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Research paper

Epicardial adipose tissue volume but not density is an independent predictor for myocardial ischemia

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ABSTRACT

Background: Epicardial adipose tissue (EAT) volume is associated with plaque formation and cardiovascular event risk, its density may reflect tissue composition and metabolic activity.
Objectives: Global and regional associations between EAT volume and density, ischemia and coronary calcium were investigated using a novel automatic quantitative measurement software.
Methods: 71 patients with an intermediate pre-test probability for coronary artery disease and inducible ischemia by SPECT were matched to two same-gender controls (total of 213 patients, 90% male, age 60 ± 10 years). Non-contrast CT for assessment of EAT volume, density (in Hounsfield Unit [HU]) and coronary calcium score (CCS) was performed.
Results: Global EAT volume was significantly increased in ischemic patients compared to controls (96 ± 49 vs. 82 ± 36 cm^3, $p = 0.04$), density showed no significant difference (−75.6 ± 4.3 vs. −75.1 ± 4.1HU, $p = 0.63$). EAT volume and density differed significantly between coronary territories (LAD: 37 ± 18 cm^3, −77.8 ± 4.5HU; LCx: 16 ± 9 cm^3, −73.9 ± 4.1HU; RCA: 36 ± 17 cm^3, −71.7 ± 4.8HU, $p < 0.001$). For regional ischemia, only LCx territory showed a significantly higher EAT volume (18 ± 8 vs. 16 ± 9 cm^3, $p = 0.048$). Multivariable logistic regression revealed a significant association with ischemia for EAT volume (OR 2.09 (1.0; 4.3), $p = 0.049$) and CCS (OR 1.43 (1.1; 1.9), $p = 0.006$). EAT volume significantly improved discrimination of ischemia over CCS (Integrated Discrimination Improvement: 3.5%, 95%CI: 1.1-6.1%, $p = 0.004$). Hypertension was the only risk factor significantly influencing EAT volume and density (98 ± 48 vs. 78 ± 31 cm^3, $p = 0.002$, −76.0 ± 4.1 vs. −74.5 ± 4.1 HU, $p = 0.01$).
Conclusions: EAT volume is associated with myocardial ischemia and improves the discriminative power for independent ischemia prediction over CCS. In hypertensive patients, EAT is characterized by lower density and higher volumes.

1. Introduction

Alterations in epicardial adipose tissue (EAT), a visceral fat depot located within the pericardial sac with immediate proximity to the coronary arteries, are associated with certain cardiac conditions. These include impaired left-ventricular systolic function, compromised diastolic filling, atrial fibrillation, atrial enlargement, cardiomyopathy and, in particular, coronary artery disease (CAD).[1]

Non-contrast cardiac computed tomography (CT) is the method of choice for quantification of EAT volume from the surrounding tissue based on density differences.[2] In a semi-automated process,

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CT, computed tomography; CAD, coronary artery disease; EAT, epicardial adipose tissue; ECG, electrocardiography; FRS, Framingham risk score; HU, Hounsfield units; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; SPECT, single-photon emission computed tomography; SRS, summed rest score; SSS, summed stress score.

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the pericardium contour is first manually traced in each transaxial slice followed by an automated step of processing all continuous voxels with a density range of −190 to −30 Hounsfield Units (HU) within the pericardial sack for calculation of global EAT volume.[3] Previous studies using CT demonstrated an association between a high global EAT volume and coronary artery plaque development and vulnerability, myocardial ischemia, increased coronary calcium as well as an increased incidence of cardiovascular adverse events.[4–9] However, only little is known about regional distribution of EAT and its relationship to myocardial ischemia and coronary calcification.[10]

Metabolic processes within the EAT are supposed to affect atherosclerosis by endocrine and paracrine mechanisms of secreted pro-inflammatory cytokines and adipokines.[5,11–16] Alterations in CT attenuation have been reported to reflect metabolic activity, composition and lipid content of adipose tissue.[17,18] In patients with no CAD, decreasing CT attenuation of pericoronary adipose tissue, defined as the layer of EAT with immediate proximity to the coronary vessels, has been associated with greater EAT volume, body mass index (BMI) and with a family history of CAD.[19] To date, information is lacking regarding the role of EAT density in patients with atherosclerosis.

In the current study, we analyzed patients from a matched cohort from the EISNER (Early Identification of Subclinical Atherosclerosis Using Non-Invasive Imaging Research) registry in order to investigate the relation between global and regional EAT volume and CT attenuation (expressed in HU) with myocardial ischemia. For this purpose, we used a novel fully automated quantitative measurement software which allows an approximated coronary artery territory-assigned EAT assessment.

2. Material and methods

2.1. Patient population

Patients were selected from the EISNER registry of 1,777 consecutive patients without known CAD and with an intermediate pre-test probability for CAD who underwent non-contrast CT for coronary calcium scoring and myocardial perfusion single-photon emission computed tomography (SPECT) within a period of 6 months (16 ± 28 days between studies). An intermediate pre-test probability was met by all men ≥55 years or women ≥65 years of age and men between 45 and 54 years or women between 55 and 64 years of age with at least 1 traditional CAD risk factor. Out of this cohort, we included all patients with inducible ischemia in SPECT and an intermediate pre-test probability for CAD within an age range of 45 to 80 years. Patients with unstable angina, history of myocardial infarction, coronary revascularization, cardiomyopathy, peripheral artery disease, or stroke were considered not eligible for the study and were excluded. 71 patients with inducible ischemia by SPECT (defined as summed difference score (SSS) ≥4) were matched to two same-gender controls (146 control cases) by using the technique of propensity score-based matching (single nearest-neighbor matching, with no replacement).[20,21] The propensity score-based matching accounted for age, body mass index, Framingham Risk Score (FRS), clinical symptoms at the time of SPECT and coronary calcium score (CCS) category (defined as Agatston score = 0, 1 to 99, 100 to 399, and >400).[22,23] Two population-cohort patients and their matched control cases were not evaluable and had to be excluded. Thus, the study cohort consisted of 213 patients (71 cases and 142 controls) who were evaluated between May 2002 and April 2008. The study was performed according to guidelines of the Cedars-Sinai Medical Center institutional review board. All patients provided written consent for use of their data.

BMI was calculated by weight (in kilograms) divided by height squared (in meters). Hypertension was defined as a systolic blood pressure >140 mmHg, a diastolic blood pressure >90 mmHg or treatment with antihypertensive drugs. Dyslipidemia was classified as a total cholesterol ≥200 mg/dl or treatment with lipid-lowering agents (though patients using lipid-lowering agents over 6 months were excluded from the study). Tobacco use was defined as smoking at least one cigarette per day at any time point of the last year. A positive family history was defined as a documented myocardial infarction or sudden death in a male (<55 years) or female (<65 years) first degree relative. FRS was calculated for estimation of a patient's 10-year risk of cardiovascular death or myocardial infarction.[24,25]

2.2. Non-contrast cardiac CT imaging and determination of coronary calcium score

Non-contrast cardiac CT imaging was performed on an electron-beam (e-Speed, GE Healthcare, Milwaukee, Wisconsin) or a 4-slice CT scanner (Somatom Volumezoom, Siemens Medical Solutions, Forchheim, Germany) calibrated daily using air and water phantoms. Images were acquired by a prospectively electrocardiography (ECG) triggered acquisition mode protocol (120 kVp tube voltage for multislice scanning, typically 45% to 60% of the R-R interval, 35-cm field of view, 512 × 512 matrix size, slice thickness 3 mm for electron-beam CT and 2.5 mm for multislice CT). Scan window extended from the aortic arch to the diaphragm and was obtained during a single breath-hold.

Using a semi-automatic commercially available software (ScImage, Los Altos, California), coronary calcium was quantified using the Agatston score.[26]

2.3. Analysis of epicardial adipose tissue volume and density

Epicardial adipose tissue volume and density (in HU) were measured using a semi-automatic software (QFAT, Version 9.5, developed at Cedars-Sinai Medical Center, Los Angeles, California) (Fig. 1).[7,22] Epicardial fat spreads between the outer wall of the myocardium and the visceral level of the pericardium, fully enclosed by the pericardial sac. As upper slice limit, the bifurcation of the pulmonary trunk was automatically determined, for the lower slice limit the slice just caudal to the posterior descending artery. In each transverse view, the pericardium was automatically defined with piecewise cubic Catmull-Rom spline functions for generating a smooth closed pericardial contour.[27] If deemed appropriate, contour and slice limits were corrected by a reader with more than 3 years of experience in cardiac CT blinded to patient characteristics and clinical data. Volume of EAT (in cm^3) was automatically calculated by including contiguous three-dimensional voxels with CT attenuations between −190 to −30 HU enclosed by the visceral pericardium.[28–30] Density was presented as mean and as histogram with 10 HU-steps (Fig. 2).

For regional EAT volume and density analysis, eight equal-sized segments based from the center of the heart in the transverse view were determined and assigned to coronary artery territories (Fig. 1).

2.4. Exercise and adenosine stress SPECT imaging protocols

Beta-blockers and calcium antagonists were discontinued for 48 h and nitrates for 24 h before testing. Heart rate, blood pressure measurements and 12-lead ECG monitoring were obtained throughout the study, horizontal or downsloping ST-segment depression ≥1 mm or upsloping ≥1.5 mm were considered positive for ischemia. Rest ^{201}Tl SPECT was performed 10 min after radionucleotid infusion (3 to 4.5 mCi, based on body weight). Patients underwent a symptom-limited Bruce treadmill exercise