

# Long-term outcome of radiofrequency catheter ablation for persistent atrial fibrillation

Wang Yubing, PhD<sup>a,b</sup>, Xu Yanping, MD<sup>a</sup>, Ling Zhiyu, PhD<sup>a</sup>, Chen Weijie, PhD<sup>a</sup>, Su Li, PhD<sup>a</sup>, Du Huaan, PhD<sup>a</sup>, Xiao Peilin, PhD<sup>a</sup>, Liu Zengzhang, MD<sup>a</sup>, Yin Yuehui, MD<sup>a,\*</sup>

## Abstract

Catheter ablation has been widely used to treat atrial fibrillation (AF) and has achieved a better efficacy for paroxysmal AF (PAF) but not for persistent AF (PerAF). Furthermore, a few data on the efficacy and safety of catheter ablation for PerAF were reported. This study aimed to investigate long-term efficacy of radiofrequency catheter ablation (RFCA) for PerAF and explore predictors of late recurrence of atrial fibrillation (LRAF).

A total of 92 consecutive patients with PerAF (64 males, aged  $56.42 \pm 11.24$  years) were enrolled in this study and accepted circumferential pulmonary vein isolation (CPVI) alone or CPVI combined additional ablation.

Maintenance rate of sinus rhythm (SR) was 40.2% after a single procedure with median follow-up of 15 months and 52.2% after mean  $1.3 \pm 0.6$  procedures with median follow-up of 26 months. Long-term SR maintenance rate was no statistical difference between patients with CPVI alone and with CPVI combined additional ablation (48.6% vs 35.1%, log rank test,  $P = .152$ ). Patients with AF duration < 24 months had a higher long-term SR maintenance rate than those with AF duration  $\geq 24$  months (55.6% vs 30.4%, log rank test,  $P = .022$ ). AF duration (OR = 1.015, 95%CI 1.001–1.030,  $P = .015$ ), and early recurrence of AF (ERAF) (OR = 10.654, 95%CI 3.853–29.460,  $P < .001$ ) were predictors of LRAF after a single procedure.

In conclusion, long-term maintenance SR rate was 52.2% in patients with PerAF after multiple procedures with a median over 2-year follow-up. Patients with AF duration < 24 months had better outcome. AF duration and ERAF were predictors of LRAF after a single procedure.

**Abbreviations:** AADs = antiarrhythmic drugs, AF = atrial fibrillation, BMI = body mass index, CPVI = circumferential pulmonary vein isolation, ERAF = early recurrence of atrial fibrillation, LAD = left atrial diameter, LCPV = left common pulmonary vein, LIPV = left inferior pulmonary vein, LRAF = late recurrence of atrial fibrillation, LSPV = left superior pulmonary vein, LVDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, PAF = paroxysmal atrial fibrillation, PerAF = persistent atrial fibrillation, PV = pulmonary vein, PVCT = pulmonary vein computed tomography, RFCA = radiofrequency catheter ablation, RIPV = right inferior pulmonary vein, RMPV = right middle pulmonary vein, RSPV = right superior pulmonary vein, SR = sinus rhythm.

**Keywords:** persistent atrial fibrillation, predictor, radiofrequency catheter ablation, recurrence

## 1. Introduction

Catheter ablation has been widely used in the treatment of atrial fibrillation (AF) since Haissaguerre et al<sup>[1]</sup> found pulmonary veins (PVs) are an important trigger of AF and has achieved a better efficacy for PAF.<sup>[2,3]</sup> Furthermore, with the development of novel technologies and strategies, as well as emerging evidence which catheter ablation as first-line therapy for PerAF is more effective than antiarrhythmic drugs (AADs),<sup>[4]</sup> current guidelines recom-

mend catheter ablation is a Class IIa indication for symptomatic perAF.<sup>[5,6]</sup> However, data on PerAF ablation relatively limited, and long-term success rate was low and marked variations with different ablation techniques and strategies.<sup>[7–9]</sup> Therefore, this study aimed to investigate the long-term efficacy of different radiofrequency catheter ablation (RFCA) strategies for PerAF and explore the predictors of late recurrence of atrial fibrillation (LRAF).

## 2. Methods

### 2.1. Study design

In this study, we defined LRAF as AF recurrence after AF ablation 3 months. According to this definition, the follow-up patients were divided into AF recurrence group and no-recurrence AF group, and a retrospective case-control study was conducted to analyze the data from our single electrophysiology center to clarify long-term efficacy of RFCA for PerAF and predictors of LRAF.

### 2.2. Study population

In this study, 92 consecutive patients (64 males) with PerAF were enrolled. PerAF is defined as continuous AF lasting more than 7 days or requiring cardioversion between 48 hours and 7 days.<sup>[5]</sup> AF duration was obtained by clinical history as well as rhythm

Editor: Ovidiu Constantin Baltatu.

The authors have no conflicts of interest to disclose.

<sup>a</sup> Department of Cardiology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing Cardiac Arrhythmia Service Center, Chongqing, <sup>b</sup> Affiliated Hospital of North Sichuan Medical College, Sichuan, China.

\* Correspondence: Yin Yuehui, Department of Cardiology, the Second Affiliated Hospital of Chongqing Medical University, Chongqing Cardiac Arrhythmia Service Center, Chongqing, 400010, China (e-mail: yinyh63@163.com).

Copyright © 2018 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2018) 97:29(e11520)

Received: 15 November 2017 / Accepted: 22 June 2018

<http://dx.doi.org/10.1097/MD.00000000000011520>

monitoring (including previous electrocardiogram [ECG] or Holter). All patients accepted transesophageal echocardiography evaluations to exclude LA thrombus. Pulmonary vein computed tomography (PVCT) was also performed before ablation to clear the PV anatomy, measure each PV diameter, and calculate the degree of roundness of each PV. The roundness of each PV was expressed by venous ostium index (VOI) of PV, which is equal to the anterior–posterior diameter (APD) of each PV divided by the superior–inferior diameter (SID). A larger VOI indicates a rounder PV. The exclusion criteria were as follows: previous ablation for AF at another institution or only focal ablation without CPVI at the first ablation; loss to follow-up after ablation; valvular heart disease; and uncontrolled heart failure. All patients provided written informed consent before the procedure, and the protocol was approved by Ethics Committee in Second Affiliated Hospital of Chongqing Medical University.

### 2.3. Catheter ablation procedure

Patients were asked to stop anti-arrhythmic drugs (AADs) for 5 half-lives before ablation and oral anticoagulation therapy was replaced by low molecular weight heparin (LMWH) for 3 days up to 12 hours before ablation. PV angiography was firstly performed to verify the PVs ostia and atrium. Subsequently, the LA three-dimensional electroanatomy was constructed guided by the CARTO mapping system (Biosense-Webster) and used Carto image integration module to obtained image integration of PVCT image with constructed electroanatomy to real-time navigate ablation catheter. Then, irrigated RFCA was performed guided by the CARTO mapping system and single Lasso ring electrode (Biosense-Webster). First, CPVI was performed at the PVs atrium with a 3.5-mm irrigated-tip ablation catheter (Navistar, Biosense-Webster). The endpoint of CPVI was to achieved complete electrical isolation of PV, that is, there is no conduction between PV and LA (entrance block and exit block). If AF did not terminate after CPVI, additional ablation (including linear, complex fractionated atrial electrograms (CFAE) ablation or both) would be performed. First, an additional roof line and/or a mitral isthmus line were performed. Subsequent, if this additional line ablation still did not terminate AF, other additional different atrial linear ablations were performed at LA anterior and posterior wall, septum, ridge between the LA appendage and LSPV, coronary sinus, the superior vena cava, or tricuspid isthmus based on the CARTO map. After that, if AF termination still failed, CFAE-targeted ablation was performed based on the CARTO map. The linear ablation endpoint was bidirectional conduction block across the linear lesions. CFAE was defined as described previously<sup>[10]</sup> and the endpoints are the elimination of detectable CFAE site. Finally, if AF was not terminated by the above ablation procedures, we administered intravenous pharmacologic cardioversion, direct current cardioversion or both methods.

### 2.4. Postablation care

After the procedure, all patients were hospitalized for 3 days to continuously monitor rhythm. All patients were routinely administered AADs for 3 months and were administered with LMWH via subcutaneous injection for 3 days followed by warfarin with a target international normalized ratio of 2 to 3 or dabigatran for 2 to 3 months, and thereafter whether anticoagulation was continued according to the CHADS2 score. If CHADS2 score  $\geq 2$ , anticoagulation should be continued.

### 2.5. Follow-up

In this study, 3-month blanking period was applied. AF recurrence was defined as the occurrence of AF, atrial flutter (AFL), atrial tachycardia (AT) of at least lasting 30 seconds that was confirmed by an ECG or Holter monitoring. ERAF was defined as AF recurrence within 3-month blanking period; LRAF was defined as AF recurrence after the blanking period. After discharge, patients were followed-up routinely at 1, 3, 6, 9, 12, 18, and 24 months and once yearly thereafter, and BP measurement, 12-lead surface ECG, 24-hour Holter, and echocardiography were performed. In addition, patients may return to the outpatient clinic for follow-up when they had palpitations or other symptoms at any time. If AF recurrence was observed, AADs were first administered to restore and maintain SR and repeat ablation were recommended after the blanking period.

### 2.6. Repeat ablation

The PV-LA conduction was first evaluated in reablation procedure. If PV-LA conduction restored, CPVI was performed to close all PV-LA conduction gaps. If necessary, additional ablation strategies, similar with the first procedure, were performed. If no PV reconnection was observed, linear, CFAE or both ablations were performed except CPVI.

### 2.7. Statistical analysis

Statistical analysis was performed using SPSS 20.0 software. Continuous variables were presented as mean  $\pm$  SD or median with interquartile range (IQR) (25th, 75th percentile), and categorical variables were expressed as percentages. The differences between groups were compared using an Independent-sample Student's *t*-test. Chi-square statistics (or Fisher's exact test if applicable) were used for categorical variables to compare differences between groups. All the variables with *P*-value (*P*)  $< .1$  in the univariate analysis were selected to the multiple variables logistic regression model. Multiple logistic regression analysis (forward selection method) was used to evaluate predictors of LRAF after a single procedure, calculating the odds ratio (OR), and 95% confidence intervals (CI). Survival analysis was completed using Kaplan–Meier survival curves and log-rank test. A 2-tailed value of *P*  $< .05$  was regarded as statistically significant.

## 3. Results

### 3.1. Patient profile

Clinical baseline characteristics of 92 patients are presented in Table 1. The mean age was  $56.42 \pm 11.24$  years, mean AF duration  $41.33 \pm 39.52$  months (median 24 months, IQR, 9–60 months), mean LAD was  $41.38 \pm 4.22$  mm and mean LVEF (%) was  $63.89 \pm 9.19$ ; right-side PVs were larger than left-side PVs (*P*  $< .001$ ); superior PVs were larger than inferior PVs (*P*  $< .001$ ); and VOI of right-side PVs was larger than that of left-side PVs (*P*  $< .001$ ). According to the long-term follow-up results after a single procedure, 92 patients were divided into recurrence group (55 patients) and no recurrence group (37 patients). Ablation strategies were no difference between groups (*P* = .226); AF duration between the recurrence group and no recurrence group were  $50.22 \pm 42.40$  mm vs  $28.11 \pm 30.85$  mm (*P* = .005), and variations in the number of PVs also exhibited statistical differences between groups (*P* = .037) (Table 2).

**Table 1****Baseline characteristics before catheter ablation.**

Variable	All patients (n=92)
Ages, years	56.42 ± 11.24
Gender, male, n (%)	64 (69.6)
BMI, kg/m <sup>2</sup>	25.24 ± 3.06
AF duration, months, m	41.33 ± 39.52
Associated diseases	
Hypertension, n (%)	36 (39.1)
CHD, n (%)	7 (7.6)
Thyroid disorders	
Hyperthyroidism, n (%)	4 (4.3)
Hypothyroidism, n (%)	10 (10.9)
Diabetes mellitus, n (%)	11 (12.0)
Stroke before ablation, n (%)	10 (10.9)
Echocardiography	
LAD, mm	41.38 ± 4.22
LVDd, mm	47.52 ± 4.97
LVEF (%)	63.89 ± 9.19
Medications before ablation	
Amiodarone, n (%)	13 (14.1)
β-block, n (%)	27 (29.3)
Propafenone, n (%)	4 (4.3)

PVCT	SID, mm	P-value	APD, mm	P-value	VOI	P-value
LSPV	22.45 ± 4.77	<.001	16.03 ± 3.25	<.001	0.73 ± 0.14	.002
LIPV	18.85 ± 3.46		12.31 ± 2.75		0.66 ± 0.14	
RSPV	22.75 ± 4.99	.099	18.70 ± 4.25	.015	0.82 ± 0.09	.147
RIPV	21.56 ± 4.77		17.13 ± 4.77		0.80 ± 0.13	
Left-side PV	20.66 ± 4.53	.003	14.17 ± 3.53	<.001	0.69 ± 0.14	<.001
Right-side PV	22.15 ± 4.90		17.91 ± 4.37		0.81 ± 0.12	
Superior PV	22.60 ± 4.87	<.001	17.36 ± 4.00	<.001	0.78 ± 0.13	.002
Inferior PV	20.21 ± 4.37		14.72 ± 4.37		0.73 ± 0.15	
Variations of PV number, n (%)			23 (25.0)			
LCPV, n (%)			1 (1.1)			
RMPV, n (%)			20 (21.7)			
Others variations, n (%)			2 (2.2)			

AF = atrial fibrillation, APD = anterior–posterior diameter, BMI = body mass index, CHD = coronary heart disease, LAD = left atrial diameter, LCPV = left common pulmonary vein, LIPV = left inferior pulmonary vein, LSPV = left superior pulmonary vein, LVDd = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, PVCT = pulmonary vein computed tomography, RIPV = right inferior pulmonary vein, RMPV = right middle pulmonary vein, RSPV = right superior pulmonary vein, SID = superior–inferior diameter, VOI = venous ostium index.

### 3.2. Clinical outcome

All 92 patients underwent RFCA were followed-up and no death occurred during follow-up period.

### 3.3. Clinical outcome after a single procedure

After a median follow-up 15 (IQR 12–34) months, 55 (59.8%) patients experienced AF recurrence. AF recurrence after a single procedure was 48.9%, 55.4%, 58.7%, and 59.8% at 1, 2, 3, and 4 years, respectively, and 92.7% of AF recurrences occurred in the first 2 years. Long-term free-AF survival after a single procedure was 40.2% (Fig. 1).

In the first procedure, 33 (35.9%) patients underwent CPVI alone, 46 (50.0%) CPVI plus linear ablation, 1 (1.1%) CPVI combined CFAE ablation and 12 (13.0%) CPVI combined linear and CFAE ablation. Long-term SR maintenance was no different between CPVI alone and CPVI plus additional ablation (48.5% vs 35.6%, log-rank test,  $P = .165$ ). In addition, 52 patients experienced ERAF and long-term SR maintenance was lower in patients with ERAF than those without (17.3% vs 70%, log rank test,  $P < .001$ ). Furthermore, arrhythmia types in 55 patients with LRAF included 42 cases of AF, 11 cases of AFL and 2 cases

of AT, and 23 of LRAF patients (13 AF, 10 AFL) received the second procedure. In the second procedure, we found PV-LA reconstruction restored in 15 patients (65%), and the prevalence of PV-LA reconstructions were similar in patients with ERAF and initial AF recurrence after the blanking period (66.7% vs 50.0%,  $P = .636$ ).

### 3.4. Clinical outcome after multiple procedures

After a mean of 1.3 ± 0.6 procedures with median follow-up 26 (IQR, 14–42) months, 44 (47.8%) patients suffered AF recurrence. AF recurrence after multiple procedures was 32.6%, 44.6%, 46.7%, 46.7%, 46.7%, and 47.8% at 1, 2, 3, 4, 5, and 6 years, respectively, and 93.2% of AF recurrence still occurred in the first 2 years. Long-term free-AF survival after multiple procedures was 52.2% (Fig. 2). Around 28 repeat procedures were performed and the distribution of which was 2 in 19 patients, 3 in 3 patients, 4 in 1 patient. The maintenance rate of SR was 40.2%, 51.1%, 52.2%, 52.2% after the 1, 2, 3, and 4 procedures, respectively. The distribution of ablation strategies was as follows: 39 (32.5%) CPVI alone, 70 (58.3%) CPVI combined additional ablation, and 11 (9.2%) other ablation strategies without combined CPVI.

**Table 2**  
Comparisons of clinical characteristics based on recurrence status.

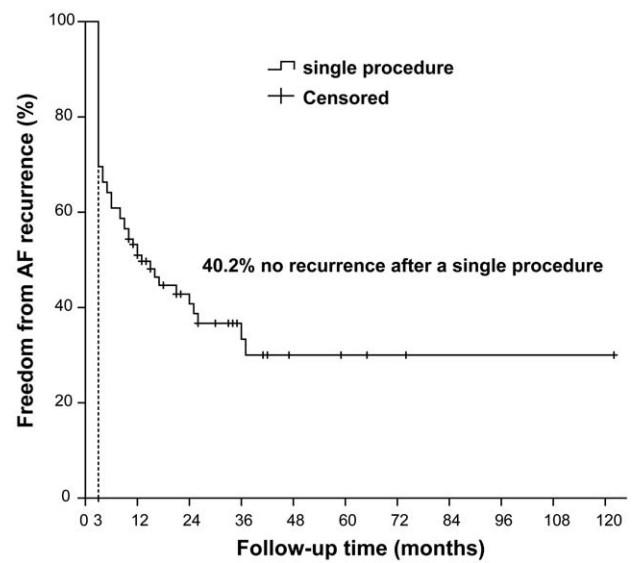
Variable	Recurrence (n=55)	No-recurrence (n=37)	P-value
Age, years	56.93 ± 11.39	55.68 ± 11.14	.603
Gender, male	69.1%	70.3%	.904
BMI, kg/m <sup>2</sup>	24.64 ± 2.74	26.13 ± 3.34	.022
AF duration, months, m	50.22 ± 42.40	28.11 ± 30.85	.005
Associated diseases			
hypertension	38.2%	40.5%	.820
CHD	9.1%	5.4%	.513
Thyroid disorders			
Hyperthyroidism	1.8%	8.1%	0.120
Hypothyroidism	7.3%	16.2%	
Diabetes mellitus	12.7%	10.8%	0.781
Echocardiography			
LAD, mm	41.58 ± 4.37	41.08 ± 4.04	0.580
LVDd, mm	47.27 ± 5.24	47.89 ± 4.57	0.561
LVEF (%)	63.67 ± 8.53	64.22 ± 10.20	0.790
PVCT			
LSPVSID, mm	22.67 ± 3.50	22.14 ± 6.24	0.643
LSPVAPD, mm	16.38 ± 3.23	15.51 ± 3.26	0.211
VOI <sub>LSPV</sub>	0.73 ± 0.13	0.73 ± 0.16	0.979
LIPVSID, mm	18.75 ± 2.70	19.00 ± 4.41	0.734
LIPVAPD, mm	12.41 ± 2.78	12.17 ± 2.74	0.690
VOI <sub>LIPV</sub>	0.67 ± 0.15	0.65 ± 0.13	0.627
RSPVSID, mm	21.96 ± 4.81	23.92 ± 5.09	0.064
RSPVAPD, mm	18.05 ± 4.22	19.66 ± 4.16	0.073
VOI <sub>RSPV</sub>	0.82 ± 0.09	0.83 ± 0.09	0.824
RIPVSID, mm	22.03 ± 4.23	20.86 ± 5.46	0.252
RIPVAPD, mm	17.40 ± 4.44	16.73 ± 4.28	0.481
VOI <sub>RIPV</sub>	0.79 ± 0.15	0.81 ± 0.11	0.537
Variations of PV number	32.7%	13.5%	0.037
Ablation strategies			
CPVI	30.9%	43.2%	0.226
CPVI+ additional ablation	69.1%	56.8%	
ERAF	78.2%	24.3%	<0.001
Medications after procedure			
AADs therapy	100.0%	100.0%	
β-blocker	30.9%	45.9%	0.143
ACEI	65.5%	70.3%	0.629

AADs = antiarrhythmia drugs, ACEI = angiotensin converting enzyme inhibitor, AF = atrial fibrillation, BMI = body mass index, CHD = coronary heart disease, ERAF = early recurrence of atrial fibrillation, LAD = left atrial diameter, LIPV = left inferior pulmonary vein, LSPV = left superior pulmonary vein, LVDd = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, PVCT = pulmonary vein computed tomography, RIPV = right inferior pulmonary vein, RMPV = right middle pulmonary vein, RSPV = right superior pulmonary vein, SID = superior-inferior diameter, VOI = venous ostium index.

**3.5. Predictors of the LRAF after a single procedure**

In univariate analysis, the factors of AF recurrence ( $P < .1$ ) included AF duration, BMI, RSPVSID, RSPVAPD, variations in the number of PVs, and ERAF after a single procedure. These factors were included in a multivariate logistic regression model and regression analysis results demonstrated that AF duration (OR = 1.015, 95%CI 1.001–1.030,  $P = .038$ ) and ERAF (OR = 10.654, 95%CI 3.853–29.460,  $P < .001$ ) were predictors of LRAF after a single procedure (Table 3).

Additionally, according to the median (24 months) of AF duration, patients were divided into those with AF duration of < 24 months ( $n = 36$ ) and those with AF duration of  $\geq 24$  months ( $n = 56$ ). The baseline characteristics are summarized in Table 4. It can be seen from Table 4, except for younger age in patients

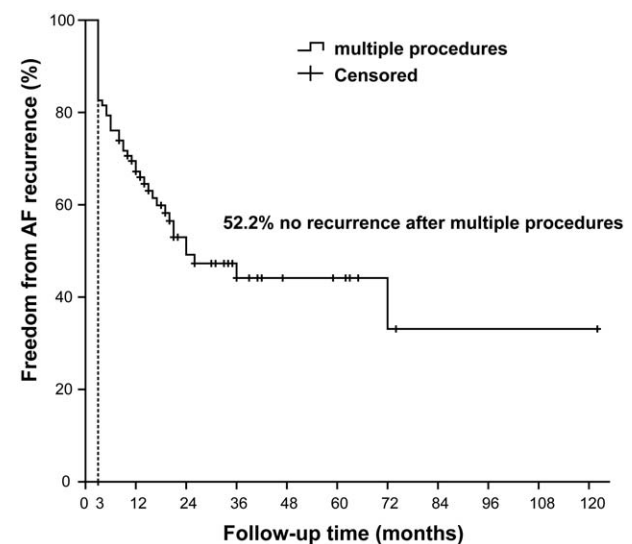


**Figure 1.** Kaplan–Meier analysis of the freedom from AF after a single procedure. AF = atrial fibrillation.

with AF duration of < 24 months ( $P = .001$ ), other baseline data was no difference between 2 groups. Survival analysis indicated long-term SR maintenance rate was higher in patients with AF duration of < 24 months than those with AF duration of  $\geq 24$  months (55.6% vs 30.4%, log rank test,  $P = .021$ ) after a single procedure.

**3.6. Complications**

There was no procedure-related death and the complication rate for all 120 procedures was 5.8%. Details were as follows: 3 (2.5%) cardiac tamponade, 1 (0.8%) transient ischemic attack (TIA), 1 (0.8%) symptomatic PV stenosis, 1 (0.8%) hematoma, and 1 (0.8%) pseudoaneurysm.



**Figure 2.** Kaplan–Meier analysis of the freedom from AF after multiple procedures. AF = atrial fibrillation.



**Table 3****Predictors of LRAF after a single procedure by logistic regression analysis.**

Variable	B	S.E.	Wald	df	Sig.	OR	95% CI for OR
AF duration	0.015	0.007	4.306	1	0.038	1.015	1.001–1.030
ERAF	2.366	0.519	20.786	1	<0.001	10.654	3.853–29.460
Constant	–1.399	0.455	9.466	1	0.002	0.247	

ERAF = early recurrence of atrial fibrillation, LRAF = late recurrence of atrial fibrillation.

## 4. Discussions

### 4.1. Main findings

In this study, the main findings are the following: Long-term SR maintenance rate was 52.2% with 2-year follow-up after multiple RFCA procedures; almost all AF recurrence occurred in the first 2 years regardless of after single- and multiple-procedure; repeat ablation increased the maintenance rate of SR; More than half of all ablation strategies was CPVI plus additional ablation regardless of after single- and multiple-procedure but CPVI plus additional ablation did not decrease AF recurrence; and AF duration and ERAF were predictors of LRAF after a single procedure; furthermore, patients with AF duration of < 24 months had better outcome.

**Table 4****Comparisons of baseline data before ablation based on AF duration.**

Variable	<24 months (n=36)	≥24 months (n=56)	P-value
Age, years	51.53 ± 12.13	59.57 ± 9.47	.001
Gender, male	66.7%	71.4%	.628
BMI, kg/m <sup>2</sup>	25.31 ± 2.73	25.19 ± 3.28	.847
Associated diseases			
hypertension	38.9%	39.3%	.970
CHD	5.6%	8.9%	.551
Thyroid disorders	13.9%	16.1%	.776
Diabetes mellitus	13.9%	10.7%	.647
Echocardiography			
LAD, mm	41.44 ± 4.21	41.34 ± 4.27	.908
LVDd, mm	47.53 ± 4.69	47.52 ± 5.18	.993
LVEF (%)	63.53 ± 9.51	64.13 ± 9.05	.763
PVCT			
LSPVSID, mm	22.68 ± 4.46	22.32 ± 4.10	.728
LSPVAPD, mm	15.83 ± 3.47	16.16 ± 3.13	.642
VOI <sub>LSPV</sub>	0.71 ± 0.14	0.74 ± 0.14	.264
LIPVSID, mm	18.26 ± 2.62	19.24 ± 3.88	.186
LIPVAPD, mm	12.07 ± 2.47	12.47 ± 2.93	.498
VOI <sub>LIPV</sub>	0.66 ± 0.12	0.66 ± 0.15	.881
RSPVSID, mm	23.36 ± 4.99	22.36 ± 5.00	.349
RSPVAPD, mm	18.90 ± 4.31	18.57 ± 4.24	.715
VOI <sub>RSPV</sub>	0.81 ± 0.08	0.83 ± 0.10	.198
RIPVSID, mm	21.29 ± 5.04	21.73 ± 4.62	.672
RIPVAPD, mm	16.78 ± 3.93	17.36 ± 4.65	.541
VOI <sub>RIPV</sub>	0.80 ± 0.11	0.80 ± 0.15	.794
Variations of PV number	19.4%	28.6%	.324

Data are expressed as mean ± SD or n (%).

AF = atrial fibrillation, APD = anterior–posterior diameter, BMI = body mass index, CHD = coronary heart disease, LAD = left atrial diameter, LIPV = left inferior pulmonary vein, LSPV = left superior pulmonary vein, LVDd = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, PVCT = pulmonary vein computed tomography, RIPV = right inferior pulmonary vein, RMPV = right middle pulmonary vein, RSPV = right superior pulmonary vein, SID = superior-inferior diameter, VOI = venous ostium index.

### 4.2. Ablation strategy and long-term efficacy of catheter ablation for PerAF

The mechanism of trigger and maintenance of PerAF is complex. Non-PV triggers of AF are common and play an important role in patients with PerAF.<sup>[11,12]</sup> Therefore, additional ablation targeting non-PV triggers based on PVI is often required in patients with PerAF. However, whether additional ablations can improve outcome remains contentious and the success rate varies with studies.<sup>[7–9,13–16]</sup> Brooks et al<sup>[7]</sup> reported the success rate was higher with PVI plus additional ablation than with PVI alone (38%–62% vs 21%–22%); Elayi et al<sup>[13]</sup> reported additional ablation increased 16-months SR maintenance rate after a single procedure; Scherr et al<sup>[14]</sup> reported stepwise ablation strategy ending with AF termination improve 5-year AF ablation success rate. However, RASTA study indicated that in PerAF patients, additional substrate modification beyond PVI does not improve single procedure outcome.<sup>[15]</sup> Atienza et al<sup>[16]</sup> reported CPVI plus high-frequency source ablation offered no incremental value for PerAF. Furthermore, a recent large randomized controlled trial reported neither linear ablation nor CFAE ablation in addition to PVI decrease AF recurrence.<sup>[9]</sup> In this study, we also found additional ablation based on CPVI did not increased long-term SR maintenance rate compared with CPVI alone after a single procedure. Its reason is unclear. Additional ablation may cause new arrhythmogenic substrates formation and these substrates may result in AF recurrence, which may impair any benefits regarding additional ablation. However, a meta-analysis showed PVI with limited linear ablation within the left atrium significantly reduced AF recurrence while more extensive linear lesion or biatrial ablation not.<sup>[17]</sup> Therefore, accurately localizing non-PV foci and limited additional ablation using different ablation strategies such as combined cryoballoon and radio-frequency ablation method<sup>[18]</sup> is necessary. In this study, except 2 empirical lines, we also ablate in other non-PV triggers based on the CARTO mapping results because ablation of these triggers maybe benefits.<sup>[19]</sup> We did not perform subanalysis of each specific additional ablation line because sample is small. Now, we are continuing to expand our sample size to further analyze the impact of each specific ablation line on ablation outcomes to detect more accurate additional ablation line and develop optimal ablation strategies for PerAF.

### 4.3. Predictors of LRAF after a single procedure

Previous studies have identified some predictors for LRAF, including early recurrence, LA size, AF duration, and failure to terminate AF by ablation and so on,<sup>[8,10,14,20–22]</sup> but the predictors of AF recurrence were inconsistent among different studies. In present study, we found AF duration and ERAF were predictors of LRAF after a single procedure while LAD not. In this study, LAD was not a predictor of LRAF probably because LAD was only 41 mm much smaller than that in other studies.<sup>[14,22]</sup>

AF duration is a predictor of LRAF and has been confirmed by many studies.<sup>[8,10,14,20,21]</sup> Matsuo et al<sup>[20]</sup> reported AF duration was longer in patients with recurrence than those without ( $57 \pm 54$  months vs  $23 \pm 21$  months,  $P < .0001$ ), further identified AF recurrence after the final ablation was higher in patients with AF duration  $> 21$  months. Scherr et al<sup>[14]</sup> identified AF duration  $\geq 18$  months predicted AF recurrence. Tilz et al<sup>[8]</sup> also reported AF duration independently predicted AF recurrence and patients with AF duration  $< 2$  years had a significantly higher success rate than those of AF duration  $> 2$  years. In this study, we found AF duration was a predictor of LRAF. Furthermore, Patients with AF duration  $\leq 24$  months had higher long-term SR maintenance rate. This may be attributed to an increase of arrhythmogenic substrates with longer AF duration.<sup>[11,12,23]</sup> Therefore, ablation for PerAF should be performed at early phase of AF.

Additionally, in this study, we found ERAF was also a predictor of LRAF after a single procedure. ERAF is common after ablation and some patients with ERAF did not again experience AF recurrence during the subsequent long-term follow-up.<sup>[24]</sup> Furthermore, ERAF is generally considered to be due to acute thermal injury and inflammatory response caused by radiofrequency energy and a transient reversible process.<sup>[25,26]</sup> However, previous studies also found patients with ERAF have lower long-term SR maintenance rate than patients without ERAF and identified ERAF can predict LRAF.<sup>[21,27]</sup> These results suggest ERAF, except for catheter-induced transient trauma, also has other mechanisms. Indeed, Lellouche et al<sup>[28]</sup> reported in 143 PAF and PerAF patients with ERAF underwent a second ablation, 59% of cases had PV-LA reconnection. Yanagisawa et al<sup>[29]</sup> reported in 66 PAF and PerAF patients with ERAF underwent early reablation, 77% patients had PV reconnection. Furthermore, Miyazaki et al<sup>[30]</sup> reported the prevalence of PV reconnections and non-PV foci were similar between patients with ERAF and those with recurrence beyond the blanking period. In this study, we also found that the prevalence of PV-LA reconnections was no difference between patients with ERAF and initial AF recurrence after the blanking period in second procedure. These results implied PV-LA reconnections are responsible for ERAF. Therefore, ERAF is attributed to not only catheter-induced transient trauma but also PV-LA reconnection and non-PV foci. In addition, Lellouche et al<sup>[28]</sup> reported early reablation within the blanking period can improve LRAF but increased the number of procedures. Yanagisawa et al<sup>[29]</sup> reported early reablation increased the number of procedures and was not beneficial for PerAF. These suggest reablation of ERAF may be more appropriate after blanking period to avoid potential risks and some unnecessary reablation.

#### 4.4. Limitation

Because ECG and 24-hour Holter was performed at intermittent regular follow-up time and the time of symptoms to detect AF recurrence, some asymptomatic AF may have remained undetected, which may lead to underestimate AF recurrence. Therefore, it is necessary to continuously monitor the patient's rhythm during the follow-up period to know the real world of AF recurrence. In addition, we only found that PV-LA reconnection and non-PV foci accounted for a large proportion in patients with AF recurrence in the second ablation procedure but cannot identify their respective triggering role in the AF recurrence. Also, this study is a retrospective study therefore its results need further confirmed by prospective studies.

## 5. Conclusion

Approximately 50% or more patients with PerAF can maintain SR with a median over 2-year follow-up by multiple ablation procedures. Additional ablation based on CPVI did not increased long-term SR maintenance rate. AF duration and ERAF were predictors of LRAF after a single procedure. Patients with AF duration  $< 24$  months had superior outcome. Therefore, PerAF should be performed at early stage in the course of the AF journey.

### Author contributions

**Conceptualization:** Wang Yubing, Ling Zhiyu, Su Li, Liu Zengzhang, Yin Yuehui.

**Data curation:** Wang Yubing, Xu Yanping, Yin Yuehui.

**Formal analysis:** Wang Yubing, Chen Weijie, Yin Yuehui.

**Investigation:** Wang Yubing, Xu Yanping.

**Methodology:** Wang Yubing, Ling Zhiyu, Chen Weijie, Du Huaan, Xiao Peilin.

**Project administration:** Wang Yubing, Ling Zhiyu, Su Li, Yin Yuehui.

**Resources:** Wang Yubing, Xu Yanping, Chen Weijie.

**Software:** Wang Yubing.

**Supervision:** Wang Yubing, Ling Zhiyu, Su Li, Du Huaan, Xiao Peilin, Yin Yuehui.

**Writing – original draft:** Wang Yubing.

**Writing – review & editing:** Ling Zhiyu, Su Li, Liu Zengzhang, Yin Yuehui.

### References

- [1] Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;339:659–66.
- [2] Ganesan AN, Shipp NJ, Brooks AG, et al. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *J Am Heart Assoc* 2013;2:e004549.
- [3] Takigawa M, Takahashi A, Kuwahara T, et al. Long-term follow-up after catheter ablation of paroxysmal atrial fibrillation: the incidence of recurrence and progression of atrial fibrillation. *Circ Arrhythm Electrophysiol* 2014;7:267–73.
- [4] Mont L, Bisbal F, Hernandez-Madrid A, et al. Catheter ablation vs antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J* 2014; 35:501–7.
- [5] Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *Europace* 2012;14:528–606.
- [6] January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014;130:2071–104.
- [7] Brooks AG, Stiles MK, Laborde J, et al. Outcomes of long-standing persistent atrial fibrillation ablation: a systematic review. *Heart Rhythm* 2010;7:835–46.
- [8] Tilz RR, Rillig A, Thum AM, et al. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy. *J Am Coll Cardiol* 2012;60:1921–9.
- [9] Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med* 2015;372:1812–22.
- [10] Cai L, Yin Y, Ling Z, et al. Predictors of late recurrence of atrial fibrillation after catheter ablation. *Int J Cardiol* 2013;164:82–7.
- [11] Bhargava M, Di Biase L, Mohanty P, et al. Impact of type of atrial fibrillation and repeat catheter ablation on long-term freedom from atrial fibrillation: results from a multicenter study. *Heart Rhythm* 2009;6: 1403–12.

- [12] Lim HS, Hocini M, Dubois R, et al. Complexity and distribution of drivers in relation to duration of persistent atrial fibrillation. *J Am Coll Cardiol* 2017;69:1257–69.
- [13] Elayi CS, Verma A, Di Biase L, et al. Ablation for longstanding permanent atrial fibrillation: results from a randomized study comparing three different strategies. *Heart Rhythm* 2008;5:1658–64.
- [14] Scherr D, Khairy P, Miyazaki S, et al. Five-year outcome of catheter ablation of persistent atrial fibrillation using termination of atrial fibrillation as a procedural endpoint. *Circ Arrhythm Electrophysiol* 2015;8:18–24.
- [15] Dixit S, Marchlinski FE, Lin D, et al. Randomized ablation strategies for the treatment of persistent atrial fibrillation: RASTA study. *Circ Arrhythm Electrophysiol* 2012;5:287–94.
- [16] Atienza F, Almendral J, Ormaetxe JM, et al. Comparison of radiofrequency catheter ablation of drivers and circumferential pulmonary vein isolation in atrial fibrillation: a noninferiority randomized multicenter RADAR-AF trial. *J Am Coll Cardiol* 2014;64:2455–67.
- [17] Wynn GJ, Das M, Bonnett LJ, et al. Efficacy of catheter ablation for persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomized and nonrandomized controlled trials. *Circ Arrhythm Electrophysiol* 2014;7:841–52.
- [18] Guler TE, Aksu T, Yalin K, et al. Combined cryoballoon and radiofrequency ablation versus radiofrequency ablation alone for longstanding persistent atrial fibrillation. *Am J Med Sci* 2017;354:586–96.
- [19] Liang JJ, Elafros MA, Muser D, et al. Pulmonary vein antral isolation and nonpulmonary vein trigger ablation are sufficient to achieve favorable long-term outcomes including transformation to paroxysmal arrhythmias in patients with persistent and long-standing persistent atrial fibrillation. *Circ Arrhythm Electrophysiol* 2016;9:11.
- [20] Matsuo S, Lellouche N, Wright M, et al. Clinical predictors of termination and clinical outcome of catheter ablation for persistent atrial fibrillation. *J Am Coll Cardiol* 2009;54:788–95.
- [21] Ciconte G, Baltogiannis G, de Asmundis C, et al. Circumferential pulmonary vein isolation as index procedure for persistent atrial fibrillation: a comparison between radiofrequency catheter ablation and second-generation cryoballoon ablation. *Europace* 2015;17:559–65.
- [22] McCready JW, Smedley T, Lambiase PD, et al. Predictors of recurrence following radiofrequency ablation for persistent atrial fibrillation. *Europace* 2011;13:355–61.
- [23] Haissaguerre M, Hocini M, Denis A, et al. Driver domains in persistent atrial fibrillation. *Circulation* 2014;130:530–8.
- [24] Andrade JG, Khairy P, Verma A, et al. Early recurrence of atrial tachyarrhythmias following radiofrequency catheter ablation of atrial fibrillation. *Pacing Clin Electrophysiol* 2012;35:106–16.
- [25] Koyama T, Tada H, Sekiguchi Y, et al. Prevention of atrial fibrillation recurrence with corticosteroids after radiofrequency catheter ablation: a randomized controlled trial. *J Am Coll Cardiol* 2010;56:1463–72.
- [26] Lim HS, Schultz C, Dang J, et al. Time course of inflammation, myocardial injury, and prothrombotic response after radiofrequency catheter ablation for atrial fibrillation. *Circ Arrhythm Electrophysiol* 2014;7:83–9.
- [27] Liang JJ, Elafros MA, Chik WW, et al. Early recurrence of atrial arrhythmias following pulmonary vein antral isolation: timing and frequency of early recurrences predicts long-term ablation success. *Heart Rhythm* 2015;12:2461–8.
- [28] Lellouche N, Jais P, Nault I, et al. Early recurrences after atrial fibrillation ablation: prognostic value and effect of early reablation. *J Cardiovasc Electrophysiol* 2008;19:599–605.
- [29] Yanagisawa S, Inden Y, Kato H, et al. Effect and significance of early reablation for the treatment of early recurrence of atrial fibrillation after catheter ablation. *Am J Cardiol* 2016;118:833–41.
- [30] Miyazaki S, Taniguchi H, Nakamura H, et al. Clinical significance of early recurrence after pulmonary vein antrum isolation in paroxysmal atrial fibrillation—insight into the mechanism. *Circ J* 2015;79:2353–9.