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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

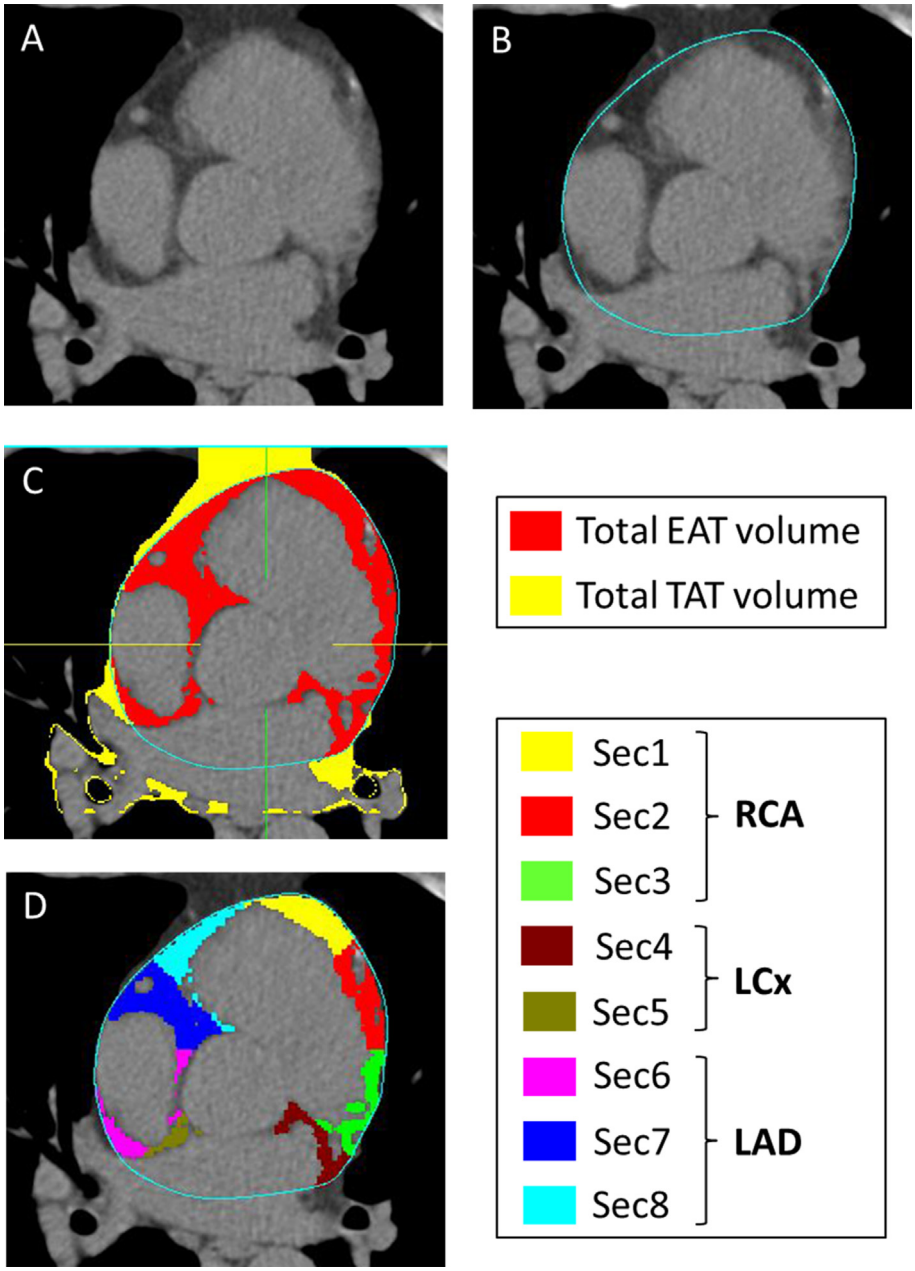

Fig. 1. Measurement of global and segmental epicardial adipose tissue volume and density by automated software. Individual steps for measurements of global and segmental epicardial adipose tissue (EAT) volume and density are presented for a non-contrast CT data set of a 56 year old male patient. (A) Axial slice at the level of the pulmonary arteries with a clear visible pericardium. (B) 20 control points on the pericardium are automatically defined. If deemed appropriate, contour and slice limit corrections could be modified by the reader blinded to patient characteristics and clinical data. (C) After performing these steps for all axial slices from the bifurcation of the pulmonary trunk to the posterior descending artery, the software automatically detects all voxels within the pericardial contour in the preset threshold of −190 to −30 HU and calculates the global EAT volume and density. Additionally, voxels within the threshold outside the pericardium are detected as thoracic adipose tissue (TAT) volume. (D) For segmental analysis, eight equal-sized sectors (Section 1–8) based from the centre of the heart in the transverse view were determined. Myocardial blood territories were assigned to the best suitable coronary artery. RCA, right coronary artery; LCx, left circumflexus artery; LAD, left anterior descending artery.

protocol or adenosine stress protocol, as described previously.[31] In brief, ^{99m}Tc-sestamibi (32 to 40 mCi) was injected intravenously at near-maximal exercise and, when tolerated, exercise was continued at maximal workload for an additional minute and at reduced workload for an additional 2 minutes. ^{99m}Tc-sestamibi SPECT acquisition was started 15 to 30 minutes after radiopharmaceutical injection. For pharmaceutical testing, adenosine (140 μg/kg/min) was infused for 5 minutes, ambulatory patients were additionally treadmill-exercising at a low-level during infusion.[32] ^{99m}Tc-sestamibi was injected at the end of the second minute, myocardial perfusion imaging was started approximately 60 minutes later.[33]

SPECT imaging was performed on a 2-detector gamma camera (Philips Adac Forte or Vertex, Philips Medical Systems, Cleveland, Ohio, or E-Cam, Siemens Medical Solutions) with a high-resolution collimator. Stress ^{99m}Tc-sestamibi images were acquired from 64 projections over 180° orbit, with 64 projections at 25 seconds/projection for supine acquisition followed immediately by 15 seconds/projection for prone acquisition.[34] For Rest ^{201} Tl images, acquisition was performed at 35 seconds/projection in supine

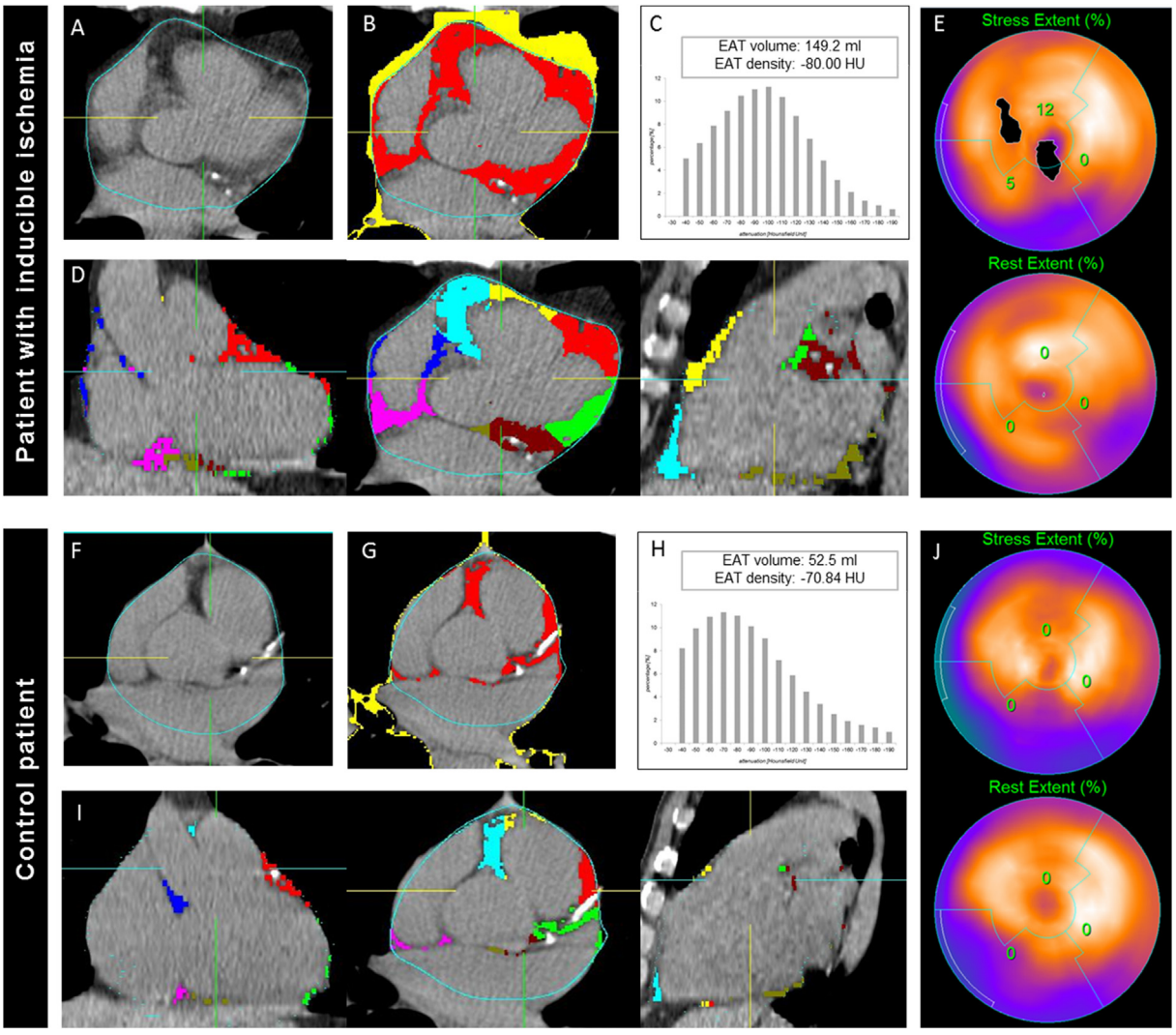

Fig. 2. Representative examples of EAT volume and attenuation analysis in a patient with inducible myocardial ischemia and matched control patient. Top panel images are from a 54-year old male patient with inducible myocardial ischemia (SSS 5, SDS 5, CCS 691). Axial slice with automatically generated pericardial contour (A) and detected epicardial adipose tissue (EAT, red filling) and thoracic adipose tissue (TAT, yellow filling) volume (B). (C) shows histogram for total EAT density for the range −190 to −30 HU, global EAT volume is 149.2 ml, mean EAT density is −80.00 HU. (D) presents standard coronal, axial and sagittal views with sector analysis of EAT. (E) presents corresponding SPECT data (top: stress image, bottom: rest image). Bottom images are from a 59-year old male matched control patient (SSS 0, SDS 0, CCS 1054). Axial slice with automatically generated pericardial contour (F) and detected EAT (red filling) and TAT volume (yellow filling) (G). (H) shows histogram for total EAT density for the range −190 to −30 HU with a definite left shift compared to histogram from patient with inducible myocardial ischemia. Global EAT volume is 52.5 ml, mean EAT density is −70.84 HU. (I) presents standard coronal, axial and sagittal views with sector analysis of EAT. (J) presents corresponding SPECT data (top: stress image, bottom: rest image).

position only. At each of the 64 projection angles, the image data were recorded into 16 equal ECG-gated time bins with no attenuation or scatter correction. Transverse images were generated by iterative reconstruction (12 iterations) with Butterworth prefiltering (cutoff 0.66 cycle/pixel for supine ^{99m}Tc-sestamibi, 0.55 cycle/pixel for prone ^{99m}Tc-sestamibi; order 5) and reoriented to short-axis images automatically by the SPECT analysis software.[35]

2.5. Computer-assisted visual quantification of SPECT images

Quantitative evaluation of perfusion defects was performed using computer-assisted visual interpretation of the 17-myocardial segment model by an expert reader (over 15 years of experience with SPECT) blinded to patient identity, clinical and CT results. Assignment of the myocardial segments to the coronary artery territories was performed according to American Heart Association guidelines.[36] Extent and severity of perfusion defects were quantified as SSS and summed rest score (SRS), the extent and severity of ischemia were expressed by summed stress score (SSS). For global ischemia analysis, a SDS $\geq$4 was defined as pathological.[37,38] For vessel-assigned ischemia, a SDS $\geq$2 was defined as pathological.

2.6. Follow up

All patients enrolled in the EISNER cohort were part of a follow up program including a yearly mailed detailed questionnaire and a 4-year clinic visit.[39] The questionnaire investigated cardiac risk factor status, ongoing medical therapies as well as cardiovascular procedures or hospitalizations. Procedures analyzed on follow up visit included exercise treadmill resting, stress myocardial perfusion imaging, stress echocardiography, coronary CT angiography and invasive coronary angiography. Invasive procedures including

percutaneous coronary intervention or coronary bypass surgery were confirmed by source documentation or through confirmation with the subject's primary care physician. A nonfatal myocardial infarct included admission with a primary or secondary diagnosis confirmed by enzymatic elevation and ECG changes consistent with acute infarction. A hospitalization event for acute myocardial infarct was confirmed by the subject's primary care physician and/or medical record review. A cardiovascular disease death was defined as fatal myocardial infarct or stroke and death related to heart failure or peripheral arterial disease. Death status was confirmed by medical record review, through the Social Security Death Index, or from Los Angeles County Public Health records. Each year of follow up, timing and occurrence of cardiac death or myocardial infarct was collected. Follow up rates at years 1, 2, 3, and 4 were 99%, 96%, 95%, and 99%, respectively. No patient was lost to follow up.

2.7. Statistical analysis

Statistical analysis was performed using STATA (version 12; StataCorp LP, College Station, TX). Continuous variables were assessed for normality using Shapiro-Wilk Test and expressed as mean ± SD. Categorical variables were described as frequencies and percentage. Parametric data was compared using *t*-test and non-parametric data using Mann-Whitney *U* test for continuous variables. Chi-square test was used to compare categorical variables. All tests were performed two-sided. Conditional multivariate logistic regression, adjusted for age, presence of symptoms and traditional risk factors, was applied to evaluate the relationship between EAT volume and CCS with ischemia. Correlation was assessed using Spearman's correlation test. Integrated discrimination improvement analysis was performed using SAS 9.2 (Cary, NC). $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. Patient characteristics

The total study cohort of 213 patients had a mean age of 60 ± 10 years with 192 males (90%). There was no significant difference in age, FRS, BMI and cardiovascular risk factors except hypertension. Detailed information on patient characteristics is presented in Table 1.

Out of those patients with inducible ischemia on SPECT, 46 patients showed defects in the left anterior descending artery (LAD) territory, 25 patients in the left circumflex artery (LCx) territory and 47 patients in the right coronary artery (RCA) territory. Mean SSS in those patients was 10.9 ± 7.5 (median 8, range 4-38) and mean SDS was 9.6 ± 7.2 (median 4, range 2-12). No inducible ischemia was present in the control cohort of 142 matched patients (SSS 0.3 ± 0.7, SDS 0.0 ± 0.3). Total coronary calcium was significantly increased in patients with ischemia compared to control cohort (Agatston score 1174 ± 1371 vs. 581 ± 664, $p = 0.003$). Significantly increased coronary calcium was found in patients with ischemia on a per-vessel basis for the LAD (Agatston score: 533 ± 608 vs. 276 ± 314, $p = 0.003$) and the RCA (Agatston score: 431 ± 651 vs. 197 ± 315, $p = 0.009$). For the LCx, there was a trend of higher coronary calcium scores in ischemic patients (Agatston score: 162 ± 284 vs. 86 ± 173, $p = 0.133$). In the myocardial ischemia cohort, at least one event occurred in 36 patients (17%). There was no event documented in the control cohort during follow up. Results of SPECT analysis, coronary calcium and follow up are presented in Table 2.

3.2. Global and regional epicardial adipose tissue volume and density and relationship to myocardial ischemia

Mean global EAT volume was 88 ± 42 cm^3, mean global EAT density was −75.2 ± 4.2 HU. EAT volume and density differed significantly between the 8 cardiac sectors ($p < 0.001$) and the vessel territories (LAD: 37 ± 18 cm^3, −77.8 ± 4.5 HU; LCx: 16 ± 9 cm^3, −73.9 ± 4.1 HU; RCA: 36 ± 17 cm^3, −71.7 ± 4.8 HU, $p < 0.001$). Global EAT volume (96 ± 49 cm^3 vs. 82 ± 37 cm^3, $p = 0.041$) was significantly increased in patients with ischemia compared to non-ischemic patients, whereas global EAT density showed no significant alterations (−75.6 ± 4.3 HU vs. −75.1 ± 4.1 HU, $p = 0.627$). EAT volume but not density was significantly increased in patients with inducible ischemia in each vessel territory (LAD: 40 ± 22 cm^3 vs. 35 ± 16 cm^3, $p = 0.049$, LCX: 18 ± 10 cm^3 vs. 15 ± 8 cm^3, $p = 0.011$, RCA: 40 ± 19 cm^3 vs. 34 ± 15 cm^3, $p = 0.024$). When vessel-assigned ischemia scores were considered, only LCx showed a significant increase in EAT volume (18 ± 8 cm^3 vs. 16 ± 9 cm^3, $p = 0.048$) in ischemic patients. A correlation of EAT volume and SSS was found for LCX ($r = 0.20$, $p = 0.006$) and RCA ($r = 0.16$, $p = 0.024$) territories but not for the LAD territory. Table 3 summarizes results on global and regional EAT volume and density between the two cohorts.

Table 1
Patient characteristics.

	Total patient cohort n = 213	Non-ischemic cohort n = 142	Ischemic cohort n = 71	*p*-value
Age (y), mean ± SD	59.6 ± 9.9	59.1 ± 9.5	60.5 ± 10.6	0.364
Male sex, n (%)	192 (90)	128 (90)	64 (90)	0.900
BMI (kg/m^2), mean ± SD	27.6 ± 4.2	27.3 ± 3.9	28.2 ± 4.7	0.252
Body weight (kg), mean ± SD	84 ± 15	84 ± 14	85 ± 17	0.879
Heart rate (bpm), mean ± SD	68 ± 12	68 ± 13	69 ± 12	0.795
Cholesterol (mg/dl)				
Total	202.8 ± 44.0	203.5 ± 42.3	201.6 ± 47.5	0.642
Low-denstity lipoprotein	121.9 ± 38.3	122.5 ± 36.6	120.7 ± 41.8	0.409
High-density lipoprotein	50.8 ± 14.8	51.7 ± 14.1	48.9 ± 16.0	0.108
Triglycerides (mg/dl)	149.3 ± 120.7	141.9 ± 97.8	163.9 ± 156.7	0.293
Glucose (mg/dl)	102.2 ± 25.8	101.2 ± 25.7	104.4 ± 26.1	0.168
Framingham risk score	12.3 ± 7.5	11.9 ± 7.0	13.2 ± 8.4	*0.435*
Cardiovascular risk factors, n (%)				
Hypertension	109 (51)	65 (46)	44 (62)	0.031*
Diabetes	14 (7)	7(5)	7 (10)	0.239
Dyslipidemia	157 (74)	103 (73)	54 (76)	*0.624*
Tobacco abuse	17 (8)	14 (10)	3 (4)	*0.187*
CAD family history	46 (22)	31 (22)	15 (21)	*0.906*

BMI, body mass index; bpm, beats per minute; CAD, coronary artery disease. *$p < 0.05$.

Table 2
Summary of Ischemia and Coronary Calcium.

	Total patient cohort n = 213	Non-ischemic cohort n = 142	Ischemic cohort n = 71	*p*-value
SPECT analysis				
Coronary territory of ischemia				
LAD	46	0	46	
LCx	25	0	25	
RCA	47	0	47	
Non-contrast CT analysis				
Agatston score				
Total	779 ± 996	581 ± 665	1174 ± 1371 (850; 1499)	0.003*
LAD	362 ± 450	276 ± 314	533 ± 608	0.003*
LCx	111 ± 219	86 ± 173	162 ± 284	0.133
RCA	275 ± 467	197 ± 315	431 ± 651	0.009*
Follow up				
Cardiovascular events				
Total	36 (17)	0 (0)	36 (51)	<0.001*
PTCA	26 (12)	0 (0)	26 (37)	<0.001*
CABG	13 (6)	0 (0)	13 (18)	<0.001*
Myocardial infarction	1 (1)	0 (0)	1 (1)	0.333
Stroke	*1 (1)*	*0 (0)*	*1 (1)*	0.333
Death	*0 (0)*	*0 (0)*	*0 (0)*	

LAD, left anterior descending artery, LCx, left circumflex artery; RCA, right coronary artery; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; #revascularization events within 30 days were not included; *p < 0.05.

3.3. Global epicardial adipose tissue volume and density and relationship to biophysical parameter

Global EAT density was negatively correlated to global EAT volume (r = −0.70, p < 0.001), per-vessel and per-sector EAT volume, thoracic adipose tissue volume (r = −0.60, p < 0.001), BMI (r = −0.25, p < 0.001), cholesterol plasma level (r = −0.5, p = 0.021), LDL plasma level (r = −0.15, p = 0.032), triglyceride plasma levels (r = −0.22, p = 0.001) and positively correlated with HDL plasma levels (r = 0.22, p < 0.001). Global EAT volume was positively correlated to thoracic adipose tissue volume (r = 0.84, p < 0.001), BMI (r = 0.37, p < 0.001), FRS (r = 0.25, p = 0.002), triglyceride plasma levels (r = 0.19, p = 0.004) and negatively correlated with HDL plasma levels (r = −0.17, p = 0.010). No correlation was found for Agatston Score.

EAT volume (90 ± 42 cm^3 in male vs. 71 ± 36 cm^3 in female, p = 0.023) but not density (−75.2 ± 4.2 HU vs. −75.3 ± 3.7 HU, p = 0.082) was significantly different between gender given the unbalance of gender in this study. Independently of ischemia, hypertension was the only cardiovascular risk factor that showed significantly influence on EAT volume (98 ± 48 cm^3 vs. 78 ± 31 cm^3 in non-hypertensive patients, p = 0.002) and density (−76.0 ± 4.1 HU vs. −74.5 ± 4.1 HU in non-hypertensive patients, p = 0.010). Patients with tobacco consumption showed a trend to lower EAT density (−73.6 ± 4.9 vs. −75.4 ± 4.1 in non-smoking patients; p = 0.063). See Table 4 for details.

3.4. Multivariable analysis and discrimination of ischemia

Multivariable analysis by conditional logistic regression adjusted for age, presence of symptoms and traditional risk factors showed a significant association with ischemia for log-transformed EAT volume and coronary calcium. The odds ratio (OR) of ischemia for log-transformed EAT volume was 2.09 (95% confidence interval [CI]: 1.00 to 4.33, p = 0.049) and for log-transformed Agatston score 1.43 (95% CI: 1.11 to 1.86, p = 0.006), see Table 5. Global EAT volume improves significantly the discriminative power for independent prediction of ischemia over coronary calcium (Integrated Discrimination Improvement score 3.5%, 95% CI: 1.1–6.1%, p = 0.004).

4. Discussion

This present case-control study is, to our knowledge, the first study which investigated the relation between global and regional

Table 3
Epicardial adipose tissue volume and density analysis in relationship to myocardial ischemia.

	Total patient cohort n = 213	Non-ischemic cohort *mean ± SD (95% CI)*	Ischemic cohort *mean ± SD (95% CI)*	*p*-value
EAT Volume [cm^3]				
In relation to global ischemia				
Global	88.2 ± 42.0	81.5 ± 36.2 (75.6; 87.4)	96.0 ± 48.5 (84.5; 107; 4)	0.041*
LAD	36.5 ± 18.2	34.8 ± 15.8 (32.2; 37.4)	40.0 ± 21.9 (34.8; 45.1)	0.049*
LCx	15.9 ± 8.7	14.8 ± 7.8 (13.5; 16.1)	18.1 ± 9.9 (15.8; 20.5)	0.011*
RCA	35.8 ± 17.0	33.8 ± 15.3 (31.2; 36.3)	39.8 ± 19.4 (35.2; 44.4)	0.024*
In relation to vessel-assigned ischemia				
LAD		35.9 ± 18.4 (33.1; 38.7)	38.7 ± 17.2 (33.6; 43.8)	0.240
LCx		15.6 ± 8.7 (14.3; 16.8)	18.2 ± 7.9 (14.9; 21.5)	0.048*
RCA		34.7 ± 16.2 (32.2; 37.1)	39.8 ± 19.2 (34.1; 45.4)	0.055
EAT Density [HU]				
Global	−75.2 ± 4.2	−75.1 ± 4.1 (−75.7;−74.4)	−75.6 ± 4.3 (−76.6;−74.6)	0.627
LAD	−77.8 ± 4.5	−77.4 ± 4.3 (−78.1;−76.6)	−77.9 ± 4.3 (−78.0;−76.9)	0.569
LCx	−73.9 ± 4.1	−73.6 ± 4.0 (−74.2;−72.9)	−74.2 ± 4.2 (−75.2;−73.2)	0.313
RCA	−71.7 ± 4.8	−71.5 ± 4.7 (−72.3;−70.7)	−72.1 ± 4.9 (−73.3;−71.0)	0.437

95% CI, 95% confidence interval; EAT, epicardial adipose tissue; LAD, left anterior descending artery, LCx, left circumflex artery; RCA, right coronary artery; HU, Hounsfield Unit.
*p < 0.05.

Table 4
Influence of cardiovascular risk factors on epicardial adipose tissue volume and density independently from myocardial ischemia.

	Volume [cm^3]			Density [*HU*]		
	Without risk factor	With risk factor	*p*-Value	Without risk factor	With risk factor	*p*-Value
Hypertension	77.6 ± 31.0	98.3 ± 48.4	0.002*	−74.5 ± 4.1	−76.0 ± 4.1	0.010*
Diabetes	86.9 ± 41.0	106.2 ± 53.7	0.224	−75.2 ± 4.0	−76.2 ± 5.8	0.549
Dyslipidemia	87.0 ± 41.0	88.6 ± 42.5	0.753	−74.7 ± 4.4	−75.4 ± 4.1	0.369
Tobacco abuse	89.1 ± 42.5	78.0 ± 36.9	0.300	−75.4 ± 4.1	−73.6 ± 4.9	0.063
CAD family history	89.6 ± 43.2	83.2 ± 37.5	0.622	−75.3 ± 4.3	−75.1 ± 3.9	0.924

CAD, coronary artery disease. *p < 0.05.

EAT volume and CT attenuation with myocardial ischemia. We used a novel fully automated quantitative measurement software which allows a sector-based EAT assessment. We found an increased global EAT volume but not density in patients with inducible ischemia. Between the three coronary artery territories, EAT volume and density differed significantly. Furthermore, we found that hypertension has a significantly influence on EAT density and volume, independently of ischemia.

An association between increased EAT volume and positive myocardial ischemia has been described in several studies.[10,40–42] Janik et al. first reported that global EAT volume as assessed by CT is an independent predictor of ischemia by PET in a CAD naïve population with intermediate pre-test probability.[42] Furthermore, EAT volume was found to be a better predictor of ischemia than total coronary calcium. A larger matched cohort study by Tamarappoo et al. identified increased global EAT and thoracic adipose tissue volume as parameters predicting myocardial ischemia using SPECT.[40] Otaki et al. identified EAT volume adjusted to body-surface-area as an independent significant predictor of impaired myocardial flow reserve after accounting for standard cardiovascular risk factors and coronary calcium using Rb-82 myocardial PET/CT.[4] Our present study showed concordant results with an increased EAT volume in patients with myocardial ischemia in SPECT imaging who have an intermediate risk profile for CAD. Additionally, we also found that global EAT volume improves significantly the discriminative power for independent prediction of ischemia over coronary calcium. In contrast to previous studies and our present results, a recent study by Tanami et al. could not find a significant association between EAT volume and myocardial perfusion abnormalities in the CORE 320 trial cohort.[43] This result was explained by great ethnic diversity of the cohort and a higher risk profile for CAD of their enrolled patients. In fact, many of the other risk factors and components of the metabolic system which were investigated in these studies are associated with epicardial fat and their complex relationships complicate the conclusion of independent associations.[44]

Among other adipose tissue depots, alterations in EAT have been attributed a special role in prediction of CAD. This has been explained by its diverse molecular signature of cytokine and adipokine expression as well as tissue composition.[11,12] Especially the immediate proximity to the coronary arteries suggests that regional alterations in EAT may be responsible for myocardial ischemia. A recent published study by Khawaja et al. investigated global and regional EAT volume by determination of the specific amount of perivascular epicardial fat adjacent to each major coronary artery.[10] They found a regional specific adipose tissue distribution with higher EAT volume around the RCA and LAD compared to the LCx territory independently from the presence of myocardial ischemia. This was in concordance with our findings showing the lowest EAT volume in the LCx territory. For patients with verified myocardial ischemia, Khawaja et al. reported significant increased EAT volume around the LAD and RCA but not around the LCx independently from the localization of the perfusion defect. They further reported that increased regional EAT volume was limited to the coronary artery supplying that specific ischemic area of the myocardium while those coronary arteries without ischemia had a normal EAT volume. In our cohort, EAT volume was increased in all three coronary artery territories in patients with myocardial ischemia independently from ischemia localization. The distribution of ischemia segments in the cohort was approximated equal between the LAD and the RCA, the number of segment with ischemia attributed to the LCx territory was significantly less. This was in concordance with the EAT volume for all three coronary arteries in terms of global ischemia. When regional segmental ischemia scores were considered, we only found a significant increase in EAT volume for the LCx territory in patients with ischemia. For coronary artery territory-assigned EAT volume analysis, we applied a sector-based model simplified from the model used in nuclear analysis. It has to be mentioned that this mapping only allows an estimation of territory assigned EAT volume as patient-specific coronary artery territories and the various orientation of the axis of the heart is not taken into account. Whereas we assessed territory-assigned EAT volume, Khawaja et al. investigated perivascular epicardial fat volume just adjacent to each major coronary artery, so called pericoronary adipose tissue.

Metabolic processes within the EAT have been suggested to affect atherosclerotic plaque formation by endocrine and paracrine mechanisms of secreted pro-inflammatory cytokines and adipokines.[11,12] Invasive excision of tissue samples followed by extensive molecular and histological work-up is the method of choice to analyze tissue composition. However, this is a time- and resource-consuming technique limited to autopsy samples and patients undergoing cardiac surgery which is ethically not acceptable in patients undergoing non-invasive cardiac imaging. There have been reports that alterations in CT attenuation reflect metabolic activity, composition and lipid content of adipose tissue. Baba et al. found a significant increase in CT attenuation of non-cardiac adipose tissue in rodents upon metabolic activity as determined by histopathological analysis.[17] In a clinical setting, Torriani et al. demonstrated reduced CT attenuation levels of abdominal visceral adipose tissue in patients 12 months after undergoing Roux-en-Y gastric bypass surgery.[18] In the present study, no difference in EAT density was found in patients with ischemia (who likely also had significant CAD) compared to control cohort. While we found a negative correlation between EAT density and volume, EAT volume rather than density identified myocardial ischemia by SPECT. A recent study by

Table 5
Results of conditional multivariable analysis adjusted for age, presence of symptoms and traditional risk factors.

	Odds ratio (95% CI)	p-Value
Log_2 (Agatston score)	1.43 (1.11; 1.86)	0.006*
Log_2 (EAT volume)	2.09 (1.00; 4.33)	0.049*
Log_2 (EAT volume)	0.96 (0.90; 1.02)	0.200

95% CI, 95% confidence interval; EAT, epicardial adipose tissue. *p < 0.05.

our group on pericoronary adipose tissue density of patients with *non-atherosclerotic* coronary arteries analyzed in coronary CTA data sets found that CT-measured attenuation of PCAT is influenced by EAT volume and body mass.[19] To date, no studies have specifically investigated the EAT density in patients with significant CAD.

Regarding an influence of risk factors on EAT volume and density, we currently observed an association with BMI, FRS, HDL and triglyceride plasma levels. Out of the traditional cardiovascular risk factors, we only found that hypertension had a significant influence on EAT volume and density. Several studies reported an association between EAT volume or thickness and arterial hypertension.[45–48] On a pathophysiological level, the rise in blood pressure related to increased EAT volume has been explained by an increase in plasma catecholamine concentration induced by cardiac fatty acids, by endothelial dysfunction and heightened sympathetic activity due to paracrine effects of EAT and by EAT-derived hypoadinopectinemia leading to decreased arterial elastic properties and impaired endothelial vasodilation.[49–51] However, those studies have only investigated the relationship between EAT volume or thickness and hypertension, but not EAT density. In our recent study on pericoronary adipose tissue density, we found lower density levels in patients with increased BMI and a trend of lower density levels in patients with a family history of CAD.[19] Further studies are necessary to elucidate the relationship between pericoronary adipose tissue and total EAT density and cardiovascular risk factors.

5. Limitations

Several limitations in this study need to be acknowledged. First, we performed a case-control study which has been shown to be more sensitive to the effects of confounding factors than a cohort study design.[27,52] As the result, there was an unbalanced gender rate with a large percentage of male patients in the present study. Additionally, there was a significant difference in total Agatston score and in the Agatston score for the LAD and the RCA territory between the two cohorts as we applied a probit model accounting for the general Agatston score category and not the Agatston score. Furthermore, this was a one-center study subjected to local effects on diet and lifestyle habits. The current study did not include an invasive angiography to confirm relevant coronary artery stenoses in patients with myocardial ischemia. As the inclusion criterion was an intermediate risk for CAD, the use of myocardial perfusion imaging was clinically appropriate. Conformation through longitudinal whole-cohort evaluation is needed. Furthermore, it has to be taken into account that the CT attenuation measured as EAT reflects a mixture of different tissue types and is rather non-specific.

6. Conclusions

EAT volume, but not density, is associated with myocardial ischemia. Global EAT volume improves significantly the discriminative power for independent prediction of ischemia over coronary calcium. However, in hypertensive patients, EAT is characterized by significantly lower density and higher volumes.

Conflict of interest

There is no conflict of interest/financial disclosure.

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