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**Original**

# Epicardial Adipose Tissue in the Right Atrium Is Associated with Progression of Atrial Fibrillation and Recurrence after Pulmonary Vein Catheter Ablation in Patients with Atrial Fibrillation

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**Abstract**: An increase in epicardial adipose tissue (EAT) in the left atrium (LA) predicts the progression of atrial fibrillation (AF) and AF recurrence after pulmonary vein catheter ablation (CA). We hypothesized that EAT in the right atrium (RA) is also associated with the progression of AF and post-CA AF recurrence. Using 128-slice multidetector computed tomography, EAT volume and atrial volume were measured 3-dimensionally before CA in 68 patients who had proven AF (paroxysmal AF, 42; persistent AF, 26; mean age, 65±11 years; 42.6% female) with successful CA and 21 volunteers with sinus rhythm (age, 63±13 years; 52.3% female). In both atria, EAT and atrial volumes were largest in patients with persistent AF, followed, in order, by those with paroxysmal AF, and then healthy volunteers ($P$ <0.001). Increased EAT and atrial volumes in both atria predicted persistent AF ($P$<0.001). Fifteen patients had AF recurrence (22.1%) during the 2-year period after CA. Increased EAT volume in both atria were independent predictors for AF recurrence, and a RA EAT volume ≥6.2ml was an independent predictor, with a hazard ratio of 5.47 (95% confidence interval, 1.2-24.3; $P$=0.03). The combination of EAT and atrial volume in both atria was a more powerful independent prognostic factor, with a hazard ratio of 4.8 (95% confidence interval, 1.7-3.7; $P$=0.003), and a sensitivity of 60% in 9 of 15 patients, and specificity of 81.1% in 43 of 53 patients, ($P$=0.003). RA EAT is associated with the progression of AF and post-CA AF recurrence.

**Key words**: atrial fibrillation, adipose tissue, right atrium epicardium, catheter ablation, recurrence

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## Introduction

Several studies demonstrate that the volume of epicardial adipose tissue (EAT) is associated with the progression of atrial fibrillation (AF) and AF recurrence after catheter ablation (CA), and these close relationships result from inflammation leading to remodeling of the left atrium (LA)[1–3]. A recent study indicated that the distribution of EAT in the LA is an important trigger for AF[4]. On the other hand, right atrial (RA) remodeling has also been reported in patients with AF, and the fibrosis associated with remodeling of not only the LA but also the RA plays an important role in AF recurrence[5]because AF is sometimes initiated by non-pulmonary vein (PV) ectopic beats which arise from the RA side rather than the PV[6, 7]. Atrial size and EAT volume can be quantified using multidetector computed tomography (MDCT) imaging[8, 9]. We hypothesized that RA EAT volume, measured using MDCT, is associated with progression of AF and AF recurrence after CA.

## Materials and methods

*Study population*

We recruited consecutive patients who had a history of palpitations and were initially diagnosed with AF at Showa University Hospital, Tokyo, Japan. A diagnosis of AF was made and differentiation between paroxysmal and persistent AF was carried out based on the American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines[10]. Before the present study, left ventricular ejection fractions and LA dimensions were measured with 2-dimensional echocardiography. Patients with diseases that could cause pathological fibrosis and adipose tissue replacement in the atrium were excluded from the study. Patients who had ischemic heart disease, valvular heart disease, cardiomyopathy, congenital heart disease, thyroid disease, chronic kidney disease, collagen disease, hematologic disease, inflammatory disease, or malignancy were also excluded from this study. Additionally, patients were excluded if they had pre-excitation syndrome, atrioventricular tachycardia or ventricular tachyarrhythmia, or an implanted pacemaker before the start of the study. After application of the exclusion criteria, 42 patients with paroxysmal AF and 26 patients with persistent AF (mean age, 65±11 years; 42.6% female) were recruited for this study. Further, for those who did not meet the exclusion criteria, 21 volunteers who had normal sinus rhythm and no history of AF were recruited as the control group (age, 63±13 years; 52.3% female). All participants provided written informed consent before the study, and the protocol was approved by the institutional review board. This research was approved by the Ethics Committee for Human Research of Showa University (Authorization number, 2592).

*Scan protocol and acquisition of MDCT data*

Within one week before CA, all patients and volunteers underwent scanning with a 128-slice single-source MDCT system (SOMATOM Definition AS+Siemens Medical Solutions, Forchheim, Germany) when they had less variable rhythm and were not experiencing tachyarrhythmia (<

75 bpm). The procedure was conducted without contrast media to measure atrial volume and EAT volume. Each scan was performed in a single breath hold in the craniocaudal direction, from the aortic arch to the diaphragm. The scan was gated to the cardiac cycle through electrocardiogram (ECG) synchronization with the following parameters: collimation, 2×64×0.6 mm; rotation time, 300 msec; tube voltage, 120 kV; effective tube current, 800 mA; and pitch, 0.3. Raw CT data were reconstructed with algorithms that were optimized for retrospectively ECG-gated segmental reconstruction with a slice thickness of 0.6 mm and increment of 0.3 mm. ECG-gated data sets were reconstructed at the point of the cardiac cycle that corresponded to atrial end diastole[9].

*Measurement of atrial volume and EAT volume with MDCT*

Reconstructed CT image data were transferred to a workstation for post-processing (Synapse Vincent; Fujifilm, Tokyo, Japan). EAT volume and atrial volume were measured 3-dimensionally in all patients with non-contrast-enhanced images (Fig. 1). The area of EAT was calculated

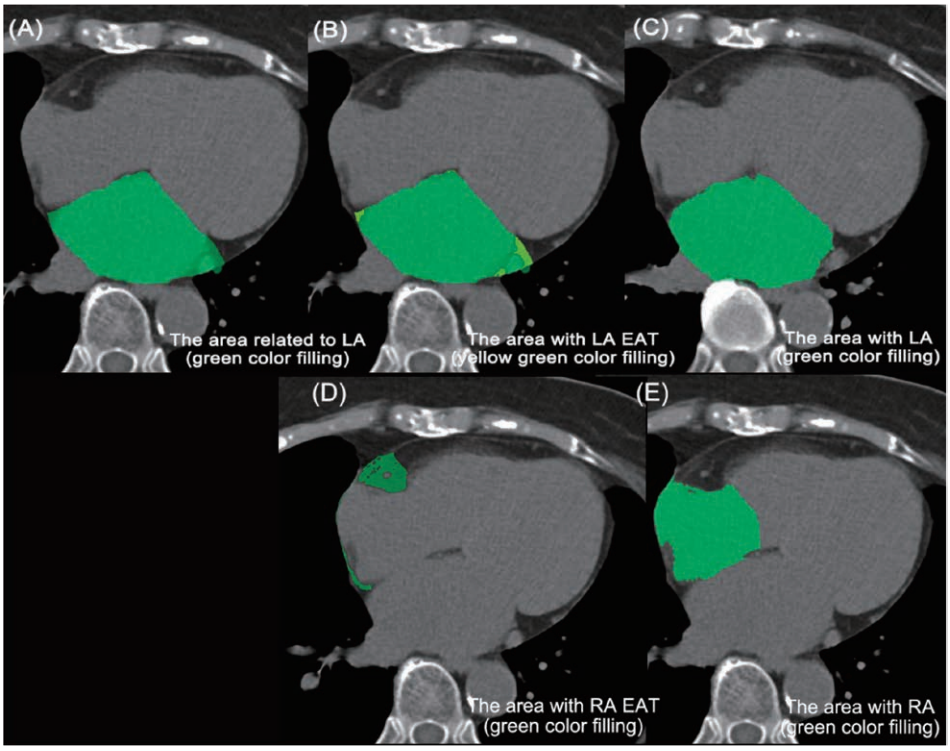


Fig. 1. Quantitative measurement of epicardial adipose tissue (EAT) volume and atrial volume

(A) The area related to the left atrium (LA) was traced in green.
(B) The area related to the LA EAT (yellow-green) was detected by assigning Hounsfield units (HU) of −50 to −200.
(C) The LA area (green) was detected by assessing HU of more than 0.
(D) The area related to the right atrium (RA) EAT (green) was detected in a similar manner to the LA volume measurement.
(E) The area related to the RA (green) was detected in a similar manner to the LA volume measurement.

by tracing the region of interest (ROI), which included each atrium with EAT. The ROI was manually placed outside the line of the visceral pericardium on a cross-sectional axial image. The area outside the traced pericardium was excluded[11]. Areas of EAT surrounding the LA and RA were separately assessed by tracing the ROI containing atrium and EAT. EAT volume was detected by assessing Hounsfield units (HU) of −50 to −200, and atrial volume was detected by assigning HU of more than 0. Volumes were reconstructed from contiguous slices of axial images from the left main coronary artery to the apex and were summed automatically[12]. The measurements were performed offline by two blinded observers. To determine the reproducibility of MDCT, two investigators repeated the EAT measurements at two different time points for 30 randomly selected participants. The inter-observer and intra-observer correlations for RA EAT were r=0.951 and r=0.953, respectively ($P<0.001$), and r=0.96 and r=0.944, respectively, for LA EAT ($P<0.001$).

*PV CA*

The NAVX-Ensite system (St.Jude Medical, Inc., St.Paul, MN, USA) was used for nonfluoroscopic 3-dimensional catheter orientation and CT image integration. After one transseptal puncture and two long-sheath insertions in the LA, radiofrequency ablation and ring catheters were positioned, and the CA procedure was performed with a steerable sheath (Agilis; St.Jude Medical, Inc.). The PV ablation procedure was essentially ipsilateral PV isolation. Line ablations (mitral isthmus, roof, and bottom lines in the LA) were added in patients with persistent AF. An irrigated catheter was used with an initial maximum power of 25−35W, depending on each physician and by the dragging method used with a steerable sheath. Electrical isolation of all PVs was attempted with bidirectional conduction block in all patients. After the procedure, successful CA was confirmed by PV stimulation.

*Follow-up after PV CA*

After CA, all patients had prospective follow-up at least once every 4 weeks without antiarrhythmic drugs. Recurrence of AF was assessed from one month to two years, and recurrence was defined as documented AF by 12-lead ECG and at least one 24-hour Holter monitoring to observe cardiac rhythm. In addition, external loop recording was performed for as long as possible. Further, 12-lead ECG and Holter monitoring were performed during follow-up for patients who reported an irregular heart beat or palpitations.

*Statistical analysis*

Comparisons between groups were performed with 1-way analysis of variance, unpaired t test, Fisher's exact test, or a Bonferroni test for continuous variables, and the chi-square test for categorical variables. Associations between predictors and AF recurrence were formally tested by construction of a Cox proportional hazards model with regression analysis. The tolerance of the variance inflation factor (VIF) was calculated to evaluate multicollinearity in the multiple regression analysis model. For descriptive purposes, receiver operator characteristic analysis

was performed to define thresholds for those factors, and the difference was compared using the area under curve (AUC) with the jackknife method. The cutoff values were defined by minimizing the expression of $(1-\text{sensitivity})^2 + (1-\text{specificity})^2$ on the AUC. Statistical analysis was performed with SPSS for Windows, version 20 (SPSS Inc., IBM, Chicago, IL, USA). A probability value of $<0.05$ was considered significant.

## Results

*Patient characteristics*

There were no significant differences in age, gender, body mass index (BMI), or coronary risk factors between the patients with persistent AF, paroxysmal AF, and the control group. Low-density lipoprotein (LDL) -cholesterol was similar between the three groups ($P=0.10$), but high-sensitivity C-reactive protein (hsCRP) was higher in patients with persistent AF than in those with paroxysmal AF or controls ($P=0.003$; Table 1). LA diameter on echocardiography was greater in patients with persistent AF than in those with paroxysmal AF (46 ± 5.3 mm vs. 40.7 ± 5.3 mm, respectively; $P=0.001$), but left ventricular ejection fractions were similar in patients with

Table 1. Baseline characteristics of patients with persistent AF, paroxysmal AF, and control participants

| Group | Persistent AF (n=26) | Paroxysmal AF (n=42) | Control (n=21) | *P*-value (ANOVA) |
|---|---|---|---|---|
| Age (years) | 64 ± 10 | 66 ± 11 | 63 ± 5 | 0.55 |
| Female, n (%) | 7 (26.9%) | 22 (52.4%) | 11 (52.4%) | 0.09 |
| Body mass index (kg/m$^2$) | 25.2 ± 2.9 | 23.7 ± 4.5 | 23.3 ± 1.7 | 0.09 |
| Diabetes mellitus, n (%) | 4 (15.4%) | 4 (9.5%) | 4 (19.0%) | 0.57 |
| Hypertension, n (%) | 15 (57.7%) | 24 (57.1%) | 12 (57.1%) | 1.00 |
| Dyslipidemia, n (%) | 9 (34.6%) | 20 (47.6%) | 8 (38.1%) | 0.53 |
| History of stroke, n (%) | 1 (3.8%) | 3 (7.1%) | 0 | 0.32 |
| Smoker, n (%) | 14 (53.8%) | 15 (35.7%) | 8 (38.1%) | 0.32 |
| Triglyceride (mg/dl) | 172 ± 136 | 145 ± 92 | 165 ± 144 | 0.64 |
| High-density lipoprotein-cholesterol (mg/dl) | 50 ± 13 | 56 ± 15 | 60 ± 15 | 0.07 |
| Low-density lipoprotein-cholesterol (mg/dl) | 124 ± 29 | 120 ± 31 | 106 ± 26 | 0.10 |
| High-sensitivity C-reactive protein (mg/dl) | 0.15 ± 0.12** †† | 0.08 ± 0.10 | 0.07 ± 0.04 | 0.003 |
| N-terminal brain natriuretic peptide (pg/ml) | 88 ± 33* | 64 ± 26 | 16 ± 15 | 0.03 |
| Creatinine (mg/dl) | 0.9 ± 0.2* | 0.8 ± 0.2 | 0.7 ± 0.2 | 0.02 |
| Medications before catheter ablation, n (%) | | | | |
| Use of ARB | 12 (46.2%) | 12 (28.6%) | 7 (33.3%) | 0.37 |
| Use of ß-blocker | 9 (34.6%) | 24 (57.1%) | 2 (9.5%) | 0.001 |
| Use of calcium channel antagonist[a] | 15 (57.7%) | 18 (42.9%) | 6 (28.6%) | 0.14 |
| Use of sodium channel blocker | 3 (11.5%) | 3 (7.1%) | 0 | 0.41 |
| Use of statin[b] | 5 (19.2%) | 15 (35.7%) | 7 (33.3%) | 0.37 |

Values are mean ± standard deviation, unless otherwise indicated. *$P<0.05$, **$P<0.01$ vs. control; ††$P<0.01$ vs. paroxysmal AF group. aCalcium channel antagonist includes bepridil; bStatin is hydroxymethylglutaryl-CoA reductase inhibitor. AF; atrial fibrillation, ANOVA; analysis of variance, ARB; angiotensin converting enzyme inhibitor or receptor blocker.

different types of AF (persistent, 61.6% ± 9.8%; paroxysmal, 58.7% ± 8.4%).

*EAT volume for progression of AF*

In both atria, EAT and atrial volumes were largest in patients with persistent AF, followed, in order, by patients with paroxysmal AF, and then control individuals with sinus rhythm ($P<0.001$; Fig. 2). In patients with AF, persistent AF was predicted by RA EAT volume (AUC=0.82;

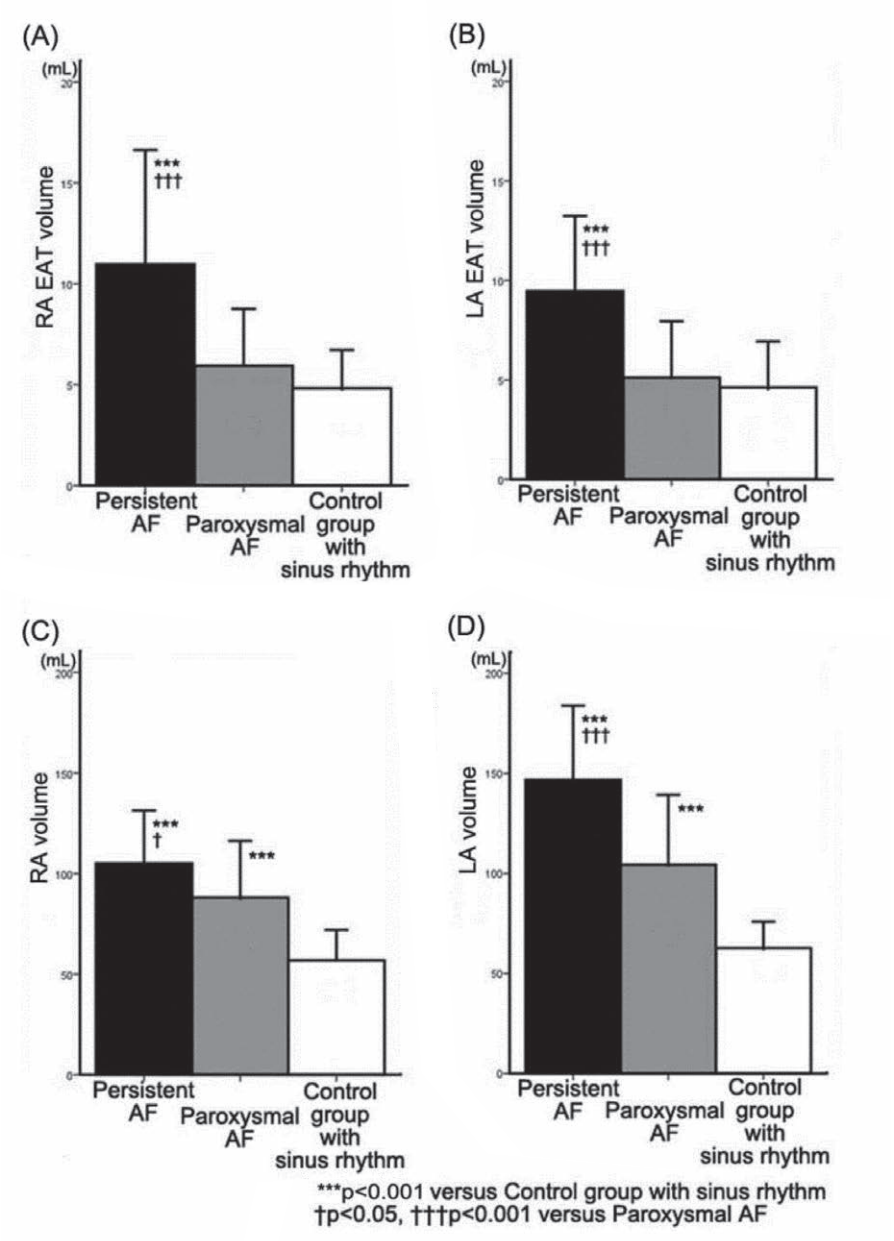


Fig. 2. Comparison of epicardial adipose tissue (EAT) and atrial volume. EAT and atrial volumes were greatest in patients with persistent atrial fibrillation (AF), followed, in order, by patients with paroxysmal AF, and then control individuals with sinus rhythm. RA; right atrium, LA; left atrium.

$P<0.001$), LA EAT volume (0.82; $P<0.001$), RA volume (0.67; $P=0.02$), and LA volume (0.8; $P<0.001$). RA EAT volume was correlated with LA EAT volume (r=0.69), RA volume (r=0.32), LA volume (r=0.42), and BMI (r=0.47) in patients with AF ($P<0.001$ for each).

*Continuous variables for predicting AF recurrence*

All patients had follow-up for two years after CA, and 15 patients had AF recurrence (22.1%). Patients with persistent AF and paroxysmal AF had a similar number of recurrences of AF (persistent, 8 of 26 patients [30.8%]; paroxysmal, 7 of 42 patients [16.7%]; $P=0.23$).

LDL-cholesterol levels were higher in patients with AF recurrence than in those without AF recurrence ($P=0.04$; Table 2). Patients receiving statin treatment were not likely to develop AF recurrence ($P=0.05$). AF recurrence was associated with RA EAT volume ($P=0.001$), LA EAT volume ($P=0.02$), and LA volume ($P=0.006$) on MDCT, as well as LA dimension

Table 2. Patient characteristics after pulmonary vein catheter ablation

| Variable | Recurrence of AF (n=15) | No recurrence of AF (n=53) | *P*-value |
|---|---|---|---|
| Age (years) | 67±11 | 65±11 | 0.39 |
| Female, n (%) | 7 (46.7%) | 8 (41.5%) | 0.77 |
| Body mass index (kg/m$^2$) | 25±2.6 | 24.1±4.4 | 0.45 |
| Diabetes mellitus, n (%) | 2 (13.3%) | 6 (11.3%) | 0.85 |
| Hypertension, n (%) | 6 (40.0%) | 33 (62.0%) | 0.15 |
| Dyslipidemia, n (%) | 3 (20.0%) | 26 (49.0%) | 0.07 |
| History of stroke, n (%) | 2 (13.3%) | 2 (3.8%) | 0.21 |
| Smoker, n (%) | 7 (46.7%) | 22 (41.5%) | 0.77 |
| Triglyceride (mg/dl) | 218±31 | 202±36 | 0.41 |
| High-density lipoprotein-cholesterol (mg/dl) | 50±13 | 54±15 | 0.37 |
| Low-density lipoprotein-cholesterol (mg/dl) | 135±28 | 117±30 | 0.04 |
| High-sensitivity C-reactive protein (mg/dl) | 0.12±0.09 | 0.10±0.12 | 0.70 |
| N-terminal brain natriuretic peptide (pg/ml) | 112±101 | 62±89 | 0.07 |
| Creatinine (mg/dl) | 0.8±0.2 | 0.8±0.2 | 1.00 |
| Echocardiographic findings | | | |
| Left ventricular ejection fraction (%) | 62±8 | 60±10 | 0.39 |
| Left atrial diameter (mm) | 47±7 | 42±6 | 0.005 |
| Medications before catheter ablation, n (%) | | | |
| Use of ARB | 4 (26.7%) | 20 (37.7%) | 0.55 |
| Use of ß-blocker | 6 (40.0%) | 27 (50.9%) | 0.56 |
| Use of calcium channel antagonista | 4 (26.7%) | 20 (37.7%) | 0.55 |
| Use of sodium channel blocker | 2 (13.3%) | 4 (7.5%) | 0.61 |
| Use of statinb | 1 (6.7%) | 19 (35.8%) | 0.05 |

Values are mean±standard deviation, unless otherwise indicated. [a]Calcium channel antagonist includes bepridil; [b]Statin is hydroxymethylglutaryl-CoA reductase inhibitor.

AF; atrial fibrillation, ARB; angiotensin converting enzyme inhibitor or receptor blocker.

on echocardiography ($P=0.007$). When the VIFs, such as RA and LA volume, were excluded from the multivariable analysis model, the predictive factors for AF recurrence were analyzed, including RA EAT and LA EAT volumes. After adjustment for potential confounding variables, such as age, BMI, LDL-cholesterol, and hsCRP, increased RA EAT and LA EAT volumes were found to be independent predictive factors for AF recurrence ($P=0.001$ and $P=0.02$, respectively; Table 3).

*Categorical variables and AF recurrence*

The AUC for RA EAT volume (0.70) was similar to LA EAT volume (0.69; $P=0.83$), RA volume (0.63; $P=0.41$), and LA volume (0.73; $P=0.69$) for predicting AF recurrence, but the AUC was greater for LA volume than RA volume ($P=0.04$) (Fig. 3). A RA EAT volume $>$ 6.2 ml was predictive of AF recurrence (Table 4). A LA EAT volume$>$6.8 ml and LA volume $>$117 ml were also significant predictive factors of AF recurrence, but a RA volume$>$88 ml did not reach significance (Fig. 4). An LDL-cholesterol level$>$125 mg/dl, hsCRP level $>$0.067 mg/dl, and N-terminal brain natriuretic peptide level$>$75 pg/ml were also significant predictive markers of AF recurrence. The VIFs, such as atrial volume for both RA and LA, were excluded from this model for multivariable analysis.

*LA volume, RA volume, LA EAT volume, and RA EAT volume for predicting AF recurrence*

When the predictive factors for AF recurrence were analyzed with RA EAT volume included, after adjustment for potential confounding variables, such as older age, higher BMI, a history of persistent AF, higher LDL-cholesterol level, higher hsCRP level, and higher N-terminal brain

Table 3. Continuous variable risk factors for recurrence of atrial fibrillation after pulmonary vein catheter ablation

| Variable | Regression Analysis | Univariable Analysis | | | Tolerance of VIF |
|---|---|---|---|---|---|
| | Coefficient (Beta) | Hazard Ratio (95% CI) | Wald Chi-Square | *P*-value | |
| Increase in age (years) | 0.018 | 1.02 (1.00–1.07) | 0.46 | 0.50 | 0.83 |
| Increase in body mass index (kg/m$^2$) | 0.059 | 1.06 (0.90–1.20) | 0.88 | 0.35 | 0.58 |
| Increase in low-density lipoprotein-cholesterol (mg/dl) | 0.015 | 1.06 (1.00–1.03) | 3.53 | 0.06 | 0.95 |
| Increase in high-sensitivity C-reactive protein (mg/dl) | 0.942 | 2.57 (0.05–143.80) | 0.21 | 0.65 | 0.77 |
| Increase in N-terminal brain natriuretic peptide (pg/ml) | 0.003 | 1.003 (1.00–1.01) | 2.45 | 0.12 | 0.63 |
| Increase in LA EAT volume (ml) by MDCT | 0.142 | 1.15 (1.02–1.31) | 5.08 | 0.02 | 0.45 |
| Increase in LA volume (ml) by MDCT | 0.018 | 1.02 (1.01–1.03) | 7.43 | 0.006 | 0.23 |
| Increase in RA EAT volume (ml) by MDCT | 0.134 | 1.14 (1.06–1.24) | 10.70 | 0.001 | 0.45 |
| Increase in RA volume (ml) by MDCT | 0.015 | 1.02 (1.00–1.04) | 2.64 | 0.10 | 0.31 |
| Increase in left ventricular ejection fraction (%) | 0.025 | 1.03 (0.97–1.09) | 0.71 | 0.40 | 0.82 |
| Increase in LA dimension (mm) by echocardiography | 0.110 | 1.12 (1.03–1.22) | 7.29 | 0.007 | 0.49 |

VIF; variance inflation factor, CI; confidence interval, LA; left atrium. EAT; epicardial adipose tissue, MDCT; multi-detector computed tomography, RA; right atrium.

natriuretic peptide level, a RA EAT volume 6.2 ml was found to be an independent predictive factor for AF recurrence with a hazard ratio (HR) of 5.47 (95% confidence interval [CI], 1.2-24.3; $P=0.03$). When the predictive factors for AF recurrence were analyzed with LA EAT volume included, a LA EAT volume>6.8 ml was not an independent predictive factor, but high LDL-

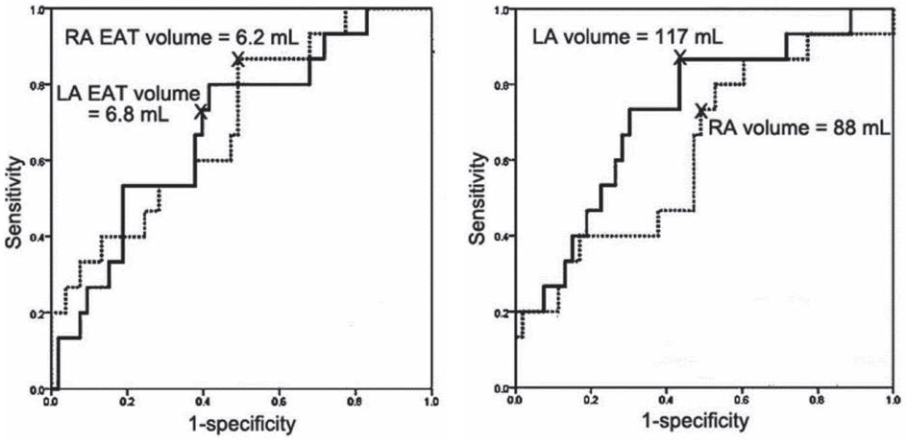


Fig. 3. Receiver operator characteristic curves of epicardial adipose tissue (EAT) volume and atrial volume for diagnosing atrial fibrillation (AF) recurrence after catheter ablation. The area under the curve (AUC) for right atrium (RA) EAT volume was similar to left atrium (LA) EAT volume, RA volume, and LA volume for predicting

Table 4. Categorical variable risk factors for recurrence of atrial fibrillation after pulmonary vein catheter ablation

| Variable | Regression Analysis | Univariable Analysis | | |
|---|---|---|---|---|
| | Coefficient (Beta) | Hazard Ratio (95% CI) | Wald Chi-Square | *P*-value |
| Age > 68 years | 1.12 | 3.1 (1.0-9.0) | 4.18 | 0.04 |
| Body mass index ≥ 25 kg/m$^2$ | 0.96 | 2.6 (0.9-74) | 3.32 | 0.07 |
| Persistent AF | 0.71 | 2.0 (0.7-5.6) | 1.88 | 0.17 |
| Low-density lipoprotein-cholesterol ≥ 125 mg/dl | 1.27 | 3.6 (1.1-11.2) | 4.70 | 0.03 |
| High-sensitivity CRP ≥ 0.067 mg/dl | 1.20 | 3.3 (1.1-10.5) | 4.24 | 0.04 |
| N-terminal brain natriuretic peptide ≥ 75 pg/ml | 1.14 | 3.1 (1.1-8.6) | 4.82 | 0.03 |
| Echocardiographic findings | | | | |
| LA dimension ≥ 48 mm | 1.37 | 3.9 (1.4-10.9) | 6.99 | 0.008 |
| Left ventricular ejection fraction < 63% | -0.39 | 0.7 (0.2-2.0) | 0.51 | 0.50 |
| MDCT findings | | | | |
| LA volume ≥ 117 ml | 1.90 | 6.7 (1.5-26.7) | 6.22 | 0.01 |
| RA volume ≥ 88 ml | 1.10 | 3.0 (0.8-10.7) | 2.91 | 0.09 |
| LA EAT volume ≥ 6.8 ml | 1.19 | 3.3 (1.0-10.3) | 4.13 | 0.04 |
| RA EAT volume ≥ 6.2 ml | 1.69 | 5.4 (1.2-24.0) | 4.93 | 0.03 |

CI; confidence interval. AF; atrial fibrillation. CRP; C-reactive protein. LA; left atrium. MDCT; multidetector computed tomography. RA; right atrium. EAT; epicardial adipose tissue.

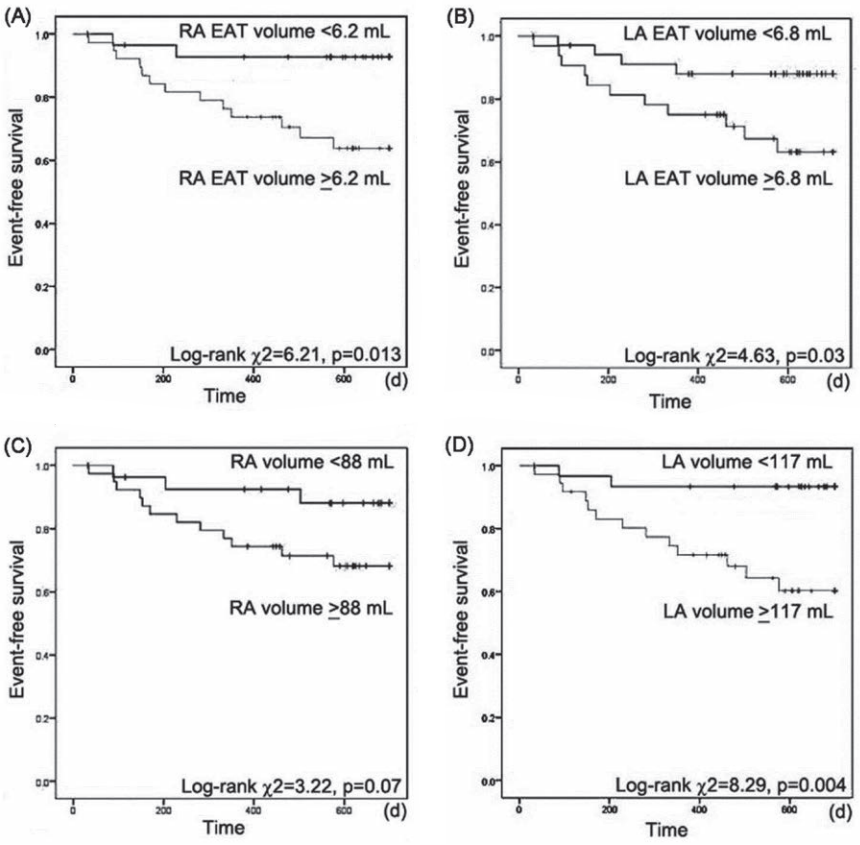


Fig. 4. Kaplan-Meier survival curves of the epicardial adipose tissue (EAT) volume and atrial volume of each atria for predicting atrial fibrillation (AF) recurrence after catheter ablation. Increased EAT volume in both atria and left atrial (LA) volume were significant predictive markers of AF recurrence, while an increased right atrial (RA) volume failed to reach significance.

cholesterol levels＞125 mg/dl predicted AF recurrence independently, with a HR of 4.87 (95% CI, 1.4–12.7; $P=0.008$).

The combined estimate of the four factors of LA volume, RA volume, LA EAT volume, and RA EAT volume provided incremental and additive prognostic power of AF recurrence, compared with LA volume alone (Table 5). After adjustment for potential confounding variables, the combination of these four factors had the most powerful independent prognostic power for AF recurrence, with a HR of 4.8 (95% CI, 1.7–13.7; $P=0.003$; Table 5).

## Discussion

RA EAT volume is associated with the progression of AF and post-CA AF recurrence.

*Atrial EAT and progression of AF*

Al Chekakie *et al*[1] compared whole heart EAT volume among patients with persistent AF, paroxysmal AF, and sinus rhythm, and found a close relationship between EAT volume and

Table 5. Combination of EAT volumes and right and left atrial volumes for atrial fibrillation recurrence after pulmonary vein catheter ablation

| Variable | Regression Analysis | Univariable Analysis | | |
|---|---|---|---|---|
| | Coefficient (Beta) | Hazard Ratio (95% CI) | Wald Chi-Square | *P*-value |
| Combined estimate of atrial and EAT volumes | | | | |
| LA volume ≥ 117 ml and RA volume ≥ 88 ml | 1.77 | 5.9 (1.7-20.9) | 7.48 | 0.006 |
| LA EAT volume ≥ 6.8 ml and RA EAT volume ≥ 6.2 ml | 1.48 | 4.4 (1.4-13.8) | 6.41 | 0.01 |
| LA volume ≥ 117 ml and LA EAT volume ≥ 6.8 ml | 1.44 | 4.2 (1.4-12.4) | 6.87 | 0.009 |
| RA volume ≥ 88 ml and RA EAT volume ≥ 6.2 ml | 1.42 | 4.2 (1.3-13.1) | 5.92 | 0.02 |
| LA volume ≥ 117 ml, RA volume ≥ 88 ml, LA EAT volume ≥ 6.8 ml, and RA EAT volume ≥ 6.2 ml | 1.58 | 4.8 (1.7-13.7) | 8.85 | 0.003 |

EAT; epicardial adipose tissue, CI; confidence interval, LA; left atrium, RA; right atrium.

progression of AF. They showed that whole heart EAT volume is correlated with LA volume. Nagashima *et al*[4] also reported that patients with persistent AF, in comparison with those with paroxysmal AF, had increased total heart EAT and LA EAT volumes, and serum hsCRP and interleukin-6 levels were elevated as biomarkers of inflammation and collagen turnover. We found that EAT volume in not only the LA, but also the RA, is associated with the progression to persistent AF.

*Atrial EAT and post-CA AF recurrence*

Previous studies[9, 13, 14] showed that myocardial damage, atrial enlargement, and a symmetric change in electric remodeling were similar in magnitude between the LA and RA in patients with AF. Although there are some distinct differences in anatomy between the atria[15], atrial dyssynchrony with AF leads to structural remodeling in both atria simultaneously[16], and systemic inflammation and endothelial dysfunction may target both atria equally[17].

Local fatty infiltration causes the fibrosis of adjacent myocardium, which leads to AF recurrence[18]. A close relationship between the AF focus and distribution of EAT in the LA was recently reported using LA high-dominant-frequency sites during an electrophysiological study[4]. Patients with AF concomitant with sick sinus syndrome are at higher risk for AF recurrence[19], and the specific characteristics of ionic remodeling in sinoatrial node tissue within the RA may affect the triggered activity mechanism and the prevalence of non-PV foci other than the LA[20]. However, Hasebe *et al*[21] demonstrated that the RA EAT volume was not larger in eight patients with AF characterized by RA ectopic initiation and right-to-left dominant-frequency gradients, compared to 32 patients characterized by initiation in the LA. These results indicate that the pathophysiology of AF is not simple, and the recurrence of AF following ablation is multifactorial and complex. However, we found that RA EAT volume is important in the recurrence of AF in the present study.

*Other factors for predicting the progression of AF and post-CA AF recurrence*

EAT is associated with clinical characteristics of the metabolic syndrome, including waist circumference and LDL-cholesterol levels[22]. Soucek *et al*[23] showed in post-CA AF patients that atorvastatin produced a significant reduction in EAT volume, CRP level, and LDL-cholesterol after three months of therapy, while BMI, high-density lipoprotein-cholesterol and triglycerides did not change appreciably. Similarly, in the present study, high LDL-cholesterol was associated with AF recurrence ($P=0.04$), and the use of statin had a tendency for no recurrence of AF ($P=0.05$). Lin *et al*[24] also reported that CRP levels and LA diameter had independent prognostic values in predicting AF recurrence. In the present study, the hsCRP level was higher in patients with persistent AF than in those with paroxysmal AF, and higher hsCRP levels ($>$ 0.067 mg/dl) predicted AF recurrence. However, after adjustment for these factors, a RA EAT volume $>$ 6.2 ml was an independent predictive factor for AF recurrence.

*Diagnostic accuracy of RA EAT for predicting AF recurrence*

Sanghai *et al*[25] showed that a LA EAT volume $>$ 0.95 $cm^2$/body surface area ($m^2$) using a 128-slice MDCT had a sensitivity of 45% and a specificity of 25.5% for predicting AF recurrence over 12 months of follow-up in patients with mixed AF. In a population of patients with mixed AF at a median follow-up time of 10.2 months, Nagashima *et al*[2] showed that a 320-slice MDCT LA EAT volume $>$ 63.4 $cm^3$ was predictive of AF recurrence, with a sensitivity of 60.0% and a specificity of 96.0%. In the present study, we found that a RA EAT volume $>$ 6.2 ml was predictive of AF recurrence in a population of patients with mixed AF at approximately two years of follow-up, with a sensitivity of 86.7% and a specificity of 50.9%. Further, the combination of EAT volume in both RA and LA was a powerful prognostic factor of AF recurrence, with a HR of 4.4 (95% CI, 1.4–13.8; $P=0.01$), and the combination of EAT volume and atrial volume for both atria was more predictive of AF recurrence than either factor alone (sensitivity, 60%; specificity, 81.1%).

*Study limitations*

In the present study, the small sample size was a major limitation, and a study with a large cohort should be conducted to verify these findings. The different technical protocols or procedures of CA may result in different cutoff values for atrial volume and atrial EAT volume in predicting AF recurrence. Our values of EAT volume were smaller than those of Sanghai *et al*[25] and Nagashima *et al*[2], but the EAT volume may differ according to the machine accuracy of MDCT, the measurement method, the extent of measurement around the heart, and the time course of persistent AF[26]. However, the EAT volume in the present study was measured in a similar manner to the report by Shin *et al*[12], and our values were similar to their values (mean total heart EAT in patients with paroxysmal AF, 86 ml vs. 76.6 ml).

## Conclusion

RA EAT volume is associated with the progression of AF and post-CA AF recurrence. Our findings may have important implications for considering the condition of the RA in patients with AF undergoing PV isolation.

### Compliance with Ethical Standards

*Funding*: none.

*Conflict of interest*: none.

*Ethical approval*: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

*Informed consent*: Informed consent was obtained from all individual participants included in the study.

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