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Prognostic value of coronary artery calcium and epicardial adipose tissue assessed by non-contrast cardiac computed tomography

Eiji Kunita [a], Hideya Yamamoto [a,*], Toshiro Kitagawa [a], Norihiko Ohashi [a], Toshiharu Oka [a], Hiroto Utsunomiya [a], Yoji Urabe [a], Hiroshi Tsushima [a], Kazuo Awai [b], Matthew J. Budoff [c], Yasuki Kihara [a]

[a] Department of Cardiovascular Medicine, Hiroshima University Graduate School of Biomedical and Health Sciences, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan
[b] Department of Diagnostic Radiology, Hiroshima University Graduate School of Biomedical and Health Sciences, Hiroshima, Japan
[c] Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, Torrance, CA, USA

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ABSTRACT

Objective: Epicardial adipose tissue (EAT) accumulation is believed to be associated with development of coronary atherosclerosis. We investigated whether EAT volume as assessed by computed tomography (CT) has value in prediction of future cardiac events.
Methods: We studied 722 patients without proven coronary artery disease (CAD) who underwent non-contrast cardiac CT. EAT volume and coronary artery calcium (CAC) score were measured simultaneously. Patients were followed as to the occurrence of coronary events (cardiac death, nonfatal myocardial infarction, unstable angina requiring hospitalization, and late coronary revascularization ≥3 months after CT examination).
Results: During a 3.7 ± 1.7 years follow-up period, 37 coronary events were documented. Annual event rates increased across CAC score categories (0.3%, 1.0%, 2.4%, and 4.3%, in 0, 1–99, 100–399, and ≥400, respectively, $p < 0.001$); these were significantly higher in the higher EAT volume group (>median; 107.2 mL, 0.7% vs., 2.1%, adjusted hazard ratio; 2.65, $p = 0.0090$). Cox-proportional hazard analysis demonstrated that a combination of CAC score ≥ 100 and high EAT volume had a significantly higher event rate than CAC score < 100 and low EAT volume group (adjusted hazard ratio 11.6, $p < 0.0001$). Using Cox regression models, incremental prognostic values were identified by adding high EAT volume to clinical risks plus CAC score ≥ 100 (global χ^2, 6.7; $p = 0.059$).
Conclusion: We suggest that high EAT volume may be an independent predictor of future coronary events and increases predictive values of CAC score in patients without proven CAD.

1. Introduction

Epicardial adipose tissue (EAT), which shares a common embryological origin with intra-abdominal visceral adipose tissue, serves as a source of inflammatory cytokines and mediators [1–3]. Thus, EAT may directly affect vessel walls, as well as progression of atherosclerosis. Non-contrast cardiac computed tomography (CT) images for calcium scoring can simultaneously provide additional clinical information, such as the amount of EAT confined within the pericardial sac. Recently, several studies using cardiac CT have demonstrated that increased EAT volume is associated with the presence of coronary artery disease (CAD) [4], induced myocardial ischemia [5,6], acute coronary syndrome [7], coronary plaque characteristics by CT angiography [8–11], and adverse cardiovascular events [12].

Previous studies using computed tomography (CT) have suggested that the presence and extent of coronary artery calcium (CAC) are associated with the overall atherosclerotic plaque burden [13] and with development of subsequent cardiovascular events [14–16].

However, it has not been established that simultaneous evaluation of CAC scores and EAT volumes by non-contrast cardiac CT can help to improve prediction of future cardiac events. The aim of the present study was to investigate the value of using non-contrast CT to simultaneously assess CAC score and EAT volume for predicting the risk of future cardiac events.

* Corresponding author. Tel.: +81 82 257 5540; fax: +81 82 257 1569.
E-mail address: hideyayama@hiroshima-u.ac.jp (H. Yamamoto).

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2. Methods

2.1. Subjects

Of a total of 1081 patients who underwent non-contrast cardiac CT for calcium scoring between November 2004 and September 2009, patients without proven CAD; a history of myocardial infarction (MI), prior coronary revascularization, status of acute coronary syndrome, or typical effort angina were recruited [17]. Patients with proven cardiomyopathy, severe valvular heart disease, renal impairments (serum creatinine level $\geq$1.5 mg/dL), or serious life-threatening illness were also excluded. Of the remaining 850 patients, those with early coronary revascularizations within 3 months from CT ($n = 76$) and follow-up duration <1 year ($n = 52$) were excluded from the analysis. Ultimately, 722 patients were enrolled. The subjects constituted patients with atypical or non-cardiac chest pain ($n = 459$) and asymptomatic high-risk patients such as those with stress or rest ECG abnormality, major vascular complications, or diabetes mellitus ($n = 263$), of whom 106 underwent non-contrast CT for CAC scoring alone and the remainder also underwent CT angiography. This study was approved by our hospital's ethics committee and written informed consent was obtained from all patients.

2.2. Risk factor assessments

Details of patient demographics, medical history, and medication use were provided by all patients during a clinical consultation. Patients were classified as hypertensive if their systolic blood pressure was $\geq$140 mm Hg, diastolic blood pressure was $\geq$90 mm Hg, and/or they were receiving antihypertensive therapy. Fasting blood samples were obtained from an antecubital vein before CT. Concentrations of high-density and low-density lipoprotein cholesterol, triglycerides, and hemoglobin A1c were measured in the hospital laboratory. Hypercholesterolemia was defined as low-density lipoprotein cholesterol concentration $\geq$140 mg/dL on direct measurement, or the current use of lipid-lowering drugs [18]. Diabetes mellitus was defined by self-report, a glycohemoglobin A1c level $\geq$6.5% [19], and/or the current use of hypoglycemic agents. Based on Japanese criteria, obesity was defined as body mass index (BMI) $\geq$ 25.0 kg/m^2 [20]. Metabolic syndrome was defined according to Japanese criteria as a waist circumference level of at least 85 cm in men and at least 90 cm in women and two or more of the following three risk factors: blood pressure $\geq$130/85 mm Hg, dyslipidemia (high-density lipoprotein cholesterol concentration $\leq$40 mg/dL or triglyceride concentration $\geq$ 150 mg/dL), and glucose intolerance (fasting plasma glucose concentration $\geq$ 110 mg/dL) [21]. BMI $\geq$ 25 kg/m^2 was used if waist circumference had not been measured.

2.3. CT scan protocol and CAC scoring

Either a 16-slice CT scanner (LightSpeed Ultrafast16, GE Healthcare, Waukesha, Wisconsin) (between November 2004 and November 2005; $n = 111$) or a 64-slice CT scanner (LightSpeed VCT, GE Healthcare) (between December 2005 and September 2009; $n = 601$) was used for coronary evaluation. Prospective ECG-triggered scans were performed in mild inspiration from the root of aorta to the apex of the heart with the following parameters (16-slice CT and 64-slice CT): axial scan; gantry rotation times, 500 ms and 350 ms; X-ray exposure times, 333 ms and 233 ms; tube voltage, 120 kV; tube currents, 100 mA and 140 mA; center of imaging window, 75% of R–R interval. Forty-eight contiguous images of 2.5-mm thickness were obtained, and the total CAC score was calculated based on the Agatston method with dedicated software (Smartscore, version 3.5, GE Healthcare) [22].

2.4. EAT volume using CT

EAT volume was measured according to a previous report [4], the details have previously been described [8]. Briefly, the EAT area within the manually traced parietal pericardium was defined as having a density range between −250 and −30 Hounsfield units and was automatically quantified using commercial software (Virtual Place, AZE INC., Tokyo, Japan). EAT volume was calculated as the sum of the EAT areas from the atrial appendage (i.e. 1.0 cm above the left main coronary artery) to the apex with 1.0 cm thick spacing between each image.

2.5. Patient follow-up and coronary events

Relevant patient information was obtained from medical records, telephone interviews with patients or their families, or from their primary care physicians. All end points were determined by consensus between two blind reviewers. The endpoint was defined as a coronary event, including cardiac death, non-fatal MI, or unstable angina requiring hospitalization, and late coronary revascularizations (percutaneous coronary intervention or coronary artery bypass grafts) $\geq$3 months after CT [23]. Coronary death was defined as death caused by acute MI, ventricular arrhythmias, or cardiogenic shock. Patients with acute MI had two of three criteria: chest pain lasting over 30 min, increased serum creatine kinase with an MB fraction, and new pathological Q waves of 0.04 s duration. Unstable angina was defined according to the European Society of Cardiology guidelines [24].

2.6. Statistics

The CAC score and serum triglycerides and hemoglobin A1c levels are expressed as median values (interquartile range). Other measurements are expressed as mean ± SD. We used the Mann–Whitney test and analysis of variance, including Tukey's test, for multiple comparisons and to compare continuous variables between the groups. Categorical variables were reported as number (%) and were compared using Pearson's χ^2 test. Pearson's correlation coefficient was used for correlation analysis. Event rates were estimated by Kaplan–Meier curves and compared by log-rank tests. Cox proportional hazards models were used to determine predictors of future coronary events. Hazard ratios (HR) with 95% confidence interval (CI) were calculated in univariate and multivariate models adjusted for clinical risks including age, sex, BMI, hypertension, hypercholesterolemia, diabetes mellitus, and current smoking. The incremental prognostic values of EAT volume beyond clinical risks and CAC score were analyzed using Cox regression analysis. Global χ^2 and p values for the incremental significance between each model (Basal model, clinical risks; Model 1, Base model + CAC score $\geq$ 100; Model 2, Model 1 + high EAT volume) were also calculated. Statistical analyses were performed using SPSS 21.0 (IBM Inc., Chicago, IL). A p value of <0.05 was considered statistically significant.

3. Results

3.1. Follow-up results

During a period of 3.7 ± 1.7 years, 37 patients experienced coronary events, consisting of 5 cardiac deaths, 4 non-fatal MIs, 9 unstable anginas requiring urgent hospitalization, and 19 late coronary revascularizations. The annual rate of coronary events was 1.4%.