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Impact of right atrial structural remodeling on recurrence after ablation for atrial fibrillation

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Abstract

Background: Recurrence of atrial fibrillation (AF) after pulmonary vein isolation (PVI) is associated with left atrial (LA) remodeling; however, its association with right atrial (RA) remodeling remains unclear.

Objective: This study aimed to identify whether RA structural remodeling could predict recurrence of AF after PVI.

Methods: This study prospectively analyzed 245 patients with AF who had undergone PVI. RA and LA volumes were determined by contrast-enhanced computed tomography. Atrial structural remodeling was defined as an atrial volume of ≥110 mL according to previous reports and receiver operating characteristic curve analysis.

Results: After excluding 32 patients, 213 patients were analyzed. During a follow-up period of 12 months, 41 patients (19%) demonstrated atrial arrhythmia recurrence after PVI. With the Cox proportional-hazards model, RA structural remodeling was the only predictor of arrhythmia recurrence (hazard ratio, 1.012; 95% confidence interval 1.003-1.021; $P = .009$). Kaplan–Meier analysis showed that arrhythmia recurrence was more frequent in the RA structural remodeling group compared with the group without RA remodeling (log-rank, $P < .001$), and the arrhythmia-free survival rates in these groups at 12 months were 68.0% and 91.4%, respectively. Additionally, there was a significant difference in recurrence-free survival after RA structural remodeling in each type of AF (log-rank, $P < .001$).

Conclusions: RA structural remodeling is a useful predictor of clinical outcome after PVI regardless of the type of AF. Our results suggest that patients without RA structural remodeling may be good candidates for successful ablation with PVI.

KEYWORDS

arrhythmia recurrence, atrial fibrillation, catheter ablation, left atrial remodeling, right atrial remodeling

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac rhythm disturbance encountered in clinical practice and is associated with decreased quality of life and increased morbidity and mortality.[1] AF recurrence after catheter ablation has been reported with long-term follow-up despite application of novel techniques and technologies. Thus, identifying patients with AF who are likely to experience treatment failure is important. In addition to conventional risk factors, such as left atrial diameter (LAD), AF duration, and age, new predictors of procedural outcome are needed to increase the ability of identifying patients at a high risk of recurrence following AF ablation. Previous evidence has highlighted structural and electrical remodeling in the atria as substrates for AF.[2-6] It is well known that pulmonary veins and the left atrium (LA) have been closely associated with AF.[7] AF is not a disease solely of the LA; it also affects the right atrium (RA). A previous study showed that RA diameter can affect the early recurrence of AF after ablation.[8] Others have also reported that RA anatomical remodeling can predict the success of AF cardioversion,[9] and the ratio of the RA volume index to the LA volume index is a risk factor for AF recurrence.[10] However, it is unclear to what extent RA contributes to the ablation outcome in the general population with AF. The present study aimed to evaluate atrial volume in patients with AF to investigate the influence of RA volume on recurrence of AF after pulmonary vein isolation (PVI).

2 | METHODS

2.1 | Study participants

We enrolled 245 patients who received initial catheter ablation for symptomatic drug-refractory paroxysmal or non-paroxysmal AF at Toho University Ohashi Medical Center between June 2016 and June 2019. Paroxysmal AF was defined as AF that terminated spontaneously within 7 days of onset, and non-paroxysmal AF was defined as other types of persistent and longstanding AF. Patients were excluded if LA thrombus was detected on transthoracic echocardiography and transesophageal echocardiography, and second-session cases were excluded. Patients were also excluded if they could not receive sufficient examination by contrast-enhanced computed tomography (CT) because of contrast media allergy and if they were already using a respiration device, such as a continuous positive airway pressure oral appliance for the treatment of sleep-disordered breathing. Patients with a history of cardiac surgery were excluded from the study because atrial tachyarrhythmias related to surgical incisions or cannulation scars may have appeared. In addition, patients with atrial septal defect, patients with asthma or chronic obstructive pulmonary disease, and patients who could not undergo follow-up were excluded. Written informed consent to undergo catheter ablation for AF and contrast-enhanced CT was obtained from all patients.

2.2 | Study protocol

Contrast-enhanced CT, transthoracic echocardiography, and transesophageal echocardiography were performed before catheter ablation. The study protocol was approved by the hospital's institutional review board, and informed consent was obtained from all patients before participation in the study and before release of study data. The study flow chart and protocol are shown in Figure 1.

2.3 | Echocardiography

Transthoracic echocardiography provided two-dimensional echocardiographic images using standard parasternal and apical views of the atria and ventricles before ablation. The LA dimensions were measured in M-mode, and left ventricular ejection fraction (LVEF) was calculated using Simpson's method. Tissue Doppler imaging of the septal mitral annulus was recorded to measure early diastolic

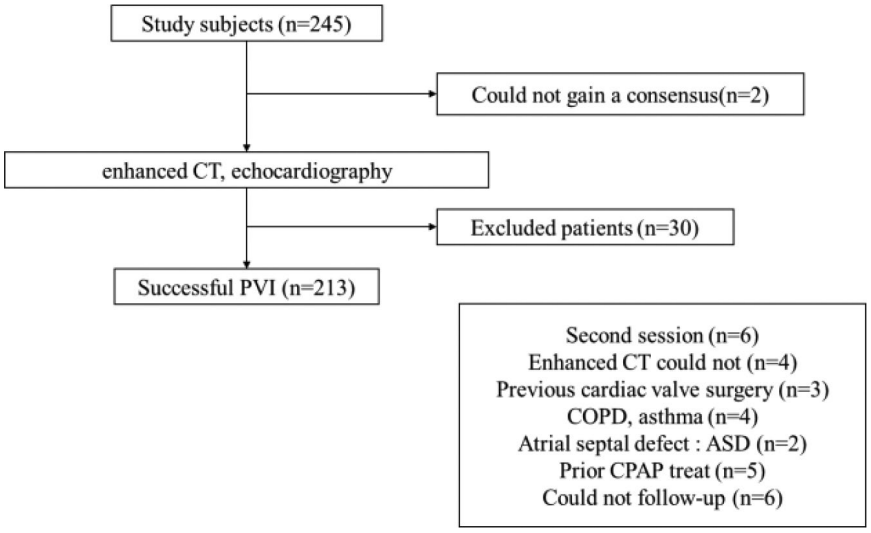

FIGURE 1 Flow diagram and study protocol. CT, computed tomography; PVI, pulmonary vein isolation; CPAP, continuous positive airway pressure

velocity (e′), and the ratio of early transmitral flow velocity to mitral annular velocity (E/e′) was calculated. According to the American Society of Echocardiography guidelines, tricuspid regurgitation is defined as none, mild, moderate, or severe. In this study, tricuspid regurgitation was scored according to a previous report as follows: none, 0; non-mild, 0.5; mild, 1; mild–moderate, 1.5; moderate, 2; moderate–severe, 2.5; and severe, 3.[11] Transesophageal echocardiography was performed only for non-paroxysmal AF to rule out intracardiac thrombi.

2.4 | Computed tomography

All patients underwent contrast-enhanced electrocardiogram-gated CT with an 80-slice multidetector CT scanner (Aquilion; Canon Medical Systems, Tochigi, Japan) before catheter ablation. CT data acquisition was performed by intravenous injection of 22.5 mgI/kg/s of a non-ionic contrast agent. Datasets were reconstructed using a retrospective electrocardiogram gating technique with a slice thickness of 0.5 mm and a section width of 0.5 mm, and image reconstruction was performed at 75% of the electrocardiogram R-to-R interval, corresponding to atrial end-diastole. The LA and RA volumes were calculated during atrial end-diastole using a semi-automated three-dimensional reconstruction technique. Multidetector CT parameters were assessed using visualization and analysis software (AZE Virtual Place; AZE, Tokyo, Japan). The atria and pulmonary veins were reconstructed and segmented using image integration software (EnSite Verismo, St. Jude Medical, Inc, St. Paul, MN, USA). In LA volume measurements, the LA appendage at its basal portion and pulmonary veins at their ostia were manually excluded. In the RA volume measurements, the inferior and superior vena cava at their ostia were manually excluded. In this study, we defined an atrial volume on CT of ≥110 mL as atrial structural remodeling based on receiver operating characteristic (ROC) analysis and previous reports.[12-16]

2.5 | Electroanatomic mapping

The NavX system (NavX with CFE software; St. Jude Medical, Inc) was used for catheter ablation. The three-dimensional bi-atrial geometry was created on the NavX system, and sequential contact mapping was performed using a 7-F decapolar circular catheter (Reflexion™ HD; St. Jude Medical, Inc). Voltage mapping was performed to investigate the relationship between structural remodeling and electrical remodeling. Mapping was performed during sinus rhythm. In patients with non-paroxysmal AF, voltage mapping was obtained during sinus rhythm after ablation. Mapping points were acquired to fill all color gaps on the voltage map using an electroanatomical mapping system. Each acquired point was classified according to the peak-to-peak electrogram as follows: healthy, >0.5 mV; diseased, 0.2-0.5 mV; and scarred, <0.1 mV. The low-voltage area was defined as sites of ≥3 adjacent to low-voltage points of <0.5 mV, as described previously.[17]

2.6 | Radiofrequency catheter ablation

PVI was guided by one 7-F decapolar circular catheter (Optima™; St. Jude Medical, Inc) positioned at the ostia of the ipsilateral pulmonary vein, and a three-dimensional CT reconstruction was integrated into the electroanatomical mapping system (EnSite NavX system, St. Jude Medical, Inc). We created bilateral circular lesions with wide-area circumferential ablation encircling the ipsilateral pulmonary vein, and each radiofrequency energy application was delivered for 30-60 s. A 3.5-mm irrigated tip radiofrequency catheter (FlexAbility™; St. Jude Medical, Inc) was used, with the temperature limited to 42°C and a power output of 25-35 W (with a flow rate of 13 mL/min). Biphasic direct current cardioversion restored sinus rhythm if AF did not terminate spontaneously after successful PVI. The end point of PVI was the creation of bidirectional conduction block between the LA and pulmonary veins.[18] After PVI, dormant pulmonary vein conduction was provoked by intravenous administration of adenosine triphosphate (10-20 mg). We determined whether AF was sustained or induced by burst atrial pacing from the coronary sinus at a cycle length of 250 ms with 20-ms decrements until atrial refractoriness. If a pulmonary vein reconnection was documented, any reconnected gaps were eliminated by additional radiofrequency applications. Cavo-tricuspid isthmus ablation was additionally performed in patients with ECG-documented or burst atrial pacing-induced typical atrial flutter. At the end of the procedure, all pulmonary veins were successfully isolated.

2.7 | Follow-up

All antiarrhythmic drugs before ablation were prescribed only if early recurrence of AF was observed prior to discharge. Antiarrhythmic drugs were discontinued 3 months after ablation (blanking period) if a patient had no recurrence of atrial tachyarrhythmia. All patients were followed up with a 12-lead electrocardiogram at each follow-up or emergency visit and 24-hour Holter monitoring. Arrhythmia recurrence was defined as any atrial tachyarrhythmia lasting more than 30 s documented by a 12-lead electrocardiogram or 24-hour Holter monitoring after a three-month blanking period from the ablation procedure.

2.8 | Statistical analysis

All group data are presented as mean ± SD or count (%). Continuous variables were analyzed by analysis of variance to compare differences among groups. Student's *t*-tests and Mann–Whitney *U*-tests were used to compare two groups depending on the data distribution. Proportional differences were evaluated using the chi-squared test. N-terminal pro–B-type natriuretic peptide (BNP) was non-normally distributed, so the log-transformed N-terminal pro-BNP levels were used as variables for regression analysis. The relationships between recurrence and various clinical parameters

were analyzed using simple regression analysis. A multivariate Cox proportional-hazards model, which included potential confounders based on clinical significance or a *P* value of <.1 in the simple linear regression analysis, was generated to identify significant predictors of arrhythmia recurrence. To compare the strength of the parameters to predict arrhythmia recurrence, the area under the ROC curve for each parameter was estimated. The Kaplan–Meier analysis and log-rank test were used to compare arrhythmia-free survival rates between the two groups, which were divided based on the optimal cutoff value according to our previous report[16] and the results of ROC analysis. A multivariate analysis using stepwise regression with backward elimination was performed to identify independent risk factors associated with RA volume. For comparison between groups with and without remodeling, an analysis of covariance was used to correct the effect of atrial volume. *P* values of <.05 were considered statistically significant. All analyses were performed using SPSS version 21.0 for Microsoft Windows (SPSS, Inc, Chicago, IL, USA).

3 | RESULTS

3.1 | Baseline characteristics

3.1.1 | Participants and descriptive data

The study flowchart and protocol are shown in Figure 1. We included 245 patients with symptomatic drug-refractory AF. Patients with second-session cases (n = 6) were excluded. Patients were also excluded if they could not undergo contrast-enhanced CT (n = 4) and if they were already using a respiration device for the treatment of sleep-disordered breathing (n = 5). Patients with a history of cardiac surgery (n = 3), patients with atrial septal defect (n = 2), patients with asthma or chronic obstructive pulmonary disease (n = 4), and patients who could not undergo follow-up (n = 6) were excluded. After excluding 32 patients, we finally enrolled 213 patients (Figure 1) who had undergone successful catheter ablation. During a mean follow-up period of 13.4 ± 3.8 months, atrial tachyarrhythmias recurred in 41 (19%) of 213 patients (23 paroxysmal AF, 14 non-paroxysmal AF, 4 paroxysmal atrial tachycardia, and 1 atrial flutter). The demographic characteristics of the study population are summarized in Table 1. Between the categorized arrhythmia recurrence groups (n = 41) and the group without arrhythmia recurrence (n = 172), no significant differences were observed in age, gender, body surface area, body mass index (BMI), $CHADS_2$ score, plasma creatinine, plasma N-terminal pro-BNP level, and LVEF; however, patients with arrhythmia recurrence had a significantly higher ratio of non-paroxysmal AF (*P* = .020), LAD (*P* = .004), TR grade (*P* = .044), LA volume (*P* < .001), and RA volume (*P* < .001) compared with the group without arrhythmia recurrence. In addition, fortunately with ablation, all cases returned to sinus rhythm, allowing us to obtain voltage mapping during sinus rhythm.

3.2 | Predictors of clinical outcomes after PVI

Simple linear regression analysis revealed that LAD, E/e′, TR, NT-pro-BNP, LA volume, RA volume, and LA low-voltage area were associated with recurrence in all the subjects. Furthermore, TR, LA volume, and RA volume were associated with recurrence in the paroxysmal and non-paroxysmal AF groups (Table 2). A multivariate Cox regression analysis indicated that RA volume (hazard ratio [HR] 1.011, 95% confidence interval [CI] 1.002-1.021, *P* = .019) was the only predictor of arrhythmia recurrence after ablation (Table 3). ROC curves were built to establish the values that represented the cutoff point of RA volume with the greatest sensitivity and specificity to predict arrhythmia recurrence. The cutoff value of RA volume was 111.5 mL with an area under the curve of 0.735 and a standard deviation of 0.041 (95% CI 0.654-0.816, *P* < .001), a sensitivity of 73.8%, and a specificity of 36.8% (Figure S1). In addition, similar results were obtained for RA volume index (hazard ratio [HR] 1.019, 95% CI 1.002-1.035, *P* = .024) and LA volume index (hazard ratio [HR] 1.015, 95% CI 0.989-1.042, *P* = .250) in the multivariate Cox regression analysis.

3.3 | Association of arrhythmia recurrence and RA structural remodeling

Based on RA volume, patients were classified into two groups: 116 patients (54%) without RA structural remodeling and 97 patients (46%) with RA structural remodeling (Table 4). There were no significant differences in age, BMI, $CHADS_2$ score, plasma creatinine, LVEF, and LA low-voltage area. However, significant differences were observed between sex (*P* < .001), body surface area (*P* = .002), LAD (*P* < .001), AF type (*P* < .001), N-terminal pro-BNP levels (*P* = .033), TR (*P* < .001), and LA volume (*P* < .001; Table 4). In patients with RA structural remodeling, paroxysmal AF was observed in 46 (47%) and non-paroxysmal AF was observed in 51 (53%), and no significant difference was found in the severity of RA structural remodeling depending on the AF (paroxysmal AF vs. non-paroxysmal AF, ie, 141.6 ± 39.0 mL vs. 150.5 ± 41.2 mL; *P* = .276). A Kaplan–Meier analysis and log-rank test showed a significant difference in recurrence-free survival between patients with RA structural remodeling compared with patients without remodeling (log-rank, *P* < .001), and the recurrence-free survival rates at 12 months were 68.0% and 91.4%, respectively (Figure 2).

3.4 | Proportion of atrial remodeling

Patients were also classified into four groups according to the atrial volume: no remodeling (n = 98 [46%]; paroxysmal AF = 82), LA remodeling (n = 14 [7%]; paroxysmal AF = 10), RA remodeling (n = 37 [17%]; paroxysmal AF = 24), and bi-atrial remodeling (n = 64 [30%]; paroxysmal AF = 26). In this study, the number

TABLE 1 Baseline characteristics of the study population shown by AF recurrence

Clinical parameter	Total (n = 213)	Recurrence (n = 41)	No Recurrence (n = 172)	*P* value
Age (yrs, mean ± SD)	64.7 ± 10.5	66.1 ± 11.7	64.4 ± 10.2	.349
Male (%)	167 (78)	35 (85)	132 (77)	.228
BMI (kg/m^2)	24.8 ± 5.3	24.7 ± 4.5	24.6 ± 4.5	.856
Body surface area (m^2)	1.75 ± 0.2	1.75 ± 0.20	1.76 ± 0.20	.820
Paroxysmal AF	142 (67)	21 (51)	121 (70)	.020
Hypertension	104 (49)	23 (57)	81 (47)	.860
Diabetes mellitus	38 (18)	6 (15)	32 (19)	.551
Heart failure	33 (15)	6 (15)	27 (16)	.866
Stroke/TIA	17 (8)	2 (5)	15 (9)	.415
$CHADS_2$ score	1.16 ± 1.02	1.19 ± 0.89	1.15 ± 1.06	.827
Medication				
β-blocker	116 (54)	26 (63)	90 (52)	.200
Amiodarone	11 (5)	1 (2)	10 (6)	.380
Bepridil	38 (18)	6 (15)	32 (19)	.551
Class I antiarrhythmic drugs	64 (30)	11 (27)	53 (31)	.617
LAD (mm)	40.6 ± 5.6	42.9 ± 5.9	40.0 ± 5.4	.004
LVEF (%)	61.1 ± 14.1	64.1 ± 17.9	60.4 ± 12.9	.146
TR	0.85 ± 0.59	1.08 ± 0.83	0.79 ± 0.49	.044
Creatinine (mg/dL)	0.92 ± 0.2	0.92 ± 0.21	0.92 ± 0.20	.942
N-terminal pro–BNP (pg/mL)	558 ± 754	631 ± 547	540 ± 797	.489
LA only volume (mL)	100 ± 33.0	127 ± 45.4	94 ± 25.4	<.001
RA only volume (mL)	111 ± 43.7	145 ± 62.4	103 ± 32.9	<.001

Note: Data are presented as mean ± SD or number (%) of subjects.

Abbreviations: BMI, body mass index; BNP, brain natriuretic peptide; LA, left atrial; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; Paf, paroxysmal atrial fibrillation; RA, right atrial; SDB, sleep-disordered breathing; TIA, transient ischemic attack; TR, tricuspid regurgitation.

of patients with LA structural remodeling was much lower than that of the other group, and a Kaplan–Meier analysis and log-rank test showed that the group with bi-atrial remodeling had the highest recurrence rate (log-rank, $P < .001$; Figure 3A). Although there was no significant difference in recurrence between the RA remodeling group and the LA remodeling group, the RA remodeling group had a significantly higher recurrence rate compared with the group without remodeling (log-rank, $P = .045$; Figure 3A).

3.5 | Analysis of recurrence by type of AF

We examined the involvement of RA structural remodeling in recurrence of each type of AF. In patients with non-paroxysmal AF, the RA remodeling group showed a significant difference in recurrence (log-rank, $P = .035$). In addition, RA structural remodeling was a significant predictor of recurrence in patients with paroxysmal AF (log-rank, $P < .001$; Figure 3B).

4 | DISCUSSION

4.1 | Main findings

In this study, RA structural remodeling was observed in 46% of the patients regardless of the AF type. The principal finding of this study is that a greater incidence of recurrence was observed in the presence of RA structural remodeling regardless of the AF type and that RA structural remodeling was an important predictor of recurrence after PVI. Although LA is known to play a key role in the pathophysiology of AF, our study suggests that bi-atrial, including RA, remodeling is involved in AF recurrence after PVI.

4.2 | Atrial structural remodeling in AF

It is believed that atrial structural remodeling, which includes atrial enlargement, cellular hypertrophy, dedifferentiation, fibrosis, apoptosis, and myolysis, is a main contributor to the initiation and

TABLE 2 Simple linear regression analysis correlation between recurrence and various clinical parameters

	All subjects (111)		Paroxysmal AF (66)		non-Paroxysmal AF (45)	
	r	*P* value	*r*	*P* value	*r*	*P* value
vs Age	.063	NS	.137	NS	−.034	NS
vs male	.083	NS	.067	NS	.050	NS
vs BMI	.014	NS	−.090	NS	.129	NS
vs Body surface area	−.016	NS	−.108	NS	.038	NS
vs $CAHD_2$	.017	NS	.098	NS	−.107	NS
vs LAD	.217	.002	.181	.040	.186	NS
vs LVEF	.113	NS	.169	NS	.092	NS
vs E/e′	.171	.024	.257	.005	.038	NS
vs MR	.108	NS	−.010	NS	.163	NS
vs TR	.208	.004	.044	NS	.288	.020
vs Creatinine	.005	NS	.004	NS	−.008	NS
vs NT pro-BNP	.163	.018	.157	.066	.011	NS
vs LA only volume	.402	<.001	.398	<.001	.342	.003
vs RA only volume	.396	<.001	.356	<.001	.383	.001
vs LA low-voltage area	.152	.028	.223	.008	.041	NS

Abbreviations: BMI, body mass index; BNP, brain natriuretic peptide; LA, left atrial; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; RA, right atrial; TR, tricuspid regurgitation.

TABLE 3 Multivariate Cox proportional-hazards analysis of the predictors of arrhythmia recurrence after PVI

Multivariate analyses of recurrence			
	Hazard ratio	95% CI	*P* value
LAD	1.019	0.923-1.124	.713
E/e′	1.063	0.994-1.137	.075
TR	1.648	0.921-2.948	.092
N-terminal pro–BNP	1.000	0.999-1.000	.305
LA volume	1.011	0.995-1.027	.168
RA volume	1.011	1.002-1.021	.019
LA low voltage area	1.793	0.690-4.661	.231

Abbreviations: BMI, body mass index; BNP, brain natriuretic peptide; LA, left atrial; LAD, left atrial diameter; PVI, pulmonary vein isolation; RA, right atrial; TR, tricuspid regurgitation.

persistence of AF. The relationship between atrial enlargement and AF has been established by numerous research studies.[19-21] However, these studies have mainly focused on the LA, and data regarding the structure and remodeling of the RA is rare. In this study, we defined an atrial volume on CT of ≥110 mL as atrial structural remodeling. To date, there have been few reports defining RA structural remodeling, and cutoff values were determined with reference to the data from the present study and previous reports. Fuchs et al reported normal cardiac chamber volumes assessed using 320-detector CT angiography and stated that the normal RA volume was 106 mL.[12] Keller et al measured LA volume by performing CT in healthy subjects and reported a mean LA volume of 67 mL (range, 25-110 mL).[13] Previous reports have identified a correlation between atrial volume on CT and AF recurrence after catheter ablation. These studies have shown that an LA volume >106 mL[14] and >117 mL[15] is highly predictive of AF recurrence following ablation. Based on these results, using an ROC curve cutoff value of 111.5 mL in this study, we defined an atrial volume on CT of ≥110 mL as atrial structural remodeling (Figure S1). To compare our data with those obtained using right atrial volume index as a parameter, the same analysis was conducted. Similar results were obtained for RA and LA volume indexes in the multivariate Cox regression analysis. On the ROC curve, the cutoff RA volume index was 66.9 mL/m^2, with area under the curve of 0.751, standard deviation of 0.042 (95% CI 0.668-0.834, $P < .001$), sensitivity of 73.2%, and specificity of 20.7%. Although there have been some reports on LA volume index, only few reports have indicated that RA volume index can be used as a reference; hence, this study was examined with reference to the atrial volume data reported so far.

TABLE 4 Baseline characteristics of the study population shown by RA remodeling

Clinical parameter	No remodeling (n = 116)	RA remodeling (n = 97)	*P* value
Age (yrs., mean ±SD)	65.2 ± 10.1	64.1 ± 11.0	.427
Male (%)	80 (69)	87 (90)	<.001
BMI (kg/m^2)	24.5 ± 5.9	25.1 ± 4.5	.512
Body surface area (m^2)	1.72 ± 0.19	1.80 ± 0.2	.002
Paroxysmal AF	96 (83)	46 (47)	<.001
Hypertension	56 (48)	48 (49)	.860
Diabetes mellitus	26 (22)	12 (12)	.057
Heart failure	17 (14)	16 (16)	.712
Stroke/TIA	12 (10)	5 (5)	.164
$CHADS_2$ score	1.28 ± 1.12	1.01 ± 0.87	.051
Medication			
β-blocker	59 (51)	57 (58)	.249
Amiodarone	7 (6)	4 (4)	.530
Bepridil	18 (16)	20 (21)	.333
Class I antiarrhythmic drugs	50 (43)	14 (14)	<.001
LAD (mm)	38.4 ± 5.0	42.8 ± 5.4	<.001
LVEF (%)	62.2 ± 12.1	59.9 ± 16.0	.247
TR	0.66 ± 0.37	1.06 ± 0.70	<.001
Cr (mg/dl)	0.9 ± 0.2	0.95 ± 0.19	.063
N-terminal pro-BNP (pg/ml)	457 ± 712	681 ± 790	.033
LA volume (mL)	84.4 ± 23.2	119.6 ± 32.8	<.001
RA volume (mL)	81.4 ± 23.2	146.3 ± 40.2	<.001
LA low voltage area (%)	1.1 ± 2.8	2.4 ± 6.3	.061

Note: Data are presented as mean ± SD or number (%) of subjects.
Abbreviations: BMI, body mass index; BNP, brain natriuretic peptide; LA, left atrial; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; RA, right atrial; TIA, transient ischemic attack; TR, tricuspid regurgitation.

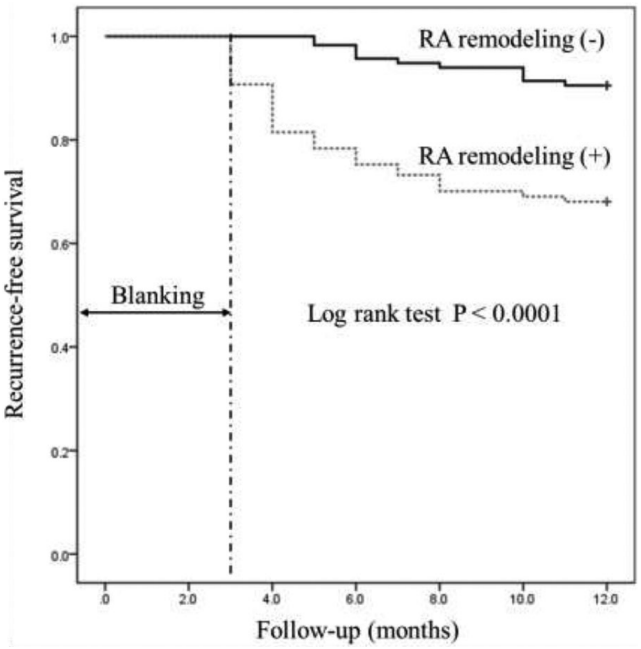

FIGURE 2 Kaplan–Meier analysis categorized using the cutoff value of the RA volume. The Kaplan–Meier curve shows a significant difference in the recurrence-free survival between patients with RA structural remodeling and patients without remodeling (log-rank, $P < .001$). RA, right atrial; LA, left atrial

4.3 | Effect of RA volume on clinical outcomes

Clinical data on the effect of RA size on the outcomes in patients with AF are limited. Luong[9] suggested that RA size and volume are predictors of AF recurrence after electrical cardioversion. Houltz et al reported that RA size and LV diastolic function may be important variables in the prediction of long-term rhythm outcomes after intraoperative ablation for AF.[22] Moon et al investigated the relationship between RA structural remodeling and the outcomes of AF after catheter ablation.[8] They found that RA structural remodeling determined by the RA volume index might affect early recurrence (ie, recurrence within the first 3 months after AF ablation), but it was not a determinant of the one-year success rate. Of note, patients were highly selected in Moon's study and those with severe LA enlargement were excluded before catheter ablation. Song et al investigated whether RA diameter measured by two-dimensional transthoracic echocardiography is a predictor of recurrence after PVI.[23] RA diameter predicts ablation outcomes only in patients with paroxysmal AF and concurrent LA enlargement. In recent years, Sasaki et al reported that the ratio of RA volume index to LA volume index is a risk factor for AF recurrence.[10] This previous study enrolled patients with only persistent AF. We examined recurrence after 12 months by measuring RA volume using CT in patients with paroxysmal AF and non-paroxysmal AF. Our study showed that RA structural remodeling may be a good predictor of arrhythmia recurrence at 12 months regardless of the AF type. In this study, AF recurrence was observed not only in the bi-atrial remodeling group but also in the RA remodeling group. RA structural remodeling is a predictor of AF recurrence in the groups with and without LA remodeling. Various pathologies that cause RA structural remodeling may be associated with AF recurrence, and further research is needed on the involvement of RA structural remodeling in AF recurrence. Many studies have shown an association between LA structural remodeling and AF recurrence.[24-26] The results of this study show that RA structural remodeling is the only predictor, but we thought that this result does not replace previous reports. RA structural remodeling may not directly affect pulmonary vein (PV) reconnection but may represent the progress of LA remodeling. Prabhu et al showed a correlation between LA and RA remodeling and that RA mapping studies provide useful insights

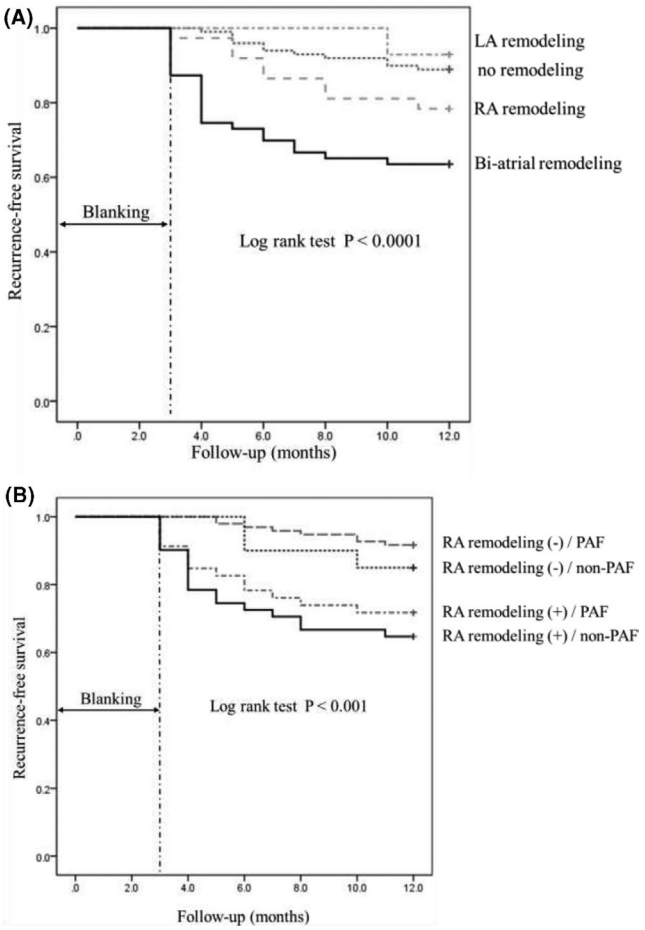

FIGURE 3 (A) Kaplan–Meier analysis divided into four groups based on the atrial volume. Kaplan–Meier curves show that the bi-atrial group had the highest recurrence rate (log-rank, $P < .001$). The RA remodeling group demonstrated significant recurrence compared with the group without remodeling ($P = .045$). RA, right atrial; LA, left atrial. (B) Kaplan–Meier analysis classified by the RA volume for each AF type (log-rank, $P < .001$). A significant difference in the recurrence-free survival was observed in the RA structural remodeling group in each patient with paroxysmal AF (log-rank, $P < .001$) and non-paroxysmal AF (log-rank, $P = .035$). RA, right atrial; LA, left atrial; PAF, paroxysmal AF

into the pathophysiological processes occurring in the LA.[27] Mutlak et al reported that the load on the RA is determined mainly by risk factors resulting from increased left-sided filling pressures (pulmonary hypertension, AF, and LA enlargement) and by age. Load on the RA is accompanied by a marked parallel increase in the associated left-sided cardiac comorbidities.[28] In addition, RA pressure has been reported to increase with the progression of AF, such as increased AF burden and sustained AF, which is thought to promote bi-atrial and LA remodeling in AF.[29,30] In this study, LA volume was significantly increased in the group with recurrence in both the paroxysmal and non-paroxysmal AFs as compared with the group without recurrence (paroxysmal AF: 87.0 ± 23.1 mL vs 119.8 ± 43.8 mL, $P = .003$; non-paroxysmal AF: 110.5 ± 23.0 mL vs 135.7 ± 47.1 mL, $P = .032$). The multivariate regression analysis revealed that LA volume and LA low-voltage area were independent predictors of increased RA volume (LA volume: $\beta = 0.629$, $P < .001$; LA low-voltage area: $\beta = 0.144$, $P = .020$). RA remodeling is considered to represent the progression of LA remodeling by AF, which may have caused more recurrences in the bi-atrial remodeling group. In addition, the impact of sleep apnea on recurrence may be considered in only the RA remodeling group without LA remodeling. We previously reported a correlation between RA structural remodeling and sleep apnea and showed that RA structural remodeling correlated with the severity of sleep apnea regardless of the AF type.[16] Importantly, previous studies have found that sleep apnea was a predictor of failure of rhythm control strategies, such as AF ablation.[31] RA structural remodeling indicates a potential coexistence of sleep apnea, and it is thought that AF recurrence after PVI can be predicted. In addition, a previous study reported that non-PV foci from the RA are involved in maintaining AF,[32] and it cannot be denied that non-PV foci may affect AF recurrence. We examined the second-session cases excluded in this study and the cases of re-ablation due to AF recurrence during the period. Most of the AF recurrences were PV reconnection, and no association was found between RA structural remodeling and non-PV foci, including a low-voltage area. Moreover only two cases of RA low-voltage area were presented, wherein there was no correlation between the RA low-voltage area and the other parameters in this study. RA structural remodeling is caused not only by LA structural remodeling but also by different mechanisms that are thought to be significantly involved in the onset and recurrence of AF, such as sleep apnea. Therefore, RA structural remodeling might have been a stronger predictor of recurrence in this study. The results may help better predict AF recurrence by adding RA structural remodeling to the previously reported association between LA structural remodeling and recurrence. Although we cannot provide a definite conclusion in this study, it may be clinically significant that RA structural remodeling is a predictor of AF recurrence.

4.4 | Study limitations

This study has some limitations. First, the evaluation method for RA volume was not completely established. There have been few reports on RA structural remodeling, and there are several ways to define RA structural remodeling. Second, the data was obtained from a single center and a small sample was enrolled with a short follow-up duration. To confirm our findings, further evaluation is required in a multicenter prospective study with a larger sample size and assessment of long-term clinical outcomes. Third, arrhythmia recurrence was determined by 12-lead electrocardiogram or 24-hour Holter monitoring, but not multiday event monitoring. This method of follow-up might underestimate arrhythmia recurrence after ablation. Finally, the type of recurrent arrhythmia and mode of reconnection in RA remodeling could not be fully investigated. Most of the recurrences were paroxysmal AF cases (56%), but no significant correlation was found between RA remodeling and the type of recurrent arrhythmia. For AF recurrence, PV reconnection was recognized in most cases, and the relationship between RA remodeling

and non-PV foci or substrate was not clarified in this study; hence, further research is necessary in the future. Despite these limitations, our results provide important new insights to better understand the prognostic impact of the RA in patients with AF.

5 | CONCLUSIONS

Right atrial structural remodeling predicts recurrence of AF after PVI irrespective of AF classification. Our results show that RA structural remodeling is strongly associated with outcomes after ablation for AF.

CONFLICTS OF INTEREST

The authors have no conflict of interests to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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