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Epicardial fat volume and concurrent presence of both myocardial ischemia and obstructive coronary artery disease

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ABSTRACT

Objective: Epicardial fat volume (EFV) is linked to cardiovascular event risk. The aim of this study was to evaluate whether EFV is independently related to concurrent presence of both myocardial ischemia and obstructive coronary stenosis.
Methods: We studied 92 consecutive patients without known coronary artery disease (CAD) who underwent Rb-82 PET, coronary calcium scoring (CCS) and invasive coronary angiography (ICA) within 6 months. EFV was computed from non-contrast CT by validated software and indexed to body surface-area (EFVi, cm^3/m^2). Ischemia was defined by ≥5% difference of total perfusion deficit (quantified by validated software) between stress and rest. Obstructive stenosis was defined ≥50% luminal diameter stenosis.
Results: Fifty three patients had both ischemia and stenosis. Compared to those without, patients with both having ischemia and stenosis had significantly higher CCS (1125 ± 1230 vs. 626 ± 690, $p = 0.02$) and EFVi (64.6 ± 20.6 vs. 49.7 ± 14.2 cm^3/m^2, $p = 0.0002$). On multivariable analysis after adjusting age, gender, cardiovascular risk factors, chest pain, and CCS (≥400), only elevated EFVi (>68.1 cm^3/m^2) significantly predicted concurrent presence of both ischemia and stenosis (odds ratio 6.18, 95% confidence interval 1.73–22.01, $p = 0.005$). Area under the receiver-operator-characteristic analysis demonstrated a trend towards improved incremental prediction of concurrent myocardial ischemia and obstructive stenosis over age, gender, chest pain, and high CCS (0.73 vs. 0.65, $p = 0.09$).
Conclusions: Our study suggests that elevated EFVi measured using non-contrast CT may be related to concurrent presence of both ischemia and stenosis.

1. Introduction

Epicardial fat volume (EFV) quantified from non-contrast CT is associated with the presence of coronary calcium [1–3], coronary artery disease (CAD) assessed by invasive coronary angiography (ICA) [4], myocardial ischemia by single photon emission computed tomography (SPECT) [5], and adverse clinical outcomes [6,7]. In an early small study of 45 patients with myocardial ischemia by positron-emission tomography (PET), epicardial fat was demonstrated to be superior to coronary calcium score (CCS) for predicting myocardial ischemia by PET [8]. To date, the additive value of EFV to CCS for the prediction of myocardial ischemia associated with obstructive CAD is unknown. We thus conducted a study of patients without known CAD who underwent non-contrast cardiac CT evaluation, PET myocardial perfusion imaging, and ICA to evaluate whether EFV is independently related to concurrent presence of both myocardial ischemia and obstructive coronary stenosis.

2. Methods

2.1. Study population

We retrospectively identified 112 consecutive patients without known CAD. All patients were clinically referred to Cedars-Sinai Medical Center (Department of Imaging, Division of Cardiac Imaging) by physicians for assessment of myocardial perfusion. Cedars-Sinai Medical Center serves the Los Angeles County in southern California and our patient population represents both genders and includes all minorities. All patients were underwent invasive coronary angiography within a 6-month period after the PET/CT study due to clinical indications. None of the patients experienced myocardial infarction or revascularization in the interscan

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period. CT was used for attenuation correction and non-contrast coronary calcium scan at the time of PET/CT study. Twenty patients were excluded since non-contrast coronary calcium scan was not performed at the time of PET/CT study. Thus, the current study consists of 92 consecutive patients who underwent PET/CT, non-contrast CT for CCS, and ICA. All patients provided written informed consent prior to the PET/CT study. This consent form includes the use of their clinical and imaging data for further research, and the study was approved by our Institutional Review Board.

2.2. PET/CT scan acquisition

All image data were acquired in list mode on a Siemens Biograph-64 TruePoint PET/CT (Siemens Medical Solutions) with the TrueV option. This 3D system consists of a 64-slice CT and a PET scanner with 4 rings of lutetium oxyorthosilicate (LSO) detectors with element dimensions of 4 mm × 4 mm × 20 mm [9]. Patients were instructed to avoid caffeine for 24 h before the test. Beta-blockers and calcium-channel antagonists were discontinued for 48 h, and nitrates were withheld for at least 6 h before testing. After a 2.8 s topogram acquisition (120 kVp) used for patient positioning, a CT transmission scan (120 kVp, pitch 1.5) was acquired. Subsequently, patients were injected with 925–1850 MBq (25–50 mCi, dose based on body mass) of Rb-82 at rest. Rest imaging began immediately with 6 min of data acquisition. Immediately after completion of rest imaging, a second stress CT transmission scan was performed (120 kVp, pitch 1.5). Pharmacologic stress was performed using adenosine infusion (n = 69, 0.14 mg/kg/min for 7 min) or regadenoson (n = 23, Lexiscan®, Astellas Pharma, Chicago, IL: 0.4 mg regadenoson in 5 ml solution), and 925–1850 MBq (25–50 mCi) of Rb-82 was administered (infusion rate 35–50 ml/min) beginning 2 min after the adenosine infusion or 30 s after the regadenoson injection (followed by a 10 ml saline flush after regadenoson). Rest and stress CT transmission scans were acquired at end-expiration breath-hold and patients were instructed to breathe normally during of the PET acquisition. Patients' emission data were reconstructed with 2D Attenuation Weighted Ordered Subsets Expectation Maximization (2 iterations and 21 subsets). CT-based attenuation, scatter, including prompt gamma, decay, and random corrections were applied to the reconstructed images.

A separate non-contrast CT scan for coronary calcium scoring and EFV analysis was performed using prospective gating typically at 45–60% of R–R interval (120 kVp, 1.4 s per cycle). Breath-holding instructions were given to minimize misregistration. Scans were reconstructed with 3 mm thickness, 512 × 512 matrix, 190 mm field of view with B35f reconstruction kernel and transferred to a ScImage (ScImage Inc., Los Altos, CA) workstation for CCS quantification.

The quality of the registration between PET and CT was first estimated by experienced nuclear cardiology technologists using fused images on a 3D workstation (Syngo 6.0, Siemens Medical Solution, Hoffman Estates, IL). When misalignment was identified, a manual registration matrix with 3D-translations was generated by an experienced technologist and applied before the final reconstruction process. Both the original CT-PET alignment and the alignment after manual registration were re-checked using QPET software by an experienced imaging cardiologist as previously described [10,11]. Visual quality control identified patient motion in 10 cases out of 92 cases, and manual motion-correction was applied in these cases.

2.3. Imaging data analysis

Automated software was used to quantify the extent and severity of PET myocardial perfusion abnormality expressed as % total perfusion deficit (TPD) [12,13]. Ischemia was defined by ischemic TPD (stress TPD–rest TPD) ≥5%. All coronary calcium scans were reviewed by an expert reader using semiautomatic commercially available software (ScImage Inc., Los Altos, CA) to quantify coronary calcium. Total Agatston CCS was calculated as the sum of calcified plaque scores of all coronary arteries [14]. Epicardial fat was defined as adipose tissue enclosed by the visceral pericardium, including fat directly surrounding the coronary arteries, and was quantified using QFAT software developed at our center, as previously described [3,5]. EFV was indexed to body surface-area (EFVi, cm^3/m^2). EFVi >68.1 cm^3/m^2 was considered the threshold for severely elevated EFVi, based on the distribution of normal epicardial fat volumes in a healthy population recently reported by our group [15]. All patients underwent ICA using a standard technique within 6 months of the index PET/CT study. All ICA were interpreted visually by experienced cardiologist who was unaware of myocardial perfusion imaging (MPI) results. Obstructive stenosis was defined ≥50% luminal diameter stenosis in major coronary artery.

2.4. Radiation dose

The average effective radiation dose for the scout, coronary calcium scan and attenuation scan was estimated to be 2.5 mSv. The dose contribution from the two Rb-82 injections was calculated using recently published human dosimetry data [16] and estimated to be 3.1 mSv, giving an average total estimated effective radiation dose of 5.6 mSv for the PET/CT and CCS protocol.

2.5. Statistical analysis

Continuous variables were described as mean ± SD. Variables with non-normal distributions were also described with medians and ranges. CCS ≥400 was used to categorize patients as high-risk for obstructive coronary stenosis [17–19]. For the further assessment, to correct for non-normal distribution, EFVi and CCS data were logarithmically transformed for the analysis (logEFVi, logCCS). Chest pain typicality was categorized as typical or atypical [20]. Multivariable logistic regression analysis including age, gender, chest pain and CCS was performed to evaluate the relationship between EFVi and concurrent presence of ischemia and stenosis. To examine the discriminatory power of EFVi, receiver–operator-characteristic (ROC) curves were constructed and areas under the ROC curve (AUC) were compared [21]. For 2 group comparisons, t-test or Wilcoxon rank-sum test was used as appropriate. Categorical variables were compared using Pearson Chi-squared tests or Fisher exact tests as appropriate. Correlation between EFVi and rest left ventricular ejection fraction (LVEF) was assessed by calculating Spearman's correlation coefficient. Associations and differences with p values <0.05 were considered significant. Statistical analyses were performed using STATA software (version 11, StataCorp LP, College Station, TX).

3. Results

Of the 92 study patients, 62 (67%) were men, and 33 (36%) had diabetes. Mean age was 69 years, and mean body mass index (BMI) was 28 kg/m^2. Overall, mean EFVi was 58.2 ± 19.6 cm^3/m^2 and mean CCS was 886 ± 1040 [median 497, range (0–4514)].

Fifty-three had both myocardial ischemia on PET and obstructive stenosis on ICA, 11 had obstructive stenosis without ischemia, 6 had ischemia without obstructive stenosis, and 22 had neither ischemia nor obstructive stenosis. As shown in Table 1, there was no significant difference in age, gender, BMI and traditional cardiovascular risk factors when patients with both ischemia and stenosis were compared to others. Patients with both ischemia and stenosis had significantly higher CCS [1125 ± 1230 (median 751, range