

Association Between Posterior Left Atrial Adipose Tissue Mass and Atrial Fibrillation

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Background—Epicardial adipose tissue located close to the atrial wall can change the electric conduction of the left atrium, potentially leading to atrial fibrillation (AF). The aim of this study was to assess whether an increased atrial adipose tissue mass posterior to the left atrium is related to AF independent of demographical and cardiovascular risk factors.

Methods and Results—Two hundred patients with AF and 200 patients without AF who underwent computed tomographic angiography were included. The posterior left atrial adipose tissue mass was quantified on computed tomographic angiography images as tissue with Hounsfield Units between -195 and -45 . The adipose tissue mass was significantly larger in patients with AF compared with patients with sinus rhythm: 10.6 ± 5.5 versus 4.7 ± 3.5 g, $P < 0.001$. In a multiple variable model (including age, body mass index, sex, coronary artery calcium score, diabetes mellitus, hypertension, hypercholesterolemia, family history of coronary artery disease, and known coronary artery disease), each gram increase of posterior left atrial adipose tissue was associated with 1.32 odds ratio of having AF (95% confidence interval, 1.22–1.43; $P < 0.001$). Furthermore, the addition of the adipose tissue mass to the multiple variable analysis significantly increased the discriminatory ability to predict AF: increase in the area under the receiver operating characteristic, 0.88 (95% confidence interval, 0.84–0.91) versus 0.81 (0.76–0.85), $P < 0.001$.

Conclusions—Posterior left atrial adipose tissue mass is significantly larger in patients with AF versus without AF. An increase in adipose tissue was independently associated with AF and provided incremental value over well-known predictors of AF. These findings add to the hypothesis that the posterior left atrial adipose tissue mass contributes to structural and electric remodeling leading to AF. (*Circ Arrhythm Electrophysiol.* 2017;10:e004614. DOI: 10.1161/CIRCEP.116.004614.)

Key Words: adipose tissue ■ atrial fibrillation ■ body mass index ■ computed tomographic angiography
■ left atrium

Epicardial adipose tissue (EAT) is defined as adipose tissue located between the myocardium and the visceral pericardium. It should be distinguished from paracardial adipose tissue (located outside the visceral pericardium) as these 2 entities are embryologically, anatomically, and functionally different.¹ EAT serves as a lipid depot and functions as an endocrine organ, secreting hormones, and inflammatory cytokines.² There exists an equilibrium between the physiological and pathophysiological effects of EAT on the heart. EAT might modulate the myocardium through systemic release of proinflammatory and anti-inflammatory cytokines (adipokines),^{1,3} but there is no direct evidence for local EAT secretion of adipokines in the coronary veins (based on a step-up in adipokine gradients across the coronary bed). Furthermore, besides these hypothetical systemic effects, EAT elicits local effects on the structure and function of the myocardium through several

pathways.¹ As EAT is not separated from the underlying myocardium by fascia, paracrine and vasocrine crosstalk between EAT and myocardium has been suggested.

Several studies addressed the association between increased EAT (volume and thickness) and atrial fibrillation (AF).^{4–6} The proposed pathophysiological mechanisms on how EAT induces AF, include structural and electric remodeling of the atria by direct (fatty infiltration and fibrosis of the adjacent myocardium) or indirect mechanisms (EAT as source for myocardial inflammation).^{7–9} Furthermore, EAT could influence trigger formation from the pulmonary veins, which may initiate AF.¹⁰

However, local (and direct) effects are most likely only caused by EAT surrounding the atria rather than surrounding the entire heart. Few studies assessed the association between left atrial (LA) adipose tissue and AF.^{11–13} In these studies, computed tomographic (CT) images were used to measure the

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WHAT IS KNOWN

- Epicardial adipose tissue has been associated with structural and electrical remodeling of the atria.
- Fatty infiltration and fibrosis of the atrial myocardium may potentially lead to atrial fibrillation.
- An excess of epicardial adipose tissue located adjacent to the posterior wall of the left atrium may be associated with the occurrence of atrial fibrillation and can be measured with computed tomography imaging.

WHAT THE STUDY ADDS

- In patients with atrial fibrillation, the amount of epicardial adipose tissue located posterior to the left atrium, measured on computed tomography, is significantly larger compared with patients in sinus rhythm.
- Increasing mass of epicardial adipose tissue adjacent to the posterior wall of the left atrium was independently associated with the presence of atrial fibrillation.
- Assessment of the epicardial adipose tissue mass in the posterior wall of the left atrium may have important clinical implications for management of patients with atrial fibrillation.

thickness of the adipose tissue surrounding the atrium as the shortest distance between the LA and several anatomic landmarks around the LA (pulmonary artery, descending aorta, and esophagus). Of these measurements, adipose tissue posterior to the LA (between the LA and the esophagus) had the strongest relationship with AF.^{11,12} However, this measurement may not represent the total mass of adipose tissue posterior to the LA because a wide variability exists in adiposity thickness at different craniocaudal levels and marked variation in anatomic relationship between the esophagus and the LA posterior wall has been reported.^{14,15} Volumetric quantification may overcome these limitations and can provide a robust measurement of the posterior LA adipose tissue mass.

The aim of this study was (1) to quantify the posterior LA adipose tissue mass in patients with and without AF and (2) to evaluate the relationship between posterior LA adipose tissue mass and AF, adjusted for demographical and cardiovascular risk factors.

Methods

Patients

From an ongoing coronary computed tomographic angiography (CTA) registry, 200 patients with and 200 patients without AF were randomly selected. The presence of AF was defined according to the European Society of Cardiology guidelines for AF management.¹⁶ Patients with AF were referred for coronary CTA before radiofrequency catheter ablation (to assess the LA anatomy and location of the pulmonary veins) and for the evaluation of suspected or known coronary artery disease (CAD). Patients without AF were referred for coronary CTA for the evaluation of suspected or known CAD. Contrast-enhanced coronary CTA data were analyzed for quantification of the atrial adipose tissue mass posterior to the LA. Demographic and clinical data were prospectively collected in the departmental electronic information

system (EPD-Vision, Leiden University Medical Center, Leiden, The Netherlands) and retrospectively analyzed. To correct for potential differences between groups, multiple variable logistic regression analyses were performed (see Statistical Analysis section). For retrospective analysis of clinically acquired data, the Institutional Review Board waived the need for patient written informed consent.

CT Acquisition

Coronary CTA 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, gantry rotation time of 350 ms, and a temporal resolution of 175 ms. To maximize image quality, 25 to 150 mg metoprolol was administered orally 1 hour before the scan if the patient's heart rate exceeded 60 beats per minute; an additional dose of intravenous metoprolol (up to 15 mg) was administered if the heart rate remained >65 beats per minute during the scout images. Sublingual nitroglycerin (0.4 mg) was administered before coronary CTA acquisition, unless contraindicated. First, a noncontrast 120 kV scan was performed for the calculation of the coronary artery calcium (CAC) score. Second, coronary CTA was acquired with prospective ECG gating covering 70% to 80% of the R–R interval. For patients with a regular heart rate of >65 beats per minute, 30% to 80% of the R–R interval was scanned to allow reconstructions of diastolic and systolic phases. A triphasic injection protocol was used to administer 60 to 90 mL of contrast agent (Iomeron 400, Bracco, Milan, Italy). CTA data were acquired the next heart beat after reaching the threshold of 300 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.

Coronary CT and Posterior LA Adipose Tissue Measurements

The CAC score was measured using the Agatston algorithm.¹⁷ All coronary arteries with a diameter of ≥ 1.5 mm were assessed for obstructive (defined as $\geq 50\%$ stenosis) CAD using a 17-segment model, as previously described.¹⁸ Coronary artery segments with stents were classified as obstructive CAD. Adipose tissue measurements were performed using the Mass software (LKEB, research version 2012, Leiden University Medical Center). Standard 2- and 4-chamber views were reconstructed with slices of 2-mm thickness and a perpendicular plane was set to obtain the cross-sectional view of the LA from the mitral annulus to the LA roof (Figure 1). The posterior LA adipose tissue mass was quantified in the short-axis views by manually tracing the pericardium posterior to the LA (Figure 2). The cranial and caudal limits were defined as the base of the LA and the mitral annulus respectively, resulting in ≈ 28 slices (Figure 3). The Hounsfield Units of the tissue within the space demarcated by the posterior LA wall and the manually traced pericardium were automatically determined. Tissue with Hounsfield Units between -190 and -45 was defined as adipose tissue.

Statistical Analysis

Continuous variables were presented as mean \pm SD or median with 25% to 75% interquartile range, according to the distribution. Normally distributed variables were compared with the Student *t* test. Non-normally distributed variables were compared with the Mann–Whitney *U* test. Categorical variables were presented as number and percentage and compared with the χ^2 test. To assess the independent association of posterior LA adipose tissue mass with AF, single and multiple variable logistic regression analyses were performed. Age, sex, body mass index (BMI), log transformed CAC, diabetes mellitus, hypertension, hypercholesterolemia, family history positive for CAD, and known CAD were included in a clinical model. Posterior LA adipose tissue mass was added to the clinical model to investigate its independent association with AF. Odds ratios (OR) and 95% confidence intervals (CI) were derived. To assess the incremental value of posterior LA adipose tissue mass to the clinical model, the Akaike Information Criterion and area under the receiver operating characteristic curve were calculated for the clinical model and model containing the clinical variables with the posterior LA adipose tissue

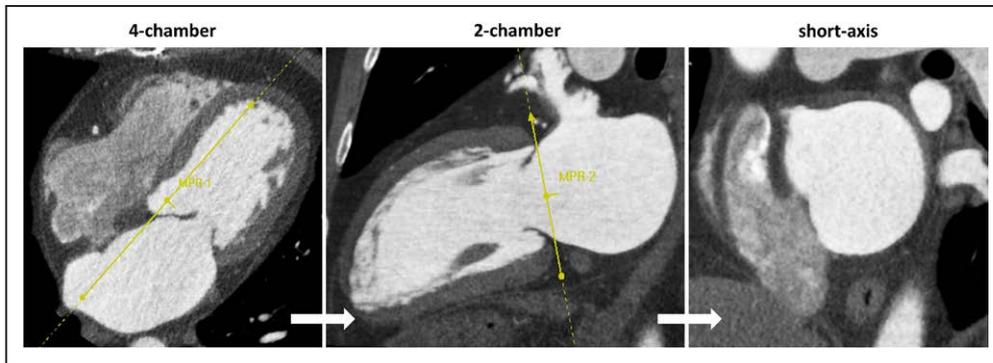


Figure 1. Computed tomography reconstructions for the measurement of posterior left atrial adipose tissue mass. 4-Chamber: a standard 4-chamber view of the heart was reconstructed. 2-Chamber: a 2-chamber view was created as a multiplanar reconstruction parallel to the yellow line in the 4-chamber view. Short-axis: a short-axis view was created as a multiplanar reconstruction parallel to the yellow line in the 2-chamber view.

mass. A P value of <0.05 in a 2-sided test was considered statistically significant. Statistical analyses were performed with the use of IBM SPSS Statistics software (version 22, IBM Corp, Armonk, New York, NY). Receiver operating characteristic curve analyses were performed with MedCalc software (version 16.2.1, Ostend, Belgium).

Results

Patients

Table 1 shows the baseline clinical characteristics of the 400 patients (mean age 58.7 ± 10.9 years; 62% male). Patients were randomly selected and not matched for clinical characteristics leading to significant differences between patients with AF and patients without AF for demographics, cardiovascular risk profile, and medication use. Patients with AF were significantly older (61.9 ± 8.8 versus 55.4 ± 11.8 years, $P < 0.001$), were more frequently male (75 versus 48%, $P < 0.001$), had a higher BMI (27.3 ± 4.3 versus 25.9 ± 11.8 kg/m², $P = 0.002$), and had a higher CAC score (23 [0–304] versus 11 [0–142], $P = 0.012$). The presence of obstructive CAD was similar between groups: 27 versus 30%, $P = 0.762$. Concerning cardiovascular risk factors, the prevalence of diabetes mellitus was lower (6% versus 21%, $P < 0.001$) for patients with AF, whereas the prevalence of hypertension was higher (66% versus 43%, $P < 0.001$) and fewer patients had a positive family history of CAD (21% versus 40%, $P < 0.001$) compared with patients without AF.

Posterior LA Adipose Tissue

The mean posterior LA adipose tissue mass in the total population was 7.7 ± 5.5 g. The mass was significantly higher in patients with AF compared with patients with sinus rhythm: 10.6 ± 5.5 versus 4.7 ± 3.5 g, $P < 0.001$. The distribution of adipose tissue between groups is shown in Figure 4.

Association Between Posterior LA Adipose Tissue Mass and AF

Single and multiple variable logistic regressions of the clinical model (including age, BMI, sex, CAC score, diabetes mellitus, hypertension, hypercholesterolemia, family history of CAD, and known CAD) and the final model (clinical model+posterior LA adipose tissue mass) are presented in Table 2. Posterior LA adipose tissue mass was independently associated with AF; the OR per gram increase was 1.32 (95% CI, 1.22–1.43, $P < 0.001$). The addition of posterior LA adipose tissue mass to the clinical model reduced the Akaike Information Criterion value (from 414 to 351), indicating better fit of the final model. The results of the analysis did not change when BMI was excluded from the model. Independent association between posterior LA adipose tissue mass and AF was also tested in a model containing the following variables: age, sex, log-transformed CAC score, diabetes mellitus, and family history of CAD. Each gram increase in posterior

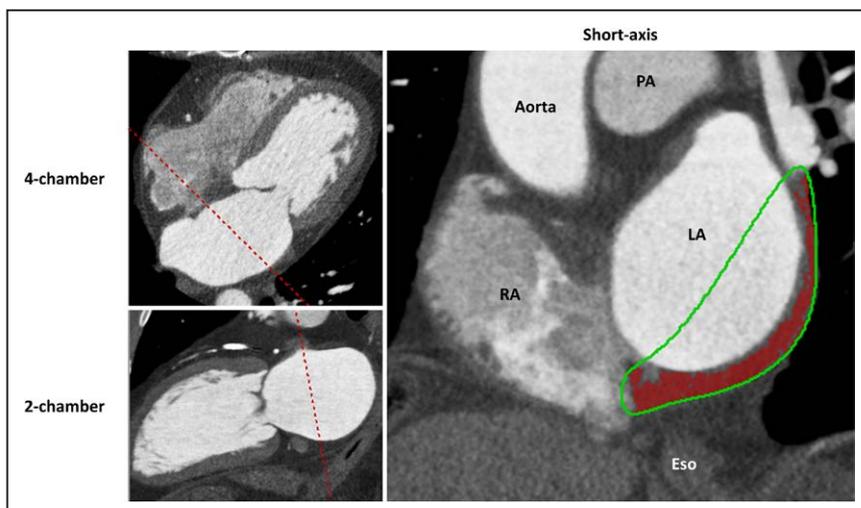


Figure 2. Example of assessment of the posterior LA adipose tissue mass. 4-Chamber: the red dotted line indicates the level of the short-axis view. 2-Chamber: the red dotted line indicates the level of the short-axis view. Short-axis: in the short axis view, the pericardium posterior to the LA was manually traced and all adipose tissue was incorporated into the green circle. The red-colored tissue has Hounsfield Units between -195 and -45 and indicates adipose tissue. Eso indicates esophagus; LA, left atrium; PA, pulmonary artery; and RA, right atrium.



Figure 3. The caudal and cranial limits for the measurement of posterior left atrial adipose tissue mass. The dotted red lines in the 2-chamber view indicate the cranial (left atrium base) and caudal (mitral annulus) levels; between these levels, the epicardial adipose tissue was measured as indicated by the red-colored tissue.

LA adipose tissue mass was associated with 32% increase in the risk of presenting AF (OR, 1.32; 95% CI, 1.22–1.43; $P < 0.001$). Furthermore, the discriminatory ability of the final

model to predict AF was significantly higher than the clinical model demonstrated by an increase in the area under the receiver operating characteristic curve: 0.88 (95% CI, 0.84–0.91) versus 0.81 (0.76–0.85), $P < 0.001$. The receiver operating characteristic curves are shown in Figure 5.

Discussion

This study demonstrated that the mass of posterior LA adipose tissue was significantly larger in patients with AF compared with patients without AF. Furthermore, after adjustment for demographics (age, BMI, and sex), cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, family history of CAD, and known CAD) and CAC score, the posterior LA adipose tissue mass retained the significant association with AF and improved the discriminatory power of the clinical model to identify patients with AF.

AF and EAT

Increasing age, hypertension, diabetes mellitus, obesity, and smoking are well-known risk factors for the development of AF.¹⁹ These risk factors have been also associated with an excess of global adiposity and particularly with an excess of EAT,^{20,21} an

Table 1. Patient Characteristics

	Total (N=400)	Atrial Fibrillation (N=200)	Sinus Rhythm (N=200)	P Value
Age, y	58.7±10.9	61.9±8.8	55.4±11.8	<0.001
BMI, kg/m ²	26.6±4.4	27.3±4.3	25.9±4.4	0.002
Male	246 (62)	150 (75)	96 (48)	<0.001
CAC score	16 (0–291)	23 (0–304)	11 (0–142)	0.012
Obstructive CAD	114 (29)	54 (27)	60 (30)	0.762
Posterior LA adipose tissue mass, g	7.7±5.5	10.6±5.5	4.7±3.5	<0.001
Cardiovascular risk factors				
Diabetes mellitus	53 (13)	11 (6)	42 (21)	<0.001
Hypertension*	218 (55)	132 (66)	86 (43)	<0.001
Hypercholesterolemia†	114 (29)	65 (33)	49 (25)	0.076
Family history of CAD‡	121 (30)	41 (21)	80 (40)	<0.001
Currently smoking	85 (21)	45 (23)	40 (20)	0.541
Known CAD§	39 (10)	25 (13)	14 (7)	0.064
Medication				
β-Blocker	142 (36)	122 (61)	20 (10)	<0.001
ACE-I/ARB	147 (37)	101 (51)	46 (23)	<0.001
Statin	93 (23)	74 (37)	19 (10)	<0.001
Diuretics	107 (27)	50 (25)	57 (29)	0.429
Calcium antagonist	55 (14)	32 (16)	23 (12)	0.191
Nitrates	22 (6)	3 (2)	19 (10)	<0.001

Values are mean±SD, median (25%–75% interquartile range) or n (%). ACE-I indicates angiotensin-converting enzyme-inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CAC, coronary artery calcium; CAD, coronary artery disease; LA, left atrium; and PCI, percutaneous coronary intervention.

*Systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or the use of antihypertensive medication.

†Defined as a self-reported history of hypercholesterolemia or therapeutic treatment with lipid lowering drugs.

‡Presence of CAD in first-degree family members at <55 years of age in men and <65 years of age in women.

§Previous PCI, CABG, or myocardial infarction.

Table 2. Odds Ratios From Single and Multiple Logistic Regression Models

	Single Model*		Clinical Model		Final Model	
	Univariable, Odds Ratio (95% CI)	P Value	Multivariable, Odds Ratio (95% CI)	P Value	Multivariable, Odds Ratio (95% CI)	P Value
Age, y	1.06 (1.04–1.09)	<0.001	1.08 (1.05–1.11)	<0.001	1.05 (1.02–1.09)	0.004
BMI, kg/m ²	1.08 (1.03–1.13)	0.002	1.10 (1.03–1.16)	0.004	1.01 (0.94–1.09)	0.815
Male	3.25 (2.13–4.96)	<0.001	3.94 (2.31–6.72)	<0.001	2.67 (1.46–4.89)	0.001
Ln CAC (+1)	1.09 (1.01–1.18)	0.021	0.90 (0.80–1.00)	0.055	0.86 (0.76–0.98)	0.022
Diabetes mellitus	0.22 (0.11–0.44)	<0.001	0.13 (0.06–0.31)	<0.001	0.14 (0.05–0.37)	<0.001
Hypertension	2.57 (1.72–3.86)	<0.001	1.52 (0.89–2.60)	0.123	1.44 (0.79–2.63)	0.238
Hypercholesterolemia	1.45 (0.96–2.30)	0.077	1.41 (0.78–2.52)	0.254	1.13 (0.58–2.19)	0.721
Family history of CAD	0.39 (0.25–0.60)	<0.001	0.43 (0.25–0.74)	0.002	0.54 (0.30–0.98)	0.041
Known CAD	1.90 (0.96–3.80)	0.067	0.69 (0.25–1.92)	0.477	0.74 (0.25–2.18)	0.584
Posterior LA adipose tissue mass, g	1.35 (1.27–1.44)	<0.001			1.32 (1.22–1.43)	<0.001

AIC of the Clinical Model: 414; AIC of the Final Model: 351. AIC indicates Akaike's information criterion; BMI, body mass index; CAC, coronary artery calcium; CAD, coronary artery disease; CI, confidence interval; and LA, left atrium.

*Only 1 independent variable is entered into each model.

important component of the visceral adipose tissue, which has been associated with the increased risk of AF.^{4,22} In addition, the treatment of these risk factors, specifically with the use of statins and novel oral anti-diabetic medications, has shown to reduce the volume of EAT.²³ Of 3217 patients included in the Framingham Heart Study and imaged with multidetector CT to assess EAT, intrathoracic and abdominal fat, 54 (1.6%) presented with AF.⁵ The volume of EAT was independently associated with prevalent AF (OR per SD of EAT, 1.28; 95% CI, 1.03–1.58; $P=0.03$) after adjusting for age, sex, systolic blood pressure, antihypertensive treatment, PR interval, and significant valvular heart disease. This association was retained after adjusting for BMI. In contrast, intrathoracic or visceral fat were not significantly associated with the occurrence of AF. The stronger association between EAT and the occurrence of AF, in comparison to other markers

of overall adiposity, may be explained by several pathophysiological mechanisms.²⁴ EAT may induce structural and electric remodeling of the LA by fatty infiltration of the LA myocardium causing slow conduction. Mahajan et al⁸ recently demonstrated in an animal model that obese sheep had larger LA volumes and pressures, reduced atrial conduction velocity, increased conduction heterogeneity, increased fractionated electrograms, and decreased posterior LA voltage as compared with control non-obese sheep. In addition, obese sheep had more frequent and longer-lasting episodes of AF than their counterparts, suggesting the association between obesity and AF. Interestingly, obese animals showed moderate to severe LA posterior wall infiltration by surrounding epicardial fat and larger areas of fibrosis compared with nonobese animals explaining the electrophysiological findings of reduced endocardial voltage in that area.

Furthermore, the EAT may be a source for paracrine modulators of myocardial inflammation and oxidative stress that facilitate arrhythmogenesis. In a retrospective case-control analysis, including 21 patients with AF and 21 without AF who were imaged with positron emission tomography-CT, the uptake of F18-fluorodeoxyglucose by the EAT and intrathoracic fat, as a marker of inflammatory activity, was compared.²⁵ The F18-fluorodeoxyglucose uptake by the EAT surrounding the LA roof was significantly greater in patients with versus without AF (1.66 ± 0.36 versus 1.23 ± 0.32 ; $P<0.001$), whereas no differences were observed in the uptake by the intrathoracic fat (0.89 ± 0.22 versus 0.81 ± 0.17 ; $P=0.24$). These findings underscore the clinical relevance of EAT over other forms of visceral fat in the pathogenesis of AF. However, it remains unclear how to assess the amount of EAT to refine the stratification of patients at risk of developing AF.

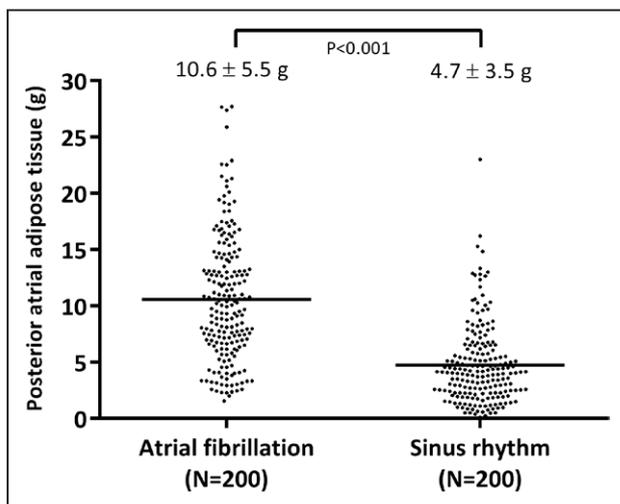


Figure 4. Individual patient data of posterior left atrial (LA) adipose tissue mass comparing patients with atrial fibrillation (AF) and sinus rhythm. A larger mass of posterior LA adipose tissue was observed in patients with AF compared with patients without AF: 10.6 ± 5.5 g vs 4.7 ± 3.5 g ($P<0.001$).

Increase in Posterior LA Adipose Tissue Mass and AF

The high spatial resolution of CT permits accurate and reproducible measurements of the volume, thickness and area of

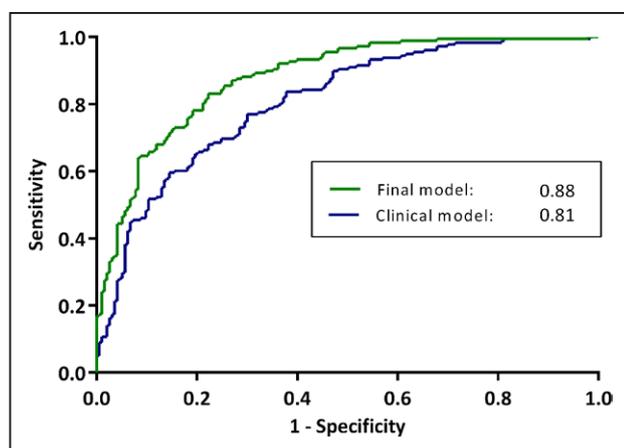


Figure 5. Receiver operating characteristics curves. Adding the posterior left atrial adipose tissue mass to the clinical model significantly improved the area under the receiver operating characteristics curve values: 0.88 (95% confidence interval, 0.84–0.91) vs 0.81 (0.76–0.85), $P < 0.001$.

the EAT, and the different regions where the EAT is distributed. This study, using CT and measuring the mass of adipose tissue immediately adjacent to the posterior LA wall, demonstrated that increasing mass of adipose tissue in this particular location was independently associated with increased risk of AF. These results are in line with previous experimental and clinical studies.^{11–13} Batal et al¹² evaluated the impact of EAT pad thickness measured on CT at different locations on the AF burden in 96 patients with AF (63% paroxysmal and 37% persistent). The thickness of the EAT located between the esophagus and the posterior LA wall, between the pulmonary artery and the anterior LA wall, and between the descending thoracic aorta and the posterior LA wall were larger among patients with AF when compared with controls. However, only the thickness of the EAT located between the esophagus and the posterior LA wall was significantly larger among patients with persistent AF when compared with patients with paroxysmal AF and controls (0.56 cm versus 0.39 cm and 0.34 cm, respectively; $P < 0.015$).¹² An independent association between the thickness of EAT between the esophagus and the posterior LA wall was observed (OR, 5.3; 95% CI, 1.39–20.24; $P = 0.015$) after adjusting for age, BMI, and LA area. Currently, the use of CT in clinical practice is increasing in patients with AF who are referred for radiofrequency catheter ablation techniques. The addition of information on extent and location of EAT may add to the risk stratification models to predict the success of radiofrequency catheter ablation techniques by identifying the patients with larger amount of EAT who may be at higher risk for AF recurrences. From the imaging point of view, the assessment of EAT mass with semiautomated postprocessing tools may help to increase accuracy and reduce variability of the measurement, leading to better risk stratification.

Limitations

The present evaluation is a retrospective study with all the inherent limitations of selection bias. The patients with AF were referred for CT before radiofrequency catheter ablation, whereas the control group was referred for CT due to

other clinical indications, and the presence of AF was ruled out based on self-reporting symptomatology and not with the systematic use of ECG Holter monitoring.

Conclusions

The posterior LA adipose tissue mass is significantly larger in patients with versus without AF. Increasing posterior LA adipose tissue mass was independently associated with AF and provided incremental value to a clinical model to identify patients with AF. These findings add to the hypothesis that posterior LA adipose tissue mass contributes to structural and electric remodeling leading to AF.

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Disclosures

None.

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