Association between non-ablated left atrial surface area and rhythm outcome in patients treated with cryoballoon and radiofrequency ablation

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BACKGROUND Cryoballoon (CB) pulmonary vein isolation (PVI) offers outcomes comparable to radiofrequency PVI (RF-PVI) in patients with atrial fibrillation (AF) but has limitations for wide circumferential PVI and extra-pulmonary vein (PV) trigger (ExPVT) ablations.

OBJECTIVE This study aimed to compare long-term outcomes of CB-PVI vs RF-PVI in patients without ExPVT and explore underlying electroanatomical mechanisms.

METHODS We identified 1902 patients undergoing de novo AF ablation without ExPVT. After propensity matching for age, sex, AF type, and left atrium anteroposterior (LAAP) diameter in patients, we compared AF recurrence in 403 CB-PVI and 403 RF-PVI cases, considering AF type and LAAP diameter. Using a Cox model, we identified the optimal LAAP diameter cutoff for differentiating outcomes and examined the relationship between PVI modality and reduction in electrically active LA area via computational modeling.

RESULTS During a median follow-up of 24 months, CB-PVI had poorer rhythm outcomes than RF-PVI in propensity-matched patients (log-rank $P = .009$). Outcomes were comparable in those with an LAAP diameter <40 mm or paroxysmal AF. However, CB-PVI was associated with higher AF recurrence in patients with a LAAP diameter ≥40 mm (hazard ratio [HR] 1.54 [1.01–2.36]; log-rank $P = .047$) or persistent AF (HR 2.17 [1.36–3.45]; log-rank $P = .001$). In computational modeling, a larger non-ablated LA area post-PVI was independently related to a higher AF recurrence risk. RF-PVI reduced LA surface area more than CB-PVI, especially in patients with a large LA or persistent AF.

CONCLUSION CB-PVI showed inferior rhythm outcomes compared with RF-PVI in patients with a LAAP diameter ≥40 mm or persistent AF, possibly because of a smaller reduction in LA critical mass.

KEYWORDS Atrial fibrillation; Catheter ablation; Cryoballoon; Radiofrequency; Critical mass

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Introduction

Atrial fibrillation (AF) is a prevalent arrhythmia that increases morbidity and socioeconomic burden worldwide.[1,2] The clinical usefulness of early rhythm control in AF has been established,[3] and the demand for AF catheter ablation (AFCA) is rising. As a result, the interest in a simple, effective and safe AFCA technology is growing.[4] Cryoballoon (CB) ablation is a medical procedure that involves the application of a specialized 28-mm CB to ablate the pulmonary vein (PV) orifice in a single contact.[5] CB PV isolation (CB-PVI) requires less catheter manipulation than radiofrequency PVI (RF-PVI).[6] Previous randomized controlled trials demonstrated comparable rhythm outcomes between CB-PVI and conventional RF-PVI in patients with paroxysmal AF.[5,7–9] For patients with persistent AF, recent randomized trials demonstrated that CB-PVI and RF-PVI were equally effective for rhythm control.[10,11] However, the prolonged follow-up of the CB or Irrigated Radiofrequency Ablation (CIRCA-DOSE) trial demonstrated that contact-force guided RF ablation was associated with a lower incidence of progression to persistent atrial arrhythmia, compared with CB ablation.[12]

As the disease progresses, atrial structural remodeling has been proposed as a contributing factor to the recurrence of AF.[13] Critical reduction in electrically active LA area by AFCA can reduce wave break and disrupt AF maintenance.[14] However, ablations using a 28-mm CB have limitations in wide circumferential PVI. Additionally, CB-PVI has limitations in extra-PV trigger (ExPVT) mapping and ablation.[5] To investigate the impact of different thermal energy source and technologies on outcome after PVI, excluding the effect of ExPVTs is needed.

This study aimed to compare long-term outcomes after AFCA between CB-PVI and RF-PVI according to left atrial

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KEY FINDINGS

- Cryoballoon (CB) pulmonary vein isolation (PVI) was independently associated with a higher risk of atrial fibrillation (AF) recurrence after ablation compared with radiofrequency (RF)-PVI in patients with a large left atrium (LA) size and those with persistent AF.
- A larger remaining non-ablated LA area after PVI correlated with an increased risk of AF recurrence.
- The additional LA surface area reduction by RF-PVI, compared with CB-PVI, was more significant in patients with a large LA size and those with persistent AF than in their counterparts.

(LA) size, and AF type in patients without ExPVT. We also evaluated the potential electroanatomical mechanisms underlying these differences.

Methods

Study population

The study protocol adhered to the principles of Declaration of Helsinki and was approved by the Institutional Review Board of Yonsei University Health System. All patients provided written informed consent for inclusion in the Yonsei AF Ablation Cohort Database (ClinicalTrials.gov Identifier: NCT02138695). We identified 4783 patients who underwent first-time AFCA in the Yonsei AF Ablation Cohort between September 2009 and August 2021. The exclusion criteria were as follows: (1) absence of a post-procedural isoproterenol provocation test; (2) confirmed ExPVT(s) on isoproterenol provocation testing; (3) presence of a common ostium in the pulmonary veins; and (4) lack of LA diameter measurement on echocardiography. Among 1902 patients without ExPVT, propensity score matching was performed for age, sex, AF type, and LA anteroposterior (LAAP) diameter. A total of 403 patients who underwent CB-PVI and 403 patients who underwent RF-PVI were enrolled in the study (75.4% male, mean age 61.8 ± 10.9 years, 53.2% with paroxysmal AF) (Figure 1). All patients were assigned to either the CB-PVI or RF-PVI group based on the ablation modality received. Propensity score matching was then performed using baseline characteristics, including age, sex, AF type, and LA diameter.

Comprehensive descriptions of echocardiographic and computed tomography image acquisition, ablation procedures, 3D modeling of the left atrium, and computational analysis of ablation and non-ablated areas are available in the Supplemental Appendix.

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation (SD) and compared using the *t* test or the Mann-Whitney U test. Categorical variables were reported as counts (percentages) and compared using the χ^2 or Fisher exact tests. Propensity scores were estimated using a non-parsimonious multiple logistic regression model for the CB-PVI and RF-PVI groups. Age, sex, AF type, and LAAP diameter were considered as variables. Patients were then matched, without replacement, with the CB-PVI group based on the closest possible propensity score (nearest neighbor matching). A matching caliper of 0.2 SDs of the logit of the estimated propensity score was enforced to ensure that matches with a poor fit were excluded. Cox regression analysis was performed to investigate variables related to AF/AT recurrence after AFCA. Variables with p-values <0.05 in each univariable analysis were selected for the multivariable analysis. Kaplan–Meier analysis with a log-rank test was used to analyze the probability of freedom from AF/atrial tachycardia (AT) recurrence after AFCA. To determine the LA cutoff size for differentiating long-term AF recurrence between RF-PVI and CB-PVI, we compared the log-likelihood values of multivariate Cox proportional hazard models at each possible cutoff value for LAAP diameter. The cutoff value with maximum likelihood was chosen as the optimal value.

Results

Patient characteristics

Patients who underwent CB-PVI had a higher prevalence of hypertension and a lower prevalence of vascular disease compared with those who underwent RF-PVI (Table 1). We determined the appropriate cutoff value of LAAP diameter (40 mm) and LA volume index (38 mL/m^2) predicting the difference in long-term AF recurrence between RF-PVI and CB-PVI using the log-likelihood values of multivariate Cox proportional hazard models (Supplemental Figure 1). Supplemental Table 1 shows baseline characteristics according to LA size.

Comparisons between CB-PVI vs RF-PVI according to LA size

During a median follow-up of 24 months (interquartile range [IQR], 12–33 months), the overall recurrence rate of AF was 19.6% in the CB-PVI group and 17.2% in the RF-PVI group. The mean follow-up durations were 13.5 ± 9.8 months for CB-PVI and 32.0 ± 30.6 months for RF-PVI. CB-PVI showed poorer AF recurrence than RF-PVI in all matched patients (log-rank *P* = .009; hazard ratio [HR] 1.605, 95% confidence interval [CI] 1.130–2.279) (Supplemental Table 2). To account for differences in follow-up duration between the groups, an additional analysis was conducted by restricting the follow-up period to 24 months (Supplemental Tables 3–5). There was no difference was observed in AF recurrence between the 2 groups among patients with a LAAP diameter <40 mm (log-rank *P* = .180; HR 1.484, 95% CI 0.836–2.634) (Figure 2A and Supplemental Table 6). In the group with a large LA size (LAAP diameter ≥40 mm), patients who underwent CB-PVI had a higher risk of AF recurrence compared with those who underwent RF-PVI (log-rank *P* = .030; HR 1.540, 95% CI 1.006–2.358) (Figure 2A and Table 2). Consistent results were shown when LA volume index 38 mL/m^2 was used as

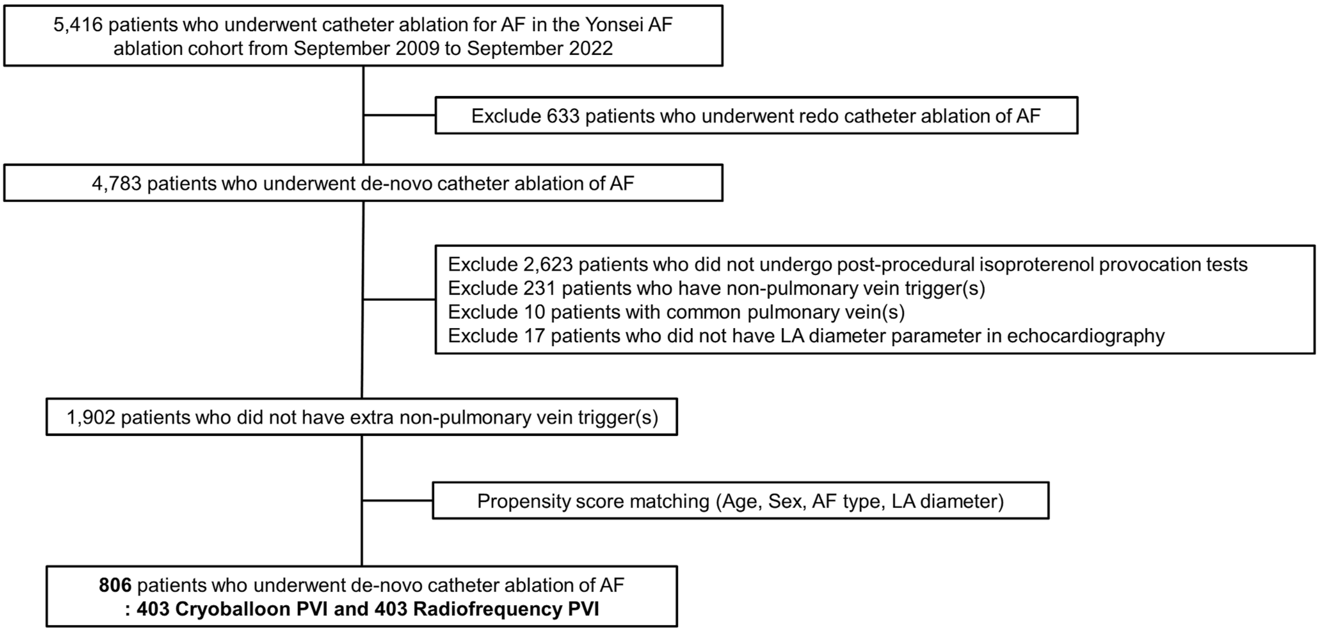

Figure 1 Study flow diagram. AF = atrial fibrillation; LA = left atrium; PVI = pulmonary vein isolation.

the cutoff for LA size (Supplemental Figure 2). At 24-months post-ablation, the cumulative incidence rates of AF/AT recurrence were 26.7% in the RF-PVI group and 43.5% in the CB-PVI group among patients with a large LA, and 16.2% and 21.3%, respectively, among those with a small LA (Figure 2A).

Comparisons between CB-PVI vs RF-PVI according to AF type

There was no difference was observed in AF recurrence between the RF-PVI and CB-PVI groups among patients with paroxysmal AF (log-rank $P = .370$; HR 0.759, 95% CI 0.416–1.387) (Figure 2B and Supplemental Table 7). In those with persistent AF, patients who underwent CB-PVI had a higher risk of AF recurrence than that of patients who underwent RF-PVI (log-rank $P = .001$; HR 2.168, 95% CI 1.363–3.447) (Figure 2B and Table 3). In a sensitivity analysis using an Akaike information criterion-based model selection approach (forcing age and sex into the model), similar predictors of AF recurrence were identified in both the persistent AF and large LA (Supplemental Table 8). When stratified by AF type, the 24-months cumulative incidence rates of AF/AT recurrence were 20.3% in the RF-PVI group and 15.3% in the CB-PVI group among patients with paroxysmal AF, and 23.7% and 47.2%, respectively, among those with persistent AF (Figure 2B). Univariate and multivariate regression analyses for predictors of AF/AT recurrence were additionally performed separately in the CB-PVI and RF-PVI groups, and the results are presented in Supplemental Tables 9 and 10. AF/AT recurrence rates were compared across 4 subgroups stratified by AF type (paroxysmal vs persistent) and LA diameter (<40 mm vs ≥40 mm), as shown in Supplemental Figure 3.

Comparison of LA surface areas using computational modeling

Figure 3 represents the LA surface areas following CB-PVI and RF-PVI according to the LA size estimated using computational modeling. RF-PVI lesions might be optimized to include the PV antrum based on the LA size and shape. However, in the case of CB-PVI lesions using a 28-mm fixed-sized balloon, the size and shape of the PV ostium play a crucial role in determining the effectiveness of the lesions.

The non-abated LA area after PVI measured using computational modeling was independently associated with AF recurrence after CA in patients with a LAAP diameter ≥40 mm (HR per 1 cm^2 increase 1.012, 95% CI 1.004–1.021; Table 2) or persistent AF (HR 1.009, 95% CI 1.001–1.016; Table 3). Figure 4 presents the LA surface area before and after RF- or CB-PVI simulated using computational modeling. The additional LA surface area reduction by RF-PVI, compared with CB-PVI, was more pronounced in patients with a large LA size (LAAP diameter ≥40 mm) than in those with a smaller LA ($P < .001$) (Figure 4A). Likewise, this difference was greater in patients with persistent AF than in those with paroxysmal AF ($P < .001$) (Figure 4B). Regardless of LA size or AF type, RF-PVI resulted in a greater relative reduction in LA area compared with CB-PVI. However, this difference was more pronounced in patients with a large LA or persistent AF (Figure 4C).

A larger non-ablated LA area after PVI was linearly associated with a higher risk of AF recurrence, particularly when exceeding 100 cm^2 (Figure 5). In these patients, each 1 cm^2 increase in the non-ablated area was associated with a higher risk of AF recurrence (HR 1.07, 95% CI 1.03–1.11 for RF-PVI; HR

Table 1 Baseline characteristics of overall study population according to strategy of ablation after propensity score matching

	Overall (N = 806)	Cryoballoon ablation (N = 403)	Radiofrequency ablation (N = 403)	*P*-value	SMD
Clinical variables					
Age, years	61.8 ± 10.9	61.7 ± 11.6	61.9 ± 10.2	.862	0.012
Paroxysmal AF, %	429 (53.2)	215 (53.3)	214 (53.1)	1.000	0.005
Men, %	608 (75.4)	301 (74.7)	307 (76.2)	.682	0.035
Body mass index, kg/m2	24.7 ± 3.2	24.7 ± 3.3	24.8 ± 3.1	.758	0.022
CHA_2DS_2-VASc score	1.8 ± 1.5	1.9 ± 1.4	1.8 ± 1.5	.698	0.027
Diabetes mellitus, %	126 (15.6)	63 (15.6)	63 (15.6)	1.000	<0.001
Hypertension, %	376 (46.7)	204 (50.6)	172 (42.7)	.029	0.160
Stroke, %	94 (11.7)	45 (11.2)	49 (12.2)	.742	0.031
Vascular disease, %	57 (7.1)	19 (4.7)	38 (9.4)	.013	0.185
Echocardiographic findings					
LAAP diameter, mm	40.4 ± 5.7	40.2 ± 5.7	40.5 ± 5.7	.349	0.006
LA volume index, mL/m^2	38.0 ± 12.2	37.9 ± 11.6	38.1 ± 12.8	.836	0.015
LVEDD, mm	49.7 ± 4.5	49.4 ± 4.3	49.9 ± 4.7	.168	0.097
LVEF, %	63.6 ± 8.6	64.5 ± 8.1	62.7 ± 9.0	.002	0.219
E/Em	10.1 ± 4.1	9.8 ± 3.5	10.3 ± 4.6	.146	0.105
RVSP, mmHg	26.5 ± 6.6	26.2 ± 6.2	26.7 ± 6.9	.287	0.078
LVMI, g/m^2	93.7 ± 20.8	93.0 ± 18.5	94.6 ± 23.0	.287	0.077
LA related parameter					
LA pressure, peak, mmHg	21.4 ± 8.7	21.4 ± 8.8	21.3 ± 8.7	.935	0.006
LA wall stress	172.2 ± 101.2	178.9 ± 1123.0	165.9 ± 88.5	.084	0.128
3D computed tomography					
LA volume/BSA, mL/m^2	84.2 ± 22.5	81.9 ± 22.2	86.4 ± 22.6	.006	0.200
Epicardial adipose tissue, mL	117.2 ± 46.4	119.8 ± 47.5	114.6 ± 45.2	.124	0.112
Catheter ablation					
Ablation time, min	38.7 ± 24.8	21.6 ± 7.0	56.0 ± 24.4	<.001	1.914
Fluoroscopic time, min	23.4 ± 10.9	18.3 ± 7.8	28.6 ± 11.1	<.001	1.082
Procedure time, min	110.4 ± 48.2	75.7 ± 18.3	145.3 ± 436	<.001	2.084
Recurrence					
ER	211 (26.4)	106 (26.6)	105 (26.2)	.949	0.010
LR	147 (18.2)	78 (19.4)	69 (17.1)	.466	0.058
Sustained AF	31 (5.5)	21 (8.4)	10 (3.2)	.013	0.222
Heart rate variability (baseline)					
Mean HR	67.2 ± 12.6	66.9 ± 11.7	67.4 ± 13.5	.673	0.040
Max HR	132.9 ± 33.1	131.0 ± 30.9	135.3 ± 35.5	.173	0.129
LF	16.1 ± 15.6	15.3 ± 13.9	16.8 ± 16.8	.428	0.099
HF	10.4 ± 8.8	9.6 ± 7.5	11.1 ± 9.6	.160	0.176
LF/HF	1.4 ± 0.7	1.4 ± 0.8	1.4 ± 0.6	.676	0.051
rMSSD	27.0 ± 17.8	24.3 ± 16.5	29.1 ± 18.5	.029	0.271

3D = 3 dimensional; AF = atrial fibrillation; BSA = body surface area; E/Em = the ratio of the early diastolic mitral inflow velocity (E) to the early diastolic mitral annular velocity (Em); EAT = epicardial adipose tissue; ER = early recurrence; HF = high frequency; HR = heart rate; LA = left atrium; LAAP = left atrium anteroposterior; LF = low frequency; LR = late recurrence; LVEDD = left ventricle end diastolic diameter; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; rMSSD = root mean square of the successive difference; RVSP = right ventricular systolic pressure.

1.04, 95% CI 1.01–1.08 for CB-PVI). The non-ablated area after PVI showed a correlation with the LAAP diameter (Supplemental Figure 4), and the LAAP diameter corresponding to 100 cm^2 of the non-ablated area was 39 mm.

Discussion

Main findings

In this retrospective cohort study, we compared the long-term outcomes of AF between CB-PVI and RF-PVI and explored the potential electroanatomical mechanisms explaining this difference. The present study includes 4 principal findings, as follows: (1) CB-PVI was independently associated with a higher risk of AF recurrence after ablation compared to RF-PVI in patients with a large LA size (LAAP diameter ≥40 mm) and those with persistent AF; (2) however, no significant differences were observed between CB-PVI and RF-PVI in patients with paroxysmal AF or a small LA size; (3) a larger remaining non-ablated LA area after PVI correlated with an increased risk of AF recurrence; and (4) the additional LA surface area reduction by RF-PVI, compared with CB-PVI, was more significant in patients with a large LA size and those with persistent AF than in their counterparts.

Efficacy and safety of CB-PVI vs RF-PVI

Unlike the point-by-point focused delivery of RF energy, cryothermal energy-based CA simplifies the procedure of creating a circumferential transmural lesion using a balloon-based technique, providing a homogeneous freezing area.[15] Regarding efficacy, several studies showed no

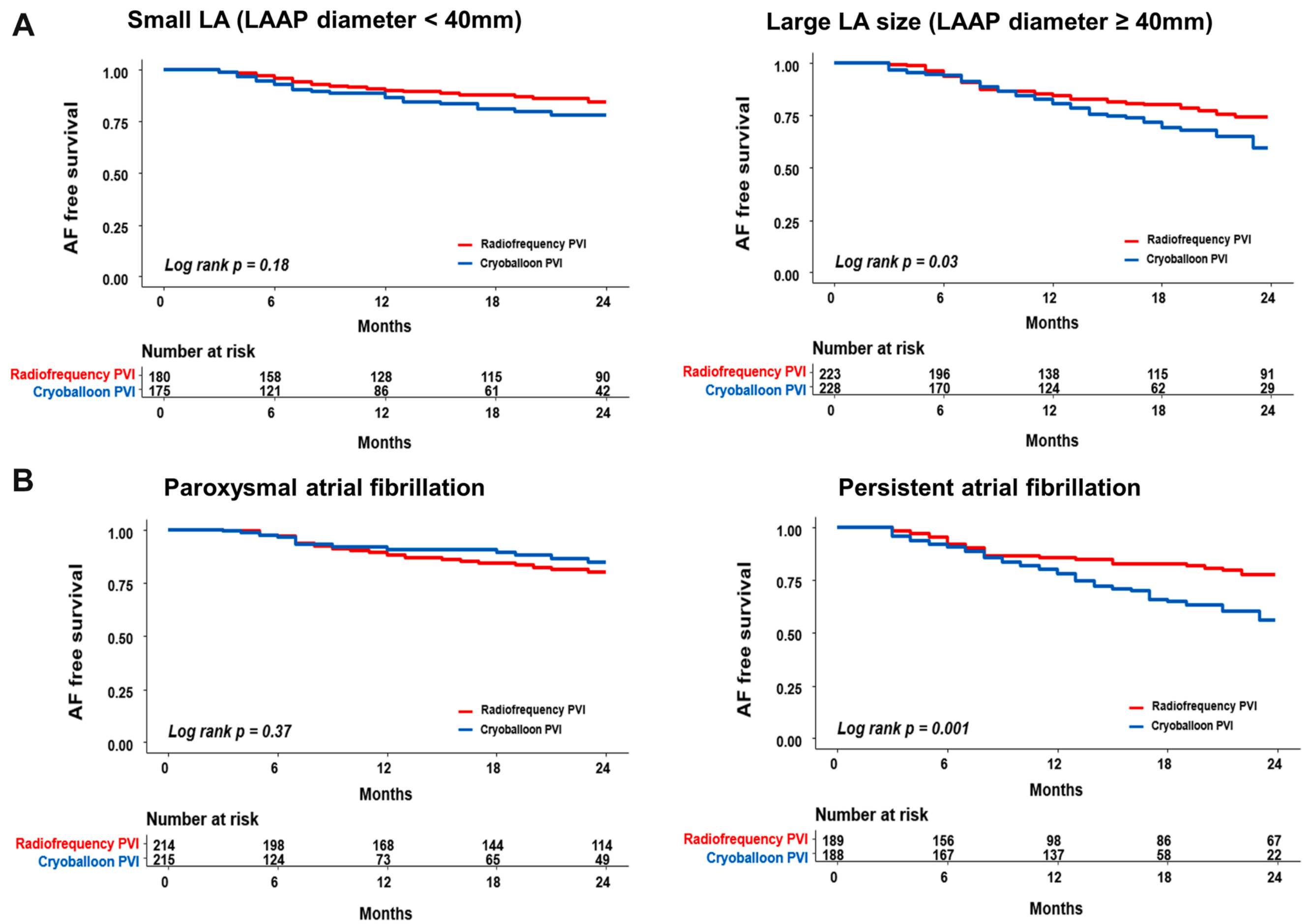

Figure 2 Freedom from atrial fibrillation recurrence after pulmonary vein isolation using cryoballoon or radiofrequency stratified by left atrial size (**A**) and atrial fibrillation type (**B**). AF = atrial fibrillation; LA = left atrium; LAAP = left atrial anteroposterior; PVI = pulmonary vein isolation.

Table 2 Predictors for atrial fibrillation recurrence in patients with a large left atrium (left atrial anteroposterior diameter ≥40 mm)

	Univariate analysis		Multivariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	0.996 (0.977–1.015)	0.677				
Men	0.636 (0.411–0.985)	0.043	0.594 (0.379–0.931)	.023	0.623 (0.397–0.976)	.039
Paroxysmal AF	0.739 (0.486–1.123)	0.156				
Body mass index	1.027 (0.966–1.092)	0.393				
Diabetes mellitus	0.640 (0.364–1.126)	0.122				
Hypertension	1.144 (0.772–1.696)	0.502				
Stroke	0.902 (0.651–1.251)	0.538				
Vascular disease	0.977 (0.492–1.938)	0.946				
LAAP diameter	1.069 (1.016–1.124)	0.009				
LVEF	0.990 (0.971–1.010)	0.315				
E/Em	1.012 (0.973–1.052)	0.547				
RVSP	1.032 (1.005–1.060)	0.021	1.023 (0.993–1.054)	.142	1.029 (0.998–1.061)	.070
LA volume/BSA	1.014 (1.006–1.023)	0.001				
Epicardial adipose tissue	1.001 (0.997–1.005)	0.599				
Atrial EAT	1.004 (0.995–1.012)	0.377				
Ventricular EAT	1.001 (0.993–1.008)	0.859				
LA pressure, peak	1.024 (1.004–1.044)	0.018	1.022 (1.001–1.044)	.038	1.027 (1.005–1.049)	.017
LA wall thickness	0.606 (0.357–1.028)	0.063				
Cryoballoon PV isolation	1.546 (1.039–2.301)	0.032	1.540 (1.006–2.358)	.047		
Post-PVI non-ablated LA area, cm^2	1.012 (1.004–1.021)	0.002			1.012 (1.004–1.021)	.003

AF = atrial fibrillation; BSA = body surface area; CI = confidence interval; E/Em = the ratio of the early diastolic mitral inflow velocity (E) to the early diastolic mitral annular velocity (Em); EAT = epicardial adipose tissue; LA = left atrium; LAAP = left atrium anteroposterior; LVEF = left ventricular ejection fraction; OR = odds ratio; PV = pulmonary vein; PVI = pulmonary vein isolation; RVSP = right ventricular systolic pressure.

Table 3 Predictors for atrial fibrillation recurrence in patients with persistent AF

	Univariate analysis		Multivariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	0.996 (0.978–1.014)	.649				
Men	0.644 (0.410–1.010)	.056				
Body mass index	1.005 (0.940–1.074)	.887				
Diabetes mellitus	0.671 (0.374–1.205)	.182				
Hypertension	1.032 (0.689–1.545)	.879				
Stroke	0.857 (0.626–1.173)	.334				
Vascular disease	1.273 (0.640–2.529)	.492				
LAAP diameter	1.007 (0.965–1.050)	.756				
LVEF	1.004 (0.981–1.028)	.746				
E/Em	1.009 (0.955–1.066)	.750				
RVSP	1.016 (0.986–1.047)	.296				
LA volume/BSA	1.012 (1.004–1.020)	.003	1.013 (1.004–1.022)	.004		
Epicardial adipose tissue	1.001 (0.997–1.005)	.804				
Atrial EAT	1.002 (0.994–1.011)	.563				
Ventricular EAT	1.000 (0.993–1.007)	.964				
LA pressure, peak	1.023 (1.001–1.046)	.043	1.024 (1.001–1.049)	.042	1.027 (1.004–1.050)	.021
LA wall thickness	0.657 (0.377–1.146)	.139				
Cryoballoon PV isolation	1.988 (1.292–3.059)	.002	2.168 (1.363–3.447)	.001		
Post-PVI non-ablated LA area, cm^2	1.009 (1.001–1.016)	.020			1.009 (1.001–1.016)	.022

AF = atrial fibrillation; BSA = body surface area; CI = confidence interval; E/Em = the ratio of the early diastolic mitral inflow velocity (E) to the early diastolic mitral annular velocity (Em); EAT = epicardial adipose tissue; LA = left atrium; LAAP = left atrium anteroposterior; LVEF = left ventricular ejection fraction; OR = odds ratio; PV = pulmonary vein; PVI = pulmonary vein isolation; RVSP = right ventricular systolic pressure.

statistical difference between the 2 ablation strategies,[7,16,17] whereas 2 studies showed higher efficacy of CB-PVI than that of RF-PVI.[18,19] CB-PVI was not inferior to RF-PVI regarding efficacy and safety in patients with drug-refractory paroxysmal AF.[5] Phrenic nerve injury was the most common adverse event (2.7%) in the CB group, and the most common adverse events (4.3%) in the RF group were groin site complications.[5] Several large cohort studies and randomized trials have demonstrated the comparable efficacy of CB-PVI and RF-PVI in patients with persistent AF.[10,11,20] The NOrwegian randomized study of PERSistent Atrial Fibrillation (NO-PERSAF) showed no difference in AF recurrence was observed between CB-PVI and RF-PVI for persistent AF, but less atrial flutter and higher proportion

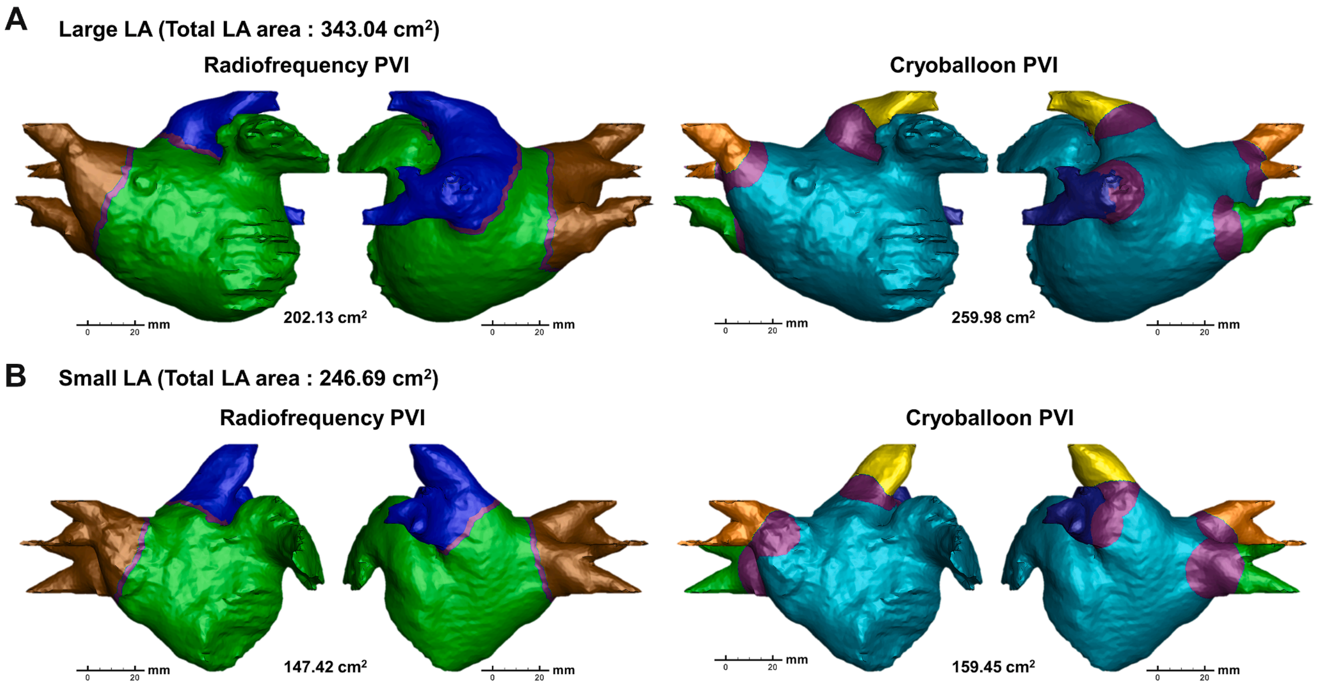

Figure 3 Representative examples of non-ablated left atrial areas following pulmonary vein isolation using cryoballoon or radiofrequency in patients with a large left atrium (**A**) and a small left atrium (**B**). AF = atrial fibrillation; LA = left atrium; PVI = pulmonary vein isolation.

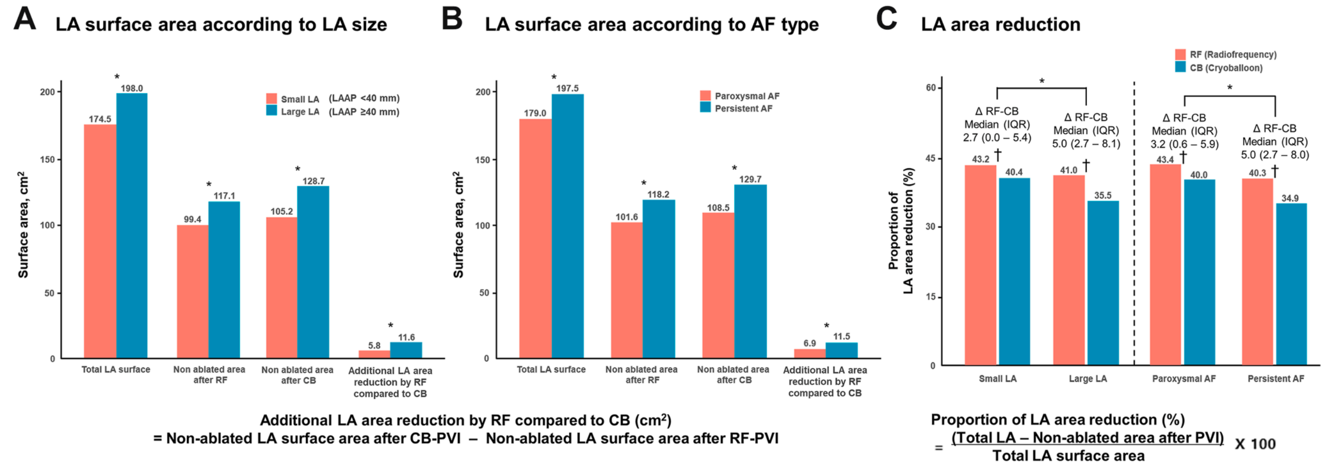

Figure 4 Computational simulation results estimating the left atrial surface area based on LA size (**A**) and atrial fibrillation type (**B**), along with the proportion of left atrial area reduction (**C**) following pulmonary vein isolation using either cryoballoon or radiofrequency. AF = atrial fibrillation; CB = cryoballoon; LA = left atrium; RF = radiofrequency. *$P < .001$. † $P < .001$ (estimated using the Wilcoxon signed rank test). Computational modeling was used to simulate the non-ablated left atrial (LA) surface area after ablation with both cryoballoon and radiofrequency in the same patient. As a result, each patient in this Figure has 2 corresponding values.

AF recurrence in persistent form was observed in the CB-PVI group, hypothesizing that the lesion size, depth, and durability, and coverage of LA posterior wall by CB may differ from wide antral PVI by RF and lead to different presenting of AF.[10]

As our results indicate, CB-PVI was associated with significantly shorter procedure and fluoroscopy times compared with RF-PVI. However, despite these advantages, the trade-off is a more limited ablation area and the inability to perform precise lesion titration, which might explain its inferior long-term outcomes in patients with larger LA sizes or persistent AF.

Reduction in electrically active LA area by CB-PVI vs RF-PVI

Critical reduction in electrically active LA area by CA may reduce wave breaks and inhibit AF maintenance.[13] Atrial structural remodeling, which occurs as a result of disease progression in AF, has also been proposed as a contributing factor in determining the type of recurrence following AF ablation.[13]

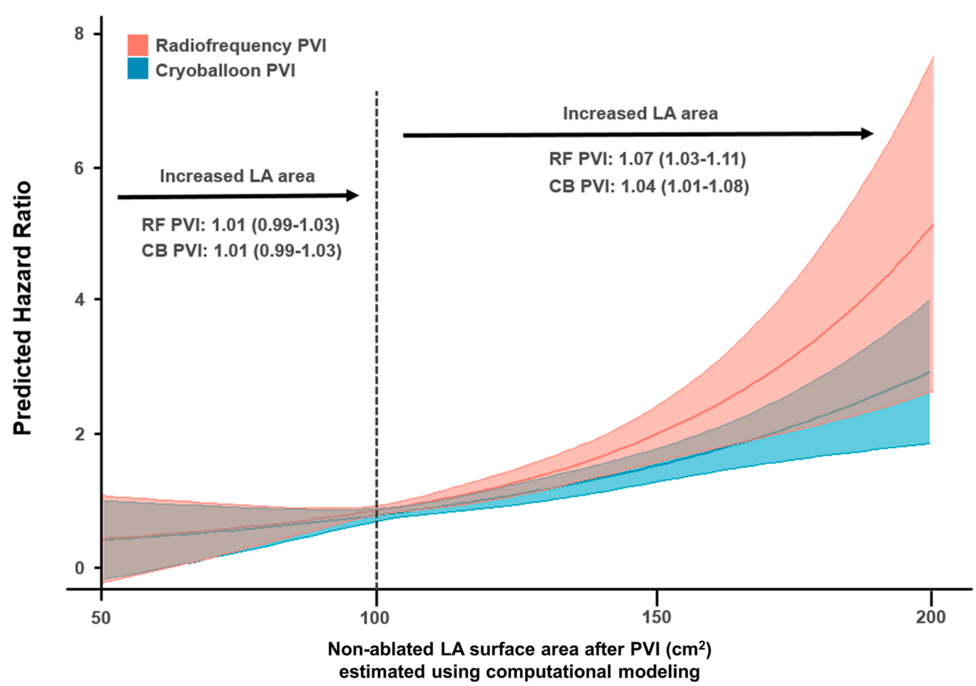

Figure 5 Relationships between non-ablated left atrial areas after pulmonary vein isolation and the risk of atrial fibrillation recurrence. AF = atrial fibrillation; CB = cryoballoon; LA = left atrium; PVI = pulmonary vein isolation; RF = radiofrequency.

Fibrillation maintenance requires an appropriate critical mass size[14,21] and short wave length.[22] The presence of critical reduction in electrically active LA area has been reported in large animal,[23] simulation,[24] and clinical studies.[14] These concepts are consistent with recent expert consensus, which recommends substrate-based ablation strategies tailored to individual atrial characteristics, particularly in patients with advanced structural remodeling.[25] Furthermore, recent reviews on the evolution of AF ablation techniques have emphasized the importance of lesion durability and anatomical targeting, supporting the rationale for critical reduction in electrically active LA area in selected patient populations.[26] Importantly, our results build upon rather than contradict the established role of PV durability,[27,28] indicating that even when durable PVI is achieved, the residual electrically active LA tissue may still influence long-term rhythm outcomes.

After excluding the cases of ExPVTs in this study, CB-PVI showed poorer rhythm outcomes than RF-PVI in patients with a large LA size. Recently, CB-PVI has gained widespread use and typically involves the use of a fixed 28-mm balloon. Although previous studies showed that RF and CB ablation result in a comparable extent of tissue injury and a similar range of isolation area,[29,30] our computational simulation showed that PVI using the 28-mm CB had the potential to cover the PV antrum in small-sized LA; however, it spared some area of the PV antrum in large-sized LA.

Kujiraoka et al[31] investigated the association between the ablated area and risk of recurrence after durable CB-PVI. The study demonstrated that a larger non-ablated area of the LA posterior wall was associated with a higher risk of atrial arrhythmia recurrence although there were no PV reconnections, underscoring the significance of the LA antrum isolation area.[31] Although recent trials showed adjunctive posterior wall isolation achieved by CB, compared with CB-PVI alone, resulted in better clinical outcomes in patients with persistent AF,[32,33] further randomized investigation is warranted to identify electroanatomic characteristics that would derive additional benefits from additional CB applications at antral area.

Limitations

This study had several limitations. First, it was a single-center, retrospective, observational cohort study. Consequently, the findings cannot be used to establish causal relationships. Second, although propensity score matching was performed to minimize selection bias, residual confounding may still exist. Third, we did not collect data on PV reconnection patterns in patients with recurrence, which could have provided additional mechanistic insights into the differential effects of CB-PVI and RF-PVI. Future studies with systematic remapping data are warranted to further elucidate the impact of lesion durability on long-term outcomes. Fourth, we included patients who underwent an isoproterenol provocation test and excluded those who did not. This might have resulted in selection bias and even the provocation test cannot fully ascertain the existence of ExPVTs. Fifth, the long study period (2009–2021) may have limited the reflection of evolving ablation technologies and increasing procedural experience over time, including the introduction of contact-force sensing catheters. Sixth, rhythm follow-up was mainly based on scheduled 24-hour Holter recordings at relatively wide intervals, which may have underestimated asymptomatic or short-duration atrial arrhythmias. However, the same follow-up schedule was uniformly applied to both RF and CB groups, and the therapeutic efficacy is unlikely to have been biased or overestimated by under-ascertainment of the outcome. Lastly, the computational modeling used in this study to estimate non-ablated LA areas relies on assumptions and simplifications that may not fully capture the complexity of real-world atrial tissue remodeling and ablation effects. Although it provides valuable insights into electroanatomical mechanisms, it may not perfectly reflect in vivo conditions, necessitating further validation through prospective studies. Furthermore, the inclusion of PV secondary branches in the 3D segmentation—aimed at maintaining anatomical consistency—may have contributed to an overestimation of the LA surface area reduction. Additionally, PV isolation in the model was inferred from anatomical surrogates rather than confirmed by electrograms in all patients, which may have led to an overestimation of actual lesion durability.

Conclusion

In this observational retrospective study, CB-PVI was associated with less favorable rhythm outcomes, in terms of sinus rhythm maintenance, as compared with RF-PVI in patients with an LAAP diameter $\geq$40 mm or persistent AF. This finding may be related to a lower reduction in LA critical mass.

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Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: All patients provided written informed consent for inclusion in the Yonsei AF Ablation Cohort Database.

Ethics Statement: The study protocol adhered to the principles of Declaration of Helsinki and was approved by the Institutional Review Board of Yonsei University Health System.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2025.11.009.

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