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Mahdiui, M. el; Simon, J.; Smit, J.M.; Kuneman, J.H.; Rosendael, A.R. van; Steyerberg, E.W.; ... ; Maurovich-Horvat, P.

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ORIGINAL ARTICLE

Posterior Left Atrial Adipose Tissue Attenuation Assessed by Computed Tomography and Recurrence of Atrial Fibrillation After Catheter Ablation

Mohammed El Mahdiui, MD*; Judit Simon, MD*; Jeff M. Smit, MD; Jurrien H. Kuneman, MD; Alexander R. van Rosendael, MD; Ewout W. Steyerberg, PhD; Rob J. van der Geest, PhD; Lili Száraz, MS; Szilvia Herczeg, MD; Nándor Szegedi, MD; László Gellér, MD, PhD; Victoria Delgado MD, PhD; Bela Merkely MD, PhD; Jeroen J. Bax MD, PhD; Pál Maurovich-Horvat, MD, PhD, MPH

BACKGROUND: Atrial fibrillation (AF) recurrence following catheter ablation remains high. Recent studies have shown a relation between epicardial adipose tissue and AF. epicardial adipose tissue secretes several proinflammatory and anti-inflammatory adipokines that directly interact with the adjacent myocardium. The aim of the current study was to evaluate whether posterior left atrial (LA) adipose tissue attenuation, as marker of inflammation, is related to AF recurrences after catheter ablation.

METHODS: Consecutive patients with symptomatic AF referred for first AF catheter ablation who underwent computed tomography were included. The total epicardial adipose tissue and posterior LA adipose tissue were manually traced and adipose tissue was automatically recognized as tissue with Hounsfield units (HU) between −195 and −45. The attenuation value of the posterior LA adipose tissue was assessed, and the population was divided according to the mean HU value (−96.4 HU).

RESULTS: In total, 460 patients (66% male, age 61±10 years) were included in the analysis. After a median follow-up of 18 months (interquartile range, 6–32), 168 (37%) patients had AF recurrence. Patients with higher attenuation (≥−96.4 HU) of the posterior LA adipose tissue showed higher AF recurrence rates compared with patients with lower attenuation (<−96.4 HU; log-rank test P=0.046). Univariate analysis showed an association between AF recurrence and higher posterior LA adipose tissue attenuation (≥−96.4 HU; P<0.05). On multivariable analysis, posterior LA adipose tissue attenuation (hazard ratio, 1.26 [95% CI, 0.90–1.76]; P=0.181) remained a promising predictor of AF recurrence following catheter ablation.

CONCLUSIONS: Posterior LA adipose tissue attenuation is a promising predictor of AF recurrence in patients who undergo catheter ablation. Higher adipose tissue attenuation might signal increased local inflammation and serve as an imaging biomarker of increased risk of AF recurrence.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: atrial fibrillation ■ atrial fibrillation recurrence ■ catheter ablation ■ computed tomography ■ epicardial fat

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Atrial fibrillation (AF) remains the most prevalent arrhythmic disease worldwide and is associated with increased morbidity and mortality. Currently, it is projected that AF prevalence will continue to rise, which is partially explained by increasing prevalence of obesity worldwide. Body mass index (BMI) is related

Correspondence to: Pál Maurovich-Horvat, MD, PhD, MPH, DSc, Department of Radiology, Medical Imaging Centre, Semmelweis University, 2 Korányi Sándoru, 1083, Budapest, Hungary. Email maurovich-horvat.pal@med.semmelweis-univ.hu

*M. El Mahdiui and J. Simon contributed equally and share first authorship

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WHAT IS KNOWN?

- Epicardial adipose tissue is a unique energy depot that secretes both proinflammatory and anti-inflammatory adipokines.
- Inflamed epicardial adipose tissue has been linked with cardiovascular diseases.
- Epicardial adipose tissue located posterior to the left atrial wall has been demonstrated to be strongly associated with atrial fibrillation.

WHAT THE STUDY ADDS?

- Volumetrically assessed posterior left atrial adipose tissue attenuation on computed tomography as a measure of inflammation is a promising predictor of atrial fibrillation recurrence following catheter ablation.
- Assessment of the left atrial posterior adipose tissue attenuation might be an important biomarker before catheter ablation.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
BMI	body mass index
CT	computed tomography
EAT	epicardial adipose tissue
HU	Hounsfield units
LA	left atrium

to new-onset AF and patients with weight loss have reduced AF burden, symptom severity, and less AF recurrences following AF catheter ablation.[1,2] However, AF recurrence rates are high following AF catheter ablation and adequate patient selection is crucial.[3] Recently, the relation between epicardial adipose tissue (EAT) surrounding the myocardium and AF has been reported.[4,5] EAT is a unique energy depot and is composed of adipocytes, stromovascular cells, immune cells, ganglia, and interconnecting nerves.[6] There is no fascial layer separating the EAT and the myocardium which allows for direct paracrine and vasocrine effects on the myocardium.[6] This is important since EAT secretes both proinflammatory and anti-inflammatory adipokines and direct effect on the myocardium has been demonstrated.[4] Computed tomography (CT) attenuation values for adipose tissue range between −195 and −45 Hounsfield units (HU).[7] Inflammation shifts the attenuation of the adipose tissue from a more lipid phase, closer to −195 HU, towards a more aqueous phase, closer to −45 HU. Attenuation of EAT on CT as a marker of inflammation has been linked to culprit coronary lesions in acute coronary syndrome[8] and cardiac mortality.[9] One study suggested a correlation between AF recurrence after AF catheter ablation and higher EAT attenuation, that is, closer to −45 HU, obtained from one slice on a 4-chamber view.[10] Volumetric assessment of EAT however may further increase accuracy since variability exists in EAT thickness at different myocardial regions.[11] Furthermore, recent studies have demonstrated that adipose tissue posterior to the left atrium (LA) had the strongest relationship with AF.[12,13] Whether the posterior LA adipose tissue mass or attenuation are related to AF recurrence following AF catheter ablation is evaluated in the current study.

METHODS

Patient Population

The data that support the findings of this study are available upon reasonable request to the corresponding author. Consecutive patients with symptomatic AF who underwent preprocedural CT imaging for a first AF catheter ablation between January 2014 and June 2018 at the Heart and Vascular Center of the Semmelweis University Hungary, were included. CT was performed for evaluation of LA anatomic characteristics and location of pulmonary veins. Patients with uninterpretable CT images or who did not undergo a catheter ablation procedure after CT were excluded. Patients were followed at the outpatient clinic and a 3-month blanking period was implemented for AF recurrence following catheter ablation. Outpatient clinical visits were scheduled at 3, 6, and 12 months and at least yearly thereafter or when patients experienced symptoms. Follow-up visits included clinical assessment, 12-lead ECG, and 24-hour Holter monitoring. Recurrence was prospectively recorded in the electronical medical records and defined as documented AF or atrial tachycardia episode lasting for >30 seconds. Echocardiographic data, including left ventricular ejection fraction and E/A-ratio, were collected from the echocardiographic database. Demographic and clinical data were collected from the electronic medical records. For retrospective analysis of clinically acquired data, the institutional review board waived the need for written patient informed consent. All data used for this study were acquired for clinical purposes and handled anonymously.

CT Acquisition

Patients were scanned using a 256-slice CT scanner (Brilliance iCT 256, Phillips Healthcare, Best, the Netherlands) with 270 ms rotation-time, 128×0.625 mm collimation, and tube voltage of 100 to 120 kV. Patients were pretreated with beta-blockers if the heart rate exceeded 65 beats per minutes. Four-phasic injection protocol with 85 to 95 mL of iodinated contrast agent was used (Iomeron 400, Bracco Ltd, Milan, Italy) at a rate of 4.5 to 5.5 mL/s. CT was acquired using prospective ECG-gating covering 75 to 81% of the RR-interval. The CT datasets were reconstructed with 0.8 mm slice thickness and 0.4 mm increment with hybrid iterative reconstruction technique (iDose5, Philips Healthcare, Best, the Netherlands).

CT Image and LA Adipose Tissue Analysis

LA adipose tissue measurements were performed using MASS software (Leiden University Medical Centre, Leiden,

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the Netherlands), as described previously.[14] In short, a cross-sectional view of the LA was obtained from the mitral annulus to the LA roof from reconstructed 2-and 4-chamber views with a slice thickness of 2 mm. The LA adipose tissue located posterior of the LA was manually traced from the base of the LA until the mitral annulus. Adipose tissue was automatically recognized by the software as tissue with HU between −195 and −45, and the mean HU of the adipose tissue was calculated (Figure I in the Data Supplement). LA volume was calculated on CT images using IntelliSpace Portal (Philips Healthcare, Best, the Netherlands).

Catheter Ablation Procedure

The indications for performed AF ablation procedures were in accordance with the current guidelines.[15] Paroxysmal AF was defined as self-terminating AF, whereas persistent AF was defined as AF lasting longer than 7 days.[15] Intravenous fentanyl, midazolam, and propofol were used in all cases for conscious sedation. Femoral venous access was used for all procedures. Transseptal puncture was performed under fluoroscopy positioning and pressure monitoring. Intracardiac echocardiography was used for visualization of the interatrial septum in case of difficulty in performing safe transseptal puncture. An electroanatomical mapping system (CARTO, Biosense Webster, Inc, Diamond Bar, CA or ENSITE, St. Jude Medical, Inc, MN) and left atrial fast anatomic map was merged with the cardiac CT images to guide ablation. Temperature-controlled ablation was performed with an irrigated 4 mm tip catheter, with an standard target power delivery of 25 to 35 W in the majority of cases. Pulmonary vein isolation was the goal of each initial procedure.

Statistical Analysis

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean±SD if normally distributed and median and interquartile range if not normally distributed. Categorical variables were compared using the χ^2 test. Continuous variables were compared using the Student *t* test if normally distributed and the Mann-Whitney *U* test if not normally distributed. The relation of BMI with total EAT, posterior LA adipose tissue mass, and attenuation was investigated using Pearson correlation. Recurrent AF incidence rates were calculated from the end of the blanking period. Kaplan-Meier analysis was performed for cumulative AF recurrence. The study population was divided into 2 groups according to the mean posterior LA adipose tissue attenuation (−96.4 HU) and compared with a log-rank test. We performed a multivariable Cox proportional-hazards analyses and adjusted posterior LA adipose tissue mass and attenuation for age,[16] sex,[3] type of AF,[3] BMI,[2] antiarrhythmic drugs,[17] left ventricular ejection fraction,[18] E/A-ratio,[18] and LA volume.[19] Any missing values among these variables were statistically imputed. Four observers independently performed all measurements and were blinded to patient outcome data. Ten patients were randomly selected for interobserver agreement and analyzed using interclass correlation coefficient. A $P<0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 23.0 (SPSS, Armonk, NY).

RESULTS

Patient Characteristics

A total of 460 patients (66% male, age 61±10 years) were included in the analysis. Clinical characteristics are shown in Table 1. There were 168 (37%) patients that developed AF recurrence after catheter ablation during a median follow-up period of 18 months (interquartile range, 6–32). Patients with AF recurrence after catheter ablation were older (62±10 versus 60±10 years; $P=0.038$), more often females (42 versus 30%, $P=0.012$), and had more often persistent AF (33 versus 18%, $P<0.001$).

Imaging Variables

Imaging variables of the total population, patients with AF, and patients without AF recurrence are shown in Table 2. Patients with AF recurrence had significantly more often left ventricular ejection fraction dysfunction (6% versus 2%, $P=0.031$), larger LA volumes (108±32 versus 97±24 mL, $P<0.001$), and more often higher attenuation (≥−96.4 HU) of the posterior LA adipose tissue (60% versus 50%, $P=0.041$). The sensitivity and specificity for the mean posterior LA adipose tissue were 60% and 50%, respectively. There was a weak but significant correlation between BMI and total EAT ($r=0.27$, $P<0.0001$) and between BMI and posterior LA adipose tissue mass ($r=0.26$, $P<0.0001$). No significant correlation was found for BMI and posterior LA adipose tissue attenuation ($r=0.03$, $P=0.571$; Figure 1).

Posterior LA Adipose Tissue Attenuation and AF Recurrence

Patients with higher posterior LA adipose tissue attenuation (≥−96.4 HU) had more cumulative recurrence rates of AF than patients with lower posterior LA adipose tissue attenuation (<−96.4 HU) by Kaplan-Meier analysis (log-rank test $P=0.046$; Figure 2). Table 3 summarizes the Cox regression analysis of the posterior LA adipose tissue mass and attenuation for AF recurrence following catheter ablation. After correcting for known associates of AF, recurrence posterior LA adipose tissue attenuation (hazard ratio, 1.26 [95% CI, 0.90–1.76]; $P=0.181$) remained a promising predictor of AF recurrence following catheter ablation.

The interclass correlation coefficient for interobserver variability for posterior LA adipose tissue mass was 0.995 (95% CI, 0.988–0.999; $P<0.001$) and for LA adipose tissue attenuation 0.990 (95% CI, 0.971–0.997; $P<0.001$).

DISCUSSION

The current study demonstrated that patients with higher posterior LA adipose tissue attenuation had significantly more often AF recurrences following AF catheter

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Table 1. Patient Characteristics

	Total patients (n=460)	With recurrence (n=168)	No recurrence (n=292)	*P* value
Clinical variables				
Age, y	61±10	62±10	60±10	0.038
Male, n (%)	302 (66)	98 (58)	204 (70)	0.012
BMI, kg/m^2	29±5	29±5	29±4	0.285
Persistent AF, n (%)	106 (23)	54 (32)	52 (18)	<0.001
Hypertension, n (%)	330 (72)	125 (74)	205 (70)	0.335
Diabetes n (%)	70 (15)	22 (13)	48 (16)	0.336
Hyperlipidemia, n (%)	116 (25)	43 (26)	73 (25)	0.887
Smoking, n (%)	130 (28)	59 (35)	71 (24)	0.054
Prior myocardial infarction, n (%)	14 (3)	6 (4)	8 (3)	0.689
Medication				
Antiarrhythmic drugs	252 (55)	98 (58)	154 (53)	0.347
β-Blocker	147 (32)	53 (32)	94 (32)	0.702
Calcium antagonist	70 (15)	23 (14)	47 (16)	0.393
ACE inhibitor/ARB	144 (31)	51 (30)	93 (32)	0.551
Diuretics	91 (20)	34 (20)	57 (20)	0.996
Statins	164 (36)	64 (38)	100 (34)	0.583
Aspirin	52 (11)	18 (11)	34 (12)	0.660
Coumarins	193 (42)	79 (47)	114 (39)	0.095
DOAC's	153 (33)	55 (33)	98 (34)	0.857
Laboratory findings				
eGFR, mL/(min·1.73 m^2)	82 (60-90)	83 (60-90)	80 (60-90)	0.779

Values are mean±SD if normally distributed and median (interquartile range) if not normally distributed. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; DOACs, directly acting oral anticoagulants; and eGFR, estimated glomerular filtration rate.

ablation. After correction for several known risk factors for AF recurrences following catheter ablation, higher posterior LA adipose tissue attenuation remained a promising predictor of AF recurrence.

EAT and AF

Recently, obesity has been recognized as an important, and modifiable risk factor for AF development.[1,2] Although BMI has been used as a marker of general adiposity, it incorporates both subcutaneous and visceral adipose tissue, despite both structures being distinct.[20] Of note, higher levels of proinflammatory adipokines are secreted by visceral adipose tissue as compared to subcutaneous adipose tissue, and visceral adipose tissue has been associated with a greater risk for cardiovascular diseases.[6,8,9,20] EAT, the adipose tissue within the visceral layer of the pericardium, has

Table 2. Imaging Variables of the Total Population and Stratified According to Recurrence

	Total patients (n=460)	With recurrence (n=168)	No recurrence (n=292)	*P* value
Echocardiographic variables				
LVEF<50%, n(%)	16 (4)	10 (6)	6 (2)	0.031
E/A-ratio	1.2±0.4	1.2±0.4	1.2±0.4	0.557
CT variables				
LA volume, mL	101±28	108±32	97±24	<0.001
Posterior LA adipose tissue mass, g	10.1±5.1	10.0±5.0	10.1±5.1	0.923
Total epicardial adipose tissue mass, g	109±44	111±43	108±45	0.488
Posterior LA adipose tissue attenuation (HU)	−96.4±7.9	−95.6±6.2	−96.8±8.7	0.098
Posterior LA adipose tissue attenuation ≥−96.4 HU, n (%)	245 (53)	100 (60)	145 (50)	0.041

Values are mean±SD if normally distributed and median (interquartile range) if not normally distributed. CT indicates computed tomography; HU, Hounsfield units; LA, left atrial; and LVEF, left ventricular ejection fraction.

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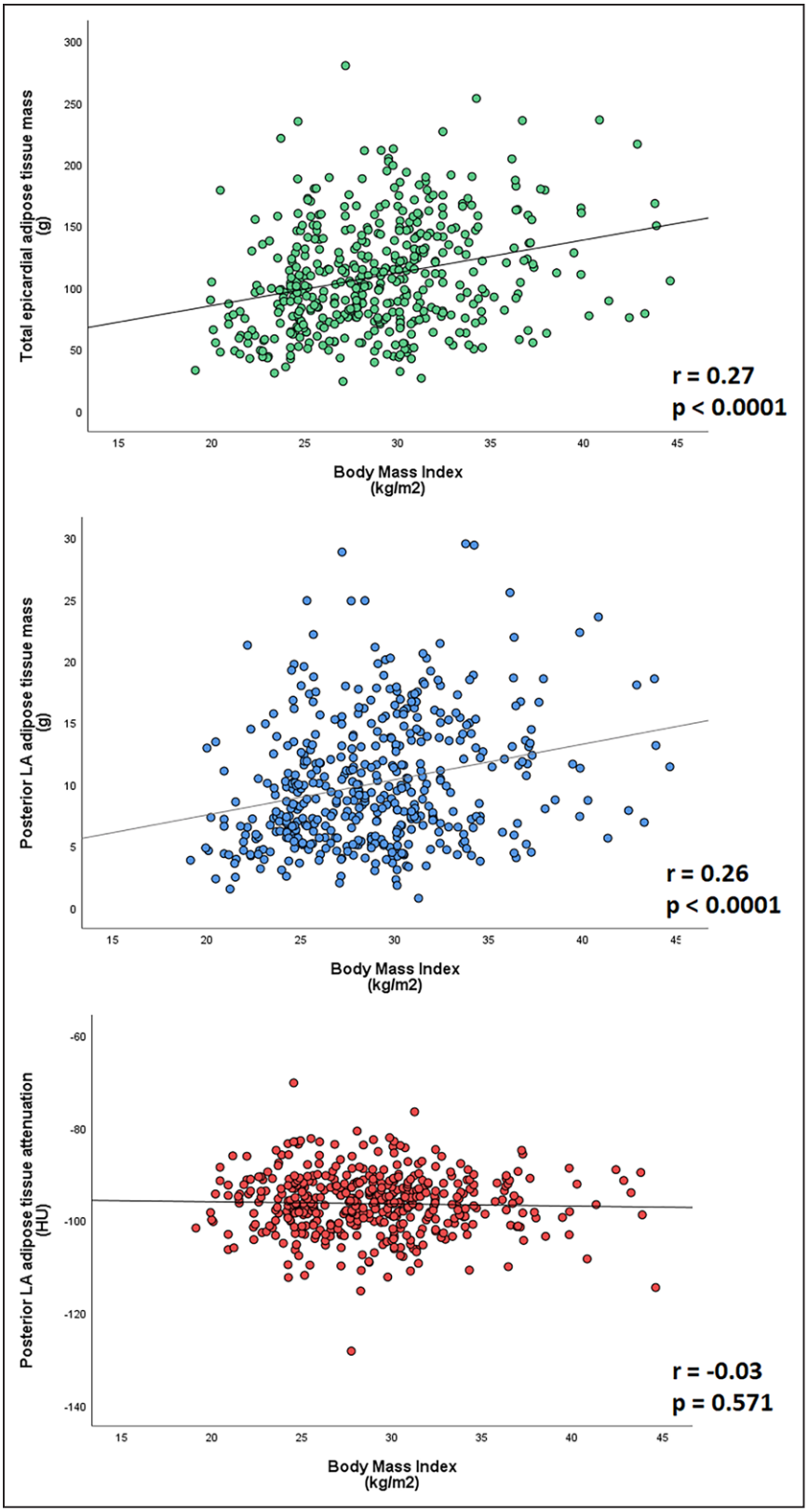

Figure 1. Correlations between body mass index (BMI), total epicardial adipose tissue (EAT), posterior left atrial (LA) adipose tissue mass, and attenuation.
The relation between BMI and total EAT, BMI, and posterior LA adipose tissue mass and attenuation. HU indicates Hounsfield units.

been demonstrated to be an important source of adipokines.[6] Total EAT is a stronger predictor for the presence of AF as compared to BMI.[5] More specifically, the relation between peri-atrial EAT and AF was examined in a population of 618 patients in sinus rhythm or with AF. Although peri-atrial EAT thickness was higher in patients with AF compared with those in sinus rhythm, posterior LA adipose tissue thickness had the strongest

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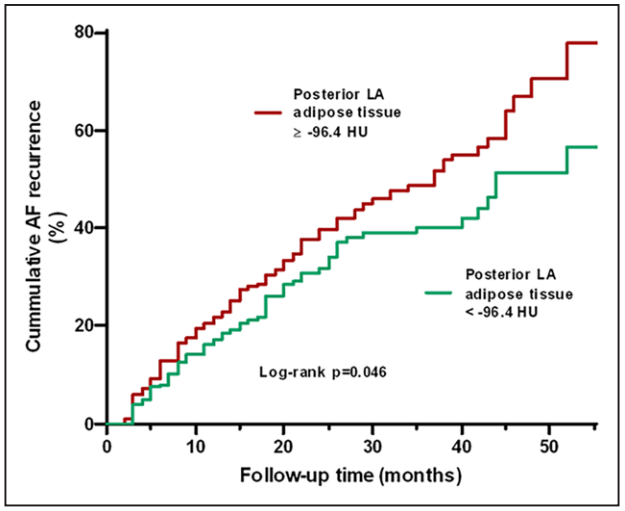

Figure 2. Kaplan-Meier curve for atrial fibrillation recurrence following catheter ablation according to posterior left atrial (LA) adipose tissue attenuation.
AF indicates atrial fibrillation; and HU, Hounsfield units.

correlation with the occurrence of AF of all LA adipose tissue pads.[13] Moreover, Batal et al[12] reported that only posterior LA adipose tissue thickness was significantly associated with AF burden. Subsequently, van Rosendael et al[14] quantified the posterior LA adipose tissue and found that each gram increase in posterior LA adipose tissue mass was associated with an increase of 32% in the risk of AF. Although some studies also demonstrated a relation between peri-atrial EAT assessed on CT and late AF recurrence after ablation,[21–23] others could not confirm this relation.[24,25] This discrepancy could be explained by methodological differences in assessment of peri-atrial EAT. Likewise, in the current study, we could not demonstrate an association indicating that the quantity of posterior LA adipose tissue might not be an important measure for predicting AF recurrence. Another explanation could be related to the large posterior LA adipose tissue mass (mean, 10.1 g) found in our population. The higher BMI in the current population, compared to populations in previous studies, suggest higher adiposity and higher peri-atrial EAT in the current population. It may be that the posterior LA adipose tissue mass has reached the maximum mass in both the recurrence and no-recurrence groups. This is further supported by the higher total EAT in the current population compared to previous studies.[21,25]

Inflammation and AF

Histological examination of atrial tissue in patients with AF has shown evidence of inflammation.[26] Various clinical studies have also reported a relation between inflammation and AF.[27,28] Specifically, systemic inflammatory biomarkers are increased in AF patients, whereas anti-inflammatory therapy decreases the AF risk.[27–29] However, systemic inflammatory biomarkers might not represent inflammatory activity at the tissue level.[30] The close proximity of EAT to the LA, the ability of EAT to produce inflammatory adipokines, and its association with AF makes EAT an attractive target for measuring inflammation in AF patients. Mazurek et al[31] quantified the inflammatory activity of EAT, visceral thoracic adipose tissue, and subcutaneous adipose tissue using 18F-fluorodeoxyglucose positron emission tomography in 21 patients with AF and 21 controls. Inflammatory activity of EAT in AF patients was significantly higher compared with controls. Moreover, inflammatory activity of EAT was higher compared with subcutaneous adipose tissue and even thoracic visceral adipose tissue in AF patients.[31] Ciuffo et al[10] demonstrated in 143 patients that increased attenuation (as a marker of inflammation) of peri-atrial adipose tissue measured from a single slice 4-chamber view on CT was a predictor of AF recurrence after catheter ablation. However, in the same study, attenuation of the peri-atrial adipose tissue measured from the 2-chamber view was not associated with AF recurrence, highlighting the variability of the EAT at different myocardial regions and the importance of volumetric quantification of EAT.[11] The results from the current study demonstrate similar findings, using volumetric quantification in a larger patient population: more inflamed peri-atrial adipose tissue is associated with AF recurrence after catheter ablation. Several explanations for this relation could be considered. A more inflamed atrial wall might impede adequate lesion transmurality during ablation through the formation of edema.[32] Another explanation might be the formation of atrial fibrosis through localized inflammatory processes induced by EAT.[30] Atrial fibrosis might enable the formation of intra-atrial reentry circuits, and the presence of atrial fibrosis reduces catheter ablation success.[33] Although we observed similar posterior LA adipose tissue mass between those patients that experienced AF recurrence and those patients that did not, patients with AF recurrence had larger LA volumes. Increasing LA

Table 3. Univariable and Multivariable Cox Regression Analysis for Atrial Fibrillation Recurrence Following Catheter Ablation

	Univariable; hazard ratio (95% CI)	*P* value	Multivariable*; hazard ratio (95% CI)	*P* value
Posterior LA adipose tissue mass (per one unit increase)	1.00 (0.97–1.03)	0.970	1.01 (0.97–1.04)	0.759
Posterior LA adipose tissue attenuation ≥ −96.4 HU (yes/no)	1.37 (1.00–1.86)	0.047	1.26 (0.90–1.76)	0.181

AF indicates atrial fibrillation; HU, Hounsfield units; and LA, left atrial.
*Adjusted for age, sex, AF type, body mass index, use of antiarrhythmic drugs, left ventricular ejection fraction <50%, E/A-ratio, and LA volume.

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volumes leads to more enhanced stretching of the LA wall allowing for a larger contact area between the EAT and the LA wall. As the inflammatory adipokines of EAT directly exert their action on the LA wall through paracrine effects,[6] in addition to the attenuation of the posterior LA adipose tissue, the contact area between the EAT and the LA wall might also be an important factor in AF recurrences.

Assessment of the posterior LA adipose tissue attenuation on CT is a novel and easily accessible tissue-specific biomarker of inflammation before AF catheter ablation. Moreover, attenuation of peri-vascular EAT assessed from CT could be a marker to track response to anti-inflammatory therapy.[34] In addition, several studies have demonstrated that anti-inflammatory therapy reduces the risk for AF.[28,29] Assessment of posterior LA adipose tissue attenuation may potentially guide/personalize the use of anti-inflammatory therapy to reduce AF recurrences.

Study Limitations

This was a single-center study with a retrospective design. Patients with inadequate CT quality were excluded, which may have introduced selection bias. Moreover, the attenuation values reported in this study may be limited to this specific CT scanner and should be validated with other CT scanners. The optimal cut-off values found in this study population should be confirmed in future studies including larger populations and using different CT scanners. Such validation is important to further assess the role of posterior LA adipose tissue attenuation before clinical implementation. Because AF recurrences were defined as documented episodes, and we did not solely rely on reported complaints, some patients with recurrences might have been missed.

Conclusions

Posterior LA adipose tissue attenuation is a promising novel and tissue-specific biomarker of AF recurrence. Higher attenuation of the posterior LA adipose tissue might signal local inflammation and serve as an imaging biomarker of increased risk of AF recurrence.

ARTICLE INFORMATION

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Affiliations

Department of Cardiology (M.E.M., J.M.S., J.H.K., A.R.v.R., V.D., J.J.B.), Department of Biomedical Data Sciences (E.W.S.), and Division of Image Processing (R.J.v.d.G.), Leiden University Medical Center, the Netherlands. MTA-SE Cardiovascular Imaging Research Group, Heart & Vascular Center (J.S., L.S., S.H., N.S., L.G., B.M., P.M.-H.) and Department of Radiology, Medical Imaging Centre (P.M.-H.), Semmelweis University, Budapest, Hungary.

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Supplemental Material

Data Supplement Table I
Data Supplement Figure I

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