

The effect of left atrial remodeling after cryoballoon ablation and radiofrequency ablation for paroxysmal atrial fibrillation

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Abstract

Background: Cryoballoon ablation (CBA) and radiofrequency ablation (RFA) are the most common procedures used to treat refractory atrial fibrillation (AF) and are performed through pulmonary vein isolation (PVI). Studies have shown that CBA can approximately match the therapeutic effects of RFA against AF. However, few studies have investigated the difference between CBA and RFA of the effects on left atrial remodeling for paroxysmal AF.

Objective: Atrial remodeling is considered pivotal to the occurrence and development of AF, therefore we sought to assess the influence of atrial remodeling in patients with paroxysmal AF after CBA and RFA in this study.

Methods: In this nonrandomized retrospective observational study, we enrolled 328 consecutive patients who underwent CBA or RFA for refractory paroxysmal AF in May 2014 to May 2017 in our hospital. After propensity score matching, 96 patients were included in the CBA group, and 96 were included in the RFA group. Patients were asked to undergo a 12-lead electrocardiogram, a 24-h Holter monitor, and an echocardiogram and to provide their clinical history and symptoms at 6 months and 1, 2, and 3 years postprocedurally. Electrical remodeling of the left atrium was assessed by P wave dispersion (Pdis); structural remodeling was assessed by the left atrium diameter (LAD) and left atrial volume index (LAVI) during scheduled visits.

Results: As of January 2020, compared with baseline, at 1 year, 2 years, and 3 years after ablation, the average changes in Pdis (Δ Pdis), LAD (Δ LAD), and LAVI (Δ LAVI) were significant in both the CBA and RFA groups. Six months after ablation, Δ Pdis, Δ LAD, and Δ LAVI were greater in the CBA group than in the RFA group. There was no significant difference between the two groups in AF/flutter recurrence, but the AF/flutter-free survival time of CBA group may be longer than RFA group after 2 years after ablation. A higher Δ Pdis, Δ LAD, or Δ LAVI at 1 year after ablation may increase AF/flutter-free survival.

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Conclusions: Although CBA and RFA are both effective in left atrial electrical and structural reverse-remodeling in paroxysmal AF, CBA may outperform RFA for both purposes 6 months after ablation. However, during long-term follow-up, there was no significant intergroup difference.

KEYWORDS

atrial remodeling, cryoballoon ablation, paroxysmal atrial fibrillation, radiofrequency ablation

1 | INTRODUCTION

Previous studies have shown that the occurrence and development of AF are closely related to atrial remodeling, which includes neural remodeling, electrical remodeling and structural remodeling.¹⁻³ In recent years, as catheter ablation based on pulmonary vein isolation (PVI) has become accepted as the cornerstone of all AF ablation procedures to maintain sinus rhythm, studies have been performed to observe the clinical outcomes of both cryoballoon ablation (CBA) and radiofrequency ablation (RFA). Evaluations of the differences in the safety and effectiveness of these two procedures have shown that CBA can achieve therapeutic effects similar to those of RFA in the treatment of paroxysmal AF.⁴⁻⁷

Several studies have explored the effects of catheter ablation on left atrial size⁸⁻¹¹ and electrical conduction¹²⁻¹⁵ in patients with AF, but no one has compared the influence of atrial remodeling caused by CBA and RFA in paroxysmal AF.

2 | METHODS

2.1 | Patients

We searched for patients who underwent CBA or RFA for paroxysmal AF in May 2014 to January 2017 at the First Affiliated Hospital of Zhengzhou University. Patients were selected according to the inclusion and exclusion criteria. All patients were required to have complete medical records, including age, sex, height, weight, and history of AF and comorbidities, as well as a preprocedural transesophageal echocardiogram to verify the absence of intracardiac thrombus and a computed tomography angiography (CTA) imaging to review the anatomy of the left atrium and PVs before the procedure. The management of oral anticoagulation during the perioperative period was determined by the physician according to the CHA2DS2-VASc score. We enrolled patients according to the following criteria: patients aged 18 to 75 years with paroxysmal AF who had undergone RFA or CBA. Exclusion criteria included a previous history of catheter ablation for AF, complicated with valvular heart disease, hepatic and renal insufficiency, hyperthyroidism, cardiomyopathy, and implanted pacemakers or defibrillators.

2.2 | Follow-up

Patients were followed up by WeChat platform and outpatient service at 6 months and 1, 2, and 3 years after ablation, assessed for clinical history and symptoms, and asked for a 12-lead electrocardiogram, a 24-h Holter monitor, and an echocardiogram. Patients who presented with symptoms such as palpitations and chest tightness were asked to undergo a 12-lead electrocardiogram or a 24-h Holter monitor immediately and to transmit the ECGs to us. Atrial fibrillation (AF)/flutter-free survival was defined as the absence of AF and atrial flutter recurrence ≥ 30 seconds following a 3-month blanking period. AF/flutter recurrence was defined as documented recurrence of AF or atrial flutter (lasting more than 30 s) after the 90-day blanking period or repeat ablation.⁶ Electrical remodeling of the left atrium was assessed by P wave dispersion (Pdis)¹⁶⁻¹⁸ as measured by a 12-lead electrocardiogram, while structural remodeling was assessed by the left atrium diameter (LAD) and left atrial volume index (LAVI) as measured by echocardiogram during scheduled visits.¹⁹⁻²¹ Pdis was defined as the difference between the maximum and minimum P-wave durations recorded by the 12 ECG leads.^{17,22} Minimum three consecutive beats were measured in all simultaneous 12 leads to calculate P-wave duration. LAD and left atrial volume (LAV) were measured using real-time three-dimensional echocardiography technology, then, the LAV was converted to LAVI by dividing by body surface area. Evaluation of each measurement was repeated three times to obtain the mean value for analysis. The post-procedural Pdis, LAD, and LAVI of each patient were subtracted from the Pdis, LAD, and LAVI at baseline to obtain the changes in Pdis, LAD, and LAVI of each patient, and then we could obtain the mean values of the changes in Pdis, LAD, and LAVI, that is, Δ Pdis, Δ LAD, and Δ LAVI, in the CBA group and the RFA group. Follow-up was ended once the patient underwent a repeat ablation after AF/flutter recurrence.

2.3 | Ablation procedure

During CBA, a second-generation cryoablation catheter and *Achieve* electrodes were advanced to the orifice of the PV. Once or twice cryoballoon freezes (each with a duration of 180 seconds) was

performed to achieve PV isolation in each pulmonary vein. For RFA, after a three-dimensional reconstruction of the left atrium, saline-irrigated electrode was used to perform pulmonary vein antrum isolation (PAVI) until complete PVI is obtained.

2.4 | Statistical analysis

Analyses were conducted with IBM SPSS Statistics, version 23. Given the differences in baseline characteristics between the CBA group

TABLE 1 Characteristics of the patients at baseline

Characteristic	Before PSM			After PSM		
	RFA (N = 223)	CBA (N = 105)	P value	RFA (N = 96)	CBA (N = 96)	P value
Age (yr)	57.74 ± 10.17	57.12 ± 10.12	.50	57.59 ± 11.23	57.67 ± 10.00	.62
Male sex—no. (%)	143 (54.3)	55 (52.4)	.63	48 (50.0)	47 (49.0)	.69
BMI	25.83 ± 2.77	25.88 ± 2.86	.79	25.75 ± 2.99	25.82 ± 2.78	.80
Months since first AF diagnosis	30.83 ± 38.53	30.75 ± 65.45	.91	32.81 ± 39.97	31.33 ± 71.70	.88
LAD (mm)	37.25 ± 6.51	37.12 ± 5.80	.91	37.25 ± 6.51	37.11 ± 6.04	.90
Pdis (ms)	44.17 ± 11.90	43.64 ± 11.57	.83	44.16 ± 13.32	44.24 ± 11.76	.97
LAVI (mL/m ²)	39.44 ± 8.18	39.63 ± 8.50	.85	39.32 ± 7.04	39.52 ± 7.58	.88
CHA2DS2-VASc score						
Distribution—no. (%)						
0	77 (34.5)	28 (26.7)	.15	32 (33.3)	28 (29.2)	.53
1	60 (26.9)	41 (39.0)	.03	28 (29.2)	37 (38.5)	.17
2	42 (18.8)	19 (18.1)	.87	18 (18.8)	18 (18.8)	1.00
3	33 (14.8)	15 (14.3)	.90	13 (13.5)	11 (11.5)	.66
4	9 (4.0)	2 (1.9)	.51	5 (5.2)	2 (2.1)	.44
5	2 (0.9)	0 (0)	1.00	0 (0)	0 (0)	1.00
6	0	0		0	0	
NYHA classification—no. (%)						
No heart failure	14 599 (65.0)	8537 (81.0)	.03	44 (45.8)	36 (37.5)	.24
Class I	4453 (19.7)	1126 (10.5)	.04	22 (22.9)	26 (27.1)	.51
Class II	2058 (9.0)	8438 (7.6)	.68	27 (28.1)	32 (33.3)	.43
Class III	1513 (6.7)	42 4 (3.8)	.29	3 (2.1)	2 (3.1)	1.00
Medical history—no. (%)						
Previous DCCV	0 (0)	1 (1.0)	.14	0 (0)	1 (1.0)	1.00
Previous stroke/TIA	22 (9.9)	13 (12.4)	.49	9 (9.4)	12 (12.5)	.49
Previous MI	5 (2.2)	1 (1.0)	.67	2 (2.1)	1 (1.0)	1.00
Previous PCI	13 (5.8)	3 (2.9)	.24	6 (6.3)	3 (3.1)	.50
Coronary artery disease	66 (29.6)	18 (17.1)	.02	23 (24.0)	18 (18.8)	.38
Hypertension—no. (%)	99 (44.4)	45 (42.9)	.79	44 (45.8)	45 (50.6)	.89
T2DM—no. (%)	50 (22.4)	17 (16.2)	.19	20 (20.8)	16 (16.7)	.46
Medication use—no. (%)						
Antiarrhythmic drug	148 (66.4)	50 (47.6)	<.001	50 (52.1)	46 (47.9)	.56
ACEI/ARB	95 (42.6)	46 (43.8)	.84	42 (43.8)	44 (45.8)	.77
Beta-blocker	99 (44.4)	48 (45.7)	.82	47 (49.0)	46 (47.9)	.89
Anticoagulation drug	86 (38.6)	37 (35.2)	.56	33 (34.4)	36 (37.5)	.65

Note: The plus-minus values are mean ± SD. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body-mass index, defined as the weight in kilograms divided by the square of the height in meters; CBA, cryoballoon ablation; CHA2DS2-VASc, (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke/transient ischemic attack/thromboembolism)-(vascular disease, age range from 65 to 74, sex [female]), with hypertension defined as blood pressure higher than 140/90 mmHg; DCCV, direct current cardioversion; LAD, left atrial diameter; LAVI, left atrial volume index; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; Pdis, P wave dispersion; PSM, propensity score match; RFA, radiofrequency ablation; TIA, transient ischemic attack; T2DM, type 2 diabetes.

TABLE 2 Average P-wave dispersion, left atrial diameter, and left atrial volume index

	Pdis (ms)		LAD (mm)		LAVI (mL/m ²)	
	CBA group	RFA group	CBA group	RFA group	CBA group	RFA group
Before ablation	44.24 ± 11.76	44.16 ± 13.32	37.11 ± 6.04	37.25 ± 6.51	39.52 ± 7.58	39.32 ± 7.04
6 months after ablation	35.20 ± 9.24	39.83 ± 13.78	35.33 ± 4.84	37.46 ± 6.06	36.24 ± 7.54	38.06 ± 8.87
1 year after ablation	34.81 ± 13.47*	38.43 ± 15.70*	34.72 ± 5.93*	35.06 ± 5.93*	34.52 ± 9.62*	35.77 ± 8.38*
2 years after ablation	30.48 ± 10.84*	35.60 ± 14.17*	32.68 ± 4.59*	33.18 ± 5.68*	31.74 ± 8.76*	33.48 ± 7.75*
3 years after ablation	29.09 ± 13.40*	33.86 ± 15.54*	30.11 ± 3.66*	31.64 ± 4.64*	30.27 ± 12.08*	31.02 ± 10.18*

Note: CBA, cryoballoon ablation; LAD, left atrial diameter; LAVI, left atrial volume index; Pdis, P-wave dispersion; RFA, radiofrequency ablation.
**P* < 0.05: the difference between measurements obtained at baseline and after the procedure was significant.

and RFA group, we matched the CBA group to the RFA group using propensity score matching at a 1:1 ratio.

Continuous data are reported as the mean and standard deviation (SD), and categorical data are expressed as percentages. A *t*-test was used to compare the differences in Pdis, LAD, and LAVI obtained at baseline and postprocedurally; another *t*-test was used to compare the differences in the average changes in Pdis, LAD, and LAVI between the CBA group and the RFA group; a chi-square test was used to evaluate the difference in the postoperative AF/flutter recurrence rate; and the Kaplan-Meier method was used to compare the AF/flutter-free survival times between the two groups. Logistic regression was used to explore the association between changes in indices (Δ Pdis, Δ LAD, and Δ LAVI) and AF/flutter-free survival. Values of *P* < .05 were considered significant.

3 | RESULTS

A total of 328 consecutive patients were enrolled in this study. Of these patients, 223 (68.0%) underwent RFA, while 105 (32.0%) underwent CBA. The RFA group was more likely than the CBA group to have coronary artery disease or to have used an antiarrhythmic drug before matching. Five patients in the CBA group and 22 patients in the RFA group underwent repeat ablation after recurrence. After propensity score matching, 96 patients in the CBA group and 96 patients in the RFA group met our study inclusion criteria. The distributions of the propensity scores were comparable and all baseline characteristics were similar between the two groups (shown in Table 1). Of 192 patients, 50 (52.1%) in RFA group and 46 (47.9%) in CBA group received Antiarrhythmic drug after cryoablation, and stopped by the end of the blanking period.

3.1 | Structural and electrical remodeling

In the per-protocol analysis, as shown in Table 2, compared with baseline, at 1, 2, and 3 years after ablation, the changes in Pdis, LAD, and LAVI were significant in both the CBA and RFA groups. At 6 months after ablation, the average changes in Pdis, LAD, and LAVI were larger

TABLE 3 Average changes in P-wave dispersion, left atrial diameter, and left atrial volume index

	CBA group	RFA group
Δ Pdis-6 months (ms)	6.45 ± 8.31*	2.22 ± 7.63*
Δ Pdis-1 year (ms)	9.15 ± 11.10	5.54 ± 9.48
Δ Pdis-2 years (ms)	11.82 ± 12.97	8.00 ± 13.39
Δ Pdis-3 years (ms)	12.36 ± 14.14	8.25 ± 12.24
Δ LAD-6 months (mm)	1.76 ± 2.36*	0.56 ± 1.91*
Δ LAD-1 year (mm)	2.49 ± 3.28	1.85 ± 2.96
Δ LAD-2 years (mm)	3.67 ± 5.30	3.27 ± 2.90
Δ LAD-3 years (mm)	4.22 ± 3.53	4.03 ± 3.16
Δ LAVI-6 months (mL/m ²)	3.56 ± 4.73*	1.23 ± 3.66*
Δ LAVI-1 year (mL/m ²)	4.99 ± 5.47	3.55 ± 5.56
Δ LAVI-2 year (mL/m ²)	7.68 ± 7.78	6.29 ± 6.65
Δ LAVI-3 year (mL/m ²)	8.85 ± 11.09	8.14 ± 8.50

Note: LAD, left atrial diameter; Δ LAD, the mean value of the change in LAD; LAVI, left atrial volume index; Δ LAVI, the mean value of the change in LAVI; Pdis, P-wave dispersion; Δ Pdis, the mean value of the change in Pdis.

**P* < 0.05: the difference between the CBA group and the RFA group was significant.

in the CBA group than in the RFA group (shown in Table 3). However, there were no significant group differences in the other indices.

3.2 | Atrial fibrillation/flutter recurrence and atrial fibrillation/flutter-free survival time

As of January 2020, AF/flutter recurrence had recurred in 33(34.4%) patients in the CBA group and 39(40.6%) in the RFA group, but there was no significant difference between the two groups (Chi-square = 1.047, *P* = .592).

The Kaplan-Meier method was used to compare the AF/flutter-free survival time between the two groups (shown in Figure 1). The mean AF/flutter-free survival times of the two groups are shown in Table 4. The log rank method was used to evaluate the difference in AF/flutter-free survival time, and there was no significant difference

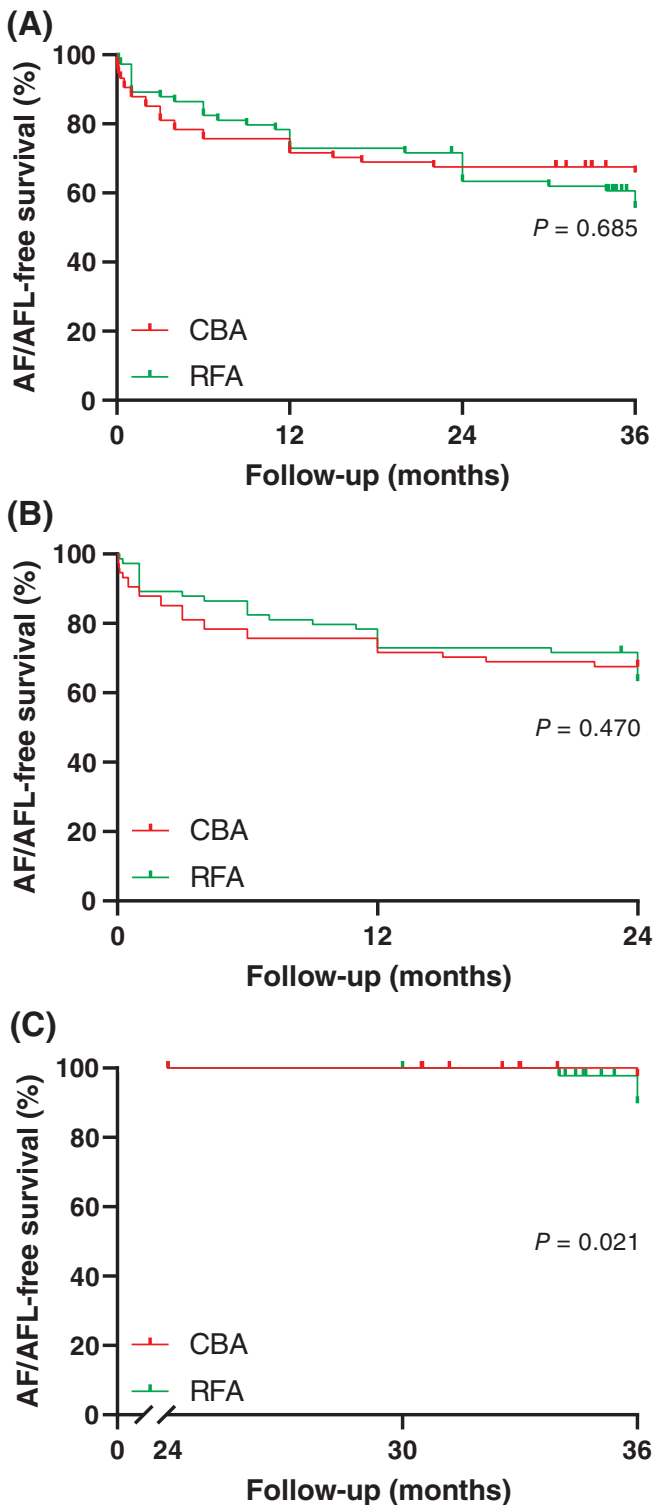


FIGURE 1 Survival plots of patients. A, Survival plots of all enrolled patients after propensity score matching. B, Survival plots of patients with an atrial fibrillation/flutter-free survival time < 24 months after propensity score matching. C, Survival plots of patients with an atrial fibrillation/flutter-free survival time \geq 24 months after propensity score matching. CBA, cryoballoon ablation; RFA, radiofrequency ablation

between the two groups (Chi-square = 0.164, $P = .685$). Then, we compared the AF/flutter-free survival times in cases with recurrence within 2 years and after 2 years between the CBA and RFA groups

and found that the survival time of CBA group may be longer than RFA group after 2 years after ablation (shown in Figure 1 and Table 4).

3.3 | Associations of Δ Pdis, Δ LAD, and Δ LAVI with atrial fibrillation/flutter-free survival

A logistic regression model analysis was performed, and we found that a higher Δ Pdis, Δ LAD, or Δ LAVI at 1 year after ablation increased AF/flutter-free survival (OR 1.307, 95% CI 1.039-1.605, $P = .035$; OR 1.301, 95% CI 1.089-1.522, $P < .001$; OR 1.879, 95% CI 1.711-1.963, $P < .001$, respectively).

4 | DISCUSSION

4.1 | Main findings

This is an observational clinical study aimed at exploring differences in atrial reverse-remodeling in paroxysmal AF patients who underwent CBA or RFA. In this study, we found that Pdis, LAD, and LAVI significantly decreased in both groups during the follow-up period. CBA may have performed better than RFA with regard for electrical and structural reverse-remodeling at 6 months after ablation, but over the long-term follow-up period, there was no significant difference between the two groups. CBA may have a longer AF/flutter-free survival time, and left atrial electrical and structural reverse-remodeling may have a positive effect on AF/flutter-free survival after ablation.

4.2 | Structural and electrical remodeling

The mechanism of occurrence and maintenance of AF remains unclear, but evidence indicates that rapid focal activation originating from the pulmonary veins may play a pivotal role. However, catheter ablation for AF remains challenging, with a low success rate over long-term follow-up.^{5,19} Previous studies have shown that RFA can reduce left atrium size and volume in patients without recurrence.^{9,10} Similarly, Canpolat et al¹² found that successful CBA improved electrical conduction in the left atrium and decreased the left atrium volume index. The results of our study are consistent with those presented in previous studies. The average changes in Pdis, LAD, and LAVI in patients with AF who underwent ablation clearly increased over time, indicating that ablation can indeed lead to reverse left atrial remodeling. A comparison between the two groups showed that Δ Pdis, Δ LAD, and Δ LAVI were significantly larger in the CBA group than in the RFA group at 6 months after ablation. As Jun Kurse et al reported that the PVI lesions after CBA were wider and more continuous than RFA,²³ we supposed the extension of ablation area produced by CBA may favor a higher entity of left atrial remodeling as compared to RFA. Wiecek M.'s study²⁴ compared RFA and CBA and found that CBA achieved a lower early pulmonary vein reconnection rate and may perform better in left atrial reverse-remodeling in the early

TABLE 4 Comparison of mean atrial fibrillation/flutter-free survival time between the CBA group and the RFA group

Patients	CBA group		RFA group		Chi-square	P value
	Mean atrial fibrillation/ flutter-free survival time	95% CI	Mean atrial fibrillation/ flutter-free survival time	95% CI		
All enrolled	25.820	(22.347, 29.294)	26.127	(22.982, 29.273)	0.164	.685
Recurrence within 2 years	12.930	(10.056, 15.803)	11.447	(8.249, 14.645)	0.522	.470
Recurrence after 2 years	36.000	(36.000, 36.000)	34.129	(32.813, 35.445)	5.306	.021

Note: CBA, cryoballoon ablation; RFA, radiofrequency ablation.

postablation period, similar to our finding that CBA may have longer AF/flutter-free survival times. But we did not find a significant difference between the two groups over long-term follow-up, a larger sample size may be helpful to find an obvious difference.

4.3 | Atrial fibrillation/flutter recurrence and atrial fibrillation/flutter-free survival time

Compared with RFA, CBA has several advantages, such as better catheter stability, continuous and complete scar boundaries, and less damage to the endocardial surface and adjacent tissue and structures²⁵; hence, CBA could potentially be noninferior to RFA with regard for safety and efficacy, as the FIRE AND ICE Trial showed over a 1.5-year follow-up duration.⁶ In terms of long-term follow-up, the STOP AF Trial obtained a ratio of 64.1% for freedom from AF and symptomatic atrial flutter/atrial tachycardia at 36 months after CBA in patients with paroxysmal AF.⁵ Another study reported a ratio of 41% freedom from atrial tachyarrhythmia recurrence after 31 ± 16 months of follow-up following a single RFA procedure in nonparoxysmal AF.²⁶ Our study compared the difference in the AF/flutter-free survival rate between CBA and RFA during a three-years-follow-up but did not show a significant difference. An important difference between our study and the aforementioned studies is that we evaluated clinical benefits according to the AF/flutter-free survival time and sought to explore the relationship between reverse left atrial remodeling and clinical benefits. In our study, the AF/flutter recurrence rates and AF/flutter-free survival times were not significantly different between the CBA and RFA groups, but the CBA group may have a longer survival time over 2 years after ablation.

4.4 | Associations of Δ Pdis, Δ LAD, and Δ LAVI with atrial fibrillation/flutter-free survival

The DECAAF study found that progressive remodeling of the left atrium might be responsible for failure after ablation²⁷; hence, we sought to explore whether AF/flutter-free survival after ablation is associated with left atrial reverse-remodeling. We found that Δ Pdis, Δ LAD, and Δ LAVI at 1 year after ablation were positively correlated

with AF/flutter-free survival, indicating that left atrial electrical and structural reverse-remodeling may have a positive effect on AF/flutter-free survival after ablation.

5 | LIMITATIONS

This study is a single-center study with a small sample size, and large randomized studies are needed to confirm these data. Regrettably, we did not require long-term continuous electrocardiographic monitoring after ablation, and the effects of ablation on the AF/flutter recurrence rate and AF/flutter-free survival time may have been exaggerated. A more obvious difference may be found if a longer follow-up time and a larger sample size are used to explore the difference in long-term AF/flutter-free survival time using these two methods.

6 | CONCLUSIONS

Our results show that both CBA and RFA are effective in left atrial electrical and structural reverse-remodeling in AF, and CBA may perform better in electrical and structural reverse-remodeling at 6 months after ablation. However, over the long-term follow-up period, there was no significant difference between the two groups.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS STATEMENT

Informed written consent was signed by all patients. This study was approved by the ethics review committee of the First Affiliated Hospital of Zhengzhou University.

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