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Original article

Inflammation of left atrial epicardial adipose tissue is associated with paroxysmal atrial fibrillation

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ABSTRACT

Background: Although an increased epicardial adipose tissue (EAT) volume around the left atrium (LA) is related to the atrial fibrillation (AF) burden, the role of EAT inflammation in AF is unclear. We investigated the association between AF and inflammation of the EAT around the LA.
Methods: We retrospectively identified regions of EAT around the LA and measured the density of these areas using computed tomography (CT).
Results: A total of 32 patients who underwent their first catheter ablation for paroxysmal AF (PAF) were enrolled (mean age 62.5 ± 11.1 years). Patients without a history of AF (n = 32), but who underwent cardiac CT and were matched by age, sex, and metabolic risk factors, were enrolled in the control group (62.2 ± 12.1 years). The mean EAT density around the LA was significantly higher in the PAF group than in the control group (−108.1 ± 6.7 vs. −111.6 ± 5.5 Hounsfield units; p = 0.02), while the densities of subcutaneous adipose tissue (SAT) in the abdomen and thorax did not differ between the two groups. In a multiple logistic regression analysis, a higher EAT density was significantly associated with the presence of PAF after adjusting for other risk factors (odds ratio: 1.25; 95% confidence interval: 1.08–1.45, p = 0.003).
Conclusions: This study supports the hypothesis that inflammation of EAT around the LA, but not SAT, is related to the presence of PAF.

Introduction

Atrial fibrillation (AF) is a commonly encountered arrhythmia that is associated with high morbidity and mortality [1]. Obesity as defined by body mass index (BMI) is one of the risk factors for developing AF, as are advanced age, diabetes, hypertension, and coronary artery disease (CAD) [2–5]. Ectopic fat deposits in muscle, liver, and the pancreas correlate with insulin resistance and CAD [4]. Epicardial adipose tissue (EAT) is ectopic visceral fat that surrounds the heart, and increased EAT volumes correlate with the prevalence of AF, as well as with the recurrence of AF after ablation therapy [6,7]. Increased fat thickness at the posterior left atrium (LA) may be particularly related to the AF burden, independent of age, BMI, and the LA area [8,9]. Nevertheless, the mechanisms of AF pathogenesis and the formations of AF substrate due to EAT are not well understood.

Chronic inflammation is not only associated with the presence of AF, but also predicts patients at increased risk of developing AF [10]. In CAD, the extent of EAT accumulation is associated with disease severity, and perivascular adipocytes are known to secrete inflammatory cytokines [4,11–14]. The presence of inflammation in pericardial fat results in a higher density in computed tomography (CT) images and is correlated with culprit lesions in patients with CAD [15]. However, the association between EAT-associated inflammation and AF remains unclear.

This study investigated the hypothesis that increased EAT density around the LA as determined by CT is associated with the presence of paroxysmal AF (PAF).

Methods

Study group

The study population consisted of 64 patients who underwent cardiac CT. In total, 51 consecutive patients underwent their first catheter ablation for AF with cardiac CT between January 2011 and September 2013 at our hospital; 19 of these patients were

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excluded, leaving 32 patients in the PAF group. The exclusion criteria were as follows: persistent or long-lasting persistent AF, moderate or severe valvular disease, left ventricular ejection fraction (LVEF) < 55%, BMI > 30 kg/m^2, heart failure, B-type natriuretic peptide level > 200 pg/mL, history of open heart surgery, and evidence of active infection or inflammation. Persistent AF was defined as AF lasting > 7 days, and long-lasting persistent AF was AF lasting > 1 year.

An additional 347 consecutive patients underwent cardiac CT to examine their coronary artery regions between April 2011 and March 2012. Of these, 32 patients without a documented history of AF and who were matched for age, sex, BMI, the presence of hypertension, diabetes mellitus, and dyslipidemia with the PAF group were enrolled in the control group.

This study was approved by our local institutional review boards and ethics committees, and was performed in accordance with institutional policies, national legal requirements, and the revised Helsinki declaration. Written informed consent was obtained from each PAF patient. This study is registered in the Universal Hospital Medical Information Network Clinical Trials Registry (UMIN000012606; http://www.umin.ac.jp/ctr).

Cardiac CT protocol

A 128-section DSCT SOMATOM Definition Flash scanner (Siemens Healthcare, Erlangen, Germany) was used for all patients in this study. If necessary, the patients were given an intravenous β-blocker to reduce their heart rate. The raw data were reconstructed using algorithms optimized for electrocardiogram-gated multi-slice spiral reconstruction. For contrast-enhanced scans, 90 mL of nonionic contrast agent (Optiray 310; Covidien Japan, Tokyo, Japan) were injected intravenously at a flow rate of 4.5 mL/s.

Cardiac CT image analysis

EAT regions containing the five major LA ganglionated plexuses (GPs) were identified: superior left (SL), inferior left (IL), anterior right (AR), inferior right (IR), and Marshall tract (MT). The anatomic areas of the GPs were presumed based on previous reports of the autonomic innervation of the heart (Fig. 1) [16,17].

A predefined image display setting was used [window width −195 to −45 Hounsfield units (HU), window center −120 HU] to identify pixels that corresponded to fat tissue (Fig. 1) [4].

The cardiologists interpreting the results were blinded to the clinical results of the patients. They trimmed along the LA, pulmonary veins, and left atrial appendages using axial, coronal, and sagittal slices. EAT areas were defined as any adipose tissue located within the pericardial sac. The EAT densities in the CT images were measured around the LA using plain CT images in both groups. The cardiologists interpreting the results only referred to enhanced CT images when they had difficulty detecting the anatomical locations of the EAT. The mean value of the five regions of interest was recorded at each EAT. The regions of interest were set as follows: circular shape, size ≥ 5 mm^2, and the whole region was fully contained in each local EAT area (Fig. 2). When the EAT area could not contain five regions in a single axial level, some regions of interest were set at upper or lower axial levels. The densities of subcutaneous adipose tissue (SAT) in the abdomen and thorax were measured similarly.

Assessment of risk factors and covariates

The following patient data were collected: the presence of hypertension, the presence of dyslipidemia, the presence of diabetes mellitus, high-sensitivity C-reactive protein (hs-CRP), BMI, and current medication. Hypertension was defined as blood pressure > 140/90 mmHg on repeated measurements, or current treatment with antihypertensive agents. Blood samples were obtained at the time of cardiac CT to measure the serum levels of the indicated markers. Dyslipidemia was defined as low-density lipoprotein cholesterol (LDL-C) levels > 140 mg/dL, high-density lipoprotein cholesterol (HDL-C) levels < 40 mg/dL, triglyceride levels > 150 mg/dL, or the use of a statin. LDL-C was examined directly or was calculated using the Friedewald method [18]. Diabetes mellitus was defined as a fasting plasma glucose > 126 mg/dL, hemoglobin A_{1c} > 6.5%, or current treatment with hypoglycemic agents. Echocardiography was performed to measure the size of each cardiac chamber and to assess cardiac function at approximately the same time as the cardiac CT. The LA diameter was measured at the end of systole in the parasternal long-axis view, and LA enlargement was defined as a diameter > 42 mm. LVEF was measured using the M-mode or modified Simpson's method; an LVEF of <55% was considered abnormal. Moderate or high valvular regurgitation was diagnosed using echocardiography.

Statistical analyses

Categorical variables are presented as numbers (%), and continuous variables are presented as means ± standard deviations (SDs). Student's *t*-test or the Mann–Whitney *U*-test was used to analyze differences between the two study groups in baseline continuous variables, and the chi-square test was used for dichotomous variables. The values for hs-CRP and triglycerides were log-transformed to improve normality. The results were finally expressed on the original scale, after exponentiation, as geometric means and the corresponding asymmetric 95% confidence intervals (CIs).

The non-LA EAT densities in the PAF group were calculated by two operators and intra- and inter-observer reliability for the EAT density measurements was examined using intra- and inter-class correlation coefficients, respectively, with their 95% CIs. Additionally, inter-observer agreements were also shown using the Bland and Altman plot. The mean difference was presented as the bias and 95% limits of agreement around the bias expressed as the mean difference ± 1.96 SDs.

Multiple logistic regression analysis was used to compare the association between the density of the EAT and PAF between the control and PAF groups. A value of $p < 0.05$ was considered statistically significant. All analyses were performed using SPSS version 19.0 for Windows (SPSS; Chicago, IL, USA).

Results

Baseline characteristics

Between January 2011 and September 2013, 32 patients underwent their first catheter ablation for PAF with cardiac CT, and were included in the PAF group (mean age 62.5 ± 11.1 years; 19 males). The mean disease duration of PAF was 4.6 ± 5.2 years. In addition, 32 patients were enrolled in the control group (mean age 62.2 ± 12.1 years; 19 males). The baseline characteristics of the two groups are shown in Table 1. The PAF group had a larger LA diameter, and more patients in this group used β-blockers.

EAT density and PAF

The EAT density was calculated by two independent operators. The intra- and inter-observer correlations were 0.890 and 0.910, respectively ($p < 0.001$). The Bland and Altman plot showed a good agreement between the observers, with a bias of −0.75 ± 7.25 HU and the 95% limits of agreement was −14.97 to 13.47 HU (Fig. 3).

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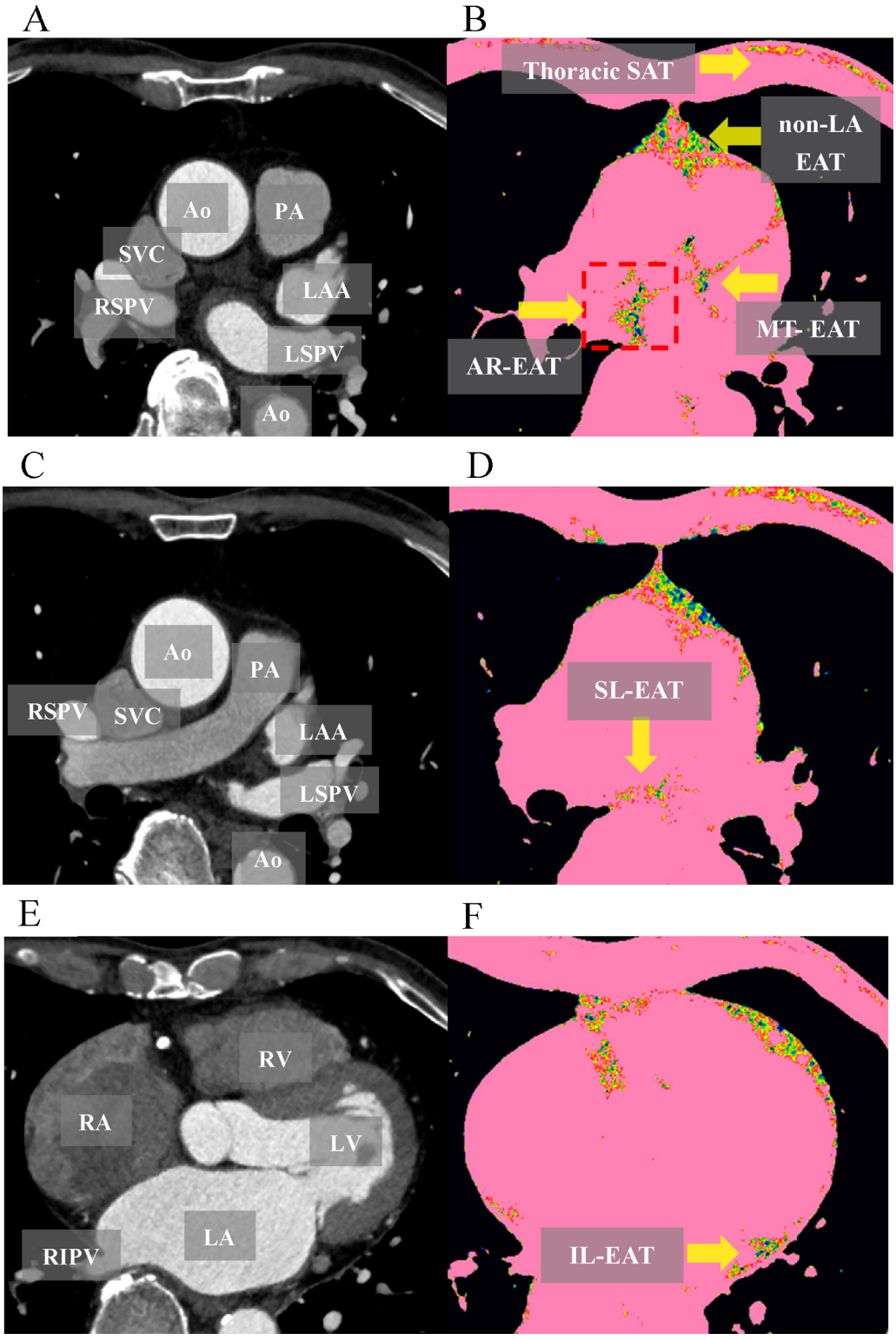

Fig. 1. Computed tomography (CT) image settings and location of the EATs. (A, C, and E) Enhanced CT images from a paroxysmal atrial fibrillation patient. (B, D, and F) Predefined plain CT image display settings (window width −195 to −45 HU, window center −120 HU) were used to identify pixels corresponding to fat tissue. Each image in B, D, and F shows the same axial level with the image of A, C, and E respectively. Yellow arrows indicate typical EAT and thoracic SAT regions. Ao, aorta; PA, pulmonary artery; SVC, superior vena cava; LA, left atrium; LAA, left atrial appendage; RS, right superior; LS, left superior; RI, right inferior; PV, pulmonary vein; RA, right atrium; RV, right ventricle; LV, left ventricle; EAT, epicardial adipose tissue; SAT, subcutaneous adipose tissue; MT, Marshall tract; AR, anterior right; SL, superior left; IL, inferior left.

The mean density of the EATs containing all five EAT areas (LA-EAT) in the PAF group was significantly higher than that in the control group (-108.1 ± 6.7 HU vs. -111.5 ± 5.5 HU, $p = 0.02$; Table 2). In the regional analysis of EAT, the densities of the AR-EAT and MT-EAT were significantly higher, and that of the SL-EAT and IR-EAT tended to be higher, in the PAF group than in the controls. In comparison, the densities of SAT in the abdomen and thorax did not differ between the two groups. Several parameters were included in the multiple logistic regression analysis: age, sex, BMI, LA diameter, and LA-EAT density. The density of LA-EAT was significantly

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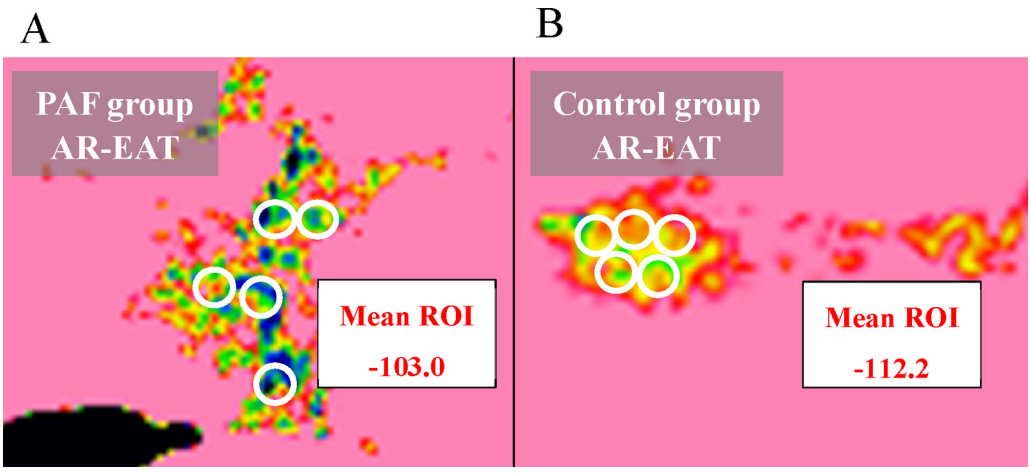

Fig. 2. Representative measurement of EAT density. (A) Predefined plain computed tomography image from a paroxysmal atrial fibrillation patient, and (B) a control patient. Figure A shows the magnified image of the area encircled by dashed square in Fig. 1B. Among the colors corresponding to adipose tissue, blue area indicates relatively higher HU, and red area indicates lower HU. White circles indicate regions of interest (ROI) contained in each AR-EAT area. The mean value of the five ROIs was recorded at each EAT area. AR, anterior right; EAT, epicardial adipose tissue.

Table 1
Baseline patient characteristics.

	Control ($n=32$)	PAF ($n=32$)	p-Value
Age, years	62.2 ± 12.1	62.5 ± 11.1	0.91
Sex, male	19 (59.4)	19 (59.4)	1.00
BMI, kg/m^2	23.1 ± 2.8	23.3 ± 2.7	0.79
LVEF, %	69.0 ± 6.2	66.2 ± 5.6	0.06
LA diameter, mm	33.7 ± 4.2	39.7 ± 7.1	<0.01
Hypertension	17 (53.1)	17 (53.1)	1.00
Dyslipidemia	21 (65.6)	21 (65.6)	1.00
Diabetes mellitus	4 (12.5)	4 (12.5)	1.00
hs-CRP, mg/dL[a]	0.07 (0.04–0.10)	0.04 (0.03–0.06)	0.07
TG, mg/dL[a]	113.1 (94.6–144.2)	117.9 (99.0–141.8)	0.75
HDL-C, mg/dL	53.4 ± 13.9	52.9 ± 11.5	0.87
LDL-C, mg/dL	106.7 ± 36.5	101.6 ± 20.1	0.50
HbA_{1c}, %	5.75 ± 0.50	5.78 ± 0.69	0.86
β-Blockers, %	3 (9.4)	16 (50.0)	<0.01
ACEI/ARB, %	11 (34.4)	13 (40.6)	0.61
Statins, %	10 (31.3)	13 (40.6)	0.43

All values are presented as means ± SDs or n (%).
[a] The values are the geometric mean and corresponding asymmetric 95% confidence intervals.
PAF, paroxysmal atrial fibrillation; BMI, body mass index; LVEF, left ventricular ejection fraction; LA, left atrium; hs-CRP, high-sensitivity C-reactive protein; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA_{1c}, hemoglobin A_{1c}; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

Table 2
Density of EAT around the LA and SAT.

	Control	PAF	p-Value
LA-EAT, HU	−111.6 ± 5.5 ($n=32$)	−108.1 ± 6.7 ($n=32$)	0.02
SL-EAT, HU	−110.7 ± 8.5 ($n=26$)	−107.5 ± 7.7 ($n=30$)	0.15
IL-EAT, HU	−114.4 ± 8.4 ($n=22$)	−112.4 ± 8.7 ($n=29$)	0.41
AR-EAT, HU	−111.8 ± 5.8 ($n=19$)	−107.7 ± 7.4 ($n=31$)	0.045
IR-EAT, HU	−111.7 ± 7.6 ($n=23$)	−108.7 ± 10.8 ($n=31$)	0.25
MT-EAT, HU	−112.2 ± 7.1 ($n=28$)	−105.0 ± 10.4 ($n=26$)	< 0.01
Abdominal SAT, HU	−121.5 ± 3.7 ($n=32$)	−123.0 ± 5.8 ($n=32$)	0.21
Thoracic SAT, HU	−122.7 ± 6.3 ($n=32$)	−124.9 ± 5.5 ($n=32$)	0.40

All data are presented as means ± SDs.
PAF, paroxysmal atrial fibrillation; LA, left atrium; EAT, epicardial adipose tissue; SAT, subcutaneous adipose tissue; SL, superior left; IL, inferior left; AR, anterior right; IR, inferior right; MT, Marshall tract; HU, Hounsfield units.
LA-EAT is shown as the mean density of EATs containing all five EAT areas.

associated with the presence of PAF (odds ratio: 1.25; 95% CI: 1.08–1.45, $p = 0.003$), as well as the LA diameter after adjusting for AF risk factors, including age, sex, and BMI (Table 3).

Discussion

Our results show that the EAT density around the LA in CT images was associated with the presence of PAF. The density of LA-EAT was significantly greater in the PAF group than in the controls. Furthermore, this difference was significantly correlated with the presence of PAF, and was independent of other metabolic risk factors.

EAT around the LA

EAT is contiguous with cardiac structures; it overlies the right ventricle, coronary arteries, left ventricular apex, and atria, without forming an intervening fascia between these

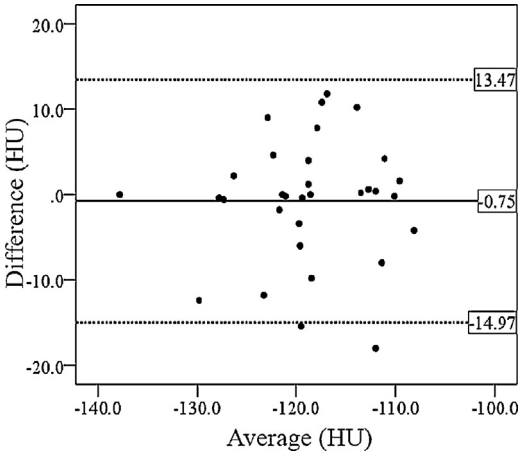

Fig. 3. Bland and Altman plots of inter-observers agreements. Bland and Altman plots shows inter-observer agreements for the epicardial adipose tissue density measurements with mean difference (thick line) and 95% limits of agreement (±1.96 standard deviations, dashed lines).

Table 3
Multiple logistic regression analysis comparing the PAF and control groups.

	Wald statistics	Odds ratio (95% CI)	*p*-Value
LA-EAT, HU	9.008	1.25 (1.08–1.45)	0.003
LA diameter, mm	14.087	1.36 (1.16–1.59)	<0.001
Age, years	0.927	0.97 (0.91–1.03)	0.34
Sex, male	1.18	2.21 (0.53–9.34)	0.28
BMI, kg/m^2	0.001	1.00 (0.75–1.35)	0.98

CI, confidence interval; PAF, paroxysmal atrial fibrillation; LA, left atrium; EAT, epicardial adipose tissue; BMI, body mass index.

structures [19]. Our study targeted EAT surrounding the LA because the LA plays an important role in AF, particularly around the pulmonary veins. We identified sites of EAT anatomically, corresponding to five major LA GPs based on reports of the autonomic innervation of the heart [8,16,17]. In fact, EAT around the LA was found in these five major GP regions. Clinically, GPs have a large effect on the initiation and perpetuation of AF, and their existence has been confirmed by the induction of hypotension and bradycardia with high-frequency pacing at that site. Although we assessed the density of EAT in each anatomical GP region, we did not confirm that each EAT area actually contained a GP in this study.

Inflammation and density

Inflamed tissue has higher attenuation values than non-inflammatory tissue on CT [20]. Furthermore, Konishi et al. [15] reported that a higher density in CT images reflects the presence of pathological inflammation in pericardial fat and is significantly correlated with CAD. We measured the density of the EAT to assess EAT inflammation in PAF patients, and we found that the density of LA-EAT was significantly higher in the PAF group than in the control group.

Inflammation of EAT and AF

Several prospective epidemiological studies confirmed that inflammation might confer an increased risk of AF [10]. A previous study assessed inflammation of EAT that was harvested from patients undergoing cardiac surgery, and showed that it represented an important local source of the inflammatory mediators tumor necrosis factor-α and interleukin-6 [21,22], which might have direct arrhythmogenic effects on atrial tissue and be associated with AF pathogenesis [23]. Moreover, lone AF and rapid acute pacing were recently reported to provoke significant changes in atrial adipogenesis and to promote adipocyte differentiation and adipose tissue expansion [24]. These mechanisms might play an important role in the formation of the AF substrate during the pathogenesis of AF. Therefore, these qualitative changes in EAT may be related to higher EAT density.

Recently, the relationship between PAF and persistent AF and inflammatory activity of the EAT measured using fluorodeoxyglucose-positron emission tomography was reported [25]. In our study, the density of LA-EAT in CT images was significantly higher in the PAF group, while that of SAT was not. In addition, hs-CRP as a marker of systemic inflammation did not differ between the two groups; however, the EAT density was higher in the PAF group. These results support the existence of local inflammation in the fat pads surrounding the atria, but not in subcutaneous fat in the PAF patients. It is well known that hs-CRP levels are often increased in AF patients [26]. However, in our study, it did not differ between the two groups. In this study, more CAD patients were included in the control group (control: $n = 6$ vs. PAF: $n = 1$), and the usage ratio of β-blockers, which has been reported to associate with lower CRP levels [27], was higher in the PAF group (Table 2). These might be the reasons why hs-CRP levels in this study were not different between the groups. Further study is needed to determine whether atrial EAT causes inflammation and subsequent AF.

In this study, the LA diameter was significantly larger in the PAF group. Although increased LA size is a strong risk factor for AF [28], the EAT density on CT was a significant predictor of the presence of PAF in the multiple logistic regression analysis including LA diameter in our study.

Study limitations

There were some limitations to this study that must be considered. For example, it was a retrospective study with a relatively small number of PAF patients. The subjects were not randomly selected from the general population, and our data contained risk factors, including blood pressures and lipid profiles, that were likely to be modified by therapeutic agents. Future studies should investigate the relationship between electrophysiological and pathological changes in the atrial myocardium in patients with AF and inflammation of the EAT around the LA.

Conclusions

In this study, the mean EAT density around the LA as determined by CT was higher in PAF patients, and this result was significantly correlated with the presence of PAF, which was independent of other metabolic risk factors. This supports the hypothesis that inflammation of EAT around the LA (but not of SAT) is related to the presence of PAF.

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Conflict of interest

The authors declare that there is no conflict of interest.

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