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Increase in epicardial fat volume is associated with greater coronary artery calcification progression in subjects at intermediate risk by coronary calcium score: A serial study using non-contrast cardiac CT

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ABSTRACT

Objective: Epicardial fat volume (EFV) is related to calcified coronary plaques. However, it is unknown whether baseline EFV or changes in EFV affect the progression of coronary artery calcification over time.
Methods: We identified 375 consecutive asymptomatic subjects with an intermediate risk of developing coronary artery disease, who underwent serial non-contrast CT at least 3–5 years apart. Subjects were divided into tertiles of CCS progression (% increase) between the 2 scans. Subjects from the upper tertile (High Progressors) were matched by age and gender to 81 subjects from the lower tertile (Low Progressors). All subjects underwent serial measurements of CCS and EFV. Relationships between EFV and CCS progression, and change in plaque number were examined.
Results: At baseline, there was no difference in EFV, and EFV indexed to body surface area (EFVi) between the groups. At follow-up, EFV, EFVi and percent increase in EFVi-change were higher in High Progressors than Low Progressors (EFV, $102 \pm 38\,cm^3$ vs. $90 \pm 35\,cm^3$, $p = 0.03$; EFVi, $50 \pm 16\,cm^3/m^2$ vs. $46 \pm 15\,cm^3/m^2$, $p = 0.03$; percent increase in EFVi-change, $15 \pm 22\%$ vs. $7 \pm 20\%$, $p = 0.02$). On multivariate analysis, after adjusting for conventional risk factors, EFVi increase $\geq 15\%$ [odds ratio (OR) 2.3, $p < 0.05$], log (baseline CCS) [OR 0.3, $p < 0.0001$] and scan interval time [$p = 0.003$, OR 1.0] were predictive of being a High Progressor. EFVi increase $\geq 15\%$ ($\beta = 3.0$, $p = 0.02$) and hypertension ($\beta = 3.1$, $p = 0.01$) were independent predictors of number of new calcified plaques on follow-up.
Conclusion: Increase in EFV is associated with greater progression of coronary artery calcification in intermediate-risk subjects.

1. Introduction

Epicardial fat volume (EFV) describes the volume of adipose tissue around the heart that is constrained by the visceral pericardium. Recent studies have demonstrated that EFV measured from non-contrast computed tomography (NCT) may be an important marker of coronary disease. EFV has been shown to be related to the presence and severity of coronary calcification [1–3], myocardial ischemia [4,5] and adverse cardiovascular outcomes [6,7]. Although it has been suggested that epicardial fat may exert its pathogenic effect by the release of inflammatory cytokines that mediate atherosclerosis [8,9], it is unknown whether elevated epicardial fat volume indicates which subjects are likely to develop greater atherosclerosis over time, and whether increases in epicardial fat volume are accompanied by a parallel increase in coronary calcification. The aim of the current study was to determine whether baseline EFV and EFV change are related to progression of coronary atherosclerosis, as measured by the coronary calcium score (CCS).

2. Methods

2.1. Study population

From 2054 subjects enrolled in the EISNER (Early Identification of Subclinical Atherosclerosis using Non-invasive Imaging

Abbreviations: CCS, coronary calcium score; EFV, epicardial fat volume; EFVi, epicardial fat volume indexed to body surface area; NCT, non-contrast computed tomography.

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Research) Registry, we identified 375 consecutive asymptomatic subjects without prior CAD (249 from a randomized trial of healthy volunteers and 126 from a registry of patients referred for CCS) found to have a baseline CCS (Agatston score) of 50–399 [10]. All subjects underwent repeat scan to quantify CCS 3–5 years after the index scan. All scans were performed between September 1998 and May 2007. Inclusion criteria were intermediate pre-test probability for developing coronary heart disease (CHD) (6–20% 10-year risk) [11] as evidenced by being: (1) a man ≥55 years or woman ≥65 years or (2) a man 45–54 years or woman 55–64 years with at least 1 traditional CHD risk factor [11], and a CCS of between 50 and 399 Agatston units (AU) [12]. Exclusion criteria were history of myocardial infarction, coronary revascularization, cardiomyopathy, peripheral artery disease, angina, or stroke. Diabetes was also an exclusion criterion due to its independent relationship to both epicardial fat and coronary calcium [13,14].

Pre-scan Risk factor Assessment: Prior to CT imaging, a fasting lipid profile [total cholesterol (TC), high density lipoprotein (HDL) cholesterol, and triglycerides, with calculated low density lipoprotein (LDL) cholesterol] and glucose were obtained on each study participant using a Cholestech (Hayward, California) desktop chemical analyzer. Weight, height [for calculation of body mass index (BMI) – weight in kg/height squared in meters], and two readings of blood pressure (with mean systolic and diastolic readings used for analysis) were also measured. A brief medical history was collected to assess prior history of cardiac disease, typical cardiovascular event risk factors, and medication usage. Hypertension was defined as history of physician-diagnosed high blood pressure, or blood pressure medication usage or blood pressure ≥140/90 mmHg (systolic/diastolic). Hypercholesterolemia was defined as history of physician-diagnosed high cholesterol, or cholesterol medication usage or LDL ≥140 mg/dl or TC ≥240 mg/dl. Presence of metabolic syndrome was defined as recommended by the recent joint American Heart Association-National Heart Lung Blood Institute statement [15], based on the Third Adult Treatment Panel (ATP III) criteria of the National Cholesterol Education Program (NCEP) [16], with the modification of replacing waist circumference cutpoints with BMI, as described in our previous work [17]. Smoking was defined as self-reported history of current smoking.

Subjects were divided into tertiles of % CCS change ($n = 125$ in each group). This subgrouping allowed standardized referencing of CCS change to the baseline CCS (i.e. a measure of change in the atherosclerotic activity). Absolute CCS change was calculated as [CCS at follow-up − CCS at baseline]. % CCS change was calculated using the equation (absolute CCS change/CCS at baseline) × 100%. Eighty-one subjects in the high tertile ("High Progressors") were then matched to 81 subjects from the low tertile ("Low Progressors") by gender and age decade. If there was more than 1 candidate for matching from the Low Progressors, the candidate was chosen randomly using a pseudo-random number generator. The study had Institutional Review Board (IRB) approval, and all patients gave written informed consent.

2.2. Imaging protocol (non-contrast computed tomography)

NCT for CCS was performed on an electron-beam (e-Speed, GE Healthcare, Milwaukee, Wisconsin) or 4-slice CT scanner (Somatom Volumezoom, Siemens Medical Solutions Forcheim, Germany) at baseline, and a dual-source CT scanner (Somatom, Siemens Medical Solutions, Forchheim, Germany) at follow-up. Each scan extended from the aortic arch to the diaphragm and was obtained during a single breath-hold. Scan parameters included: heart-rate dependent prospective ECG-triggering (typically 45–60% of the R–R interval), 35 cm field-of-view, 512 × 512 matrix size, and peak tube voltage of 120 kVp. Slice thickness was 3 mm for electron-beam CT and 2.5 mm for multislice CT. Acquired images were then transferred to a remote research workstation (Leonardo, Siemens Medical Systems) for analysis. All coronary calcium score measurements were performed on a ScImage workstation with dedicated ScImage software reporting CCS (ScImage, Los Altos, CA) to quantify coronary calcification as described by Agatston [10]. In addition to the total CCS score, the numbers of discrete calcified plaques were recorded to assess whether increases in coronary calcium were due to progression of existing calcified plaques or the formation of de-novo calcified plaques.

2.3. Epicardial fat volume quantification

Epicardial fat was defined as in our previous work [1] and included all adipose tissue outside of the myocardium enclosed by the visceral pericardium. Epicardial fat volume was quantified using dedicated software (QFAT) developed by our group [1]. The superior boundary of epicardial fat was set at the level of the pulmonary artery bifurcation. The inferior boundary was set at the first axial slice displaying posterior descending artery (PDA). Experienced readers blinded to the CCS determined the superior and inferior boundaries, and at each axial slice, traced contour points to define the pericardium. From these control points, piecewise cubic Catmull-Rom spline function [1] was automatically generated to create a smooth, closed pericardial contour. EFV was then automatically calculated by identifying contiguous 3D voxels displaying Hounsfield Units (HU) between −190 and −30 [14,18]. EFV was reported in cubic centimeters (cm^3) and indexed to body surface-area (EFVi). Percent EFVi-change was calculated using EFVi as reference.

2.4. Statistical analysis

This study was a matched case–control study, in which each High Progressor was matched to a unique Low Progressor by age decade and gender. CCS was compared after logarithmic transformation (LogCCS) to adjust for its non-normal distribution. Based on our previously determined mean inter-scanner variability of 8.8–14.4% [19] and same-scan inter-observer variability of 8.0 ± 5.3% [1], a ≥15% increase from baseline EFVi was set as the criterion for significant EFVi increase. Continuous variables were expressed as the mean ± standard deviation, and for highly skewed variables medians and ranges were also presented. The unpaired Student's *t*-test (for normally distributed variables) or the Wilcoxon rank-sum test (for non-parametrically distributed variables) was used to conduct intergroup comparisons, while paired *t*-test or Wilcoxon signed-rank tests were done whenever comparing baseline to follow-up measurements. Categorical variables were compared using Pearson Chi-squared tests or Fisher exact tests for cell counts <6. Multiple pairwise comparisons were adjusted using the Bonferroni method. Multivariable logistic regression analyses controlling for hypertension, hypercholesterolemia, smoking, BMI, baseline CCS, and scan interval time were performed to examine the relationship of baseline EFVi and EFVi increase ≥ 15% with high progression of CCS. We also performed secondary multivariate analyses replacing BMI with metabolic syndrome or waist circumference as a covariate. Additionally, multivariable linear regression analysis was used to examine whether hypertension, hypercholesterolemia, smoking, BMI, baseline CCS, scan interval time, baseline EFVi and EFVi increase ≥ 15% predicted the number of newly identified calcified plaques at the follow up NCT. Newly calcified plaques were defined as [number of calcified plaque at follow-up NCT – the number of calcified plaque at baseline NCT]. *P*-values <0.05 were considered statistically significant. All statistical calculations were