

Association between functional mitral regurgitation and recurrence of paroxysmal atrial fibrillation following catheter ablation: a prospective cohort study

Fusheng Ke^{1, #}, Yinhui Huang^{2, #}, Zhexiu Jin¹,
Lei Huang¹, Qiang Xiong³, Fang Jia¹, Yu Chen⁴
and Gang Chen⁵ 

Abstract

Objective: The present study aimed to investigate the effect of functional mitral regurgitation (FMR) on recurrence of paroxysmal atrial fibrillation (PAF) in patients undergoing radiofrequency catheter ablation.

Methods: This prospective cohort study comprised 107 patients with PAF. The patients were divided into the FMR and non-FMR groups. FMR was assessed by Doppler echocardiography before index ablation. All patients initially underwent circumferential pulmonary vein isolation (CPVI) and were followed up for 12 months after ablation. PAF, atrial tachycardia, or atrial flutter served as the endpoint indicator.

Results: The median duration of PAF was 24 (3–60) months. Binary logistic univariate and multivariate analyses showed that FMR was not a risk factor for recurrence of catheter ablation for PAF (hazard ratio=0.758, 95% confidence interval: 0.191–3.004; hazard ratio=0.665, 95% confidence interval: 0.134–3.300, respectively). Kaplan–Meier analysis showed no significant

¹Department of Cardiology, The Second Affiliated Hospital of Xiamen Medical College, Xiamen, China

²Department of Neurology, Jinjiang Municipal Hospital, Jinjiang, China

³Department of Emergency, The Second Affiliated Hospital of Xiamen Medical College, Xiamen, China

⁴Department of Pediatrics, The Second Affiliated Hospital of Xiamen Medical College, Xiamen, China

⁵Department of Cardiology, Shanghai General Hospital, Shanghai, China

[#]These authors contributed equally to this work.

Corresponding author:

Gang Chen, Shanghai General Hospital, Shanghai, No. 100 Haining Road, Hongkou District 200080, China.
Email: 415638906@qq.com



difference in the recurrence rate between the groups. Fifteen (15/107, 14%) cases of PAF were triggered by the pulmonary vein. Three (3/107, 2.8%) cases of PAF were triggered by the superior vena cava.

Conclusions: FMR is not an independent risk factor for predicting recurrence of catheter ablation for PAF. FMR does not affect patients undergoing radiofrequency catheter ablation for PAF.

Keywords

Atrial fibrillation, catheter ablation, mitral regurgitation, left atrium, pulmonary vein, Doppler echocardiography

Date received: 25 August 2020; accepted: 9 April 2021

Introduction

Atrial fibrillation (AF) is a common clinical arrhythmia. At the age of 40 years, the lifetime risk for AF is 26% (95% confidence interval [CI], 24%–27%) for men and 23% (21%–24%) for women. At the age of 80 years, this risk is 22.7% (20.1%–24.1%) in men and 21.6% (19.3%–22.7%) in women.¹ The incidence and prevalence of AF increase with age and are higher in men than in women in different age groups.^{2,3} A meta-analysis showed that cryoballoon ablation is an equally effective alternative procedure to standard radiofrequency treatment with a slightly high alleviation from AF at 1 year after ablation.⁴ Catheter ablation has a significantly low recurrence rate for AF ablation.⁵ With the widespread use of radiofrequency catheter ablation of AF, many patients, especially those with paroxysmal atrial fibrillation (PAF), show a satisfactory therapeutic effect.⁵ The grades of severity of mitral regurgitation (MR) are correlated with the rate of recurrent AF; a severe grade of MR indicates recurrent AF.⁶ However, considerable functional mitral regurgitation (FMR) can be identified in 7.4% to 29% of AF.^{7,8} These previous studies suggest that PAF has a low

ratio of clinically significant FMR. Whether this low ratio affects the recurrence of PAF after circumferential pulmonary vein isolation (CPVI) remains unclear. Therefore, this study aimed to investigate the association between FMR and the recurrence of PAF after CPVI.

Materials and methods

Selection criteria

AF was determined by an electrocardiogram (ECG) and 24-hour Holter monitoring. PAF was defined as AF that terminates spontaneously or with intervention within 7 days of onset.⁹ PAF was based on clinical symptoms, ECG, and 24-hour Holter. Informed consent was obtained from all participants. The left ventricular ejection fraction (LVEF) was normal ($\geq 50\%$).¹⁰ None of the patients underwent radiofrequency ablation.

Exclusion criteria

We excluded patients with primary valve involvement by echocardiography, such as infective endocarditis, rheumatic valvular disease, chordae or papillary muscle

rupture, congenital heart disease or significant mitral calcification, cardiomyopathy, or a LVEF <50%, those who had radiofrequency ablation, and those who presented with a history of CPVI.

Diagnostic criteria of FMR and definition of recurrence after AF ablation

An echocardiographic examination before index ablation was performed. MR was assessed according to recommendations of the American Society of Echocardiography criteria. The ratio of the maximum MR color jet area to the left atrial (LA) area (MR/LA) was measured by Doppler echocardiography to assess the degree of MR. MR was classified as mild (MR/LA ≥ 0.1 and < 0.2), moderate (MR/LA ≥ 0.2 and < 0.4), and severe MR (MR/LA > 0.4).¹¹ FMR was defined as secondary MR as follows: normal anatomy of the valve, excluding valve thickening, prolapse, and rheumatic valvular disease; a normal or mildly dilated left ventricular (LV) size with fixed (infarction) or inducible (ischemia) regional wall motion abnormalities; or primary myocardial disease with LV dilation and systolic dysfunction.¹² FMR was assessed by skilled doctors using Doppler echocardiography (Philips EPIQ7 and S5-1 probe; Philips Healthcare, Best, the Netherlands). Data were collected, recorded, and checked by specialized personnel.

Early recurrence was defined as AF, atrial tachycardia, or atrial flutter occurring within 3 months after radiofrequency ablation if the duration was > 30 s. Late recurrence was defined as AF, atrial tachycardia, or atrial flutter occurring within 3 to 12 months after radiofrequency ablation if the duration was > 30 s. Very late recurrence was defined as AF, atrial tachycardia, or atrial flutter occurring 12 months after radiofrequency ablation of AF if the duration was > 30 s.⁹

Perioperative management

All patients discontinued antiarrhythmic drugs for at least five half-lives before ablation, while amiodarone was stopped for > 3 months. The CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥ 75 years [doubled], diabetes, stroke/transient ischemic attack/thromboembolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65 to 75 years, sex category [female]) score was used to assess the risk of stroke.¹⁰ Pulmonary vein (PV) computed tomography was performed before ablation to determine the anatomy of the PV and left atrium (LA). Esophageal echocardiography was performed within 24 hours before ablation to exclude LA or LA appendage thrombosis.

Electrophysiological examination and catheter ablation procedure

Procedures, such as puncture and catheter placement, were performed in accordance with the interventional operation specifications. An electrophysiological examination was conducted to discover other arrhythmias. CPVI is the cornerstone of catheter ablation for AF.^{13–15} The 4-mm tip electrode of the ablation catheter was passed through a cold saline solution at 30 W, a temperature of 43°C, and flow rate of 17 mL/minute using the three-dimensional mapping system Rhythmia (Boston Scientific, MA, USA) to guide the ablation. The PV vestibule was the ablation target and PV electrical isolation was the ablation endpoint. In the process of AF catheter ablation, the extrapulmonary vein-triggering lesion was found and ablated.

Postoperative management and follow-up

The patients were followed up for 12 months (1st, 3rd, 6th, 9th, and 12th months). The endpoint indicator was

whether AF, atrial tachycardia, or atrial flutter occurred after 3 months post-ablation. The follow-up included recording any symptoms of palpitations, ECG, and 24-hour Holter monitoring. Additionally, a cardiologist instructed the patients to monitor the symptoms of palpitations, pulse rate, and rhythm to identify arrhythmias in a timely manner. If an abnormal pulse was found, ECG and 24-hour Holter were promptly performed. In the case of AF, atrial tachycardia, or atrial flutter occurring in patients in the 3-month blanking period after ablation, antiarrhythmic drugs were not used.

Statistical analysis

The data were statistically processed by SPSS software version 18.0 (SPSS, Chicago, IL, USA). Continuous variables are described as the mean \pm standard deviation for normally distributed data and the median (25%–75% quartiles) for non-normally distributed data. Comparisons between groups were performed with the Student's t-test (normally distributed data) or the Mann–Whitney U test (non-normally distributed data). Categorical variables are described as counts and were compared by χ^2 analysis and Fisher's exact test. Survival curves were generated using Kaplan–Meier analysis and compared by the log-rank test. Binominal logistic regression was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) for the presence of FMR. Binominal logistic regression analysis (univariate and multivariate analyses) was used to determine the independent predictors of recurrence of AF by determining the HR and 95% CI for each variable in the model. The variables that were selected for multivariate analysis were those with $P < 0.05$ in the univariate models. In univariate analysis, HR values and 95% CIs were calculated, while in multivariate analysis, FMR,

interventricular septal thickness (IVS), and other risk factors for the recurrence of AF ablation were determined on the basis of HR values and 95% CIs. All tests were two-tailed and statistical significance was established at $P < 0.05$.

Ethical approval

This work was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved by the Human Research Ethics Committee of Shanghai General Hospital (no: AF08060004, date of approval: 23 January 2017), and written informed consent was obtained from every participant. In error, we did not prospectively register this trial, but we have now registered it retrospectively at the Research Registry (<https://www.researchregistry.com/>, registration number: 6707). We followed the STROBE Statement-Case control study guidelines from the Enhancing the QUALity and Transparency Of health Research (EQUATOR) Network.

Results

Baseline characteristics of the study population

A total of 120 patients with PAF who did not undergo CPVI from February 2017 to March 2018 at the Shanghai General Hospital were enrolled in this study to achieve a $>80\%$ power for detecting a difference in the AF recurrence rate after CPVI at a 5% level of significance. Of these, 13 were excluded during the run-in period (8 were excluded in accordance to the protocol and 5 were lost to follow-up). Finally, 107 patients participated in the current study after CPVI (Figure 1).

Using echocardiography, the patients were divided into two groups before AF ablation (with FMR and without FMR)

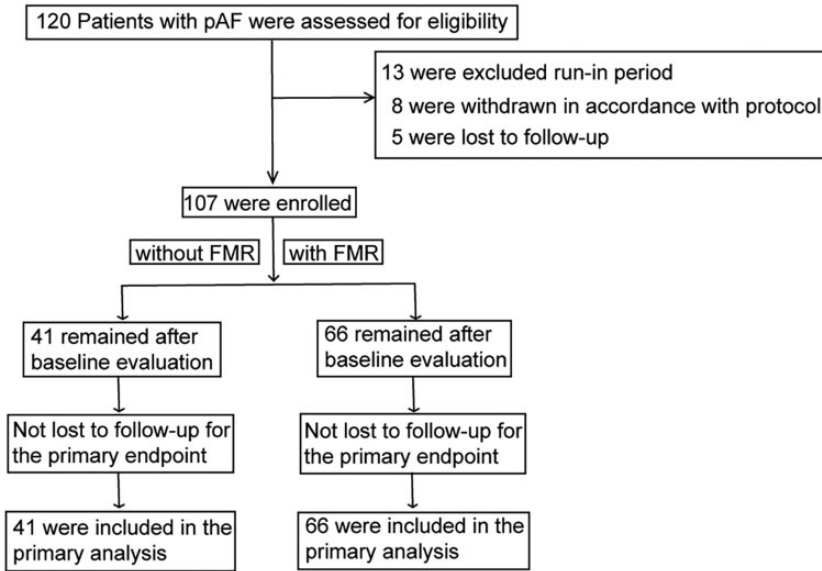


Figure 1. Flowchart of the study

PAF, paroxysmal atrial fibrillation; FMR, functional mitral regurgitation.

and they were in sinus rhythm at the time of echocardiography. The cohort consisted of 56 (52.33%) men, and the mean age of the participants was 65.66 ± 10.15 years. The median duration of AF was 24 months (range: 3–60 months). The mean age of patients in the FMR group was 66.41 ± 9.34 years, while that of patients in the non-FMR group was 64.46 ± 11.35 years. In the FMR and non-FMR groups, 42.2% and 68.3% were men, respectively. FMR was observed in 66 (61.68%) patients. Among these, 60 had mild FMR, while 6 showed moderate FMR, and severe FMR was not detected. Furthermore, five patients had recurrence of PAF in the FMR group. Forty-one patients in the non-FMR group experienced recurrence of PAF. The mean brain natriuretic peptide level in the FMR group was significantly higher than that in the non-FMR group ($P < 0.05$). However, the mean body mass index (BMI) was not significantly different between the two groups. The rate of AF

triggered by the PV was 14% (15/107, Table 2, Figure 2) and three cases relapsed. The rate of AF triggered by the superior vena cava (SVC) was 2.8% (3/107) and one case relapsed (Figure 3). For catheter ablation, three patients had the atrioventricular nodal pathway used and atrioventricular node reentrant tachycardia was shown by an electrophysiological examination.

The patients were further divided into subgroups of the normal IVS group (IVS ≤ 11 mm) and the IVS thickening group (IVS > 11 mm) based on echocardiographic measurement of the ventricular septum. The mean age of patients in the IVS thickening group was 64.50 ± 11.96 years and that of patients in the normal IVS group was 65.71 ± 10.14 years, and the male ratios were 75% and 51.5%, respectively.

There was a significantly higher rate of male sex, higher height, lower BNP levels, smaller left atrial diameter, higher low-



Figure 2. Lasso in the pulmonary vein. The arrows shows atrial fibrillation triggered by a pulmonary vein potential

density lipoprotein levels, and higher creatinine levels in the non-FMR group than in the FMR group (all $P < 0.05$) (Table 2).

A case of vagueness of speech 48 hours post-ablation was observed and the right limb muscle strength was grade III. Acute cerebral infarction was confirmed by cranio-cerebral magnetic resonance imaging. However, after treatment, there were no sequelae. None of the other patients showed any severe complications during and after ablation.

Association between FMR and recurrence of PAF with CPVI

A total of 107 patients with PAF initially received CPVI. The mean follow-up time was 11.36 ± 2.23 months (range: 3–12 months). None of these patients were lost to follow-up. Among these, 41 patients did not have FMR of whom 4 (9.8%) patients

relapsed, and 66 patients had FMR of whom 5 (7.6%) patients relapsed.

Binary logistic univariate and multivariate analyses showed that FMR did not affect recurrence of PAF post-ablation (hazard ratio [HR]=0.758, 95% confidence interval [CI]: 0.191–3.004, $P=0.694$; HR=0.665, 95% CI: 0.134–3.300, $P=0.617$, respectively; Table 1). Kaplan–Meier analysis did not show a significant difference in the recurrence rate between the two groups (log-rank test, $P=0.679$) (Figure 4). Additionally, binary logistic univariate analysis, but not multivariate analysis, showed that statins affected recurrence of PAF post-ablation (HR=5, 95% CI: 1.169–21.391, $P=0.030$; HR=4.216, 95% CI: 0.883–20.135, $P=0.071$; Table 1). Binary logistic multivariate analysis showed that LA enlargement was associated with FMR (HR=1.12; 95% CI: 1.031–1.218, $P=0.007$).



Figure 3. Lasso in the superior vena cava. The arrow shows atrial fibrillation triggered by a superior vena cava potential

Association between IVS and recurrence of PAF with CPVI

Binary logistic univariate and multivariate analyses of the IVS showed the following: HR=1.937, 95% CI: 1.024–3.662, $P=0.042$; HR=1.787, 95% CI: 0.868–3.680, $P=0.115$, respectively (Table 1). Kaplan–Meier analysis showed a significant difference between the IVS thickening group and the normal IVS group (log-rank test, $P=0.001$) (Figure 5).

Discussion

Associations between FMR and ablation outcome post-CPVI

Various clinical factors, including LA enlargement, LA scarring, and elevated troponin levels, have been proposed as indicators for recurrence of AF post-ablation.^{16–18} A previous study compared 95

patients with moderate or greater baseline MR (defined by an MR/LA ratio ≥ 0.2) who underwent AF ablation with 95 patients without clinically significant MR who underwent AF ablation.¹⁹ These patients with MR had a higher recurrence rate of AF than controls (61% vs. 46%, $P=0.04$). The degree of MR and the LA dimension were higher in patients with recurrence compared with those with no recurrence. (MR/LA ratio: 0.25 vs. 0.20, $P=0.03$; LA dimension: 4.5 vs. 4.1 cm, $P<0.0001$).¹⁹ The grades of severity of MR are correlated with the rate of recurrent atrial tachyarrhythmia; a more severe grade of MR indicates more recurrent atrial tachyarrhythmia.⁶ Although AF triggered by the PV is the main mechanism of PAF, matrix remodeling is also considered to be a mechanism of AF, but provides unsatisfactory results after AF ablation.^{20–22} In the current study, 66 patients had FMR

Table 2. Baseline demographics and clinical characteristics

Baseline characteristics	FMR group n=41	Non-FMR group n=66	P
Age, years	64.46±11.35	66.41±9.34	0.337
Male sex, n (%)	28 (68.3)	28 (42.4)	0.009
AF duration, months	24 (5.5–60)	24 (3–36.5)	0.403
Cigarette history, n (%)	10 (24.39)	15 (22.7)	0.843
Alcohol history, n (%)	4 (9.8)	4 (6.1)	0.742
Brain infarction/TIA, n (%)	2 (4.9)	6 (9.1)	0.669
Weight, kg	69.95±9.88	66.92±9.96	0.128
Height, m	1.68±0.09	1.64±0.08	0.018
BMI, kg/m ²	24.7±2.77	24.8±2.92	0.865
CHA ₂ DS ₂ -VASc score	2.76±1.68	2.95±1.66	0.551
BNP (pg/mL)	62 (31.5–96.5)	90.0 (43.75–163)	0.036
LAD (mm)	37.95±5.26	40.91±5.22	0.005
IVS (mm)	8.95±1.18	8.79±0.95	0.628
LVPW (mm)	8.63±0.89	8.59±0.78	0.793
LVDd (mm)	47.07±4.06	48.65±4.89	0.087
LVEF (%)	64.17±3.61	62.95±4.3	0.134
CHO (mmol/L)	4.42±0.95	4.09±0.954	0.096
LDL (mmol/L)	2.59±0.71	2.25±0.84	0.034
TG (mmol/L)	2.05±1.32	1.73±1.42	0.230
UA (μmol/L)	369.15±90.08	337±92.11	0.085
GLU (mmol/L)	5.39±1.15	5.51±1.51	0.644
Cr (μmol/L)	77.73±18.94	68.66±119.07	0.018
BUN (mmol/L)	6.08±1.73	5.87±1.49	0.503
ALB g/L	42.91±2.62	42.0±3.54	0.158
HT, n (%)	25 (61.0)	34 (51.5)	0.339
DM, n (%)	11 (26.83)	12 (19.69)	0.390
CHD, n (%)	6 (14.63)	9 (13.64)	0.885
ACEI/ARB, n (%)	17 (41.5)	26 (39.4)	0.832
Beta-blocker, n (%)	17 (41.5)	34 (51.5)	0.311
AS, n (%)	29 (70.7)	50 (75.8)	0.565
Statin, n (%)	14 (34.15)	20 (30.3)	0.678
SVC trigger, n (%)	1 (2.4)	2 (3.0)	0.857
PV trigger, n (%)	5 (12.2)	10 (15.2)	0.668

Data are mean ± standard deviation, median (range), or n (%).

FMR, functional mitral regurgitation; TIA, transient ischemic attack; BMI, body mass index; CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, stroke/transient ischemic attack/thromboembolism (doubled), vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), age 65–75 years, sex category (female); BNP, brain natriuretic peptide; LAD, left atrial diameter; IVS, interventricular septum, LVPW, left ventricular posterior wall; LVDd, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; CHO, cholesterol; LDL, low-density lipoprotein; TG, triglycerides; UA, uric acid; GLU, glucose; Cr, creatinine; BUN, blood urea nitrogen; ALB, albumin; HT, hypertension; DM, diabetes; CHD, coronary heart disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AS, atherosclerosis; SVC, superior vena cava; PV, pulmonary vein.

Table 1. Binary logistic regression analysis for recurrence of AF after CPVI

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age, years	1.007 (0.940–1.080)	0.835	1.014 (0.937–1.098)	0.733
Sex	1.152 (0.292–4.548)	0.840	0.930 (0.195–4.442)	0.927
AF duration	1.002 (0.991–1.013)	0.791	1.001 (0.987–1.015)	0.898
Weight	1.041 (0.972–1.114)	0.249		
BMI	1.010 (0.794–1.285)	0.936		
CHA ₂ DS ₂ -VASc score	1.190 (0.799–1.772)	0.392		
LAD	0.953 (0.833–1.089)	0.478		
FMR	0.758 (0.191–3.004)	0.694	0.665 (0.134–3.300)	0.617
CHO	0.665 (0.310–1.427)	0.295	1.095 (0.202–5.933)	0.916
LDL	0.508 (0.198–1.307)	0.160	0.657 (0.081–5.330)	0.694
TG	1.010 (0.622–1.639)	0.969	0.966 (0.533–1.75)	0.909
Statin	5 (1.169–21.391)	0.030	4.216 (0.883–20.135)	0.071
IVS	1.937 (1.024–3.662)	0.042	1.787 (0.868–3.680)	0.115

AF, atrial fibrillation; CPVI, circumferential pulmonary vein isolation, HR, hazard ratio; CI, confidence interval; BMI, body mass index; CHA₂DS₂-VASc, congestive heart failure, hypertension, age \geq 75 years (doubled), diabetes, stroke/transient ischemic attack/thromboembolism (doubled), vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), age 65–75 years, sex category (female); LAD, left atrial diameter; FMR, functional mitral regurgitation; CHO, cholesterol; LDL, low-density lipoprotein; TG, triglycerides; IVS, interventricular septum.

(recurrence in 5 patients, mild FMR) and 41 patients did not have FMR (4 patients with recurrence). In the FMR group, 60 patients had mild FMR, 6 had moderate FMR, and no severe FMR was detected. Recurrence of PAF in the FMR group occurred in those with mild FMR, while no recurrence was detected in those with moderate FMR. Univariate and multivariate analyses showed that FMR did not increase the risk of recurrence of PAF after the CPVI procedure (Table 1). Survival analysis suggested that the recurrence rate of PAF in the FMR group was not higher than that in the non-FMR group. Therefore, FMR does not appear to be an independent predictor of recurrence of PAF post-ablation.

Main findings

The current study included 15 (15/107, 14%) cases of PAF triggered by the PV, among which 3 relapsed (3/15, 20%).

Three (3/107, 2.8%) cases of PAF were triggered by the SVC, among which one (1/3, 33%) relapsed. There was no evidence to suggest that the SVC and PV could trigger PAF (89/107, 83% not triggered by the PV or SVC); however, five (5/89, 5.6%) cases relapsed (Table 2). In the current study, the FMR group accounted for 62% of patients, and a large diameter of the LA was closely related to occurrence of FMR. Therefore, FMR may be a predictor of LA remodeling, and enlargement of the LA might be closely related to FMR.

FMR in patients with AF

MR increases the LA and LV preload, enlarges the LA and LV, and increases reflux.²³ Previous studies have shown that LA enlargement is closely related to FMR (odds ratio=1.130, 95% CI: 1.006–1.269, $P=0.04$).²⁴ Enlargement of the LA increases the incidence of AF.²⁵ A canine model of MR reproduced mechanical and electrical

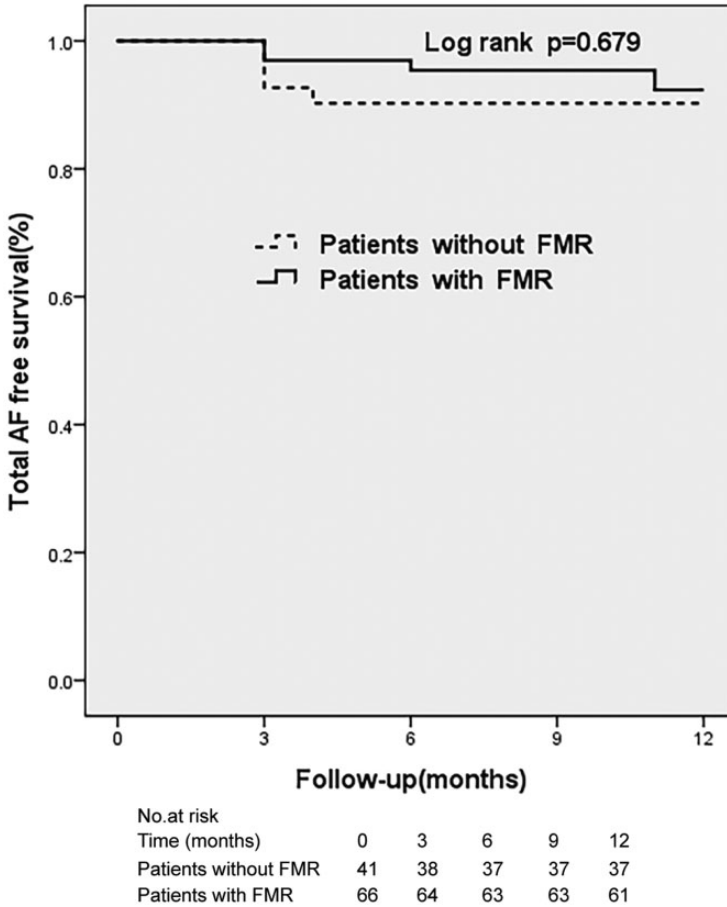


Figure 4. Kaplan–Meier curves for recurrence of AF in the FMR group and the non-FMR group
AF, atrial fibrillation; FMR, functional mitral regurgitation.

remodeling similar to clinical MR.²⁶ In this model, the LA size increased with a corresponding decrease in LV systolic function, and elevated atrial activation lowered the effective refractory period and increased inducibility of AF. Maintaining sinus rhythm after successful catheter ablation promotes reverse remodeling in the mitral valve apparatus and improves atrial FMR. The positive geometric effect of catheter ablation might contribute to improved outcomes in patients with AF in addition to the post-procedural freedom from disturbance

of rhythm.²⁷ MR increases the size of the LA and increases the incidence of AF, and the occurrence of AF increases regurgitation of the mitral valve. In patients with PAF, severe FMR is rare, most cases are mild FMR, and a few cases are moderate FMR. A previous study showed that patients with FMR had a substantial risk for recurrence of AF post-ablation, and the total recurrence rate of PAF after ablation was 28% (38/132).²⁴ However, survival analysis in our study suggested that the recurrence rate of PAF in the FMR group

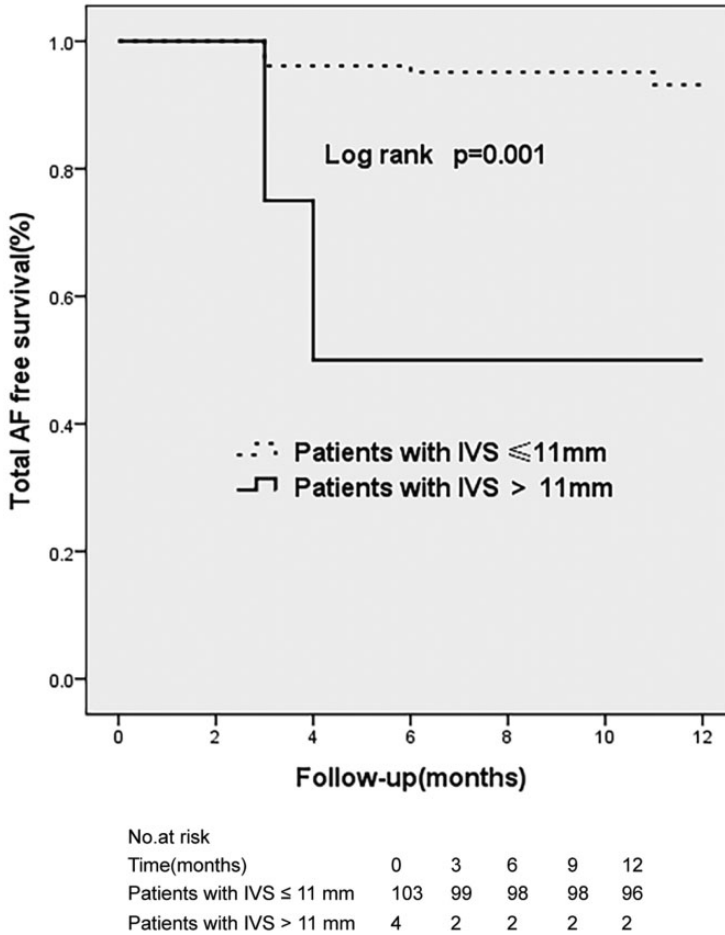


Figure 5. Kaplan–Meier curves for recurrence of AF in the IVS \leq 11 mm cohort and IVS > 11 mm cohort. AF, atrial fibrillation; FMR, functional mitral regurgitation; IVS, interventricular septum.

was not higher than that in the non-FMR group. Enlargement of the LA elevates MR, which in turn increases the incidence of AF. However, a small proportion of PAF has clinically significant FMR, and therefore, PAF has a small effect on FMR. FMR has not yet been determined as an independent predictor of recurrence of ablation of PAF. Therefore, the effect of FMR on patients undergoing radiofrequency catheter ablation of PAF requires further investigation.

Associations of FMR with LA substrate remodeling, cardiac chamber size, heart failure, and obesity

The function of the LA plays a critical role in adequate functioning of the mitral valve. Timely atrial contraction is critical for appropriate closing of the mitral valve, and the strength and timing of atrial contraction contribute to normal function of the mitral valve.^{28,29} Our study showed that LA enlargement was associated with

FMR. The result is in accordance with previous studies.³⁰ The mechanism of atrial function and MR is complicated; some patients with AF develop moderate to severe MR (atrial functional MR). This mechanism involves multiple factors, such as dilatation of the mitral area, flattening of the annular saddle shape, and leaflet tethering, which are the most influential factors affecting deterioration. A larger effective regurgitation orifice area was found to be associated with a greater annular area and annular circumference.³⁰ The mitral leaflet area increases in AF with isolated annular dilation and normal LV function. This compensatory enlargement becomes insufficient with high annular dilation, and the leaflets fail to match asymmetrical annular remodeling, thereby increasing MR.³¹ The current study suggested that the LA diameter in the FMR group was larger than that in the non-FMR group, and binary regression analysis suggested that LA enlargement was associated with FMR.

A case report showed considerable improvement in the severity of MR after catheter ablation for AF in a patient with severe functional MR and normal LV systolic function.³² Loss of this shape and annular flattening with LV remodeling result in increased leaflet stress with secondary MR. Additionally, LV systolic dysfunction reduces the strength of closing of the mitral valve, which opposes the leaflet tethering forces created by papillary muscle displacement. These pathological changes culminate in failure of leaflet coaptation and decreased valvular closing forces due to LV dysfunction, resulting in MR.³³ In most cases, as a consequence of LV dysfunction, valvular incompetence occurs. Therefore, FMR is the most common type of MR encountered in patients with chronic heart failure. Additionally, obesity is associated with a higher recurrence of AF in patients undergoing

catheter ablation. A high BMI might also be associated with a higher risk for adverse events.³⁴

IVS thickening and recurrence of PAF after ablation

In this study, the IVS thickening group showed recurrence of PAF in 2/4 patients within 1 year after AF ablation. Survival analysis showed a significant difference between the IVS thickening and normal IVS groups. In patients with hypertrophic cardiomyopathy, the incidence of AF is approximately 2%/year. LV hypertrophy causes an increase in the LA end-diastolic pressure, leading to mechanical distraction of atrial muscle and secondary atrial remodeling as vital mechanisms underlying AF in patients with hypertrophic cardiomyopathy.³⁵ Absolute LA end-diastolic volume is significantly greater in patients with hypertrophic cardiomyopathy and AF than in patients with hypertrophic cardiomyopathy without AF. After adjusting for the LA ejection fraction and age, every 10% increase in LA end-diastolic volume is associated with a 6% increase in odds of developing AF. Therefore, recurrence after AF ablation is related to LA end-diastolic volume or pressure.³⁶ In a previous study, 72 catheter ablations (i.e., PV isolation) were performed in 49 patients for recurrent symptomatic AF.³⁷ This previous study showed that LA size was significantly larger in patients with recurrence of AF post-ablation than in patients without recurrence.

Non-PV trigger and recurrence after AF ablation

Identification of a non-PV trigger that can be eliminated during a single procedure is associated with a low long-term recurrence rate of atrial tachyarrhythmia.³⁸ In the current study, the rate of AF triggered by the

SVC was 2.8% (3/107, Table 2), and one patient relapsed. Therefore, identifying a non-PV trigger is critical.

Limitations

This was a single-center prospective study with a small number of patients and it was not double blind. Additionally, only a few indicators were assessed. The present study also did not evaluate MR and the size of the LA after CPVI. Furthermore, the follow-up time was short, and therefore, long-term effects were not reported.

Conclusion

FMR is not an independent risk factor for predicting recurrence of catheter ablation for PAF. Additionally, FMR does not appear to affect patients undergoing radiofrequency catheter ablation of PAF, thereby requiring further investigation of this issue.

Acknowledgments

The authors would like to thank the doctors and nurses at the Cardiology Department of Shanghai General Hospital.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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.

Author contributions

FK and GC carried out the study, participated in collecting data, performed statistical analysis, participated in design of the study, and drafted

the manuscript. YH, ZJ, LH, QX, FJ, and YC participated in acquisition, analysis, or interpretation of data, and drafted the manuscript. All authors read and approved the final manuscript.

ORCID iD

Gang Chen  <https://orcid.org/0000-0002-9584-3259>

References

1. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004; 110: 1042–1046.
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. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet* 2015; 386: 154–162.
4. 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.
5. Packer DL, Mark DB, Robb RA, et al. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA* 2019; 321: 1261–1274.
6. Zhao L, Jiang W, Zhou L, et al. The role of valvular regurgitation in catheter ablation outcomes of patients with long-standing persistent atrial fibrillation. *Europace* 2014; 16: 848–854.
7. Gertz ZM, Raina A, Saghy L, et al. Evidence of atrial functional mitral regurgitation due to atrial fibrillation: reversal with arrhythmia control. *J Am Coll Cardiol* 2011; 58: 1474–1481.
8. Van Rosendael PJ, Katsanos S, Kamperidis V, et al. New insights on Carpentier I mitral regurgitation from multidetector row computed tomography. *Am J Cardiol* 2014; 114: 763–768.

9. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm* 2017; 14: e275–e444.
10. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; 37: 2129–2200.
11. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003; 16: 777–802.
12. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 63: e57–e185.
13. Ouyang F, Bänsch D, Ernst S, et al. Complete isolation of left atrium surrounding the pulmonary veins: new insights from the double-Lasso technique in paroxysmal atrial fibrillation. *Circulation* 2004; 110: 2090–2096.
14. Hocini M, Sanders P, Jaïs P, et al. Techniques for curative treatment of atrial fibrillation. *J Cardiovasc Electrophysiol* 2004; 15: 1467–1471.
15. Augello G, Vicedomini G, Saviano M, et al. Pulmonary vein isolation after circumferential pulmonary vein ablation: comparison between Lasso and three-dimensional electroanatomical assessment of complete electrical disconnection. *Heart Rhythm* 2009; 6: 1706–1713.
16. Verma A, Wazni OM, Marrouche NF, et al. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. *J Am Coll Cardiol* 2005; 45: 285–292.
17. Aksu T, Baysal E, Guler TE, et al. Predictors of atrial fibrillation recurrence after cryoballoon ablation. *J Blood Med* 2015; 6: 211–217.
18. Aksu T, Golcuk SE, Guler TE, et al. Prediction of mid-term outcome after cryoballoon ablation of atrial fibrillation using post-procedure high-sensitivity troponin level. *Cardiovasc J Afr* 2015; 26: 165–170.
19. Gertz ZM, Raina A, Mountantonakis SE, et al. The impact of mitral regurgitation on patients undergoing catheter ablation of atrial fibrillation. *Europace* 2011; 13: 1127–1132.
20. Haïssaguerre M, Jaïs 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.
21. Dinov B, Kosiuk J, Kircher S, et al. Impact of metabolic syndrome on left atrial electroanatomical remodeling and outcomes after radiofrequency ablation of nonvalvular atrial fibrillation. *Circ Arrhythm Electrophysiol* 2014; 7: 483–489.
22. Rolf S, Kircher S, Arya A, et al. Tailored atrial substrate modification based on low-voltage areas in catheter ablation of atrial fibrillation. *Circ Arrhythm Electrophysiol* 2014; 7: 825–833.
23. Neilan TG, Ton-Nu TT, Kawase Y, et al. Progressive nature of chronic mitral regurgitation and the role of tissue Doppler-derived indexes. *Am J Physiol Heart Circ Physiol* 2008; 294: H2106–H2111.
24. Qiao Y, Wu L, Hou B, et al. Functional mitral regurgitation: predictor for atrial substrate remodeling and poor ablation outcome in paroxysmal atrial fibrillation. *Medicine (Baltimore)* 2016; 95: e4333.
25. Vaziri SM, Larson MG, Benjamin EJ, et al. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. *Circulation* 1994; 89: 724–730.
26. Ruaengsri C, Schill MR, Lancaster TS, et al. The hemodynamic and atrial electrophysiologic consequences of chronic left atrial volume overload in a controllable canine model. *J Thorac Cardiovasc Surg* 2018; 156: 1871–1879.e1871.
27. Nishino S, Watanabe N, Ashikaga K, et al. Reverse Remodeling of the Mitral Valve Complex After Radiofrequency Catheter

- Ablation for Atrial Fibrillation: A Serial 3-Dimensional Echocardiographic Study. *Circ Cardiovasc Imaging* 2019; 12: e009317.
28. David D, Michelson EL, Naito M, et al. Diastolic "locking" of the mitral valve: the importance of atrial systole and intraventricular volume. *Circulation* 1983; 67: 640–645.
 29. Dell’Era G, Rondano E, Franchi E, et al. Atrial asynchrony and function before and after electrical cardioversion for persistent atrial fibrillation. *Eur J Echocardiogr* 2010; 11: 577–583.
 30. Cong T, Gu J, Lee APW, et al. Quantitative analysis of mitral valve morphology in atrial functional mitral regurgitation using real-time 3-dimensional echocardiography atrial functional mitral regurgitation. *Cardiovasc Ultrasound* 2018; 16: 13.
 31. Kim DH, Heo R, Handschumacher MD, et al. Mitral Valve Adaptation to Isolated Annular Dilation: Insights Into the Mechanism of Atrial Functional Mitral Regurgitation. *JACC Cardiovasc Imaging* 2019; 12: 665–677.
 32. Udo EO and Hassink RJ. Pulmonary vein isolation as a treatment for severe atrial functional mitral regurgitation in a patient with atrial fibrillation. *Int J Cardiol* 2014; 175: 578–579.
 33. Carpentier A. Cardiac valve surgery: the 'French correction'. *J Thorac Cardiovasc Surg* 1983; 86: 323–337.
 34. Pranata R, Henrina J, Yonas E, et al. BMI and Atrial Fibrillation Recurrence Post Catheter Ablation: A Dose-Response Meta-analysis. *Eur J Clin Invest* 2021: e13499.
 35. Nijenkamp LLAM, Güçlü A, Appelman Y, et al. Sex-dependent pathophysiological mechanisms in hypertrophic cardiomyopathy: implications for rhythm disorders. *Heart Rhythm* 2015; 12: 433–439.
 36. Maron BJ, Haas TS, Maron MS, et al. Left Atrial Remodeling in Hypertrophic Cardiomyopathy and Susceptibility Markers for Atrial Fibrillation Identified by Cardiovascular Magnetic Resonance. *Am J Cardiol* 2014; 113: 1394–1400.
 37. Rowin EJ, Maron MS and Maron BJ. Response by Rowin et al to Letter Regarding Article, "Clinical Profile and Consequences of Atrial Fibrillation in Hypertrophic Cardiomyopathy". *Circulation* 2018; 137: 2541–2542.
 38. Lee KN, Roh SY, Baek YS, et al. Long-Term Clinical Comparison of Procedural End Points After Pulmonary Vein Isolation in Paroxysmal Atrial Fibrillation: Elimination of Nonpulmonary Vein Triggers Versus Noninducibility. *Circ Arrhythm Electrophysiol* 2018; 11: e005019.