

Radiofrequency catheter ablation for paroxysmal atrial fibrillation: outcomes during a 3-year follow-up period

Journal of International Medical Research

2019, Vol. 47(4) 1636–1648

© The Author(s) 2019

Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/0300060519828522

journals.sagepub.com/home/imr



Yubing Wang^{1,2}, Yanping Xu¹, Zhiyu Ling¹,
Weijie Chen¹, Li Su¹, Huan Du¹, Peilin Xiao¹,
Zengzhang Liu¹ and Yuehui Yin¹ 

Abstract

Objective: This study was performed to observe the effect of radiofrequency catheter ablation (RFCA) in patients with paroxysmal atrial fibrillation (PAF) and to explore the risk factors for late recurrence of atrial fibrillation (LRAF) after a single RFCA session.

Methods: In this retrospective study, 243 patients with PAF underwent RFCA and were followed up regularly.

Results: At a median follow-up of 37 months after a single procedure, 60.5% of patients maintained sinus rhythm (SR), and at a median follow-up of 42 months after multiple procedures, 74.9% of patients maintained SR. The statistically significant risk factors for LRAF after a single RFCA session were the left atrial diameter (LAD), left inferior pulmonary vein superior–inferior diameter (LIPV SID), PV number variation, circumferential pulmonary vein isolation (CPVI) combined with additional ablation, and early recurrence of atrial fibrillation (ERAF). The best cut-off value for LAD was 35.5 mm.

Conclusions: During a 3-year follow-up, about 70% of the patients with PAF maintained SR. LRAF after a single procedure was associated with the LAD, LIPV SID, PV number variation, CPVI combined with additional ablation, and ERAF.

Keywords

Atrial fibrillation, radiofrequency catheter ablation, recurrence, predictor, left atrial diameter, pulmonary vein

Date received: 25 September 2018; accepted: 14 January 2019

¹Department of Cardiology, the Second Affiliated Hospital of Chongqing Medical University, Chongqing Cardiac Arrhythmia Service Center, Chongqing, China

²Affiliated Hospital of North Sichuan Medical College, Sichuan, China

Corresponding author:

Yuehui Yin, Department of Cardiology, the Second Affiliated Hospital of Chongqing Medical University, Chongqing Cardiac Arrhythmia Service Center, No. 74 Linjiang Road, Yuzhong District, Chongqing 400010, China.

Email: yinyh63@163.com



Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice, and the prevalence rate of AF in the general population is high.^{1,2} Catheter ablation is a well-established treatment for AF and can lead to a long-term sinus rhythm (SR) maintenance rate of >70% in patients with paroxysmal AF (PAF) after multiple procedures.^{3,4} Catheter ablation for AF significantly improves the prognosis of patients with heart failure.⁵ Thus, catheter ablation has been recommended as the first-line therapy in patients with PAF.^{6,7} However, the AF recurrence rate remains high. Different ablation strategies,^{8,9} energy levels,¹⁰ and types of AF^{11,12} have different prognoses. Therefore, selection of the most appropriate patients and optimal ablation strategy has a decisive impact on the prognosis. The present study was performed to investigate the long-term efficacy of radiofrequency catheter ablation (RFCA) for PAF and explore the predictors of late recurrence of AF (LRAF) in an effort to provide the basis for choosing the optimal strategy and best candidate patients.

Material and methods

Study population

Symptomatic patients with PAF who underwent catheter ablation from April 2004 to June 2015 in our center were consecutively enrolled in this retrospective study. PAF is defined as spontaneous termination of AF within 7 days.⁶ All patients underwent transesophageal echocardiography evaluations to rule out a left atrial (LA) thrombus. Pulmonary vein (PV) computed tomography (PVCT) was also performed before ablation to clarify the PV anatomy, measure each PV diameter, and calculate the degree of roundness of each PV as expressed by the venous ostium

index (VOI) of the 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. In addition, variations in the PV anatomy were recorded. The presence of two single PVs (a separate right and left PV) was defined as normal; otherwise, the patient was considered to have a PV number variation. The exclusion criteria were as follows: (1) previous ablation for AF at another institution or only focal ablation without circumferential PV isolation (CPVI) at the first ablation, (2) loss to follow-up after ablation, (3) valvular heart disease requiring surgery, and (4) New York Heart Association functional class >II. All patients provided written informed consent before the procedure, and the protocol was approved by the institutional ethics review committee.

Catheter ablation procedure

The patients were asked to stop taking antiarrhythmic drugs (AADs) for five half-lives before ablation, and oral anticoagulation therapy was replaced by low-molecular-weight heparin for 3 days up to 12 hours before ablation. PV angiography was first performed to verify the ostia and antrum of the PV. We then constructed the LA three-dimensional electroanatomy guided by the CARTO mapping system (Biosense Webster, Irvine, CA, USA) and used the CARTO image integration module to obtain the image integration of the PVCT image with the constructed electroanatomy to navigate the ablation catheter in real time. Irrigated RFCA was then performed with guidance by the CARTO mapping system and a single Lasso ring electrode (Biosense Webster). The ablation steps were as follows. First, CPVI was performed at the atrium of the PV with a 3.5-mm irrigated-tip ablation catheter (Navistar; Biosense Webster). The endpoint of the CPVI procedure was abolition or dissociation of the PV potentials or

failure to induce AF. The AF induction protocol involved burst pacing with a 20-mA pacing output and 2-ms pulse width from the proximal coronary sinus. AF of ≥ 30 s was considered inducible. If AF continued or was induced, linear ablation was performed at the LA roof and mitral isthmus. The linear ablation endpoint was a bidirectional conduction block across the linear lesions. If AF persisted or was induced after the above-described procedure, ablation of the complex fractionated atrial electrogram (CFAE) was performed. The CFAE was defined as previously described,¹³ and the endpoint was the elimination of detectable CFAE sites. Finally, if AF was not terminated using the above-described ablation procedures, we performed intravenous pharmacologic cardioversion, direct current cardioversion, or both.

Post-ablation care

After the procedure, all patients were hospitalized for 1 week for continuous rhythm monitoring to observe for recurrence. The patients were not routinely administered AADs. If AF, atrial flutter (AFL), atrial tachycardia (AT), or frequent atrial premature beats were confirmed, AADs were administered to these patients for 3 months. Moreover, all patients were administered low-molecular-weight heparin via subcutaneous injection for 3 days followed by warfarin or dabigatran for 3 months, and anticoagulation was thereafter continued according to the CHADS₂ score. If the CHADS₂ score was ≥ 2 , anticoagulation was continued. The dose of warfarin was adjusted to maintain an international normalized ratio of 2.0 to 3.0.

Follow-up

In this study, a 3-month blanking period was applied. AF recurrence was defined as the occurrence of AF, AFL, or AT lasting

at least 30 s as confirmed by electrocardiography or Holter monitoring. Early recurrence of AF (ERAF) was defined as AF recurrence within a 3-month blanking period, and LRAF was defined as AF recurrence after the blanking period. After discharge, the patients were followed up at 1, 3, 6, 9, 12, 18, and 24 months and once yearly thereafter, and BP measurement, 12-lead surface electrocardiography, 24-hour Holter monitoring, and echocardiography were performed. In addition, the patients were instructed to 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 the patients to restore and maintain SR, and repeat ablation was considered after the blanking period.

Repeat ablation

The PV-LA conduction was first evaluated during the reablation procedure. If the PV-LA conduction was restored, CPVI was performed to close all PV-LA conduction gaps. If necessary, additional ablation strategies similar to the first procedure were performed. If no PV reconnection was observed, then linear ablation, CFAE ablation, or both was performed (CPVI was not performed).

Statistical analysis

Statistical analysis was performed using SPSS 20.0 software (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean \pm standard deviation or median with interquartile range (IQR) (25th, 75th percentile), and categorical variables are expressed as percentage. The differences between the groups were compared using the independent-samples Student's t-test. Chi-square statistics (or Fisher's exact test if applicable) were used to compare categorical variables between groups.

A multivariate Cox stepwise regression model was used to determine the predictors of LRAF after a single procedure, and the hazard ratio (HR) and 95% confidence interval (CI) were calculated. Clinical variables with a P-value of <0.1 in the univariate analysis were included in the multivariate Cox regression model. A receiver operating characteristic curve analysis was performed to determine the optimal cut-off value for the LA diameter (LAD) in predicting LRAF after a single procedure. Survival analysis was completed using Kaplan–Meier survival curves and the log-rank test. A two-tailed test with a P value of <0.05 was considered statistically significant.

Results

Patient profiles

In total, 243 symptomatic patients with PAF (147 men) were enrolled in this study. The patients' clinical baseline characteristics are presented in Table 1. Their mean age was 58.55 ± 11.19 years, mean LAD was 36.47 ± 5.09 mm, and mean left ventricular ejection fraction was $69.60\% \pm 8.51\%$. The right-side PVs were significantly larger than the left-side PVs ($P < 0.001$), and the superior PVs were significantly larger than the inferior PVs ($P < 0.001$). Furthermore, the VOI of the right-side PVs was significantly larger than that of the left-side PVs ($P < 0.001$). According to the long-term follow-up results, after a single procedure, the 243 patients were divided into a recurrence group (96 patients) and a no-recurrence group (147 patients). The LAD and left ventricular end-diastolic diameter in the recurrence group and no-recurrence group were 38.10 ± 4.92 and 35.41 ± 4.92 mm, respectively ($P < 0.001$) and 47.23 ± 4.95 and 45.63 ± 4.11 mm, respectively ($P = 0.004$). The left inferior PV (LIPV)

SID was also significantly different between the groups ($P = 0.002$) (Table 2).

Clinical outcomes

All 243 patients who underwent RFCA were followed up. During the follow-up, three patients died: one died of heart failure, one of lung cancer, and one of unknown cause.

Clinical outcomes after a single procedure

After a median follow-up of 37 (IQR, 17, 58) months, 96 (39.5%) patients developed AF recurrence. The AF recurrence rate at 1, 2, 3, 4, 5, and 6 years after a single procedure was 29.2%, 33.3%, 35.8%, 37.4%, 38.3%, and 39.5%, respectively, and 74% of AF recurrences occurred in the first year. The long-term AF-free survival rate after a single procedure was 60.5% (Figure 1).

In the first procedure, 183 (75.3%) patients underwent CPVI alone, 47 (19.4%) patients underwent CPVI plus linear ablation, 2 (0.8%) patients underwent CPVI combined with CFAE ablation, and 11 (4.5%) patients underwent CPVI combined with linear and CFAE ablation. We analyzed two groups with matched baseline data (Table 3); that is, one group of patients who underwent CPVI alone ($n = 123$) and another group of patients who underwent CPVI combined with additional ablation ($n = 60$). The results showed a long-term SR maintenance rate of 64.2% in patients who underwent CPVI alone and 41.7% in patients who underwent CPVI combined with additional ablation (log rank test, $P = 0.001$). In addition, 115 patients developed ERAF, and the long-term SR maintenance was significantly lower in patients with than without ERAF (37.4% vs. 81.2%, respectively; log rank test, $P < 0.001$). The types of arrhythmia in 96 patients with LRAF were AF ($n = 72$), AFL ($n = 20$), and AT ($n = 4$);

Table 1. Patients' baseline characteristics before catheter ablation

Variable	All patients (n = 243)					
Age, years	58.55 ± 11.19					
Male sex	147 (60.5)					
BMI, kg/m ²	23.80 ± 2.78					
AF duration, months	51.65 ± 60.05					
Associated diseases						
Hypertension	118 (48.6)					
CHD	39 (16.0)					
Hyperthyroidism	6 (2.5)					
Hypothyroidism	27 (11.1)					
Diabetes mellitus	29 (11.9)					
COPD	9 (3.7)					
Stroke before ablation	16 (6.6)					
Echocardiographic parameters						
LAD, mm	36.47 ± 5.09					
LVDd, mm	46.26 ± 4.52					
LVEF, %	69.60 ± 8.51					
Medications before ablation						
Amiodarone	57 (23.5)					
β-blocker	92 (37.9)					
Propafenone	24 (9.9)					
PVCT	SID, mm	P-value	APD, mm	P-value	VOI	P-value
LSPV	20.67 ± 4.25	<0.001	15.18 ± 3.31	<0.001	0.75 ± 0.14	0.146
LIPV	17.73 ± 3.97		12.76 ± 3.67		0.73 ± 0.16	
RSPV	21.52 ± 5.50	0.001	17.31 ± 4.25	0.158	0.81 ± 0.12	0.004
RIPV	20.05 ± 4.64		16.79 ± 3.86		0.85 ± 0.11	
Left-side PV	19.21 ± 4.37	<0.001	13.97 ± 3.69	<0.001	0.74 ± 0.15	<0.001
Right-side PV	20.79 ± 5.14		17.05 ± 4.07		0.83 ± 0.12	
Superior PV	21.10 ± 4.93	<0.001	16.25 ± 3.95	<0.001	0.78 ± 0.14	0.541
Inferior PV	18.89 ± 4.47		14.77 ± 4.27		0.79 ± 0.15	
PV number variation	41 (16.9)					
LCPV	8 (3.3)					
RCPV	1 (0.4)					
RMPV	27 (11.1)					
Other variations	5 (2.1)					

Data are presented as mean ± standard deviation or n (%).

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

furthermore, AFL (including AT) was present in 16.4% of the patients who underwent CPVI alone and 42.9% of the patients who underwent CPVI plus

additional ablation (P = 0.004). A total of 50 patients with AF recurrence (AF, n = 30); AFL, n = 17; and AT, n = 3) underwent the second procedure. In the second

Table 2. Univariate and multivariate Cox regression analysis to recognize the predictors of AF recurrence after a single procedure

Variable	Recurrence (n = 96)	No recurrence (n = 147)	P-value	HR	95% CI
Age, years	59.49 ± 10.21	57.93 ± 11.78	0.261	1.010	0.992–1.028
Male sex	60.4%	60.5%	0.925	0.981	0.651–1.476
BMI, kg/m ²	23.90 ± 2.81	23.73 ± 2.76	0.419	1.030	0.959–1.107
AF duration, months	52.04 ± 55.27	51.40 ± 63.15	0.850	1.000	0.996–1.003
Associated diseases					
Hypertension	53.1%	45.6%	0.177	1.319	0.882–1.972
CHD	14.6%	17.0%	0.484	0.817	0.463–1.440
Normal thyroid function	85.4%	87.1%	reference		
Hyperthyroidism	3.1%	2.0%	0.553	1.417	0.448–4.488
Hypothyroidism	11.5%	10.9%	0.828	1.072	0.571–2.013
Diabetes mellitus	12.5%	11.6%	0.745	1.106	0.604–2.026
COPD	4.2%	3.4%	0.914	1.057	0.388–2.876
Echocardiographic parameters					
LAD, mm	38.10 ± 4.92	35.41 ± 4.92	<0.001	1.092	1.051–1.135
LVDd, mm	47.23 ± 4.95	45.63 ± 4.11	0.004	1.062	1.020–1.107
LVEF, %	68.75 ± 8.86	70.16 ± 8.26	0.219	0.986	0.963–1.009
PVCT parameters					
LSPV SID, mm	21.13 ± 4.41	20.39 ± 4.14	0.102	1.041	0.992–1.091
LSPV APD, mm	15.63 ± 3.32	14.89 ± 3.28	0.136	1.047	0.986–1.112
VOI _{LSPV}	0.75 ± 0.14	0.74 ± 0.15	0.897	0.912	0.223–3.179
LIPV SID, mm	18.55 ± 3.86	17.20 ± 3.95	0.002	1.066	1.024–1.109
LIPV APD, mm	13.13 ± 3.51	12.52 ± 3.76	0.198	1.033	0.983–1.085
VOI _{LIPV}	0.71 ± 0.15	0.74 ± 0.16	0.128	0.383	0.111–1.319
RSPV SID, mm	22.08 ± 6.03	21.17 ± 5.11	0.046	1.039	1.001–1.079
RSPV APD, mm	17.72 ± 4.61	17.05 ± 4.00	0.096	1.043	0.993–1.096
VOI _{RSPV}	0.81 ± 0.12	0.82 ± 0.12	0.628	0.671	0.134–3.364
RIPV SID, mm	20.40 ± 4.26	19.82 ± 4.88	0.111	1.033	0.993–1.076
RIPV APD, mm	17.07 ± 4.01	16.61 ± 3.76	0.147	1.039	0.987–1.094
VOI _{RIPV}	0.84 ± 0.11	0.85 ± 0.12	0.342	0.431	0.076–2.444
PV number variation	20.8%	14.3%	0.050	1.644	1.000–2.703
Ablation strategies					
CPVI	63.5%	83.0%	reference		
CPVI + additional ablation	36.5%	17.0%	<0.001	2.171	1.430–3.296
ERAF	75.0%	29.3%	<0.001	4.577	2.876–7.284
Medications after procedure					
AAD therapy	68.8%	41.5%	<0.001	2.351	1.526–3.624
β-blocker	43.8%	44.9%	0.914	1.023	0.683–1.531
ACEI	65.6%	57.8%	0.509	1.153	0.756–1.757
Multivariate Cox regression analysis*					
LAD, mm	38.10 ± 4.92	35.41 ± 4.92	<0.001	1.078	1.034–1.123
LIPV SID, mm	18.55 ± 3.86	17.20 ± 3.95	0.001	1.074	1.028–1.121
PV number variation	20.8%	14.3%	0.028	1.767	1.065–2.934
CPVI + additional ablation	36.5%	17.0%	0.005	1.858	1.209–2.857
ERAF	75.0%	29.3%	<0.001	5.595	2.854–7.398

Data are presented as mean ± standard deviation unless otherwise indicated

Definitions of BMI, CHD, COPD, LAD, LVDd, LVEF, PVCT, LSPV, LIPV, RSPV, RIPV, SID, APD, and VOI are listed in the footnote of Table 1

AF, atrial fibrillation; CPVI, circumferential pulmonary vein isolation; ERAF, early recurrence of atrial fibrillation; AADs, antiarrhythmic drugs; ACEI, angiotensin-converting enzyme inhibitor

*Variables with a P value of <0.10 in the univariate Cox analysis were included in the multivariate analysis

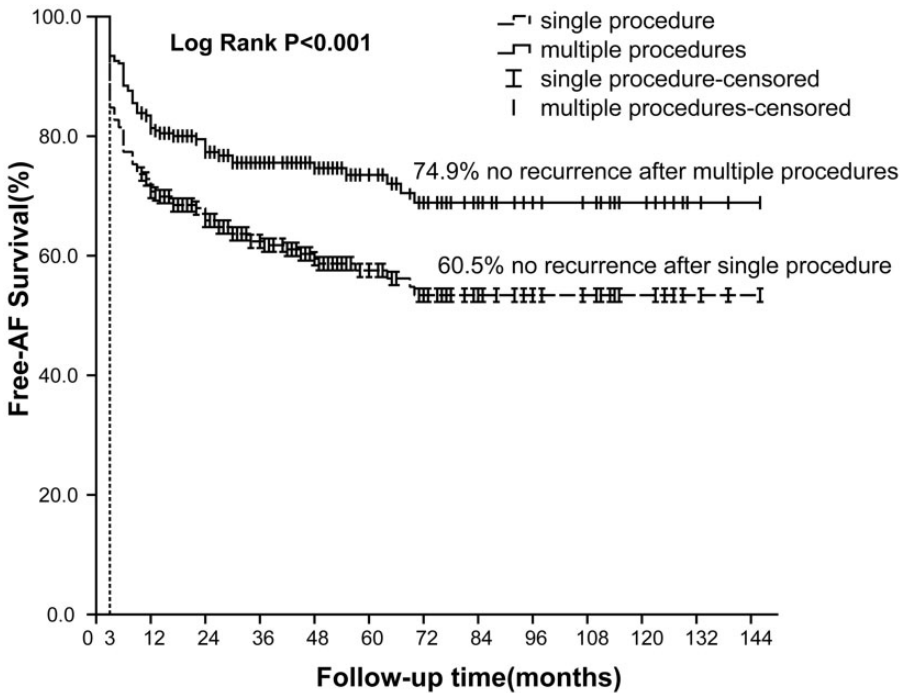


Figure 1. Kaplan–Meier analysis of AF-free rate after a single procedure and multiple procedures. AF, atrial fibrillation

procedure, we found that PV-LA conduction was restored in 40 patients (80.0%), and the prevalence of PV-LA reconnections was not significantly different between the patients with ERAF and those with initial AF recurrence after the blanking period (74.4% vs. 100.0%, respectively).

Clinical outcomes after multiple procedures

After a mean of 1.3 ± 0.6 procedures with a median follow-up of 42 (IQR, 22, 66) months, 61 (25.1%) patients developed AF recurrence. The rate of AF recurrence at 1, 2, 3, 4, 5, and 6 years after multiple procedures was 18.5%, 21.8%, 23.0%, 23.5%, 23.9%, and 25.1%, respectively, and 73.8% of AF recurrences occurred in the first year. The long-term AF-free survival rate after multiple procedures was 74.9%

(Figure 1). In total, 67 repeat procedures were performed with a distribution of 2 in 38 patients, 3 in 8 patients, 4 in 3 patients, and 5 in 1 patient. The cumulative maintenance rate of SR after one, two, three, four, and five procedures was 60.5%, 71.1%, 73.3%, 74.5%, and 74.9%, respectively. The distribution of the ablation strategies was as follows: 211 (68.0%) patients underwent CPVI alone, 82 (26.5%) underwent CPVI combined with additional ablation, and 17 (5.5%) underwent other ablation strategies not combined with CPVI.

Predictors of LRAF after a single procedure

In the univariate analysis, the factors associated with AF recurrence were the LAD, left ventricular end-diastolic diameter, LIPV SID, right superior PV SID, right superior

Table 3. Comparisons of baseline data before ablation based on ablation strategy

Variable	CPVI alone (n = 123)	CPVI + additional ablation (n = 60)	P-value
Age, years	59.43 ± 11.00	58.40 ± 11.49	0.558
Male sex	61.0%	63.3%	0.758
BMI, kg/m ²	24.08 ± 2.69	24.12 ± 2.78	0.923
AF duration, months	51.05 ± 58.64	50.68 ± 69.25	0.970
Associated diseases			
Hypertension	52.8%	43.3%	0.227
CHD	19.5%	13.3%	0.302
Hyperthyroidism	2.4%	1.7%	0.684
Hypothyroidism	12.2%	8.3%	
Diabetes mellitus	14.6%	13.3%	0.813
COPD	5.7%	1.7%	0.211
Echocardiographic parameters			
LAD, mm	37.63 ± 4.04	38.08 ± 4.68	0.504
LVDd, mm	46.65 ± 4.62	47.42 ± 4.67	0.295
LVEF, %	69.63 ± 8.07	67.47 ± 9.11	0.105
PVCT parameters			
LSPV SID, mm	20.94 ± 4.45	19.98 ± 3.95	0.159
LSPV APD, mm	15.40 ± 3.42	14.77 ± 3.22	0.238
VOI _{LSPV}	0.75 ± 0.13	0.76 ± 0.16	0.666
LIPV SID, mm	17.91 ± 4.70	17.33 ± 2.94	0.378
LIPV APD, mm	12.97 ± 3.84	12.35 ± 3.65	0.301
VOI _{LIPV}	0.74 ± 0.16	0.71 ± 0.16	0.390
RSPV SID, mm	20.90 ± 4.92	21.69 ± 5.65	0.336
RSPV APD, mm	17.02 ± 4.01	17.43 ± 3.85	0.510
VOI _{RSPV}	0.82 ± 0.12	0.82 ± 0.12	0.826
RIPV SID, mm	19.87 ± 4.64	19.05 ± 3.70	0.236
RIPV APD, mm	16.83 ± 3.97	16.49 ± 3.11	0.558
VOI _{RIPV}	0.85 ± 0.09	0.87 ± 0.10	0.180
PV number variation	19.5%	15.0%	0.456

Data are presented as mean ± standard deviation unless otherwise indicated

Definitions of BMI, AF, CHD, COPD, LAD, LVDd, LVEF, PVCT, LSPV, LIPV, RSPV, RIPV, SID, APD, and VOI are listed in the footnote of Tables 1 and 2.

PV APD, PV number variation, ablation strategies, ERAF, and AAD therapy within the blanking period after a single procedure ($P < 0.1$ for all). These factors were included in the Cox regression model, and the multivariate analysis results demonstrated that the following factors were predictors of LRAF after a single procedure: LAD (HR, 1.092; 95% CI, 1.051–1.135; $P < 0.001$), LIPV SID (HR, 1.066; 95% CI, 1.024–1.109; $P = 0.001$), PV number

variation (HR, 1.767; 95% CI, 1.065–2.934; $P = 0.028$), CPVI combined with additional ablation (HR, 2.171; 95% CI, 1.430–3.296; $P = 0.005$), and ERAF (HR, 4.577; 95% CI, 2.876–7.284; $P < 0.001$) (Table 2). The receiver operating characteristic curve analysis showed that the optimal cut-off value for the LAD was 35.5 mm for predicting LRAF after a single procedure with a sensitivity of 70.8% and specificity of 55.1% (Figure 2). The Kaplan–Meier survival

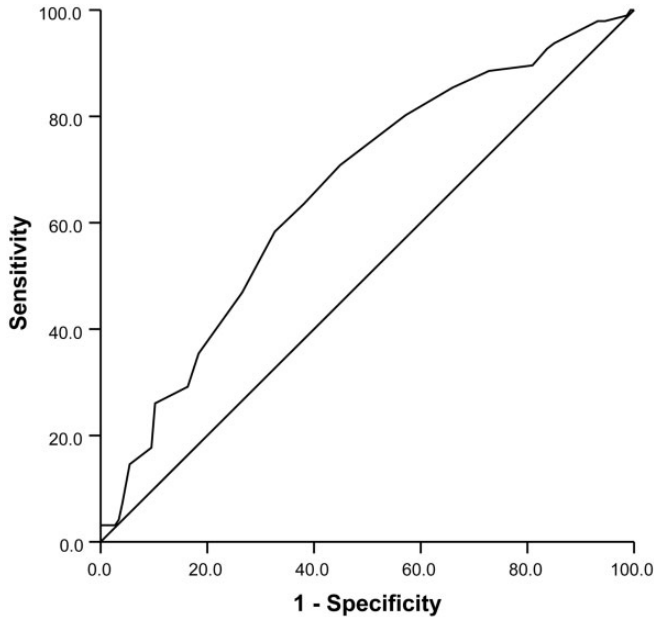


Figure 2. Receiver operating characteristic curve analysis with different left atrial diameters. A left atrial diameter of 35.5 mm had the highest accuracy (sensitivity, 70.8%; specificity, 55.1%) for predicting late recurrence of atrial fibrillation after a single procedure. The area under the curve was 0.66 ($P < 0.001$)

analysis revealed that patients with an LAD of <35.5 mm had a higher SR maintenance rate than those with an LAD of >35.5 mm (74.3% vs. 49.5%, respectively; log-rank test, $P < 0.001$).

Complications

No procedure-related deaths occurred, and the complication rate for all 310 procedures was 6.8%. The details for these complications are as follows: seven (2.3%) cases of cardiac tamponade, two of which were treated by surgical intervention; one (0.3%) transient ischemic attack; three (1.0%) cases of symptomatic PV stenosis; four (1.3%) hematomas; three (1.0%) pseudoaneurysms; two (0.6%) arteriovenous fistulas; and one (0.3%) phrenic nerve injury.

Discussion

The main findings in this study are as follows. 1) RFCA resulted in maintenance of SR in 74.9% of the patients during 3 years of follow-up after multiple procedures; 2) more than two-thirds of AF recurrence occurred in the first year after a single procedure and multiple procedures; 3) repeat ablation increased the maintenance rate of SR; 4) CPVI remained the cornerstone of AF ablation, and CPVI plus additional ablation did not provide additional benefits but increased the incidence of AFL; and 5) LAD, LIPV SID, PV number variation, CPVI combined with additional ablation, and ERAF were predictors of LRAF after a single procedure.

The predictors of AF recurrence are inconsistent among different studies. Previous studies identified some predictors

of LRAF, such as hypertension, ERAF, LA size, LA volume, atrial tissue fibrosis, ablation strategies, natriuretic peptides, and others.^{4,13-19} In the present study, we found that the LAD, LIPV SID, PV number variation, CPVI combined with additional ablation, and ERAF were predictors of LRAF after a single procedure.

The LAD as a predictor of LRAF has been confirmed in previous studies.^{4,13,14,18} In the present study, we found that the LAD was larger in patients with than without recurrence and was a predictor of LRAF after a single procedure. Furthermore, we found that the optimal cutoff value for the LAD was 35.5 mm, which is almost equivalent to normal, and the patients with an LAD below the optimal cutoff value had better outcomes. LA enlargement is considered a sign of structural and electrical remodeling of the left atrium that leads to atrial conduction abnormalities and accumulation of arrhythmogenic substrate, which increases the risk of AF recurrence. These results suggest that RFCA is more suitable for patients with PAF without enlargement of the LA.

ERAF is common after ablation and can predict LRAF during the long-term follow-up. Previous studies have shown that the rate of ERAF ranged from approximately 38.2% to 58.6% after a single ablation of PAF and that ERAF significantly predicted LRAF.²⁰⁻²⁴ In the present study, the incidence of ERAF was 47.3%, and ERAF was identified as a predictor of LRAF. The mechanism of ERAF was unclear but is generally considered to involve acute thermal injury and an inflammatory response caused by radiofrequency energy and a transient reversible process.^{25,26} However, previous studies^{13,14,21} and the present study showed that patients with ERAF had a lower long-term SR maintenance rate than patients without ERAF, and ERAF was identified as a predictor of LRAF. These results suggest that ERAF

develops by other mechanisms in addition to catheter-induced transient trauma. Indeed, Lellouche et al.²⁷ reported that among 143 patients with PAF and persistent AF who developed ERAF and underwent a second ablation, 59% had PV-LA reconnection. Yanagisawa et al.²⁴ reported that among 66 patients with PAF and persistent AF who developed ERAF and underwent early reablation, 77% had PV reconnection. Furthermore, Miyazaki et al.²¹ reported that the prevalence of PV reconnections and non-PV foci were similar between patients with ERAF and those with recurrence beyond the blanking period. In the present study, we found that the prevalence of PV-LA reconnections was not different between patients with and without ERAF. These results illustrate that one of the mechanisms of ERAF is PV-LA reconnection, which is a mechanism of LRAF. In addition, Lellouche et al.²⁷ and Yanagisawa et al.²⁴ reported that early reablation within the blanking period can improve LRAF but increase the number of procedures. This suggests that a 3-month blanking period is reasonable and that reablation may be more appropriate after a blanking period to avoid potential risks associated with early reablation and some unnecessary reablation procedures, although PV reconnection was already present in ERAF.

Notably, we identified LIPV SID as a predictor of LRAF after a single procedure. Although previous studies²⁸⁻³⁰ investigated the anatomy of the PVs, several previous studies^{29,30} only showed the relationship between the PV anatomy and the efficacy of RFCA; they did not identify the relationship of the PV ostia diameter with the efficacy of RFCA. In the present study, we found that a PV number variation was a predictor of LRAF, which is similar to the findings of previous studies.^{29,30} Furthermore, we found that the LIPV was larger in patients with than without LRAF

and that the LIPV SID was a predictor of LRAF after a single procedure. The reason for the effect of the LIPV on the long-term efficacy of RFCA is unclear, but several possible reasons are as follows. 1) In the baseline data, the LIPV was small and more oval; thus, a small, irregularly shaped LIPV may affect the location and stability of Lasso catheter placement and consequently lead to incomplete linear ablation. 2) The LIPV was larger in patients with than without recurrence group, implying that the LIPV may undergo more significant electroanatomical remodeling and making incomplete ablation more likely. 3) Operators do not pay enough attention to the inferior PVs because most of the AF triggers originate from the bilateral superior PVs and rarely from the inferior PVs.³¹ 4) The anatomical position of the LIPV is also a factor. Takatsuki et al.³² reported that a high take-off LIPV hampered the formation of complete linear lesions in the lateral mitral isthmus. Further investigations of the relationship between the PV and the efficacy of RFCA are necessary because of variations in PVs.

The effect of additional ablation based on CPVI for PAF has also been controversial. Nam et al.³³ and Gaita et al.³⁴ respectively reported that CPVI + CFAE as well as CPVI + linear ablation for PAF can reduce AF recurrence. However, other studies showed that additional ablation based on CPVI did not improve AF recurrence.^{35,36} Sawhney et al.³⁶ reported that additional linear ablation increased the incidence of atypical LA flutter. In the present study, we also found similar results that CPVI combined with additional ablation did not yield an additional benefit, but rather increased the incidence of AFL compared with CPVI alone and was a predictor of LRAF after a single procedure. The reason for this may be the presence of gaps resulting from previous incomplete ablation lines or new arrhythmogenic

substrate formation induced by additional ablation. These results suggest that additional ablation for PAF should be carefully considered.

This study has several limitations. Besides the inherent limitations of retrospective studies, electrocardiography and 24-hour Holter monitoring were performed at intermittent regular follow-up times and at the time of symptoms to detect AF recurrence; thus, some asymptomatic AF may have remained undetected, and AF recurrence may have been underestimated. Further research using long-term constant monitoring of patients' heart rhythm is needed for a more realistic view of AF recurrence.

Conclusion

RFCA resulted in an SR maintenance rate of 74.9% during 3 years of follow-up after multiple ablation procedures. The LAD, LIPV diameter, PV number variation, ERAF, and CPVI plus additional ablation were predictors of LRAF after a single procedure. Therefore, RFCA is more suitable for patients without enlargement of the LA, and additional ablation for PAF should be carefully considered.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Yuehui Yin  <http://orcid.org/0000-0001-9769-435X>

References

1. Wolf PA, Abbott RD and Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991; 22: 983–988.
2. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. *Circulation* 2014; 129: 837–847.
3. 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–e004549.
4. 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: 267–273.
5. Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018; 378: 417–427.
6. 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.
7. 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: 2071–2104.
8. Narayan SM, Baykaner T, Clopton P, et al. Ablation of rotor and focal sources reduces late recurrence of atrial fibrillation compared with trigger ablation alone: extended follow-up of the CONFIRM trial (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation). *J Am Coll Cardiol* 2014; 63: 1761–1768.
9. Vogler J, Willems S, Sultan A, et al. Pulmonary vein isolation versus defragmentation: the CHASE-AF clinical trial. *J Am Coll Cardiol* 2015; 66: 2743–2752.
10. Murray MI, Arnold A, Younis M, et al. Cryoballoon versus radiofrequency ablation for paroxysmal atrial fibrillation: a meta-analysis of randomized controlled trials. *Clin Res Cardiol* 2018; 107: 658–669.
11. 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: 1921–1929.
12. Ouyang F, Tilz R, Chun J, et al. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. *Circulation* 2010; 122: 2368–2377.
13. Cai L, Yin Y, Ling Z, et al. Predictors of late recurrence of atrial fibrillation after catheter ablation. *Int J Cardiol* 2013; 164: 82–87.
14. Arya A, Hindricks G, Sommer P, et al. Long-term results and the predictors of outcome of catheter ablation of atrial fibrillation using steerable sheath catheter navigation after single procedure in 674 patients. *Europace* 2010; 12: 173–180.
15. Themistoclakis S, Schweikert RA, Saliba WI, et al. Clinical predictors and relationship between early and late atrial tachyarrhythmias after pulmonary vein antrum isolation. *Heart Rhythm* 2008; 5: 679–685.
16. Hof I, Chilukuri K, Arbab-Zadeh A, et al. Does left atrial volume and pulmonary venous anatomy predict the outcome of catheter ablation of atrial fibrillation? *J Cardiovasc Electrophysiol* 2009; 20: 1005–1010.
17. Marrouche NF, Wilber D, Hindricks G, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. *JAMA* 2014; 311: 498–506.
18. den Uijl DW, Tops LF, Delgado V, et al. Effect of pulmonary vein anatomy and left atrial dimensions on outcome of circumferential radiofrequency catheter ablation for atrial fibrillation. *Am J Cardiol* 2011; 107: 243–249.
19. Zhang Y, Chen A, Song L, et al. Association between baseline natriuretic peptides and atrial fibrillation recurrence after catheter ablation. *Int Heart J* 2016; 57: 183–189.

20. Pokushalov E, Romanov A, Corbucci G, et al. Use of an implantable monitor to detect arrhythmia recurrences and select patients for early repeat catheter ablation for atrial fibrillation: a pilot study. *Circ Arrhythm Electrophysiol* 2011; 4: 823–831.
21. 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: 2353–2359.
22. 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: 2461–2468.
23. Willems S, Khairy P, Andrade JG, et al. Redefining the blanking period after catheter ablation for paroxysmal atrial fibrillation: insights from the ADVICE (Adenosine Following Pulmonary Vein Isolation to Target Dormant Conduction Elimination) Trial. *Circ Arrhythm Electrophysiol* 2016; 9: pii: e003909.
24. 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: 833–841.
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: 1463–1472.
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: 83–89.
27. 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.
28. Anselmino M, Blandino A, Beninati S, et al. Morphologic analysis of left atrial anatomy by magnetic resonance angiography in patients with atrial fibrillation: a large single center experience. *J Cardiovasc Electrophysiol* 2011; 22: 1–7.
29. Sohns C, Sohns JM, Bergau L, et al. Pulmonary vein anatomy predicts freedom from atrial fibrillation using remote magnetic navigation for circumferential pulmonary vein ablation. *Europace* 2013; 15: 1136–1142.
30. Mulder AA, Wijffels MC, Wever EF, et al. Pulmonary vein anatomy and long-term outcome after multi-electrode pulmonary vein isolation with phased radiofrequency energy for paroxysmal atrial fibrillation. *Europace* 2011; 13: 1557–1561.
31. 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: 659–666.
32. Takatsuki S, Extramiana F, Hayashi M, et al. High take-off left inferior pulmonary vein as an obstacle in creating a conduction block at the lateral mitral isthmus. *Europace* 2009; 11: 910–916.
33. Nam GB, Jin ES, Choi H, et al. Effect of substrate modification in catheter ablation of paroxysmal atrial fibrillation: pulmonary vein isolation alone or with complex fractionated electrogram ablation. *Tex Heart Inst J* 2012; 39: 372–379.
34. Gaita F, Caponi D, Scaglione M, et al. Long-term clinical results of 2 different ablation strategies in patients with paroxysmal and persistent atrial fibrillation. *Circ Arrhythm Electrophysiol* 2008; 1: 269–275.
35. Arbelo E, Guiu E, Ramos P, et al. Benefit of left atrial roof linear ablation in paroxysmal atrial fibrillation: a prospective, randomized study. *J Am Heart Assoc* 2014; 3: e000877.
36. Sawhney N, Anousheh R, Chen W, et al. Circumferential pulmonary vein ablation with additional linear ablation results in an increased incidence of left atrial flutter compared with segmental pulmonary vein isolation as an initial approach to ablation of paroxysmal atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010; 3: 243–248.