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Increased epicardial adipose tissue is associated with coronary artery disease and major adverse cardiovascular events

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ABSTRACT

Background: Increased-epicardial-adipose tissue (EAT) is associated with the presence and severity of subclinical-atherosclerosis. This study investigates the long-term clinical-outcome of subjects with and without increased-EAT. **Methods**: Two hundred and forty-five subjects, aged 61 ± 9 years and 34% women underwent clinically-indicated computed-tomography-angiography (CTA), and body-surface-area adjusted EAT was measured and were followed prospectively. CTA-diagnosed coronary-artery-disease (CAD) was defined as obstructive (luminal-stenosis ≥50%), non-obstructive (luminal-stenosis: 1–49%) and zero-obstruction. Major-adverse-cardiac-event (MACE) was defined as myocardial-infarction or cardiovascular-death. **Results**: EAT increased significantly from subjects with zero-obstruction-coronaries (93 ± 37 cm^3/m^2) to non-obstructive-CAD (132 ± 25 cm^3/m^2) to obstructive-CAD (145 ± 35 cm^3/m^2) ($P = 0.01$). During the 48-month follow-up, the event-rate was 8.6% (21). The event free survival-rate decreased significantly from 99% in the lowest-quartile to 86.6% in the highest-quartile of EAT. After adjustment for risk-factors, the hazard ratio of MACE was 1.4, 3.1 and 5.7 in lower mid-, upper mid- and highest-quartiles of EAT as compared to lowest-quartile of EAT ($P < 0.05$). **Conclusion**: Increased EAT is directly associated with CAD and predicts MACE independent of the age, gender and conventional-risk-factors.

1. Introduction

Increased regional fat distribution plays an important part in the development of an unfavorable metabolic and cardiovascular risk profile [1]. Epicardial adipose tissue (EAT) is associated with multiple markers of inflammation, vascular dysfunction and oxidative stress, atherosclerosis, the presence and extent of subclinical and clinical coronary atherosclerosis [2–4]. Furthermore EAT is associated with fatal and nonfatal coronary events in the general population independent of traditional cardiovascular risk factors [5,6]. This study investigates the long term clinical outcome of increased EAT measured by cardiac computed tomography (CT) in subjects without any prior documentation of coronary artery diseases (CAD), also compares the prognostic value of increased EAT and severity of CAD measured by CT over traditional risk factors measured as Framingham risk score (FRS) in predicting major adverse cardiovascular events (MACE).

2. Methods

Two hundred and forty five consecutive subjects with suspected CAD, aged 61 ± 9 years and 34% women, who underwent clinically indicated computed tomography angiography (CTA) in 2008–2009, were studied. After obtaining informed consent, the presence and severity of CAD as well as body surface area adjusted EAT was measured, and subjects were followed prospectively for median of 48-months. Subjects with irregular heart rates, allergies to contrast media, any prior documentation of CAD, liver disease, stroke, systemic inflammation, or impaired renal function were excluded. The study protocol and consent form were approved by the Institutional Review Board Committee at our institution.

2.1. Cardiac CTA

Beta blockers were administered for pulses greater than 65 bpm. A test IV bolus of 15 ml of contrast agent was followed by 20 ml of

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normal saline flush at a rate of 4.5 ml/s. Using a dual-head power injector (Stellant, Medrad, Indianola, PA), a prospective ECG gated cardiac CT angiography was performed with a tri-phasic consecutive injection sequence beginning with 50 ml nonionic IV contrast material (Iopamidol 370; Bracco Diagnostics, Plainsboro, NJ) injected at a rate of 5.0 ml followed by 50 ml of a mixture of 60% contrast and normal saline and ended with a 50-ml flush of normal saline. Contrast was injected through an 18- to 20-gauge angiocatheter in an antecubital vein. Mean heart rate during the scan was 56 ± 3 bpm.

2.2. Data acquisition

A snapshot pulse acquisitions axial ECG-Triggering mode with prospective gating using the 64- Multi-detector Computed Tomography (MDCT) Lightspeed VCT scanner (General Electric Healthcare Technologies, Milwaukee, WI) was used for all patients. Imaging was started 1 inch above the left main ostium and continued to 1 inch below the bottom of the heart. The following imaging and reconstruction parameters were applied: data acquisition collimation 0.625 mm × 64 = 4 cm; 120 kVp; 220–670 mAs; pitch 0.18–0.24 (depending on heart rate); rotation time 0.35 s; slice width 0.625 mm; matrix 512 × 512 and pixel size 0.39 mm^2. ECG-triggered dose modulation with padding was applied in each case with 400–600 mA in 70–80% R–R interval.

2.3. CTA measurement

EAT, adipose tissue inside the pericardial sac, was measured in axial images starting 15 mm above the superior extent of the left main coronary artery to the bottom of the heart. Volume Analysis software (GE Healthcare, Waukesha, WI) was used to discern EAT on the basis of a corresponding HU threshold of −190 to −30 HU (mean, −120 HU) [7]. EAT was measured by a semiautomatic segmentation technique in each slice with the above display settings.

CTA diagnosed coronary artery disease (CAD) was defined as obstructive (luminal stenosis≥50%), non-obstructive (luminal stenosis 1–49%) and zero-obstruction. Disease coronaries were defined as luminal stenosis ≥1.

Two experienced computed tomography readers, blinded to each other, patient characteristics, treatment status, and outcome measured EAT as well as presence and severity of CAD. Mutual consensus was reached in cases of disagreement ($n = 3$).

Epidemiologic methods for follow-up included all those that ascertained of major adverse cardiac event (MACE) and outcome were blinded to CT status. The primary end point was the occurrence of myocardial infarction or cardiovascular death, which was verified by telephone interview follow-ups and primary physician verifications (i.e., 100% follow-up). As part of consent, all subjects were agreed to provide the contact information of their primary physician, themselves and minimum of 2 other authorized relatives/friends. All subjects had a primary physician. In case of lack of answer to phone calls or last physician visit>6-month at the time of ascertainment ($n = 15$), the end points were verified by contacting authorized relatives/friends.

2.4. Statistical analysis

Analyses were performed with SPSS version 21 (IBM SPSS, Inc., Chicago, Illinois). All continuous data are presented as mean ± SD, and all categorical data are reported as percentages or absolute numbers. Kruskal–Wallis tests and analysis-of-variance tests were used to assess differences between groups. Kaplan–Meier survival curves were constructed for quartiles of CT measured EAT and compared using the log-rank test. Multivariate Cox regression analyses were employed to assess the relation of increased EAT with MACE. The hazard ratio of MACE was calculated with: a) each quartile increase in EAT as compared to lowest EAT quartile, and b) each standard deviation increase in EAT (40 cm^3/m^2) before and after adjustment for age, gender, smoking status, diabetes mellitus, hypertension, hypercholesterolemia, family history of premature CAD, presence and severity of CTA diagnosed CAD. Receiver operating characteristic (ROC) curves were constructed, and the area under the ROC curve (AUC) was calculated to predict the ability of each model (FRS, EAT (continues data), CTA diagnosed CAD and combination) to predict MACE. *The likelihood ratio* statistic *tests* the significance of the addition of each *variable to predict MACE; assessing independent prognostic value of models.*

3. Results

Table 1ashows that there is no significant differences in age, gender, prevalence of hypertension, hyperlipidemia, diabetes mellitus, family history of premature CAD and smoking across quartiles of EAT ($P > 0.05$). The prevalence of diseased coronaries, but not obstructive CAD, increased with each quartile increase of EAT ($P < 0.05$). EAT increased significantly from subjects with zero-obstruction coronaries (93 ± 37 cm^3/m^2) to non-obstructive CAD (132 ± 25 cm^3/m^2) to obstructive CAD (145 ± 35 cm^3/m^2) ($P = 0.01$) that was more robust in subjects with MACE as compared to those without MACE (Fig. 1a).

During the median of 48 month follow-ups, the event rate was 8.6% (21). The event free survival rate decreased significantly from 99% in the lowest quartile of EAT to 86.6% in the highest quartile of EAT ($p = 0.001$). Table 1breveals that after adjustment for risk factors, the hazard ratio of MACE was 1.4(95%CI 1.2–4.2), 3.1(95%CI 1.4–6.9) and 5.7(95%CI 1.6–9.8) in lower mid, upper mid and highest quartiles of EAT as compared to lowest quartile of EAT ($P < 0.05$). Similarly, the hazard ratio of MACE increased 2.23 (95%CI 1.5–3.3) folds with each standard deviation increase in EAT ($p < 0.05$).

The area under ROC curve to predict MACE was 0.60 (95%CI 0.52–0.68), 0.73 (95%CI 0.58–0.86, $p = 0.0001$) for each 10 cm^3/m^2 increase in EAT, 0.72 (95%CI 0.61–0.74, $p = 0.0001$) for presence and severity of CTA diagnosed CAD, and 0.87 (95%CI 0.81–0.89, $p = 0.0001$) for the combination of increased EAT and CTA diagnosed CAD. The likelihood ratio test revealed EAT predicts MACE

Table 1a
Clinical characteristics of studied subjects across quartiles of epicardial adipose tissue.

Model	Lowest Q EAT $n = 62$	Lower mid Q EAT $n = 61$	Upper mid Q EAT $n = 61$	Highest Q EAT $n = 61$	P value
Age	63 ± 10	63 ± 12	64 ± 10	64 ± 14	0.8
Gender	73%	73%	76%	79%	0.9
Diabetes mellitus	17%	21%	21%	18%	0.9
Hypertension	21%	20%	35%	28%	0.2
Hypercholesterolemia	27%	32%	26%	44%	0.4
Family history of CHD	58%	46%	65%	62%	0.9
Smoker	3%	5%	8%	5%	0.7
Diseased coronaries	40%	63%	69%	71%	0.01
Obstructive CAD	12%	16%	21%	21%	0.2
MACE (%)	1%	3.3%	11.4%	13.4%	0.001

Q: quartile.
MACE: major adverse cardiovascular events.
CAD: coronary artery disease.
CHD: coronary heart disease.
Diseased Coronaries: coronary artery obstruction of 1–99%.