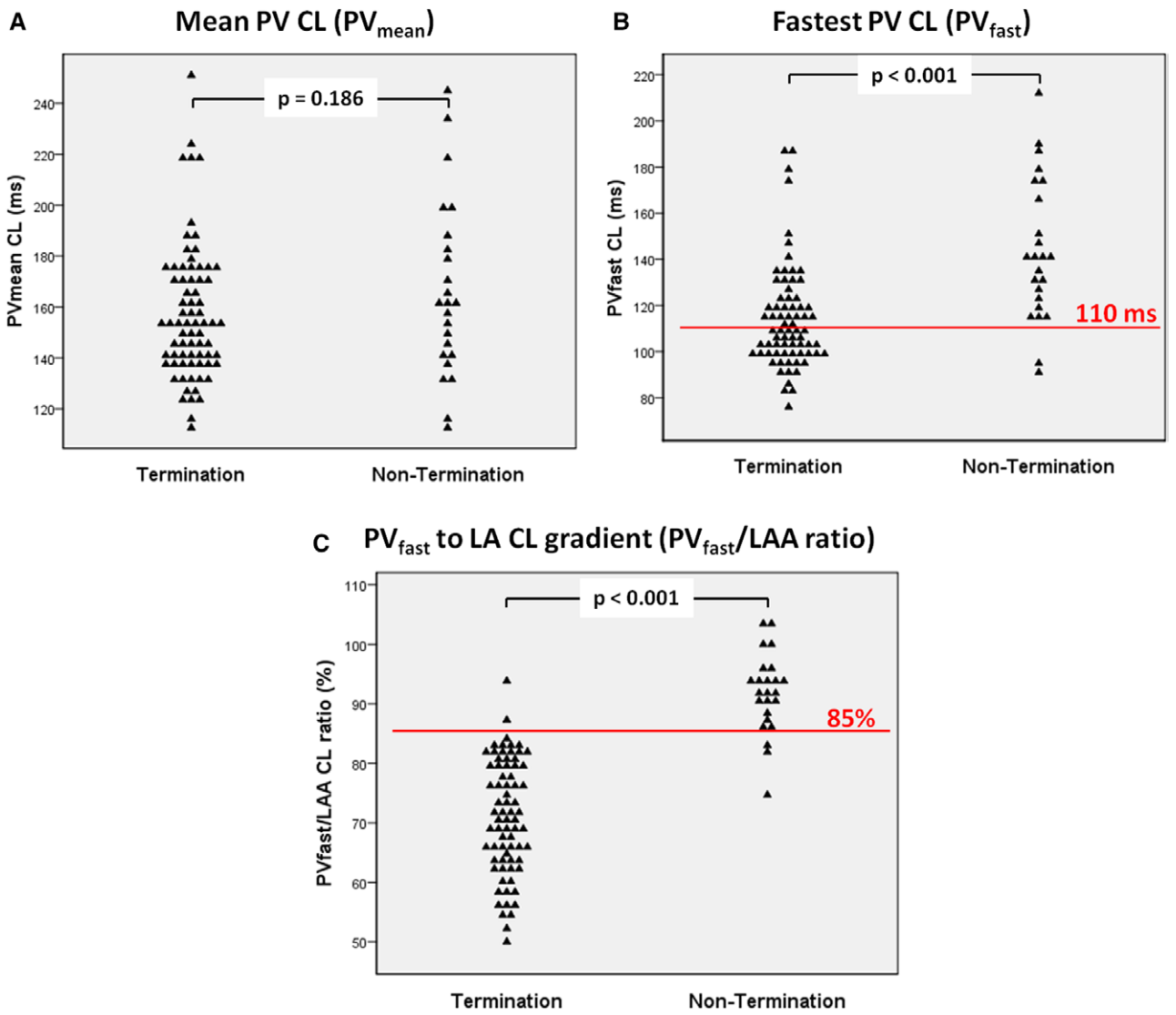

Figure 2. Scatterplot showing the individual values of (**A**) the mean PV CL (PV_{mean}), (**B**) the fastest PV CL (PV_{fast}), and (**C**) the PV_{fast} to left atrial AF CL gradient (PV_{fast}/LAA ratio) in patients with and without procedural AF termination. Horizontal line indicates optimal diagnostic cut-off values to predict AF termination. AF indicates atrial fibrillation; CL, cycle length; LAA, left atrial appendage; and PV, pulmonary vein.

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; *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 preablation clinical and procedural variables, both the PV_{fast}/LAA ratio (adjusted OR, 0.772; 95% CI, 0.688–0.866; *P*<0.001) and the presence of structural heart disease (adjusted OR, 0.071; 95% CI, 0.012–0.438; *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 nontermination group compared with the termination group (52% versus 18%; *P*=0.001).

A repeat ablation procedure was performed in 41 out of 61 patients with arrhythmia recurrence. Ten patients underwent >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 with the nontermination 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%

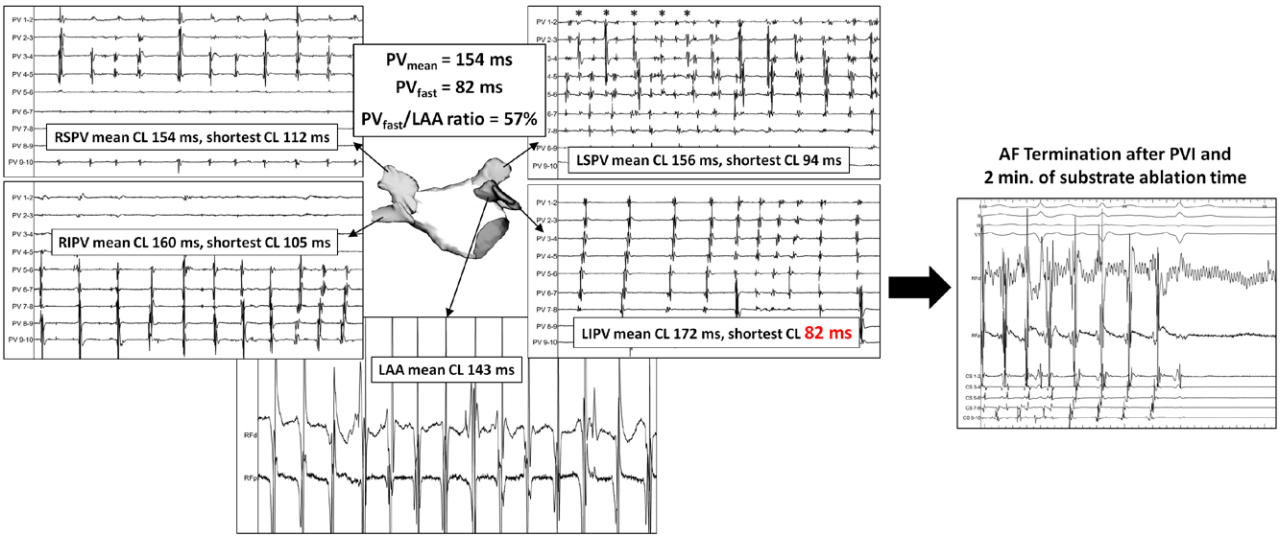

Figure 3. Baseline tracings of the LAA and 4 PVs from a 45-year-old man with continuous AF for 8 months. **Left**, The fastest recorded PV activities observed over a 1-min observation window are illustrated for each vein. Far-field LAA activity is apparent in the left superior PV (asterisks). Rapid PV activities are observed in all 4 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). Although 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. AF indicates atrial fibrillation; CL, cycle length; LAA, left atrial appendage; and PV, pulmonary vein.

of cases (44% taking AADs) against 80% (29% taking AADs) in patients with a ratio ≤85% (P<0.001).

With regard to the subgroup of patients with PV$_{fast}$/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 <69% provided additional outcome stratification over an 85% cut-off as, among the patients without arrhythmia recurrence, only 8% were on AADs compared with 44% in the subgroup with a 69% to 85% PV$_{fast}$/LAA ratio (P=0.002). Therefore, even among the patients with a more favorable outcome (ie, with PV$_{fast}$/LAA ratio ≤85%), a higher clinical success rate off-AADs was observed in patients with a ratio <69% compared with those with a 69% to 85% ratio (80% versus 55%;

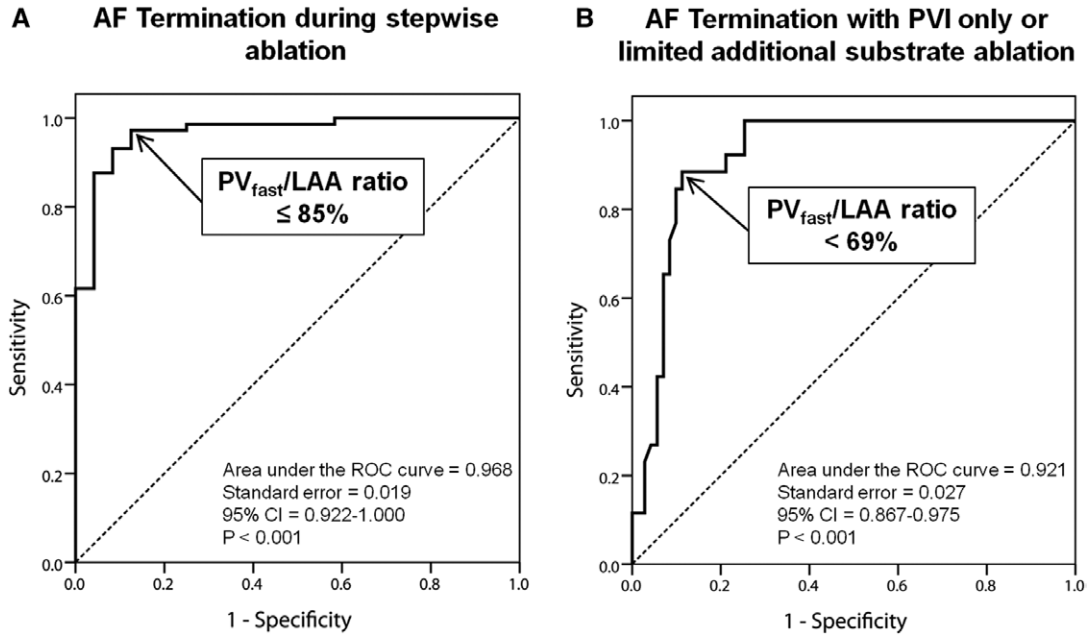

Figure 4. Procedural outcome according to the PV$_{fast}$ to left atrial AF CL gradient. Receiver-operating characteristic curve analysis of the PV$_{fast}$/LAA ratio to predict (**A**) AF termination during stepwise ablation and (**B**) AF termination with only PV isolation or limited substrate-based ablation (first quartile of ablation time). Arrows show optimal cut-off point for sensitivity and specificity. AF indicates atrial fibrillation; CI, confidence interval; CL, cycle length; LAA, left atrial appendage; and PV, pulmonary vein.

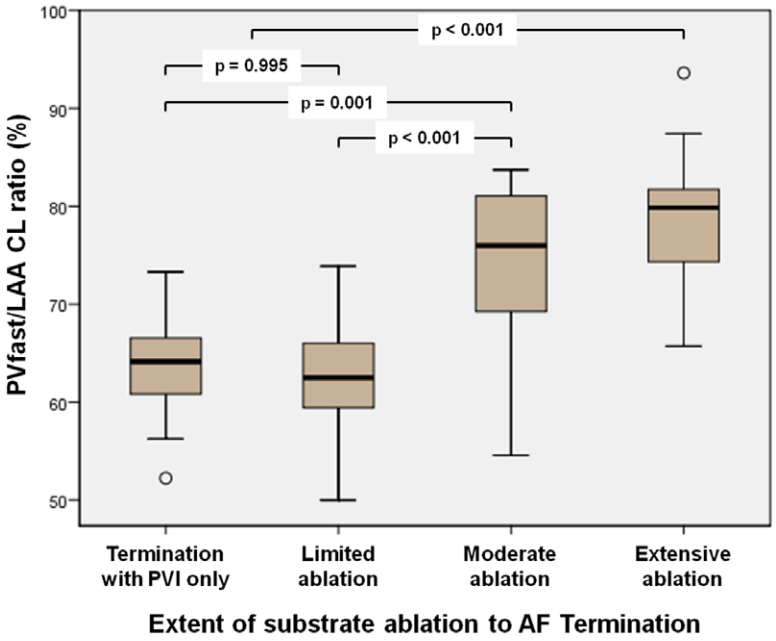

Figure 5. Boxplot showing the values of the PV_{fast} to left atrial AF CL gradient (PV_{fast}/LAA ratio) in patients with AF termination achieved during PV isolation versus substrate-based ablation. The extent of substrate ablation is categorized as limited, moderate, and extensive according to the quartiles of ablation time needed to terminate AF after completion of PV isolation. AF indicates atrial fibrillation; CL, cycle length; LAA, left atrial appendage; and PV, pulmonary vein.

P=0.032). Also, among the patients with arrhythmia recurrence, paroxysmal forms of AF were more often observed in the subgroup with PV_{fast}/LAA ratio <69% than in the rest of the study population (25% versus 6%; *P*=0.032; Figure 6). Figure 7 displays Kaplan–Meier arrhythmia-free survival curves stratified according to PV_{fast}/LAA cut-off 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±10 versus 63±9 years; *P*=0.002), had lower LA dimension (45±6 versus 50±7 mm; *P*=0.003),

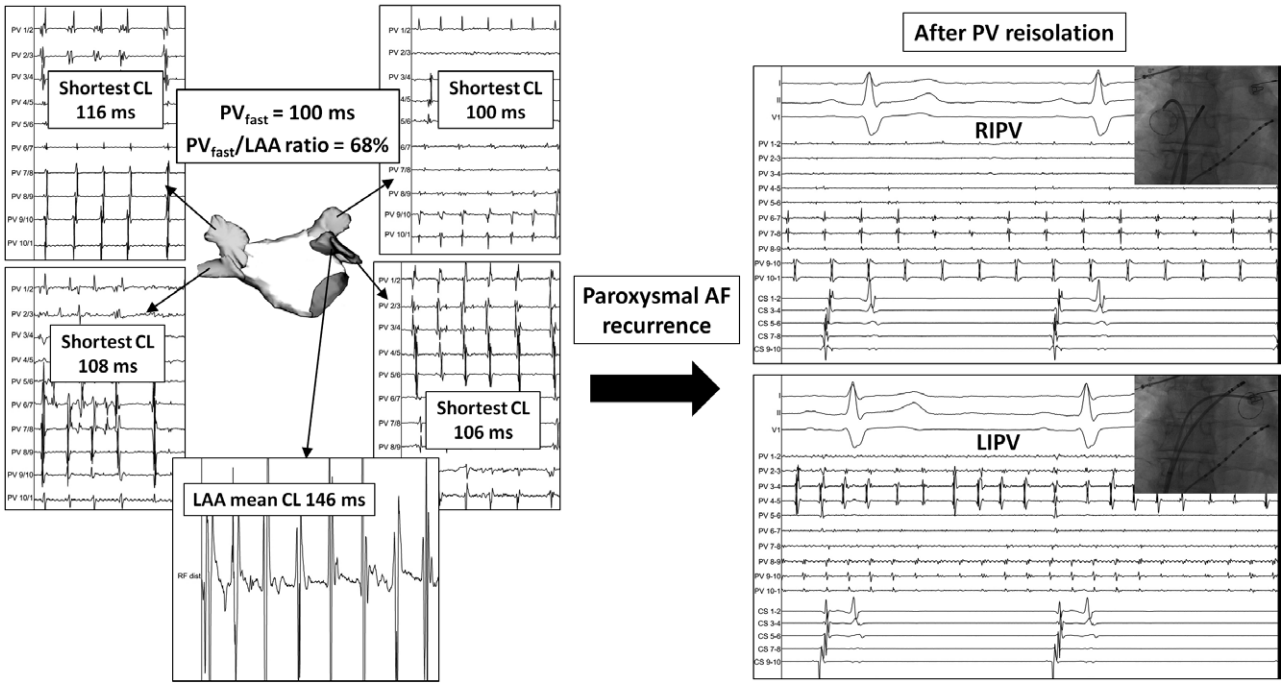

Figure 6. Tracings from a 40-year-old man with continuous AF for 12 months recorded during the index procedure (**left**) and the repeat procedure 3 years later for paroxysmal AF recurrence (**right**). **Left**, At baseline, fast PV activities are recorded in all 4 PVs with a high gradient between the fastest PV activity and the LA AF CL (PV_{fast}/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 3 reconnected PVs was performed in sinus rhythm (**right**). **Right**, Subsequently, intermittent bursts of fast PV activities with exit block were observed in 2 of them. Isoproterenol and rapid burst pacing failed to induce AF afterward. 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. AF indicates atrial fibrillation; CL, cycle length; LAA, left atrial appendage; and PV, pulmonary vein.

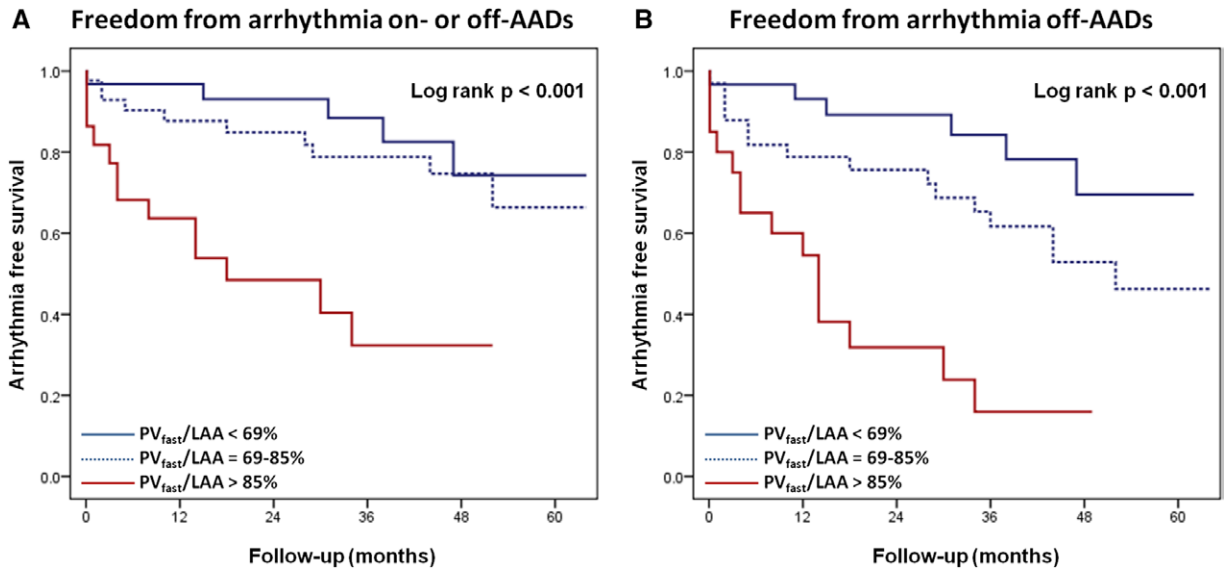

Figure 7. Kaplan–Meier curves of the arrhythmia-free survival after the last procedure for (**A**) the entire population and (**B**) the population off-AADs. Patients are stratified according to the baseline PV_{fast}/LAA ratio. AAD indicates antiarrhythmic drug; AF, atrial fibrillation; CL, cycle length; LAA, left atrial appendage; and PV, pulmonary vein.

and a trend toward shorter duration of continuous AF (16±17 versus 26±28 months; *P*=0.056). In the multivariate analysis incorporating preablation clinical and procedural variables, both the PV_{fast}/LAA ratio (adjusted OR, 0.939; 95% CI, 0.899–0.981; *P*=0.004) and the LA dimension (adjusted OR, 0.905; 95% CI, 0.840–0.974; *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: (1) 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; (2) 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; (3) 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[5] observed reproducible immediate recurrences of AF after cardioversion in 27% of 263 patients with persistent AF. 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 patients with persistent AF where PVs play a major role. Previous studies including mostly patients with paroxysmal AF 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 toward 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 contrary, the absence of a significant gradient between the fastest PV and the AF CL pointed toward 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 from 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 although 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.[14] 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.[15–18] These studies consistently demonstrated that these dominant frequency sources of activity often emanated from the PV region in paroxysmal AF.[15,19–21] On the contrary, 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 1 per minute and they may occur in temporal clusters of less than few seconds.[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 toward more tailored ablation strategies.

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Disclosures

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References

1. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res*. 2002;54:230–246.
2. Haïssaguerre M, Sanders P, Hocini M, Takahashi Y, Rotter M, Sacher F, Rostock T, Hsu LF, Bordachar P, Reuter S, Roudaut R, Clémenty J, Jaïs P.

Catheter ablation of long-lasting persistent atrial fibrillation: critical structures for termination. *J Cardiovasc Electrophysiol*. 2005;16:1125–1137.
3. Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, Khunnawat C, Ngarmukos T. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. *J Am Coll Cardiol*. 2004;43:2044–2053.
4. Haïssaguerre M, Jaïs P, Shah DC, Arentz T, Kalusche D, Takahashi A, Garrigue S, Hocini M, Peng JT, Clémenty J. Catheter ablation of chronic atrial fibrillation targeting the reinitiating triggers. *J Cardiovasc Electrophysiol*. 2000;11:2–10.
5. Inoue K, Kurotobi T, Kimura R, Toyoshima Y, Itoh N, Masuda M, Higuchi Y, Date M, Koyama Y, Okamura A, Iwakura K, Fujii K. Trigger-based mechanism of the persistence of atrial fibrillation and its impact on the efficacy of catheter ablation. *Circ Arrhythm Electrophysiol*. 2012;5:295–301.
6. Oral H, Ozaydin M, Tada H, Chugh A, Scharf C, Hassan S, Lai S, Greenstein R, Pelosi F Jr, Knight BP, Strickberger SA, Morady F. Mechanistic significance of intermittent pulmonary vein tachycardia in patients with atrial fibrillation. *J Cardiovasc Electrophysiol*. 2002;13:645–650.
7. O'Donnell D, Furniss SS, Bourke JP. Paroxysmal cycle length shortening in the pulmonary veins during atrial fibrillation correlates with arrhythmogenic triggering foci in sinus rhythm. *J Cardiovasc Electrophysiol*. 2002;13:124–128.
8. Oral H, Knight BP, Ozaydin M, Chugh A, Lai SW, Scharf C, Hassan S, Greenstein R, Han JD, Pelosi F Jr, Strickberger SA, Morady F. Segmental ostial ablation to isolate the pulmonary veins during atrial fibrillation: feasibility and mechanistic insights. *Circulation*. 2002;106:1256–1262.
9. Tse HF, Lau CP, Kou W, Pelosi F, Oral H, Kim M, Michaud GF, Knight BP, Moscucci M, Strickberger SA, Morady F. Prevalence and significance of exit block during arrhythmias arising in pulmonary veins. *J Cardiovasc Electrophysiol*. 2000;11:379–386.
10. O'Neill MD, Jaïs P, Takahashi Y, Jönsson A, Sacher F, Hocini M, Sanders P, Rostock T, Rotter M, Pernat A, Clémenty J, Haïssaguerre M. The stepwise ablation approach for chronic atrial fibrillation–evidence for a cumulative effect. *J Interv Card Electrophysiol*. 2006;16:153–167.
11. Lin D, Frankel DS, Zado ES, Gerstenfeld E, Dixit S, Callans DJ, Riley M, Hutchinson M, Garcia F, Bala R, Verdino R, Cooper J, Marchlinski FE. Pulmonary vein antral isolation and nonpulmonary vein trigger ablation without additional substrate modification for treating longstanding persistent atrial fibrillation. *J Cardiovasc Electrophysiol*. 2012;23:806–813.
12. Tilz RR, Chun KR, Schmidt B, Fuernkranz A, Wissner E, Koester I, Baensch D, Boczor S, Koektuerk B, Metzner A, Zerm T, Ernst S, Antz M, Kuck KH, Ouyang F. Catheter ablation of long-standing persistent atrial fibrillation: a lesson from circumferential pulmonary vein isolation. *J Cardiovasc Electrophysiol*. 2010;21:1085–1093.
13. Haïssaguerre M, Sanders P, Hocini M, Hsu LF, Shah DC, Scavée C, Takahashi Y, Rotter M, Pasquié JL, Garrigue S, Clémenty J, Jaïs P. Changes in atrial fibrillation cycle length and inducibility during catheter ablation and their relation to outcome. *Circulation*. 2004;109:3007–3013.
14. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation*. 1995;92:1954–1968.
15. Lazar S, Dixit S, Marchlinski FE, Callans DJ, Gerstenfeld EP. Presence of left-to-right atrial frequency gradient in paroxysmal but not persistent atrial fibrillation in humans. *Circulation*. 2004;110:3181–3186.
16. Mandapati R, Skanes A, Chen J, Berenfeld O, Jalife J. Stable microreentrant sources as a mechanism of atrial fibrillation in the isolated sheep heart. *Circulation*. 2000;101:194–199.
17. Mansour M, Mandapati R, Berenfeld O, Chen J, Samie FH, Jalife J. Left-to-right gradient of atrial frequencies during acute atrial fibrillation in the isolated sheep heart. *Circulation*. 2001;103:2631–2636.
18. Skanes AC, Mandapati R, Berenfeld O, Davidenko JM, Jalife J. Spatiotemporal periodicity during atrial fibrillation in the isolated sheep heart. *Circulation*. 1998;98:1236–1248.
19. Lin YJ, Tai CT, Kao T, Tso HW, Higa S, Tsao HM, Chang SL, Hsieh MH, Chen SA. Frequency analysis in different types of paroxysmal atrial fibrillation. *J Am Coll Cardiol*. 2006;47:1401–1407.
20. Sanders P, Berenfeld O, Hocini M, Jaïs P, Vaidyanathan R, Hsu LF, Garrigue S, Takahashi Y, Rotter M, Sacher F, Scavée C, Ploutz-Snyder R, Jalife J, Haïssaguerre M. Spectral analysis identifies sites of high-frequency activity maintaining atrial fibrillation in humans. *Circulation*. 2005;112:789–797.
21. Sanders P, Nalliah CJ, Dubois R, Takahashi Y, Hocini M, Rotter M, Rostock T, Sacher F, Hsu LF, Jönsson A, O'Neill MD, Jaïs P, Haïssaguerre M. Frequency mapping of the pulmonary veins in paroxysmal versus permanent atrial fibrillation. *J Cardiovasc Electrophysiol*. 2006;17:965–972.

CLINICAL PERSPECTIVE

Pulmonary vein (PV) triggers play a major role in the initiation of atrial fibrillation (AF), and PV isolation is the cornerstone of catheter ablation for paroxysmal AF. The success of this approach is limited in nonparoxysmal forms of AF, and adjunctive ablation strategies have been developed to target the alterations in the underlying substrate that may perpetuate AF. Nonetheless, the mechanisms underlying AF persistence are not uniform, and a trigger-based mechanism may be operative in a subset of patients. Identifying these patients remains a challenge. Intermittent rapid rhythms arising in the PVs are commonly observed during sustained episodes of paroxysmal AF. These rapid activities represent an active phenomenon that may have a critical role in the maintenance of AF by providing continued refueling of the fibrillatory process. We therefore evaluated in persistent AF the cycle length gradient between PVs and the left atrium in an attempt to identify patients where PVs play an important role. Our study demonstrates that 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 PV isolation 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 in whom the PVs still play an important role in AF persistence, these findings may be a step toward more tailored ablation strategies.

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

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