Pericardial Fat Is Associated With Prevalent Atrial Fibrillation
The Framingham Heart Study

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Background—Obesity represents an important risk factor for atrial fibrillation (AF). We tested the hypothesis that pericardial fat, a unique fat deposit in close anatomic proximity to cardiac structures and autonomic fibers, is associated with prevalent AF.

Methods and Results—Participants from the Framingham Heart Study underwent multidetector computed tomography from 2002 to 2005. We estimated the association between quantitative pericardial, intrathoracic and visceral adipose tissue volumes (per standard deviation of volume) with prevalent AF adjusting for established AF risk factors (age, sex, systolic blood pressure, blood pressure treatment, PR interval, and clinically significant valvular disease). Of the 3217 eligible participants (mean age, 50.6±10.1 years; 48% women), 54 had a confirmed diagnosis of AF. Pericardial fat but not intrathoracic or visceral abdominal fat was associated with prevalent AF in multivariable-adjusted models (odds ratio per standard deviation of pericardial fat volume, 1.28; 95% confidence intervals, 1.03 to 1.58). Further adjustments for body mass index, heart failure, myocardial infarction, and intrathoracic fat volume did not materially change the association between pericardial fat and AF.

Conclusions—Pericardial fat was associated with prevalent AF even after adjustment for AF risk factors, including body mass index. If this association is replicated, further investigations into the mechanisms linking pericardial fat to AF are merited. (Circ Arrhythm Electrophysiol. 2010;3:345-350.)

Key Words: atrial fibrillation ■ pericardial adipose tissue ■ obesity ■ epidemiology ■ risk factor

Atrial fibrillation (AF) is expected to affect more than 6 million individuals in the United States by 2010 and is associated with significant morbidity and mortality. Obesity represents an important risk factor for new-onset AF. Even after adjustment for hypertension and heart failure (HF), measures of obesity remain significant predictors of AF, suggesting that obesity may predispose to AF. Pericardial fat represents a unique ectopic fat deposit because of its proximity to cardiac structures and its shared blood supply with the cardiac microcirculation. Pericardial fat is highly metabolically active and may be a potential mechanism by which obesity increases the risk of AF.

Clinical Perspective on p 350
To our knowledge, the association between pericardial fat and AF has not been evaluated previously. The aim of the present study was to evaluate the cross-sectional associations between pericardial fat volume and other regional fat deposits, measured by multidetector computed tomography (MDCT), with AF in the Framingham Heart Study, a middle-aged to elderly community-based cohort. Because of its contiguity to cardiac structures, we hypothesized that pericardial fat would be cross-sectionally associated with AF, even after adjustment for known AF risk factors, including body mass index (BMI) and other fat depots.

Methods

Study Sample
Participants for the current study were from the Framingham Heart Study Offspring and Third Generation Cohorts who underwent thoracic and abdominal MDCT as part of a substudy between June
defined as a systolic murmur grade ≥3/6 or any diastolic murmur noted on examination by the Framingham clinic physician. HF and myocardial infarction events were adjudicated by a committee of Framingham investigators, based on the clinical encounter with the study physician and available medical records. Participants with HF or myocardial infarction event at any point before MDCT assessment were deemed to have HF or myocardial infarction, respectively.

### Statistical Analysis

Intrathoracic, pericardial, and visceral fat were normally distributed and were standardized, within each sex, to a mean of 0 and standard deviation (SD) of 1 to allow comparisons of the effect estimates between fat depots from regression models. Age- and sex-adjusted logistic regression models were fit to assess the association between pericardial, intrathoracic, and visceral abdominal fat volumes (per 1 standard deviation of fat volume) and prevalent AF in separate models. Estimates also were adjusted for AF risk factors (age, sex, PR interval, hypertension, hypertension treatment, and clinically significant valvular disease) were entered into the multivariate model, based on the recently reported Framingham AF risk score.15 All of the AF risk factor covariates were retained in the model, regardless of statistical significance, because they represent important predictors of AF. Because of the correlation between pericardial fat and BMI (r = 0.41 and 0.46 for women and men, respectively12), BMI was entered into the model at a second step after the addition of the other covariates and was retained in the model. In addition, we constructed a final model in which both intrathoracic and pericardial fat were entered into the same AF risk-adjusted model to evaluate and compare the separate effect of each of these fat deposits. Interactions between fat volumes and age or sex were evaluated for all analyses, but, because of limited power, these did not reach statistical significance and were not included in the models presented. Results are reported as odds ratios (ORs) with 95% confidence intervals (CI). Analyses were performed in SAS 9.13; a 2-tailed probability value <0.05 was considered statistically significant.

In secondary analyses, we further adjusted for HF and myocardial infarction. In addition, because of the familial structure of our data and the potential correlations between family members, we used generalized estimating equations to reanalyze the associations between regional fat deposits and AF, incorporating indicator variables for relatedness between subjects.

### Results

The study comprised 1657 men and 1560 women with a mean age of 50.6 ± 10.1 years. There were 54 (1.7%) participants with prevalent AF. Of the 54 patients with prevalent AF or atrial flutter, 44 (81.5%) were classified as AF, 2 (3.7%) were classified as atrial flutter, and 8 (14.8%) were classified as mixed subtype (AF/atrial flutter). For offspring, AF occurred from July 25, 1985, through December 18, 2003 (a period of 18.4 years). For Gen 3, AF occurred from July 25, 1980, through May 13, 2003 (a period of 22.7 years). The median time from first AF diagnosis to CT scan was 4.7 years (range, 0.03 to 22.7 years) and median time from PR interval measurement to AF was 0.9 years (range, −4.8 to 22.6 years). None of the subjects were in AF at the time of the scan. Only 5 (0.16%) participants had HF and 48 (1.5%) had a history of myocardial infarction. Other characteristics of the sample are described in Table 1.

### Age- and Sex-Adjusted Associations Between Regional Fat Deposits and AF

Pericardial fat but not intrathoracic fat or visceral abdominal fat volume was associated with prevalent AF in age- and sex-adjusted models. The odds ratios per 1 SD of pericardial, intrathoracic, and visceral abdominal fat volume were 1.30...
Table 1. Clinical Characteristics of Overall Sample

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1560</td>
<td>1657</td>
</tr>
<tr>
<td>Age, y</td>
<td>51.9±9.8</td>
<td>49.4±10.4</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.1±5.8</td>
<td>28.4±4.5</td>
</tr>
<tr>
<td>PR interval, ms</td>
<td>157±23</td>
<td>166±25</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>405 (26)</td>
<td>511 (30.8)</td>
</tr>
<tr>
<td>Significant heart murmur, n (%)</td>
<td>13 (0.8)</td>
<td>17 (1.0)</td>
</tr>
<tr>
<td>Hypertension treatment, n (%)</td>
<td>281 (18.0)</td>
<td>306 (18.5)</td>
</tr>
<tr>
<td>History of myocardial infarct, n (%)</td>
<td>10 (0.6)</td>
<td>38 (2.3)</td>
</tr>
<tr>
<td>History of HF, n (%)</td>
<td>2 (0.2)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Prevalent AF, n (%)</td>
<td>19 (1.2)</td>
<td>35 (2.1)</td>
</tr>
</tbody>
</table>

Fat volumes, cm³

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Pericardial</td>
<td>100±38</td>
<td>124±46</td>
</tr>
<tr>
<td>Intrathoracic</td>
<td>66±40</td>
<td>129±64</td>
</tr>
<tr>
<td>Visceral abdominal</td>
<td>1353±827</td>
<td>2209±1010</td>
</tr>
</tbody>
</table>

Values represent means±SD, except where otherwise specified.

(95% CI, 1.05 to 1.60; \( P=0.02 \)), 1.12 (95% CI, 0.85 to 1.49; \( P=0.41 \)), and 0.97 (95% CI, 0.74 to 1.28; \( P=0.84 \)), respectively.

Table 2. Associations Between Regional Fat Deposits and Prevalent AF

<table>
<thead>
<tr>
<th></th>
<th>Age- and Sex-Adjusted OR (95% CI)</th>
<th>P</th>
<th>AF Risk Factor-Adjusted OR (95% CI)</th>
<th>P</th>
<th>*BMI-Adjusted OR (95% CI)</th>
<th>P</th>
<th>*Fat Deposit-Adjusted† OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardial</td>
<td>1.30 (1.05–1.60)</td>
<td>0.02</td>
<td>1.28 (1.03–1.58)</td>
<td>0.03</td>
<td>1.28 (1.01–1.63)</td>
<td>0.04</td>
<td>1.37 (1.02–1.85)</td>
<td>0.04</td>
</tr>
<tr>
<td>Intrathoracic</td>
<td>1.12 (0.85–1.49)</td>
<td>0.41</td>
<td>1.13 (0.85–1.52)</td>
<td>0.82</td>
<td>0.83 (0.57–1.21)</td>
<td>0.34</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Visceral fat</td>
<td>0.97 (0.74–1.28)</td>
<td>0.84</td>
<td>0.97 (0.72–1.29)</td>
<td>0.82</td>
<td>0.83 (0.57–1.21)</td>
<td>0.34</td>
<td>…</td>
<td>…</td>
</tr>
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</table>

*Adjusted for the following covariates: age, sex, systolic blood pressure, blood pressure treatment, PR interval, clinically significant valvular disease (defined as grade ≥3 systolic murmur or any diastolic murmur).

†Fat deposit-adjusted model included both pericardial and intrathoracic fat and was adjusted for all other covariates in the AF risk-adjusted model (including BMI).

Discussion

In participants of the Framingham Heart Study, a middle-aged to elderly community-based cohort, we observed that higher pericardial fat volumes were associated with a nearly 40% higher odds of prevalent AF. This association remained significant and of the same magnitude even after serial adjustments for clinical AF risk factors including BMI, HF, myocardial infarction, and other regional fat depots. Interestingly, we found a significant association with prevalent AF and pericardial fat but not with intrathoracic fat or visceral abdominal fat.

In the Context of the Current Literature

Obesity is an important risk factor for AF.2–4 In the United States, it has been projected that the rising prevalence of obesity is responsible for nearly 60% of the increasing incidence of AF at the population level.1 Mounting evidence suggests that obesity-related diseases may be mediated, at least in part, by regional fat deposits.12,13,16–23 For example, it has been hypothesized that visceral abdominal fat deposits, which are strongly associated with glucose intolerance and the metabolic syndrome,22,23 may act by local ‘‘vasocrine’’ mechanisms.24 Other regional fat depots, such as pericardial fat, may also have important local cardiovascular effects.

Emerging evidence suggests that pericardial fat may represent an important risk factor for cardiovascular disease because of its unique properties and its proximity to cardiac structures. Pericardial fat has been associated with an adverse cardiovascular risk profile,12,18,25 coronary artery calcium,12,20,21 and prevalent cardiovascular disease18,20 in several studies from diverse populations. As previously reported for coronary artery calcification and prevalent cardiovascular disease, the association with AF appears to be limited to pericardial fat,13,18 which is suggestive of a possible local cardiovascular effect of this depot.

Pericardial fat is significantly correlated with localized atrial septal fat, a finding known as lipomatous septal hypertrophy, which has been historically associated in several small studies with sick sinus syndrome27 and atrial arrhythmias.28–29 Using necropsy data, Shirani et al27 have shown that interatrial fat correlated closely with epicardial fat thickness over the atrioventricular groove and the right ventricle. Larger fat deposits in the atrial septum were associated with a significantly higher prevalence of atrial
tumor necrosis factor—an important local source of inflammatory mediators, including infiltrating adipose tissue.33 Pericardial fat also represents an important source of inflammation and resultant fibrosis requiring further study.

Whether this finding could be partially explained by changes in infiltrating adipose tissue and resultant inflammation and fibrosis requires further study.

Pericardial fat may also modulate activity of the intrinsic autonomic nervous system, which is known to increase the propensity for AF.42 The intrinsic autonomic system consists of nerves and ganglia contained entirely within the pericardium and encased within pericardial fat pads. Animal models have demonstrated that parasympathetic nerve activity within such fat pads promotes inducibility for AF, primarily by shortening the atrial refractory period.43,44 Increased pericardial fat could locally influence these autonomic ganglia, enhancing vagal tone and increasing propensity for AF.

Clinical and Research Implications

Our findings, if confirmed, suggest that pericardial fat may represent a novel risk factor for AF. Increased pericardial fat is prevalent in the community and may mediate part of the recent increase in obesity-related vascular disease. Increased pericardial fat is associated with other markers of adiposity12 highlighting the potential importance of maintaining optimal body weight to reduce the burden of cardiovascular disease, including AF. Weight loss has been shown to lead to marked reductions in pericardial fat and may limit the potentially deleterious effects of this fat deposit.45,46 Further studies examining the effect of weight loss on pericardial fat and AF risk are warranted.

Strengths and Limitations

The major strengths of the present study were the relatively large sample drawn from a community-based cohort and the use of a highly reliable MDCT-based volumetric quantification of fat deposits. We were also able to adjust odds ratio estimates using risk factors based on the recently reported Framingham AF risk score.15

Our study also had a number of important limitations. First, because of the use of prevalent cases of AF and the cross-sectional design of our study, our results could be explained by reverse causality. However, we are unaware of any mechanism in AF patients that could specifically increase pericardial fat without concomitant increases in other fat depots. Second, despite adjustments for major AF risk factors, we cannot exclude residual confounding. For example, atrial dimension was not included as a covariate in the multivariable model; it is conceivable that the observed association between pericardial fat and AF may be mediated through changes in atrial dimensions. Third, because of limited power, the confidence intervals for the association between AF and the various fat depots were wide. Therefore, the lack of association between intrathoracic and visceral abdominal fat and AF may represent false-negative findings. However, because all fat volumes were standardized to allow comparisons between fat depots, our inability to detect a significant association with intrathoracic or visceral abdominal fat while finding a significant association with pericardial fat suggests that any potential association with these other fat depots and AF was weaker than that observed for pericardial fat. Fourth, we also acknowledge that the AF cases were heterogeneous in origin; given the small number of prevalent AF cases, we were unable to conduct many important analyses including the relation between pericardial fat and specific forms of AF and the anatomic distribution of pericardial fat (anterior versus posterior fat) and AF. We hope that future studies with more events will confirm our findings.
and examine important subgroup analyses. Fifth, our sample consisted of primarily white middle-aged to elderly individuals; our results may not be generalizable to other ethnicities or age groups.

Conclusion

We have shown that pericardial fat but not other fat deposits is associated with prevalent AF. Prospective studies are needed to validate the association between pericardial fat and AF. If the association is replicated, further investigations into the mechanisms linking pericardial fat to AF are merited.

Sources of Funding

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Disclosures

None.

References


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**CLINICAL PERSPECTIVE**

Obesity is a major risk factor for cardiovascular disease. However, the mechanisms for this association are not well understood. Pericardial fat represents a potentially novel risk factor for obesity-related cardiovascular disease and could partially explain the association between obesity and atrial fibrillation. The present study evaluated the association between pericardial fat volume by computed tomography and prevalent atrial fibrillation in 3217 Framingham Offspring participants who underwent cardiac computed tomography. Each increment in the standard deviation of pericardial fat volume was associated with a 28% increase in the prevalence of atrial fibrillation (odds ratio, 1.28; 95% confidence interval, 1.03 to 1.58). This association remained significant despite adjustment for known risk factors for atrial fibrillation, including body mass index. A similar association was not found for intrathoracic fat, a thoracic fat deposit that is not contiguous to cardiac structures. Our results are consistent with the hypothesis that adipose tissue in contact with cardiac structures may have deleterious effects. However, our findings must be confirmed in other cohorts.
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