

Article

Correlation Analysis of Pulmonary Vein Anatomy and Paroxysmal Atrial Fibrillation Recurrence after Cryoballoon Ablation

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Submitted: 28 November 2023 Revised: 3 January 2024 Accepted: 11 January 2024 Published: 29 February 2024

Abstract

Background: Cryoballoon ablation (CBA) is a reliable therapy for paroxysmal atrial fibrillation (pAF). However, the relatively high recurrence rate poses a perplexing challenge for clinicians; thus, a more detailed understanding of the pulmonary vein anatomy and the left atrial (LA)-pulmonary vein (PV) conjunction mode is needed. This study aimed to explore the correlation between the PV anatomy and pAF recurrence in patients who underwent the index CBA. **Methods:** We included 274 consecutive pAF patients (men: 60%, mean age: 58.8 ± 11.5 years, median AF history: 25 (8, 63) months) with pAF who underwent their first cryoballoon ablation between October 2019 and March 2022. All data were collected from the patient's medical records. Subsequent post-procedural long-term follow-up and statistical analysis were conducted. **Results:** Amongst the total patients, 220 (80%) remained AF-free. Multivariate analysis showed that the right inferior PV (RIPV) vertical angle (hazard ratio (HR): 1.097, 95% CI: 1.071–1.124, $p < 0.001$) and PV variation (HR: 1.905, 95% CI: 1.079–3.362, $p = 0.026$) correlated with postoperative AF recurrence. The study investigated the effectiveness of the RIPV vertical angle, either alone or in combination with other recognized factors. **Conclusions:** In patients with pAF who underwent the index CBA, the RIPV vertical angle and PV variation served as reliable prognostic predictors. Specifically, the RIPV vertical angle, either alone or in combination with recognized factors, demonstrated effective predictive performance.

Keywords

paroxysmal atrial fibrillation; cryoballoon ablation; pulmonary vein anatomy; prognosis; recurrence predictor

Introduction

Patients with symptomatic atrial fibrillation (AF) have considerably impaired quality of life and an increased risk of stroke, heart failure, and all-cause mortality [1]. The

electrically active venous-atrial junction plays a crucial role in the initiation and maintenance of AF [2,3], making circumferential pulmonary vein isolation (CPVI) a fundamental intervention for AF. However, a considerable number of pulmonary veins (PVs) were reconnected in patients with AF recurrence (varying between 19% and 67% [4–6]). Left atrial (LA)-PV re-connection contributes to AF recurrence following cryoballoon ablation (CBA)-CPVI [7,8]. The success of CPVI is highly dependent on the presence or absence of circumferential homogeneous lesions around the PV ostia. Consequently, understanding the anatomical factors contributes to the efficacy of ablation and long-term maintenance of sinus rhythm [8–10]. In this context, a comprehensive understanding of the PV anatomy and LA-PV conjunction mode is essential. However, data on the relationship between PV anatomy and paroxysmal AF (pAF) recurrence in a central Chinese cohort are limited. The present study aimed to explore the correlation between PV anatomy and pAF recurrence after index CBA.

Patients and Methods

Among 412 consecutive patients with AF who completed their first CBA between October 2019 and March 2022 at our institution, 274 were deemed eligible for the study. All patients were aged >18 years and presented with medicine-refractory symptomatic pAF (AF that terminated either spontaneously or with intervention within 7 days of onset). Patients with a previous history of LA ablation (e.g., due to AF or paroxysmal supraventricular tachycardia), an LA diameter of >60 mm (echocardiography in the parasternal long-axis view), severe valvular heart disease, congenital heart disease (except patent foramen ovale detected during CBA), intracardiac thrombus, AF from a potentially reversible cause (e.g., hyperthyroidism), New York Heart Association class IV, or contraindications to post-interventional oral anticoagulation (Fig. 1) were excluded. The study was approved by the human research committee of the Second Xiangya Hospital of Central South University. All data were collected from the patient's medical records, and no additional experiments were conducted. Informed consent was not obtained owing to the use of anonymized data.

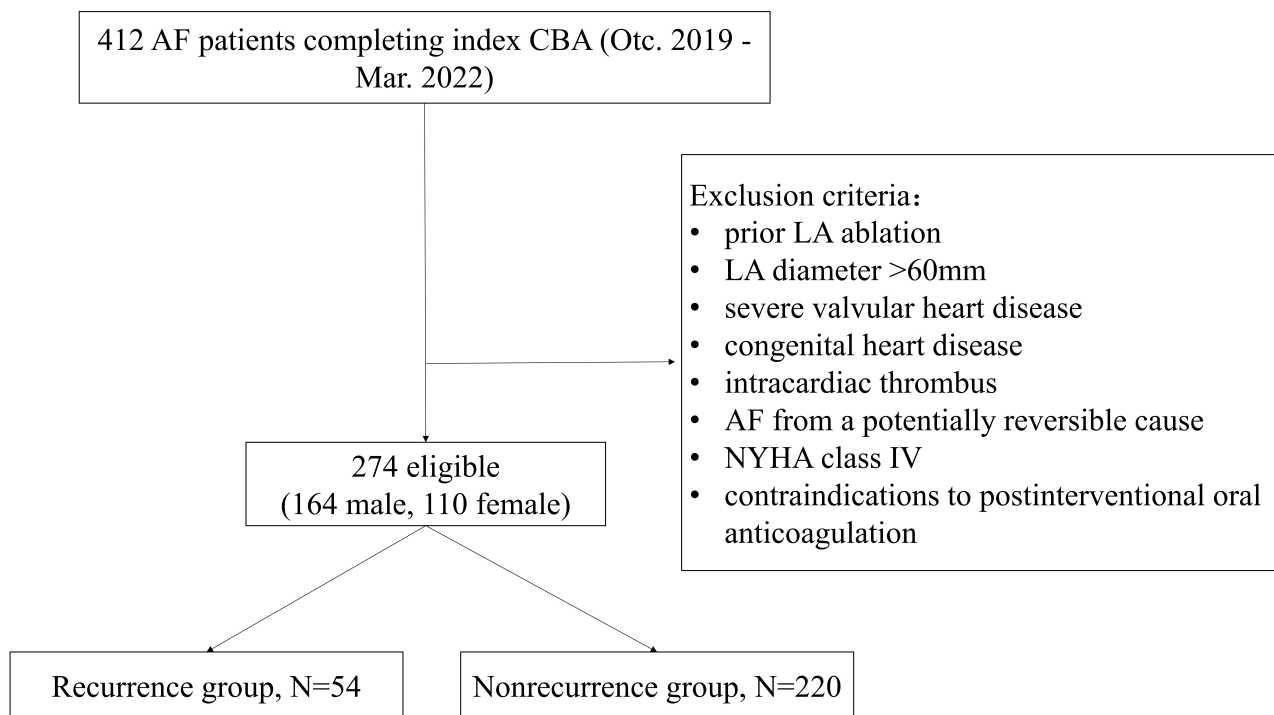


Fig. 1. Flowchart for the study population. AF, atrial fibrillation; CBA, Cryoballoon ablation; LA, left atrium; NYHA, New York heart association.

Contrast-Enhanced Computed Tomography Image

Twenty-four hours prior to ablation, all patients underwent contrast-enhanced computed tomography (CT) to examine the PV anatomic characteristics and rule out an intracardiac thrombus. Three orthogonal planes were used to obtain the optimal sight, and three-dimensional images of the LA and PVs were subsequently reconstructed (Fig. 2). Two independent well-trained researchers evaluated the PV drainage pattern, the number of PV ostia, PV parameters, and the presence of left atrial thrombus. Discordances (e.g., confusing classification and deviations in diameter exceeding 0.2 cm/angle over 5°) were resolved through consensus discussions. The averages of the two researchers' measurements were calculated and utilized in the analysis. PV variation was determined by assessing the presence of additional PV(s) (Fig. 2D,F) or a common trunk (Fig. 2E), following the classifications of Marom *et al* [8]. The ostial major and minor axes of the PV, and the angle between the PV and the sagittal axis (SA)/vertical axis (VA) were measured (Fig. 2B,C). These angles ranged from 0° to 180° (0° at the top and 180° at the bottom of the picture), indicating the orientation of the PVs from ventral to dorsal or cranial to caudal. PV eccentricity was defined as the deviation from perfect circularity and quantitatively calculated as follows: $e = \sqrt{1 - (b/a)^2}$ (where a is the length of the major axis and b is the minor axis). Thus, a higher value indicates a more oval-shaped PV. In this study, an e value of <0.4 was considered indicative of a circle.

Echocardiography

Transesophageal echocardiography was conducted 24 h before surgery to rule out intracardiac thrombus, except in patients whose last examination was performed within 2 weeks and were on regular anticoagulation treatment. Transthoracic echocardiography was performed regularly to assess the cardiac structure and left ventricular ejection fraction (LVEF).

Cryoballoon Ablation Procedure

All procedures were carried out by four qualified and experienced experts. The risks of the procedure were discussed in detail, and all patients provided written informed consent prior to ablation. The surgical procedures were performed under local anesthesia. Catheter electrodes were inserted into the femoral veins through a transseptal puncture or the open fossa ovalis to access the LA. A bolus of heparin was infused to maintain an activated clotting time of >300 s, which was reevaluated every 30 min. Before CPVI, a mapping catheter was placed to determine the baseline electrical patterns. Temperature was automatically recorded using a thermos-sensor. Considering the confounding effects of repeated applications, only the initial freezing at each PV was analyzed. The degree of a 28-mm balloon occlusion was rated from 1 (very poor, contrast agent immediate rapid outflow from the PV) to 4 (excellent, full retention without visible outflow) [11]. At least one attempt was made to achieve a grade 4 ablation on every target PV. The unaf-

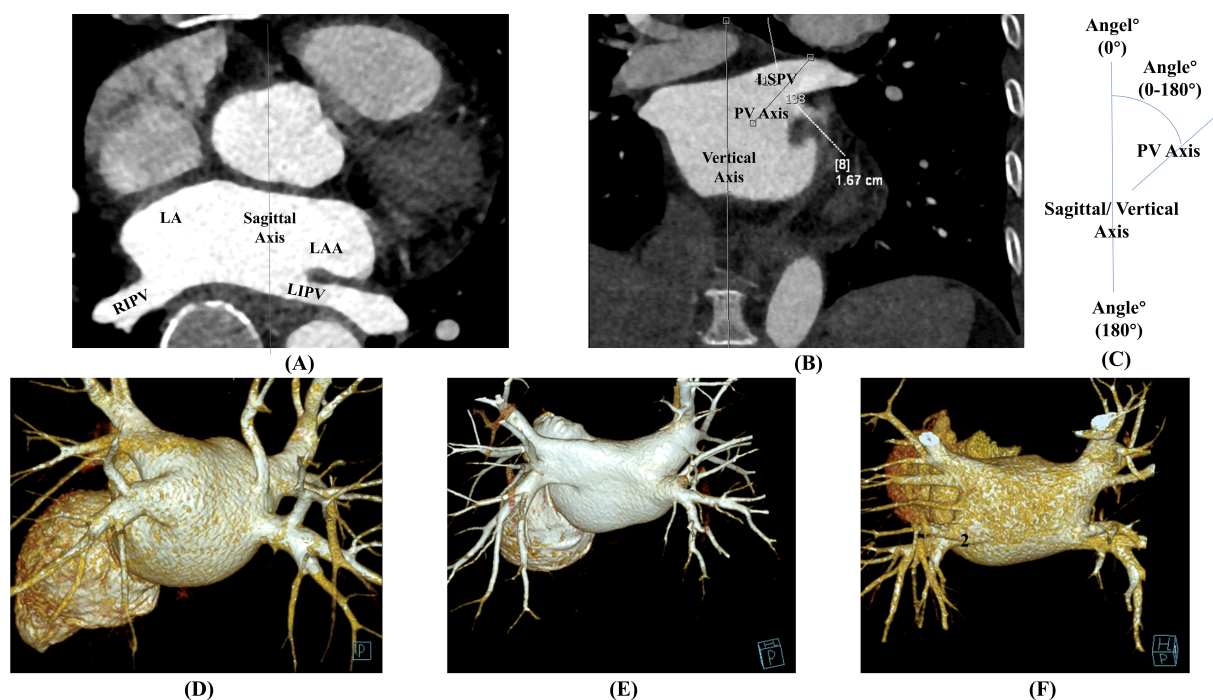


Fig. 2. Computed tomography scans of pulmonary veins. (A) A transverse image of a computed tomography scan. (B) A direct coronal reformatted image shows LSPV ostia and LSPV vertical angle. (C) Example of the angle between the PV axis and sagittal/vertical axis. (D) An example of RMPV. (E) An example of LCT. (F) An example of the left addition PV. AO, aorta; LAA, left atrial appendage; LSPV, left superior pulmonary vein; PV, pulmonary vein; RMPV, right middle pulmonary vein; LCT, left common trunk; LIPV, left inferior pulmonary vein; RIPV, right inferior pulmonary vein.

affected phrenic nerve movement was monitored by assessing the tactile feedback of diaphragmatic contraction and nerve action potential [12,13] during right PV ablation. Energy delivery was discontinued when a decrease or loss of phrenic nerve activity was observed or when the temperature fell below -55°C . Supplementary PV ablation (e.g., superior vena cava, linear lesions on mitral/cavotricuspid isthmus, and roof lines) and isolation of additional PVs were made at the discretion of the surgeons. Sequential ablation was performed if occlusion of the common trunk was not achieved.

Post-Ablation Treatment and Follow-up

Anticoagulants were continued for at least 3 months, and antiarrhythmic treatment was allowed during the 3-month blanking period to maintain the sinus rhythm unless the patient refused or had contradictions; all patients were treated with proton pump inhibitors for at least 2 weeks. The primary endpoint of this study was AF recurrence, defined as any documented symptomatic or atrial tachycardia, atrial flutter, or AF of >30 s in the absence of antiarrhythmic drug therapy, re-prescription of antiarrhythmic drugs, or repeat ablation after a 3-month blanking period. The AF-free time (months) was defined as the episode between the procedure and recurrence. If AF recurred during the blanking period and persisted thereafter, the recurrence time was considered as 3 months after CBA.

Statistical Analysis

Normally distributed variables were expressed as the mean \pm standard deviation (SD), while non-normally variables were expressed as the median with interquartile range (IQR: Q1–Q3). Categorical variables were presented as numbers (proportions) and were analyzed using the chi-square test or Fisher's exact test. Unpaired Student's *t*-test (normally distributed variables) or the Mann-Whitney U-test (if not) was used to compare continuous variables. Prognostic factors with a *p*-value of <0.05 after univariate Cox regression analysis were included in the multivariate Cox regression analysis to determine the independent factors. The intraclass correlation coefficients (ICCs) between raters were calculated based on a mean rating ($k = 2$), an absolute agreement, and a two-way random effects model. A receiver operating characteristic curve was constructed to assess the sensitivity and specificity of the independent predictors of AF recurrence. The optimum cutoff point was selected as the combination with the highest sensitivity and specificity. All tests were two-tailed, and a *p*-value of <0.05 was considered significant. Statistical analyses and picture making were performed using SPSS software version 26 (IBM Software Inc., Armonk, NY, USA), GraphPad Prism 9.0 (GraphPad Software, Inc., San Diego, CA, USA), and R studio 4.2.1 (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline and Characteristics of the Study Population

Table 1 presents the patient's baseline characteristics. A total of 274 consecutive patients were recruited (men: 60%, mean age: 58.8 ± 11.5 years). The LA diameter and LVEF were 35.3 ± 5.6 mm (54% >35 mm, 23% >40 mm) and $60.0 \pm 5.8\%$, respectively. Approximately 37% (102/274) of the patients had hypertension, and 18% (49/274) had diabetes. After a mean follow-up duration of 14 (9, 18) months, 80% (220/274) of the patients remained free from AF recurrence. The study population was divided into non-recurrence and recurrence groups. In this study, only age (61.9 ± 10.0 years vs. 58.0 ± 11.7 years, $p = 0.017$), AF history (46 (25, 81) months vs. 20 (6,55) months, $p = 0.010$), LA diameter (37.3 ± 6.4 mm vs. 34.7 ± 5.3 mm, $p = 0.002$), and anti-renin-angiotensin system drugs (aRASD, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor-neprilysin inhibitor) usage (19% vs. 36%, $p = 0.006$) showed significant differences. Other recognized factors, such as sex ($p = 0.921$), body mass index (BMI) ($p = 0.218$), smoking or alcohol use ($p = 0.244$ and $p = 0.054$, respectively), comorbidities ($p > 0.05$), and CHA₂DS₂-VASc score ($p = 0.230$), were non-significant, even after further stratification (Table 1).

Pulmonary Vein Anatomy and AF Recurrence

Table 2 presents all the "typical" PV topographic traits. Among the total patients, 84 (31%) exhibited PV anatomical variations, with the right middle PV (RMPV) being the most common (74%, 62/84). Variations were more prevalent in the recurrence group (44% vs. 27%, $p = 0.024$). Among the 62 identified RMPVs, 20 converged into the right superior PV/right inferior PV (RSPV/RIPV), while 42 directly entered into the LA. These distinct RMPVs appeared noticeably slender (0.74×0.83 cm). Having a left common trunk (LCT) was also prevalent in our study (19%, 16/84), and it appeared thicker (1.40×2.26 cm) than the left superior PV/left inferior PV (LSPV/LIPV). Besides, 12 patients showed multiple right additional PVs, while 4 patients had additional PVs on both sides. The majority of PVs in our study were oval in shape rather than circular in shape (64% $e > 0.4$). The RIPV in the recurrence group displayed a more pronounced deviation from a circular shape (0.58 ± 0.18 vs. 0.41 ± 0.19 , $p < 0.001$) and entered the LA at a larger VA (99.0 ± 11.6 vs. 81.7 ± 14.0 , $p < 0.001$), indicating an upward convergence of RIPV into the LA (from caudal to cranial). Typical RIPV VAs are depicted in Fig. 3. As for the other three PVs, no obvious differences were noted between the two groups (p all >0.05).

Procedural Parameters

In total, 1078 PVs were successfully isolated, including 14 solitary RMPVs (5 recurrences) and 16 LCTs (6 recurrences) (Table 3). Most PVs achieved satisfactory occlusion prior to isolation. Moreover, 82 (30%) patients required additional ablation (72 linear lesions, 16 lesions in the superior vena cava (SVC), and 14 lesions in the RMPVs). The majority of PVs were successfully isolated during the initial ablation, but some (30%, 320/1078) required another cycle of ablation. However, no difference was observed between AF recurrence and ablation cycle. Similarly, no significant association was found between AF recurrence and any procedural parameters.

Predictors of AF Recurrence

The prognostic factors for AF recurrence were investigated using univariate and multivariate Cox hazard analyses (Table 4). Univariate analysis demonstrated that age (HR: 1.028, 95% CI: 1.004–1.053, $p = 0.024$), AF history (HR: 1.005, 95% CI: 1.000–1.010, $p = 0.031$), LA diameter (HR: 1.068, 95% CI: 1.019–1.119, $p = 0.006$), aRASD usage (HR: 0.482, 95% CI: 0.243–0.958, $p = 0.037$), RIPV eccentricity (HR: 30.563, 95% CI: 6.737–138.639, $p < 0.001$), RIPV VA (HR: 1.082, 95% CI: 1.061–1.104, $p < 0.001$), and PV variation (HR: 1.891, 95% CI: 1.105–3.235, $p = 0.020$) were significant. Intriguingly, after dividing the AF history and LA diameter, an LA diameter of >35 mm was not significant ($p = 0.108$). After including gender, age, hypertension, diabetes, cigarette usage, alcohol usage, AF history, an LA diameter of >40 mm, aRASD usage, an RIPV eccentricity of >0.4, RIPV VA, RIPV SA, and PV variation in the Cox multivariate analysis, only RIPV VA (HR: 1.097, 95% CI: 1.071–1.124, $p < 0.001$), PV variation (HR: 1.905, 95% CI: 1.079–3.362, $p = 0.026$), age (HR: 1.053, 95% CI: 1.026–1.081, $p < 0.001$), an LA diameter of >40 mm (HR: 3.093, 95% CI: 1.688–5.665, $p < 0.001$), and aRASD usage (HR: 0.372, 95% CI: 0.170–0.816, $p = 0.014$) were still significant. The receiver operating characteristic analysis showed that RIPV VA (area under curve: 0.840, 95% CI: 0.780–0.900, cutoff point: 98.5°, sensitivity: 64.7%, specificity: 89.4%, $p = 0.000$), age (area under curve: 0.590, 95% CI: 0.509–0.672, cutoff point: 56.5 years, sensitivity: 74.1%, specificity: 46.4%, $p = 0.049$), RIPV VA + age (area under curve: 0.857, 95% CI: 0.800–0.913, $p = 0.000$), and RIPV VA + age + LA diameter > 40 mm + PV variation + aRASD usage (area under curve: 0.902, 95% CI: 0.853–0.951, $p = 0.000$) were effective predictors of AF recurrence (Fig. 4). The median time without AF was 12 months (95% CI: 6.263–17.737) in patients with an RIPV VA of >98.5°. At the end of our study, more than half of the patients aged <56.5 years, with an LA diameter of <40 mm, with no PV variation, and who used aRASD remained recurrence free (Fig. 5).

Table 1. Characteristics of 274 patients completing index CBA.

	N = 274	Recurrence group	Nonrecurrence group	p value
		N = 54	N = 220	
Age, years	58.8 ± 11.5	61.9 ± 10.0	58.0 ± 11.7	0.017
Age ≥65, %	101 (37%)	22 (41%)	79 (36%)	0.511
Age ≥75, %	30 (11%)	14 (26%)	16 (7%)	0.056
Male, n (%)	164 (60%)	32 (59%)	132 (60%)	0.921
BMI (Kg/m ²)	23.6 ± 3.5	23.1 ± 3.1	23.8 ± 3.6	0.218
BMI <18.5 Kg/m ² , n (%)	15 (6%)	2 (4%)	13 (6%)	0.517
BMI >24 Kg/m ² , n (%)	114 (42%)	18 (33%)	96 (44%)	0.146
Course of disease, months	25 (8, 63)	46 (25, 81)	20 (6, 55)	0.010
Course >12 months, n (%)	164 (60%)	45 (83%)	119 (54%)	<0.001
Alcohol, n (%)	89 (32%)	12 (22%)	77 (35%)	0.054
Cigarette, n (%)	98 (36%)	23 (43%)	75 (34%)	0.244
Hypertension, n (%)	102 (37%)	20 (37%)	82 (37%)	0.975
Diabetes, n (%)	49 (18%)	8 (15%)	41 (19%)	0.513
Stroke, n (%)	33 (12%)	9 (17%)	24 (11%)	0.302
Vascular disease, n (%)	43 (16%)	10 (19%)	33 (15%)	0.755
CHA ₂ DS ₂ -VASc score	1.5 (0.5, 2.7)	1.6 (0.7, 2.9)	1.5 (0.5, 2.7)	0.230
CHA ₂ DS ₂ -VASc score ≥3, n (%)	75 (27%)	16 (30%)	59 (27%)	0.679
aRASD usage	89 (32%)	10 (19%)	79 (36%)	0.006
Statins usage	118 (43%)	24 (44%)	94 (43%)	0.820
Echocardiography				
LA, mm	35.3 ± 5.6	37.3 ± 6.4	34.7 ± 5.3	0.002
LA >35 mm, n (%)	149 (54%)	36 (67%)	113 (51%)	0.039
LA >40 mm, n (%)	62 (23%)	21 (39%)	41 (19%)	0.006
LV, mm	43.0 ± 5.6	42.9 ± 6.0	43.0 ± 5.6	0.888
RA, mm	29.1 ± 4.7	30.1 ± 4.6	29.0 ± 4.7	0.089
RV, mm	30.8 ± 3.8	31.0 ± 3.5	30.7 ± 3.9	0.617
LVEF, %	60.0 ± 5.8	60.3 ± 5.1	59.9 ± 6.0	0.692

Data were presented as the mean ± SD or n (%) or median (Q1–Q3), where N is the total number of patients with available data. CBA, cryoballoon ablation; BMI, body mass index; CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke [doubled]-vascular disease, age 65–74 years, sex category [female]; aRASD, anti-renin-angiotensin system drugs; LA, left Atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; LVEF, left ventricle ejection fraction.

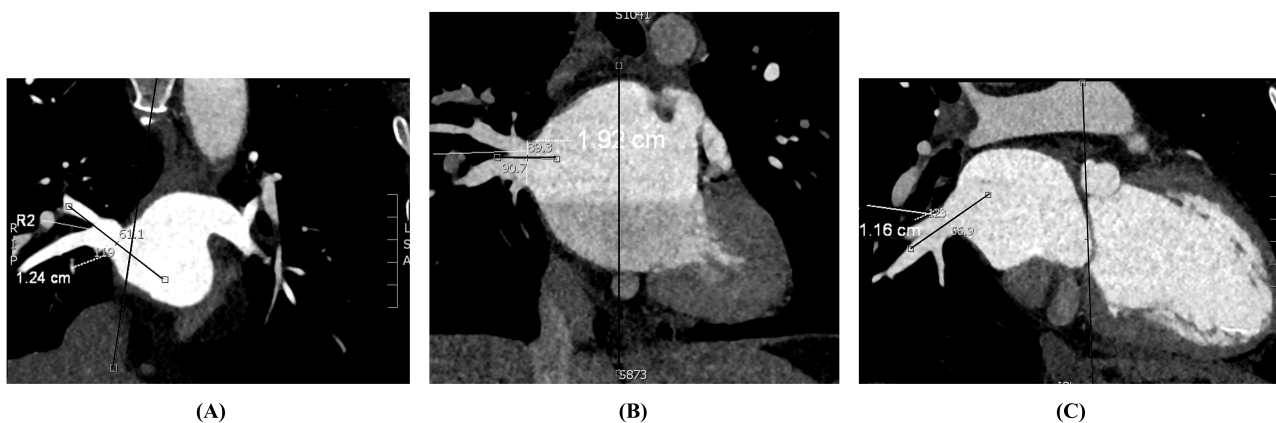


Fig. 3. Typical RIPV vertical angles. (A) RIPV VA 61°. (B) RIPV VA 90°. (C) RIPV VA 123°. RIPV, right inferior pulmonary vein; VA, vertical angle.

Complications

One patient, suspected of cardiac tamponade, underwent a thorough medical examination and was relieved

Table 2. Pulmonary vein anatomic characteristics.

	N = 274	Recurrence group	Nonrecurrence group	p value
		N = 54	N = 2220	
LSPV eccentricity	0.52 ± 0.20	0.52 ± 0.18	0.52 ± 0.21	0.947
LSPV eccentricity >0.4	187 (73%)	37 (74%)	150 (73%)	0.866
LSPV SA (°)	76.7 ± 22.4	73.0 ± 22.5	77.5 ± 22.3	0.194
LSPV VA (°)	52.2 ± 15.8	50.8 ± 11.3	52.6 ± 16.7	0.370
LIPV eccentricity	0.65 ± 0.22	0.62 ± 0.19	0.65 ± 0.22	0.401
LIPV eccentricity >0.4	216 (84%)	43 (86%)	173 (84%)	0.726
LIPV SA (°)	112.7 ± 19.7	114.9 ± 16.0	112.2 ± 20.5	0.388
LIPV VA (°)	90.2 ± 20.8	88.7 ± 15.4	90.6 ± 21.9	0.482
RSPV eccentricity	0.52 ± 0.20	0.51 ± 0.16	0.52 ± 0.20	0.704
RSPV eccentricity >0.4	180 (66%)	40 (75%)	140 (65%)	0.930
RSPV SA (°)	80.6 ± 21.7	80.5 ± 12.6	80.6 ± 23.4	0.950
RSPV VA (°)	66.4 ± 12.5	65.3 ± 10.1	66.7 ± 13.0	0.391
RIPV eccentricity	0.45 ± 0.20	0.58 ± 0.18	0.41 ± 0.19	<0.001
RIPV eccentricity >0.4	176 (64%)	44 (86%)	132 (61%)	<0.001
RIPV SA (°)	121.6 ± 17.8	124.7 ± 16.1	120.9 ± 18.2	0.170
RIPV VA (°)	85.0 ± 15.2	99.0 ± 11.6	81.7 ± 14.0	<0.001
Variation, n (%)	84 (31%)	24 (44%)	60 (27%)	0.024

Data were presented as the mean ± SD or n (%), where N is the total number of patients with available data. LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; SA, the angle between the axis of the pulmonary vein and sagittal Axis; VA, the angle between the axis of the pulmonary vein and vertical axis. No additional PVs or common trunks were included.

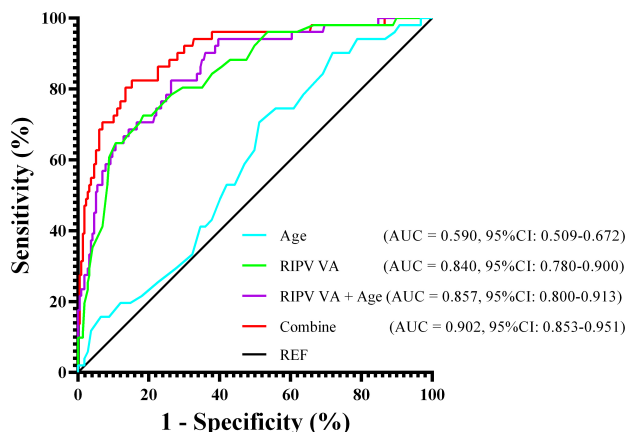


Fig. 4. ROC curves. ROC curve for RIPV VA, age, RIPV + age, combine. RIPV, right inferior pulmonary vein; VA, vertical angle; combine, RIPV VA + age + left atrial diameter > 40 mm + PV variation + anti-renin-angiotensin system drug usage. ROC, receiver operating characteristic; AUC, Area under the ROC Curve.

without additional handling before discharge. One patient was admitted to the hospital due to hemiparalysis and experienced a stroke 12 months after CBA and left atrial appendage closure with standard postoperative anticoagulation therapy. None of the patients complained of symptoms indicating the occurrence of PV stenosis, phrenic nerve palsy, atrial-esophageal fistula, or any other major complications.

Discussion

A comprehensive understanding of the pulmonary vein anatomy is crucial for creating effective circumferential lesions using the cryoballoon technique. The key findings of our study were as follows: (1) the recurrence rate of pAF after the index CBA was 20%, which was in accordance with the reports of previous studies [4,14]; (2) patients with AF recurrence exhibited a larger RIPV VA, a more oval-shaped RIPV, additional anatomic variants (RMPV, LCT, etc.), noticeably enlarged LA, longer AF history, and older age; and anatomical characteristics of RIPV proved to be reliable predictors of recurrence.

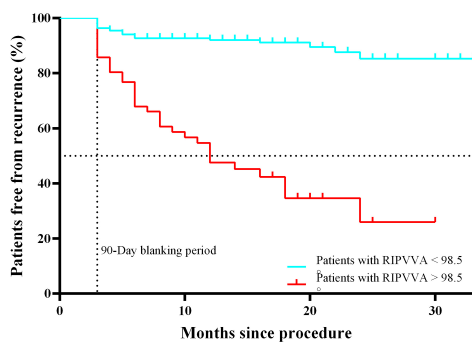
PV Anatomy and AF Recurrence

Ensuring the complete formation of transmural lesions is essential for achieving stable chronic CPVI. Previous studies have highlighted the significance of creating robust lesions, rather than acute CPVI, in ensuring long-term success against AF recurrence. Although CBA is an attractive technique, its efficacy heavily relies on the PV characteristics. Contrary to assumptions, variations in PV are more prevalent, ranging from 11% to 38.5% [8,10,15–19], with a higher incidence in the RMPV and LCT. In our study, we detected anatomical variants in 31% of the patients, with RMPV being the most common (62/84). The majority of the RMPVs (42/62) directly drained into the LA and had

Table 3. Procedural parameters.

	N = 274	Recurrence group	Nonrecurrence group	p value
		N = 54	N = 220	
LSPV n	1.4 (1, 1.9)	1.4 (1, 1.9)	1.4 (1, 1.9)	0.819
LSPV n >1, n (%)	91 (35%)	19 (38%)	72 (35%)	0.654
LSPV 30 s, (°C)	-29.1 ± 5.4	-29.7 ± 4.3	-28.9 ± 5.6	0.302
LSPV 60 s, (°C)	-37.8 ± 4.8	-37.5 ± 3.9	-37.8 ± 5.0	0.670
LSPV NT, (°C)	-44.8 ± 5.7	-44.9 ± 3.4	-44.8 ± 6.2	0.854
LSPV TTI, (s)	68.0 ± 23.1	67.2 ± 22.9	68.1 ± 23.2	0.819
LSPV O	3.9 ± 0.4	3.9 ± 0.3	3.9 ± 0.4	0.329
LIPV n	1.2 (1, 1.7)	1.1 (1, 1.6)	1.2 (1, 1.8)	0.097
LIPV n >1, n (%)	51 (20%)	7 (14%)	44 (21%)	0.191
LIPV 30 s, (°C)	-28.1 ± 4.1	-28.1 ± 3.8	-28.1 ± 4.2	0.951
LIPV 60 s, (°C)	-36.2 ± 4.3	-36.5 ± 5.0	-36.1 ± 4.22	0.606
LIPV NT, (°C)	-45.3 ± 4.0	-45.4 ± 4.0	-45.3 ± 4.0	0.948
LIPV TTI, (s)	57.7 ± 23.9	55.0 ± 19.8	58.2 ± 24.7	0.411
LIPV O	3.9 ± 0.4	3.8 ± 0.6	3.9 ± 0.4	0.415
RSPV n	1.3 (1, 1.9)	1.4 (1, 1.9)	1.3 (1, 1.8)	0.497
RSPV n >1, n (%)	80 (29%)	18 (33%)	62 (28%)	0.457
RSPV 30 s, (°C)	-32.1 ± 4.4	-32.2 ± 3.7	-32.0 ± 4.6	0.793
RSPV 60 s, (°C)	-39.7 ± 4.8	-40.5 ± 4.5	-39.5 ± 4.9	0.208
RSPV NT, (°C)	-46.6 ± 4.5	-47.6 ± 3.0	-46.4 ± 4.8	0.058
RSPV TTI, (s)	53.4 ± 20.5	53.7 ± 21.2	53.3 ± 20.5	0.905
RSPV O	3.8 ± 0.6	3.8 ± 0.5	3.8 ± 0.6	0.585
RIPV n	1.4 (1, 2.0)	1.5 (1, 2.2)	1.4 (1, 2.0)	0.203
RIPV n >1, n (%)	98 (36%)	24 (44%)	74 (34%)	0.155
RIPV 30 s, (°C)	-28.9 ± 5.2	-28.5 ± 6.1	-29.0 ± 5.0	0.544
RIPV 60 s, (°C)	-37.5 ± 5.7	-37.4 ± 5.3	-37.6 ± 5.8	0.828
RIPV NT, (°C)	-45.6 ± 5.1	-45.3 ± 4.3	-45.7 ± 5.3	0.679
RIPV TTI, (s)	76.4 ± 23.2	70.9 ± 23.3	77.6 ± 23.1	0.137
RIPV O	3.8 ± 0.5	3.8 ± 0.5	3.8 ± 0.5	0.414
Additional ablation, n (%)	82 (30%)	13 (25%)	69 (31%)	0.370

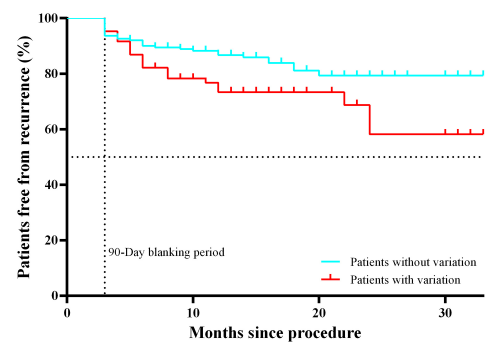
Data were presented as the mean ± SD or n (%), where N is the total number of patients with available data. n, ablation cycle; n >1, circumferential pulmonary vein isolation requiring ablation for more than one cycle; 30 s, temperature at 30 s during ablation; 60 s, temperature at 60 s during ablation; NT, nadir temperature; TTI, time to isolation; O, occlusion grade.



No. at Risk
RIPVVA < 98.5°
RIPVVA > 98.5°

	218	163	56	17
	56	30	6	2

(A)



No. at Risk
Without variation
With variation

	190	140	44	11
	84	53	18	8

(B)

Fig. 5. Kaplan-Meier analysis. (A) Kaplan-Meier analysis of patients classified according to the right inferior pulmonary vein vertical angle. (B) Kaplan-Meier analysis of patients classified according to pulmonary vein variation.

Table 4. Predictors of AF recurrence.

	Univariate			Multivariate		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Male	0.927	0.539–1.596	0.785	-	-	-
Age	1.028	1.004–1.053	0.024	1.053	1.026–1.081	<0.001
Hypertension	0.981	0.564–1.704	0.945	-	-	-
Diabetes	0.846	0.399–1.794	0.662	-	-	-
Cigarette	1.412	0.823–2.4323	0.208	-	-	-
Alcohol	0.613	0.322–1.165	0.131	-	-	-
Course of disease	1.005	1.000–1.010	0.031	-	-	-
Course >12 months	3.427	1.675–7.010	<0.001			
CHA ₂ DS ₂ -VASc score	1.11	0.938–1.314	0.225			
LA	1.068	1.019–1.119	0.006			
LA >35 mm	1.587	0.900–2.798	0.108			
LA >40 mm	2.232	1.290–3.863	0.004	3.093	1.688–5.665	<0.001
aRASD usage	0.482	0.243–0.958	0.037	0.372	0.170–0.816	0.014
RIPV eccentricity	30.563	6.737–138.639	<0.001			
RIPV eccentricity >0.4	2.672	1.202–5.942	0.016	-	-	-
RIPV SA	1.011	0.995–1.028	0.180	-	-	-
RIPV VA	1.082	1.061–1.104	<0.001	1.097	1.071–1.124	<0.001
Variation	1.891	1.105–3.235	0.020	1.905	1.079–3.362	0.026

HR, hazard ratio; CI, confidence interval. For other abbreviations, see Tables 1,2,3.

a smaller diameter (0.74 ± 0.24 cm \times 0.83 ± 0.31 cm). Among the 42 patients, 37 (7 with AF recurrence) had no other variations. In our study, the isolated RMPV in these patients showed no significant difference (3/7 vs. 9/30, $p = 0.659$). None of the LCTs in our study exceeded the balloon size, ensuring satisfactory ablation efficacy. Some researchers argue that there is no correlation between anatomical variations and AF recurrence. The occurrence of LCT did not influence CBA efficiency [16] and disregarding the RMPV during the intervention showed no difference [17]. This seems contradictory to our findings indicating that PV variation is correlated with AF recurrence. However, these samples were relatively small. Moreover, the role of other characteristics should not be ignored; therefore, more studies with larger sample sizes are needed. Different venous drainage patterns result in different tissue characteristics of the surrounding myocardium. To date, adaptive changes in the LA due to PV variations have not been described in detail. Given that myocardial sleeves are known triggers for AF, untreated PVs could potentially serve as triggers, with sleeves being more prominent on the upper side [20]. The epicardial structures may also vary. The epicardial adipose tissue (EAT) is in direct contact with the surface of the myocardium and affects myocardial function in several ways. Approximately 80% of the heart surface and 20% of the heart weight comprise the EAT [21]. Cardiac magnetic resonance imaging revealed increased EAT accumulation on the posterior and inferior LA surfaces [22]. One study showed that EAT-based ablation is more effective [23]. The EAT was independently associated with post-ablation AF recurrence [24]. Various studies have been carried out to explore how EAT affects myocardial function, including

endocrine, paracrine, extracellular vesicles [21], exosomes [25], and direct infiltration. EAT promotes inflammatory microenvironment formation, myocardial fibrosis, oxidative stress, and autonomic dysfunction [21,22]. Moreover, a close relationship exists between the cardiovascular autonomic nervous system and EAT, with the autonomic denervation reinforcing PVI efficiency [26]. In conclusion, PV variations might promote unexpected cardiac and epicardial structural alterations, thus further contributing to AF occurrence and recurrence.

Consistent balloon contact during ablation reduces conduction gaps and ensures complete occlusion, leading to stable CPVI formation [9,27]. Numerous studies indicate that recurrent AF after CBA is associated with PV reconnections [7,28,29]. Additionally, the anatomic characteristics of the PV (diameter, ovality, *etc.*) have been shown to affect procedural parameters (e.g., nadir temperature) [30,31]. In alignment with the report of a previous study, the RIPV eccentricity and VA were closely related to AF recurrence. The challenging positioning of the RIPV and the complexities in achieving and maintaining catheter co-axis hinder the effective formation of lesions. This may result in temporary CPVI but subsequent conduction recovery. The RIPV is most challenging to reach [13,32–34]. The mean endoluminal distance between the fossa ovalis and RIPV was 20.2 mm [35]. Several maneuvers, such as “hockey stick” and “pull-down” [36], were established to assist, but almost all of them required the rotation of the entire system. In both acute PVI procedures, repeat applications and additional ablation in RIPV were frequently required [37,38]. During chronic follow-up, reconnections were frequently observed in the RIPV [32,33,39]. Indeed,

frequent reconnections occurred at the inferior LA-PV junction [39,40]. This occurrence is possibly due to the enhanced muscle thickness of the inferior ridge between the LA and PV ostia [39] and the cumulative EAT. However, these findings remain controversial. Some studies have reported that RIPVs have the highest isolation rates [7,41]. Meanwhile, some researchers have found that left-sided PVs tended to appear more oval in shape, more difficult to isolate, and have a higher recurrence rate [17,19,42]. LSPV reconnections [7,41] have also been proposed to be the most frequent. Possible explanations for these paradoxes could be the different definitions, energy applications, and protocols used in these studies. For example, a more distal position inside an LCT might achieve more stable isolation but increases the risk of missing the patent proximal foci and post-ablation PV stenosis. In our study, RIPV eccentricity and VA were related to postoperative AF recurrence, but only RIPV VA counts showed significance in the multivariate analysis. The satisfactory occlusion effect of the 28-mm balloon may partly counteract PV ovality. However, the relatively large RIPV VA makes it difficult to maintain desirable contact, which contributes significantly to a successful PVI.

As for the recognized factors (e.g., age, sex, BMI, and hypertension), after performing a multivariate analysis, only age, an LA diameter of >40 mm, and aRASD usage were proven to be credible predictors of postoperative AF recurrence. In our study, the pulmonary vein anatomy proved to be effective in predicting postprocedural AF recurrence, especially when combined with the aforementioned factors for a comprehensive evaluation.

Previous studies have reported a relatively low ablation proportion. Wiczorek *et al.* [7] enrolled 151 out of 965 patients over 5 years (approximately 15%), and Scala *et al.* [29] recruited 148 patients over 4 years. When a recurrence was identified during follow-up, we carefully reevaluated the patient's condition and provided recommendations accordingly. Due to the considerations of the ablation process and cost, only a very small proportion of patients opted to retry, with the majority opting for renouncing cardioversion. During follow-up, 4 out of 54 patients (7%) underwent a second ablation. During the re-ablation procedure, LSPV + RSPV reconnection was detected in a 53-year-old woman, SVC foci in a 42-year-old man, and RIPV + LSPV + SVC in a 68-year-old man. Due to strong patient demand, we had to reschedule surgery 1 month after CBA for a 66-year-old male patient who was confirmed to have perimitral flutter. Even with these data, it remains challenging to make a conclusive judgment. Therefore, further studies are warranted.

Limitation

First, the study used a sample small size. Second, the high incidence (30%) of additional ablation and the allowance of anti-arrhythmic drugs post-procedure could be

regarded as limitations. Third, the absence of adenosine or isoproterenol challenge might result in the non-detection of concealed reconnection in some patients.

Conclusions

In pAF patients who underwent the initial CBA, the RIPV vertical angle and PV variation are reliable prognostic predictors. Whether RIPV vertical angle alone or in combination with those recognized factors demonstrated consistent predictive efficacy.

Availability of Data and Materials

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

Author Contributions

QL and HT completed the study design and performed quality control of data authenticity. YW collected and analyzed these data and drafted the manuscript. XW and YW finished the follow-up visit. NL helped with the echocardiography and computed tomography. YW, HT and QL revised the paper and all authors approved the final version. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The study was approved by the ethic committee of The Second Xiangya Hospital, Central South University (2023-0271). Informed consent forms were obtained from all participants.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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