

Pericardial Fat Is Associated With Atrial Fibrillation Severity and Ablation Outcome

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Objectives	The aim of this study was to characterize the relationship between pericardial fat and atrial fibrillation (AF).
Background	Obesity is an important risk factor for AF. Pericardial fat has been hypothesized to exert local pathogenic effects on nearby cardiac structures above and beyond that of systemic adiposity.
Methods	One hundred ten patients undergoing first-time AF ablation and 20 reference patients without AF underwent cardiac magnetic resonance imaging for the quantification of periatrial, periventricular, and total pericardial fat volumes using a previously validated technique. Together with body mass index and body surface area, these were examined in relation to the presence of AF, the severity of AF, left atrial volume, and long-term AF recurrence after ablation.
Results	Pericardial fat volumes were significantly associated with the presence of AF, AF chronicity, and AF symptom burden (all p values <0.05). Pericardial fat depots were also predictive of long-term AF recurrence after ablation ($p = 0.035$). Finally, pericardial fat depots were also associated with left atrial volume (total pericardial fat: $r = 0.46$, $p < 0.001$). Importantly, these associations persisted after multivariate adjustment and additional adjustment for body weight. In contrast, however, systemic measures of adiposity, such as body mass index and body surface area, were not associated with these outcomes in multivariate-adjusted models.
Conclusions	Pericardial fat is associated with the presence of AF, the severity of AF, left atrial volumes, and poorer outcomes after AF ablation. These associations are both independent of and stronger than more systemic measures of adiposity. These findings are consistent with the hypothesis of a local pathogenic effect of pericardial fat on the arrhythmogenic substrate supporting AF. (J Am Coll Cardiol 2011;57:1745–51) © 2011 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common sustained arrhythmia, and its prevalence has been projected to continue to increase significantly in the coming decades (1–3). Recent studies have highlighted obesity and body size as risk

factors for AF (4–7). This is particularly significant given the obesity epidemic (8).

Although many studies have evaluated the relationship between systemic measures of adiposity and AF, pericardial

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Abbreviations and Acronyms

- AF** = atrial fibrillation
- BMI** = body mass index
- BSA** = body surface area
- LA** = left atrial
- MRI** = magnetic resonance imaging

adipose tissue depots have only recently been shown to be associated with AF (9,10). In addition, no study has quantified periatrial and periventricular fat volumes in relation to AF.

The aim of the present study was thus to characterize the relationship between specific pericardial fat depots, as measured by cardiac magnetic resonance imaging (MRI), and AF. We sought to determine whether pericardial fat depots were associated with the presence and severity of AF, as assessed by AF chronicity and symptom burden. In addition, we also explored the association of these depots with left atrial (LA) volume and ablation outcome. Because of its contiguity to cardiac structures, we hypothesized that specific pericardial fat depots would be associated with the presence and severity of AF, larger LA volumes, and poorer outcomes after AF ablation.

Methods

Study population. Consecutive patients (n = 110) undergoing first-time ablation with no contraindications to MRI were recruited into 3 groups on the basis of AF chronicity, in accordance with the Heart Rhythm Society expert consensus statement (11). Paroxysmal AF was defined as recurrent AF that terminates spontaneously within 7 days. Persistent AF was defined as AF that is sustained beyond 7 days or that lasts <7 days but necessitates pharmacological or electrical cardioversion. Permanent AF was defined as AF of >1 year in duration in which cardioversion has either failed or not been attempted. AF symptom burden was

evaluated in these patients using the University of Toronto Atrial Fibrillation Severity Scale (12). A reference group of 20 volunteers without AF was also studied. The 2 groups were well matched with regard to cardiovascular risk factors and systemic adiposity (Table 1).

All patients provided written informed consent for the study protocol, which was approved by the Clinical Research and Ethics Committee of the Royal Adelaide Hospital.

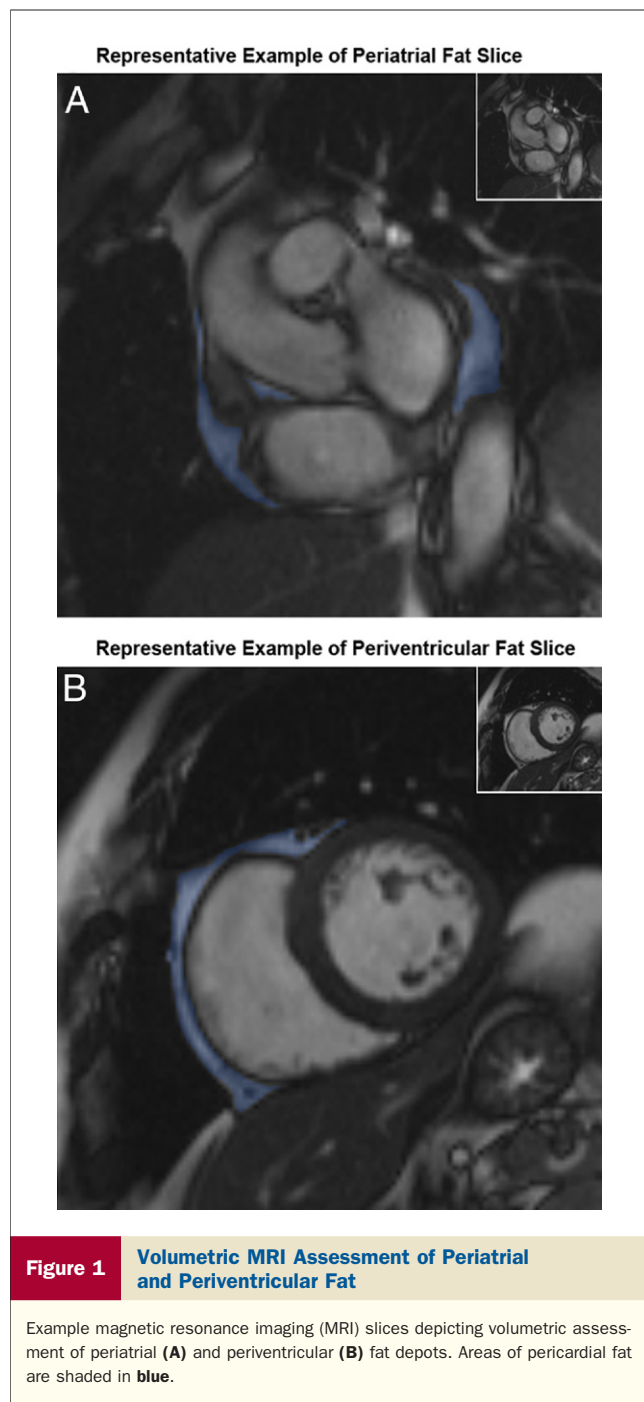
MRI protocol and analysis. Patients underwent cardiac MRI at 1.5 T (Siemens Avanto, Siemens Medical Solutions, Erlangen, Germany) in the week before ablation. Sequential steady-state free-precession short-axis cine sequences were acquired with 6-mm slice thickness and no interslice gaps through the atria and 6-mm slice thickness with 4-mm gaps through the ventricles. Slices were taken from the most cranial aspect of the left atrium and sequentially to the cardiac apex at end-expiration. The atria were additionally imaged in the horizontal long-axis plane with 6-mm slice-thickness and no interslice gaps. Typical imaging parameters were as follows: echo time 1.2 ms, repetition time 63.7 ms, flip angle 80°, matrix size 192 × 156, and field of view 360 to 440 mm. Of 110 subjects, 8 scans were uninterpretable because of motion artifacts, leaving 102 in the study sample.

Pericardial fat volumes were measured offline by 2 blinded observers using proprietary software (Argus, Siemens Medical Solutions). Fat volumes were quantified using a previously validated technique found to be highly accurate and reproducible by our group in an ex vivo ovine model (13). Pericardial fat was defined as regions of high signal intensity between the myoepicardium and the parietal pericardium. Periatrial and periventricular fat was defined as any pericardial fat subtending the atria and ventricles, respectively (Fig. 1).

Table 1 Study Sample Characteristics

Variable	AF (n = 102)	Reference (n = 20)	p Value
Age (yrs)	58 ± 9	54 ± 6	0.15
Men	76% (72)	11% (55)	0.20
BMI (kg/m ²)	28.0 ± 3.5	27.2 ± 3.4	0.46
BSA (m ²)	2.04 ± 0.22	1.93 ± 0.20	0.08
Periatrial fat (cm ³)	118.5 (70.8–173.8)	69.7 (47.7–88.0)	<0.001
Periventricular fat (cm ³)	154.7 (114.4–233.8)	101.2 (84.9–111.2)	<0.001
Total pericardial fat (cm ³)	299.9 (192.2–407.2)	168.8 (130.4–189.0)	<0.001
Paroxysmal AF	37% (38)	—	—
Persistent AF	33% (34)	—	—
Permanent AF	29% (30)	—	—
AF episode frequency score	8.5 ± 1.9	—	—
AF episode duration score	8.5 ± 2.1	—	—
LA volume (ml)	123 ± 36	90 ± 26	0.006
Valvulopathy	6.9% (7)	0.0% (0)	0.60
Hypertension	56.9% (58)	55.0% (11)	0.99
Diabetes	5.9% (6)	10.0% (2)	0.61
Ischemic heart disease	17.6% (18)	10.0% (2)	0.52
Left ventricular dysfunction	14.7% (15)	5.0% (1)	0.47
Obstructive sleep apnea	17.6% (18)	10.0% (2)	0.52

Data are expressed as mean ± SD, as % (n), or as median (interquartile range).
AF = atrial fibrillation; BMI = body mass index; BSA = body surface area; LA = left atrial.



Areas of fat were traced on consecutive end-diastolic short-axis images and multiplied by the slice thickness to derive volume (13). Intraobserver and interobserver reproducibility with this technique was excellent (coefficients of variation 3.5% and 4.9%, respectively). LA volumes were determined by manually tracing endocardial borders in the horizontal long-axis views in ventricular end-systole and calculated using a modified Simpson's rule (14).

Risk factor definitions. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters, and body surface area (BSA) was calcu-

lated using the Mostellar formula (15). The following risk factors were ascertained as categorical variables: sex, hypertension, diabetes mellitus, ischemic heart disease, left ventricular dysfunction, valvulopathy, and obstructive sleep apnea. LA volume was determined as previously discussed. **Electrophysiology study and ablation.** The electrophysiological procedure was performed in the post-absorptive state with conscious sedation using midazolam and fentanyl. The ablation technique has been previously described (16). In brief, a conventional transseptal puncture was used to advance both a circular mapping catheter (Lasso, Biosense Webster, Diamond Bar, California) and a 3.5-mm-tip externally irrigated ablation catheter (ThermoCool, Biosense Webster). After transseptal puncture, unfractionated heparin was administered (100 IU/kg), with repeated boluses to maintain an activated clotting time of 300 to 350 s. Electroanatomic mapping (CARTO, Biosense Webster; or NavX, St. Jude Medical, St. Paul, Minnesota) was used for nonfluoroscopic navigation. The ablation strategy included wide-encircling ablation of the pulmonary veins with an endpoint of pulmonary vein isolation and further substrate modification using linear ablation or electrogram-based ablation in those with AF paroxysms >48 h, large atria (largest diameter >57 mm), or evidence of structural heart disease. Radiofrequency power of 30 W was used, with irrigation rates of 30 to 60 ml/min.

Follow-up. Patients were followed at 3, 6, 9, 12, 18, and 24 months, and then yearly, until AF recurrence. At each review, patients underwent ambulatory monitoring for a 7-day period. All patients received either flecainide or sotalol for 6 weeks after the procedure. Antiarrhythmic drugs were ceased at the discretion of the treating physician at the 6-week follow-up visit. Warfarin was continued in all patients for at least 3 months. In patients with CHADS₂ scores <2, warfarin was ceased in the absence of any arrhythmia; otherwise, it was continued for a minimum of 12 months. Procedural success was determined as the absence of any atrial arrhythmia >30 s without the use of antiarrhythmic drugs after a blanking period of 3 months.

Statistical analysis. To study the relationship between pericardial fat and AF presence, we used binary logistic regression models. Each adiposity measure was then studied separately, adjusting for the 2 strongest univariate risk factors (LA volume and obstructive sleep apnea) to avoid overfitting and then additionally for weight.

To determine the relationship between pericardial fat depots and AF chronicity, we compared pericardial fat depots according to AF chronicity using the Kruskal-Wallis test and post hoc Wilcoxon rank sum tests as appropriate. We then dichotomized the study sample into 2 groups: paroxysmal and nonparoxysmal AF (persistent or permanent AF). Each adiposity measure was then studied separately, adjusting for the 4 strongest univariate risk factors (LA volume, left ventricular dysfunction, sex, and valvulopathy) to avoid overfitting and then additionally for weight. To determine the relationship between pericardial fat and AF symptom burden

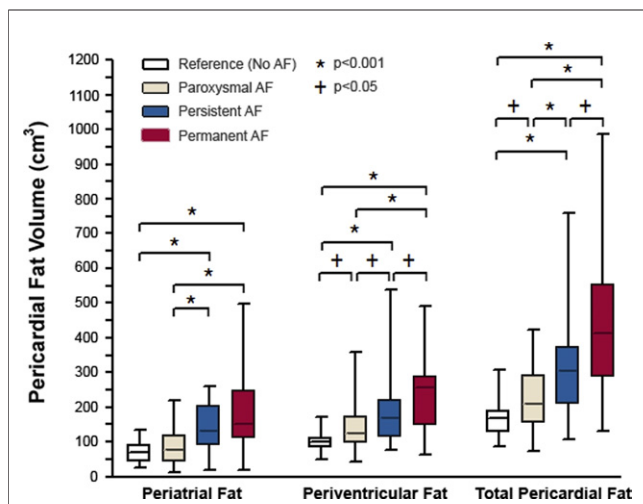


Figure 2 Pericardial Fat According to the Presence and Severity of AF

Box plots are shown depicting specific pericardial fat depot volumes according to the presence and chronicity of atrial fibrillation (AF). There is a clear dose-response relationship between pericardial fat volumes and both the presence of and chronicity of AF.

scores, multivariate linear regression models were used, adjusting for all the aforementioned risk factors and AF chronicity and then additionally for weight.

To determine the relationship between pericardial fat and AF recurrence, patients were first divided into tertiles according to total pericardial fat, and Kaplan-Meier methods were used. Second, a time-to-event Cox proportional-hazards regression method was used to study the individual relationships of specific adiposity measures as continuous variables to long-term AF recurrence. Multivariate Cox proportional-hazards regression models were used adjusting for all the aforementioned risk factors and AF chronicity and then additionally for weight. The proportional-hazards assumption was confirmed by means of the Schoenfeld residuals test; no relevant violations of the assumption were found.

To determine the relationship between pericardial fat and LA volume, Pearson’s correlations between adiposity measures and LA volume were calculated. Multivariate linear regression models were then constructed to determine which specific adiposity measures were associated with LA volumes, adjusting for all the aforementioned risk factors and then additionally for weight.

Continuous variables are reported as mean ± SD or as median and interquartile range as appropriate. Study sample characteristics according to group were compared using the unpaired Student *t* tests, Wilcoxon rank sum tests, or Fisher exact tests as appropriate. All adiposity measures were standardized to a mean of 0 and an SD of 1 to facilitate comparison between different fat depots. Statistical tests were performed using SPSS version 16 (SPSS, Inc., Chicago, Illinois), and 2-tailed *p* values <0.05 were considered significant.

Results

Patient characteristics. Patient characteristics are summarized in Table 1. The 2 groups were well matched for age, sex, and risk factors. However, patients with AF had larger left atria (*p* = 0.006).

Pericardial fat and AF presence. Patients with AF had greater pericardial fat volumes than reference patients (Fig. 2). By logistic regression modeling, pericardial fat depots were individually predictive of the presence of AF (Table 2), whereas systemic adiposity measures were not. Additional adjustment for risk factors and weight did not change these associations.

Pericardial fat and AF severity. Worsening baseline AF chronicity was associated with greater adiposity measures (Fig. 2). All adiposity measures were individually predictive of nonparoxysmal AF (Table 3). However, only pericardial fat volumes were associated with nonparoxysmal AF in multivariate-adjusted models, and additional adjustment for weight did not change these associations.

Similarly, although all adiposity measures were individually associated with AF burden score, only pericardial fat volumes were still associated after multivariate adjustment (Table 4). Additional adjustment for weight also did not change these associations.

Pericardial fat and AF recurrence. There was no loss to follow-up after 16.7 ± 11.1 months. Of 102 patients, 43 (42.6%) remained free of recurrence while off antiarrhythmic drugs after a single ablation procedure. Of those with recurrence (*n* = 59), 32 were recommenced on antiarrhythmic drugs, and 14 (43.8%) responded favorably to previously ineffective antiarrhythmic drugs after ablation and maintained normal sinus rhythm. Of the 59 patients with recurrence, 37 went on to have second procedures, and 5 went on to have third procedures. After 1.4 ± 0.6 procedures and 21.0 ± 12.0 months after the last procedure, 90

Table 2 Multivariate-Adjusted Odds Ratios (Confidence Intervals) of Adiposity Measures and the Presence of AF

Variable	Univariate	p Value	Multivariate Adjusted	p Value	With Additional Adjustment for Body Weight	p Value
BMI	1.26 (0.74–2.15)	0.391	1.16 (0.61–2.22)	0.645	—	—
BSA	1.61 (0.94–2.73)	0.081	1.25 (0.65–2.41)	0.509	—	—
Periatrial fat	4.61 (1.72–12.39)	0.002	5.35 (1.30–2.19)	0.020	5.33 (1.25–22.66)	0.023
Periventricular fat	13.63 (3.04–61.15)	0.001	10.94 (1.69–70.73)	0.012	11.97 (1.69–84.88)	0.013
Total pericardial fat	10.47 (2.87–38.21)	<0.001	11.25 (2.07–61.24)	0.005	13.28 (2.23–79.98)	0.005

Abbreviations as in Table 1.

Table 3 Multivariate-Adjusted Odds Ratios (Confidence Intervals) of Adiposity Measures and AF Chronicity

Variable	Univariate	p Value	Multivariate Adjusted	p Value	With Additional Adjustment for Body Weight	p Value
BMI	1.76 (1.08-2.87)	0.024	1.72 (0.89-3.32)	0.108	—	—
BSA	2.05 (1.27-3.30)	0.003	1.57 (0.74-3.33)	0.243	—	—
Periatrial fat	4.64 (2.20-9.76)	<0.001	4.87 (1.87-12.69)	0.001	4.84 (1.75-13.4)	0.002
Periventricular fat	2.67 (1.46-4.89)	0.001	2.10 (1.08-4.09)	0.030	1.96 (1.01-3.82)	0.047
Total pericardial fat	4.33 (2.08-9.02)	0.005	3.56 (1.41-9.00)	0.007	3.28 (1.25-8.59)	0.015

Abbreviations as in Table 1.

patients (88.2%) were free of recurrence while off antiarrhythmic drugs.

By Kaplan-Meier analysis, patients with more extensive total pericardial fat had recurrence at earlier time points after the index ablation procedure ($p = 0.035$ by log-rank test) (Fig. 3).

Pericardial fat volumes were predictive of AF recurrence by Cox regression modeling, whereas BMI and BSA were not (Table 5). After multivariate adjustment, periventricular fat ($p = 0.024$) remained predictive of AF recurrence. This association remained significant after additional adjustment for weight ($p = 0.025$).

Pericardial fat and LA volume. Periatrial ($r = 0.43$), periventricular ($r = 0.48$), and total pericardial ($r = 0.49$) fat volumes were correlated with LA volume (all p values < 0.001). In contrast, neither BMI nor BSA was significantly correlated with LA volume ($p = 0.22$ and $p = 0.38$, respectively).

In multivariate-adjusted models, all pericardial fat depots were associated with LA volume. Per 1-SD increase in periatrial fat, periventricular fat, and total pericardial fat, LA volume was 12.10 ml ($p = 0.004$), 12.34 ml ($p = 0.003$), and 14.04 ml ($p = 0.001$) larger, respectively. These associations persisted after additional adjustment for weight ($p = 0.041$ for periatrial, $p = 0.024$ for periventricular, and $p = 0.022$ for total pericardial fat).

Discussion

Major findings. In consecutive patients with AF presenting for first-time radiofrequency ablation and a group of reference patients, we undertook detailed MRI examination to present new information regarding the interrelationships between localized pericardial fat depots and AF.

First, we showed there to be an association between pericardial fat and the presence of AF. Second, we demonstrated there to be a strong dose-response association

between pericardial fat and AF severity, as assessed by AF chronicity and symptom burden. Third, our data demonstrate that pericardial fat was independently predictive of AF recurrence after ablation. Finally, we found independent associations between pericardial fat depots and LA volume.

These associations were not seen with more systemic measures of adiposity. Our findings are consistent with the hypothesis of a local pathogenic effect of pericardial fat promoting an arrhythmogenic substrate.

Pericardial fat and AF. Significant associations between BMI and the development of AF have been reported (4-7,17). Prior studies have shown that the association with BMI is stronger for sustained AF than it is for less severe forms and that obesity causes progression to more severe AF (6,18). Short-term increases in BMI have also been associated with increased AF risk (4). A recent report has suggested that total pericardial fat volume measured on computed tomography is associated with prevalent AF (9). Another recent study reported an association between epicardial thickness over the left atrium on computed tomography and AF chronicity (10). The present investigation extends the results of these studies to a cohort of patients who had specific pericardial fat volumes measured with a previously validated MRI technique (13). After multivariate adjustment, only pericardial fat, and not systemic adiposity measures, remained independently predictive of both the presence and severity of AF. Although studies with larger samples have previously reported associations between systemic adiposity and AF, the finding that pericardial fat but not systemic adiposity was significantly associated with AF in our study suggests that pericardial fat depots may be more influential than BMI or BSA. Furthermore, we found that pericardial fat was predictive of ablation outcomes, providing evidence of the deleterious role that pericardial fat may also have on substrate remodeling after ablation.

Table 4 Multivariate-Adjusted Regressions (Confidence Intervals) Between Adiposity Measures and AF Burden

Variable	Univariate	p Value	Multivariate Adjusted	p Value	With Additional Adjustment for Body Weight	p Value
BMI	1.10 (0.33 to 1.88)	0.005	0.87 (-0.49 to 2.24)	0.205	—	—
BSA	1.18 (0.42 to 1.94)	0.003	1.00 (-0.32 to 2.33)	0.133	—	—
Periatrial fat	1.57 (0.88 to 2.27)	<0.001	1.71 (0.79 to 2.64)	<0.001	1.59 (0.59 to 2.60)	0.003
Periventricular fat	1.46 (0.74 to 2.19)	<0.001	1.21 (0.23 to 2.19)	0.017	1.11 (0.11 to 2.11)	0.031
Total pericardial fat	1.69 (0.99 to 2.39)	<0.001	1.71 (0.73 to 2.68)	0.001	1.57 (0.54 to 2.60)	0.003

Abbreviations as in Table 1.

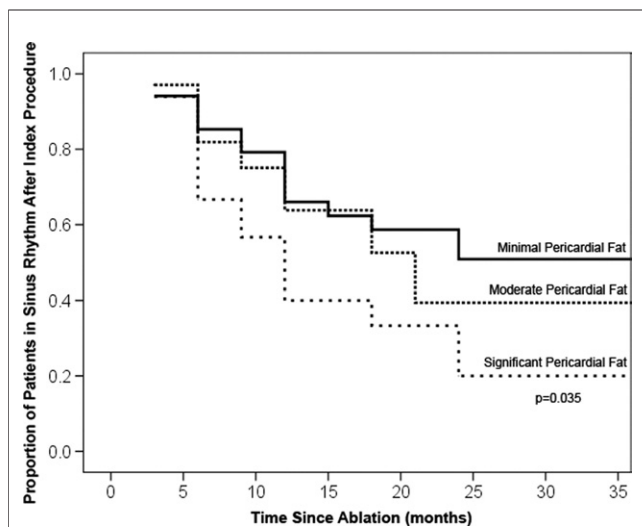


Figure 3 Pericardial Fat and Ablation Outcome

Kaplan-Meier curves showing the proportion of patients who maintained sinus rhythm after a single ablation procedure according to total pericardial fat tertiles.

Pericardial fat and cardiac structure. Pericardial fat has been previously shown to be associated with LA dimensions (19–22). However, periatrial and periventricular fat has not been previously studied in relation to LA volume, a superior predictor of outcome to LA dimension (23). We found that specific pericardial fat depots were associated with MRI-assessed LA volumes. In contrast, we observed no such association between systemic adiposity and LA volume. This may reflect our small sample size compared with previous epidemiological studies, our use of LA volume, or the AF population studied. Nevertheless, our data suggest that pericardial fat may have a pathogenic effect on the anatomically contiguous atria, above and beyond systemic effects of generalized adiposity.

Potential mechanisms. The association between pericardial fat and AF was not weakened by risk factor adjustment, suggesting that they play a lesser role in mediating the relationship. Previous studies have reported that the association between BMI and AF was attenuated when LA dimension was accounted for, suggesting that LA enlargement accounts for this association (17). We found that pericardial fat, but not systemic adiposity, was associated with LA volume. Furthermore, adjustment for LA volume

did not attenuate the association between pericardial fat, the presence and severity of AF, and ablation outcomes. Thus, although previous reports have explained the association between obesity and AF as due to LA enlargement, our findings suggest that the association between pericardial fat measures and AF are independent of LA size.

Circulating markers of inflammation, microvasculopathy, and hemodynamic strain have been linked to AF and obesity (24,25). At a local level, pericardial fat has been associated with increased expression of numerous inflammatory markers (26). Intracardiac inflammatory markers have also been observed to be greater than peripheral inflammatory markers, and greatest in the left atrium, which plays a critical role in AF genesis (27). Cytokines have also been shown to activate fibroblasts, with the extracellular matrix deposition and fibrosis causing electro-anatomical remodeling (28). Therefore, the present finding that only pericardial fat measures are associated with AF supports the notion that pericardial fat, the local fat depot, may exert deleterious effects on the anatomically contiguous atria and promote arrhythmogenesis.

Implications. We demonstrate that pericardial fat volumes are associated with the presence and severity of AF, independent of other risk factors and systemic adiposity. With the increasing use of cardiac MRI, pericardial fat measurement may yield additional information on the risk for developing AF, the risk for AF progressing, and the risk for recurrence after ablation and thereby constitute a novel risk marker. With the emerging significance of obesity in cardiovascular disease, further investigation is required into the underlying pathophysiological mechanisms.

Study limitations. The cross-sectional study design limits inferences of causality. The predominantly white Australian patient sample also limits the generalizability of our findings to nonwhite subjects. We also did not measure waist circumference or waist-to-hip ratio; these measures may have added incremental information on the effects of local versus systemic adiposity. Finally, because of small subgroup sizes, the number of variables adjusted for in the binary logistic regression models was limited to avoid overfitting models.

Conclusions

Pericardial fat is associated with the presence and severity of AF, LA volumes, and poorer outcomes after AF ablation. These associations are both independent of and stronger

Table 5 Multivariate-Adjusted Hazard Ratios (Confidence Intervals) of Adiposity Measures and AF Recurrence

	Univariate	p Value	Multivariate Adjusted	p Value	With Additional Adjustment for Body Weight	p Value
BMI	1.03 (0.79–1.34)	0.842	0.72 (0.35–1.47)	0.364	—	—
BSA	1.27 (0.96–1.67)	0.096	1.07 (0.47–2.42)	0.874	—	—
Periatrial fat	1.34 (1.05–1.71)	0.020	0.69 (0.30–1.55)	0.366	0.60 (0.25–1.46)	0.259
Periventricular fat	1.55 (1.23–1.96)	<0.001	3.83 (1.19–12.29)	0.024	3.95 (1.19–3.34)	0.025
Total pericardial fat	1.51 (1.19–1.90)	0.001	1.42 (0.56–3.59)	0.465	1.39 (0.52–3.67)	0.509

Abbreviations as in Table 1.

than more systemic measures of adiposity. Our findings are consistent with the hypothesis of a local pathogenic effect of pericardial fat on the arrhythmogenic substrate supporting AF.

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