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Epicardial adipose tissue volume assessed by cardiac CT as a predictor of atrial fibrillation recurrence following catheter ablation

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ABSTRACT

Introduction: In patients with atrial fibrillation (AF), up to one third have recurrence after a first catheter ablation (CA). Epicardial adipose tissue (EAT) has been considered to be closely related to AF, with a potential role in its recurrence. We aimed to evaluate the association between the volume of EAT measured by cardiac computed tomography (CT) and AF recurrence after CA.
Methods: Consecutive AF patients underwent a standardized cardiac CT protocol for quantification of EAT, thoracic adipose volume (TAV) and left atrium (LA) volume before CA. An appropriate cut-off of EAT was determined and risk recurrence was estimated.
Results: 305 patients (63.6 % male, mean age 57.5 years, 28.2 % persistent AF) were followed for 24 months; 23 % had AF recurrence at 2-year mark, which was associated with higher EAT ($p = 0.037$) and LAV ($p < 0.001$). Persistent AF was associated with higher EAT volumes ($p = 0.010$), TAV ($p = 0.003$) and LA volumes ($p < 0.001$). EAT was predictive of AF recurrence ($p = 0.044$). After determining a cut-off of 92 cm^3, survival analysis revealed that EAT volumes > 92 cm^3 showed higher recurrence rates at earlier time points after the index ablation procedure ($p = 0.006$), with a HR of 1.95 ($p = 0.008$) of AF recurrence at 2-year. After multivariate adjustment, EAT > 92 cm^3 remained predictive of AF recurrence ($p = 0.028$).
Conclusion: The volume of EAT measured by cardiac CT can predict recurrence of AF after ablation, with a volume above 92 cm^3 yielding almost twice the risk of arrhythmia recurrence in the first two years following CA. Higher EAT and TAV are also associated with persistent AF.

1. Introduction

Epicardial adipose tissue (EAT) refers to the layer of fat located between the outer surface of the heart and the pericardium. The EAT serves as a natural buffer and insulation for the heart, but it is also associated with various cardiovascular conditions and metabolic disorders, gaining significant attention in recent years.[1,2] Studies have shown that excessive amounts of EAT may contribute to the development of

Abbreviations: AAD, anti-arrhythmic drugs; AF, atrial fibrillation; BMI, body mass index; CA, catheter ablation; CT, computed tomography; EAT, epicardial adipose tissue; LA, left atrium; LAV, left atrial volume; LVEF, left ventricle ejection fraction; PAF, paroxysmal atrial fibrillation; PersAF, persistent atrial fibrillation; TAV, thoracic adipose volume.

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cardiovascular diseases, such as coronary artery disease, heart failure, and atrial fibrillation (AF).[3–6] It has been suggested that EAT might function as a lipid-storing depot, as an endocrine organ secreting hormones, and as an inflammatory tissue producing cytokines and chemokines.[1] Pro-inflammatory and profibrotic cytokines can interact with cardiomyocytes or coronary artery endothelial cells and can have harmful effects.[2] Because of its proximity to the heart, EAT may play a role in the pathogenesis of cardiovascular disease, through proinflammatory signals and fatty infiltration, ultimately promoting myocardium fibrosis.[7,8]

The thickness or volume of epicardial fat can be measured by multiple medical imaging techniques, such as echocardiography, computed tomography (CT), and magnetic resonance imaging.[9] Measuring the EAT may provide insights into an individual's cardiovascular health and help risk stratification for certain diseases, including AF.[5,10–13]

AF is the most common sustained arrhythmia encountered in clinical practice and is associated with significant morbidity and mortality.[14] Catheter ablation (CA) aims to restore sinus rhythm and improve quality of life in symptomatic patients. However, despite advancements in ablation techniques, AF recurrence remains a significant challenge, with up to one third of patients undergoing CA of AF have recurrence of the arrhythmia after the first ablation.[15] Owing to this fact, it's of utmost importance to predict and identify which patients are at higher recurrence risk after CA. Ongoing research aims to elucidate the contributing factors involved in the maintenance of sinus rhythm or its recurrence, as the conventional factors are not without limitations.[15–18]

Mounting evidence suggests that EAT may play a pivotal role in the pathophysiology of AF.[5,7,9,10,13,19,20] Moreover, several studies have demonstrated that increasing thickness or volume of EAT is associated with higher recurrence rates after CA of AF.[11,12,21–25] However, current studies on the relationship between EAT volume, assessed by cardiac CT, and AF recurrence suffer from limited sample sizes and/or by focusing solely on paroxysmal AF. Thus, there is a need for larger studies to validate these findings.

The primary objective of this investigational study is to evaluate the relationship between EAT volume, as measured by cardiac CT, and the recurrence of AF after CA. We aim to investigate whether increased EAT volume is an independent predictor of AF recurrence, beyond traditional risk factors and left atrial characteristics.

2. Material and methods

2.1. Study population

A cohort of 350 consecutive patients who underwent pulmonary vein isolation procedure to treat paroxysmal AF (PAF, spontaneous termination within 7 days) or persistent AF (PersAF, lasting >7 consecutive days) in a single tertiary center from September 2011 to March 2020 was retrospectively analyzed. All patients underwent cardiac CT before CA. AF ablation was performed in all cases using a 3-dimensional electroanatomic mapping system and an irrigated ablation catheter.

The inclusion criteria were patients 18 years or older, undergoing CA as a first procedure and refractory to at least one anti-arrhythmic drug agent. The exclusion criteria were patients with having also left atrial flutter or undergoing a repeated (redo) ablation for AF.

Information was collected regarding demographics, anthropometric data, medical history, baseline bleeding and thrombotic risk, anti-arrhythmic drugs (AAD) before the CA. All patients had an echocardiogram performed, and left atrium (LA) dimensions, left ventricular ejection fraction (LVEF) and the presence of structural heart disease were analyzed.

The database was registered at the local Institutional Review Board. The hospital ethics committee approved the study protocol (Ethics Committee approval number 974/2020). All participants provided written consent for data collection, and the study was conducted according to the Declaration of Helsinki guidelines.

2.2. Study protocol

2.2.1. Cardiac computed tomography analysis

A pre-procedural assessment was conducted using a 128-slice dual-source cardiac scanner (*Somaton Definition Flash*, *Siemens*, *Erlangen*, *Germany*), equipped with electrocardiographic gating, with the administration of iodinated contrast product. Acquisition protocols, interpretation and reporting were performed according to local standardized practice.[26] This evaluation aimed to examine the pulmonary veins and the anatomy of the LA, to aid operators during AF ablation, as well as to ensure the absence of thrombus in the LA appendage. Data regarding the pulmonary vein count and LA anatomy were not analyzed in this study. Nevertheless, all CT examinations ruled out LA appendage thrombus before CA. Additionally, measurements of left atrial volume (LAV), EAT volume and thoracic adipose volume (TAV), using a standardized protocol, were performed. All evaluation and measurements were performed offline using a dedicated three-dimensional *Aquarius* Workstation CT-image processing software.

LAV was measured at end-systole. LA walls were manually traced, on axial planes, and after three-dimensional reconstruction, volume (in cm^3) was automatically calculated by the software.

EAT volume was obtained with volume tool in Aquarius workstation (Fig. 1). The fibrous pericardium was manually traced, every 10 mm on axial planes, from the pulmonary artery bifurcation to the diaphragm. Afterwards, by assigning an attenuation threshold from −30 to −190 Hounsfield units to fat, EAT volume was defined as total volume of fat enclosed by the fibrous pericardium previously traced. Finally, using three-dimensional reconstruction, the software automatically calculated volume (in cm^3).

We chose to evaluate EAT volume rather than thickness, as it offers a more accurate assessment of the total EAT burden.[1,9] Moreover, prior investigations into EAT thickness in coronary artery disease have produced conflicting results.[27]

TAV was detected by only assigning the attenuation threshold from −30 to −190 Hounsfield units to fat and its volume (in cm^3) was calculated automatically by the software of the all the slices detected by the scanner.

Measurements of LAV, TAV and EAT volume from cardiac CT were performed manually by two independent observers. However, due to the lack of documentation regarding the specific measurements conducted by each observer, calculation of inter-observer variability was not feasible.

2.3. Electrophysiological study and ablation procedure

Procedural details and protocol regarding catheter ablation were previously described in detail.[28]

2.4. Postablation follow-up

Oral anticoagulation was re-initiated 4 h after the procedure and maintained for at least 3 months. Patients were discharged on AAD at the operator's discretion. Patients were observed for routine follow-up in the outpatient clinic 1–3 months after the procedure and every six months (or earlier if symptoms) during the first two years post-ablation. At each visit, a standard 12-lead ECG was obtained. After the first 3 months, patients were followed up with a 24-hour Holter at each outpatient visit. AAD was continued for six months after CA and was withdrawn - except for beta-blockers - if the patients were free from arrhythmia-related symptoms. Oral anticoagulation was re-evaluated in the third month, and the decision to continue was based on the CHA2DS2-VASc score.[29] Clinical events and AF recurrence occurring during the follow-up were evaluated. The first 3 months after AF ablation were considered as the blanking period and atrial arrhythmias during this period were not considered for recurrence. Recurrence of AF was defined as detection of AF (>30 s duration) by 12-lead ECG or 24-

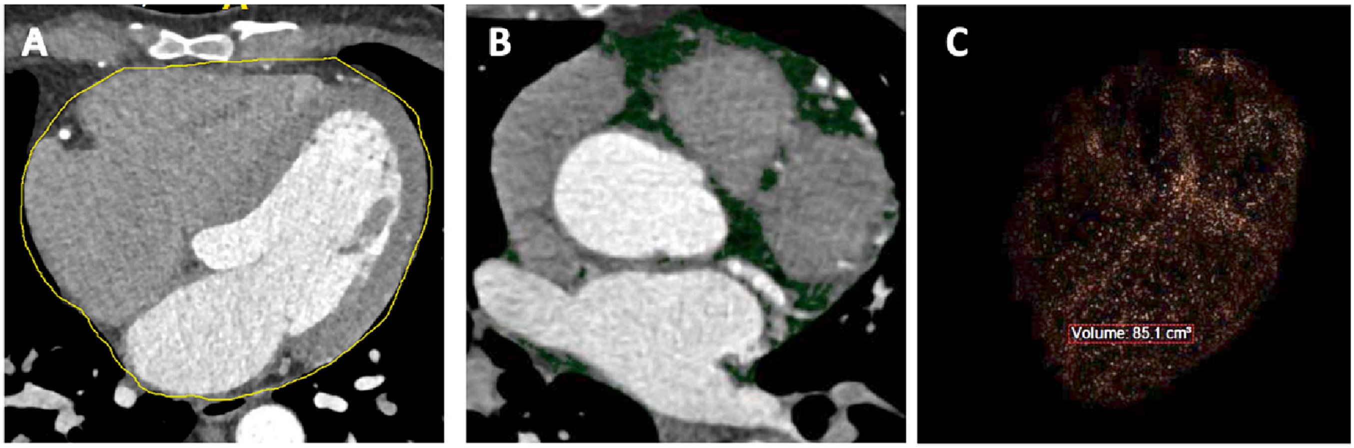

Fig. 1. A – EAT measurement starts with the tracing of the fibrous pericardium (green). B – Assigning an attenuation threshold from −30 to −190 Hounsfield units to fat, EAT volume (dark green) is defined as total volume of fat enclosed by the fibrous pericardium previously traced. C – Using three-dimensional reconstruction, the software automatically calculated volume (in cm^3). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

hour Holter after 3 months following the ablation. Even without documentation, symptomatic and clinically typical sustained episodes were also considered recurrences.

2.5. Statistical analysis

Patients were divided according to recurrence at 24 months of follow-up and analyzed regarding baseline characteristics, procedure data and outcomes. Continuous variables are presented in mean value and standard deviation (SD) when normal data distribution was found, or median and interquartile ranges (IQR) when non-normal distribution was found. Normal distribution was confirmed using the Kolmogorov-Smirnov test, or skewness and kurtosis. The categorical variables are presented as absolute frequency (n) and relative frequency (%).

Group comparison was tested with independent sample *t*-test for normal distribution continuous variables, Mann-Whitney test for non-normal distribution continuous variables, chi-square and Fisher's exact test for categorical variables.

Simple Cox regression analysis was conducted to identify a relationship between adiposity measurements (EAT, TAV and body mass index (BMI)) and time to AF recurrence. Then, using receiver operating characteristic (ROC) curve analysis, an appropriate cut-off level, using the Youden index method,[30] of EAT volume in the prediction of AF recurrence during follow-up for our population was determined. After dividing the patients according to the optimal cut-off, Kaplan-Meier survival curves were used to estimate the risk of AF recurrence. Afterwards, a multivariate Cox proportional-hazards regression analysis was used to assess the prognostic relevance of EAT volume, after adjustment for age, AF risk factors, TAV, BMI and type of AF. Statistical significance was defined as a p-value < 0.05. All tests were two-sided. The software used for statistical analysis was SPSS version 25.0 (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 305 patients were included (63.6 % male; 71.8 % with PAF), with a mean age of 57.5 ± 11 years and a median follow-up time of 24 months. There were 28.2 % of patients with PersAF. At 2-year follow-up, 23 % ($n = 70$) had recurrence of AF.

The population was divided into 2 groups – with and without AF recurrence. Baseline characteristics were similar between groups, except for PersAF and LVEF: patients with recurrence of AF were more likely to have PersAF (42.9 % vs 23.8 %, $p = 0.002$) and lower LVEF (55 ± 9.9 % vs 58 ± 6.7 %, $p = 0.013$), compared with those who remained in sinus rhythm (Table 1).

As for CT characteristics, AF recurrence was associated with higher EAT ($p = 0.037$) and higher LAV ($p < 0.001$), but statistical differences were not found in regards of TAV ($p = 0.061$) nor BMI ($p = 0.133$) (Table 1 and Fig. 2).

Moreover, PersAF was associated with higher EAT volumes ($p = 0.010$), TAV ($p = 0.003$) and higher LAV ($p < 0.001$) when compared with PAF (Fig. 3). This difference wasn't found with BMI ($p = 0.227$).

In univariate Cox proportional hazard regression analysis, EAT was predictive of AF recurrence at 2 years ($p = 0.044$), whereas TAV ($p = 0.084$) and BMI ($p = 0.161$) were not. After carefully selecting an optimal cut-off level of 92 cm^3 for EAT using ROC curve analysis (AUC 0.682, $p = 0.037$) in our population, survival analysis comparing patients with EAT below and above the aforementioned value was performed. Kaplan Meyer survival curves revealed that patients with EAT volume > 92 cm^3 had higher recurrence rates at earlier time points after the index ablation procedure ($p = 0.006$ by log-rank test), with a HR of 1.95 (95 % CI 1.195–3.181, $p = 0.008$) of the endpoint of AF recurrence at 2-year follow-up (Fig. 4). This was supported by multivariate Cox regression analysis: after multivariate adjustment for age, risk factors, TAV, BMI and persAF, EAT > 92 cm^3 remained predictive of AF recurrence, with a HR of 1.74 (95 % CI 1.160–2.858, $p = 0.028$).

4. Discussion

In accordance with previous studies,[21–24] our findings revealed a significant association between increased EAT volume and AF recurrence after CA and can predict AF recurrence independently from traditional risk factors, adiposity parameters and type of AF. Interestingly, we did not find a significant association between TAV or BMI and AF recurrence, suggesting that the specific distribution of adipose tissue, particularly EAT, may have a more direct impact on the pathophysiology of AF recurrence. These findings are also corroborated by previous studies.[12,22,31] The hypothesis that the distribution of fat is important in the role of AF was also raised by Nagashima et al., where 3-D electroanatomical maps were produced during AF ablation procedures and found that areas of fragmented signals were adjacent to epicardial fat.[32] Consistent with prior research, larger LA volumes were linked to AF recurrence and persistent forms of AF.[17,22]

In contrast, our analysis shows an association between not only EAT volume, but also TAV, and the presence of PersAF, suggesting a different role of adiposity in the chronicity of AF versus its recurrence. Thanassoulis et al.,[10] conclude that pericardial fat, but not other fat deposits, is associated with prevalent AF. However, in this study, conducted at

Table 1
Baseline characteristics and imaging (echocardiography and cardiac CT) data. CT – computer tomography. IQR – interquartile range. LA – left atrium. LVEF – left ventricle ejection fraction. SD – standard deviation. Bold indicates significant value.

Clinical and image data characteristics	All (*n* = 305)		Recurrence (n = 70)		No recurrence (*n* = 235)		*p* value
Age in years - mean ± SD	57.5 ± 11		59.1 ± 8.1		56.9 ± 11.6		0.151
Male - n (%)	194	(63.6)	50	(71.4)	144	(61.3)	0.121
BMI - median (IQR)	28.1	(5.1)	28.6	(4.6)	28	(5.3)	0.133
Smoking - n (%)	29	(9.5)	5	(7.1)	24	(10.2)	0.442
Hypertension - n (%)	181	(59.3)	38	(54.3)	143	(60.9)	0.326
Diabetes mellitus - n (%)	19	(6.2)	5	(7.1)	14	(6)	0.778
Dyslipidemia - n (%)	87	(28.5)	19	(27.1)	68	(28.9)	0.771
Obstructive sleep apnea - n (%)	41	(13.4)	9	(12.9)	32	(13.6)	0.870
Heart failure - n (%)	24	(7.9)	6	(8.6)	18	(7.7)	0.804
CHA2DS2-VASC score ≥ 2 - n (%)	140	(45.9)	28	(40)	112	(47.7)	0.259
Persistent atrial fibrillation - n (%)	86	(28.2)	30	(42.9)	56	(23.8)	**0.002**
Echocardiography measurements							
LA diameter (AP) in mm - median (IQR)	44	(8.6)	44	(10)	44	(8)	0.583
LA volume in ml - mean ± SD	76	± 29.1	83	± 31.2	74	± 28.2	0.088
LA volume indexed in ml/m2 - mean ± SD	39	± 14.6	42	± 15.0	38	± 14.4	0.154
LVEF in % - median (IQR)	60	(5)	60	(10)	60	(3)	**0.013**
Cardiac CT measurements							
LA volume in cm^3 - median (IQR)	99.4	(54.5)	134	(51)	96	(43)	**<0.001**
Thoracic adipose tissue volume in cm^3 - median (IQR)	206	(137.5)	239	(136)	200	(146)	0.061
Epicardial adipose tissue volume in cm^3 - median (IQR)	92	(75)	102	(70)	87.9	(71.4)	**0.037**

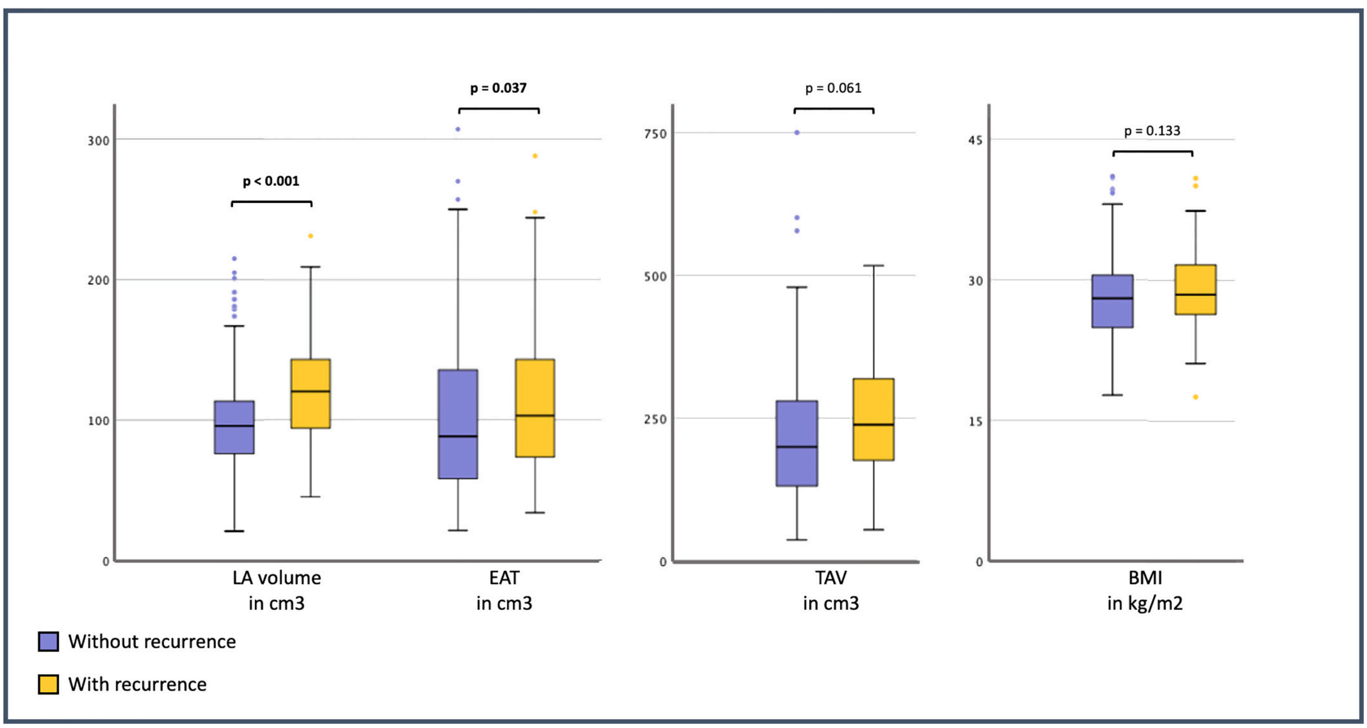

Fig. 2. Box plots comparing left atrium, epicardial adipose tissue and thoracic adipose volumes among patients with and without AF recurrence. Box plots comparing BMI between patients with and without recurrence is also shown.

population level, prevalent AF was defined on the basis of presence of any episode of confirmed atrial flutter or AF. This differs from ours, where all patients were diagnosed with AF (paroxysmal or persistent) proposed to pulmonary vein isolation. We can, therefore, speculate that EAT plays a decisive role in recurrence after CA and also on the progress to chronic forms of arrhythmia in a broader population. Recently, a study demonstrated that EAT was associated with AF recurrence after PersAF ablation, but not following PAF ablation, suggesting that the role of the metabolic atrial substrate in PAF pathophysiology is less obvious than in PersAF.[25] An interesting study showed a weak correlation between EAT and LA fibrosis, suggesting that LA fibrosis is not the main mechanism linking EAT and AF and that EAT was more strongly associated with AF recurrence than LA fibrosis, supporting the existence of other more important mediators linking EAT and AF recurrence.[33]

Our study also establishes an optimal cut-off value of 92 cm^3 of EAT volume being associated with AF recurrence, as patients with EAT above 92 cm^3 have nearly twice the risk of AF recurrence during the first two years after CA in our cohort. Thus, the measure of EAT using cardiac CT provides useful clinical information regarding risk of recurrence that could potentially impact the management of these patients, leading, for example, to the use of extended periods of AAD therapy and closer follow-up. To our knowledge, this is the first study to show this finding, being this cut-off a helpful tool in identifying patients with higher risk of AF recurrence, independently of other risk factors, adiposity parameters and type of AF.

As cardiac CT is performed routinely to assess LA and pulmonary

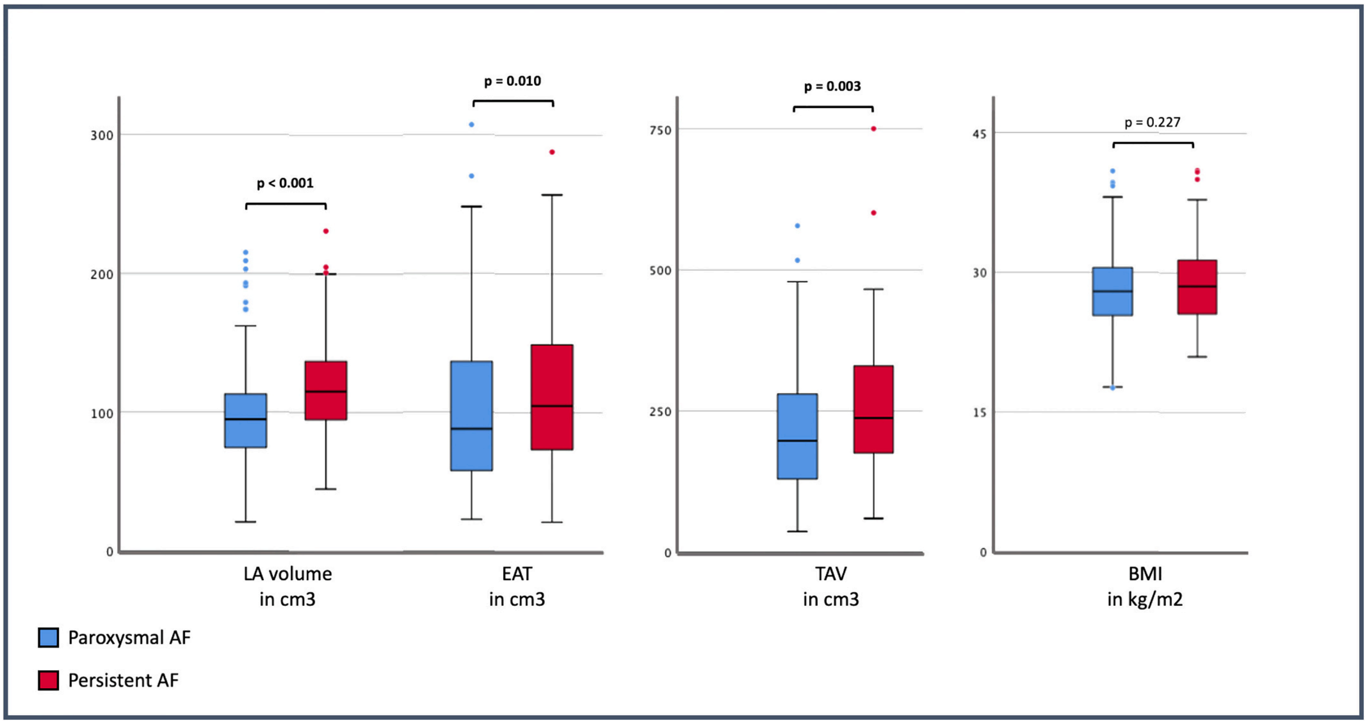

Fig. 3. Box plots comparing left atrium, epicardial adipose tissue and thoracic adipose volumes according to the type of AF (PAF vs PersAF). Box plots comparing BMI according to the type of AF is also shown.

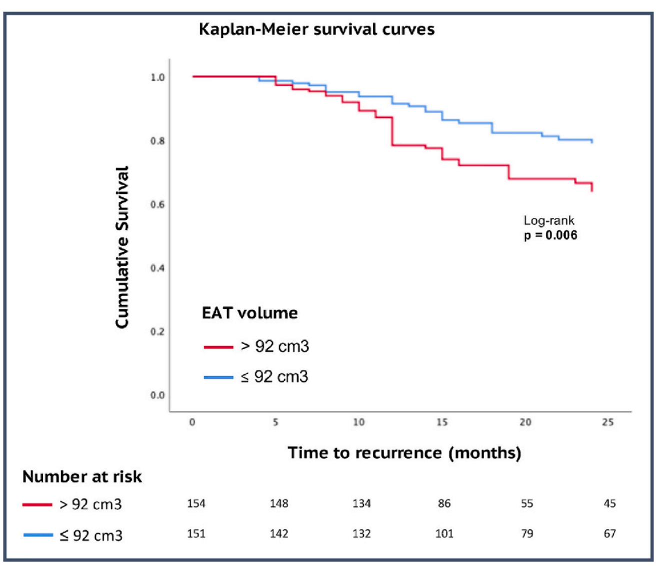

Fig. 4. Kaplan Meier survival curves estimates of AF recurrence during a follow-up of 24 months, in patients with AF undergoing catheter ablation, stratified by EAT volume below or above 92 cm^3 (log-rank p = 0.006).

veins morphology previously to CA procedures, the routine measurement of epicardial fat could provide valuable information regarding risk stratification, treatment planning, and prognostication for AF patients undergoing ablation, without significant costs. Furthermore, measuring EAT volume, through cardiac CT, instead of EAT thickness (measured by the same or other imaging techniques) is more direct and reliable since is not based in geometrical assumptions. Indeed, cardiac CT provides the noninvasive gold standard measurement of EAT volume because of its excellent spatial resolution.[34] Although manual quantification of EAT is laborious and currently falls outside the scope of routine CT interpretation, there have been studies to demonstrate and validate automated quantification of EAT using machine-learning.[34,35]

Moreover, this study also provides further insights about the multifactorial pathogenic mechanisms that lead to AF progression and poor response to anti-arrhythmic therapies such as CA, leading the authors to believe that aggressive lifestyle modifications, such as healthy diet and rigorous weight management should be mandatory in these patients' approach.

Further studies evaluating the use of different post-ablations strategies guided by EAT volume are needed. Also, studies evaluating the use of pharmacological measures that target EAT, for example lipid lowering therapies could further elucidate the complete role of EAT in the development, progression and recurrence in patients with AF.

5. Study limitations

The limitations of this study are mainly related to those inherent to the retrospective design in a single center, which could potentially include some selection bias and confounding factors. However, the population was selected and all patients underwent the same standard protocol. Additionally, although we adjusted data for various clinical and echocardiographic variables, unmeasured confounders may still exist. Other limitation was that the measurement of the left-atrium, epicardial and thoracic fat volumes in CT were performed manually by two different operators, subjecting the study to inter-observer variability. The determined cut-off value for EAT in our study population may not be universally applicable to broader populations due to differences regarding baseline demographic and clinical characteristics. To establish a standard reference limit for healthy populations and define specific cut-off values for cardiac pathologies, it is imperative to conduct extensive population-based studies on a larger scale. Lastly, although we performed the analysis with a follow-up of 2 years, the observed results may not contemplate potential recurrence of AF that can happen later.

6. Conclusions

The volume of EAT measured by cardiac CT can predict recurrence of AF after CA, independently from traditional risk factors, TAV, BMI and type of AF, with a volume above 92 cm^3 causing twice the risk of arrhythmia recurrence in the first two years following CA. Higher LA volumes are associated with persistent AF and AF recurrence. Higher EAT and TAV are also associated with the chronicity of AF.

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CRediT authorship contribution statement

Bárbara Lacerda Teixeira: Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis. **Pedro Silva Cunha:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Guilherme Portugal:** Writing – review & editing, Methodology. **Sérgio Laranjo:** Writing – review & editing, Methodology. **Bruno Valente:** Writing – review & editing, Methodology. **Ana Lousinha:** Writing – review & editing, Methodology. **Madalena Coutinho Cruz:** Writing – review & editing, Methodology. **Ana Sofia Delgado:** Writing – review & editing, Data curation. **Manuel Brás:** Data curation. **Margarida Paulo:** Data curation. **Cátia Guerra:** Data curation. **Ruben Ramos:** Methodology, Investigation. **Iládia Fontes:** Supervision, Methodology. **Rui Cruz Ferreira:** Supervision. **Mário Martins Oliveira:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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