Association Between Epicardial Adipose Tissue Volumes on 3-Dimensional Reconstructed CT Images and Recurrence of Atrial Fibrillation After Catheter Ablation

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Background: Whether epicardial adipose tissue (EAT) is independently associated with atrial fibrillation (AF) and outcome after catheter ablation (CA) for AF remains unclear.

Methods and Results: Three-dimensional volume-rendering reconstructed images of EAT (total EAT) and EAT surrounding the left atrium (LA-EAT) were measured on 320-row multidetector computed tomography in 40 patients with AF (paroxysmal AF [PAF], n=24; persistent AF [PerAF], n=16) who underwent CA, and in 37 age-matched control patients. EAT volumes were as follows for the control, PAF and PerAF patients: total EAT, 138.3±45.2 cm³ vs. 158.3±47.2 cm³ vs. 226.4±93.3 cm³ (P<0.01 for control or PAF vs. PerAF); LA-EAT, 32.9±14.5 cm³ vs. 41.3±15.3 cm³ vs. 66.8±35.1 cm³ (P=0.001 for control or PAF vs. PerAF). EAT volume was independently associated with the presence of AF after adjustment for possible confounding factors. EAT volume was significantly greater in patients with lone AF than in control patients (total EAT, 132.8±33.3 cm³ vs. 106.2±27.3 cm³, P=0.021; LA-EAT: 34.0±10.6 cm³ vs. 21.8±6.9 cm³, P=0.0006). EAT volumes were greater in the 15 AF patients (37.5%) with post-ablation recurrence than in patients without recurrence (total EAT: 239.0±90.2 cm³ vs. 153.5±42.7 cm³, P=0.0002; LA-EAT: 69.6±35.5 cm³ vs. 40.7±13.9 cm³, P=0.0008).

Conclusions: EAT volume increases in AF patients independent of conventional risk factors and is greater in patients with lone AF than in non-AF patients. EAT volume might be useful for predicting AF recurrence after CA. (Circ J 2011; 75: 2559–2565)

Key Words: Atrial fibrillation; Catheter ablation; Epicardial adipose tissue

The association of atrial fibrillation (AF) with metabolic syndrome and inflammation is well established. Recent studies have suggested that epicardial adipose tissue (EAT) may also be associated with AF, and EAT volume has been shown to predict the association of AF. EAT contains abundant ganglionic plexi, which can be responsible for the occurrence of AF. EAT has been reported to secrete several activated pro-inflammatory cytokines, such as tumor necrosis factor-α, transforming growth factor-β (TGF-β), and interleukin-6 (IL-6). Furthermore, because of its proximity to the heart and its shared blood supply with the coronary arteries, EAT may induce electrical and structural remodeling of the atria leading to AF. Although AF is often observed in patients with valvular heart disease, congestive heart failure, or ischemic heart disease, it is also observed in patients without structural heart disease or metabolic disorder, referred to as lone AF. Whether the association between the volume of EAT and the presence of AF is truly applicable to any AF patients with and without structural heart disease or metabolic disorder remains controversial.

Over the past decade, catheter-based ablation mainly targeting the pulmonary veins (PVs) has become a widely accepted therapy for patients with symptomatic drug-refractory AF. Several recent studies have suggested, however, that high levels of biomarkers of inflammation, and metabolic syndrome resulted in a poor outcome after catheter ablation (CA) for AF. Therefore, we hypothesized that EAT volume may influence outcome after CA for AF. Computed tomography (CT), echocardiography, and magnetic resonance imaging have been used to assess adipose tissue volume, and the majority of recent studies have used a 64-row CT scanner. A 320-row scanner was recently developed that (in comparison to the 64-row scanner) results in less radiation and less i.v. contrast dose over a shorter period of...
time. With 320-row CT, the whole heart can be scanned in 1 rotational X-ray during 1 heart beat, which allows for more accurate acquisition of the EAT volume with less artifact. We conducted a study to assess whether (1) volumes of total EAT and EAT surrounding the left atrium (LA; LA-EAT) are related to the development of AF; (2) an association exists between EAT and lone AF; and (3) EAT volume assessed using 320-row CT can predict recurrence of AF after CA.

**Methods**

**Study Groups**

The study included 40 consecutive patients who underwent CA for AF and 37 age- and sex-matched control patients without a history of AF. In the AF group, 24 patients had paroxysmal AF (PAF; spontaneous termination within 7 days), and 16 had persistent AF (PerAF; AF lasting >7 days). To minimize confounding effects, patients with coronary artery disease diagnosed using multislice CT were excluded. Patients >80 years of age or who had a previous history of ischemic heart disease, cardiomyopathy, valvular heart disease, congenital heart disease, chronic hepatic or renal disease, thyroid disease, malignancy, connective tissue disease, inflammatory disease, or hematologic disease were also excluded. The study was approved by the Institutional Review Board of Nihon University Inabashi Hospital, and all patients provided written informed consent for their participation.

**Multidetector CT and EAT Measurements**

EAT volumes were calculated from non-contrast images obtained with a 3-D spiral CT scanner (320-row detector, dynamic volume CT scanner; Aquilion One, Toshiba Medical Systems, Tokyo, Japan; 0.35-s gantry rotation time, 120 kV, and 350–450 mA). Gated assessments were performed before ablation using the use of an electrocardiogram-triggered scanning protocol. To minimize motion artifact, patients were given β-blockers and underwent CT only if their heart rate was >80 beats/min. Representative 3-D reconstructed volume renderings of total EAT and LA-EAT are given in Figure. On a workstation (Zio M900 Quadra; Amin, Tokyo, Japan), total EAT was detected by assigning Hounsfield units from −50 to −200 to fat, and the total EAT volume was semi-automatically reconstructed from contiguous 0.5-mm slices of the axial images from the bifurcation of the pulmonary artery to the diaphragm. Thereafter, the LA-EAT volume was manually segmented from the total EAT, that is, it was obtained by deleting EAT volume off the left ventricular side anterior to the mitral annulus and the right atrial side anterior to the right superior PV, and then from the lower side of the coronary sinus from the total EAT, leaving the EAT surrounding the LA. The measurements of the EAT volume were performed by 2 independent operators. The interobserver and intraobserver correlations for total EAT were 0.983 and 0.962, respectively (P<0.0001), and 0.976 and 0.975, respectively for LA-EAT (P<0.0001).

**Echocardiography**

Transesophageal echocardiography was performed before ablation with an Acuson Sequoia C256 echocardiography system (Siemens Medical Solutions USA, Malvern, PA, USA). The LA diameter (LAD) was measured in the parasternal long-axis view at the end-systole, and the left ventricular ejection fraction was assessed by means of M-mode echocardiography (Teichholz method). The maximum LA volume was calculated by the prolate-ellipsoid method. Measurements from 3 consecutive beats were averaged.

**Hematologic Measurements**

Baseline blood samples were obtained from a peripheral vein before the CT examination. Levels of standard biomarkers including serum hemoglobin A1c (HbA1c), total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride were measured in all patients. In the AF group, serum high-sensitivity C-reactive protein (hs-CRP) levels were measured using particle-enhanced immunonephelometry (Siemens Healthcare Diagnostics, Eschborn, Germany). Serum IL-6 level was measured with a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Fujirebio, Tokyo, Japan), and TGF-β1 level was also measured with a commercially available ELISA kit (Funakoshi, Tokyo, Japan).

**Electrophysiology and CA**

Details of the electrophysiology and ablation strategy have been described previously. In brief, all anti-arrhythmic drugs were discontinued for at least 5 half-lives before the procedure. With the patient under i.v. sedation with propofol and fentanyl, vascular access was obtained, and catheters were placed in standard fashion. After single trans-septal puncture, i.v. heparin was given to maintain an activated clotting time >300 s. After 3 long sheaths (2 SL0 sheaths and 1 SL1 sheath; St Jude Medical, St Paul, MN, USA) were inserted into the LA via trans-septal puncture, rotational angiography of the LA and 4 PVs was performed during right ventricular pacing at a cycle length of 300 ms. A 3.5-mm irrigated-tip catheter (Celsius ThermoCool, Biosense Webster, Diamond Bar, CA, USA) was advanced into the LA for mapping and ablation. Extensive ipsilateral PV isolation (PVI) was performed under guidance using double Lasso catheters (Biosense Webster) and a 3-D geometric NavX map (St Jude Medical). Radiofrequency energy was delivered at a maximum power output of 30 W and upper temperature limit of 41°C at a saline irrigation rate of 17 ml/min. The endpoint of the PVI was elimination or dissociation of all PV potentials and attainment of complete entrance block. In patients in whom AF was not terminated by PVI or in whom sustained AF was inducible after PVI, additional ablation was performed in the LA according to the results of post-PVI complex fractionated atrial electrogram (CFAE) mapping. The endpoint of this ablation step was termination of the AF during the procedure or abolition of all CFAEs in the LA if AF was not terminated. Anti-arrhythmic drugs previously prescribed to the patients were resumed after the procedure but were stopped 6 months later. Other previously prescribed drugs including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and statins were not changed during the follow-up period. All procedures were performed under local anesthesia with propofol and fentanyl, and statins were not changed during the follow-up period. All procedures were performed under local anesthesia with propofol and fentanyl, and statins were not changed during the follow-up period.

**Statistical Analysis**

Continuous variables are expressed as mean±SD. The serum triglyceride, hs-CRP, and IL-6 levels had a skewed distribution and are expressed as median and interquartile ranges. Student’s t-test or Mann–Whitney U-test was used to analyze differences between the 2 main study groups in baseline con-
Figure. Representative sample of 3-D volume renderings of (A) total epicardial adipose tissue (EAT) and (B) left atrium EAT (LA-EAT) in control patients and patients with paroxysmal atrial fibrillation (PAF) or persistent AF (PerAF). (A, Upper) 2-D horizontal slices of total EAT (pink) after semi-automatic detection based on assignment of Hounsfield units from −50 to −200 to fat; (Lower) 3-D reconstructed volumes of total EAT. (B, Upper) 2-D coronal slices of LA-EAT (pink) and (Lower) 3-D LA-EAT volumes. Note that LA-EAT is predominantly observed in the PV antrum, LA appendage, LA roof, and mitral annulus in patients with PAF and PerAF. Ao, aorta; LAA, left atrium appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; MA, mitral annulus; PA, pulmonary artery; RA, right atrium; RSPV, right superior pulmonary vein; RV, right ventricle; SVC, superior vena cava.
Table 1. Baseline Characteristics of Control Patients and Patients With PAF or PerAF

<table>
<thead>
<tr>
<th></th>
<th>Control (n=37)</th>
<th>Total (n=40)</th>
<th>PAF (n=24)</th>
<th>PerAF (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.1±11.1</td>
<td>58.0±10.2</td>
<td>56.9±8.3</td>
<td>59.8±12.7</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>28 (75.7%)</td>
<td>31 (77.5%)</td>
<td>17 (70.8%)</td>
<td>14 (87.5%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.6±2.5</td>
<td>23.9±2.6</td>
<td>22.2±2.6</td>
<td>24.2±2.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (35.1%)</td>
<td>15 (37.5%)</td>
<td>9 (37.5%)</td>
<td>6 (37.5%)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.6±1.4</td>
<td>5.5±0.5</td>
<td>5.4±0.3</td>
<td>5.7±0.7</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>195.8±28.5</td>
<td>205.0±30.5</td>
<td>211.5±29.4</td>
<td>195.1±30.4</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>60.8±15.7</td>
<td>60.7±22.3</td>
<td>66.1±24.2</td>
<td>52.4±16.4</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>113.3±30.0</td>
<td>113.8±23.1</td>
<td>119.3±20.8</td>
<td>105.7±24.6</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>95.0 (75.0, 120.0)</td>
<td>121.5 (90.3, 163.5)</td>
<td>113.5 (70.0, 137.0)</td>
<td>144.5 (97.5, 198.3)*</td>
</tr>
<tr>
<td>History of CHF</td>
<td>0 (0%)</td>
<td>4 (10.0%)</td>
<td>0 (0%)</td>
<td>4 (25.0%)†,‡**</td>
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<tr>
<td>Echocardiography</td>
<td></td>
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<tr>
<td>LVEF (%)</td>
<td>71.1±5.4</td>
<td>65.9±9.3**</td>
<td>66.7±5.6</td>
<td>64.5±13.4*</td>
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<tr>
<td>LAD (mm)</td>
<td>34.3±5.3</td>
<td>36.8±8.0</td>
<td>34.7±6.3</td>
<td>40.3±9.5**</td>
</tr>
<tr>
<td>LAV (ml)</td>
<td>–</td>
<td>46.3±29.3</td>
<td>35.9±16.2</td>
<td>62.4±37.2†</td>
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<td>Biomarkers</td>
<td></td>
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<tr>
<td>hs-CRP (ng/ml)</td>
<td>–</td>
<td>3250.0 (141.0, 565.0)</td>
<td>542.0 (224.0, 1546.0)</td>
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</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>–</td>
<td>1.4 (1.0, 2.5)</td>
<td>1.9 (1.4, 2.5)</td>
<td></td>
</tr>
<tr>
<td>TGF-β (ng/ml)</td>
<td>–</td>
<td>8.9 (5.2, 13.9)</td>
<td>6.4 (4.7, 16.6)</td>
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Values are the mean±SD, median (25th, 75th interquartile range) or n (%).
*P<0.05, **P<0.01 vs. control values.†P<0.05, ‡P<0.01 vs. PAF.

PAF, paroxysmal atrial fibrillation (AF); PerAF, persistent AF; BMI, body mass index; HbA1c, hemoglobin A1c; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; LAD, left atrial (LA) diameter; LAV, LA volume; EAT, epicardial adipose tissue; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; TGF-β, transforming growth factor-β.

Results

Baseline characteristics of patients in the 2 study groups (AF and control patients) are listed in Table 1. There was no significant difference in age, sex, or body mass index (BMI) between the 2 groups. The prevalence of hypertension, hyperlipidemia, diabetes, or history of congestive heart failure also did not differ between the 2 groups. BMI, however, was significantly higher in patients with PerAF than PAF (24.2±2.1 kg/m² vs. 22.2±2.6 kg/m², P=0.037), and serum triglyceride level was significantly higher in patients with PerAF than the control (144.5 mg/dl, 97.5–198.3 vs. 95.0 mg/dl, 75.0–120.0; P=0.012; Table 1).

Representative examples of the 3-D reconstructed total-EAT and LA-EAT are shown in Figure. The EAT surrounding the LA was often observed in the PV antrum, LA appendage, LA roof, and mitral annulus. The EAT volume increased from the control level to the PAF patient level and then to the PerAF level (total EAT: 138.3±45.5 cm³ vs. 158.3±47.2 cm³ vs. 226.4±93.3 cm³; P=0.40 for control vs. PAF, P=0.0001 for control vs. PerAF, P=0.0017 for PAF vs. PerAF; LA-EAT: 32.9±14.5 cm³ vs. 41.3±15.3 cm³ vs. 66.8±35.1 cm³; P=0.27 for control vs. PAF, P=0.0001 for control vs. PerAF, P=0.0008 for PAF vs. PerAF; Table 1). LA dimension was larger in patients with PerAF than in control and PAF patients, but there was no difference between PAF patients and controls (34.3±5.3 mm for control vs. 34.7±6.3 mm for PAF, 40.3±9.5 mm for PerAF; P=0.97 for control vs. PAF, P=0.014 for control vs. PerAF, P=0.036 for PAF vs. PerAF). The association between EAT volume and variables including age; BMI; serum levels of HbA1c, cholesterol, and triglyceride; and presence of AF are given in Table 2. EAT volume was positively associated with age, BMI, triglyceride level, and presence of AF, and negatively with the HDL-C level. No association was found, however, between EAT volume and HbA1c, or LDL-C level. After adjustment for these variables, age, BMI, triglyceride level, and presence of AF remained significantly associated with EAT volume. Fifteen patients with AF but without metabolic syndrome (n=16). The EAT volume was significantly greater in the lone AF patients than in the control patients (total EAT: 132.8±33.3 cm³ vs. 106.2±27.3 cm³, P=0.021; LA-EAT: 34.0±10.6 cm³ vs. 21.8±6.9 cm³, P=0.0006).
Epicardial Fat Volume and AF

Fifteen (37.5%) of the 40 AF patients experienced recurrent AF after CA. EAT volumes were significantly greater in the patients with AF recurrence than in those without recurrence (total EAT: 239.0±90.2 cm³ vs. 153.5±42.7 cm³, P=0.0002; LA-EAT: 69.6±35.5 cm³ vs. 40.7±13.9 cm³, P=0.0008). AF recurrence was also increased in patients with PerAF, longer duration of AF, higher BMI, larger LAD and LA volume, and higher serum HDL-C and triglyceride levels (Table 3). According to the ROC curve (area under the curve: 0.80), the most sensitive cut-off for LA-EAT volume to predict AF recurrence was >63.4 cm³, with a sensitivity of 60.0% and a specificity of 96.0%.

Discussion

Main Findings

The present study has found that the 3-D reconstructed total EAT and LA-EAT volumes became increased, from the control patients to the PAF patients, and then to the PerAF patients.
In addition, greater total EAT and LA-EAT volumes were found in patients with lone AF than in the control patients. Further, the total EAT and LA-EAT volumes were associated with age, HDL-C and triglyceride levels, and presence of AF. Thus, total EAT and LA-EAT volumes might be useful for identifying patients at risk for AF recurrence after ablation.

**EAT and AF**

We found that the EAT volume was greater in patients with AF, and that EAT volume was greater in patients with PerAF than in those with PAF. Although the mechanism underlying the increased EAT volume in patients with AF is uncertain, the present data imply that EAT may contribute to the progression of atrial remodeling or that EAT may be a consequence of the atrial remodeling that develops as a result of PerAF. Recent studies clarified that EAT is a particular form of visceral adipose tissue that is in direct contact with the myocardium and acts as a biologically active endocrine organ, secreting several inflammatory cytokines, which might promote atrial structural remodeling. Generally, EAT volume has been shown to increase in patients with metabolic syndrome. In fact, several recent large population-based cohort studies confirmed the association between metabolic syndrome and AF even after adjustment for possible confounding factors. Nonetheless, the mechanisms underlying increased prevalence of AF in patients without systemic metabolic factors (ie, patients with lone AF), remain unclear. In the present study, EAT volume remained significantly greater in lone AF patients than in control patients without metabolic syndrome. CFAEs or high dominant frequency sites have been suggested to be important regions for the initiation and/or the maintenance of AF. CFAEs or high dominant frequency sites are commonly distributed at the PV antrum, LA appendage, mitral annulus, or LA roof. Of interest, these sites were similar to the location of the EAT surrounding the LA. Although a direct relationship between the location of the EAT and the electrical parameters such as CFAEs or high dominant frequency sites was not evaluated in the present study, these findings may provide additional insight into the underlying mechanism, in that a “local metabolic syndrome” caused by EAT surrounding the atrium may lead to AF.

EAT volumes were significantly greater in the AF patients than in the control patients, but the absolute 3-D rendered EAT volumes obtained in the present study were greater than those reported in other recent studies. The discrepancy may be explained by the wider 320-row detector used in the present study vs. the commonly used 64-row CT scanner. Our particular 320-row detector CT scanner acquires accurate high-resolution 3-D images because it allows full cardiac coverage in a single heart beat without table movement, and eliminates stair-step artifacts. In addition, we used plain CT images to avoid underestimation of the adipose tissue density that could be influenced by the presence of contrast medium. Our further comparison of the EAT volume with and without contrast medium in 5 patients confirmed that the EAT volume quantified from non-contrast images was significantly greater than that quantified from contrast images (total EAT: 185.3±65.0 cm³ vs. 146.5±50.4 cm³, P=0.0072; LA-EAT: 52.8±17.2 cm³ vs. 29.2±12.5 cm³, P=0.0049).

**EAT and Recurrence of AF**

We found that large 3-D EAT volumes were associated with post-ablation recurrence of AF. The patients with AF recurrence also had a larger LAD and longer duration of AF, suggestive of progressive atrial remodeling. A recent study reported that metabolic syndrome was an independent predictor of AF recurrence after CA. Therefore, the greater EAT volume in patients with post-ablation AF recurrence may reflect the consequence of progressive atrial remodeling by upregulation of inflammatory molecules. However, the follow-up period after CA was short (median, 10.2 months). A longer follow-up study may provide additional insight into the association between EAT and post-ablation recurrence of AF.

**Study Limitations**

There were several study limitations that should be noted. First was the relatively small number of patients, which might have influenced the statistical analysis. Second, the study was not designed to address whether the presence of increased EAT was the cause or consequence of AF. In addition, there were no available data regarding the relationship between EAT and the electrical information (eg, CFAEs, high-frequency activity, bipolar voltage amplitude, or conduction delay). Although EAT may influence the LA substrate via inflammation, future studies are needed to prove this hypothesis. Third, although the present subjects were well-matched, in terms of baseline characteristics the AF patients were limited to those with symptomatic AF who had not responded to anti-arrhythmic drug therapy and who were referred for ablation. We believe this is not problematic because the pathogenesis of AF is similar between symptomatic and asymptomatic AF.

**Conclusions**

The 3-D rendered EAT volume was increased in AF patients independent of conventional risk factors, and EAT volume was greater in patients with lone AF than in non-AF patients. The EAT volume might be useful for predicting recurrence of AF after ablation. The present data suggest that EAT volume is associated not only with the presence of AF but also with progressive structural remodeling of the atria in patients with persistent AF refractory to CA.

**Disclosures**

Funding: Departmental sources only. Conflict of interest: None.

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