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ORIGINAL RESEARCH

Clinical Characteristics and Rhythm Outcomes in Patients With Atrial Myopathy After Successful Catheter Ablation of Atrial Fibrillation

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BACKGROUND: Although successful atrial fibrillation (AF) ablation can maintain sinus rhythm and reduce the left atrial (LA) dimension, blunted LA reverse remodeling can be observed in patients with atrial myopathy. We explored the potential mechanisms and long-term outcomes in patients with blunted LA reverse remodeling after successful AF catheter ablation.

METHODS AND RESULTS: We included 1685 patients who underwent baseline and 1-year follow-up echocardiograms, had a baseline LA dimension ≥40 mm, and did not have a recurrence of AF within a year. The patients were divided into tertile groups according to the delta value of the change in LA dimension on the preprocedure and 1-year postprocedure echocardiography. After propensity score matching for age, sex, AF type, and LA dimension, 1272 patients were finally included in the analyses (424 in each group; the least/blunted, moderate, and the most reverse remodeling group). The patients in the T1 group (blunted LA reverse remodeling) were independently associated with higher left ventricular mass index (odds ratio [OR], 1.014 [95% CI, 1.005–1.022], P=0.001), change in ΔH_2FPEF score (heavy, hypertensive, atrial fibrillation, pulmonary hypertension, elder, filling pressure) score (OR, 1.445 [95% CI, 1.121–1.861], P=0.004), ventricular epicardial adipose tissue volume (OR, 1.010 [95% CI, 1.003–1.017], P=0.003), thinner LA wall thickness (OR, 0.461 [95% CI, 0.271–0.785], P=0.004), lower LA voltage (OR, 0.670 [95% CI, 0.499–0.899], P=0.008), and showed higher long-term AF recurrence (log-rank P<0.001) than other groups.

CONCLUSIONS: Blunted LA reverse remodeling after AF catheter ablation, which is suggestive of atrial myopathy, was independently associated with a larger ventricular epicardial adipose tissue volume and worsening of H_2FPEF score. Blunted LA reverse remodeling after AF catheter ablation was also an independent predictor for higher recurrences of AF post-1-year AF catheter ablation.

Key Words: atrial fibrillation ■ atrial myopathy ■ atrial reverse remodeling ■ catheter ablation ■ epicardial adipose tissue

Atrial fibrillation (AF) is a chronic progressive disease with atrial structural remodeling.[1] Aging, inflammation, atrial stretch caused by hemodynamic stress, and fibrosis are mechanisms of the structural atrial remodeling process that can result in atrial myopathy.[2] Sustained AF may exacerbate atrial myopathy, which in turn may perpetuate AF, thus constituting a vicious cycle that promotes AF maintenance and progression.[3] The European Heart Rhythm Association, Heart Rhythm Society, Asian Pacific Heart Rhythm Society, and Sociedad Latino Americana de Estimulacion Cardiaca y Electrofisiologia expert

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CLINICAL PERSPECTIVE

What Is New?

- The least (blunted) atrial reverse remodeling 1 year after atrial fibrillation catheter ablation, which is a potential atrial myopathy, is associated with larger ventricular epicardial adipose tissue volume and worsened diastolic function.
- The atrial fibrillation recurrence rate 1 year after the procedure was significantly higher in the group of patients with blunted atrial reverse remodeling and potential for worsening atrial myopathy than in their counterparts.

What Are the Clinical Implications?

- Among the patients who remained in sinus rhythm 1 year after the atrial fibrillation ablation procedure, 1-year left atrium reverse remodeling can be used as an index of atrial myopathy or a prognostic factor for long-term atrial fibrillation rhythm outcome.
- Strict rhythm control with appropriate anticoagulation is essential in patients with potential atrial myopathy, especially with large ventricular epicardial adipose tissue volume and diastolic dysfunction.

Nonstandard Abbreviations and Acronyms

AFCA	atrial fibrillation catheter ablation
EAT	epicardial adipose tissue
PV	pulmonary vein

consensus defined atrial myopathy as "any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations."[4] Some studies have reported that atrial fibrosis reflected atrial myopathy can be measured by late gadolinium enhancement on cardiac magnetic resonance imaging in patients with AF.[5–7] However, there are no clear clinical diagnostic criteria. Significant atrial myopathy causes atrial hemodynamic stasis, endocardial dysfunction, and hypercoagulable state,[8] satisfying the perfect conditions for a thromboembolic risk.

The left ventricle (LV) and left atrium (LA) have a hemodynamic linkage because they are in pressure equilibrium during the diastolic period. There is growing evidence for the association between LV diastolic function and LA remodeling or atrial myopathy, and between epicardial adipose tissue (EAT) and heart failure with preserved ejection fraction.[9,10] Previous studies have revealed the association between LA EAT and LA volume based on cardiac magnetic resonance imaging in patients with AF.[11] However, there was no clear proof for the associations among atrial myopathy, LV diastolic function, and EAT volume.

This study aimed to explore the characteristics of atrial myopathy and independent predictors in patients with blunted LA reverse remodeling 1 year after AF catheter ablation (AFCA) despite the absence of an AF recurrence. In addition, we also evaluated the long-term rhythm outcomes in patients with atrial myopathy.

METHODS

Raw data are available upon reasonable request to the corresponding author.

Study Population

The study protocol adhered to the principles of the Declaration of Helsinki and was approved by the institutional review board of the Yonsei University Health System. All patients provided written informed consent for inclusion in the Yonsei AF Ablation Cohort Database (ClinicalTrials.gov Identifier: NCT02138695). Among the 2756 patients who underwent AFCA in the Yonsei AF Ablation Cohort from September 2009 to August 2021, 1685 patients who had both baseline and 1-year follow-up echocardiograms and had a baseline LA dimension ≥40 mm, with no recurrence of AF during the 1-year follow-up period (327 patients) and therefore expected sufficient reverse remodeling of the LA, were enrolled in the study.[12] The patients were divided into tertile groups (LA reverse remodeling T1, T2, and T3) based on a 1-year percent change in the LA dimension. After a 1:1:1 propensity score matching for the age, sex, AF type, and LA dimension, 424 patients in each group (total of 1272 patients) were compared (Figure 1). The LA reverse remodeling (T1 group (the least/blunted reverse remodeling group) comprised patients with the smallest percent change decrease or increase in LA dimension between baseline and 1-year follow-up, which may represent a group of patients with potential atrial myopathy. Meanwhile, the LA reverse remodeling T3 group (modest reverse remodeling group) included patients with the largest percent change decrease in LA dimension within 1 year. The average percentage of LA dimension for each LA reverse remodeling group was 2.64±6.8 (T1), −8.1±2.4 (T2), and −18.0±5.3 (T3). The exclusion criteria in this study were as follows: (1) recurrence within 1 year after AFCA, (2) permanent AF refractory to electrical cardioversion, (3) AF with rheumatic valvular disease, and (4) a lack of transthoracic echocardiography data at baseline or 1 year later.

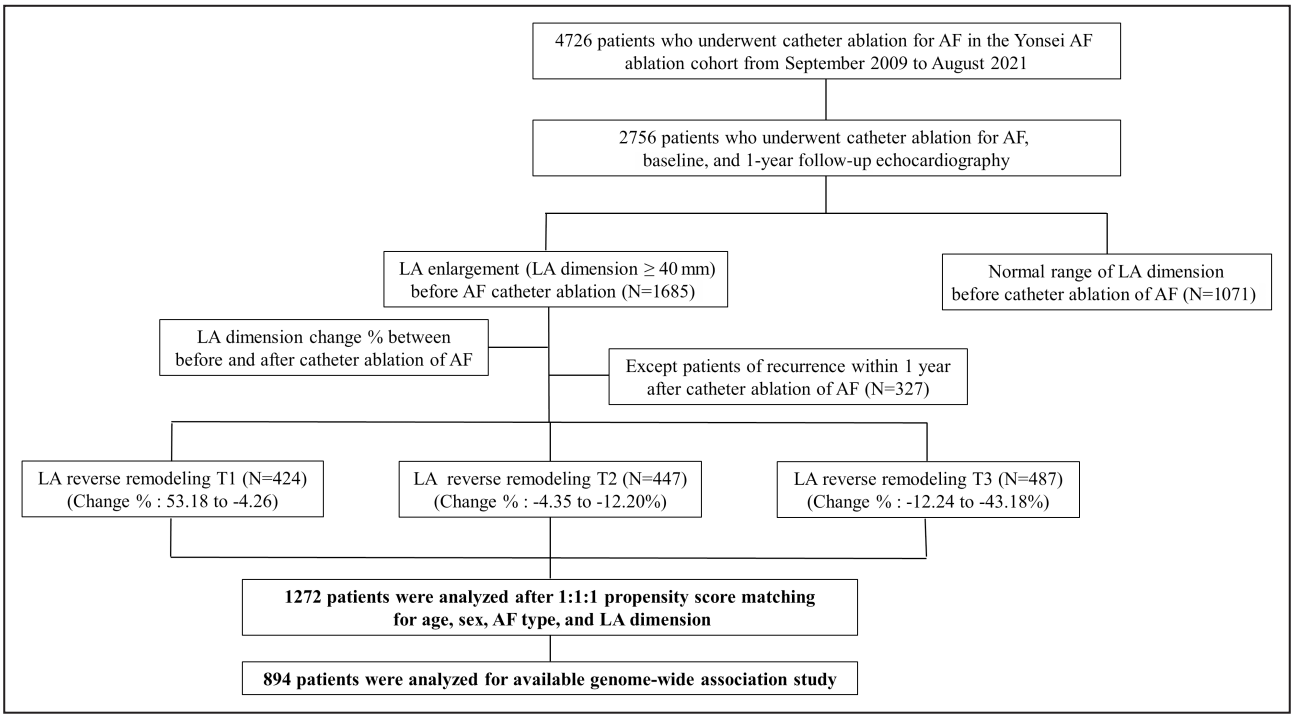

Figure 1. Study flow chart of patient enrollment.
AF indicates atrial fibrillation; and LA, left atrium.

H_2FPEF Score at Baseline and 1 Year After Catheter Ablation of Atrial Fibrillation

The heavy, hypertensive, atrial fibrillation, pulmonary hypertension, elder, filling pressure (H_2FPEF) score consists of 6 domains based on clinical and echocardiographic values: obesity (body mass index >30 kg/m^2, score 2), hypertension (use of 2 or more antihypertensive drugs, score 1), AF (paroxysmal or persistent, score 3), pulmonary hypertension (Doppler echocardiographic estimated pulmonary arterial systolic pressure >35 mm Hg, 1 point), being elderly (>60 years, 1 point), and the filling pressure (Doppler echocardiography E/Em>9, 1 point).[13] Baseline H_2FPEF scores were obtained within 3 months before the AFCA, and the 1-year H_2FPEF scores were obtained with all clinical and echocardiographic values 1 year after the AFCA.

Echocardiographic and Cardiac Computed Tomographic Evaluations

All patients underwent transthoracic echocardiography at baseline and at the 1-year follow-up. The LA dimension by M-mode measurements, left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular mass index, peak transmitral flow velocity (E), and peak septal mitral annular velocity (Em) on tissue Doppler echocardiography were measured in accordance with the American Society of Echocardiography guidelines.[14] Three-dimensional (3D) spiral computed tomography (CT) scans (64 Channel, Light Speed Volume CT, Philips, Brilliance 63; Amsterdam, the Netherlands) were performed to define the pulmonary vein (PV) anatomy and to analyze the LA using an image processing workstation (Aquarius; TeraRecon, Inc., Foster City, CA). The echo and CT measures in our study had acceptable inter- and intraobserver variabilities, as reported in previous studies.[15,16] Furthermore, our registry data containing details of more than 5000 patients who underwent AF catheter ablation showed a robust linear correlation between transthoracic echocardiography-measured LA size and CT-measured LA size (Figure S1).

LA Pressure, LA Wall Thickness, and LA Wall Stress Measurements

Intracardiac electrograms and hemodynamic measurements were recorded using a Prucka Cardio Lab electrophysiology system. A transseptal puncture approach was used for catheter access to the LA. The LA pressure was measured during sinus rhythm after a transseptal puncture using a 6-F pigtail catheter inserted into the LA through a long sheath (Schwartz left 1; St. Jude Medical, Inc.). When the initial rhythm was AF, we measured the LA pressure during sinus rhythm after terminating the AF via internal cardioversion (5–20 J biphasic shocks, Lifepak12; Physiocontrol, Ltd., Redmond, WA), followed by a 3-minute waiting period to allow for recovery from atrial stunning from the

cardioversion.[17] We analyzed the peak LA pressure (LA pressure peak; v wave), LA nadir pressure (LA pressure nadir; x wave), and LA mean pressure (LA pressure mean). Those parameters have been defined and calculated in a previous study.[18]

We developed customized software (AMBER, Laonmed Inc., Seoul, Republic of Korea) that measured the LA wall (LAW) thickness by applying Laplace's equation to the cardiac CT images.[19–22] The myocardial wall thickness calculation consists of 3 steps. In the first step, the threshold for each tissue automatically calculated on the histogram of the cardiac CT, and the investigator draws the guidelines for the basis of the myocardial wall extraction semiautomatically. The second stage extracted the myocardial wall region, and the third stage solved the Laplace equation to calculate a myocardial wall thickness. AMBER 3D-cardiac thickness map measured by cardiac CT images was verified and its feasibility was tested for radiofrequency energy titration during clinical catheter ablation.[19] Thereafter, the mean LAW thickness was used as a parameter to calculate the LAW stress. The LAW-stress (dyn/cm^2) was calculated using Laplace's law (s=[P×r]/2 h [s, wall stress; P, pressure; r, radius; h, wall thickness]).[23,24] The peak LA pressure during sinus rhythm was measured, and the LA radius was defined as half of the LA anteroposterior diameter on transthoracic echocardiography. Thus, the LAW-stress was calculated using the following equation: LAW-stress=(peak LA pressure×LA anteroposterior diameter)/(4×LAW thickness). It was expressed as dyn/cm^2 (1 mm Hg=1333 dyn/cm^2).

Electrophysiological Mapping and Radiofrequency Catheter Ablation

Three-dimensional electroanatomical mapping (NavX; St. Jude Medical, Inc., Minnetonka, MN) was performed using a circumferential PV mapping catheter (Lasso; Biosense-Webster Inc., Diamond Bar, CA) through a long sheath (Schwartz left 1; St. Jude Medical, Inc.). The 3D geometry of both the LA and PV was merged using the NavX system and then generated using 3D spiral CT images. LA voltage maps were generated during high right atrial pacing at 500 ms to prevent rate-dependent activation changes after maintaining sinus rhythm by a circumferential PV isolation with or without cardioversion. We obtained the peak-to-peak amplitude of the contact bipolar electrograms from 350 to 500 points on the LA endocardium, and the mean LA electrogram voltage was calculated.

An open-irrigated tip catheter was used for the AFCA. All patients underwent a de novo procedure involving a circumferential PV isolation. Most patients (92.3%) received a cavotricuspid isthmus block line during the procedure unless there was atrioventricular conduction disease. We conducted additional linear ablation, including a roof line, posterior inferior line, and anterior line, especially in patients with persistent AF. The procedure ended when there was no immediate recurrence of AF within 10 minutes of the cardioversion with an isoproterenol infusion (5–20 μg/min).

Postablation Management and Follow-Up

The patients were instructed to visit the outpatient clinic at 1, 3, 6, and 12 months and then every 6 months thereafter or whenever symptoms occurred after the AFCA. Electrocardiography was performed at each visit. Twenty-four-hour Holter monitoring was performed at 3, 6, and 12 months and every 6 months thereafter according to the 2012 Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society expert consensus statement guidelines.[25] Patients who experienced symptoms of palpitations underwent Holter/event-monitor examinations to investigate the possibility of an arrhythmia recurrence. AF recurrence was defined as any episode of atrial tachycardia or AF lasting >30 s. All electrocardiographic documentation of AF recurrences after a 3-month blanking period was classified as a clinical recurrence. We defined patients with progression to permanent AF as those patients who remained in a sustained AF/atrial tachycardia rhythm at the final follow-up date despite a repeat ablation, antiarrhythmic drugs, or electrical cardioversion.

Statistical Analysis

Continuous variables were expressed as the mean±SD and compared using an ANOVA. Categorical variables were reported as counts (percentages) and compared using the chi-square or Fisher's exact test. A logistic regression analysis was used to investigate the variables related to blunted LA reverse remodeling. Variables with P values <0.05 in the univariate analysis were selected for the multivariate analysis. A multivariate analysis was performed by dividing several models when variables with many missing values were included. A Kaplan–Meier analysis with a log-rank test was used to analyze the probability of the freedom from an AF/atrial tachycardia recurrence after AFCA. Statistical significance was set at a P<0.05. Propensity scores were estimated using a nonparsimonious multiple logistic regression model twice for the T1, T2 and T1, T3 groups. The following variables were considered: age, sex, AF type, and baseline echocardiographic LA diameter. Patients were then matched, without replacement, with the T1 group based on the closest possible propensity score (nearest neighbor matching). A matching caliper of 0.01 SDs of the logit of the estimated propensity score was enforced in order to ensure that matches of poor fit were excluded.[26,27] The matching

procedure was performed using R packages, including MatchIt and RItools. The Statistical Package for the Social Sciences version 25.0 for Windows (IBM Corp., Armonk, NY) and R software version 3.6.2 (The R Foundation for Statistical Computing, Vienna, Austria) were used for the data analysis.

RESULTS

Patient Characteristics With Blunted LA Reverse Remodeling

Among 1685 patients overall, we divided 1272 patients after propensity score matching for the age, sex, AF type, and baseline LA dimension into 3 groups depending on the tertile analysis for a 1-year percent change in the LA dimension. The baseline clinical characteristics of the study population before and after the propensity score matching are listed in Table 1. The standardized mean difference before and after matching are presented in Table S1. Patients with blunted LA reverse remodeling (n=424, T1 group), which reflected a potential atrial myopathy, had a greater body mass index (*P*<0.001), higher ΔH_2FPEF $score_{1\text{-}yr}$ (*P*<0.001), LA peak pressure (*P*=0.006), and EAT volume (*P*<0.001), lower LA voltage (*P*<0.001), and LA wall thickness (*P*=0.001) than those in the T2 or T3 groups (Table 1).

Figure 2 compares the representative examples of a patient with blunted LA reverse remodeling (T1 group) and a patient with significant LA reverse remodeling (T3 group) 1 year after AFCA. The T1 group (Figure 2A) shows an increase in H_2FPEF score, higher E/Em at 1-year follow-up, larger ventricular EAT volume, and lower mean LA voltage than the T3 group (Figure 2B). When comparing the prestudy and 1-year follow-up echocardiographic findings, the LA dimension (*P*<0.001), left ventricular end-diastolic diameter (*P*<0.001), E/Em (*P*<0.001), and right ventricular systolic pressure (*P*<0.001) increased in the T1 group as compared with that in the T2 and T3 groups (Table 2).

Associations Among Atrial Myopathy, Diastolic Function, and Ventricular Epicardial Adipose Tissue

The body mass index (odds ratio [OR], 1.089 [95% CI, 1.023–1.159], *P*=0.007), LV mass index (OR, 1.014 [95% CI, 1.006–1.022], *P*=0.001), LA wall thickness (OR, 0.469 [95% CI, 0.275–0.798], *P*=0.005), and LA voltage (OR, 0.674 [95% CI, 0.502–0.904], *P*=0.009) were associated with blunted LA reverse remodeling (T1) when compared with the other groups (T2 and T3). ΔH_2FPEF $score_{1\text{-}yr}$ (OR, 1.547 [95% CI, 1.182–2.024], *P*=0.001) and ventricular EAT volume/body surface area (OR, 1.019 [95% CI, 1.006–1.032], *P*=0.003) were also associated with the T1 group (Table 3). Additional regression models for the data before propensity score matching (Table S2) increased ΔH_2FPEF $score_{1\text{-}yr}$ (Table S3) and high EAT volume (Table S4), exhibited in the Supplementary materials.

Long-Term Outcome 1 Year After the Procedure in Patients With Blunted LA Reverse Remodeling

Throughout the 65.9±37.4 months of follow-up, the incidence of an AF recurrence 1 year after the procedure was significantly higher in the patients with blunted LA reverse remodeling (T1 group) than in the T2 or T3 groups (log-rank *P*<0.001, Figure 3A). That finding was consistent after including all patients who had recurrent AF within a year (log-rank *P*<0.001, Figure 3B). Patients who progressed to permanent AF (sustained AF under antiarrhythmic drug, cardioversion, or repeat ablation) were independently associated with blunted LA reverse remodeling (T1 group, OR, 2.205 [95% CI, 1.078–4.510], *P*=0.030) and low LA voltage (OR, 0.305 [95% CI, 0.147–0.633], *P*=0.001) and atrial EAT volume (OR, 1.032 [95% CI, 1.015–1.049], *P*<0.001; Table 4). There was no difference between the 3 groups in the incidence of stroke (*P*=0.344) or intracranial hemorrhage (*P*=0.555) after AF catheter ablation (Table S5).

DISCUSSION

Main Findings

The current study investigated the characteristics and long-term outcomes of patients with AF who had blunted atrial reverse remodeling without an AF recurrence within a year after the AFCA. We found that blunted atrial reverse remodeling after the AFCA was independently associated with ventricular EAT volume, ΔH_2FPEF $score_{1\text{-}yr}$, body mass index, LV mass index, thin atrial wall thickness, and low LA voltage. The AF recurrence rate 1 year after the procedure was significantly higher in the group of patients with blunted atrial reverse remodeling and potentially advanced atrial myopathy than in their counterparts.

Atrial Myopathy and AF

After Zipes et al[28] proposed the concept of atrial cardiomyopathy in 1997, it was considered a common pathological feature of AF. However, the exact pathophysiology and diagnostic criteria of atrial myopathy remain unclear.[2,4] EAT, a source of adipokines, inflammatory cytokines, and free fatty acids, also contributes to fibrotic remodeling and atrial myopathy.[29] Therefore, ever-worsening atrial myopathy increases the risk of sustained AF, which further aggravates the atrial myopathy forming a vicious cycle that increases the risk of AF progression. On the other hand, maintenance

Table 1. Baseline Characteristics of the Study Population After PSM

Variables	Overall (N=1685) before PSM	Overall (N=1272) after PSM	After PSM (N=1272)			*P* value
			LA reverse remodeling T1 (N=424)	LA reverse remodeling T2 (N=424)	LA reverse remodeling T3 (N=424)	
Clinical variables						
Age, y	60.2±10.1	60.7±10.1	60.7±10.0	60.4±10.1	60.9±10.1	0.724
Paroxysmal atrial fibrillation, %	918 (54.5)	758 (59.6)	251 (59.2)	258 (60.8)	247 (58.3)	0.738
Male sex, %	1260 (74.8)	934 (73.4)	296 (69.8)	319 (75.2)	320 (75.5)	0.107
Body mass index, kg/m^2	25.5±3.2	25.5±3.1	25.9±3.4	25.5±2.9	25.1±3.1	<0.001
CHA_2DS_2VASc score	1.9±1.5	2.0±1.6	2.1±1.6	1.9±1.6	1.9±1.6	0.013
Baseline H_2FPEF score	4.8±1.2	4.9±1.2	5.0±1.3	4.8±1.2	4.8±1.2	0.114
1-y H_2FPEF score	4.8±1.2	4.8±1.2	5.1±1.3	4.8±1.2	4.7±1.1	<0.001
Delta H_2FPEF score	0.0±0.7	0.0±0.7	0.1±0.7	0.0±0.6	−0.1±0.7	<0.001
Diabetes, %	282 (16.7)	218 (17.1)	80 (18.9)	73 (17.2)	64 (15.1)	0.342
Hypertension, %	888 (52.7)	672 (52.8)	244 (57.5)	224 (52.8)	203 (47.9)	0.019
Stroke, %	210 (12.5)	160 (12.6)	58 (13.7)	47 (11.1)	55 (13.0)	0.500
Vascular disease, %	231 (13.7)	181 (14.2)	67 (15.8)	54 (12.7)	60 (14.2)	0.441
Transthoracic echocardiography						
LA dimension, mm	45.4±4.4	44.8±3.9	44.6±4.0	44.7±3.8	45.1±3.9	0.050
LA volume index, mL/m^2	43.0±13.5	41.9±12.7	42.9±13.6	41.2±12.5	41.6±12.0	0.158
Left ventricular end-diastolic diameter, mm	51.0±4.7	50.7±4.4	50.9±4.3	50.6±4.0	50.7±4.9	0.589
Left ventricular ejection fraction, %	62.0±9.2	62.5±8.7	62.3±8.7	63.1±7.9	62.1±9.5	0.725
Ratio of the early diastolic mitral inflow velocity to the early diastolic mitral annular velocity	11.2±4.9	11.2±4.8	11.6±4.9	10.8±4.6	11.2±4.9	0.269
Right ventricular systolic pressure, mmHg	27.8±7.4	27.8±7.4	28.0±8.0	27.9±7.3	27.6±7.0	0.479
Left ventricular mass index, g/m^2	99.1±22.9	98.2±22.4	101.2±22.6	96.8±20.5	96.8±24.0	0.008
LA related parameter						
LA pressure, peak, mmHg	23.8±10.3	23.7±10.3	25.0±10.7	23.6±10.5	22.5±9.6	0.001
LA wall thickness	1.9±0.3	1.9±0.3	1.8±0.3	1.9±0.3	1.9±0.3	<0.001
LA voltage	1.3±0.7	1.3±0.7	1.2±0.7	1.4±0.7	1.4±0.7	0.001
LA wall stress	195.7±107.2	192.1±101.8	209.2±107.8	185.9±99.2	181.7±96.4	<0.001
Three-dimensional computed tomography						
LA volume/body surface area, mL/m^2	92.8±30.0	91.5±29.4	96.9±37.6	88.7±24.6	89.0±23.0	<0.001
EAT, mL	124.2±56.1	122.9±56.1	132.7±53.4	122.9±56.4	113.1±56.8	<0.001
Atrial EAT, mL	47.7±20.5	47.2±20.3	48.5±20.7	46.6±21.0	44.0±21.3	0.007
Ventricular EAT, mL	71.6±28.5	71.2±28.3	76.2±27.1	71.3±28.8	65.6±28.5	<0.001
Catheter ablation						
Ablation time, min	75.0±32.8	73.7±31.5	73.5±33.2	71.7±29.2	76.2±31.9	0.219
Fluoroscopic time, min	38.0±16.4	36.9±15.2	37.5±15.8	36.4±15.4	37.0±14.1	0.681
Procedure time, min	177.1±57.2	174.2±55.5	172.9±58.1	172.6±52.0	177.4±56.1	0.232

EAT indicates epicardial adipose tissue; H_2FPEF, heavy, hypertensive, atrial fibrillation, pulmonary hypertension, elder, filling pressure; LA, left atrium; and PSM, propensity score matching.

of sinus rhythm by catheter ablation seems to prevent and ameliorate the progression of atrial myopathy. Our study showed a significant reduction in LA dimension, especially in the T2 and T3 groups, which is similar to that reported in other studies.[30] Changes in the LA volume index were compared between ablation group and drug therapy group in the CABANA (Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation) imaging study, and the LA volume index decreased by 7.8 mL/m^2 in the catheter ablation group, which was similar to the results in our study (LA volume index decreased by 7.7 mL/m^2 in the T2 group and 12.5 mL/m^2 in the T3 group). Another study[31] showed that the LA dimension decreased from 44.0±5.8 to 40±4.5 mm in the group in whom sinus rhythm was maintained after catheter ablation, which was also

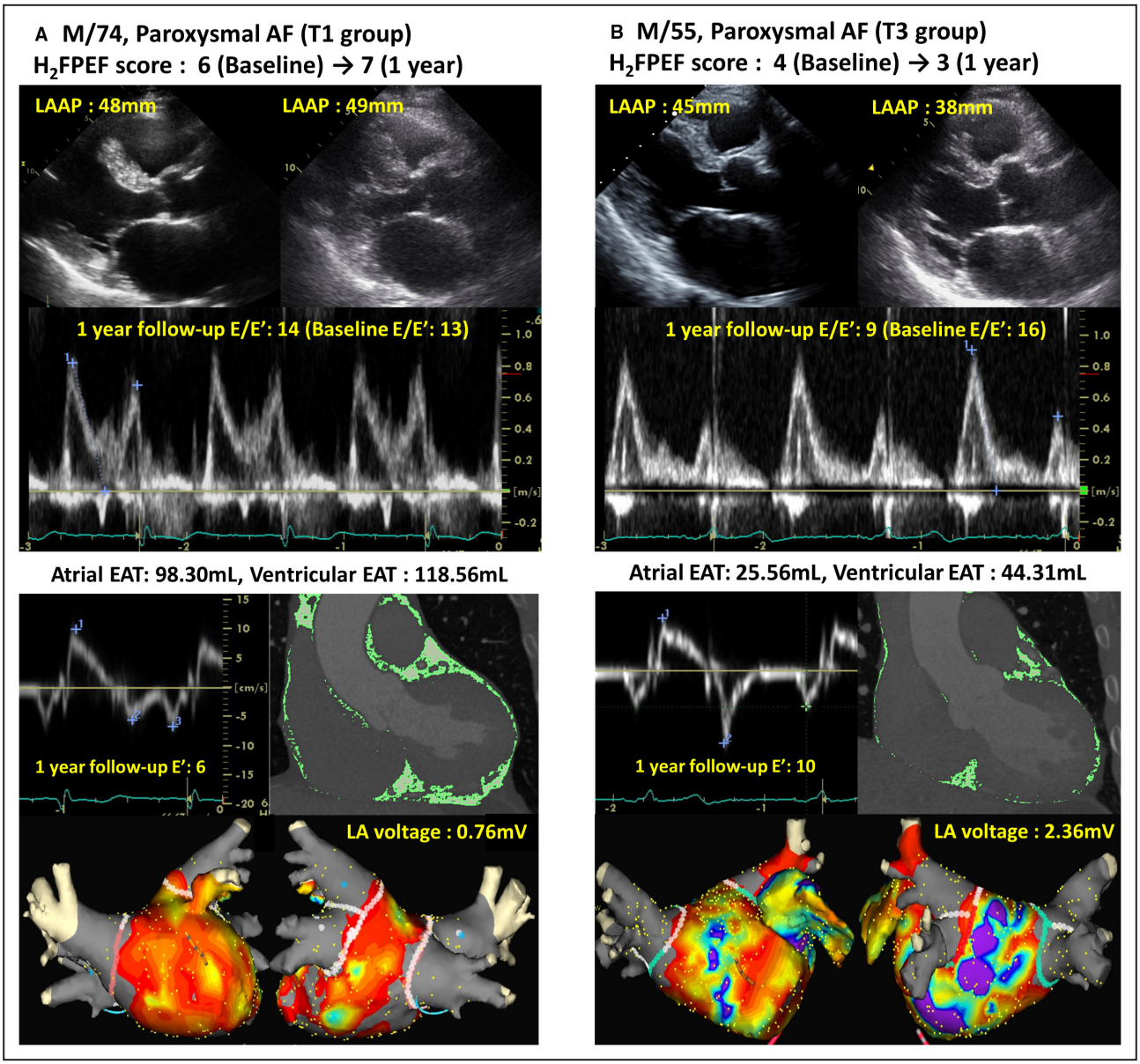

Figure 2. Patients with LA reverse remodeling T1 (A) show higher ventricular EAT and lower LA voltage than patients with LA reverse remodeling T3 (B).
AF indicates atrial fibrillation; E/Em, the ratio of the early diastolic mitral inflow velocity (E) to the early diastolic mitral annular velocity (Em); EAT, epicardial adipose tissue; H_2FPEF, heavy, hypertensive, atrial fibrillation, pulmonary hypertension, elder, filling pressure; LA, left atrium; and LAAP, left atrium anteroposterior diameter.

similar to our findings (LA dimension decreased by 3.6 mm in the T2 group and 8.2 mm in the T3 group).

A clinical diagnosis of atrial myopathy has not yet been defined. In patients with AF, atrial fibrosis as measured by late gadolinium enhancement on cardiac magnetic resonance imaging[5–7] or LA dysfunction as measured by the LA strain is associated with atrial myopathy and ischemic strokes.[32] Therefore, atrial myopathy has a diverse spectrum, from early phase AF including reversible remodeling to irreversible end-stage atrial myopathy that does not recover even after aggressive rhythm control by AFCA.[33] In our study, atrial myopathy was defined as LA reverse remodeling with blunted LA diameter change between baseline and 1 year after AFCA despite active rhythm control and was associated with poor rhythm outcome.

Ventricular EAT, LV Diastolic Function, and Atrial Myopathy

EAT volume has been known to be a prognostic factor in various cardiac diseases and is associated with LV diastolic function or heart failure with preserved ejection fraction.[9] In addition, the EAT volume is related to

Table 2. Changes in the Echocardiographic Findings Before and After Catheter Ablation of Atrial Fibrillation

Variables	Baseline				1-y follow-up				Delta value			
	LA reverse remodeling T1 (N=424)	LA reverse remodeling T2 (N=424)	LA reverse remodeling T3 (N=424)	*P* value	LA reverse remodeling T1 (N=424)	LA reverse remodeling T2 (N=424)	LA reverse remodeling T3 (N=424)	*P* value	LA reverse remodeling T1 (N=424)	LA reverse remodeling T2 (N=424)	LA reverse remodeling T3 (N=424)	*P* value
LA dimension, mm	44.6±4.0	44.7±3.8	45.1±3.9	0.050	45.7±4.6	41.1±3.6	37.0±3.7	<0.001	1.1±3.0	−3.6±1.1	−8.2±2.6	<0.001
LA volume index, mL/ m^2	42.9±13.6	41.2±12.5	41.6±12.0	0.158	41.2±14.5	33.5±11.7	29.2±8.8	<0.001	−1.6±10.8	−7.7±9.3	−12.5±9.6	<0.001
Left ventricular end-diastolic diameter, mm	50.9±4.3	50.6±4.0	50.7±4.9	0.589	51.0±4.2	50.3±3.8	49.3±4.1	<0.001	0.1±3.9	−0.4±3.5	−1.4±4.0	<0.001
Left ventricular ejection fraction, %	62.3±8.7	63.1±7.9	62.1±9.5	0.725	64.3±8.5	65.0±7.1	64.5±7.2	0.664	1.9±7.9	1.9±7.2	2.4±9.0	0.343
Ratio of the early diastolic mitral inflow velocity to the early diastolic mitral annular velocity	11.6±4.9	10.8±4.6	11.2±4.9	0.269	12.4±5.6	11.0±5.0	10.3±4.3	<0.001	0.8±4.4	0.2±3.7	−0.8±3.9	<0.001
Right ventricular systolic pressure, mmHg	28.0±8.0	27.9±7.3	27.6±7.0	0.479	28.6±7.7	26.6±7.1	24.8±5.8	<0.001	0.6±8.5	−1.5±7.2	−3.0±7.3	<0.001
Left ventricular mass index, g/m^2	101.2±22.6	96.8±20.5	96.8±24.0	0.008	103.8±23.9	97.7±21.2	94.1±22.0	<0.001	1.9±19.4	0.0±16.6	−2.0±18.9	0.004

LA indicates left atrium.

Table 3. Logistic Regression Analysis of the Predictors of Blunted LA Reverse Remodeling in the Study Population

	Univariate analysis		Multivariate analysis (Model 1)*		Multivariate analysis (Model 2)*	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.012 (0.989–1.012)	0.952				
Male sex	0.756 (0.584–0.982)	0.035	1.020 (0.688–1.512)	0.912	1.102 (0.743–1.634)	0.629
Paroxysmal atrial fibrillation	0.985 (0.778–1.250)	0.904				
Body mass index	1.064 (1.026–1.106)	0.001	1.102 (1.036–1.171)	0.002	1.089 (1.023–1.159)	0.007
Hypertension	1.337 (1.057–1.692)	0.016	1.003 (0.705–1.426)	0.988	0.953 (0.669–1.356)	0.789
Diabetes	1.207 (0.888–1.633)	0.226				
Stroke	1.077 (0.904–1.278)	0.403				
Vascular disease	1.208 (0.868–1.671)	0.257				
LA dimension	0.981 (0.952–1.011)	0.212				
LA volume index	1.009 (1.000–1.018)	0.056				
Left ventricular ejection fraction	0.996 (0.983–1.010)	0.575				
Left ventricular end-diastolic diameter	1.010 (0.984–1.038)	0.444				
Ratio of the early diastolic mitral inflow velocity to the early diastolic mitral annular velocity	1.025 (1.000–1.051)	0.050				
Right ventricular systolic pressure	1.005 (0.988–1.021)	0.570				
Left ventricular mass index	1.009 (1.003–1.014)	0.002	1.014 (1.006–1.023)	0.001	1.014 (1.006–1.022)	0.001
LA pressure, peak†	1.018 (1.006–1.031)	0.003	1.002 (0.984–1.019)	0.859	1.002 (0.985–1.020)	0.792
LA wall stress†	1.002 (1.001–1.004)	<0.001				
LA wall thickness	0.458 (0.315–0.662)	<0.001	0.466 (0.274–0.791)	0.005	0.469 (0.275–0.798)	0.005
LA voltage	0.693 (0.560–0.853)	<0.001	0.690 (0.516–0.924)	0.013	0.674 (0.502–0.904)	0.009
LA volume/BSA	1.010 (1.005–1.014)	<0.001	1.008 (1.001–1.015)	0.022	1.008 (1.001–1.015)	0.017
EAT//BSA	1.009 (1.005–1.014)	<0.001				
Atrial EAT/BSA	1.016 (1.005–1.028)	0.006	1.011 (0.994–1.029)	0.203		
Ventricular EAT/BSA	1.020 (1.012–1.028)	<0.001			1.019 (1.006–1.032)	0.003
Baseline H_2FPEF score	1.103 (1.004–1.211)	0.041				
Delta H_2FPEF score	1.431 (1.203–1.703)	<0.001	1.560 (1.194–2.038)	0.001	1.547 (1.182–2.024)	0.001
Mean HR at baseline	1.008 (0.998–1.017)	0.121				
Max HR at baseline	1.004 (1.000–1.008)	0.077				
Low-frequency/high-frequency components at baseline	0.928 (0.746–1.154)	0.501				

BSA indicates body surface area; EAT, epicardial adipose tissue; H_2FPEF, heavy, hypertensive, atrial fibrillation, pulmonary hypertension, elder, filling pressure; HR, heart rate; LA, left atrium; and OR, odds ratio.

*Multivariate analysis was performed by dividing atrial and ventricular EAT.

†LA pressure peak was included in the multivariate analysis due to the multicollinearity among 2 variables.

the occurrence, prognosis, and post-AFCA recurrence of AF.[34–36] In this study, blunted LA reverse remodeling, a potential surrogating marker for atrial myopathy, was affected by ventricular EAT volume. This suggests that ventricular EAT can affect atrial reverse remodeling by mechanical and hemodynamic mechanisms associated with LV diastolic function in addition to metabolic or inflammatory factors.[37,38] Heart failure with preserved ejection fraction and atrial myopathy are strongly associated with hemodynamic abnormalities that progressively worsen with an increasing AF burden and contribute to the morbidity and mortality.[10,39] Previously, our study reported that AF catheter ablation tended to decrease the H_2FPEF score and that patients with an increased H_2FPEF score had poor rhythm outcomes after AF catheter ablation.[40]

Clinical Implications

Atrial myopathy influences long-term rhythm control of AF, which leads to the thromboembolic condition by satisfying the Virchow triad, a hypercoagulable state and hemodynamic stasis due to AF.[8] LV diastolic

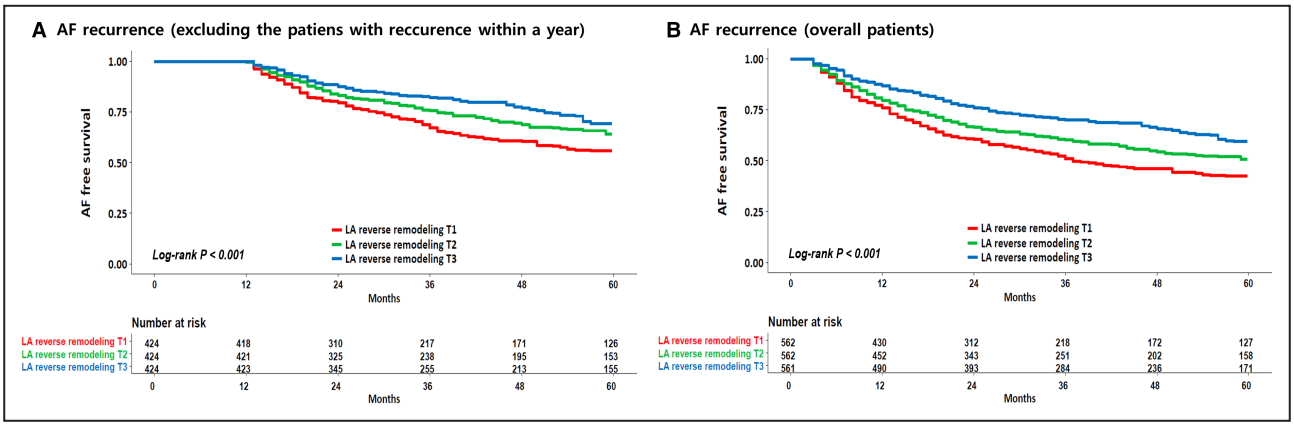

Figure 3. Kaplan–Meier analysis of AF recurrence after catheter ablation.
Clinical recurrence of AF after catheter ablation, excluding the patients with recurrence within 1 year (**A**) and in overall patients (**B**). AF indicates atrial fibrillation, and LA, left atrium.

dysfunction could contribute to increasing the atrial filling pressure, progressive atrial enlargement, atrial myopathy, and eventual thromboembolisms. On the one hand, atrial myopathy may contribute to thromboembolic stroke irrespective of atrial rhythm status.[41] Although current AF guidelines typically recommend continuation of oral anticoagulants even after a successful catheter ablation, it is not uncommon for patients or physicians to consider discontinuation of oral anticoagulation, and the desire to cease taking oral anticoagulants is a major reason for ablation. The Canadian guidelines suggest that oral anticoagulants can be discontinued after successful ablation if the patient has a minimal lifetime risk of stroke and has a persistent sinus rhythm.[42] The results of ongoing trials (ClinicalTrials.gov Identifier: NCT02168829, ClinicalTrials.gov Identifier: NCT04432220) will help physicians in determining the best antithrombotic regimen for AF patients with stroke risk factors postablation. Moreover, a subanalysis of these studies to determine which patients carry an increased risk of stroke without recurrence of AF would be helpful to better understand the relationship between atrial myopathy and stroke without AF. In our study, we could not report the research results on the relationship between atrial myopathy and thromboembolism, and further studies are warranted. The H_2FPEF score correlated with the LA longitudinal strain in patients with heart failure with preserved ejection fraction and the risk of stroke in patients with AF who have a low CHA_2DS_2-VASc score.[13,39,43] Although there is controversy about the association between stroke events and subclinical AF recorded in cardiac implantable electronic devices, a recent large-scale study showed that subclinical AF lasting more than 5.5 hours increased stroke risk.[44,45] It is true that patients with blunted LA reverse remodeling have a poorer prognosis after ablation. Patients with LA increased after AFCA had a very high rate of late recurrence (48.2% versus 35.7%) (no recurrence until 1 year, then recurrence after 1 year) with a mean follow-up of more than 5 years. Furthermore, in the group of patients with recurrent AF who had increased LA after AFCA, the AF recurrence rate was >66% even after redo ablation (Table S6 and S7). However, it is difficult to say that blunted or at least LA remodeling alone can be a cutoff point for abandoning rhythm control, and the decision should be based on the patient's symptoms, underlying disease, and other factors. Moreover, the benefits of strict rhythm control in this patient population, if successful, may be greater than leaving the patient in AF. Because even subclinical/minimal AF burden with atrial myopathy can be a significant risk factor for a stroke, lifelong anticoagulation and more stringent rhythm monitoring are likely to be important in patients with AF and severe atrial myopathy.

Limitations

This study had several limitations. First, this was an observational cohort study from a single center that included a limited number of highly selected patients referred for AF ablation. Second, atrial reverse remodeling was defined according to the change in the LA diameter; however, the LA diameter criterion did not accurately reflect atrial remodeling or a causal association with atrial myopathy. LA reverse remodeling is multifactorial and can be reflected by a variety of functional, structural, anatomical, and histological factors. Moreover, the use of tertile analysis is one of the limitations of this study, as there are no anatomical or physiologic criteria for the presence or severity of atrial myopathy. However, several variables showed a consistent and robust trend in the tertile analysis, and the T1 (blunted reverse remodeling) group was the only group among the 3 groups where LA reverse

Table 4. Logistic Regression Analysis of the Predictors of the Progression to Permanent AF Within 1 Year in Patients After Catheter Ablation in the Overall Patients (N=1685)

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	0.991 (0.976–1.007)	0.272		
Male sex	0.926 (0.645–1.327)	0.674		
Paroxysmal atrial fibrillation	0.335 (0.238–0.471)	<0.001	1.179 (0.518–2.685)	0.695
Body mass index	1.018 (0.969–1.070)	0.472		
Hypertension	0.947 (0.688–1.303)	0.738		
Diabetes	0.908 (0.591–1.395)	0.660		
Stroke	0.504 (0.274–0.927)	0.028	0.249 (0.055–1.128)	0.071
Vascular disease	0.811 (0.501–1.314)	0.395		
LA dimension	1.102 (1.066–1.140)	<0.001		
LA volume index	1.026 (1.015–1.037)	<0.0001	1.011 (0.976–1.047)	0.539
Left ventricular ejection fraction	0.988 (0.972–1.004)	0.148		
Left ventricular end-diastolic diameter	0.987 (0.953–1.022)	0.454		
Ratio of the early diastolic mitral inflow velocity to the early diastolic mitral annular velocity	0.989 (0.954–1.025)	0.556		
Right ventricular systolic pressure	0.995 (0.972–1.019)	0.705		
Left ventricular mass index	0.998 (0.990–1.005)	0.539		
LA pressure, peak*	1.030 (1.012–1.047)	0.001	0.967 (0.930–1.005)	0.087
LAW stress*	1.003 (1.002–1.004)	<0.001		
LAW thickness	0.695 (0.431–1.123)	0.137		
LA voltage	0.138 (0.085–0.225)	<0.001	0.305 (0.147–0.633)	0.001
LA volume/body surface area	1.013 (1.008–1.019)	<0.001	1.004 (0.985–1.022)	0.705
Epicardial adipose tissue	1.005 (1.002–1.008)	0.001		
Atrial EAT	1.009 (1.001–1.016)	0.023	1.032 (1.015–1.049)	<0.001
Ventricular EAT	1.004 (0.998–1.006)	0.199		
Baseline H_2FPEF score	0.944 (0.829–1.076)	0.390		
Delta H_2FPEF score	1.135 (0.894–1.442)	0.298		
Mean HR at baseline	1.006 (0.991–1.020)	0.436		
Max HR at baseline	1.002 (0.997–1.008)	0.422		
Low-frequency/high-frequency components at baseline	0.464 (0.327–0.658)	<0.001	0.500 (0.281–0.887)	0.018
The blunted LA reverse remodeling	2.428 (1.759–3.353)	<0.001	2.205 (1.078–4.510)	0.030

EAT indicates epicardial adipose tissue; H_2FPEF, heavy, hypertensive, atrial fibrillation, pulmonary hypertension, elder, filling pressure; HR, heart rate; LA, left atrium; LAW, left atrial wall; and OR, odds ratio.

*LA pressure peak was included in the multivariate analysis due to the multicollinearity among 2 variables.

remodeling did not occur despite maintaining sinus rhythm for 1 year after AFCA. Additional analyses of predictors for bunted reverse remodeling based on the change of LA size yielded similar results (Table S8 and S9). Third, although the clinical history of a stroke or transient ischemic attack has been sufficiently investigated, silent strokes could not be excluded. Fourth, other pathological factors, such as cardiomyocyte changes, fibrotic changes, and noncollagen infiltration, could influence atrial myopathic status but have not been evaluated. Fifth, among the factors that make up the H_2FPEF score, obesity varied in prevalence between the H_2FPEF score validation cohort and our study cohort. Also, because the prevalence of obesity and hypertension in our cohort was different at baseline, it could affect the H_2FPEF score and rhythm outcome. Sixth, before the results of STAR-AF2 (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II) reported in 2015, additional line ablation was performed in addition to PV isolation. Also, additional ablation other than pulmonary vein isolation may affect the physiology or reverse remodeling of the LA. However, the ablation protocol in this study was consistent for each AF type, so it is unlikely to have had a significant impact on the results of the study. Seventh, the LA volume measured by CT was not propensity

score matched, and rhythm status at the time of CT acquisition may have influenced LA size values that were not identified in our study. Also, rhythm was not reported when LA volume was measured using CT. Eighth, although ECG and Holter monitoring were performed 1, 3, 6, and 12 months after the procedure according to the previous guidelines, it is possible that AF recurrence occurred within 1 year but was not detected and may have acted as a confounding factor for atrial reverse remodeling. Lastly, data on preoperative medications were not available for analysis (Table S10).

CONCLUSIONS

Blunted atrial reverse remodeling after AFCA, which may be due to AF-induced atrial myopathy, is closely associated with worsened diastolic dysfunction, high ventricular EAT volume, high body mass index, left ventricular mass index, thin atrial wall thickness, and low LA voltage. Blunted atrial reverse remodeling has poor rhythm outcomes 1 year after AFCA. Therefore, there may be a potential mechanistic linkage of ventricular EAT volume, diastolic function, and atrial myopathy in patients with AF. Patients with atrial myopathy should be closely monitored and treated for rhythm control to prevent AF progression with aggressive lifestyle modification.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S10
Figure S1

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