Original Article

Acute and long-term outcomes of pulmonary vein isolation and left atrial substrate modification for non-paroxysmal atrial fibrillation: a non-randomized trial

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Background: The long-term success rate of nonparoxysmal atrial fibrillation (AF) treated with pulmonary vein isolation (PVI) alone is not ideal. This may indicate atrial fibrosis as a major cause of recurrence. Therefore, the aim of this study is to investigate the efficacy of left atrial substrate modification (LASM) by targeting low-voltage area.

Methods: A total of 157 consecutive patients with drug-refractory nonparoxysmal AF who underwent radiofrequency ablation during hospitalization in the Third People's Hospital of Chengdu from April 2017 to August 2021 were prospectively included. Stepwise ablation was performed in two different orders: LASM first (n=53) and PVI first (n=104) group. All patients underwent ablation during AF, and the procedural endpoint was AF termination during ablation. In the LASM first group, LASM was performed first and if AF was terminated, PVI was not performed. Similarly, in the PVI first groups, LASM was performed if AF was not terminated. The primary outcome were AF termination and freedom from AF. The secondary outcome was adverse events. Cox regression analysis was used to define predictors of AF termination, and Kaplan-Meier analysis was used to assess differences between groups in AF freedom.

Results: The baseline characteristics of the two groups were similar. At a median follow-up of 16 months, the 112 patients (39 in LASM first group and 73 in PVI first group) with AF termination had a higher success rate than the 45 patients who had no AF termination (78.6% *vs.* 57.8%; P<0.01). The AF termination rate (24/53, 45.3% *vs.* 12/104, 11.5%; P<0.01) and AF freedom (20/24, 83.3% *vs.* 7/12, 58.3%; P=0.13) by LASM alone was higher than PVI alone. There were 3 cases of heart failure and 1 case of stroke (4/53) in the LASM first group, and 1 case of pericardial tamponade, 5 cases of heart failure and 1 case of stroke (7/104) in the LASM first group (7.5% *vs.* 6.7%; P>0.05).

Conclusions: LASM provides higher immediate success and a slightly better long-term success rate compared to PVI. Patients who terminated AF were more likely to have AF freedom than those who did not. AF termination during procedure may improve symptoms and reduce hospitalization.

Keywords: Atrial fibrillation (AF); pulmonary vein isolation (PVI); substrates modification; recurrence; AF termination

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Introduction

Background

As a common tachyarrhythmia, atrial fibrillation (AF) is a progressive disease that is deemed a considerable health threat due to its association with major complications, such as stroke, heart failure, and even dementia (1). Compared with paroxysmal AF, non-paroxysmal AF has a larger left atrial volume and involves more complex triggering and maintenance substrate (2). Currently, pulmonary vein isolation (PVI) is considered as the first-line treatment for non-paroxysmal AF; however, the success rate of single ablation for non-paroxysmal AF is poor. A meta-analysis involving 18,657 patients with non-paroxysmal AF showed that the long-term success rate of a single PVI was only 43% (3). Various combined strategies to improve the success rate of persistent AF ablation are currently receiving attention in cardiac arrhythmia research.

When electrogram-guided or hybrid approaches are adopted, intraoperative endpoints of ablation are usually defined as the conversion to sinus rhythm, atrial tachycardia (AT), or a reduction of AF burden. Previous studies demonstrated that patients with AF termination during ablation have a lower rate of long-term recurrence than those without intraoperative termination (4-6). Rostock *et al.* evaluated the long-term predictors of single-procedure and multiple-procedure outcomes of 395 patients who had undergone persistent AF ablation, and AF termination was found to significantly predict multiple-procedure success and favorable outcomes (7).

Highlight box

Key findings

- Compared with pulmonary vein isolation, atrial ablation can terminate more atrial fibrillation (AF) during the procedure, and these patients can achieve ideal AF freedom. Compared with patients without AF termination, AF termination predicted higher AF freedom.

What is known and what is new?

- Pulmonary vein isolation can only terminate a small number of cases of non-paroxysmal AF, and the long-term success rate is not ideal. Although the mechanisms of AF are not fully understood, substrate modification significantly improves long-term success.
- This study attempted to analyze the effects of substrate modification and pulmonary vein isolation separately on AF termination and long-term recurrence.

What is the implication, and what should change now?

- For non-paroxysmal AF, substrate modification cannot be underestimated, and its importance is no less than that of pulmonary vein isolation. To better understand the mechanism of AF, focus should be placed on the atria.

Rationale and knowledge gap

In many cases, PVI alone has been insufficient in terminating non-paroxysmal AF and reducing late AF recurrence, and additional left atrial substrate modification (LASM) was necessary (8,9). When combined with other ablation strategies, such as complex fractionated atrial electrograms (CFAEs), rotor, low-voltage and linear ablation, better long-term AF freedom can be achieved compared to PVI alone (10-13). Although there are a large number of randomized controlled trials comparing PVI and PVI combined with other ablation strategies, there are several limitations. First, they did not explore the effect of different ablation sequences on ablation outcomes, and second, they did not define intraoperative termination of AF as procedural termination. Similarly, no study to date was designed to investigate the efficacy of LASM without PVI for the treatment of non-paroxysmal AF. Whether LASM ablation alone can elicit comparable or superior effects to PVI combined with LASM remains unclear. Indeed, unlike paroxysmal AF, the severity of non-paroxysmal AF showed a strong association with the complexity of atrial substrate and exterior triggering ectopic activities, except for pulmonary veins (14,15). The current evidence indicates that successful AF termination or ablation may depend on atrial substrates.

Objective

In this study, we aimed to establish a novel stepwise ablation strategy (LASM first and PVI first) to investigate the effect of different ablation sequences on the long-term recurrence of non-paroxysmal AF, especially the efficacy of atrial LASM alone in terminating AF. We present this article in accordance with the TREND reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-273/rc).

Methods

Study design

This study was a prospective, single-center, non-randomized controlled trial conducted in the AF Center of the Third People's Hospital of Chengdu, China. As an

exploratory study for preceding a randomized controlled trial, in order to further ensure the ethics of the trial, the principle of the different order of ablation of the admitted patients was mainly based on the wishes of the patients in the preoperative interview. In the process of conversation, all the doctors involved in this study did not introduce too much about the advantages and disadvantages of different ablation sequences, and refused to implement purposeful induction for patients to ensure the randomness of patients' independent choice. This study was derived from a larger trial on the individualized localization method of the AF maintenance substrate (2020YJ0483). This study was registered as a clinical trial (ChiCTR-OIN-17013021). This study was approved by the ethics review board of the Third People's Hospital of Chengdu (No. 2023-S-38) and conducted in accordance with the Declaration of Helsinki (as revised in 2013) and institutional guidelines. All patients signed an informed consent form for radiofrequency ablation.

Study population, inclusion and exclusion criteria

The principle of sample size calculation is the principle of superiority testing (the ratio of LASM first to PVI first group was 1:2; α=0.05, Power =0.9, loss to follow-up 5%). A total of 157 (see *Table 1* for baseline characteristics) consecutive patients with drug-refractory nonparoxysmal AF who underwent radiofrequency ablation during hospitalization in Third People's Hospital of Chengdu from April 2017 to August 2021 were prospectively included. The inclusion criteria were as follows: (I) duration >7 days and non-conversion to sinus rhythm on their own; (II) age 18 through 80 years old; (III) meeting the indications for radiofrequency ablation; and (IV) active cooperation regarding postoperative follow-up.

The exclusion criteria included: (I) presence of left atrial thrombosis or other absolute contraindications for catheter ablation surgery; (II) history of left intra-atrial catheter ablation and left atrial surgery; (III) AF caused by reversible and pathological factors, such as hyperthyroidism, drugs, or alcoholism; and (IV) left ventricular dysfunction (<30%) or severe cardiac valvular disease, including severe aortic stenosis or aortic insufficiency, severe mitral valve stenosis or incomplete closure, or mitral valve replacement surgery.

Study procedures and data collection

After obtaining the patient's consent, eligible patients were divided into two groups: LASM first and PVI first. The staff member performing the assessments was not involved in implementing any aspect of the intervention, and the operator was made aware of the patient's group assignment only prior to ablation. AF was induced in patients who were not in AF before ablation, and all patients underwent ablation during AF. In the LASM first group, LASM was performed first, and PVI was performed if AF termination could not be achieved. In the PVI first group, PVI was performed first, and LASM was performed if AF termination could not be achieved. Termination of AF was defined as conversion of AF into AT or sinus rate. If AF was terminated or converted into AT, the converted AT was mapped and ablated by means of activation mapping and entrainment maneuvers. Finally, if AT failed to convert to sinus rate or AF could not be terminated, external electrical conversion (ECV) was used to restore sinus rhythm.

The primary outcome measures were the achievement of the procedural endpoint (AF termination) and freedom from AF. The secondary outcome measures were severe early procedure-related complications and long-term adverse events. Clinical baseline, echocardiographic, and surgical records of patients were collected from the hospital's electronic information system of the Third People's Hospital of Chengdu and included in the study.

Ablation method

All patients underwent ablation under general anesthesia using a three-dimensional imaging system (CARTO-3 System, Version 6). Catheter ablation is performed by two professionally trained and experienced surgeons. The criteria for AF termination during ablation were concerted by a senior surgeon and two surgeons. During LASM, the adjustable sheath was replaced with the pentaRay electrode (Johnson & Johnson, USA) in the left chamber via the CARTO-3 navigation system to guide the descending left atrium anatomy modeling, collecting the contact bipolar cavity electrical graph signal throughout the left atrium. Subsequently, the low-voltage region of the left atrium was mapped under sinus rate and AF state, and the ablation circuit was designed according to the mapping results. Catheter ablation was performed using 50-W power at the left atrium or PVI, while 40-W was used in the right atrium if needed. The low voltage threshold calculation method can be found elsewhere (16).

Follow-up and outcome definitions

All patients were required to take antiarrhythmic drugs for

Table 1 Baseline characteristics of study cohort

Characteristics	All patients (n=157)	PVI first group (n=104)	LASM first group (n=53)	P value
Demographics				
Age, years	66.6±8.3	66.4±7.9	67.6±8.8	0.553
Male sex	82 (52.2)	55 (52.9)	27 (50.9)	0.818
BMI, kg/m^2	24.4±2.9	24.62±3.02	23.89±2.48	0.133
Ablation points	142±46	145.95±43	136±51	0.174
Course of AF, days	365 [30, 1,095]	183 [30, 730]	730 [120, 2,190]	<0.001
Follow-up time, months	16 [13, 24]	16 [13, 24]	16 [13, 24]	0.955
Medical history, n (%)				
Smoking	51 (32.5)	31 (29.8)	20 (37.7)	0.316
Hypertension	80 (51.0)	56 (53.8)	24 (45.3)	0.310
Diabetes	33 (21.0)	23 (22.1)	10 (18.9)	0.637
Stroke	22 (14.0)	17 (16.3)	5 (9.4)	0.238
Coronary artery disease	30 (19.1)	16 (15.4)	14 (26.4)	0.096
Hyperlipidemia	29 (18.5)	21 (20.2)	8 (15.1)	0.436
Heart failure	26 (16.6)	14 (13.5)	12 (22.6)	0.143
CHA_2DS_2-VASc score	3 [2, 4]	3 [2, 4]	3 [2, 4]	0.890
0–3	105 (66.9)	70 (67.3)	35 (66.0)	
4	29 (18.5)	20 (19.2)	9 (17.0)	
5–9	23 (14.6)	14 (13.5)	9 (17.0)	
Echocardiography at admission				
LAD, mm	44 [41, 47]	43 [41, 46]	44 [41, 48]	0.180
LVEF, %	59 [57, 62]	59 [56, 62]	60 [58, 62]	0.064
Laboratory parameters				
eGFR, mL/min*1.73 m^2	84.56±1.53	84.80±19.38	84.40±18.86	0.825
BNP, pg/mL	176 [92, 310]	164 [98, 375]	180 [77, 365]	0.693

Values are presented as n (%), median [interquartile range], or mean ± SD. CHA_2DS_2-VASc, stroke risk score based on congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, previous stroke, transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years, and sex category (female). PVI, pulmonary vein isolation; LASM, left atrial substrate modification; BMI, body mass index; AF, atrial fibrillation; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; SD, standard deviation.

8 weeks after ablation. In the absence of contraindications, anticoagulant treatment (warfarin or rivaroxaban) was continued in patients with a CHA_2DS_2-VASc score of ≥2. There was a 3-month blank period after ablation, during which no further ablation was performed, and patients could be treated with medical or electrotherapy if symptoms recurred. All patients were followed up regularly at the outpatient clinic of our hospital by an outpatient follow-up physician who was blinded to the study condition assignment at 3, 6, and 12 months after ablation, mainly including Holter monitoring (more than 24 hours) and were asked about any symptoms associated with arrhythmias. After ablation, patients are usually informed that if there are recurrent symptoms, it is recommended to go to the nearest hospital for a surface 12-lead electrocardiogram as soon as possible.

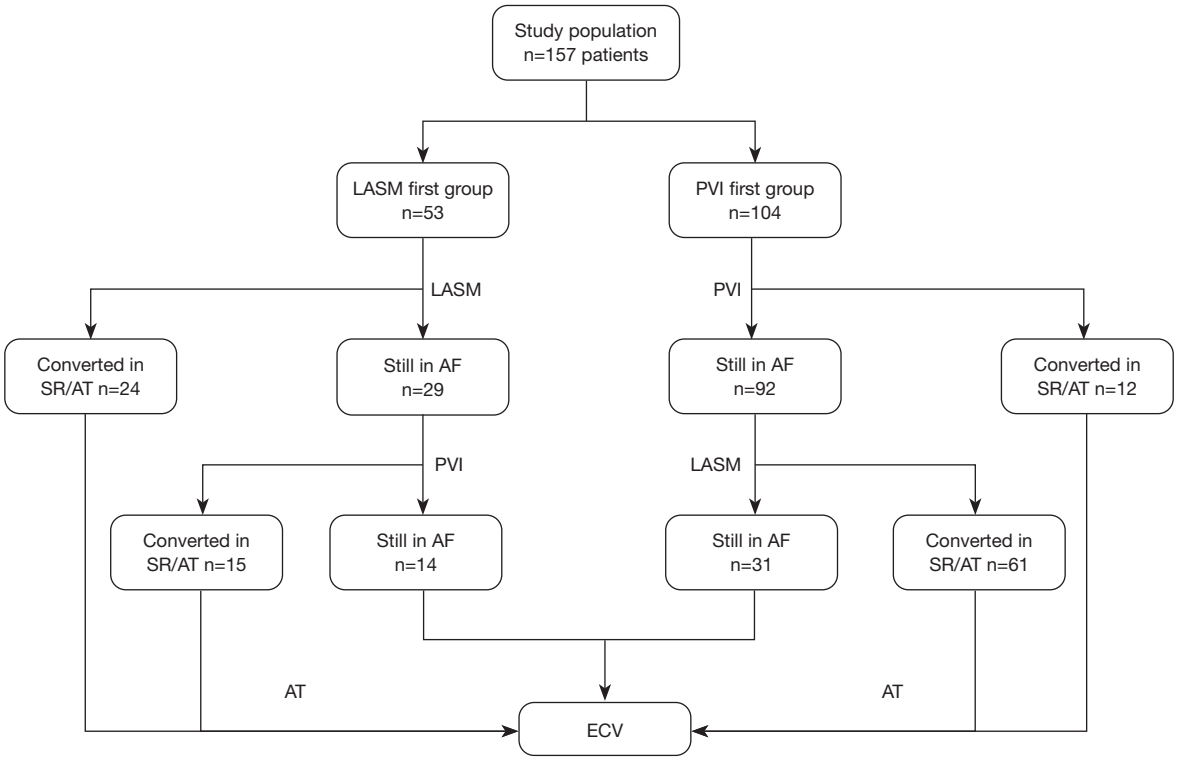

Figure 1 Study population and ablation procedure results. LASM, left atrial substrate modification; PVI, pulmonary vein isolation; SR, sinus rhythm; AT, atrial tachycardia; AF, atrial fibrillation; ECV, electric cardioversion.

AF recurrence was defined as occurrence of arrhythmia on electrocardiogram or Holter monitoring for 30-s AF events continuously after 3 months of ablation. Long-term ablation success was defined as the absence of AF, atrial flutter, or AT for more than 30 s for at least 12 months after ablation. Early serious complications (within 7 days) included atrioesophageal fistula, pericardial tamponade, myocardial perforation, major complications of vascular puncture, myocardial infarction, phrenic nerve injury, and cerebral infarction. Long-term adverse events included heart failure, stroke, and death that occurred after surgery and out of the hospital.

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate. The Kolmogorov-Smirnov test was used to determine data normality. An unpaired *t*-test was used to compare continuous variables with normal distribution, and a non-parametric test was used to compare those with skewed distribution. Categorical variables were expressed as counts or proportions (%) and were compared using the chi-squared or Fisher's exact test, as appropriate. Event-free survival plots were constructed using the Kaplan-Meier method and compared with log-rank tests. Univariate and multivariable Cox proportional hazard regression models were used to assess independent effects of the acute AF termination during ablation. Multivariate Cox regression analysis was performed to adjust for the effect of covariates on long-term ablation outcomes between groups. Statistical significance was defined as a two-sided P value of <0.05, and analyses were performed using SPSS software, version 26.0 and GraphPad Prism v9.5.0.

Results

Study population

The overall ablation results are shown in *Figure 1*. A total of 157 patients who met the inclusion criteria and agreed to participate in the study were divided into the LASM first group (n=53) and PVI first group (n=104). The clinical baseline, echocardiographic, and laboratory parameters

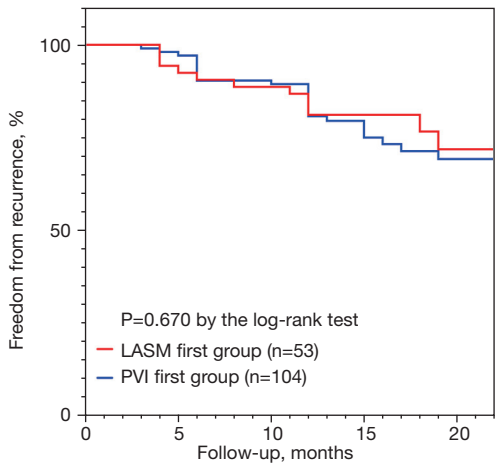

Figure 2 Kaplan-Meier survival curve for LASM first and PVI first group. The graph shows Kaplan-Meier estimates of freedom from any documented atrial arrhythmia after a single ablation procedure (log-rank P=0.670), with LASM first group (red line) and PVI first group (blue line). LASM, left atrial substrate modification; PVI, pulmonary vein isolation.

Table 2 Multivariate Cox regression analysis for predicting recurrence

Groups	HR (95% CI)	P value
Different group (model 1)	1.149 (0.599–2.202)	0.677
Different group (model 2)	1.234 (0.637–2.391)	0.532
Different group (model 3)	1.285 (0.656–2.518)	0.465
Different group (model 4)	1.230 (0.594–2.544)	0.577

Model 1: different group (PVI first group); model 2: different group + age + sex (female) + LAD + eGFR; model 3: different group + course of AF + history of coronary artery disease + LVEF; model 4: different group + age + sex (female) + LAD + eGFR + BMI + smoking + course of AF + hypertension + diabetes mellitus + coronary artery disease + heart failure + stroke + hyperlipidaemia + BNP + LVEF + ablation points + CHA_2DS_2-VASc score. CHA_2DS_2-VASc, stroke risk score based on congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, previous stroke, transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years, and sex category (female). HR, hazard ratio; CI, confidence interval; PVI, pulmonary vein isolation; LAD, left atrial diameter; eGFR, estimated glomerular filtration rate; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; BMI, body mass index; BNP, brain natriuretic peptide.

of the two groups were retrospectively collected and compared (*Table 1*). No statistically significant differences in the characteristics of the patients between the two groups were found.

Primary outcome measures

In the LASM first group, comprising 24 patients (45.3%), had AF termination after LASM, and 29 patients did not have AF termination. After continued PVI, 15 patients had AF termination, and the remaining 14 patients with AF eventually underwent ECV. In the PVI first group, 12 patients (11.5%) had AF termination after PVI, and 92 patients did not have AF termination. In the LASM first group, the immediate success rate of 45.3% was significantly higher than that of the PVI first group (11.5%, P<0.001). Among these 92 patients, LASM was continued, and AF was terminated in 61 cases, while AF required ECV in 31 cases. Finally, after the expanded ablation was completed, 14 patients in the LASM group and 31 patients in the PVI group still had AF, and the immediate success rates were 73.6% and 70.2%, respectively. At a median follow-up time of 16 months, 13 patients had recurrence in the LASM first group, including 4 patients for whom AF was terminated with LASM, 3 patients for whom AF was terminated with LASM combined with PVI, and 6 patients for whom treatment immediately failed. Recurrence occurred in 30 patients in the PVI group, including 5 patients for whom AF was terminated with PVI, 12 patients for whom AF was terminated with PVI combined with LASM, and 13 patients for whom treatment immediately failed. There were no differences in long-term success rate between the LASM first and PVI first groups (75.5% *vs.* 71.2%, respectively; log-rank test, P=0.670; *Figure 2*). Multivariate analysis with Cox regression showed consistent results after adjusting for relevant confounding factors (*Table 2*). The long-term success rate of those patients who had immediate success was 78.6%, whereas for those who had immediate failure was 57.8% (log-rank test, P=0.003; *Figure 3*). Based on comparison of the characteristics between the two groups, the Brain natriuretic peptide and ablation points of patients in the AF termination group were higher than those in the non-termination group. In addition, patients in the AF termination group had a lower estimated glomerular filtration rate and a higher prevalence of hypertension history, for which the difference bordered statistical significance (*Table 3*). Therefore, we performed univariate and multivariate cox regression analyses, which revealed that no independent predictors of AF termination were observed between the two groups (*Table 4*). Among the 24 patients who underwent ablation only in the left atrium, 20 did not experience long-term recurrence, whereas 7 of 12 patients (58.3%) who only had PVI ablation in the PVI

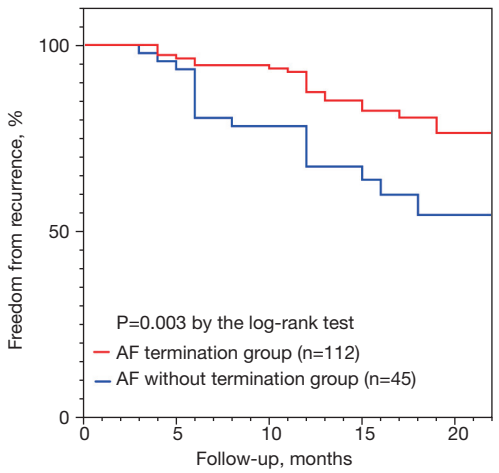

Figure 3 Kaplan-Meier survival curves for recurrence with and without AF termination during ablation. The graph shows Kaplan-Meier estimates of freedom from any documented atrial arrhythmia after a single ablation procedure (log-rank P=0.003), with AF termination group (red line) and AF without termination group (blue line). AF, atrial fibrillation.

first group were free from AF recurrence. Thus, patients for whom AF was terminated with PVI had a lower long-term success rate than those for whom AF was terminated with LASM; however, the difference did not reach statistical significance (P=0.126).

Secondary outcome measures

Table 5 shows surgery-related serious complications and long-term postoperative adverse events for all patients with non-paroxysmal AF. One patient in the PVI first group experienced an early serious procedural complication—cardiac tamponade during left atrial appendage ablation—and recovered well after adequate drainage. When the follow-up reached a median of 16 months, six cases of long-term adverse events occurred in the PVI first group, including five cases of heart failure and one case of stroke. Four adverse events occurred in the LASM first group, including three cases of heart failure and one case of stroke. No death occurred during the follow-up period. The incidence of early serious procedural complications in the LASM and PVI first groups was 0% and 1.0%, respectively. The rates of total adverse events were 7.5% and 6.9%, respectively, with no significant difference between the two groups. The long-term postoperative adverse events occurred in 4 cases (4/53) in the PVI first group and 6 cases (6/104) in the PVI-LASM group, and there was no significant difference between the two groups (7.5% *vs.* 5.8%; P=0.734).

Discussion

Key findings

This study showed that AF termination during ablation tends to predict a good long-term outcome. Moreover, non-paroxysmal AF was terminated by LASM alone in nearly half of cases, while PVI was able to terminate fewer AF cases. Finally, the two stepwise ablations of PVI first and LASM first seemed to have no effect on AF recurrence in the long-term follow-up.

Strengths and limitations

There are some limitations to our study. First, although the study was pre-designed, it was a non-randomized and single-center trial, so selection bias may have impacted the overall outcomes. Nonetheless, no significant differences in the characteristics of the two groups at baseline were identified. Secondly, the sample size of the two groups were limited and imbalance, so we should keep cautious in emphasizing the extrapolation property of our results, and the conclusions may need to be further verified in a larger patient population. Third, without continuous monitoring after ablation, the AF recurrence rate is most likely to be underestimated. Moreover, a longer follow-up time should be performed to assess the long-term safety of this innovative stepwise procedure in the future. Last but not least, the association between AF termination and long-term outcomes required further validation.

Comparison with similar research

Controversy remains as to whether substrate modification can improve AF freedom in non-paroxysmal AF. A recent study comparing the outcomes of PVI alone and PVI plus substrate ablation for the treatment of non-paroxysmal AF showed no improvement in long-term efficacy (17). In contrast, a study of low-voltage mapping in patients with AF undergoing PVI first showed that low-voltage zones are associated with AF recurrence, and the impact of low-voltage zones on outcomes was associated with higher burden in patients with persistent relative to paroxysmal AF (18). A meta-analysis of data from

Table 3 Baseline characteristics of the population between the terminated and non-terminated groups

Characteristics	AF termination (–) (n=45)	AF termination (+) (n=112)	P value
Demographics			
Age, years	65.4±7.4	67.1±8.6	0.246
Female sex	18 (40.0)	57 (50.0)	0.217
BMI, kg/m^2	24.6±2.6	24.3±3.0	0.532
Ablation points	162±38	135±47	0.001
Duration of AF, days	365 [60, 1,095]	330 [30, 1,095]	0.512
Recurrence	19 (42.2)	24 (21.4)	0.008
Medical history, n (%)			
Smoking	16 (35.6)	35 (31.3)	0.602
Hypertension	19 (42.2)	66 (58.9)	0.057
Diabetes	12 (26.7)	21 (18.8)	0.271
Stroke	6 (13.3)	16 (14.3)	0.876
Coronary artery disease	11 (24.4)	19 (17.0)	0.281
Hyperlipidemia	7 (15.6)	22 (19.6)	0.551
Heart failure	7 (15.6)	19 (17.0)	0.830
CHA_2DS_2-VASc score	2.73±1.41	2.96±1.49	0.391
Echocardiography at admission			
LAD, mm	44.04±5.07	44.11±4.50	0.939
LVEF, %	58.13±4.25	58.30±5.98	0.862
Laboratory parameters			
eGFR, mL/min*1.73 m^2	89.13±16.90	82.72±19.4	0.058
BNP, pg/mL	111 [76.5, 223]	194 [102, 365]	0.001

Values are presented as n (%), median [interquartile range], or mean ± SD. CHA_2DS_2-VASc, stroke risk score based on congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, previous stroke, transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years, and sex category (female). AF, atrial fibrillation; BMI, body mass index; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; SD, standard deviation.

885 patients with persistent AF identified that the success rate of PVI combined with LASM in a low-voltage area at a mean follow-up of 17 months was 70% (19). Recently, an increasing body of evidence supports that substrate modification can improve AF freedom (8,9).

When electrogram-guided or hybrid approaches are used, conversion to sinus rhythm or AT or a reduction in the rate of AF activation are usually the intended endpoints of ablation. In our study, patients who achieved AF termination had a lower long-term recurrence rate than those who did not, which is consistent with the results of a recent multicenter prospective randomized controlled study involving 450 patients with persistent AF (4). For patients achieving AF termination, ablation resulted in a decreased dominant frequency gradient throughout the left atrium and was associated with improved ablation outcomes (5). If AF termination is used as a reliable procedural endpoint, it would help establish the efficacy of ablation and increase the confidence of the operator.

AF termination aims to progressively target multiple drivers of persistent AF until most sources have been eliminated during an operation. There are considerable variations of the single success rate of AF termination by PVI alone between various studies, which ranges from 6%

Table 4 Univariate and multivariate COX regression analysis for predicting atrial fibrillation termination

Parameters	Univariate Cox regression		Multivariate Cox regression	
	HR (95% CI)	P value	HR (95%CI)	P value
Age	1.028 (1.004–1.052)	0.020	1.023 (0.998–1.049)	0.067
Sex, female	0.676 (0.463–0.986)	0.042	1.196 (0.796–1.796)	0.388
BMI	0.997 (0.939–1.058)	0.923		
Duration of AF	1.000 (1.000–1.000)	0.602		
Smoking	0.870 (0.582–1.300)	0.496		
Hypertension	0.942 (0.642–1.383)	0.761		
Diabetes mellitus	0.918 (0.568–1.485)	0.728		
Coronary artery disease	0.571 (0.340–0.960)	0.034	0.607 (0.361–1.023)	0.061
Heart failure	1.329 (0.807–2.186)	0.264		
Previous stroke	0.585 (0.331–1.034)	0.065		
Hyperlipidaemia	1.195 (0.747–1.910)	0.458		
eGFR	0.992 (0.983–1.002)	0.118		
BNP	1.000 (0.999–1.001)	0.787		
LAD	1.008 (0.967–1.051)	0.705		
LVEF	1.027 (0.989–1.067)	0.167		
CHA_2DS_2VASC score	1.089 (0.955–1.242)	0.205		

CHA_2DS_2-VASc, stroke risk score based on congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, previous stroke, transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years, and sex category (female). HR, hazard ratio; CI, confidence interval; BMI, body mass index; AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; LAD, left atrial diameter; LVEF, left ventricular ejection fraction.

Table 5 Adverse events of study cohort

Adverse events	LASM first group (n=53)	PVI first group (n=104)
Overall adverse events	4 (7.5%)	7 (6.7%)
Cardiac tamponade	0	1
Heart failure	3	5
Stroke	1	1
Death	0	0

There was no significant difference between two groups in overall adverse events. LASM, left atrial substrates modification; PVI, pulmonary vein isolation.

to 25.4% (20-23). In terms of the long-standing persistent AF, the single success rate of AF termination through PVI is merely 4.3% (24). Similarly, in our study, the probability of attaining the procedural endpoint by PVI alone was only 12%. Although the results are from different centers, we can also figure it out that PVI alone insufficiently achieve the rhythm control from the extremely low AF termination rate. Besides, it seems to be no different of long-term outcomes between the patients with AF termination by PVI and the patients without AF termination (25).

In our study, the patients with AF termination by LASM alone had more ideal AF freedom in the following. At least three papers reported that LASM alone can improve the AF termination rate and a relatively good long-term availability. The reason may be explained that ablation of AF triggers by PVI is not sufficient to maintain persistent AF. It is also necessary to eliminate the AF maintenance substrate within the atrium and electrical isolation of pulmonary veins is not decisive for curing persistent AF (26-28).

Explanation of findings

Unsurprisingly, no significant difference was observed in the late recurrence rate between the LASM first and

PVI first groups. This outcome is likely because the long-term success rate of patients without PVI was not lower than those receiving LASM plus PVI in the present study. However, although the long-term outcome of patients with PVI alone is not ideal, it had no significant effect on the outcomes of the whole group of patients due to the small sample size. Although there was no difference between different ablation order groups, there were significant differences between subgroups, which was the key point of this study. The high recurrence rate of PVI ablation may be related to the high reconnection of pulmonary veins (29,30). However, a similar degree of pulmonary vein reconnection was demonstrated in patients with and without AF recurrence (31). Additionally, ectopic electrical activity outside of pulmonary veins may also be a key factor in AF recurrence (32). The abnormal substrates of the atrium are associated with AF recurrence, which may be one of the key reasons for the ideal long-term efficacy after LASM (no PVI). In our study, in 45% of patients with AF, most maintenance targets were distributed in the left atrium, and the ablation targets distributed in the pulmonary vein were about 12%. Previous studies also found AF termination can also occur in the right atrium in addition to PVI and the left atrium regions (33,34). All observations above may indicate the necessity of LASM from the perspective of AF substrates.

Implications and actions needed

In addition to highlighting the importance of substrate modification for non-paroxysmal AF, this study highlights that AF termination is a reliable endpoint of procedures. However, AF termination during ablation cannot be blindly pursued without considering the adverse consequences of excessive ablation and procedure time. The ablation target should be more specific and non-generalized, and a patient-specific approach should be selected. Some ablation strategies are too extensive, and although they can help achieve very-high procedural endpoints, they are not associated with better long-term results (35). It is possible that extensive complex fractionated atrial electrogram ablation strategies may lead to iatrogenic proarrhythmic areas (36), and an increased risk of recurrence of AT can contribute to reduced success rates (37). This notion partially explains why patients with terminated AF have better ablation results after multiple ablation procedures. This study suggests that LASM may provide higher immediate success and a slightly better long-term success rate compared to those achieved with PVI. However, it is worth noting that the difference in long-term success rates between the two groups was not statistically significant, which suggests that the two treatments might be equally effective. The significant difference in immediate success rate after LASM relative to PVI is noteworthy and may have implications for patient comfort and hospital stay duration. Future research with a larger, randomized sample and long-term follow-up would further validate these findings.

Conclusions

Two stepwise ablation approaches perform the comparable effect on reducing the AF recurrence in the long-term following, while the LASM based on low-voltage mapping provide a higher AF termination rate compared to preferential PVI. LASM should not be underestimated in the treatment of non-paroxysmal AF. It's rational to focus on the atria substrates modification and individual ablation for non-paroxysmal AF.

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Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-273/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (Available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-273/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the ethics review board of the Third People's Hospital of Chengdu (No. 2023-S-38) and conducted in accordance with the Declaration of Helsinki (as revised in 2013) and institutional guidelines. All patients signed an informed consent form for radiofrequency ablation.

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