# Association between left atrial epicardial fat, left atrial volume, and the severity of atrial fibrillation

Rosendael, A.R. van; Smit, J.M.; El'Mahdiui, M.; Rosendael, P.J. van; Leung, M.; Delgado, V.; Bax, J.J.

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**CLINICAL RESEARCH**
*Atrial fibrillation*

# Association between left atrial epicardial fat, left atrial volume, and the severity of atrial fibrillation

**Alexander R. van Rosendael [1,2], Jeff M. Smit[1], Mohammed El'Mahdiui[1], Philippe J. van Rosendael[1], Melissa Leung[1], Victoria Delgado [1], and Jeroen J. Bax [1]***

[1]Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands; and [2]Department of Radiology, Dalio Institute of Cardiovascular Imaging, New York-Presbyterian Hospital and Weill Cornell Medicine, New York, NY, USA

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**Aims** Left atrial (LA) volume and LA epicardial fat are both substrates for atrial fibrillation (AF), but may relate with AF at different (early vs. late) stages in the AF disease process. We evaluated associations between LA epicardial fat and LA volume in patients with sinus rhythm (SR), paroxysmal AF (PAF), and persistent/permanent AF.

**Methods and results** In total, 300 patients (100 with SR, 100 with PAF, and 100 with persistent/permanent AF) who underwent cardiac computed tomography angiography (CTA) were included. The epicardial fat mass posterior to the LA and the LA volume were quantified from CTA and compared between patients with SR, PAF, and persistent/permanent AF. Furthermore, four groups were created by classifying LA epicardial fat and LA volume into large or small according to their median. The mean age of the population was 58.9 ± 10.5 years and 69.7% was male. Left atrial epicardial fat mass was larger in patients with PAF compared with SR, but did not further increase from PAF to persistent/permanent AF. Left atrial volume increased significantly from SR to PAF and to persistent/permanent AF. Left atrial epicardial fat and LA volume were both concordantly large or small in 184 (61%) patients, and discordant in 116 (39%). When both were small, 65.2% of the patients had SR, 23.9% PAF, and 10.9% persistent/permanent AF. When the LA epicardial fat mass was large and the LA volume small (compared with both being small), patients were significantly more often in PAF (55.2 vs. 23.9, $P < 0.05$), less frequently in SR (32.8% vs. 65.2%, $P < 0.05$) but showed comparable rates of persistent/permanent AF (12.0% vs. 10.9%, $P < 0.05$). When the LA volume was large, most patients had persistent/permanent AF.

**Conclusion** Left atrial epicardial fat mass was larger in PAF vs. SR, possibly indicating a marker of early disease, while large LA volumes were associated with a high prevalence of persistent/permanent AF. Elevated LA epicardial fat mass without large LA volume may reflect the early AF disease process.

**Keywords** Atrial fibrillation • Epicardial adipose tissue • Computed tomography • Cardiac imaging



* Corresponding author. Tel: +31 71 526 2020; fax: +31 71 526 6809. *E-mail address*: j.j.bax@lumc.nl

## What's new?

- The study shows that patient with paroxysmal atrial fibrillation (AF) have a larger left atrial epicardial fat mass than patient with sinus rhythm.
- However this mass was not different between patients with persistent/permanent AF and paroxysmal AF.
- Left atrial volume was larger with each more severe atrial fibrillation type.
- Elevated LA epicardial fat mass may reflect the early AF disease process.

# Introduction

Structural remodelling of the cardiac atria is a well-described phenomenon in patients with atrial fibrillation (AF).[1] Structural and functional changes of the atria are commonly expressed as an increase in atrial volumes, decrease in atrial contractility or relaxation and the presence of wall fibrosis. Atrial enlargement is strongly associated with the severity of AF and can easily be quantified using several non-invasive imaging techniques.[2,3] In addition to these biomarkers of atrial disease, (atrial) epicardial adipose tissue has recently attracted interest. In animal studies, increase in epicardial fat located posteriorly to the left atrium (LA) was associated with infiltration of the atrial wall by adipocytes, which intermingle with fibrous tissue and myocytes creating a substrate for AF.[4] Imaging studies have demonstrated greater volumes of epicardial fat in patients with AF.[5] Moreover, it was shown that LA volume and LA epicardial fat volume both identify patients with AF independently from each other, indicating potential differences in pathophysiology.[6] Epicardial fat (the visceral fat accumulation within the heart associated with metabolic disbalance) and LA volume (a marker of structural atrial damage) may represent two distinct substrates of AF at different stages in the disease process. We hypothesize that LA epicardial fat represents an early marker of AF, while an increase in LA volume occurs later in the disease process. Accordingly, we evaluated the association between LA epicardial fat and LA volume in patients with different disease stages of AF (PAF and persistent/permanent AF) and a control group of patients in sinus rhythm (SR).

# Methods

## Patients

From an ongoing clinical registry of patients with AF referred for cardiac computed tomography (CT) to evaluate LA size and pulmonary vein anatomy,[7] 100 patients with PAF and 100 patients with persistent or permanent AF were randomly selected. In addition, 100 patients without AF who were referred for CT coronary angiography for suspected CAD[8] were included. Patients with congenital heart disease, left ventricular ejection fraction <50% or moderate to severe heart valve disease were excluded. The type of AF was defined according to the guidelines of the European Society of Cardiology for the management of AF.[9] Self-terminating AF, usually within 48 h with paroxysms continuing for up to a maximum of 7 days was classified as paroxysmal AF, whereas persistent/permanent AF was defined as AF that lasts longer than 7 days (including episodes that are terminated by cardioversion after ≥7 days) and permanent AF was defined as AF that is accepted and rhythm control strategies are not pursued.

Demographic and clinical data were prospectively collected in the departmental electronic information system (EPD-Vision, Leiden University Medical Center, Leiden, The Netherlands) and retrospectively analysed. For retrospective analysis of clinically acquired data, the Institutional Review Board waived the need for patient written informed consent.

## Cardiac computed tomography data acquisition and left atrial epicardial fat measurements

Computed tomography data acquisition was performed with a 320-slice CT scanner (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan), using a collimation of 320 × 0.5 $mm^2$, gantry rotation time of 350 ms, and a temporal resolution of 175 ms. Heart rhythm (SR or AF) and frequency were recorded prior to CT data acquisition. Up to 150 mg metoprolol was administered orally 1 h before the scan if the patient's heart rate exceeded 60 b.p.m. to optimize image quality. An additional dose of intravenous metoprolol (up to 15 mg) was administrated if the heart rate remained >65 b.p.m. during the scout images. Sublingual nitroglycerin (0.4 mg) was systematically administered before CT acquisition unless contra-indicated. Cardiac CT was acquired with prospective ECG gating covering 70–80% of the R–R interval to allow reconstructions in diastole. A triphasic injection protocol was used and 60–90 mL of contrast agent (Iomeron 400, Bracco, Milan, Italy) was administered. CT data were acquired during the next heart beat after reaching the threshold of 300 Hounsfield Units (HU) in the descending aorta. Peak tube voltage was between 100 and 135 kV and tube current was between 140 and 580 mA depending on body habitus.

Left atrial epicardial fat mass was quantified using the contrast enhanced CT images, as previously described.[10] In short, from standard 2- and 4-chamber views, a short-axis view of the LA was created with 2-mm slice thickness (*Figure 1*). Regions of interest containing the LA epicardial fat were created by manually tracing the pericardium posterior to the LA, from the mitral annulus to the LA roof. Tissue with HU between −190 and −45 within this region of interest was defined as fat tissue by dedicated software (Mass, LKEB, research version 2012, Leiden University Medical Center, The Netherlands). The LA volume was also quantified from the short-axis view by manually tracing the endocardial border while excluding the pulmonary vein ostia and LA appendage.

## Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are presented as number and percentage. Trends between continuous variables and the heart rhythm spectrum (SR, PAF, and persistent/permanent AF) were assessed with a linear trend test and the $\chi^2$ linear by linear analysis for categorical data. Differences in LA epicardial fat mass and LA volume between the three rhythm groups were assessed with the analysis of variance (ANOVA) with Bonferroni *post hoc* correction. Patients were divided into large or small LA epicardial fat mass and LA volume according to their median and 75th percentile. Proportions were compared with the $\chi^2$ test with Bonferroni adjustment for multiple comparisons. A *P*-value <0.05 in a two-sided test was considered statistically significant. Statistical analyses were performed with the use of IBM SPSS Statistics software (version 23, IBM Corp., Armonk, NY, USA).

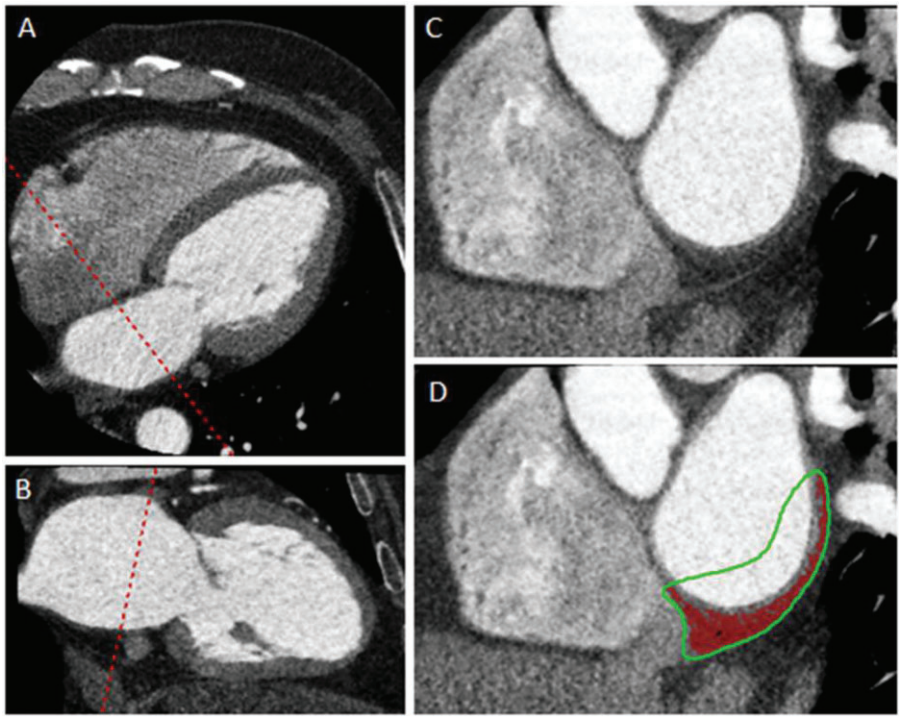


**Figure 1** Patient example illustrating the measurement of LA epicardial fat. (*A*) The axial view of the left atrium derived from computed tomography is shown. (*B*) The two-chamber view is shown. (*C*) The short-axis view of the left atrium, which was created as multi-planar reconstruction parallel to the dashed lines in (*A*) and (*B*). (*D*) The short-axis view with manual tracing of the pericardium (green line). The red marked tissue indicates fat tissue (Hounsfield Units between −190 and −45). LA, left atrium.

# Results

In total, 100 patients with SR, 100 patients with PAF and 100 patients with persistent/permanent AF (89 patients with persistent AF and 11 with permanent AF) were included in the present analysis. Of the clinical patient characteristics, increasing age, body mass index, body surface area, male sex, and hypertension were significantly associated with AF severity (*P*-value for trend <0.005) (*Table 1*). Both LA epicardial fat mass and LA volume showed a significant trend with AF severity, 5.5 ± 3.7 g for SR, 9.4 ± 5.4 g for PAF, 10.4 ± 6.7 g for persistent/permanent AF (*P*-value for trend <0.001) and 88.5 ± 31.1 mL for SR, 110.9 ± 28.2 mL for PAF, and 133.8 ± 34.4 mL for persistent/permanent AF, respectively (*P*-value for trend < 0.001).

## Left atrial epicardial fat mass and left atrial volume according to heart rhythm

Left atrial epicardial fat mass was significantly larger among patients with PAF when compared with SR ($P < 0.001$), but not different between persistent/permanent AF and PAF ($P = 0.563$, *Figure 2*). Patients with persistent/permanent AF showed the largest LA volumes, followed by patients with PAF and patients with SR, *P*-value <0.001 for both comparisons. The prevalence of SR, PAF, and persistent/permanent AF when patients were categorized above or below their median of LA epicardial fat mass and LA volume is shown in *Figure 3*. Left atrial epicardial fat and LA volume were both concordantly large or small in 184 (61%) patients, and discordant in 116 (39%). When both were small, 65.2% of the patients had SR, 23.9% PAF, and 10.9% persistent/permanent AF. When the LA epicardial fat mass was large but the LA volume small, patients were significantly more often in PAF (55.2 vs. 23.9, $P < 0.05$), less frequently in SR (32.8% vs. 65.2%, $P < 0.05$) but showed comparable rates of persistent/permanent AF (12.0% vs. 10.9%, $P < 0.05$). When the LA volume was large, most patients had persistent/permanent AF (43.1% when LA fat mass was small; 63.0% when LA fat mass was large). Comparable results were observed when groups were defined by the 75th percentile (Supplementary material online, *Appendix Figure S1*).

# Discussion

We investigated the associations between LA epicardial fat mass and LA volumes with AF at different stages of disease (PAF vs. persistent/permanent). Compared with patients in SR, LA epicardial fat mass was higher in patient with PAF, without being larger in persistent/permanent. Left atrial volumes were larger in PAF vs. SR, and also larger in persistent/permanent AF vs. PAF.

## Epicardial fat and atrial fibrillation

Epicardial fat is an endocrinologically active organ that exerts beneficial and harmful effects on the myocardium through several

**Table 1 Clinical variables according to heart rhythm**

| | SR (*N* = 100) | PAF (*N* = 100) | Persistent/permanent AF (*N* = 100) | *P*-value for trend |
|---|---|---|---|---|
| Age (years) | 56.1 ± 12.7 | 59.4 ± 8.9 | 61.2 ± 8.7 | 0.001 |
| Sex (male) | 52 (52) | 74 (74) | 83 (83) | <0.001 |
| BMI (kg/m$^2$) | 26.3 ± 4.1 | 27.1 ± 3.9 | 27.7 ± 4.1 | 0.015 |
| BSA (m$^2$) | 1.95 ± 0.21 | 2.10 ± 0.23 | 2.14 ± 0.23 | <0.001 |
| Cardiovascular risk factors | | | | |
| Diabetes | 16 (16) | 4 (4) | 9 (9) | 0.094 |
| Hypertension | 46 (46) | 59 (59) | 64 (64) | 0.010 |
| Hypercholesterolaemia | 27 (27) | 37 (37) | 34 (34) | 0.292 |
| Current smoking | 21 (21) | 6 (6) | 9 (9) | 0.298 |
| Cardiovascular medication | | | | |
| Beta-blocker | 9 (9) | 56 (56) | 61 (61) | <0.001 |
| ACE-I/ARB | 24 (24) | 54 (54) | 47 (47) | 0.001 |
| Statin | 11 (11) | 33 (33) | 39 (39) | <0.001 |
| Diuretic | 29 (29) | 28 (28) | 16 (16) | 0.060 |
| Calcium antagonist | 15 (15) | 13 (13) | 16 (16) | 0.852 |
| CTA findings | | | | |
| LA epicardial fat mass (g) | 5.5 ± 3.7 | 9.4 ± 5.4 | 10.4 ± 6.7 | <0.001 |
| LA volume (mL) | 88.5 ± 31.1 | 110.9 ± 28.2 | 133.8 ± 34.4 | <0.001 |

Values represent mean ± standard deviation or counts (percentage).
ACE-I, angiotensin-converter enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BSA, body surface area; CTA, computed tomography angiography; LA, left atrium; PAF, paroxysmal AF; SR, sinus rhythm.

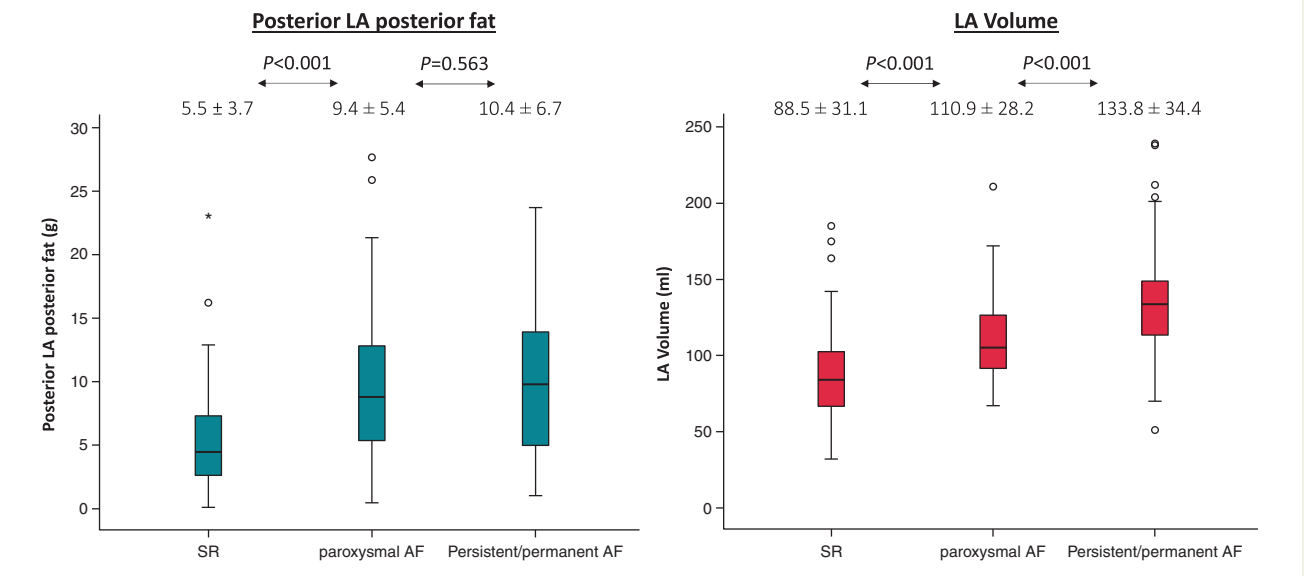


**Figure 2** LA epicardial fat and LA volume according to heart rhythm. Boxplots are shown for LA epicardial fat and LA volume according to the heart rhythm (SR, paroxysmal AF, and persistent/permanent AF). Left atrium epicardial fat was significantly larger in paroxysmal AF vs. SR, but the volume was similar between persistent/permanent AF and paroxysmal AF. LA volume increased significantly from SR to paroxysmal AF and to persistent/permanent AF. The coloured boxes represent the 25th and 75th inter-quartile range; whiskers represent 1.5 times the height of the box; additional points are outliers. AF, atrial fibrillation; LA, left atrium; SR, sinus rhythm.

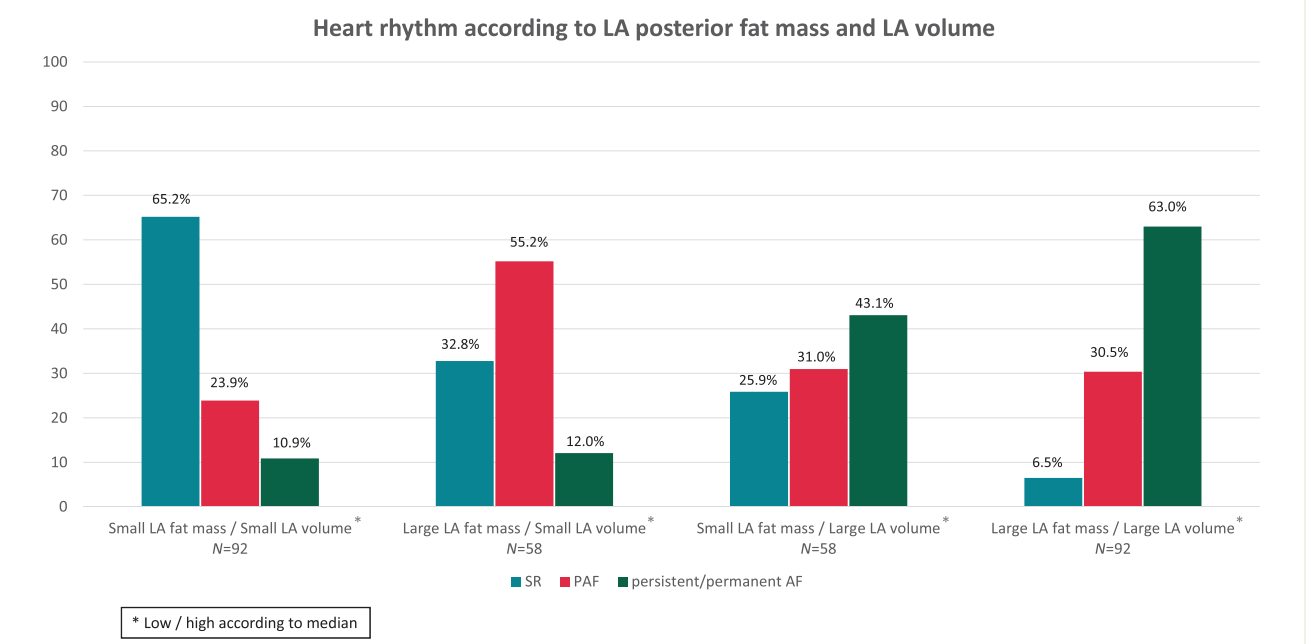


**Figure 3** Heart rhythm according to LA epicardial fat mass and LA volume. Patients are classified into four groups according to low or high (defined by median) magnitudes of LA epicardial fat mass and LA volume. The prevalence of sinus rhythm, paroxysmal atrial fibrillation (PAF), and persistent/permanent AF is shown on the *Y*-axis. AF, atrial fibrillation ; LA, left atrium.

pathways. It serves as energy depot for the myocardium, regulates heat and protects the autonomic ganglia.[11] Several pathophysiological mechanisms have been proposed that could contribute to the association of epicardial fat with AF. Two important pathways are fatty infiltration of the atrial wall leading to altered electrical conductance or paracrine modulation of the myocardial wall by inflammation and oxidative stress.[12] When epicardial fat increases in amount, bioactive molecules may accumulate in close proximity with the myocardium and accelerated fatty infiltration may follow. In an animal experiment, Mahajan *et al.*[4] demonstrated that sustained obesity is associated with increased volume of epicardial fat located posterior to the LA showing a typical pattern of fatty infiltration of the wall and increased prevalence of fibrosis. Previous imaging studies confirmed that abundance of epicardial fat associates with and increases risk for AF, independent of clinical predictors and LA size.[5,13,14] A meta-analysis including 352 275 individuals demonstrated that each standard deviation of epicardial fat volume was associated with 2.6-fold higher odds for AF, with similar associations for post ablation, postoperative and post cardioversion AF.[5]

## Association between left atrial volume, epicardial fat, and atrial fibrillation

Left atrial dilatation is an important part of atrial adverse remodelling and is a strong predictor of AF.[15] It is currently recommended that LA size and anatomy are assessed in all patients with AF.[9] Therefore, for clinical purposes, LA epicardial fat volume should demonstrate independent value from LA volume to improve risk stratification. In a population-based sample of 1990 individuals, Bos *et al.*[14] demonstrated the increased risk of epicardial fat with incident AF after extensive multivariable modelling, including LA diameter. Nakamori *et al.*[6] demonstrated that LA volume and epicardial fat both independently contribute to the identification of patients with AF. A total of 53 patients with AF and 52 age-matched patients without AF underwent cardiac magnetic resonance imaging and combined assessment of increased LA volume and epicardial fat volume provided greater discriminatory performance for detecting AF than LA volume alone (*C*-statistic 0.88 vs. 0.74 for LA volume, $P < 0.001$). Nevertheless, a previous report from the Heinz Nixdorf Recall Study demonstrated that increased LA volume can be a confounder in the association between epicardial fat and AF.[16] In 3467 healthy individuals, epicardial fat was associated with a nearly two-fold increased prevalence of AF on univariate analysis, which persisted after adjustment for AF risk factors. However, further adjustment for LA size reduced the effect to non-significant: 1.38 [95% confidence interval (CI) 1.11–1.72], $P = 0.003$ and 1.26 (95% CI 0.996–1.60), $P = 0.054$.[16] It may be that these discrepant results are caused by the fact that an increase in LA epicardial fat occurs earlier before development of AF, whereas LA dilation may occur later. Severely remodelled atria of patients with AF will be large in size, but when the LA does not show significant structural damage, AF risk may be underestimated by LA volume. Left atrial epicardial fat mass, as an indicator of overall metabolic disbalance, obesity and cardiovascular risk factor burden, can be increased significantly before the LA remodelling occurs.[17] Our study observed the largest difference in LA epicardial fat mass between patients with PAF and SR, whereas LA fat was not different between PAF and persistent/permanent AF, which supports this hypothesis. Further patients with a large LA epicardial fat mass but preserved LA

volume most frequently had PAF but similarly few had persistent/permanent AF as patients with both small LA volumes and epicardial fat. In contrast, when LA was large, most patients had persistent/permanent AF.

From a clinical point of view, increased LA epicardial fat volume may be an early marker of individuals at risk for future AF. Especially in individuals with normal LA size, improved risk stratification for AF, possibly by LA epicardial fat, would be helpful for early intervention with risk modifying medical therapy or lifestyle changes.

A confounding factor in the results may be the higher use of statin with more severe AF. Statin use has been demonstrated to reduce epicardial fat, and therefore the volume of LA epicardial fat may be reduced in those with persistent/permanent AF.[18]

## Study limitations

This study is a retrospective evaluation of clinically acquired data, with its inherent limitations including selection bias. Patients with SR underwent CCTA for clinical indications and are therefore not fully representative of healthy controls. Also, AF in these patients was ruled out based on self-reported absence of symptoms and electrocardiograms instead of systematic ECG Holter monitoring. Also, given the cross-sectional nature of the results, the findings should be replicated in prospective, longitudinal observations.

# Conclusions

Left atrial epicardial fat mass increased early in the disease process of AF while large LA volumes were associated with a high prevalence of persistent/permanent AF. Elevated LA epicardial fat mass without a large LA volume may reflect the early AF disease process.

# Supplementary material

Supplementary material is available at *Europace* online.

**Conflict of interest:** The Department of Cardiology of the Leiden University Medical Center received unrestricted research grants from Edwards Lifesciences, Biotronik, Medtronic, and Boston Scientific.

## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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