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Pericardial Fat is Associated with Prevalent Atrial Fibrillation: The Framingham Heart Study

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Abstract

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 multi-detector computed tomography from 2002–2005. We estimated the association between quantitative pericardial, intra-thoracic and visceral adipose tissue volumes (per standard deviation [SD] 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 intra-thoracic or visceral abdominal fat, was associated with prevalent AF in multivariable-adjusted models (Odds Ratio [OR] per SD of pericardial fat volume 1.28, 95% confidence intervals [CI] 1.03–1.58). Further adjustments for body mass index, heart failure, myocardial infarction and intra-thoracic 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.

Keywords

Atrial fibrillation; pericardial; adipose tissue; obesity; epidemiology; risk factor

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Disclosures

None

Atrial fibrillation (AF) is expected to affect over 6 million individuals in the US by 2010 and is associated with significant morbidity and mortality. Obesity represents an important risk factor for new-onset AF.²⁻⁴ 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 due to its proximity to cardiac structures and its shared blood supply with the cardiac microcirculation.⁵ Pericardial fat is highly metabolically active^{6,7} and may be a potential mechanism by which obesity increases the risk of AF.^{5,8}

To our knowledge the association between pericardial fat and AF has not been evaluated previously. The aim of our study was to evaluate the cross-sectional associations between pericardial fat volume and other regional fat deposits, measured by multi-detector computed tomography (MDCT), with AF in the Framingham Heart Study, a middle-aged to elderly community-based cohort. Due to 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 deposits.

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 sub-study, between June 2002 and April 2005.⁹⁻¹¹ Of the 3529 eligible participants in the MDCT substudy, we excluded individuals for the following indications: 127 for uninterpretable values for pericardial fat or intra-thoracic fat measures; 55 with previous CABG surgery; 21 for not having a corresponding physical exam in which risk factors/covariates were measured; 81 for not having all required fat volumes measured; and an additional 28 for other missing covariates. The final study sample was 3217 individuals.

The study protocol was approved by the Institutional Review Boards of the Boston University Medical Center and Massachusetts General Hospital. All subjects provided written informed consent.

MDCT Scan Protocol

The MDCT scanning protocol has been previously described.¹² Briefly, participants underwent a full thoracic scan and an 8-slice MDCT cardiac scan (LightSpeed Ultra, General Electric, Milwaukee, WI) in the supine position with an average of 48 contiguous 2.5 mm slices of the heart with a prospective ECG-triggering algorithm. In addition, abdominal imaging was performed with 25 contiguous 5 mm slices (120 kVp, 400 mA, gantry rotation time 500 ms, table feed 3:1) starting at the upper edge of S1.

Intrathoracic, Pericardial and Abdominal Fat Volume Measurements

Fat measurements for the pericardial, intra-thoracic and abdominal compartments previously have been described in detail.^{12,13} Briefly, these fat volumes were measured using a dedicated offline workstation (Aquarius 3D Workstation, TeraRecon Inc., San Mateo, CA) using a predefined image display setting based on Hounsfield units (HU) (window width -195 to -45 HU; window center -120 HU) which identified pixels corresponding to adipose tissue. Using a semi-automatic segmentation technique, both intra-thoracic and pericardial fat volumes were determined as previously described.^{12,13} Segmentation of the overall volume was automatically interpolated using the manually-defined tracings. Additional manual adjustments were made by the reader through the scan volumes to account for interpolating errors. Pericardial fat volume was defined as total adipose tissue measured within the

pericardial sac. Total thoracic fat volume was defined as total adipose tissue located within the thorax (delimited by the level of the right pulmonary artery to the diaphragm in the transverse plane and the anterior chest wall to the descending aorta in the coronal plane); intra-thoracic fat was derived by subtracting pericardial fat from total thoracic fat. Visceral adipose tissue was defined as visceral fat within the abdominal compartment as described previously.¹⁴ Intraclass correlation coefficients for intra-reader and inter-reader reproducibility were ≥ 0.97 for all fat depots as previously reported.^{12,14}

Assessment of Atrial Fibrillation

Prevalent AF was defined based on the presence of any episode of confirmed atrial flutter or atrial fibrillation on an electrocardiogram or Holter report prior to the MDCT study. Electrocardiograms were obtained at each Framingham Heart Study clinic visit. Electrocardiograms and Holter monitors also were obtained from external medical offices and hospital records. AF events were confirmed by at least two Framingham Study cardiologists.

Risk Factor Assessment

Risk factors and covariates were assessed at the seventh examination (1998–2001) and at the first examination (2002–2005) for members of the Framingham Offspring and Third Generation Cohorts, respectively. Hypertension was defined as a blood pressure $\geq 140/90$ mm Hg, or treatment with an antihypertensive agent. BMI was defined as weight (in kilograms) divided by the square of height (in meters). PR interval was assessed from the resting ECG measured from the onset of the P-wave to the onset of the QRS complex (in milliseconds). In the majority of participants, the resting ECG was obtained after AF. However, in a few cases ($n = 19$) the examination (and PR interval measurement) occurred before participants met the study definition for AF. Clinically significant valvular disease was defined as a systolic murmur grade $\geq 3/6$ 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 a HF or myocardial infarction event at any point prior to MDCT assessment were deemed to have HF or myocardial infarction, respectively.

Statistical Analysis

Intra-thoracic, pericardial and visceral fat were normally distributed and were standardized, within each sex, to a mean of 0 and standard deviation 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, intra-thoracic 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, as 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 intra-thoracic 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 due to 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 (95% CI). Analyses were performed in SAS 9.13; a two-tailed p -value < 0.05 was considered statistically significant.

In secondary analyses, we further adjusted for HF and myocardial infarction. In addition, due to the familial structure of our data and the potential correlations between family members, we used generalized estimating equations (GEE) to re-analyze 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 atrial fibrillation or atrial flutter, 44 (81.5%) were classified as atrial fibrillation, 2 (3.7%) were classified as atrial flutter, and 8 (14.8%) were classified as mixed subtype (atrial fibrillation/atrial flutter). For offspring, AF occurred from July 25, 1985 through Dec 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 yrs (range = 0.03 – 22.7 years) and median time from PR interval measurement to atrial fibrillation was 0.9 yrs (range = –4.8 to 22.6 yrs). 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 Atrial Fibrillation

Pericardial fat, but not intra-thoracic fat or visceral abdominal fat volumes, 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 (95% CI 1.05–1.60; $P=0.02$), 1.12 (95% CI 0.85–1.49; $P=0.41$) and 0.97 (95% CI 0.74–1.28; $P=0.84$), respectively.

Multivariable-adjusted Associations between Regional Fat Deposits and AF

In multivariable-adjusted models accounting for AF risk factors (excluding BMI), pericardial fat remained significantly associated with AF (OR per 1-SD of fat volume 1.28, 95% CI 1.03–1.58; $P=0.03$). Intra-thoracic fat and visceral abdominal fat were not associated with AF (Table 2). When BMI was included in the multivariable model, the association with pericardial fat was not materially changed (Table 2).

Associations of Pericardial Fat and Intrathoracic Fat and AF

To further evaluate the association between pericardial and intra-thoracic fat with AF, both of these fat depots were entered into the multivariable-adjusted model. Pericardial fat remained significantly associated with AF (OR per 1-SD of fat volume 1.37, 95% CI 1.02–1.85; $P=0.04$), whereas intra-thoracic fat was not associated with AF (Table 2). In secondary analyses, further adjustments for HF and myocardial infarction did not substantively affect the association between regional fat volumes and AF. The OR per 1-SD of pericardial fat volume after adjustment for HF and myocardial infarction was 1.38 (95% CI 1.02–1.86; $P=0.04$). Results from GEE models to account for familial correlations were not materially different from logistic regression models reported above (data not shown).

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 intra-thoracic fat or visceral abdominal fat.

In the Context of the Current Literature

Obesity is an important risk factor for AF.²⁻⁴ In the US, 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 due to 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 disease^{18,20} 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 syndrome²⁶ and atrial arrhythmias.²⁷⁻²⁹ Using necropsy data, Shirani et al. 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 arrhythmias.²⁷ Of the 80 patients with high inter-atrial fat, 20 had atrial arrhythmias, of which 7 had AF.²⁷ More recently, Heyer et al. have reported that of 75% of patients with lipomatous septal hypertrophy (21/28 patients) had increased pericardial fat by CT. Of these 21 patients, 13 had electrocardiographic abnormalities and 8 had atrial arrhythmias.²⁹ While suggestive for an association between cardiac adiposity and atrial arrhythmias, these studies relied on case reports, necropsy series or highly selected patients referred for cardiac imaging, significantly limiting the validity and generalizability of these reports. The only population-based study to evaluate lipomatous septal hypertrophy and atrial arrhythmias, failed to find any association with atrial arrhythmias in 384 patients evaluated by transesophageal echocardiography.³⁰ However that study did not report the number or type of arrhythmic events and due to the relatively small sample size may have been limited by low numbers of atrial arrhythmic events. To our knowledge the present study, using a MDCT based volumetric quantification of pericardial fat, provides the first report of an association between cardiac adiposity, as measured by pericardial fat, and AF

Potential Mechanisms for the Association between Pericardial Fat and AF

It has been hypothesized that unlike large fat deposits, such as visceral abdominal fat, which act primarily systemically, pericardial fat likely acts locally via mechano-structural or paracrine mechanisms. Pericardial fat is directly contiguous with cardiac structures, overlying the right ventricle, the coronary arteries, the left ventricular apex and the atria, with no intervening fascia between these structures.³¹ Increased pericardial fat has been associated with significant structural and functional changes that could affect the propensity for AF. Iacobellis et al. have shown that increased pericardial fat is associated with significant increases in left ventricular mass and impaired diastolic function.^{16,17} More recently, we have shown that increased pericardial fat is also associated with changes in cardiac structures and specifically increased left atrial dimensions.¹³

In addition, when epicardial fat deposits enlarge they are associated with marked fatty infiltration of the ventricular myocardium and atrial septum³² which may lead to electromechanical changes in atrial tissue. Pericardial fat, due to its contiguity with atrial tissue,

may also cause local inflammation and resultant fibrosis. Histopathological studies of lipomatous septal hypertrophy demonstrate an inflammatory infiltrate associated with myocardial fibrosis surrounding infiltrating adipose tissue.³³ Pericardial fat also represents an important local source of inflammatory mediators, including tumor necrosis factor- α and interleukin-6,⁶ which may have direct arrhythmogenic effects on atrial tissue and have been associated with AF initiation.^{34–36} P-wave dispersion, a marker of intra-atrial conduction heterogeneity³⁷ and a risk factor for AF, is frequently prolonged in obese subjects.^{38–41} 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 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 atrial fibrillation. 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 our 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, due to 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 via changes in atrial dimensions. Third, due to limited power, the confidence intervals for the association between AF and the various fat depots were wide. Therefore, the lack of association between intra-thoracic 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 intra-thoracic 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 vs. posterior fat) and AF. Future studies with more events

hopefully 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.

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Table 1

Clinical Characteristics of Overall Sample

| | Women | Men |
|--------------------------------------|------------|-------------|
| N | 1560 | 1657 |
| Age, years | 51.9 ± 9.8 | 49.4 ± 10.4 |
| Body mass index, kg/m ² | 27.1 ± 5.8 | 28.4 ± 4.5 |
| PR interval, msec | 157 ± 23 | 166 ± 25 |
| Hypertension, n (%) | 405 (26) | 511 (30.8) |
| Significant heart murmur, n (%) | 13 (0.8) | 17 (1.0) |
| Hypertension treatment, n (%) | 281 (18.0) | 306 (18.5) |
| History of myocardial infarct, n (%) | 10 (0.6) | 38 (2.3) |
| History of heart failure, n (%) | 2 (0.2) | 3 (0.1) |
| Prevalent Atrial Fibrillation (%) | 19 (1.2) | 35 (2.1) |
| Fat Volumes (cm ³) | | |
| Pericardial | 100 ± 38 | 124 ± 46 |
| Intrathoracic | 66 ± 40 | 129 ± 64 |
| Visceral abdominal | 1353 ± 827 | 2209 ± 1010 |

Values represent means±standard deviations except where otherwise specified.

Table 2

Associations between Regional Fat Deposits and Prevalent AF

| | Age- and sex-adjusted | | AF risk factor-adjusted [†] | | +BMI-adjusted | | +Fat deposit-adjusted [*] | |
|-----------------------|-----------------------|------|--------------------------------------|------|------------------|------|------------------------------------|------|
| | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) | P |
| Pericardial | 1.30 (1.05–1.60) | 0.02 | 1.28 (1.03–1.58) | 0.03 | 1.28 (1.01–1.63) | 0.04 | 1.37 (1.02–1.85) | 0.04 |
| Intra-thoracic | 1.12 (0.85–1.49) | 0.41 | 1.13 (0.85–1.52) | 0.4 | 1.09 (0.78–1.52) | 0.61 | 0.85 (0.55–1.30) | 0.45 |
| Visceral Fat | 0.97 (0.74–1.28) | 0.84 | 0.97 (0.72–1.29) | 0.82 | 0.83 (0.57–1.21) | 0.34 | - | - |

[†] 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 BMD).