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Relation of Pericardial Fat, Intrathoracic Fat, and Abdominal Visceral Fat with Incident Atrial Fibrillation (From the Framingham Heart Study)

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Abstract

Obesity is associated with increased risk of developing atrial fibrillation (AF). Different fat depots may have differential associations with cardiac pathology. We examined the longitudinal associations between pericardial, intrathoracic, and visceral fat with incident AF. We studied Framingham Heart Study Offspring and Third Generation Cohorts who participated in the multi-detector computed tomography sub-study examination 1. We constructed multivariable-adjusted Cox proportional hazard models for risk of incident AF. Body mass index (BMI) was included in the multivariable-adjusted model as a secondary adjustment. We included 2,135 participants (53.3% women; mean age 58.8 years). During a median follow-up of 9.7 years, we identified 162 cases of incident AF. Across the increasing tertiles of pericardial fat volume, age- and sex-adjusted incident AF rate per 1000 person-years of follow-up were 8.4, 7.5, and 10.2. Based on an age- and sex-adjusted model, greater pericardial fat [hazard ratio (HR) 1.17, 95% confidence interval (CI) 1.03-1.34] and intrathoracic fat (HR 1.24, 95% CI 1.06-1.45) were associated with increased risk of incident AF. The HRs (95% CI) for incident AF were 1.13 (0.99-1.30) for pericardial fat, 1.19 (1.01-1.40) for intrathoracic fat, and 1.09 (0.93-1.28) for abdominal visceral fat after multivariable adjustment. After additional adjustment of BMI, none of the associations remained significant (all

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$p>0.05$). Our findings suggest that cardiac ectopic fat depots may share common risk factors with AF, which may have led to a lack of independence in the association between pericardial fat with incident AF.

Keywords

atrial fibrillation; ectopic cardiac fat; epidemiology; pericardium

Introduction

Our prior study has shown that higher pericardial fat volume, but not intrathoracic or abdominal visceral fat, was associated with prevalent atrial fibrillation (**AF**), even after adjusting for multiple confounders and generalized obesity.¹ However, whether pericardial fat is longitudinally associated with incident AF remains uncertain. The primary goal of our study was to examine whether higher pericardial fat, intrathoracic fat, and abdominal visceral fat are associated with higher incidence of AF. We hypothesized that pericardial fat, a cardiac ectopic fat depot, is more closely associated with incident AF, as compared to intrathoracic or visceral fat. We hypothesized that the associations between fat compartments and AF are present after accounting for previously established risk factors of AF and systemic effects of obesity.

Methods

Our study drew participants from the Offspring cohort 7th examination (1998-2001) and Third Generation cohort 1st examination (2002-2005) who additionally participated in the 1st examination of the multi-detector computed tomography (**MDCT**) sub-study from 2002 to 2005.² The inclusion criteria for the MDCT sub-study were: 1) individuals residing in New England at the time of the examination; 2) women 40 years and not pregnant and men 35 years; and 3) <160 kg body weight due to the weight restriction of MDCT scanner.³ We identified 3,453 eligible individuals who underwent MDCT imaging for the quantification of pericardial fat, intrathoracic fat, and abdominal visceral fat. We excluded participants based on the following exclusion criteria: 1) prevalent AF (n=86); 2) missing follow-up information for incident AF (n=2); 3) missing covariates (n=48); 4) 45 years of age (n=1,145) as having AF under age 46 years is uncommon and is characteristically different than having AF after the age of 45; and/or 5) previous coronary artery bypass graft surgery (n=37). Compared with participants excluded from the analysis (n=1,318), participants included in the analysis (n=2,135) had higher mean age, body mass index (**BMI**), systolic blood pressure, and pericardial, intrathoracic, and abdominal visceral fat volumes; more likely to have diabetes and use antihypertensive medication; and were less likely to currently smoke, and have a history of prior heart failure and myocardial infarction (**Supplementary Table 1**). The study protocol was approved by the institutional review boards of the Boston University Medical Center and Massachusetts General Hospital. All participants provided written informed consent.

The cases of AF, which included AF and atrial flutter, were identified based on the resting 12-lead electrocardiograms recorded during the Framingham Heart Study examination or

electrocardiograms and Holter monitors from the external hospital records and primary medical doctor records.¹ All incident cases of AF were adjudicated by 2 Framingham Heart Study cardiologists.

Participants underwent MDCT imaging (LightSpeed Ultra, General Electric, Milwaukee, WI) in the chest and abdomen in the supine position for the assessment of pericardial fat, intrathoracic fat, and abdominal visceral fat by using a protocol described elsewhere.^{1, 3, 4} Briefly, 48 contiguous 2.5 mm thick MDCT scans in the chest (120 kVp, 400 mA, temporal resolution 330) were acquired for the assessment of pericardial and intrathoracic fat. A total of 25 contiguous 5 mm thick slices of the MDCT scans in the abdomen (120 kVp, 400 mA, gantry rotation time 500 ms, table feed 3:1) were obtained for abdominal VAT assessment. The state-of-the-art workstation tool (Aquarius 3D Workstation, TeraRecon Inc., San Mateo, CA) was subsequently used to quantify the adipose tissue volumes from the MDCT images in a semiautomatic manner. The trained reader outlined the pericardium to differentiate the adipose tissue accumulated in the pericardial sac and thorax. The adipose tissue detected within the pericardial sac was defined as pericardial fat. Due to the technical limitations, precisely identifying different layers of pericardium via CT imaging was challenging. Accordingly, pericardial fat included epicardial fat that was contiguous to the myocardium and the fat accumulated outside of the parietal layer of the serous pericardium. The adipose tissue quantified in the pericardium and in the thorax from the level of the right pulmonary artery to the diaphragm and the chest wall to the descending aorta was labeled as total thoracic fat.⁵ The differences in adipose tissue volume between the total thoracic fat and pericardial fat were defined as intrathoracic fat. Similarly, the abdominal muscular wall was manually outlined to differentiate and quantify abdominal subcutaneous and visceral adipose tissue. We previously reported the high reproducibility of pericardial, intrathoracic, and abdominal visceral fat measures with inter- and intra-observer reproducibility of 0.95.^{5, 6}

Covariates were selected from the AF risk prediction model previously established by the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)-AF Consortium.⁷ The covariates were assessed at the Offspring cohort 7th examination (1998-2001) and Third Generation cohort 1st examination (2002-2005). BMI was calculated by using participants' weight in kilograms and height in meters squared (kg/m^2). Resting seated systolic and diastolic blood pressures were measured. Diabetes mellitus was diagnosed as fasting plasma glucose ≥ 126 mg/dL or use of insulin or oral hypoglycemic medications. Clinic physicians asked a series of questions to ascertain participants' smoking status and use of antihypertensive medications. Current smoking was dichotomized on the basis of smoking ≥ 1 cigarette per day within the year preceding the Framingham Heart Study examination. Events of heart failure and myocardial infarction were adjudicated by 3 physician investigators at the Framingham Heart Study based on available medical records.

Age- and sex-adjusted Pearson correlation coefficients among the MDCT-measured fat depots (pericardial, intrathoracic, and abdominal visceral fat) and BMI were computed. Age- and sex-adjusted AF incidence rates were acquired according to tertiles of MDCT-assessed fat depots. The MDCT-measured fat depots were standardized to a mean of 0 and standard deviation of 1 to enable the comparison among the effect sizes of the analysis. We constructed multivariable-adjusted Cox proportional hazard regression models to determine

the association between pericardial fat, intrathoracic fat, and abdominal visceral fat with incident AF with a separate model performed for each association tested. For all Cox models, proportionality assumptions were validated. We derived hazard ratio (**HR**) and 95% confidence interval (**CI**) per 1-standard deviation (**SD**) increment in the MDCT fat measures. Two different covariate-adjustments were considered: 1) age- and sex-adjusted model; and 2) multivariable-adjusted model that accounted for sex and risk factors for AF,⁷ including age, systolic blood pressure, diastolic blood pressure, current smoking, use of antihypertensive medication, diabetes mellitus, history of heart failure, and history of myocardial infarction.

As secondary analyses, additional covariate-adjusted models were constructed. We further adjusted the multivariable-adjusted model for 1) BMI or 2) abdominal visceral fat for pericardial and intrathoracic fat models. Moreover, all of the ectopic fat depots were additionally entered in the same multivariable-adjusted model to explore the association among the different fat depots with incident AF. Tests for age- and sex-interactions were separately conducted based on the multivariable model.

We created age- and sex-adjusted cumulative AF incidence curves by the tertiles of MDCT-measured fat depots using adjusted method.⁸ Tertile 3 corresponded to higher ectopic fat volume, as compared to tertile 1. A 2-sided *p*-value less than 0.05 were considered statistically significant in all analyses. All of the statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Given that we had 162 cases of incident AF, we had 80% power to discover an adjusted HR of 1.26 or larger at 0.05 significance level.

Results

Table 1 describes the demographic and clinical characteristics of the study participants. During a median follow-up of 9.7 years (25th–75th percentile 8.8–10.5 years), 162 cases of incident AF were identified among the 2,135 participants (7.6%). For those with incident AF, the median age of AF diagnosis was 73.4 years (25th–75th percentile 65.2–79.9 years). Baseline characteristics of the participants with incident AF are shown in **Supplementary Table 2**. The ectopic fat measures were highly correlated to each other with age- and sex-adjusted Pearson correlation coefficients of 0.62 for pericardial fat and intrathoracic fat; 0.60 for pericardial fat and abdominal visceral fat; and 0.75 for intrathoracic fat and abdominal visceral fat (all *p*<0.0001). Similarly, the age- and sex-adjusted Pearson correlation coefficients with BMI were 0.43 for pericardial fat, 0.51 for intrathoracic fat, and 0.70 for abdominal visceral fat, suggesting moderate to high correlations between BMI and the ectopic fat depots (all *p*<0.0001).

The associations of incident AF per 1-SD increment in ectopic adipose tissue volumes are shown in **Table 2**. Higher pericardial fat and intrathoracic fat volume, but not abdominal visceral fat, was associated with increased incidence of AF based on the age- and sex-adjusted model (all *p*<0.05). For example, per 1-SD increment in pericardial fat and intrathoracic fat were associated with 1.17-fold and 1.24-fold increased risk of incident AF (all *p*<0.05), respectively. In the multivariable-adjusted model, only intrathoracic fat remained associated with incident AF. Regardless of the type of covariate adjustments,

abdominal visceral fat was not associated with incident AF (all $p>0.05$). Further adjustment of BMI or abdominal visceral fat did not materially affect the association between ectopic fat depots and incident AF (all $p>0.05$) (**Table 2**). The only notable exception was intrathoracic fat, in which the significant association with incident AF did not persist after additionally adjusting for BMI (HR 1.15, 95% CI 0.96-1.38). When all the ectopic fat depots were entered in the same multivariable model to explore the association among 3 different ectopic fat depots with incident AF, none of the ectopic fat depots was associated with incident AF (all $p>0.05$).

We additionally explored age- and sex-interactions for the association between ectopic adipose tissue with incident AF based on the multivariable model. None of the interaction tests were statistically significant (all $p \geq 0.13$).

Tertile-specific analyses showed an increase in the cases and rates of incident AF for greater ectopic fat depots (**Table 3**). From the lowest to the highest ectopic fat depot tertile, age- and sex-adjusted AF incident rate per 1000 person-years increased from 8.4 to 10.2 for pericardial fat; and from 8.8 to 10.2 for intrathoracic fat (**Table 3**). **Figure 1** shows the association between follow-up time in years and the cumulative incidence of AF. An increase in cumulative incidence of AF was observed for the participants in the highest tertile (i.e., higher ectopic fat volume), as compared to those in the lower tertiles for both pericardial and intrathoracic fat depots (**Figure 1**).

Discussion

We examined the relation of ectopic adipose tissue depots with incident AF during a median follow-up of 9.7 years. Our findings are 3-fold. First, pericardial and intrathoracic fat depots were longitudinally associated with incident AF based on the model adjusted for age and sex. Second, after further accounting for risk factor determinants of AF and generalized adiposity, none of the ectopic fat depots were associated with incident AF. Third, abdominal visceral fat was not associated with incident AF regardless of types of covariate adjustments. Taken together, our findings confirm that after accounting for confounding factors and obesity, the Framingham Heart Study ectopic fat depots, including the adipose tissue accumulated closely to the cardiac structure, were not longitudinally associated with incident AF.

The current study is an extension of our previous research that demonstrated the cross-sectional association between pericardial fat with prevalent AF that persisted even after taking into account potential confounders, generalized adiposity, and regional fat depot (i.e., intrathoracic fat).¹ Other cross-sectional studies underscored the importance of volumetric measures of pericardial fat on prevalence,⁹⁻¹² severity,^{9, 13} and recurrence^{9, 14} of AF. To our knowledge, only 1 study has examined the longitudinal association between pericardial fat with incident AF. A recent population-based study from the Heinz Nixdorf Recall study demonstrated that epicardial fat assessed by non-contrast cardiac computed tomography was associated with incident AF in unadjusted [odds ratio (OR) 1.78, 95% CI 1.44-2.18, $p<0.0001$] and age- and sex-adjusted models (OR 1.57, 95% CI 1.23-1.99, $p<0.0003$).¹⁵ Similar to our findings, these associations attenuated and did not persist after the model was

adjusted for risk factors of AF, including age, sex, BMI, systolic blood pressure and antihypertensive treatment (OR 1.19, 95% CI 0.88-1.61). In contrast, epicardial fat was associated with prevalent AF even after further adjusting for AF risk factors (OR 1.55, 95% CI 1.16-2.09). Collectively, we have also shown in our study that the association observed between pericardial fat with prevalent AF is not replicable in the incident analysis.

Our research question was constructed based on our prior findings and existing literature that support pericardial fat, a metabolically active ectopic fat depot, has a localized effect on cardiac structure due to the close proximity of pericardial fat and the cardiac structure, and shared blood supply with the myocardial microcirculation.¹ In addition, other potential mechanisms were proposed to support that increased pericardial fat mediates AF via electrical and structural remodeling process;^{14,16} diastolic dysfunction;¹⁷ and releasing myriad of adipo-fibrokinases,¹⁸ pro-inflammatory adipokines,¹⁹ and reactive oxygen species.²⁰ Of Interest, indirect evidence for the local toxic effect of cardiac ectopic fat on AF was recently shown by a surgical biopsy study.²¹ That study demonstrated the increased concentration of norepinephrine, a catecholamine that invokes a sympathetic response, in epicardial adipose tissue, as compared to subcutaneous adipose tissue or plasma.²¹ These findings support the biological plausibility of a relation between pericardial fat and AF as greater local catecholamine concentration may increase the occurrence of arrhythmia. Nevertheless, we did not find associations between pericardial fat with incident AF after further adjusting for risk factor determinants of AF and BMI.

The discrepant findings between the significant cross-sectional findings but negative longitudinal findings between pericardial fat with AF may be explained by several potential mechanisms. First, the borderline power to detect the significant association between pericardial fat with incident AF may explain the discrepancy in our study findings.

Second, the pathogenesis of AF is multifactorial, and it may be that only a subset of the incident AF cases in our study was mediated by factors associated with the pericardial fat depot. More specifically, the non-significant longitudinal association observed in this study may be due to the complexity of AF that cannot be explained solely by a single factor. According to the risk prediction model established by the CHARGE-AF consortium, the moderate proportion of incident AF risk was explained by an extensive list of risk factors.⁷ Thus, the heterogeneity within the cases of AF manifested by a wide variety of risk factors with different pathophysiologic properties and mechanisms may have hindered the detection of the longitudinal association between the cardiac ectopic fat with fat-mediated AF.

Third, pericardial fat may not be the optimal measure of cardiac fat deposition. In our study, the measurement of pericardial fat included epicardial fat and paracardial fat due to the technical limitation of visualizing the lining that differentiates these 2 different fat depots. It is feasible that the local toxic effect is only applicable to the epicardial fat owing to its location immediately adjacent to the heart. The paracardial fat that is accumulated in the outer layer of parietal pericardium may have distinctively pathophysiological properties, as compared to pericardial fat.²² Subsequently, we may have not fully captured the association between the cardiac ectopic fat and incident AF, which may have resulted in a disparity in the findings between cross-sectional and longitudinal settings.

Pericardial fat and risk determinants of AF may share common pathologic links with AF. Previously, it has been speculated that pericardial fat may promote the pathogenesis of AF via several properties, including secretion of inflammatory cytokines,^{23, 24} alteration in cardiac structure,⁹ and modulation of autonomic nervous system.²⁴ Nonetheless, it should be noted that these properties are not only limited to pericardial fat. For instance, multiple lines of evidence support that ectopically located cardiac adiposity plays a crucial role in the pathophysiology of AF via secreting pro-inflammatory cytokines²⁵ and increasing expression of inflammatory markers,¹⁹ in which inflammatory conditions (e.g., pericarditis and myocarditis)²⁶ and markers of inflammation²³ are closely associated with AF. Yet, the determinants of AF, such as advancing age²⁷, hypertension,²⁸ smoking,²⁹ and diabetes mellitus³⁰ are also closely associated with higher circulating levels of inflammatory cytokines and the inflammatory state. Further research is needed to elucidate the biologic mechanisms between pericardial fat with AF while disentangling the association with the commonly shared risk factors.

The strengths of our study include highly reproducible measures of ectopic fat volume acquired by MDCT. The well-defined human cohort study that was documented for approximately 10 years of median follow-up enabled the exploration of the association between ectopic fat depots with incident AF. Several limitations merit discussion. Our observational study precludes inferences of causal relations between pericardial fat with incident AF. Generalization of our study results may not apply to other ethnic groups, or ages as our study participants consisted of white, predominantly middle-aged to older adults. AF is not infrequently unrecognized, thus we may have failed to detect cases of incident AF. We had moderate power to detect associations between MDCT-assessed ectopic fat depots with incident AF. We observed differences in the baseline characteristics of participants who were included and excluded from the study, which may have introduced selection biases in our study design.

Pericardial fat and intrathoracic fat were associated with incident AF in age- and sex-adjusted models during a median follow-up of 9.7 years. However, volumes of pericardial, intrathoracic and visceral fat were not associated with incident AF after accounting for risk factor correlates of incident AF and generalized obesity. Our findings suggest that cardiac ectopic fat depots and AF may share common pathologic links with AF, which may have led to a lack of independence in the association between pericardial fat with incident AF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1a. Pericardial Fat

Number at risk	Year					
	0	2	4	6	8	10
Tertile 1	698	691	683	658	618	328
Tertile 2	698	688	671	657	599	306
Tertile 3	699	688	660	621	543	240

Figure 1b. Intrathoracic Fat

Number at risk	Year					
	0	2	4	6	8	10
Tertile 1	698	689	683	667	630	331
Tertile 2	699	692	673	651	593	291
Tertile 3	698	686	658	618	537	252

Figure 1c. Abdominal Visceral Fat

Number at risk	Year					
	0	2	4	6	8	10
Tertile 1	695	684	674	654	618	308
Tertile 2	696	686	674	660	605	307
Tertile 3	695	686	656	614	532	265

Figure 1.

Cumulative incidence of atrial fibrillation by tertiles of ectopic fat volume (**Figure 1a.** pericardial fat, **Figure 1b.** intrathoracic fat, **Figure 1c.** abdominal visceral fat) adjusting for age and sex and accounting for competing risk of death. Tertile 3 corresponded to higher ectopic fat volume, as compared to tertile 1. Abbreviation: AF, atrial fibrillation.

Table 1

Characteristics of the Study Sample at Baseline

Characteristics	Women (n=1,137)	Men (n=998)	Overall Participants (n=2,135)
Age (years)	59.1 ± 9.5	58.4 ± 9.6	58.8 ± 9.6
Weight (kg)	72 ± 16	89 ± 15	80 ± 18
Height (cm)	162 ± 6	176 ± 7	169 ± 10
Body Mass Index (kg/m ²)	27.5 ± 5.8	28.7 ± 4.5	28.0 ± 5.3
Obesity	319 (28.1%)	293 (29.4%)	612 (28.7%)
Systolic Blood Pressure (mmHg)	123 ± 18	126 ± 14	124 ± 17
Diastolic Blood Pressure (mmHg)	74 ± 9	78 ± 9	76 ± 9
Current Smoker	118 (10.4%)	116 (11.6)	234 (11.0%)
Antihypertensive Medication	285 (25.1%)	252 (25.3%)	537 (25.2%)
Diabetes Mellitus	61 (5.4%)	89 (8.9%)	150 (7.0%)
Prior Heart Failure	4 (0.4%)	2 (0.2%)	6 (0.3%)
Prior Myocardial Infarction	10 (0.9%)	29 (2.9%)	39 (1.8%)
Pericardial Fat (cm ³)	106 ± 40	133 ± 49	118 ± 46
Intrathoracic Fat (cm ³)	75 ± 42	141 ± 63	106 ± 63
Abdominal Visceral Fat (cm ³)	1,493 ± 852	2,457 ± 1,042	1,945 ± 1,061

Values are described as means ± standard deviations for continuous variables or counts (proportions) for dichotomous variables.

Table 2

Associations between Measures of Ectopic Fat Depots and Incident Arterial Fibrillation

Models [*]	Pericardial Fat		Intrathoracic Fat		Abdominal Visceral Fat	
	Hazard Ratio (95% CI)	<i>p</i> -Value	Hazard Ratio (95% CI)	<i>p</i> -Value	Hazard Ratio (95% CI)	<i>p</i> -Value
Age- and Sex-Adjusted	1.17 (1.03-1.34)	0.02	1.24 (1.06-1.45)	0.007	1.15 (0.98-1.35)	0.08
Multivariable-Adjusted	1.13 (0.99-1.30)	0.08	1.19 (1.01-1.40)	0.04	1.09 (0.93-1.28)	0.29
Multivariable + BMI-Adjusted	1.09 (0.94-1.27)	0.26	1.15 (0.96-1.38)	0.14	1.02 (0.82-1.26)	0.88
Multivariable + Visceral Fat [†] -Adjusted	1.13 (0.95-1.34)	0.18	1.19 (0.93-1.51)	0.16	–	–
Multivariable + Fat Depot [‡] -Adjusted	1.09 (0.90-1.32)	0.39	1.14 (0.87-1.48)	0.34	0.88 (0.66-1.19)	0.41

Data are shown as hazard ratios (95% confidence intervals) per 1 standard deviation increment in the ectopic adipose tissue volumes.

Abbreviations: BMI, body mass index; CI, confidence interval.

^{*} Multivariable-adjustment included sex, age, systolic blood pressure, diastolic blood pressure, current smoking, use of antihypertensive medication, diabetes mellitus, history of heart failure, and history of myocardial infarction.

[†] Visceral fat were additionally adjusted for the pericardial fat model; and visceral fat were additionally adjusted for the intrathoracic fat model.

[‡] Intrathoracic and visceral fat were adjusted for the pericardial fat model; pericardial and visceral fat were additionally adjusted for intrathoracic fat model; and pericardial and intrathoracic fat were additionally adjusted for the visceral fat model.

Table 3

Age- and Sex-Adjusted Incidence Rates of Atrial Fibrillation According to Tertiles of Ectopic Fat Depots

Ectopic Fat Depots	Cases	Incidence* (95% Confidence Interval)
Pericardial Fat		
Tertile 1	33	8.4 (5.0-11.7)
Tertile 2	46	7.5 (5.3-9.7)
Tertile 3	80	10.2 (7.8-12.6)
Intrathoracic Fat		
Tertile 1	30	8.8 (3.6-14.0)
Tertile 2	45	7.7 (5.3-10.2)
Tertile 3	84	10.2 (7.5-13.0)
Abdominal Visceral Fat		
Tertile 1	35	9.1 (5.1-13.1)
Tertile 2	41	6.8 (4.6-8.9)
Tertile 3	82	10.3 (7.7-12.9)

* Data are shown as atrial fibrillation incidence rates per 1000 person years. Rates were standardized to the study sample age and sex distribution.