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Relationship of pericardial fat with biomarkers of inflammation and hemostasis, and cardiovascular disease: The Multi-Ethnic Study of Atherosclerosis

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ABSTRACT

Objective: Pericardial fat may increase the risk of cardiovascular disease (CVD) by increasing circulating levels of inflammation and hemostasis biomarkers. We investigated the associations of pericardial fat with inflammation and hemostasis biomarkers, as well as incident CVD events, and whether there are any ethnic differences in these associations.
Methods: We analyzed results from 6415 participants from the Multi-Ethnic Study of Atherosclerosis who had measurements of pericardial fat volume and circulating levels of C-reactive protein (CRP), fibrinogen, interleukin (IL)-6, factor VIII, D-dimer and plasmin-antiplasmin complex (PAP), and had a mean follow-up period of 9.5 years. Incident CVD event was defined as any adjudicated CVD event.
Results: After adjusting for confounding factors, pericardial fat volume was positively associated with natural log (ln) of IL-6 levels, but inversely associated with ln D-dimer and ln PAP levels ($\beta = 0.067$, -0.032, and -0.105 respectively, all $P < 0.05$). Although a larger pericardial fat volume was associated with a higher risk of incident CVD, the association was attenuated to borderline significance after adjusting for traditional cardiovascular risk factors ($P = 0.050$). There was a borderline significant ethnicity interaction ($P = 0.080$), whereby the association between pericardial fat volume and incident CVD was significant in Hispanic Americans, even after further adjusting for biomarkers of inflammation and hemostasis (hazard ratio = 1.31 per SD increase, 95% confidence interval 1.09–1.57, $P = 0.004$).
Conclusion: Pericardial fat was associated with several inflammation and hemostasis biomarkers. The association of pericardial fat with incident CVD events was independent of these biomarkers only among Hispanic Americans.

1. Introduction

An excess of ectopic fat deposition, such as in the pericardium, is often found in obese subjects [1]. Recent studies suggest a role of pericardial fat (especially epicardial fat) in the pathogenesis of coronary atherosclerosis via a paracrine pathway [2,3]. Specifically, pro-inflammatory cytokines that are released from pericardial fat may act locally and lead to coronary vessel inflammation [3,4]. This includes interleukin-6 (IL-6), a key mediator of inflammatory responses, which plays an important role in atherogenesis [5,6] and is the major regulator of production of acute phase proteins, including C-reactive protein (CRP) and fibrinogen [6]. Adipose tissue may also contribute to enhanced coagulation and fibrinolysis [7]. However, there are few studies on the relationship between pericardial adipose tissue and biomarkers in relation to inflammation and hemostasis.

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Previous studies have shown an ethnic difference in circulating levels of some inflammation biomarkers and hemostatic factors such as CRP and fibrinogen [8–10]. A previous study using data from the Multi-Ethnic Study of Atherosclerosis (MESA) has shown that the associations of inflammation biomarkers with future cardiovascular events are modified by ethnicity. More specifically, the association is significant in Caucasians for CRP and in African Americans for IL-6 [9]. Given that ethnic difference in pericardial fat volume has also been reported [11], there may be an ethnic difference in the relationship of pericardial fat volume with biomarkers of systemic inflammation and hemostasis, and with future cardiovascular disease (CVD) events. In this study, we investigated the relationship of pericardial fat volume with biomarkers of systemic inflammation and hemostasis, and with future CVD events in the MESA study.

2. Methods

2.1. Participants

The MESA study is a longitudinal cohort of 6814 men and women aged 45–84 years of age, and free of clinically apparent CVD at baseline [12]. Participants of four major ethnic groups, Caucasian, African American, Hispanic American, and Chinese American were recruited from six United States communities between July 2000 and August 2002. Participants were followed up in person at four clinic visits over a 10-year period. The study was approved by the institutional review boards at all participating centers and informed written consent was obtained from all participants. The study was performed in compliance with the principles of the Declaration of Helsinki. Details of the study objectives, design, and protocol have been described previously [12]. The definitions of diabetes, hypertension, dyslipidemia, and physical activity have also been described as previously [13].

Among 6814 participants at baseline, data on pericardial fat volume were available on 6788 participants, of whom 6445 had their circulating levels of CRP, fibrinogen, IL-6, factor VIII, D-dimer and plasmin-antiplasmin complex (PAP) measured. After excluding 30 participants with missing data on incident CVD events during follow up, a total of 6415 participants were included in this analysis.

2.2. Pericardial fat measurement

At baseline, all participants underwent computed tomography (CT) of the thorax to ascertain the presence and extent of coronary artery calcium using either an electron-beam CT scanner at 3 field centers or a multidetector row helical CT scanner at the other 3 field centers. These CT scans were then analyzed for pericardial fat volume as described previously [4]. Briefly, the slices within 15 mm above and 30 mm below the superior extent of the left main coronary artery were analyzed by three experienced CT analysts. This region of the heart was selected because it includes the pericardial fat located around the proximal coronary arteries (left main coronary, left anterior descending, right coronary, and circumflex arteries). The anterior border of the volume was defined by the chest wall and the posterior border by the aorta and the bronchus. Pericardial fat volume was defined as the sum of all voxels containing fat based on the volume analysis software (GE HealthCare, Waukesha, WI), which could discern fat from other tissues with a threshold of −190 to −30 Hounsfield units. This measure of pericardial fat volume was previously found to be highly correlated with total volume of pericardial fat volume [14] in a random subset of 10 Diabetes Heart Study participants (correlation coefficient = 0.93, $P < 0.0001$) [4]. In a random sample of 80 MESA participants, their CT scans were reread and the intraclass correlation coefficients of intrareader and interreader reliability were 0.99 and 0.89, respectively, for pericardial fat [4].

2.3. Biomarker measurement

CRP and fibrinogen were measured by immunonephelometry using a BNII nephelometer (N high sensitivity CRP and N antiserum to human fibrinogen; Dade Behring Inc., Deerfield, IL). IL-6 was measured by ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN). Factor VIII levels were measured by determining the clot time of a sample in factor VIII deficient plasma in the presence of activators using the Sta-R analyzer (STA-Deficient VIII; Diagnostica Stago, Parsippany, NJ). Fibrin fragment D-dimer was measured using an immunoturbidimetric assay on the Sta-R analyzer. Plasmin-antiplasmin complex (PAP), a marker of active plasmin generation, was measured by a two-site ELISA [15]. Details on the measurement methods of these biomarkers have been described previously [9,10,16].

2.4. CVD event ascertainment

CVD end-points included myocardial infarction, resuscitated cardiac arrest, definite angina, probable angina associated with coronary revascularization, stroke, stroke death, coronary heart disease death, other atherosclerotic death, and other CVD death [17]. At intervals of 9–12 months, a trained telephone interviewer contacted each participant to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses and procedures, and deaths. Additional medical encounters were identified through follow-up visits, participant call-ins, medical record abstractions, or obituaries occasionally. Copies of all death certificates and medical records for all hospitalizations, and selected outpatient cardiovascular diagnoses and procedures were also requested to verify self-reported diagnoses. Out of hospital cardiovascular deaths were also identified through next of kin interviews. Follow-up started from the baseline examination until death, loss to follow-up, or 31 December 2011, whichever came first, with a mean follow-up period of 9.5 years.

2.5. Statistical analysis

Data analysis was performed using SPSS 22 (IBM, Armonk, NY) or STATA 13.0 (StataCorp, College Station, TX). Data were presented as mean ± SD or percentage (number). For variables with a skewed distribution, data were presented as median (interquartile range). Multivariable linear regression model was used to investigate the cross-sectional association of different characteristics with pericardial fat volume as continuous variable after adjusting for age, sex, and ethnicity. Those variables with significant trend were used as covariates in subsequent regression analysis.

Multivariable linear regression was performed to investigate the association of pericardial fat volume with different biomarker levels (all as continuous variables) after adjusting for confounding factors and regression coefficients (β) were estimated with SD as analytic unit. The association of pericardial fat volume with incident CVD events was assessed using Cox proportional hazard regression analysis and hazard ratios (HR) were estimated after adjusting for confounding factors. In all these analyses, pericardial fat volume and the six biomarkers were also assessed as binary categorical variables (i.e. elevated levels or not, defined as a level in the highest quartile) in separate analyses, and the odds ratios (OR) or HR were estimated, where appropriate. No multi-collinearity issue was detected as assessed by the variance inflation factors (<3.0 for all covariates). Survivals were estimated by the