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Article

Epicardial Atrial Fat at Cardiac Magnetic Resonance Imaging and AF Recurrence after Transcatheter Ablation

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Abstract: The relationship between epicardial adipose tissue (EAT) and atrial fibrillation (AF) has gained interest in recent years. Previous literature on the topic presents great heterogeneity, focusing especially on computed tomog-raphy imaging. Aim of the present study is to determine whether an increased volume of left atrial (LA) EAT evaluated at routine pre-procedural cardiac magnetic resonance imaging (MRI) relates to AF recurrences after catheter ablation. 50 patients undergoing AF cryoballoon ablation and pre-procedural cardiac MRI allowing quantification of LA EAT were enrolled. In one patient segmentation of LA EAT could not be achieved. After a median follow-up of 16.0 months, AF recurrences occurred in 17 patients (34%). Absolute volume of EAT was not different in patients with and without AF recurrences (10.35 ml vs. 10.29 ml; p-value=0.963), whereas volume of EAT indexed on the LA (EATi) was lower, albeit non statistically significant, in patients free from arrhythmias (12.77% vs. 14.06%; p-value=0.467). Receiver operating characteristic curve testing the ability of EATi to predict AF recurrence after catheter ablation showed sub-optimal performance (AUC: 0.588). The finest identified cut-off of EATi was 10.65%, achieving a sensitivity of 0.5, a specificity of 0.82, a positive predictive value of 0.59 and a negative predictive value of 0.76. Patients with values of EATi lower than 10.65% showed greater survival free from arrhythmias than patients with values above this cut-off (84% vs. 48%; p-value=0.04). In conclusion, indexed LA EAT volume evaluated at cardiac MRI independently relates to arrhythmia recurrence after AF cryoballoon ablation.

Keywords: atrial fibrillation; catheter ablation; epicardial adipose tissue; magnetic resonance; cryoballoon ablation

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1. Introduction

Attention to the role of epicardial adipose tissue (EAT) in the development of atrial fibrillation (AF) has increased in recent years. EAT plays several roles in the regulation of cardiac function and has a profound and complex interaction with the heart: it represents a storage of energy resources for the cardiac cells (in the older age), and it has thermogenesis properties (in the youngest)[Fainberg 2018]; through endocrine and paracrine interactions it mediates inflammatory response and modulates the immune system[Iacobellis 2004,Iacobellis 2009]; finally, ganglionated plexi, key structures of the autonomic nervous system of the heart, are located in the EAT. It has peculiar characteristics that differentiate it from the other types of visceral adipose tissue; EAT shares properties with both white and brown adipose tissue, so that the term "beige" adipose tissue has

been proposed to define it [Sacks 2013]. Excess or dysregulation of EAT has shown to be involved in the pathogenesis of heart failure with preserved ejection fraction[Van Woerden 2018,Pugliese 2021] and coronary artery disease through an imbalance in the inflammatory state that promotes atherogenesis and the development of unstable plaques[Hirata 2011,Antonopoulos 2017]. The exact pathophysiology of the interplay between EAT and AF is not yet entirely clarified: dysfunctional or excessive EAT through the secretion of adipokines and cytokines favors an inflammatory milieu and the production of reactive oxygen species which in turn can promote fibrogenesis; on the other hand, it has been postulated that its proarrhythmic effects are mediated by modification in the expression and function of cardiac ion channels, resulting in arrhythmogenic electrical remodeling[Friedman 2014,Mahabadi 2014,Wong 2016]. Indeed classic pro inflammatory cytokines – such as TNF alpha, IL 6 and IL 1 beta - as well as components of the inflammasome and of the immune response are overly expressed in the dysregulated EAT [Mazurek 2003]. Catheter ablation is an effective and safe option for the treatment of AF, and it has earned strong recommendations in guidelines for rhythm control[Hindricks 2021], also as first line option[Saglietto 2021]. Nevertheless, the correct selection of the patients is fundamental in order to avoid referring to an invasive procedures patient who have high risk of recurrences. Aim of the study is to determine whether an increased volume of atrial EAT evaluated at routine pre-procedural imaging relates to the recurrence of AF after catheter ablation.

2. Materials and Methods

All patients undergoing AF cryoballoon transcatheter ablation from January 2019 to December 2021 with a preprocedural cardiac magnetic resonance (MRI) with sequences allowing for epicardial adipose tissue quantification were retrospectively included. Key exclusion criteria were age < 18 years and any contraindication to MRI. All patients signed a written informed consent. Arrhythmia recurrences were defined as ECG-documented recurrences at 12-lead ECG and 24-hour Holter recordings or as clinically recognized symptomatic episodes. All patients were routinely followed up with 24-hour ECG Holter recording at 3 and 12 months, outpatient visits and telephonic interview. The study was approved by the local ethical committee and conducted according to the declaration of Helsinki. Before the ablation procedure, all patients underwent a transesophageal echocardiography (TEE) to rule out left atrial appendage (LAA) thrombosis and cardiac MRI to assess LA anatomy. A 1.5-T scanner (Achieva, version 2.6, Philips Medical Systems, Eindhoven, The Netherlands) using a 32-channel body phased-array coil was used. Paramagnetic contrast medium (Prohance, gadoteridol, Bracco Imaging, Italy) was administered at a dose of 0.1 mmol/kg. The sequences acquired during the exam were: Angio-MRI (non ECG-gated, 4D time resolved with keyhole 4D-TRAK); LGE-MRI (free breathing navigator and ECG gated inversion recovery gradient-echo sequence). The ablation protocol adopted has been previously detailed elsewhere[Ballatore 2023]. Briefly, through venous femoral accesses a diagnostic decapolar electrophysiological catheter was placed in the coronary sinus (CS), subsequently access to the LA was achieved through a patent foramen ovale or by single transseptal puncture and a 28-mm cryoballoon ablation catheter (Arctic Front Advance, Medtronic) and an inner lumen mapping catheter (Achieve, Medtronic) via a steerable 15Fr sheath (FlexCath Advance, Medtronic) were advanced in each pulmonary vein (PV) ostium. An activated clotting time > 350 s was maintained during the procedure. According to our standard approach, cryoenergy was delivered at each PV ostium for 180 seconds if PV isolation was achieved in less than 60 seconds, for 240 seconds for the other cases. Cryoenergy application was immediately stopped if the temperature reached -55°C or in case of loss of diaphragmatic stimulation during right PVs ablation.

Volume of left atrial epicardial adipose tissue was manually quantified on the acquired images by two trained radiologists (M.G and D.T.). Manual segmentations were performed on LGE-MRI images using open-source software 3D Slicer (slicer.org). The primary outcome of the study was to correlate left atrial adipose tissue, evaluated at cardiac MRI, with recurrence after AF cryoballoon ablation.

Both absolute LA epicardial adipose tissue and LA epicardial adipose tissue indexed on the LA were considered for the analyses.

Statistical Analysis

Categorical variables are reported as percentage. Continuous variables are reported as mean ± standard deviation (SD) or median and interquartile range (IQR). Student's t-test and Fisher exact test were used to compare continuous and categorical variables between groups, respectively. A receiver operating characteristic (ROC) curve was used to analyze the relationship between AF recurrences and the absolute LA EAT volume and the LA EAT volume indexed on the LA. The strength of the predictive ability of the variables in exam was evaluated with the area under the curve (AUC): a value greater than 0.7 was considered indicative of an acceptable association. Youden index was used to identify the best cut-offs at ROC analyses. Survival analyses were performed with Kaplan-Meier curves and log-rank test comparing two groups stratified on the cut-off identified at the ROC analysis. Univariate and multivariate Cox regression analyses were used to identify predictors of AF after ablation. A two-tailed p value<0.05 was considered statistically significant. All analyses were performed using R software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Segmentation and quantification of LA EAT at cardiac MRI could not be achieved in one case of the 50 enrolled patients. Baseline characteristics of the study population are reported in Table 1. The mean age was 59.6 years, 38% of patients were female, and the majority suffered of paroxysmal AF (86%); the mean number of previous AADs (effective, not-effective or not-tolerated) or rate control agents was 1.7 per patient. At baseline echocardiography mean ejection fraction was 61%. At MRI mean indexed LA volume was 43.3 ml/mq. After a median follow-up of 16.0 months (IQR: 12.0-21.8), AF relapsed in 17 patients (34%). No statistically significant differences in baseline characteristics were found between patients with and without recurrences, with the exception of greater use of beta-blockers at baseline (79% vs. 47%, p-value=0.019) in patients free from arrhythmic recurrences.

Mean EAT volume was 10.3 ml and the EAT volume indexed on the LA (EATi) was 13.2%. Absolute volume of EAT did not diverge in patients with and without AF recurrences (10.35 ml vs. 10.29 ml; p-value=0.963; Figure 1), whereas, the indexed volume, was lower, albeit non statistically significant, in patients not suffering relapses during follow-up (12.77% vs. 14.06%; p-value=0.467) (Figure 2)
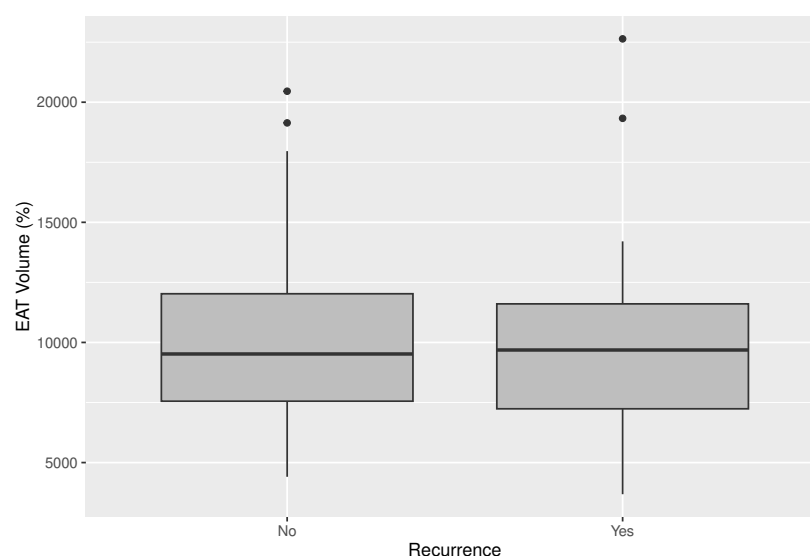

Figure 1. Direct comparison of the absolute LA EAT volume according to recurrence status.

Table 1. Baseline characteristics of the included patients stratified by arrhythmia recurrence. The reported p-value refers to the comparison between recurrence subgroup.

Variable	General population	Arrhythmic recurrence (n=17)	No recurrence (n=33)	p-value
Age (years)	59.64	59.4	59.8	ns
Gender (female)	19 (38%)	8 (47%)	11 (33%)	ns
Paroxysmal AF	43 (86%)	17 (100%)	26 (79%)	ns
AF history duration (months)	66.5	85.5	57	ns
Hypertension	26 (52%)	10 (59%)	16 (48%)	ns
Diabetes	3 (6%)	3 (18%)	0 (0%)	ns
Previous stroke	4 (8%)	2 (12%)	2 (6%)	ns
CAD	1 (2%)	1 (6%)	0 (0%)	ns
Thyroid disorders	6 (12%)	2 (12%)	4 (12%)	ns
Prior use of AADs				
Amiodarone	3 (6%)	0 (0%)	3 (9%)	ns
Flecainide	27 (74%)	12 (71%)	25 (76%)	ns
Propafenone	12 (24%)	6 (35%)	6 (18%)	ns
Sotalol	6 (12%)	3 (18%)	3 (9%)	ns
Beta-blockers	34 (68%)	8 (47%)	26 (79%)	0.019
Digoxin	1 (2%)	0 (0%)	1 (3%)	ns
Oral anticoagulants				ns
VKA	2 (4%)	0 (0%)	2 (6%)	
DOAC	32 (64%)	12 (71%)	20 (61%)	
Indexed volume ml/mq	43.3	39.4	45.2	ns

AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CAD: coronary artery disease; DOAC: direct oral anticoagulation; EF: ejection fraction; LA: left atrium; ns: non-significant; VKA: vitamin K antagonist.
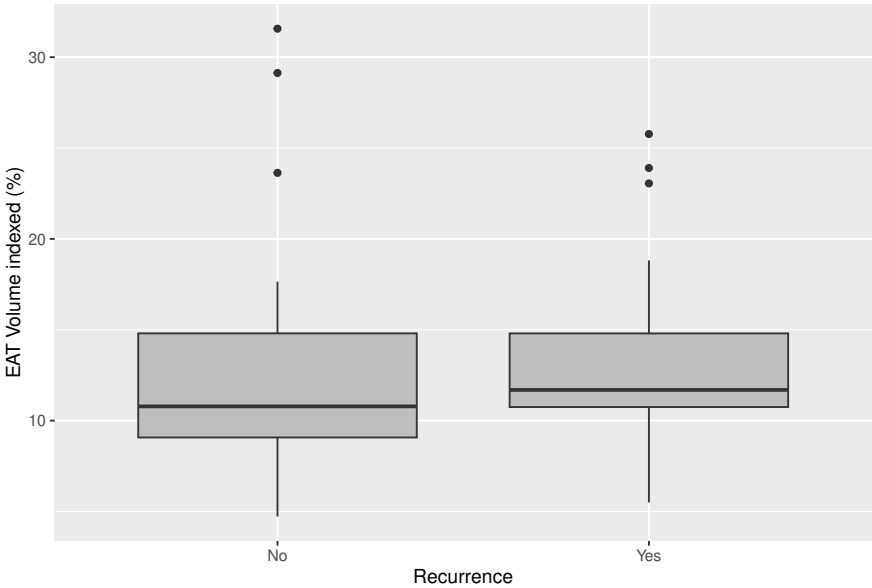

Figure 2. Direct comparison of the LA indexed EAT volume according to recurrence status.

ROC curve testing the ability of EATi to predict AF recurrence after cryoballoon ablation (Figure 3) showed a sub-optimal performance (AUC: 0.588). The finest identified cut-off, able to predict patients with AF recurrence, was 10.65% with a sensitivity of 0.5, a specificity of 0.82, a positive predictive value

of 0.59 and a negative predictive value of 0.76. Patients with an EATi value lower than the identified cut-off (10.65%) showed greater survival free from arrhythmias than patients with a value above the cut-off (84% vs. 48%; p-value=0.04; Figure 4). Figures S1 and S2 (see Supplementary Material) illustrate the ROC curve and subsequent Kaplan-Meier analysis stratified by absolute LA EAT volume.
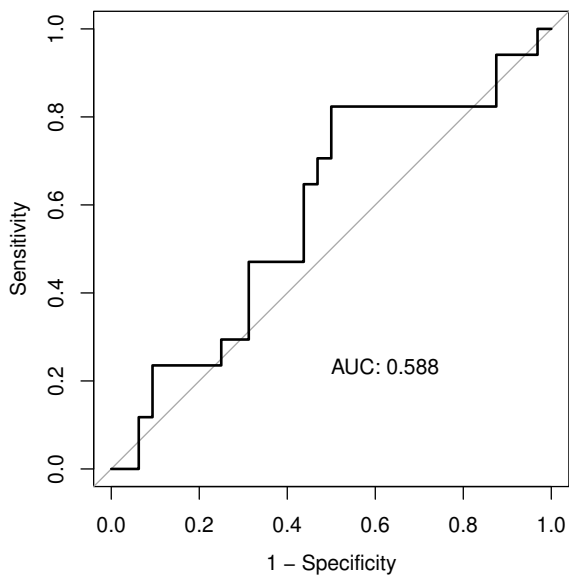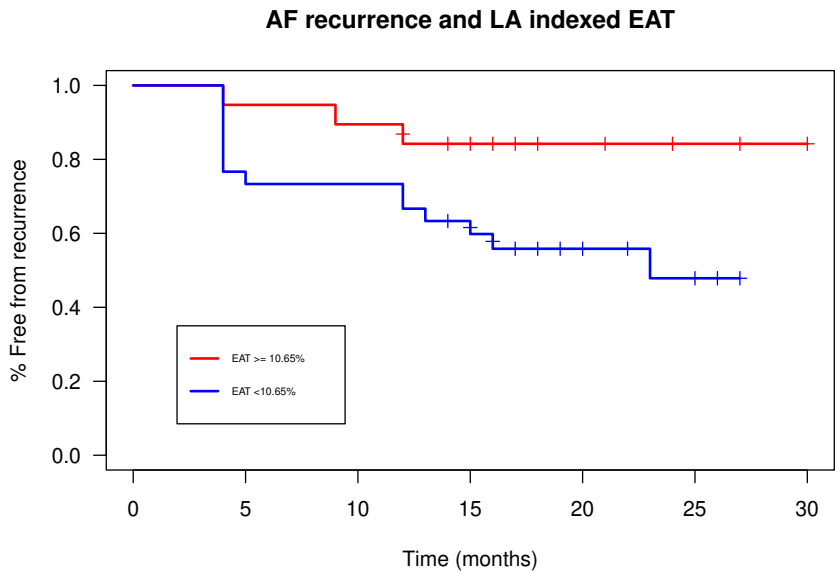

Figure 3. ROC curve for the LA indexed EAT volume.

Figure 4. Kaplan-Meier arrhythmia-free survival curves stratified by the LA indexed EAT volume above or below 10.65%.

Table 2 shows univariate and multivariate Cox regression analyses for AF recurrences. At multivariate analysis EATi above the cut-off of 10.65% was independently associated to an increased risk of AF recurrences (HR 4.5; 95%CI: 1.2-17.0; adjusted for BSA, diabetes, age and beta-blockers use). Diabetes also emerged as an independent risk factor of cryoballon catheter ablation failure (HR 5.5; 95%CI:1.2-24.4), whereas beta-blockers showed a protective effect (HR 0.31; 95%CI: 0.10-0.96).

Table 2. Univariate and multivariate analyses of predictors of AF recurrences reporting HR and 95%CI.

Variable	Univariate	Multivariate
Hypertension	1.4 (0.5-3.7)	
Diabetes	3.9 (1.1-13.9)	5.5 (1.2-24.4)
Previous stroke	1.9 (0.4-8.3)	
Thyroid disease	1.5 (0.5-4.4)	
Valvular disease	3.9 (0.9-17.1)	
Beta-blockers	0.5 (0.2-1.3)	0.3 (0.1-0.96)
Flecainide	1.0 (0.6-1.7)	
Gender	1.6 (0.6-4.3)	
LA EATi >=10.65%	3.3 (1.0-11.7)	4.5 (1.2-17.0)
BSA	0.3 (0.0-5.2)	0.1 (0.0-4.0)
Age	1.0 (0.95-1.0)	1.0 (0.9-1.0)

BSA: body surface area; EATi: epicardial adipose tissue indexed; LA: left atrium

4. Discussion

The main findings of the present study are:

- evaluation of left atrial adipose tissue by means of routine preprocedural cardiac MRI imaging is feasible;
- levels of left atrial adipose tissue indexed on LA volume are associated with a higher risk of arrhythmic recurrence after AF cryoballoon catheter ablation.

Identification of the optimal candidates for catheter ablation of AF is of paramount importance. Assessment of the risk of AF recurrence after the procedure is a fundamental step in the management of patients with AF. More importantly, in case of modifiable risk factors, such as obesity, patients can be encouraged to improve lifestyle habits, delaying ablation when and whether these risk factors have been controlled. Recently, web based risk scores have been made freely available to physicians and patients to predict the probability of AF recurrence after catheter ablation (AFA-RECUR)[Saglietto 2023]. Interestingly, BMI has a deep impact on the risk of arrhythmic recurrence and reduction in body weight is associated with a similar decrease in arrhythmic risk. Bearing in mind the recent extension of gliflozin use for the treatment of heart failure, greater attention to the metabolic aspects should be posed also for AF patients: indeed, SGLT2 inhibitors have shown to reduce the risk of new onset AF along with a reduction in body weight[Chahine 2022,Pandey 2021]. These effects are, at least partially, mediated by a reduction of epicardial adipose tissue. Another new oral antidiabetic drug, semaglutide, recently showed weight lowering properties, but its effect on prevention of atrial arrhythmias is still unclear[Lincoff 2023]. On these bases, evaluation of left atrial adipose tissue may play an important role in the management of patients with AF, both in adding a parameter to assess in search of the likelihood of AF recurrence than in identifying the correct timing of the procedure once other risk factors are controlled, in order to avoid futile procedures.

Previous literature on the topic presents great heterogeneity on both the methods of EAT quantification and the parameters analyzed. The preferred imaging modality adopted in previous studies was cardiac CT, whereas cardiac MRI has been seldom used; thickness of EAT as well as total, and LA volume of EAT have been proposed. A previous meta-analysis by Shamloo[Seperi Shamloo 2019] summarized current evidence by grouping studies on the basis of the variable analyzed: the Authors found a significant differences in LA EAT volume, analyzed at CT, in patients with and without AF recurrences after catheter ablation, however the difference was in crude values, not corrected for other risk factors that may have potentially driven the association. A more recent systematic review[Chen 2022] meta analyzed relative risk and hazard ratio of several EAT parameters and AF recurrence after catheter ablation suggesting that relative EAT thickness but not EAT volume measures related with an increased risk of recurrence. More specifically this relation was more evident in younger patients (less than 60 years old), Asian AF population and in case of longer follow-up.

Only few works have focused on the evaluation of LA EAT with cardiac MRI[Chahine 2022, Nakamori 2018]. The present study focused exclusively on the analysis of epicardial adipose tissue at the left atrium level (Figure 5): due to the reduced left atrial thickness the distinction between epicardial and pericardial adipose tissue is challenging and could have entailed a less accurate quantification; on the other hand, left atrial epicardial adipose tissue embraces ganglionated plexi, which play an important role in AF arrhythmogenesis. Indeed, we found that an amount of LA EAT equal or superior to 10.65% of the total volume of the LA was independently associated with the risk of AF recurrence after cryoballoon ablation. These findings are consistent with those recently published by Chahine et al. with a slightly different cut-off[Chahine 2022]. In fact, quantification of atrial adipose tissue by means of cardiac MRI is surely feasible if the preprocedural imaging is focused on LA, without the need of acquisition of the whole cardiac volume, significantly shortening examination time. From a practical point of view, this is very important as it allows to implement routine evaluation of this parameter without changing current protocol or adding further time-consuming acquisitions.

Figure 5. Example of segmentation and 3D reconstruction of LA EAT at cardiac MRI.

4.1. Limitations

This work presents the following limitations. The population in exam is small and includes mostly patients with paroxysmal AF, preventing generalization of the results to the entire AF population. The low numerosity may result in statistical under-power preventing to detect significant differences. In our cohort all patients underwent cryoballoon ablation: therefore, it is unclear whether the association will remain valid in case of another ablation energy.

5. Conclusions

LA EAT volume indexed on the LA volume independently related to arrhythmia recurrence after AF cryoballoon catheter ablation. Prospective studies with larger cohorts are warranted to assess the role of the evaluation of LA EAT volume for referral of patients to catheter ablation.

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