Association between Epicardial Adipose Tissue and Recurrence of Atrial Fibrillation after Ablation: A Propensity Score-Matched Analysis

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Research Article

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Abstract

Purpose: To assess the association between epicardial adipose tissue (EAT) index derived from cardiac computed tomography and atrial fibrillation (AF) recurrence after ablation by comparing with a propensity score matched non-recurrence AF patients.

Methods: A total of 506 patients with AF recurrence and 174 patients without AF recurrence were enrolled in this retrospective study. Density and volume of total EAT surrounding the heart (Total-EAT) and EAT surrounding the left atrium (LA-EAT) were measured, propensity score matching (PSM) analyses were used to compare the outcomes of the two groups while controlling for confounders.

Results: Total-EAT density (HU) value (-81.27 ± 4.67 vs -84.05 ± 3.84 , $P=0.000$) and LA-EAT density (HU) value (-72.47 ± 23.87 vs -78.83 ± 3.81 , $P=0.001$) were significantly higher in the patients with AF recurrence than in those without recurrence. LA-EAT density (HU) value was significantly higher than Total-EAT (-75.65 ± 17.36 vs -82.66 ± 4.49 , $P=0.000$). In a multiple logistic regression analysis, a higher Total-EAT density (odds ratio: 1.09; 95% CI: 1.00 – 1.19, $p = 0.047$) and LA-EAT density (odds ratio: 1.12; 95% CI: 1.03 – 1.23, $p = 0.012$) was significantly associated with the AF recurrence after adjusting for other risk factors.

Conclusion: The LA-EAT density plays an important role in the AF recurrence after ablation. Assessment of LA-EAT density can improve ablation outcomes by refining patient selection.

1. Introduction

Atrial fibrillation (AF) is the most common type of supraventricular tachyarrhythmia[1]. Serious complications, such as stroke, thromboembolism, and myocardial infarction, can be induced by AF, resulting higher rates of disability and death[2–5]. Catheter-based ablation mainly targeting the pulmonary veins (PVs) has become a widely accepted therapy for patients with symptomatic drug-refractory AF.[6] However, there is still a high recurrence rate after catheter ablation of AF (accounting for 10–30%)[7].

Epicardial adipose tissue (EAT), as a special visceral adipose tissue, has been proved to be related to the occurrence, severity of AF and the recurrence of AF after catheter ablation[8, 9]. EAT has a high metabolic activity, in which the high expression of inflammatory mediators such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) can lead to local inflammatory reaction, which promote the occurrence of arrhythmia[10–13].

Most studies have shown that EAT volume (EATV) is related to recurrence after AF ablation, but in recent years, EAT density as a newly emerging indicator has also been shown to be an independent predictor of recurrence after AF ablation[14]. The value of research on the correlation between density or volume and AF recurrence remains unknown. In addition, in these studies, the choice of EAT measurement location includes total EAT surrounding the heart (Total-EAT) and EAT surrounding the left atrium (LA-EAT). Studies have shown that the concentration of inflammatory mediators in the LA-EAT is higher than EAT surrounding other cardiac chambers[15–17]. Therefore, whether Total-EAT or LA-EAT is more suitable for studies on recurrence of AF is still inconclusive, the selection of EAT measurement location was challenging.

However, some studies found that EATV does not affect the results of surgical ablation[18]. Various studies have shown that the components of metabolic syndrome, including obesity elevated blood pressure, elevated blood sugar, and lipid metabolism disorders were related to the AF recurrence[19], therefore, the controversy in the above results may be caused by the lack of balanced these confounding factors. In observational research, propensity score matching (PSM) can match the experimental group and the control group in a certain proportion through a certain statistical method to avoid potential selection bias.

In this background, we aimed to investigate the correlation between EAT volume or density and AF recurrence after ablation by applying PSM approach to adjust potential covariate imbalance and to compare the density of the Total-EAT-LA-EAT.

2. Materials And Methods

2.1 Study population

This retrospective study was approved by the Institutional Review Board. The written informed consent was waived. 782 consecutive hospitalized patients with symptomatic, drug-refractory AF referred for catheter ablation from January 1, 2017 to December 31, 2018 were enrolled in this study, all patients underwent preprocedural cardiac computed tomography angiography (CCTA) of the LA and pulmonary veins. 689 patients were included in this study according to the exclusion criteria. The clinical characteristics were retrospectively collected from the patients' medical records. Fig. 1 shows the flowchart for inclusion and exclusion.

2.2 Ablation procedure

The patient was placed supine in the magnetic navigation room for cryoballoon ablation of atrial fibrillation, routinely sterilized drapes, and 2% lidocaine was used for local anesthesia. Then, the right jugular vein and left femoral vein were punctured and sheathed, and electrophysiological markers were inserted through the sheath. The electrodes are measured at the coronary sinus and superior vena cava. Sinus rhythm was present in the basal state. The right femoral vein was punctured and the sheath was placed, the long sheath was placed in the superior vena cava, the atrial septal puncture was performed, the guide wire was placed in the left atrium, the cryo-balloon delivery catheter was placed, and the cryo-balloon was delivered through the catheter, which were placed in the left, The right, upper, and lower pulmonary veins, angiography showed good sealing and cryoablation, and pulmonary vein isolation was performed. Postoperative verification of pulmonary vein potential isolation is complete.

2.3 Follow-up

All patients received antiarrhythmic drugs for 8 weeks to prevent any early AF recurrence after catheter ablation. AF recurrence was defined as any evidence of an episode of atrial arrhythmia lasting more than 30 s after a 3-month blanking period[20]. All patients were followed up for at least 1 year after catheter ablation.

2.4 Propensity Score Matching

We used PSM approach to create a new dataset in which the probability of patients with and without AF recurrence is equal to balance patients' baseline characteristics[21]. As shown in Table 1, before PSM, differences between the patients with and without AF recurrence in 2 variables, which were age and triglyceride. Two of the clinical variables above with a certain difference ($p < 0.05$) were selected to match the two groups. Propensity scores were obtained by utilizing logistic regression. Logit-transformed propensity scores matched to the nearest neighbor in a 1 : 1 fashion with a caliper of 0.2 were used for the matching.

Table 1
Baseline Characteristics of population

Characteristic		Before matching (689 patients)			After matching (348 patients)		
		Non-recurrence (506 patients)	Recurrence (174 patients)	P	Non-recurrence (174 patients)	Recurrence (174 patients)	P
age		62.00 (55.00, 67.00)	64.00 (57.00, 69.25)	0.007	63.00 (58.00, 69.00)	64.00 (57.00, 69.25)	0.780
BMI(Kg/m ²)		24.56 (22.65, 26.93)	24.68 (22.90, 26.75)	0.901	24.49 (22.49,27.23)	24.68 (22.90, 26.75)	0.902
TC(mmol/L)		4.31±0.98	4.21±1.01	0.281	4.18±1.00	4.22±1.01	0.739
LDL-C(mmol/L)		2.65 (1.97, 3.14)	2.53 (1.87, 3.09)	0.244	2.53±0.81	2.54±0.87	0.843
HDL-C(mmol/L)		1.16 (1.01, 1.35)	1.18 (1.02, 1.36)	0.600	1.16 (1.02, 1.39)	1.18 (1.02, 1.36)	0.604
TG(mmol/L)		1.42 (1.03, 1.91)	1.27 (0.90, 1.72)	0.019	1.26 (0.89, 1.72)	1.27 (0.90, 1.72)	0.997
gender	Male	323(63.8%)	111(63.8%)	0.992	110 (63.2%)	111(63.8%)	0.911
	Female	183(36.2%)	63(36.2%)		64 (36.8%)	63 (36.2%)	
diabetes	Absent	434(85.8%)	146(83.9%)	0.550	149 (85.6%)	146(83.9%)	0.654
	Presence	72(14.2%)	28(16.1%)		25 (14.4%)	28 (16.1%)	
hyperlipidemia	Absent	333(65.8%)	120(69.0%)	0.446	123(70.7%)	120(69.0%)	0.726
	Presence	173(34.2%)	54(31.0%)		51(29.3%)	54(31.0%)	
hypertension	Absent	254(50.2%)	80(46.0%)	0.337	90(51.7%)	80(46.0%)	0.284
	Presence	252(49.8%)	94(54.0%)		84(48.3%)	94(54.0%)	
p value < 0.05 was considered as statistically significant. BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.							

2.5 Image acquisition

All CCTA examinations were performed on a third-generation dual-source CT scanner (SOMATOM Force, Siemens Healthineers, Forchheim, Germany). CCTA was triggered 10 s after CT attenuation of region of interest (ROI) placed in the LA reached 100 HU (Hounsfield unit). A total of 50-80 mL contrast agent (Ultravist 370, Bayer Schering, Germany) was injected at the rate of 4.0-6.0 mL/s followed by a 30 mL of saline chaser. The scan mode including prospective, retrospective or high-pitch prospective modes was selected according to patients' heart rhythm. The image parameters were as follows: tube current and tube voltage automatically determined by CARE Dose4D and CARE kV technique; detector collimation 2× 68× 0.6 for single energy acquisition; gantry rotation 0.25 s; pitch 0.15-0.25; 512×512 pixel matrix size. Images were reconstructed at the kernel of Bv40, with the image thickness of 0.75 mm and increment of 0.4 mm. The phase with best image quality was picked for imaging measurements and analysis. All images were analyzed on the commercial postprocessing workstation (SyngoVia, VB20, Siemens Healthineers, Forchheim, Germany).

2.6 EAT morphological measurement

EAT were semi-automatically segmented by a dedicated software (Cardiac Risk Analysis, Research Frontier, SyngoVia, Siemens Healthineers). The EAT mask was then loaded into the Radiomics software (Research Frontier, SyngoVia, Siemens Healthineers) to delineate LA-EAT and quantify EAT and LA-EAT[22]. Axial images were used to delineate the LA-EAT mask from the pulmonary artery to the coronary sinus, then we trimmed along the LA, pulmonary veins, and left atrial appendages using axial, coronal, and sagittal slices. The contour delineation was checked and manually trimmed with EAT as a reference if necessary. Adipose tissue was defined as voxels between -190 and -30 Hu. Meanwhile, the volumes and densities of EAT and LA-EAT were measured. (Fig. 2) An experienced radiologist, who was blinded to patients' clinical characteristics, performed the measurement independently and remeasured after one month to avoid imaging recognition.

2.7 Statistical analysis

The statistical analysis was performed on SPSS version 25.0 (Statistical Product and Service Solutions, IBM; Armonk, NY, USA). Normality was examined with the *Kolmogorov-Smirnov* test. The means $\pm$ standard deviations for normally distributed variables and medians (25th-75th percentiles) for non-normally distributed variables were calculated. Categorical variables were compared by using the χ^2 test. The Student's *t*-test and the Wilcoxon rank-sum test were used for comparing continuous variables. Univariate and multivariate analyses of independent risk factors for recurrence of AF were performed using logistic regression analysis. The lesion segmentation was performed in the analysis step integrated on the Radiomics prototype (Frontier, VB10, Siemens). The intraclass correlation coefficient (ICC) was reported for intra-observer reliability. All probability values reported were 2-sided, and a probability value < 0.05 was considered statistically significant.

3. Results

3.1 Baseline Characteristics of population

A total of 9 patients (1.3%) were lost during follow-up and excluded from the results. 174 patients developed AF recurrence while 506 patients remained free of AF recurrence after ablation within 1 year. The baseline characteristics of each group are presented in Table 1. Univariate analysis revealed that 8 factors were equal in the two original groups ($p > 0.05$). Differences in 2 factors were statistically significant ($p < 0.05$). After PSM,

variables of background characteristics were equal in the matched Non-recurrence group (n = 174) and recurrence group (n = 174). consequently, the difference of other risk factors which might have impact on EAT and AF have been eliminated, permitting fully examine the association between EAT and AF recurrence. In the following sections, all statistical comparisons were based on the matched population.

3.2 Comparison of EAT between patients with and without AF recurrence After matching

The ICC of the LA-EATV and LA-EAT densities between the two observers are 0.997 and 0.988, respectively, showing an excellent agreement.

The volume of LA(mL)(133.65 ± 38.70 vs 116.62 ± 40.30, P=0.000)was significantly higher in the patients with AF recurrence than in those without recurrence. no difference of the volume of Total-EAT(mL)129.19±48.59 vs 126.53±47.03, P=0.604 and LA-EAT(mL)25.00±12.45 vs 23.63±12.30, P=0.302 was found. Total-EAT density (HU) value-81.27±4.67 vs -84.05±3.84, P=0.000) and Total-EAT density (HU) value-72.47±23.87 vs -78.83±3.81, P=0.001 were significantly higher in the patients with AF recurrence than in those without recurrence. (Table 2)

Table 2
Comparison of EAT between patients with and without AF recurrence After matching

Characteristic	Non-recurrence (174 patients)	recurrence (174 patients)	p
LAV(mL)	116.62±40.30	133.65±38.70	0.000
Total-EATV(mL)	126.53±47.03	129.19±48.59	0.604
LA-EATV(mL)	23.63±12.30	25.00±12.45	0.302
Total-EATD(HU)	-84.05±3.84	-81.27±4.67	0.000
LA-EATD(HU)	-78.83±3.81	-72.47±23.87	0.001
p value < 0.05 was considered as statistically significant. Total-EATV, Total-EAT volume; LAV, LA volume; LA-EATV, LA-EAT volume; Total-EATD, Total-EAT density; LA-EATD, LA-EAT density.			

Comparison between Total-EAT and LA-EAT density: LA-EAT density (HU) value was significantly higher than Total-EAT(-75.65±17.36 vs -82.66±4.49, P=0.000).

3.3 logistic regression analysis

The LA volume, Total-EAT density, and LA-EAT density were selected by univariate analysis (Table 3). AF risk factors and our measurement parameters were included in the multiple logistic regression analysis, including age, sex, BMI, diabetes, hypertension, hyperlipidemia, TC, TG, HDL-C, LDL-C, LA volume, EAT density and LA-EAT density. The density of EAT (odds ratio: 1.09; 95% CI: 1.00 – 1.19, p = 0.047) and LA-EAT (odds ratio: 1.12; 95% CI: 1.03–1.23, p = 0.012) were significantly associated with the AF recurrence, as well as the LA volume (odds ratio: 1.01; 95% CI: 1.00–1.02, p = 0.001) after adjusting for baseline characteristics (Table 4).

Table 3
univariate logistic regression analysis of risk factor for AF recurrence

	OR	95% CI	p
gender	1.03	0.66 – 1.59	0.911
age	1.00	0.98 – 1.02	0.923
BMI(Kg/m ²)	1.00	0.94 – 1.07	0.991
diabetes	1.14	0.64 – 2.05	0.655
TC(mmol/L)	1.04	0.84 – 1.28	0.738
LDL-C(mmol/L)	1.03	0.80 – 1.32	0.843
HDL-C(mmol/L)	1.15	0.51 – 2.60	0.735
TG(mmol/L)	0.99	0.79 – 1.24	0.933
hyperlipidemia	1.09	0.69 – 1.72	0.726
hypertension	1.26	0.83 – 1.92	0.284
LAV(mL)	1.01	1.00 – 1.02	<0.001
Total-EATV(mL)	1.00	1.00 – 1.01	0.603
LA-EATV(mL)	1.01	0.99 – 1.03	0.303
Total-EATD(HU)	1.16	1.10 – 1.23	<0.001
LA-EATD(HU)	1.19	1.12 – 1.27	<0.001
p value < 0.05 was considered as statistically significant. LAV, LA volume; Total-EATV, Total-EAT volume; LA-EATV, LA-EAT volume; Total-EATD, Total-EAT density; LA-EATD, LA-EAT density.			

Table 4
Multiple logistic regression analysis of risk factor for AF recurrence

	OR	95% CI	p
LAV(mL)	1.01	1.00 – 1.02	0.001
Total-EATD(HU)	1.09	1.00 – 1.19	0.047
LA-EATD(HU)	1.12	1.03 – 1.23	0.012
p value < 0.05 was considered as statistically significant. LAV, LA volume; Total-EATD, Total-EAT density; LA-EATD, LA-EAT density.			

3.4 cut-off value

The cut-off value of Total-EAT density was -79.61 HU for predicting AF recurrence. The cut-off value of LA-EAT density was -78.49 HU for predicting AF recurrence.

4. Discussion

The present study has found that LAV, Total-EAT density and LA-EAT density of recurrent group was significantly higher than the matched groups. In addition, LAV, Total-EAT density and LA-EAT density were independent predictors of AF recurrence. Furthermore, the density of LA-EAT was significantly higher than that of Total-EAT.

The density of inflamed tissues has a higher CT value than that of non-inflamed tissues[23]. We found that Total-EAT and LA-EAT densities were associated with post-ablation recurrence of AF. Each increase in the average CT value of Total-EAT by 1 unit increases the risk of AF recurrence by 1.09 times, and each increase in the average CT value of LA-EAT by 1 unit increases the risk of AF recurrence by 1.12 times. As a part of the visceral adipose tissue in the human body, EAT is located in the pericardial sac and is closely connected to the outer wall of the myocardium[24]. At present, the specific pathogenesis of EAT affecting AF is still unclear, previous studies thought that the occurrence and development of AF may be a process involving multiple factors, including abnormal electrophysiological conduction, EAT secretion of adipokines, EAT activates autonomic nerves, EAT releases inflammatory mediators, etc.[25, 26]. Local inflammatory processes play a role in the pathophysiology of AF. Inflammation markers, such as CRP, IL-6 and TNF- α are related to the occurrence, severity and recurrence of AF after ablation[27–30]. These markers are secreted by EAT, which may have a local pro-inflammatory effect on the adjacent atrial myocardium, thereby promoting the occurrence and development of arrhythmia. In addition, we also found that the density of LA-EAT was significantly higher than that of Total-EAT. Indeed, some studies have pointed out that LA-EAT may be a better independent risk factor associated with AF severity or prognosis than total EAT[31, 32]. Atrial biopsies from patients with AF have shown the infiltration of inflammatory cells[33]. Therefore, the study of the correlation between EAT and recurrence of AF should pay more attention to the role of LA-EAT in it.

Previous studies showed that the volume of the Total-EAT and LA-EAT are associated with AF recurrence after catheter ablation.[34, 35] In our study, the Total-EAT and LA-EAT volumes of patients with recurrence after AF ablation were higher than those of patients without recurrence, but the difference was not statistically significant. Since we balance the confounding factors with PSM, this may indicate that the density of the EAT may more accurately reflect the relationship between EAT and the prognosis of AF.

We also found that the patients with AF recurrence had a larger LA, suggestive of progressive atrial remodeling. Left atrial volume enlargement is risk predictor after ablation of AF because AF causes remodeling and fibrosis of the LA[36]. Cardiac endothelin-1 expression correlates with enlarged left atrium size and responds to the wall stress caused by enlarged left atrium, thus promoting hypertrophy of myocytes and fibrosis of myocardial interstitium. Atrial fibrosis in patches can cause slow conduction and change dynamic repolarization in some areas, consequently shifting the initiation focus and AF maintenance to the left atrium from the pulmonary veins[37, 38]. In this case, radiofrequency ablation may be insufficient, resulting in an increased rate of recurrence.

This study still has certain limitations. This study is a single-center retrospective study with a small sample size. Further study should consider expanding the sample for further confirmation. In addition, PSM can only control known risk factors, and there may be some unknown factors that bias the results, but we have tried our

best to control all the indicators that can be collected. Further, Statistics about the time of recurrence should be as accurate as possible in follow-up studies. **Conclusion**

Total-EAT density, LA-EAT density and LAV were independent predictors of AF recurrence. In addition, the density of LA-EAT was significantly higher than that of Total-EAT. LA-EAT mediated inflammation plays an important role in the prognosis of AF. Therefore, assessment of LA-EAT density can improve ablation outcomes by refining patient selection.

Declarations

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Figures

Figure 1

The patient enrollment flow diagram.

Figure 2

(a) EAT. (b) LA-EAT. EAT, epicardial adipose tissue. LA-EAT, epicardial adipose tissue around the left atrium.