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Epicardial adipose tissue and coronary artery plaque characteristics

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ABSTRACT

Objective: Epicardial adipose tissue (EAT) has been implicated in the pathogenesis of coronary atherosclerosis. The association of EAT volume with type of coronary artery plaque on computed tomography angiography (CTA) is not known.
Methods: Coronary artery calcium (CAC) scoring and EAT volume measurement were performed on 214 consecutive patients (mean age 54 ± 14 years) referred for coronary CTA. CAC was performed on non-contrast images, while EAT volume, the severity of luminal stenoses, and plaque characterization were assessed using contrast-enhanced CTA images. EAT volume was also indexed to body surface area (EAT-i).
Results: EAT volume correlated with age, height, body mass index (BMI), and CAC score. EAT volume increased significantly with the severity of luminal stenosis ($p < 0.001$), and in patients with no plaques, calcified, mixed, and non-calcified plaques (62 ± 33 mL, 63 ± 22 mL, 98 ± 47 mL, and 99 ± 36 mL, respectively, $p < 0.001$). The EAT volume was significantly larger in patients with mixed or non-calcified plaques compared to patients with calcified plaques or no plaques (all $p < 0.01$ or smaller). The trend remained significant after adjustment for traditional risk factors for coronary artery disease. In adjusted models EAT was an independent predictor of CAC [exp(B) = 3.916, $p < 0.05$], atherosclerotic plaques of any type [exp(B) = 4.532, $p < 0.01$], non-calcified plaques [exp(B) = 3.849, $p < 0.01$], and obstructive CAD [exp(B) = 3.824, $p < 0.05$]. The above results were unchanged after replacing EAT with EAT-i.
Conclusion: EAT volume was larger in the presence of obstructive CAD and non-calcified plaques. These data suggest that EAT is associated with the development of coronary atherosclerosis and potentially the most dangerous types of plaques.

1. Introduction

Epicardial adipose tissue (EAT) is fat confined within the pericardial sac. Evidence is accumulating that EAT may be linked with the development of coronary atherosclerosis through several paracrine mechanisms, such as the local release of inflammatory mediators that trigger the atherosclerotic process, and other systemic effects. The first attempts at quantifying EAT used transthoracic echocardiography and measured EAT thickness adjacent to the right ventricular free wall [1]. With recent developments in magnetic resonance imaging (MRI) and multidetector computed tomography (MDCT), more comprehensive volumetric EAT measurements have become possible [2].

Prior studies have shown an association between EAT and the presence and extent of coronary artery disease (CAD) [3–6] and coronary artery calcium (CAC) [7–9]. However, there are limited to no data regarding the association of EAT with the type of atherosclerotic plaque (calcified, mixed, or non-calcified).

2. Methods

2.1. Study population

We reviewed 214 MDCT angiography (CTA) scans performed at our institution on consecutive patients with no history of percutaneous coronary intervention, coronary artery by-pass surgery, or known cardiomyopathy (LVEF < 45%). Patients underwent coronary CTA between January 2007 and May 2009 for a variety of indications: perioperative risk assessment, atypical chest pain, or functional stress test results of indeterminate significance. The study protocol was approved by our internal institutional review board.

2.2. Data collection

Demographic data were collected on all patients through retrospective chart review. Height and weight measured at the time

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of imaging were used to calculate body mass index (BMI). The presence of risk factors for atherosclerosis was derived from the patient's chart and/or direct assessment: hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg or currently receiving antihypertensive treatment; dyslipidemia was defined as total cholesterol ≥200 mg/dL, LDL-cholesterol ≥130 mg/dL, HDL-cholesterol <30 mg/dL, or currently receiving lipid modifying agents; diabetes mellitus was defined as a fasting glucose ≥126 mg/dL or currently receiving hypoglycemic treatment. Smoking was classified as current smoking if the patient smoked or quit in the last 30 days, or not smoking if the patient never smoked or smoked in the remote past. A family history of premature coronary artery disease was considered present if a first degree relative suffered an acute coronary artery event or was submitted to coronary revascularization prior to age 45 for men and age 55 for women.

2.3. CT imaging protocol

All scans were performed on a Somatom Sensation 64-slice CT scanner or a Definition dual source 64-slice CT scanner (Siemens Medical Solutions, Forchheim, Germany). Breath holding was utilized to minimize motion artifact. Oral β-blockers were administered only when the single source CT scanner was used and only when the resting heart rate of the patient exceeded 75 beats per minute. For CAC scoring prospective ECG triggering technique in mid to late diastole was used to limit radiation exposure. Reconstructed stacked short-axis images with a 3.0-mm slice thickness were obtained via filtered back-projection, spanning from the bronchial carina to the diaphragm. Before the injection of iodinated contrast for the performance of coronary CTA, 0.4 mg of nitroglycerin were administered sublingually. After a test bolus injection to determine the timing of acquisition, the CTA was performed by retrospective ECG gating according to the following protocol: tube voltage 100–140 kV depending on patient's weight; tube current 560 mA s with dose modulation; gantry rotation time 0.33 s; pitch 0.2–0.44 adapted to heart rate; collimation 0.6 mm, leading to an isotropic voxel resolution of approximately 0.2 mm^3. A volume of contrast agent adjusted for body weight (1.25 cc/kg, Omnipaque 350, GE Healthcare, Cork, Ireland) was injected continuously at a rate of 6 cc/s. Axial images were reconstructed with 0.75 mm slice thickness and reconstruction increment of 0.4 mm.

2.4. Coronary artery calcium scoring

Each area of calcification of the coronary arteries was scored by an experienced investigator blinded to clinical variables, CTA results, and EAT volume analyses, using semiautomatic software available on the workstation (Leonardo, Siemens Medical Solutions, Forchheim, Germany). CAC was considered present if a minimum of three contiguous pixels with an attenuation of ≥130 Hounsfield Units (HU) were detected along the course of a coronary artery. CAC scores were calculated using the method described by Agatston et al. [10].

2.5. Plaque evaluation

For the analysis of coronary plaque morphology, all reconstructed data sets were evaluated at different ECG-phases for diagnostic image quality and the optimal data set was then chosen. The MDCT datasets were evaluated by two independent investigators blinded to EAT volume measurements using a dedicated cardiac workstation (Leonardo, Siemens Medical Solutions, Forchheim, Germany). No CAD was defined as no visible coronary atherosclerotic plaques; mild (non-obstructive) CAD was defined as plaques causing less than 50% luminal narrowing, moderate CAD as plaques causing 50–70% luminal narrowing, and severe CAD as plaques causing >70% luminal narrowing. Atherosclerotic plaques were classified as calcified, mixed, or non-calcified. Calcified plaques were defined as lesions with an attenuation ≥130 Hounsfield units (HU); non-calcified plaques were defined as structures clearly assignable to the vessel wall (in at least two views) with a density lower than the lumen contrast; plaques demonstrating calcification in ≤50% of the plaque area were classified as mixed.

2.6. Epicardial adipose tissue volume measurement

Epicardial fat was identified on contrast-enhanced CT as a hypodense rim surrounding the myocardium and limited by pericardium. Quantification of "total EAT volume" was done on a separate workstation (*Advantage*, GE, Milwaukee, WI) with dedicated software (*Volume Viewer*, GE, Milwaukee, WI) as described by Gorter et al. [11]. The visceral pericardium, was traced manually from the mid left atrium to the left ventricular apex, and all extra-pericardial tissue was excluded. These images were then segmented using an attenuation threshold varying between −250 HU and −30 HU providing the EAT area in each slice. This effectively excluded myocardium, coronary arteries, coronary calcium, the aorta, and blood pool. The EAT area at each level was then summed across slices and multiplied by the slice thickness and number of slices to determine "total EAT volume" (Fig. 1). The reproducibility of the method we used to measure EAT has been reported by Nichols et al. [12] and Gorter et al. [13] to be very high. We also tested the inter- and intra-reader variability of EAT measurements at our institution among 3 investigators trained on the same software. We found the average error to be 3 mL, demonstrating a high degree of reproducibility.

2.7. Statistical analysis

Normally distributed parameters are presented as mean ± standard deviation and skewed parameters are expressed as median (interquartile range). Descriptive data are presented as absolute and relative (percentage) frequencies. For parametric analyses, CAC was log-transformed. Pearson's bivariate correlations were used to test the strength of association between EAT volume and other variables. Univariable ANOVA was used to compare normally distributed variables (such as EAT volume) across various degrees of CAC score or plaque characteristics, using the Fisher LSD method for post hoc determination of significance ($p < 0.05$ considered significant).

ANCOVA was used to determine if any difference observed in the univariable analyses was independent of confounders. Multivariable logistic regression analyses were performed to assess whether an EAT volume above the median predicted the presence of CAC, plaques of any plaque, plaques with a non-calcified component and obstructive CAD. To take into account the effect of anthropometric variability on EAT volume, we repeated the statistical analyses after having indexed EAT to the body surface area (EATI-i). Statistical analyses were performed using SPSS statistical package for Windows, version 16.0 (SPSS Inc., Chicago, IL).

3. Results

Patients' demographic and clinical characteristics are shown in Table 1. A CAC score was calculated in 204 patients. The median CAC score was 0 with an interquartile range of 0–104. One hundred and eight (53%) patients had a CAC score of zero, 44 patients (22%) had a CAC score >0 and ≤100, 23 patients (11%) had a CAC score >100 and ≤400, and 29 patients (14%) had a CAC score >400. MDCT angiography data were available in the whole population and showed