Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp



# Impact of Functional, Morphological and Clinical Parameters on Epicardial Adipose Tissue in Patients With Coronary Artery Disease

Christina Doesch, MD; Dariusch Haghi, MD; Tim Suselbeck, MD;
Stefan O. Schoenberg, MD; Martin Borggrefe, MD; Theano Papavassiliu, MD

***Background:*** Because a close relationship between epicardial adipose tissue (EAT) and coronary artery disease (CAD) has been shown, the impact of functional, morphological and clinical parameters to identify potential determinants of EAT was investigated.

***Methods and Results:*** Clinical and cardiac magnetic resonance parameters were determined and correlated to the amount of EAT in 158 patients with CAD and 40 healthy subjects. Patients with CAD and left ventricular function (LVEF) ≥50% revealed significantly elevated EAT (36±11 g/m²) compared to healthy controls (31±8 g/m²) and to patients with LVEF <50% (26±8.0 g/m²). In the whole study population, only LVEF (P=0.003), body mass index (BMI) (P=0.004) and left ventricular end diastolic diameter (LV-EDD) (P=0.004) remained significantly associated with EAT after multivariate analysis. Subgroup analysis in patients with CAD and LVEF ≥50% showed that BMI (P=0.03) was the only correlate of EAT. However, in patients with CAD and LVEF <50%, indexed LV end diastolic mass (LV-EDMI) (P=0.003) and the extent of late gadolinium enhancement (LGE %) (P=0.03) remained significantly correlated with EAT in multivariate analysis.

***Conclusions:*** The amount and the determinants of EAT differ according to the LVEF in patients with CAD. Thus, different amounts of EAT reflect different stages of CAD underlining the complex interaction of EAT in the pathogenesis and progression of ischemic cardiomyopathy. (*Circ J* 2012; **76:** 2426–2434)

**Key Words:** Cardiac magnetic resonance imaging; Coronary artery disease; Determinants; Epicardial adipose tissue

Epicardial adipose tissue (EAT) is the true visceral fat deposited around the heart. It is located subepicardially around both ventricles of the heart with variable extent and distribution patterns.[1–3] Due to its proximity to coronary arteries and the myocardium, a relationship between EAT and pathological conditions of the heart has been suggested.[4,5] In obese subjects, increased epicardial fat thickness has been related to increased left ventricular (LV) mass, impaired diastolic filling and enlarged atria.[6] Additionally, recent studies have shown[7–9] that EAT produces various pro-inflammatory and pro-atherogenic cytokines and has therefore been suspected to be implicated in the pathogenesis of coronary atherosclerosis. In this context, increased EAT has been associated with the presence and extent of coronary artery disease (CAD) and coronary artery calcium[10–15] however without further stratifying patients according to LV function (LVEF). However, LVEF impairment is a well established prognostic predictor for the clinical outcome of patients with CAD.[16–18] In prior studies of our group, we found significantly decreased amounts of EAT in patients with impaired LVEF due to ischemic or non-ischemic cardiomyopathy in comparison to healthy controls,[19] suggesting a complex interaction of EAT and CAD.

Editorial p2333

To date, there are limited data regarding the association of EAT with functional and morphological cardiac magnetic resonance imaging (CMR) parameters as well as clinical variables in patients with CAD. Moreover, the identification of the determinants of EAT in different stages of CAD with regard to LVEF are of great interest because they could promote our understanding of the role of EAT in the pathogenesis of ischemic heart disease.

The aim of the study was to assess the amount and determinants of EAT in the whole spectrum of patients with CAD using CMR. Thus, subgroup analysis was performed with regard to

Received March 12, 2012; revised manuscript received May 14, 2012; accepted June 8, 2012; released online July 13, 2012 Time for primary review: 22 days

1st Department of Medicine (C.D., D.H., T.S., M.B., T.P.), Department of Clinical Radiology and Nuclear Medicine (S.O.S.), University Medical Centre Mannheim, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany
Mailing address: Christina Doesch, MD, 1st Department of Medicine, University Medical Centre Mannheim, Medical Faculty Mannheim, University of Heidelberg, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany. E-mail: Christina.Doesch@umm.de

ISSN-1346-9843 doi:10.1253/circj.CJ-12-0301

LVEF representing different stages of the disease. Additionally, the results were compared to age- and sex-matched healthy controls.

## Methods

### Study Population

One hundred and fifty-eight consecutive patients (126 males and 32 females; mean age, 64±10 years) who underwent cardiac catheterization at our hospital between January 2010 and January 2012 as part of a diagnostic evaluation for known or presumed CAD, having at least 1 stenosis ≥50% and no contraindications to CMR examination, were included in the study. Patients with valvular heart disease, patients with hypertrophic cardiomyopathy, patients with prior coronary artery bypass graft (CABG) as well as patients with severely impaired kidney function (GFR <30 ml · min$^{-1}$ · 1.73 m$^{-2}$) were excluded. In 5 patients, the CMR examination was discontinued due to claustrophobia.

Forty age- and sex-matched healthy subjects served as controls and satisfied the following criteria: normal physical examination, normal blood pressure (<130 mmHg and <85 mmHg), normal ECG findings, no history of chest pain or dyspnoea, no diabetes, no hyperlipidemia and normal 2D echocardiography and Doppler examination. None of the control subjects were on medication. Any potential subjects with evidence of heart disease, hypertension or other systemic disorders were excluded from the control group.

All patients and volunteers underwent CMR examination with identical protocols except for contrast agent administration being omitted in healthy controls. Informed consent for the CMR protocol was obtained from all subjects and the study was approved by the local ethics commission.

### Coronary Angiography and Image Interpretation

Coronary angiography was performed with a conventional angiography unit (Integris H; Philips Medical Systems). Coronary artery stenosis was imaged in the centre of the field from multiple projections, and the overlap of side branches and foreshortening of relevant coronary arteries was avoided as far as possible. The severity of coronary atherosclerotic lesions was evaluated from at least 3 projections in all the patients. All coronary angiograms were evaluated in consensus by 2 board-certified cardiologists with at least 5 years experience who were blinded to the patients' clinical information. CAD was angiographically defined as a diameter stenosis of ≥50%.

### MRI Image Acquisition

All studies were performed using a 1.5 Tesla whole-body imaging system (Magnetom Avanto, Siemens Healthcare Sector, Erlangen). A dedicated 4-element, phased-array cardiac coil was used. Images were acquired during repeated end-expiratory breath-holds. Scout images (coronal, sagittal, and axial planes) were obtained for planning of the final double-oblique long-axis and short-axis views. To evaluate functional parameters, electrocardiogram-gated cine images were then acquired using a segmented steady-state free precession [fast imaging with steady-state precession (true-FISP)] sequence (time to echo/time of repetition 1.6/3.2 ms, temporal resolution 35 ms, in-plane spatial resolution 1.4×1.8 mm, slice thickness 8 mm, interslice gap 2 mm). Seven to 12 short-axis views covering the whole left and right ventricle were obtained. For the assessment of the EAT, we used a dark blood prepared T1-weighted multislice turbo spin-echo pulse sequence with a water suppression prepulse to obtain a transversal 4-chamber view and short-axis images in the same orientations used for the cine short-axis images. Imaging parameters were as follows: time of repetition=800 ms, time to echo=24 ms, slice thickness=6 mm, interslice gap=2 mm, and field of view=30–34 cm.

Ten minutes after the injection of a gadolinium-based contrast agent (Magnevist; Bayer-Schering Pharma AG, Berlin, Germany), a segmented inversion recovery cine trueFISP pulse sequence (TI scout) acquisition was performed at a midventricular short-axis location. This acquisition was used to determine the TI at which the signal of normal myocardium is null for the subsequent late gadolinium enhancement (LGE) acquisition. After that, LGE images were acquired in the same orientation as the cine images using a 2D-segmented inversion recovery gradient-echo pulse sequence triggered to the end-diastole (repetition time/echo time=9.6/4.4 ms, flip angle 25°, matrix 208×256 and a typical voxel size of 1.6×1.3×5.0). LGE was only considered to be present if it was also present in the same slice after swapping phase encoding, thus excluding artifacts.

### Image Analysis and Determination of Ventricular Parameters

Image analysis and quantitative analysis were performed offline using dedicated software (ARGUS, Siemens). Each study was examined for abnormalities in the morphology of the right and left ventricle. End-diastolic and end-systolic volumes and LV mass was analysed with the serial short-axis trueFISP cine loops, using manual segmentation. The LV end systolic and end diastolic volume index (LV-ESVI, LV-EDVI) were calculated as LV end systolic (LV-ESV) and LV end diastolic volume (LV-EDV) divided by the body surface area. Stroke volumes and ejection fractions were calculated. The LV remodelling index (LVRI) was determined as the ratio of LV mass (LV-EDMI) to LV end-diastolic volume (LV-EDV).[20]

Additionally, left and right ventricular diameters were measured. On the 4-chamber view, the distance between the cutting edge of the tricuspid annulus with the RV free wall and the RV apex was measured in end-diastole (end-diastolic length, EDL, mm) and end-systole (ESL, mm), and the right ventricular fractional shortening (RVFS) was calculated as follows: RVFS (%)=[(EDL–ESL)/EDL)*100].[21]

### Volumetric Assessment of the Absolute Mass of EAT

For EAT mass determination, the area subtended by the manual tracings was determined on a consecutive end-diastolic short axis slice beginning with the most basal slice at the level of the mitral valve and moving apically through the stack until the most inferior margin of EAT was traced. The amount of EAT was calculated by using the modified Simpson's rule with integration over the image slices.[22] The contours of EAT were outlined manually at end-diastole in the short-axis views covering the entire left and right ventricle. For EAT mass determination, the area subtended by the manual tracings was determined in each slice and multiplied by the slice thickness to yield the fat volume. Total EAT volume was obtained after the data summation of all slices. To obtain EAT mass, the volume of EAT was multiplied by the specific weight of fat (0.92 g/cm$^3$).[22] The observer was blinded to patient details.

### Determination of the Extent of LGE%

In the present study, the extent of LGE%, expressed as the percentage of the myocardial mass, was quantified using the visual segmentation score described by Comte et al.[23] With respect to the AHA recommendations,[24] the myocardium was divided into 17 segments. A score ranging from 0 to 4 was

**Table 1. Demographic and Baseline Characteristics**

| | Patients with CAD | | All patients with CAD (n=158) | Healthy controls (n=40) | P value† |
|---|---|---|---|---|---|
| | LVEF ≥50% (n=44) | LVEF <50% (n=114) | | | |
| **Age (years)** | 64±10 | 64±10 | 64±10 | 61±11 | 0.2 |
| **Male sex, n (%)** | 35 (80) | 91 (80) | 126 (80) | 32 (80) | 0.9 |
| **Body weight (kg)** | 79±15 | 80±15 | 79±15 | 78±14 | 0.2 |
| **BMI (kg/m²)** | 26.6±4.4 | 26.9±4.6 | 26.7±4.5 | 26.0±5.9 | 0.3 |
| **Medical history, n (%)** | | | | | |
| Hypertension | 44 (100) | 113 (99) | 157 (99) | 0 (0) | – |
| Diabetes mellitus | 7 (16) | 44 (39) | 51 (32) | 0 (0) | – |
| Dyslipidemia | 42 (95) | 98 (86) | 140 (89) | 0 (0) | – |
| Current smoker | 8 (18) | 39 (34) | 47 (30) | 0 (0) | – |
| Family history of CAD | 8 (18) | 53 (46) | 61 (39) | 0 (0) | – |
| **NYHA class, n (%)** | | | | | |
| I | 41 (93) | 8 (7) | 49 (31) | 0 (0) | – |
| II | 3 (7) | 35 (31) | 38 (24) | 0 (0) | – |
| III | 0 (0) | 55 (48) | 55 (35) | 0 (0) | – |
| IV | 0 (0) | 16 (14) | 16 (10) | 0 (0) | – |
| **Vessel disease** | | | | | |
| 1 | 18 (41) | 27 (24) | 45 (28) | 0 (0) | – |
| 2 | 14 (32) | 45 (39) | 59 (37) | 0 (0) | – |
| 3 | 12 (27) | 42 (37) | 54 (34) | 0 (0) | – |
| **Atrial fibrillation, n (%)** | 1 (2) | 38 (33) | 39 (25) | 0 (0) | – |
| **Medication, n (%)** | | | | | |
| Aspirin | 44 (100) | 82 (74) | 126 (80) | 0 (0) | – |
| Marcumar | 2 (5) | 34 (30) | 36 (23) | 0 (0) | – |
| β-blocker | 42 (95) | 109 (96) | 151 (96) | 0 (0) | – |
| ACE inhibitors/ ARBs | 42 (95) | 110 (96) | 152 (96) | 0 (0) | – |
| CCBs | 3 (7) | 11 (10) | 14 (9) | 0 (0) | – |
| Diuretics | 4 (9) | 88 (77) | 92 (58) | 0 (0) | – |
| Statins | 42 (95) | 107 (94) | 149 (94) | 0 (0) | – |
| Insulin | 3 (7) | 23 (20) | 26 (16) | 0 (0) | – |
| Glucose-lowering drugs | 4 (9) | 21 (18) | 25 (16) | 0 (0) | – |

†P-value comparing all patients with CAD and healthy controls.
ACE, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCB, calcium channel blocker; LVEF, left ventricular systolic function; n, number; NYHA, New York Heart Association functional class; kg, kilogram.

visually attributed to each of the 17 segments according to the transmurality extent of the hyperenhancement: score 0=0%, 1=0–25%, 2=26–50%, 3=51–75%, 4=76–100%. All 17 scores were summed and global infarct size was expressed as a percentage of the maximum possible score of 68.

### Statistical Analysis

Body mass index (BMI) was calculated by using the common formula: BMI ($kg/m^2$) = weight (kg)/height $(m)^2$. Body surface area (BSA) was assessed by using a variation of the DuBois formula: BSA ($m^2$) = [weight $(kg)^{0.425}$*height $(cm)^{0.725}$]*0.007184.[25]

The Kolmogorow-Smirnow test was used to test for normality. Continuous variables were presented as mean±standard deviation (SD) and compared using the unpaired, 2-tailed Student's t-test or the Mann-Whitney U test, when appropriate. Categorical variables were summarized as number (n) and percentages (%) and compared using the Chi-squared or Fisher's exact test. A P value <0.05 was considered statistically significant.

The matching technique applied in this study to select the healthy controls was based on the variables of age and sex and matched the controls with the cases.[26]

The relationship between subject characteristics (age, gender, BMI), symptoms (New York Heart Association functional class [NYHA] I–IV), cardiovascular risk factors (arterial hypertension, diabetes mellitus, hyperlipidemia, current smoker, positive family history of CAD), atrial fibrillation and CMR parameters (LVEF, indexed LV-EDMI, LV-EDVI, LV-ESVI, LV-EDD, LVRI, RV-FS, RV-EDD, RAD, extent LGE) to indexed EAT mass was assessed in all CAD patients and in CAD patients with a preserved LVEF ≥50% and a LVEF <50%[27,28] using linear regression analysis.

Multivariate regression analyses were performed to test the independent association between variables with a P value <0.05 in univariate analysis and indexed EAT mass.

Analysis was performed using SPSS statistical software (version 14.0, SPSS Inc, Chicago, IL, USA).

## Results

### Patient Characteristics

Patients' baseline demographic and clinical characteristics are shown in Table 1. Our patient cohort consisted of 158 patients

**Table 2. Cardiac Magnetic Resonance Characteristics**

| | Patients with CAD | | All patients with CAD (n=158) | Healthy controls (n=40) | P value† |
|---|---|---|---|---|---|
| | LVEF ≥50% (n=44) | LVEF <50% (n=114) | | | |
| LVEF (%) | 60±6 | 30±11 | 38±17 | 59±6 | <0.0001 |
| LV-EDMI (g/m²) | 67±16 | 95±26 | 87±27 | 67±14 | <0.0001 |
| LV-EDVI (ml/m²) | 70±19 | 125±40 | 110±43 | 72±13 | <0.0001 |
| LV-ESVI (ml/m²) | 29±10 | 91±38 | 74±43 | 30±8 | <0.0001 |
| LV-EDD (mm) | 52±7 | 64±10 | 60±10 | 51±5 | <0.0001 |
| LVRI (g/ml) | 1.0±0.2 | 0.8±0.2 | 0.8±0.2 | 1.0±0.3 | <0.0001 |
| RV-FS (%) | 32±5 | 27±8 | 29±8 | 32±7 | 0.002 |
| RV-EDD (ml) | 42±7 | 42±7 | 42±7 | 43±6 | 0.6 |
| RAD (mm) | 45±8 | 46±7 | 45±8 | 44±6 | 0.4 |
| LGE% of LV mass | 6±10 | 43±20 | 33±24 | – | – |
| Indexed EAT mass (g/m²) | 36±11 | 26±8 | 29±10 | 31±8 | <0.0001 |
| EAT/EDM-ratio | 0.6±0.2 | 0.3±0.1 | 0.4±0.2 | 0.5±0.1 | <0.0001 |
| EAT/EDV-ratio | 0.6±0.2 | 0.2±0.1 | 0.3±0.2 | 0.5±0.2 | <0.0001 |

†P-value comparing all patients with CAD and healthy controls.
EAT, epicardial adipose tissue; LGE, late gadolinium enhancement; LV, left ventricular; LV-EDD, left ventricular end diastolic diameter; LV-EDMI, indexed left ventricular end diastolic mass; LV-EDVI, indexed left ventricular end diastolic volume; LVEF, left ventricular systolic function; LV-ESVI, indexed left ventricular end systolic volume; LVRI, left ventricular remodelling index; RAD, right atrial dimension; RV-EDD, right ventricular end diastolic diameter; RV-FS, right ventricular fraction shortening.

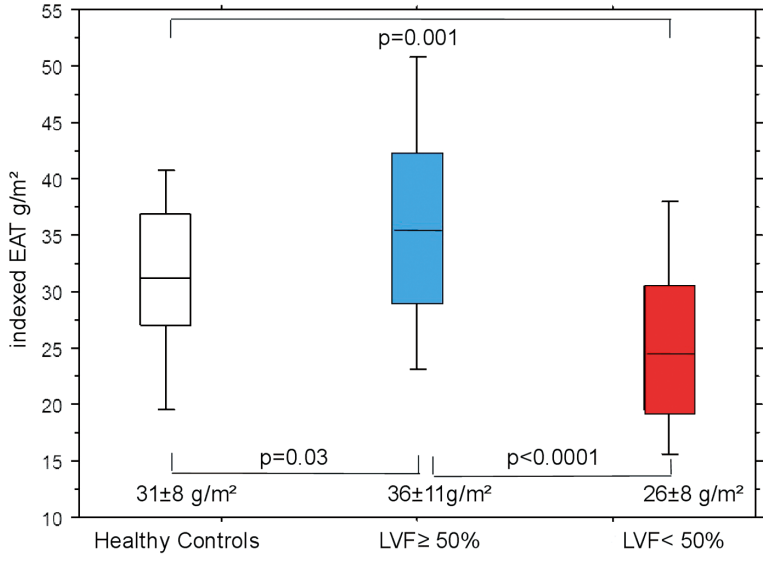


**Figure 1.** Relationship of indexed EAT and LVEF. A box-plot of EAT according to LVEF in patients with CAD and healthy controls. Patients with CAD and a LVEF of ≥50% (blue boxplot) had more indexed EAT mass compared to healthy controls (white boxplot) and CAD patients with an impaired LVEF (red boxplot) who revealed the smallest indexed EAT mass. CAD, coronary artery disease; EAT, epicardial adipose tissue; LVEF, left ventricular fraction.

with CAD [thereof 126 men (80%)] with a mean age of 64±10 years and 40 sex- and age-matched healthy controls (61±11 years). A subgroup analysis of patients was performed after dividing patients into 2 groups: patients with LVEF ≥50% and patients with LVEF <50%. The baseline characteristics of these subgroups are presented in Table 1. There were no significant differences regarding body weight, BMI and BSA between patients with CAD and healthy controls, as well as within the subgroups. However, in patients with CAD and a LVEF <50%, the presence of diabetes mellitus, hyperlipidemia, current smoking, a positive family history of CAD and 3-vessel disease was significantly more prevalent compared to patients with CAD and preserved LVEF. The severity of symptoms at admission was assessed by using the NYHA classification.

## CMR Parameters

The CMR characteristics of all CAD patients, subgroups and healthy controls are summarized in Table 2. In 44 (28%) patients, LVEF was preserved (≥50%), whereas 114 (72%) patients showed a reduced LVEF (<50%). In patients with CAD and reduced LVEF, LV-EDMI (P<0.0001), LV-EDVI (P<0.0001), LV-ESVI (P<0.0001), extent LGE% (P<0.0001) were significantly increased compared to CAD patients with a preserved LVEF. The RV-FS (P=0.0004), LVRI (P<0.0001) and the EAT/EDM-ratio (P<0.0001) were significantly reduced compared to CAD patients with a preserved LVEF.

## Relationship of Indexed EAT Mass to LV Function and Clinical Presentation

The indexed EAT mass ranged from 11 g/m² to 68 g/m² with a

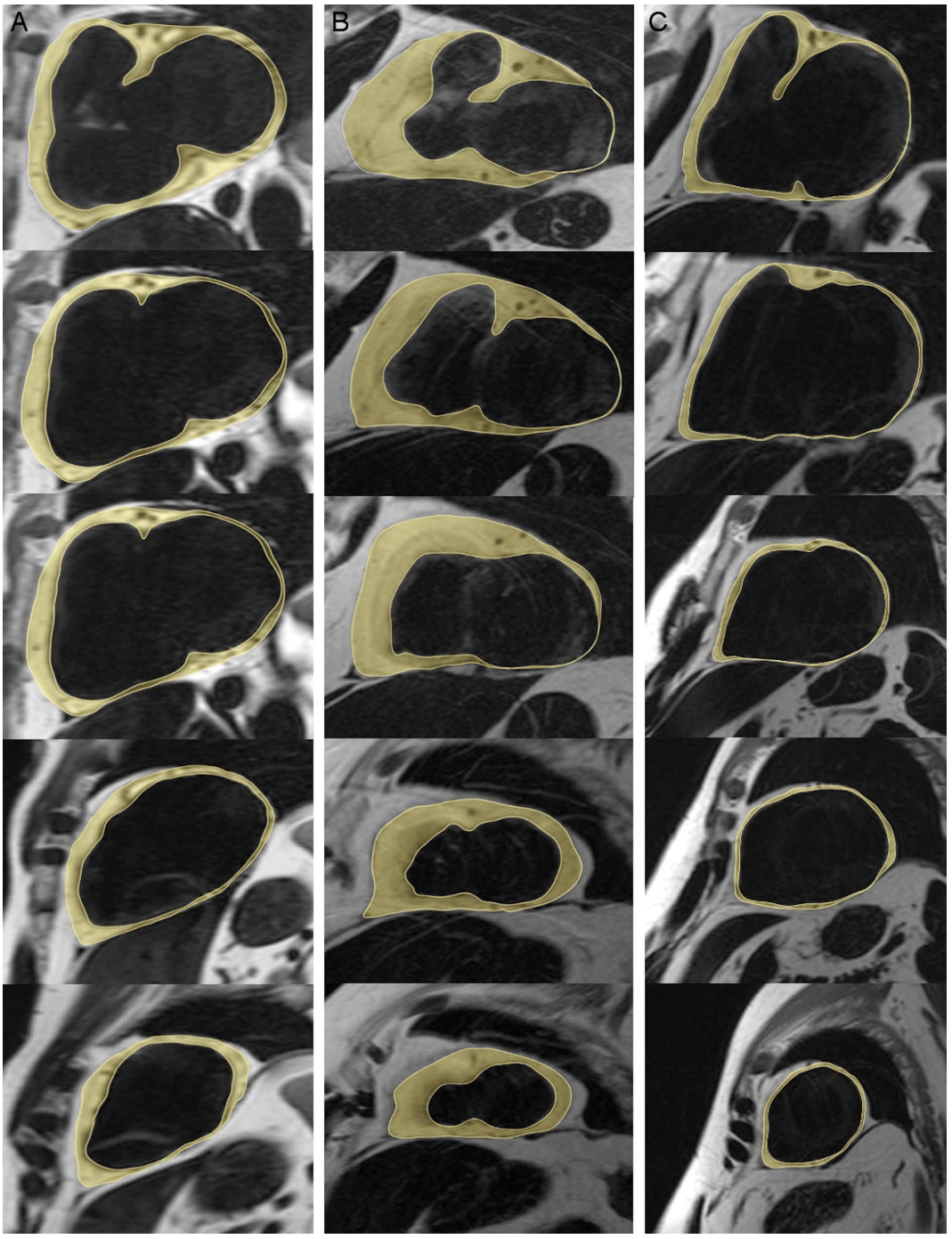


**Figure 2.** Examples of patients with different EAT masses. Patient examples to illustrate the differences in indexed EAT mass between healthy Controls (**A**), patients with CAD and a LVEF ≥50% (**B**) having significantly more indexed EAT mass than healthy controls, and patients with impaired LVEF and patients with CAD and a LVEF <50% (**C**) having significantly less EAT than healthy controls and CAD patients with a LVEF ≥50%. CAD, coronary artery disease; EAT, epicardial adipose tissue; LVEF, left ventricular function.

mean of 29±10 g/m$^2$ in the whole CAD patient cohort compared to an indexed EAT range of 16 g/m$^2$ to 56 g/m$^2$ with a mean of 31±8 g/m$^2$ (P<0.0001) in healthy controls. However, subgroup analysis with regard to LVEF showed that in patients with CAD and preserved LVEF (≥50%), the indexed EAT mass was significantly elevated compared to healthy controls (36±11 g/m$^2$ vs. 31±8 g/m$^2$, P=0.03) and CAD patients with impaired LVEF (<50%) 26±8 g/m$^2$ (P<0.0001) (**Table 2**; **Figure 1**). **Figure 2** shows patient examples illustrating these differences in indexed EAT mass in the different subgroups.

**Table 3. Correlation of Patient Characteristics and CMR Parameters With Indexed EAT**

| | Patients with CAD | | | | All patients with CAD (n=158) | |
|---|---|---|---|---|---|---|
| | LVEF ≥50% (n=44) | | LVEF <50% (n=114) | | | |
| | r/z | P value | r/z | P value | r/z | P value |
| Age | 0.032 | 0.9 | 0.047 | 0.6 | 0.07 | 0.4 |
| Male sex | –1.004 | 0.3 | –0.897 | 0.4 | –0.265 | 0.8 |
| BMI (kg/m$^2$) | 0.357 | 0.02 | 0.116 | 0.2 | 0.185 | 0.02 |
| Hypertension | – | – | –0.414 | 0.7 | –0.033 | 0.9 |
| Diabetes mellitus | –0.684 | 0.5 | –0.728 | 0.5 | –1.718 | 0.09 |
| Dyslipidemia | –0.451 | 0.7 | –0.596 | 0.6 | –0.036 | 0.9 |
| Current smoker | –0.289 | 0.8 | –0.254 | 0.8 | –0.884 | 0.4 |
| Family history of CAD | –0.289 | 0.8 | –1.917 | 0.06 | –0.139 | 0.9 |
| NYHA class I | –0.512 | 0.6 | –0.987 | 0.3 | –4.909 | <0.0001 |
| NYHA class II | –0.512 | 0.6 | –0.427 | 0.7 | –0.899 | 0.4 |
| NYHA class III | – | – | –0.870 | 0.4 | –3.210 | 0.001 |
| NYHA class IV | – | – | –0.049 | 0.9 | –1.032 | 0.3 |
| Atrial fibrillation | –0.709 | 0.5 | –0.018 | 0.9 | –2.072 | 0.04 |
| LVEF | 0.137 | 0.4 | 0.171 | 0.07 | 0.574 | <0.0001 |
| LV-EDMI | 0.305 | 0.04 | 0.336 | 0.0003 | 0.019 | 0.8 |
| LV-EDVI | 0.043 | 0.8 | 0.201 | 0.03 | 0.160 | 0.04 |
| LV-ESVI | 0.056 | 0.7 | 0.089 | 0.4 | 0.262 | 0.001 |
| LV-EDD | 0.011 | 0.9 | 0.076 | 0.4 | 0.272 | 0.001 |
| LVRI | 0.202 | 0.2 | 0.137 | 0.2 | 0.344 | <0.0001 |
| RV-FS | 0.046 | 0.8 | 0.085 | 0.4 | 0.089 | 0.3 |
| RV-EDD | 0.110 | 0.5 | 0.075 | 0.4 | 0.023 | 0.8 |
| RAD | 0.017 | 0.9 | 0.017 | 0.9 | 0.024 | 0.8 |
| Extent of LGE% | 0.047 | 0.8 | 0.229 | 0.01 | 0.435 | <0.0001 |

CMR, cardiac magnetic resonance imaging. Other abbreviations as in Tables 1,2.

With regard to clinical presentation, patients with no or only mild symptoms of dyspnoea NYHA class I/II had significantly more indexed EAT (31±7 g/m$^2$) than patients with progressive dyspnoea NYHA class III/IV (25±9 g/m$^2$, P=0.0003).

### Determinants of Indexed EAT

By using univariate regression analysis, an increasing indexed EAT mass in all 158 CAD patients correlated with increasing BMI (P=0.02) and NYHA I (P<0.0001). With decreasing EAT mass, there was a significant correlation with the presence of atrial fibrillation (P=0.04), NYHA III (P=0.001), decreasing LVEF (P<0.0001), higher LV-EDVIs (P=0.04), higher LV-ESVIs (P=0.001) as well as extended LV-EDDs (P=0.001), lower LVRIs (P<0.0001) and a higher extent of LGE% (P<0.0001) (Table 3). In a multivariate regression model including LVEF, BMI, NYHA class I and III, atrial fibrillation, LV-EDVI, LV-ESVI, LV-EDD, LVRI and extent of LGE%, the best correlates to indexed EAT mass were the independent variables of LVEF (HR 0.478, 95% CI 0.280–0.675, P<0.0001), BMI (HR 0.528, 95% CI 0.217–0.840, P=0.001), LV-ESVI (HR 0.148, 95% CI 0.083–0.213, P<0.0001) and LV-EDD (HR –0.238, 95% CI –0.408 to –0.068, P=0.01).

A subgroup analysis of patients was performed after dividing patients into 2 groups: CAD patients with a LVEF ≥50% and patients with a LVEF <50%. In patients with CAD and preserved LVEF (≥50%), an increasing indexed EAT mass was related to an increasing BMI (P=0.03, Figure 3A-1) and an increasing LV-EDMI (P=0.04, Figure 3A-2). Multivariate regression analysis showed that only BMI (HR 0.712, 95% CI 0.023–1.402, P=0.04) was independently associated with EAT mass. In the 114 CAD patients with reduced LVEF (<50%), decreasing indexed EAT mass was associated with an increasing extent of LGE% (P=0.01, Figure 3B-2), whereas an increasing indexed EAT was related to a higher LV-EDMI (P=0.0003, Figure 3B-1) and an elevated LV-EDVI (P=0.03, Table 3). Interestingly, in contrast to CAD patients with preserved LVEF, those with reduced LVEF did not show a significant correlation between BMI and indexed EAT mass (P=0.2). In multivariate regression analysis including LV-EDMI, extent LGE% and LV-EDVI, the strongest correlation with indexed EAT in patients with a LVEF <50%, was revealed by LV-EDMI (HR 0.105, 95% CI 0.022–0.189, P=0.01) and extent LGE% (HR –0.096, 95% CI –0.172 to –0.020, P=0.01).

## Discussion

The main findings of the present study are: (1) the amount of EAT differs according to the LVEF in patients with CAD. Patients with CAD and preserved LVEF reveal significantly more EAT than healthy controls and patients with reduced LVEF; (2) the determinants of EAT are also different with regards to LV function. In the whole study cohort of 158 CAD patients, the EAT mass correlated with BMI, atrial fibrillation, NYHA class, LVEF, the extent of LGE% and CMR parameters of LV dilatation and remodelling. Of these parameters BMI, LVEF, LV-ESVI and LV-EDD remained independently associated with EAT in multivariable analysis. In patients with CAD and a preserved LVEF, BMI was the only independent correlate of EAT, whereas in patients with reduced LVEF, LV-EDMI and the extent of LGE% were independent determinants of EAT.

In the development of CAD, an ambiguous role that is both

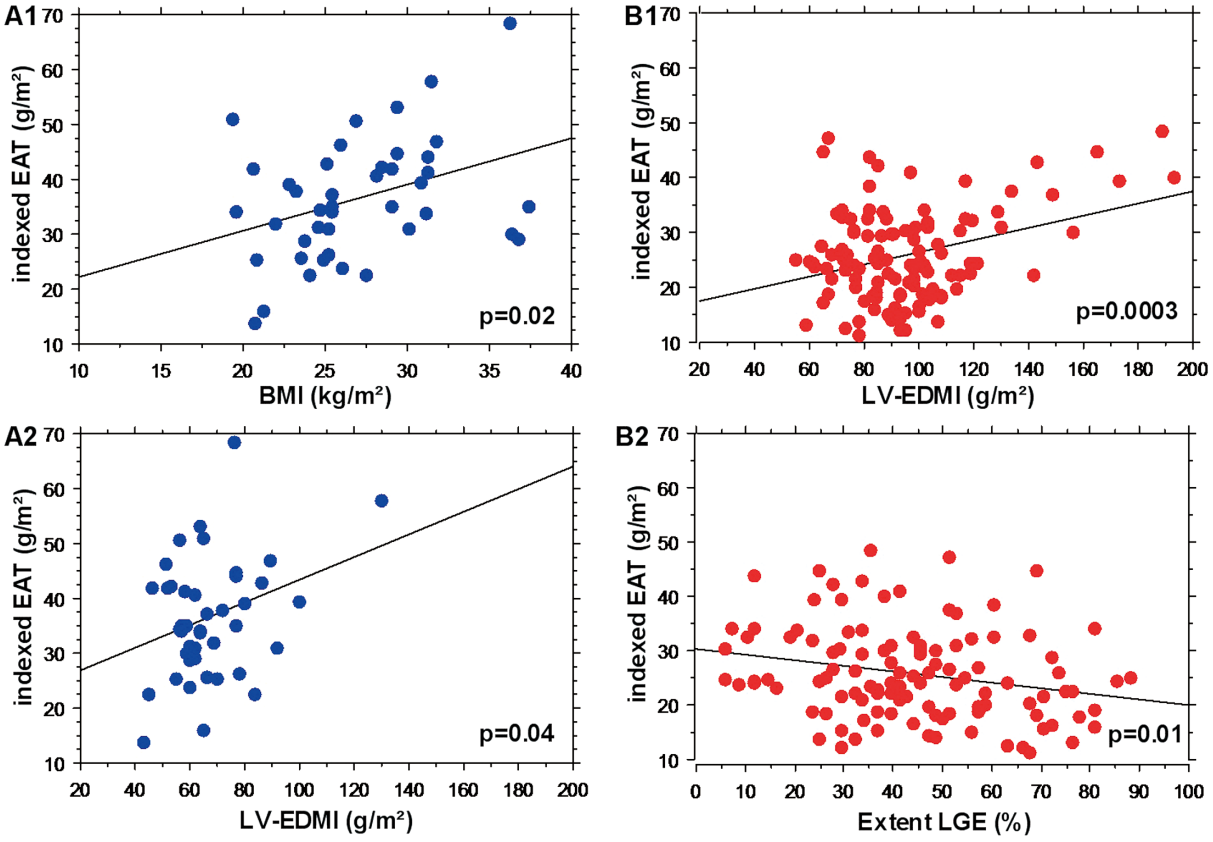


**Figure 3.** Determinants of indexed EAT mass in patients with CAD and (**A**) a LVEF of ≥50%. Correlation between indexed EAT and BMI (**A-1**) as well as LV-EDMI (**A-2**) in CAD patients with preserved LVEF (≥50%) (blue dots); and (**B**) a LVEF <50%. A correlation between indexed EAT mass and LV-EDMI (**B-1**) as well as with extent LGE% (**B-2**) in CAD patients with reduced LVEF (<50%) (red dots). BMI, body mass index; CAD, coronary artery disease; EAT, epicardial adipose tissue; LGE%, extent of late gadolinium enhancement expressed as a percentage of LV mass; LV-EDMI, left ventricular end diastolic mass index; LVEF; left ventricular function.

unfavourable and protective has been attributed to EAT.[29] The pro-inflammatory mediators are supposed to contribute to the atherosclerotic process and the development of CAD.[7,30–33] Prior studies using computed tomography (CT) have shown an association between increased amount of EAT and the presence and extent of CAD.[10,15,30,34–38] However, in these studies, the role of LV function was not taken into account. Thus, there are scarce data about the association between EAT, cardiac function and morphology. A decreased amount of EAT in patients with congestive heart failure was for the first time described in a post mortem study by Schejbal.[2] Additionally, in previous studies by our group[19,39] using CMR, we could show that patients with severely reduced LVEF (≤35%) due to ischemic or dilated cardiomyopathy revealed significantly reduced amounts of EAT compared to healthy controls. Furthermore, a more recent study by Khawaja et al[40] involving 381 consecutive patients undergoing non-invasive assessment of cardiac perfusion to rule out significant CAD using CT, showed that patients with a LVEF <55% have decreased EAT volume compared to patients with normal LVEF. This study cohort was also not homogeneous regarding the aetiology of the LV dysfunction, because only 40% of the patients with a LVEF <55% had an ischemic heart disease. Besides, the results were not compared to healthy controls.

To the best of our knowledge, the results of the present study show for the first time, that the amount of EAT differs according to the cardiac function in a study population consisting only of patients with CAD. We included the whole spectrum of CAD patients from normal to those with severely impaired LVEF and compared these results to age- and sex-matched healthy controls. Thus, it is not possible to directly compare our results to the previous studies that focused mainly on the relationship between EAT mass and CAD extent[10,13,30,34,35,37,41,42] or which consisted of different study populations.[2,19,39,40] Our present study findings showed that with decreasing LVEF, there was a linear decrease of the EAT mass in patients with CAD. Interestingly, patients with CAD and preserved LVEF revealed even more EAT than healthy controls, indicating that different amounts of EAT reflect different stages of CAD. We assume that these different EAT amounts are due to an imbalance of its favorable and unfavorable effects in the different stages of CAD. At the beginning of the disease process, the increased EAT mass might cause an excessive production of inflammatory adipokines and cytokines predisposing to the progression of atherosclerosis and the development of CAD.[7,30–33] As soon as CAD patients develop ischemic cardiomyopathy, the EAT mass decreases successively. We hypothesize that at this stage of the disease, the loss of the favorable effects of EAT acting

as a local energy source for cardiac muscle in times of high demand,[43,44] protecting the heart from fatty acid-induced cardiotoxicity through its capacity to quickly incorporate fatty acids,[44,45] and producing vasoprotective adipokines such as adiponectin,[31] is preponderate. This might contribute to a vicious circle of accelerated maladaptive cardiac remodelling and progressive LV impairment.

Due to the different amounts of EAT in different stages of CAD, we analyzed the determinants of EAT in patients with CAD in the whole study population and with regard to LVEF. Looking at the whole study population, EAT correlated with various clinical and CMR parameters. Among other clinical findings, we observed a significant correlation between decreasing EAT and the occurrence of atrial fibrillation. This finding is in contrast to previous studies[46,47] that showed elevated amounts of EAT in patients with atrial fibrillation. However, the study population of these studies[46,47] consisted of patients with atrial fibrillation and mainly preserved LVEF. In contrast, our study population of patients with atrial fibrillation presented with a reduced LVEF. Therefore, we are of the opinion that due to the different study populations, the results cannot be compared. We believe that in our study the correlation between EAT and atrial fibrillation rather reflects the correlation between EAT and the impaired LVEF than the relationship between EAT and atrial fibrillation.

Subgroup analysis in CAD patients with preserved LVEF showed a significant linear correlation between increasing EAT mass and elevated BMI. This result is in line with previous studies,[48–50] which also reported a relationship between EAT and BMI. Besides, we found a significant correlation between increasing LV-EDMI in patients with CAD and a preserved LVEF (P=0.04) as well as in patients with CAD and a reduced LVEF (P<0.0001). This finding is in line with several former autopsy studies showing a significant correlation between EAT and heart weight[2,48,51] or myocardial weight,[52] and thus suggests a close link between LV hypertrophy and EAT. This link is further supported by an echocardiographic study by Iacobellis et al,[53] who reported a correlation between EAT thickness and LV mass. In a previous CMR study of our group[19] in patients with severely impaired LVEF due to dilatative or ischemic cardiomyopathy, we have found a constant and parallel increase of LV mass and EAT mass, but with a reduced EAT mass/LV-EDMI ratio compared to healthy controls. In this larger patient collective, we found in CAD patients with a preserved LVEF an EAT/EDM-ratio that was even slightly higher than that in healthy controls, indicating the excessive augmentation of the EAT mass. Similar to our prior findings[19] in CAD patients with a reduced LVEF <50%, the EAT/EDM-ratio was significantly reduced compared to patients with preserved LVEF and healthy controls. Although a causal effect of EAT on LV mass remains to be demonstrated, the close anatomical and functional relationship of EAT to the adjacent myocardium may allow due to a lack of fascia, local, paracrine interactions between these tissues.[4] Focusing on the extent of LGE%, we found a gradual declining indexed EAT mass with progressive LV fibrosis (P<0.0001). This correlation was statistically significant in the whole patient population as well as in patients with reduced LVEF. In the latter, the extent of LGE% proved to be an important determinant of indexed EAT in the multivariate regression model.

### Clinical Implications

Determination and quantification of EAT is feasible and easy to perform using conventional CMR imaging. The current study shows that EAT amounts differ significantly depending on the LVEF in patients with CAD. It seems to underlie a dynamic process presenting with increased EAT amounts in patients with CAD but still preserved LVEF, and with successively decreasing EAT as soon as CAD patients develop LV dysfunction. Therefore, EAT quantification could potentially add to the prognostic value of the already known CMR markers for risk stratification, such as LVEF or LGE in patients with CAD. However, there is a need for further prospective longitudinal studies to evaluate the dynamic course of EAT and its independent prognostic value in the pathogenesis of ischemic cardiomyopathy.

### Study Limitations

Unfortunately, because the observed data were not assessed longitudinally, but at a single time-point, we could not prove the dynamic process of "changing" EAT. Further studies to support this hypothesis are needed.

## Conclusion

The amount and the determinants of EAT differ according to the LVEF in patients with CAD. CAD patients with preserved LVEF showed the highest amount of EAT compared to healthy controls and CAD patients with reduced LVEF. In CAD patients with preserved LVEF, EAT only correlated with the BMI and the LV-EDMI. Patients with reduced LVEF revealed the lowest EAT mass, which was associated with the LV-EDMI and the extent of LGE%. Thus, different amounts of EAT reflect different stages of CAD, which underlines the complex interaction of EAT in the pathogenesis of ischemic cardiomyopathy.

## References


1. Nelson AJ, Worthley MI, Psaltis PJ, Carbone A, Dundon BK, Duncan RF, et al. Validation of cardiovascular magnetic resonance assessment of pericardial adipose tissue volume. *J Cardiovasc Magn Reson* 2009; **11:** 15.
2. Schejbal V. Epicardial fatty tissue of the right ventricle--morphology, morphometry and functional significance. *Pneumologie* 1989; **43:** 490–499.
3. Shirani J, Berezowski K, Roberts WC. Quantitative measurement of normal and excessive (cor adiposum) subepicardial adipose tissue, its clinical significance, and its effect on electrocardiographic QRS voltage. *Am J Cardiol* 1995; **76:** 414–418.
4. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: Anatomic, biomolecular and clinical relationships with the heart. *Nat Clin Pract Cardiovasc Med* 2005; **2:** 536–543.
5. Yudkin JS, Eringa E, Stehouwer CD. "Vasocrine" signalling from perivascular fat: A mechanism linking insulin resistance to vascular disease. *Lancet* 2005; **365:** 1817–1820.
6. Iacobellis G, Leonetti F, Singh N, Sharma AM. Relationship of epicardial adipose tissue with atrial dimensions and diastolic function in morbidly obese subjects. *Int J Cardiol* 2007; **115:** 272–273.
7. Mazurek T, Zhang L, Zalewski A, Mannion JD, Diehl JT, Arafat H, et al. Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation* 2003; **108:** 2460–2466.
8. Cheng KH, Chu CS, Lee KT, Lin TH, Hsieh CC, Chiu CC, et al. Adipocytokines and proinflammatory mediators from abdominal and epicardial adipose tissue in patients with coronary artery disease. *Int J Obes (Lond)* 2008; **32:** 268–274.
9. Fain JN, Sacks HS, Buehrer B, Bahouth SW, Garrett E, Wolf RY, et al. Identification of omentin mRNA in human epicardial adipose tissue: Comparison to omentin in subcutaneous, internal mammary artery periadventitial and visceral abdominal depots. *Int J Obes (Lond)* 2008; **32:** 810–815.
10. Bastarrika G, Broncano J, Schoepf UJ, Schwarz F, Lee YS, Abro JA, et al. Relationship between coronary artery disease and epicardial adipose tissue quantification at cardiac CT: Comparison between automatic volumetric measurement and manual bidimensional estimation. *Acad Radiol* 2010; **17:** 727–734.
11. de Vos AM, Prokop M, Roos CJ, Meijs MF, van der Schouw YT, Rutten A, et al. Peri-coronary epicardial adipose tissue is related to

cardiovascular risk factors and coronary artery calcification in postmenopausal women. *Eur Heart J* 2008; **29:** 777–783.
12. Gorter PM, de Vos AM, van der Graaf Y, Stella PR, Doevendans PA, Meijs MF, et al. Relation of epicardial and pericoronary fat to coronary atherosclerosis and coronary artery calcium in patients undergoing coronary angiography. *Am J Cardiol* 2008; **102:** 380–385.
13. Jeong JW, Jeong MH, Yun KH, Oh SK, Park EM, Kim YK, et al. Echocardiographic epicardial fat thickness and coronary artery disease. *Circ J* 2007; **71:** 536–539.
14. Pracon R, Kruk M, Kepka C, Pregowski J, Opolski MP, Dzielinska Z, et al. Epicardial adipose tissue radiodensity is independently related to coronary atherosclerosis: A multidetector computed tomography study. *Circ J* 2011; **75:** 391–397.
15. Ueno K, Anzai T, Jinzaki M, Yamada M, Jo Y, Maekawa Y, et al. Increased epicardial fat volume quantified by 64-multidetector computed tomography is associated with coronary atherosclerosis and totally occlusive lesions. *Circ J* 2009; **73:** 1927–1933.
16. van der Burg AE, Bax JJ, Boersma E, Pauwels EK, van der Wall EE, Schalij MJ. Impact of viability, ischemia, scar tissue, and revascularization on outcome after aborted sudden death. *Circulation* 2003; **108:** 1954–1959.
17. Nanthakumar K, Epstein AE, Kay GN, Plumb VJ, Lee DS. Prophylactic implantable cardioverter-defibrillator therapy in patients with left ventricular systolic dysfunction: A pooled analysis of 10 primary prevention trials. *J Am Coll Cardiol* 2004; **44:** 2166–2172.
18. Min JK, Lin FY, Dunning AM, Delago A, Egan J, Shaw LJ, et al. Incremental prognostic significance of left ventricular dysfunction to coronary artery disease detection by 64-detector row coronary computed tomographic angiography for the prediction of all-cause mortality: Results from a two-centre study of 5330 patients. *Eur Heart J* 2010; **31:** 1212–1219.
19. Doesch C, Haghi D, Fluchter S, Suselbeck T, Schoenberg SO, Michaely H, et al. Epicardial adipose tissue in patients with heart failure. *J Cardiovasc Magn Reson* 2010; **12:** 40.
20. De Castro S, Caselli S, Maron M, Pelliccia A, Cavarretta E, Maddukuri P, et al. Left ventricular remodelling index (LVRI) in various pathophysiological conditions: A real-time three-dimensional echocardiographic study. *Heart* 2007; **93:** 205–209.
21. Nijveldt R, Germans T, McCann GP, Beek AM, van Rossum AC. Semi-quantitative assessment of right ventricular function in comparison to a 3D volumetric approach: A cardiovascular magnetic resonance study. *Eur Radiol* 2008; **18:** 2399–2405.
22. Flüchter S, Haghi D, Dinter D, Heberlein W, Kühl HP, Neff W, et al. Volumetric assessment of epicardial adipose tissue with cardiovascular magnetic resonance imaging. *Obesity (Silver Spring)* 2007; **15:** 870–878.
23. Comte A, Lalande A, Walker PM, Cochet A, Legrand L, Cottin Y, et al. Visual estimation of the global myocardial extent of hyperenhancement on delayed contrast-enhanced MRI. *Eur Radiol* 2004; **14:** 2182–2187.
24. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al; American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002; **105:** 539–542.
25. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **1:** 307–310.
26. Dunlay SM, Weston SA, Jacobsen SJ, Roger VL. Risk factors for heart failure: A population-based case-control study. *Am J Med* 2009; **122:** 1023–1028.
27. Meta-analysis Global Group in Chronic Heast Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: An individual patient data meta-analysis. *Eur Heart J* 2011 August 6 [Epub ahead of print].
28. Kusunose K, Yamada H, Nishio S, Tomita N, Niki T, Yamaguchi K, et al. Clinical utility of single-beat E/e' obtained by simultaneous recording of flow and tissue Doppler velocities in atrial fibrillation with preserved systolic function. *JACC Cardiovasc Imaging* 2009; **2:** 1147–1156.
29. Iacobellis G, Barbaro G. The double role of epicardial adipose tissue as pro- and anti-inflammatory organ. *Horm Metab Res* 2008; **40:** 442–445.
30. Alexopoulos N, McLean DS, Janik M, Arepalli CD, Stillman AE, Raggi P. Epicardial adipose tissue and coronary artery plaque characteristics. *Atherosclerosis* 2010; **210:** 150–154.
31. Iacobellis G, Pistilli D, Gucciardo M, Leonetti F, Miraldi F, Brancaccio G, et al. Adiponectin expression in human epicardial adipose tissue in vivo is lower in patients with coronary artery disease. *Cytokine* 2005; **29:** 251–255.
32. Baker AR, Silva NF, Quinn DW, Harte AL, Pagano D, Bonser RS, et al. Human epicardial adipose tissue expresses a pathogenic profile of adipocytokines in patients with cardiovascular disease. *Cardiovasc Diabetol* 2006; **5:** 1.
33. Chaowalit N, Somers VK, Pellikka PA, Rihal CS, Lopez-Jimenez F. Subepicardial adipose tissue and the presence and severity of coronary artery disease. *Atherosclerosis* 2006; **186:** 354–359.
34. Wang TD, Lee WJ, Shih FY, Huang CH, Chen WJ, Lee YT, et al. Association of epicardial adipose tissue with coronary atherosclerosis is region-specific and independent of conventional risk factors and intra-abdominal adiposity. *Atherosclerosis* 2010; **213:** 279–287.
35. Oka T, Yamamoto H, Ohashi N, Kitagawa T, Kunita E, Utsunomiya H, et al. Association between epicardial adipose tissue volume and characteristics of non-calcified plaques assessed by coronary computed tomographic angiography. *Int J Cardiol* 2011 May 11 [Epub ahead of print].
36. Bettencourt N, Toschke AM, Leite D, Rocha J, Carvalho M, Sampaio F, et al. Epicardial adipose tissue is an independent predictor of coronary atherosclerotic burden. *Int J Cardiol* 2012; **158:** 26–32.
37. Djaberi R, Schuijf JD, van Werkhoven JM, Nucifora G, Jukema JW, Bax JJ. Relation of epicardial adipose tissue to coronary atherosclerosis. *Am J Cardiol* 2008; **102:** 1602–1607.
38. Iwasaki K, Matsumoto T, Aono H, Furukawa H, Samukawa M. Relationship between epicardial fat measured by 64-multidetector computed tomography and coronary artery disease. *Clin Cardiol* 2011; **34:** 166–171.
39. Doesch C, Suselbeck T, Leweling H, Fluechter S, Haghi D, Schoenberg SO, et al. Bioimpedance analysis parameters and epicardial adipose tissue assessed by cardiac magnetic resonance imaging in patients with heart failure. *Obesity (Silver Spring)* 2010; **18:** 2326–2332.
40. Khawaja T, Greer C, Chokshi A, Chavarria N, Thadani S, Jones M, et al. Epicardial fat volume in patients with left ventricular systolic dysfunction. *Am J Cardiol* 2011; **108:** 397–401.
41. Ahn SG, Lim HS, Joe DY, Kang SJ, Choi BJ, Choi SY, et al. Relationship of epicardial adipose tissue by echocardiography to coronary artery disease. *Heart* 2008; **94:** e7.
42. Sarin S, Wenger C, Marwaha A, Qureshi A, Go BD, Woomert CA, et al. Clinical significance of epicardial fat measured using cardiac multislice computed tomography. *Am J Cardiol* 2008; **102:** 767–771.
43. Marchington JM, Pond CM. Site-specific properties of pericardial and epicardial adipose tissue: The effects of insulin and high-fat feeding on lipogenesis and the incorporation of fatty acids in vitro. *Int J Obes* 1990; **14:** 1013–1022.
44. Marchington JM, Mattacks CA, Pond CM. Adipose tissue in the mammalian heart and pericardium: Structure, foetal development and biochemical properties. *Comp Biochem Physiol B* 1989; **94:** 225–232.
45. Pond CM, Mattacks CA. The effects of noradrenaline and insulin on lipolysis in adipocytes isolated from nine different adipose depots of guinea-pigs. *Int J Obes* 1991; **15:** 609–618.
46. Batal O, Schoenhagen P, Shao M, Ayyad AE, Van Wagoner DR, Halliburton SS, et al. Left atrial epicardial adiposity and atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010; **3:** 230–236.
47. Nagashima K, Okumura Y, Watanabe I, Nakai T, Ohkubo K, Kofune T, et al. Association between epicardial adipose tissue volumes on 3-dimensional reconstructed CT images and recurrence of atrial fibrillation after catheter ablation. *Circ J* 2011; **75:** 2559–2565.
48. Silaghi A, Piercecchi-Marti MD, Grino M, Leonetti G, Alessi MC, Clement K, et al. Epicardial adipose tissue extent: Relationship with age, body fat distribution, and coronaropathy. *Obesity (Silver Spring)* 2008; **16:** 2424–2430.
49. Iacobellis G, Assael F, Ribaudo MC, Zappaterreno A, Alessi G, Di Mario U, et al. Epicardial fat from echocardiography: A new method for visceral adipose tissue prediction. *Obes Res* 2003; **11:** 304–310.
50. Rabkin SW. Epicardial fat: Properties, function and relationship to obesity. *Obes Rev* 2007; **8:** 253–261.
51. Womack HC. The relationship between human body weight, subcutaneous fat, heart weight, and epicardial fat. *Hum Biol* 1983; **55:** 667–676.
52. Corradi D, Maestri R, Callegari S, Pastori P, Goldoni M, Luong TV, et al. The ventricular epicardial fat is related to the myocardial mass in normal, ischemic and hypertrophic hearts. *Cardiovasc Pathol* 2004; **13:** 313–316.
53. Iacobellis G, Ribaudo MC, Zappaterreno A, Iannucci CV, Leonetti F. Relation between epicardial adipose tissue and left ventricular mass. *Am J Cardiol* 2004; **94:** 1084–1087.