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Pericardial Fat Is Independently Associated With Human Atrial Fibrillation

M. Obadah Al Chekakie, MD, Christine C. Welles, MD, Raymond Metoyer, BSRT, Ahmed Ibrahim, MD, Adam R. Shapira, MD, Joseph Cytron, MD, Peter Santucci, MD, David J. Wilber, MD, Joseph G. Akar, MD, PhD
Maywood, Illinois

Objectives The purpose of this study was to investigate the association between atrial fibrillation (AF) and pericardial fat.

Background Pericardial fat is visceral adipose tissue that possesses inflammatory properties. Inflammation and obesity are associated with AF, but the relationship between AF and pericardial fat is unknown.

Methods Pericardial fat volume was measured using computed tomography in 273 patients: 76 patients in sinus rhythm, 126 patients with paroxysmal AF, and 71 patients with persistent AF.

Results Patients with AF had significantly more pericardial fat compared with patients in sinus rhythm (101.6 ± 44.1 ml vs. 76.1 ± 36.3 ml, $p < 0.001$). Pericardial fat volume was significantly larger in paroxysmal AF compared with the sinus rhythm group (93.9 ± 39.1 ml vs. 76.1 ± 36.3 ml, $p = 0.02$). Persistent AF patients had a significantly larger pericardial fat volume compared with paroxysmal AF (115.4 ± 49.3 ml vs. 93.9 ± 39.1 ml, $p = 0.001$). Pericardial fat volume was associated with paroxysmal AF (odds ratio: 1.11; 95% confidence interval: 1.01 to 1.23, $p = 0.04$) and persistent AF (odds ratio: 1.18, 95% confidence interval: 1.05 to 1.33, $p = 0.004$), and this association was completely independent of age, hypertension, sex, left atrial enlargement, valvular heart disease, left ventricular ejection fraction, diabetes mellitus, and body mass index.

Conclusions Pericardial fat volume is highly associated with paroxysmal and persistent AF independent of traditional risk factors including left atrial enlargement. Whether pericardial fat plays a role in the pathogenesis of AF requires future investigation. (J Am Coll Cardiol 2010;56:784–8) © 2010 by the American College of Cardiology Foundation

The association between obesity and cardiovascular disease is well established (1). Recently, studies have focused on the relationship between regional fat depots and cardiovascular risk, independent of total adiposity (2,3). Pericardial fat serves an important endocrine and inflammatory function, and given its direct apposition to myocardium and coronary arteries, pericardial fat may play a central role in the pathogenesis of cardiovascular disease, mediated by its inflammatory properties (2,4,5).

Central obesity is associated with atrial fibrillation (AF); however, the relationship between visceral adiposity and AF has not been explored (6–8). Moreover, AF is associated with inflammation (9,10). Therefore, given the strong association between AF, obesity, and inflammation, and given the inflammatory characteristics of pericardial adipose tissue and its relationship to cardiovascular disease, we hypothesized that pericardial fat is independently associated with AF in humans.

Methods

Study population. The study was approved by the institutional review board and consisted of 300 consecutive patients who underwent computed tomography (CT). This included 218 patients referred for AF ablation and a control group of patients who underwent cardiac CT for evaluation of potentially cardiac symptoms but were at intermediate risk and had no history of AF (n = 82). Twenty-one patients in the AF group were excluded because of image clipping (n = 19) or significant motion artifact (n = 2). The control group consisted of 76 patients, after excluding patients for motion artifact (n = 4) and history of heart transplantation (n = 2). Body mass index (BMI) was measured in all patients. Obesity was defined as BMI >30 kg/m^2.

CT and pericardial fat measurement. CT studies were performed using a 64-slice scanner (Siemens Sensation Cardiac 64, Siemens Medical Solutions, Malvern, Pennsylvania).

From the Loyola University Medical Center, Maywood, Illinois. Dr. Al Chekakie is on the Fellowship advisory council for Biotronik. Dr. Wilber has been an investigator for Medtronic, St. Jude Medical, Biosense Webster, and Cardio Insight, and has been a consultant for Biosense Webster and Cardio Insight. All other authors have reported that they have no relationships to disclose.

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Gated studies were performed before ablation using an electrocardiogram-triggered scanning protocol. To ensure adequate gating and minimal motion artifact, patients in AF (n = 73) received beta-blockers and underwent CT scanning only if the ventricular response was <80 beats/min. The percentage of the R-R interval with the least amount of motion was used for pericardial fat measurements, which were performed offline using a semiautomated technique and dedicated workstation (Advantage Workstation 4.4, General Electric, Waukesha, Wisconsin). Contiguous 2.0-mm slices of the heart extending from the bifurcation of the pulmonary artery to the diaphragm were analyzed (average of 45). The pericardium was manually traced, and pericardial fat consisted of all adipose tissue within the pericardial sac, identified by an image display threshold setting of −190 to −30 Hounsfield units. Pericardial fat measurements were performed by 2 independent operators. The interobserver and intraobserver correlations were 0.99 and 0.97, respectively (p = 0.001). Left atrial volume was calculated at end systole using a Tera Recon workstation (Tera Recon, San Mateo, California).

Echocardiographic measurements. Left atrial diameter was measured at end systole in the parasternal long-axis view. Left atrial echocardiographic volume was calculated using the area length technique after tracing the left atrial (LA) area in the 2- and 4-chamber views. Left atrial enlargement was defined as diameter >4.2 cm. Left ventricular ejection fraction (LVEF) was measured using the Simpson method. An LVEF of <50% was considered abnormal. Structural heart disease was defined as moderate or greater amount of valvular regurgitation or left ventricular hypertrophy >1.4 cm.

Statistical analysis. Analysis was done using Stata version 9.0 (StataCorp, College Station, Texas). The Student *t* test was used to compare baseline continuous variables, and the chi-square test was used to compare dichotomous variables. Analysis of variance was used to compare the baseline continuous variables among subgroups, and the chi-square test was used for dichotomous variables. Pairwise comparisons are presented when analysis of variance was significant.

Multivariate linear regression was used to study the association between pericardial fat and baseline variables in patients with AF. Multiple logistic regression was used to study the association between AF and pericardial fat after correction for the baseline variables for the whole group. Multivariate multinomial logistic regression was used to examine the association between pericardial fat and both paroxysmal and persistent AF compared with sinus rhythm. A p value <0.05 was considered statistically significant.

Abbreviations and Acronyms

AF = atrial fibrillation

BMI = body mass index

CI = confidence interval

CT = computed tomography

LA = left atrial

LVEF = left ventricular ejection fraction

OR = odds ratio

Results

Baseline characteristics. A total of 273 patients were studied: 197 patients with AF and 76 controls with no history of AF (sinus rhythm group). The baseline characteristics of the AF and sinus rhythm groups are shown in Table 1. Within the AF group, there were 126 patients with paroxysmal AF and 71 patients with persistent AF (Table 2).

As Figure 1A demonstrates, patients with AF had significantly more pericardial fat compared with patients in sinus rhythm (101.6 ± 44.1 ml vs. 76.1 ± 36.3 ml, p < 0.001). The volume of pericardial fat was significantly larger in paroxysmal AF compared with sinus rhythm (93.9 ± 39.1 ml vs. 76.1 ± 36.3 ml, p = 0.02) (Fig. 1B). Similarly, persistent AF patients had a larger pericardial fat volume compared with patients who had paroxysmal AF (115.4 ± 49.3 ml vs. 93.9 ± 39.1 ml, p = 0.001) (Fig. 1B).

Pericardial fat and AF. Multiple risk factors have been associated with the development of AF, including age, hypertension, valvular heart disease, LVEF, obesity and associated obstructive sleep apnea, and LA enlargement. The results of univariate and multivariate linear regression analyses examining the association between pericardial fat volume and these risk factors are shown in Table 3.

Pericardial fat was associated with AF (odds ratio [OR]: 1.13; 95% confidence interval [CI]: 1.03 to 1.24, p = 0.01),

Table 1 Baseline Characteristics of Patients in Sinus Rhythm and All Patients With Atrial Fibrillation

	Sinus Rhythm (n = 76)	Atrial Fibrillation (n = 197)	p Value
Pericardial fat, ml	76.1 ± 36.3	101.6 ± 44.1	<0.001
Age, yrs	55.9 ± 14.9	58.1 ± 9.8	0.56
Male	43 (65)	141 (72)	0.36
Structural heart disease	23 (35)	76 (39)	0.39
Hypertension	31 (47)	101 (51)	0.55
Diabetes mellitus	12 (18)	16 (8)	0.02
LVEF, %	56.4 ± 9.9	56.3 ± 7.2	0.93
Left atrial diameter, mm	37.9 ± 5.9	43.4 ± 7.4	<0.001
BMI, kg/m^2	28.8 ± 6.9	30.3 ± 4.9	0.06

Values are mean ± SD or n (%).
BMI = body mass index; LVEF = left ventricular ejection fraction.

Table 2 Baseline Characteristics of Patients in Sinus Rhythm, Paroxysmal AF, and Persistent AF

	Sinus Rhythm (n = 76)	Paroxysmal AF (n = 126)	Persistent AF (n = 71)	p Value
Pericardial fat, ml	76.1 ± 36.3	93.9 ± 39.1	115.4 ± 49.3	<0.001*
Age, yrs	55.9 ± 14.9	58.3 ± 9.7	57.8 ± 10.4	0.34*
Male	43 (65)	82 (65)	59 (83)	0.02†
Structural heart disease	16 (24)	43 (34)	33 (46)	0.16†
Hypertension	31 (46)	62 (49)	39 (55)	0.62†
Diabetes mellitus	12 (18)	12 (10)	4 (6)	0.05†
LVEF, %	56.4 ± 9.9	57.5 ± 5.7	54.7 ± 8.7	0.15*
Left atrial diameter, mm	37.9 ± 5.9	41.4 ± 6.9	46.6 ± 7.0	<0.001*
BMI, kg/m^2	28.8 ± 6.9	30.1 ± 4.9	30.5 ± 5.1	0.07*

Values are mean ± SD or n (%). *p value using analysis of variance. †p value using chi square.
AF = atrial fibrillation; other abbreviations as in Table 1.

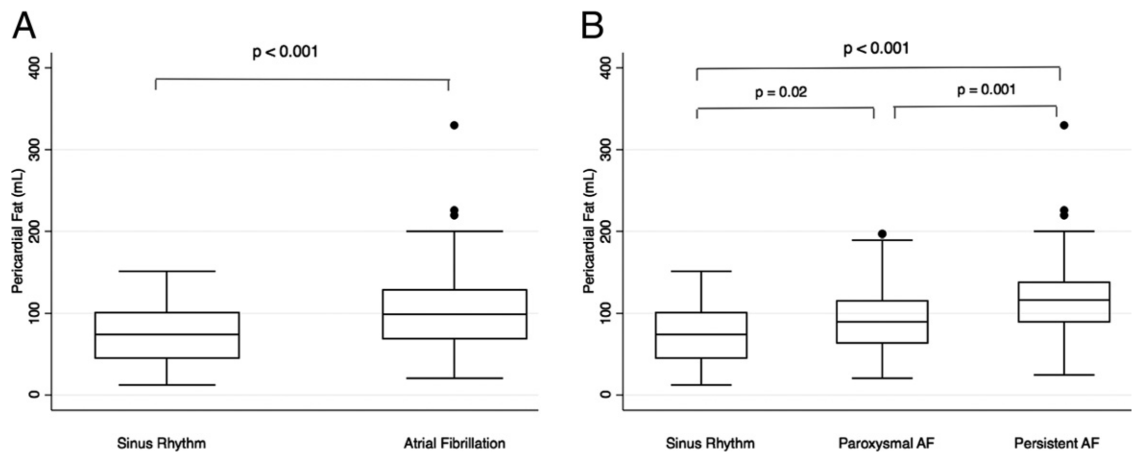

Figure 1 **Differences in Pericardial Fat Volume Among Patients With AF and Sinus Rhythm**

(A) Comparison of pericardial fat volume among patients with atrial fibrillation (AF) and patients who do not have a history of AF.
(B) Comparison of pericardial fat volume among patients with persistent AF, paroxysmal AF, and those who do not have a history of AF.

and this relationship remained significant after adjusting for AF risk factors including age, sex, hypertension, valvular heart disease, LVEF, diabetes mellitus, and BMI. The association between pericardial fat volume and AF was also independent of LA enlargement (OR: 2.22, 95% CI: 1.04 to 4.67, $p = 0.04$) (Table 4).

Pericardial fat volume was associated with both paroxysmal AF (OR: 1.11, 95% CI: 1.01 to 1.23, $p = 0.04$) and persistent AF (OR: 1.18, 95% CI: 1.05 to 1.33, $p = 0.004$) and this relationship was also completely independent of all the risk factors (Table 5).

Pericardial fat and LA size. Consistent with previous studies, LA size was larger in AF patients compared with sinus rhythm (43.4 ± 7.4 mm vs. 37.9 ± 5.9 mm, $p < 0.001$) (Table 1) and was independently associated with AF. Pericardial fat volume correlated with LA enlargement as measured by LA diameter ($b = 0.82$; 95% CI: 0.08 to 1.56, $p = 0.03$) and LA volume on 2-dimensional echocardiography ($b = 0.27$; 95% CI: 0.02 to 0.55, $p = 0.05$), as well as LA volume on CT ($b = 0.24$; 95% CI: 0.04 to 0.45, $p = 0.02$) (Fig. 2). The association between pericardial fat volume and AF was independent of LA enlargement. For every 10-ml increase in pericardial fat volume, the odds of AF increase by ~13%.

Discussion

This is the first study to examine the association between pericardial fat and AF, demonstrating a significant association with both paroxysmal and persistent AF that is completely independent of all major risk factors including LA enlargement.

Pericardial fat, obesity, and AF. The relationship between central obesity and cardiovascular disease is well established (1). Recently, attention has focused on visceral adipose tissue, such as pericardial fat, because of its inflammatory and endocrine properties (2–5). In fact, the correlation between pericardial fat and metabolic risk is stronger than that of other indexes of systemic obesity such as BMI or waist circumference (11). Although multiple studies have demonstrated that overall

Table 3 **Univariate and Multivariate Linear Regression for the Association Between Pericardial Fat (1 ml) and Baseline Variables**

	Univariate Linear Regression		Multivariate Linear Regression	
	b (95% CI)	p Value	b (95% CI)	p Value
Age, yrs	0.94 (0.48 to 1.40)	<0.001	0.83 (0.32 to 1.33)	0.001
Sex, male	21.8 (9.8 to 32.4)	<0.001	22.7 (9.94 to 34.6)	<0.001
Structural heart disease	16.5 (5.16 to 27.8)	0.004	10.4 (−1.41 to 24.3)	0.08
Hypertension	19.7 (9.3 to 30.1)	<0.001	12.8 (1.16 to 24.3)	0.03
Diabetes mellitus	−7.4 (−24.7 to 9.7)	0.39	−14.4 (−32.2 to 3.79)	0.12
Left atrial diameter, mm	1.48 (0.76 to 2.19)	<0.001	0.82 (0.08 to 1.56)	0.03
Body mass index, kg/m^2	1.52 (0.55 to 2.50)	0.002	1.71 (0.75 to 2.78)	0.001
Ejection fraction, %	0.09 (−0.62 to 0.79)	0.82	0.38 (−0.29 to 1.07)	0.27

CI = confidence interval.

Table 4 Multiple Logistic Regression Comparing Atrial Fibrillation to Sinus Rhythm

	Odds Ratio (95% CI)	p Value
Pericardial fat, 10 ml	1.13 (1.03–1.24)	0.01
Age, yrs	1.001 (0.96–1.04)	0.96
Sex, male	1.46 (0.68–3.02)	0.33
Structural heart disease	1.54 (0.68–3.48)	0.30
Hypertension	0.83 (0.41–1.92)	0.78
Diabetes mellitus	0.41 (0.15–1.06)	0.09
Left atrial diameter >42 mm	2.22 (1.04–4.67)	0.04
Body mass index, kg/m^2	1.02 (0.95–1.08)	0.52
Ejection fraction, %	1.02 (0.98–1.07)	0.23

CI = confidence interval.

obesity is associated with AF, ours is the first to examine the relationship between AF and visceral adiposity (6–8,12).

Pericardial fat, LA enlargement, and AF. LA enlargement is the final common end point of several different processes leading to the development of AF, and is one of the strongest predictors of its recurrence (13). Recent evidence has demonstrated a possible relationship between pericardial fat and LA size (14,15); however, this is the first study to correlate pericardial fat with LA size and risk of AF. Atrial enlargement has traditionally been measured using 2-dimensional echocardiography, but this may not correlate well with true LA volume measured by CT or magnetic resonance imaging (16). Accordingly, LA size was measured by 3 different methods in this study: 1) LA diameter on 2-dimensional echocardiography; 2) LA volume on 2-dimensional echocardiography; and 3) LA volume measured by gated CT. Pericardial fat volume correlated with LA size using all 3 methods. Since pericardial fat volume is completely independent of LA size and other AF risk factors, it may become an additional parameter to consider when assessing an individual patient's risk of having AF.

Pericardial fat, inflammation, and AF. Inflammation is associated with AF; however, the exact mechanisms are unclear (9,10). Pericardial adipose tissue is directly contiguous with atrial and ventricular myocardium, and it releases inflammatory cytokines that have been implicated in the genesis of coronary atherosclerosis and cardiovascular disease risk factors (2–5). These local inflammatory effects may provide a mechanism to explain the association between AF and pericardial fat. This hypothesis needs to be addressed in future studies.

Study limitations. This study was not designed to address whether increased pericardial fat is a cause or consequence of AF. Although the most likely mechanism involves inflammation, this needs to be proved in future studies. Computed tomography cannot distinguish epicardial fat separated by the visceral pericardium. This study defined pericardial fat as all adipose tissue within the pericardial sac, according to standard methodology (2,5,11,15).

Although baseline characteristics were well matched, one cannot exclude a difference other than the presence of AF between the groups. This study examined patients with symptomatic AF who had failed antiarrhythmic therapy and were referred for ablation. While this may introduce an element of selection bias, the findings are nonetheless valid and clinically relevant. In addition, if the logistic regression model is overfitted, it may not replicate well with larger datasets. However, this study is the first to demonstrate an association between pericardial fat and AF. Larger prospective studies are needed to extend this observation to other AF populations and clarify the nature of the association.

This study did not formally test for obstructive sleep apnea. However, sleep apnea is highly correlated with central obesity, and this study carefully examined the BMI of all patients enrolled. The relationship between pericardial fat and AF was independent of BMI, and BMI was not independently correlated with AF. Thus, it is extremely unlikely that sleep apnea accounts for the highly significant association between pericardial fat and AF.

Conclusions

Pericardial fat is highly associated with paroxysmal and persistent AF independent of traditional AF risk factors, including LA enlargement. The nature of the role that

Table 5 Multivariate Multinomial Logistic Regression Comparing Paroxysmal and Persistent AF to Sinus Rhythm

	Paroxysmal AF		Persistent AF	
	Odds Ratio (95% CI)*	p Value	Odds Ratio (95% CI)*	p Value
Pericardial fat, 10 ml	1.11 (1.01–1.23)	0.04	1.18 (1.05–1.33)	0.004
Age, yrs	1.01 (0.95–1.04)	0.67	0.97 (0.94–1.02)	0.48
Sex, male	1.27 (0.58–2.78)	0.52	2.01 (0.76–5.35)	0.16
Structural heart disease	1.40 (0.61–3.29)	0.44	1.83 (0.71–4.74)	0.21
Hypertension	0.83 (0.37–1.86)	0.57	0.95 (0.38–2.38)	0.73
Diabetes mellitus	0.48 (0.16–1.34)	0.17	0.29 (0.07–1.22)	0.12
Ejection fraction, %	1.04 (0.97–1.09)	0.09	1.01 (0.95–1.06)	0.79
Left atrial diameter >42 mm	1.52 (0.68–3.38)	0.32	4.57 (1.85–11.3)	0.001
Body mass index, kg/m^2	1.02 (0.93–1.09)	0.63	1.01 (0.93–1.09)	0.80

*In multinomial logistic regression, the paroxysmal atrial fibrillation (AF) group and the persistent AF group are compared with the sinus rhythm group, which acts as a reference.
CI = confidence interval.

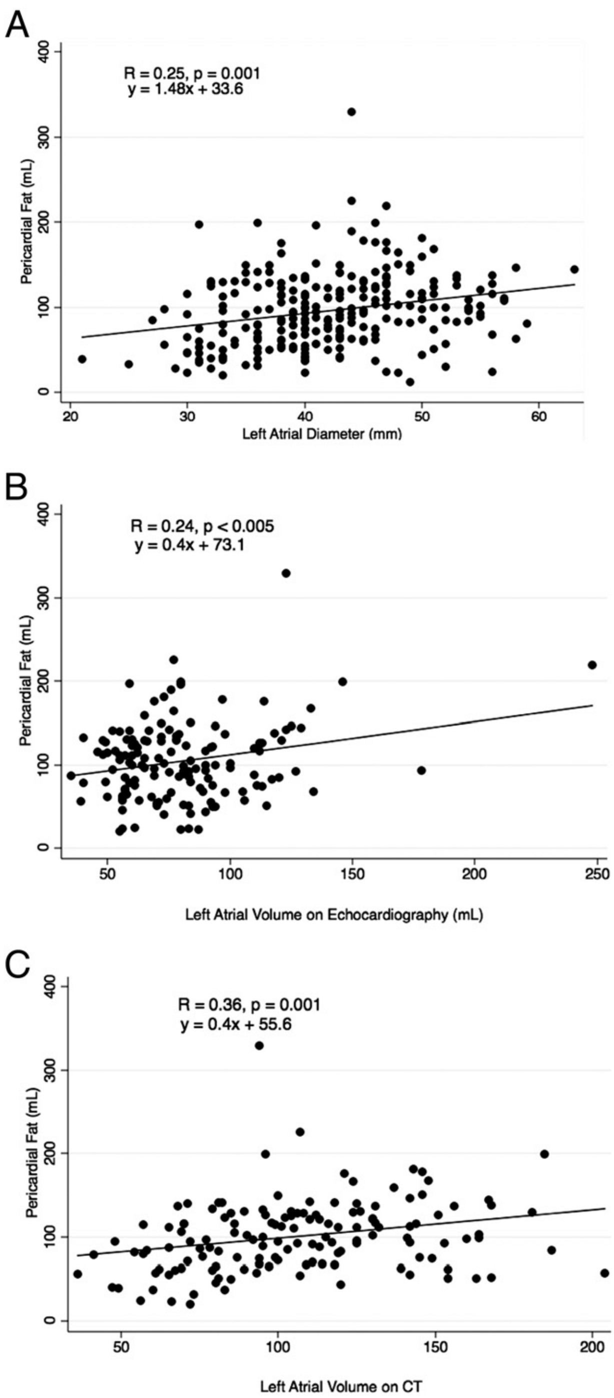

Figure 2 **Correlation Between Pericardial Fat Volume and Left Atrial Size**

Correlation between pericardial fat volume and left atrial size as measured by **(A)** left atrial diameter on echocardiography, **(B)** left atrial volume by echocardiography, and **(C)** left atrial volume using computed tomography (CT).

pericardial fat plays in AF pathogenesis requires future investigation.

Reprint requests and correspondence: Dr. Joseph G. Akar, Section of Cardiovascular Medicine, Yale University School of Medicine, 333 Cedar Street, FMP 3, New Haven, Connecticut 06511. E-mail: joseph.akar@yale.edu.

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