Echocardiographic Epicardial Adipose Tissue Thickness Is Associated with Symptomatic Coronary Vasospasm during Provocative Testing

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Background: Epicardial adipose tissue (EAT) is the ectopic visceral fat surrounding the heart, which plays an important role in atherosclerosis of the coronary arteries via endothelial damage. Several studies have also suggested that vasospasm with angina (VSA) causes endothelial dysfunction in the coronary arteries. The aim of this study was to evaluate the thickness of EAT in the anterior interventricular groove (EAT-AIG) using echocardiography in patients who had no obstructive coronary artery disease and were suspected of having VSA.

Methods: Sixty-five patients who underwent intracoronary acetylcholine provocation testing for clinical indications were prospectively enrolled. VSA was diagnosed by coronary artery stenosis increase of >90% and the presentation of chest pain with ischemic changes on electrocardiography.

Results: Subjects were divided into two groups, with and without significant coronary spasm (VSA group, 30 patients; non-VSA group, 35 patients), consistent with acetylcholine provocation testing. EAT-AIG thickness was significantly greater in the VSA group than in the non-VSA group (8.2 ± 2.7 vs 6.1 ± 2.5 mm, $P = .002$). By receiver operating characteristic analysis, EAT-AIG thickness had a high C statistic (area under the curve = 0.81, $P < .001$) after adjustment for conventional risk factors (smoking, diabetes mellitus, and dyslipidemia). EAT-AIG thickness had incremental diagnostic value over other conventional risk factors (area under the curve = 0.81 vs 0.64, P for comparison = .020).

Conclusions: EAT-AIG thickness, which is noninvasively and easily measured using transthoracic echocardiography, can be one of multiple clinical variables associated with VSA. (J Am Soc Echocardiogr 2017;30:1021-7.)

Keywords: Echocardiography, Epicardial adipose tissue, Vasospasm in patients with angina, Anterior interventricular groove

Previous studies have shown that increased epicardial adipose tissue (EAT) thickness is associated with known cardiovascular risk factors.[1] Echocardiography can determine the regional thickness of EAT and has some advantages over other methods (i.e., it is noninvasive, relatively economical, and easy to perform for screening). Echocardiographic EAT thickness has been defined as the thickness of the low-isoechoic area on the free wall of the right ventricle (RV) in the parasternal long- and short-axis views.[2] EAT is not uniformly distributed, as adipose tissue concentrates primarily in the interventricular and atrioventricular grooves rather than in nongroove segments, such as the free wall of the RV.[3] We recently reported that the echocardiographic thickness of EAT in the anterior interventricular groove (EAT-AIG), obtained using a higher frequency linear probe, was well correlated with EAT volume measured by computed tomography and associated with coronary artery disease (CAD).[4]

Vasospasm with angina (VSA) is caused by focal or diffuse spasm of a major coronary artery, resulting in a high-grade obstruction.[5,6] Although it is sometimes thought that patients with VSA have relatively favorable outcomes, their clinical outcomes strongly depend on early diagnosis. Because the treatment strategies for VSA and other chest pain or discomfort diseases are substantially different, it is important to

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This work was partially supported by JSPS Kakenhi grants (15K19381 to Dr. Kusunose and 25293184 to Dr. Sata) and a Japan Heart Foundation research grant to Dr. Kusunose.

Conflicts of Interest: None.

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0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2017.06.024

Abbreviations

ACh = Acetylcholine

AIG = Anterior interventricular groove

CAD = Coronary artery disease

EAT = Epicardial adipose tissue

LAD = Left anterior descending coronary artery

LCA = Left coronary artery

RCA = Right coronary artery

RV = Right ventricle

VSA = Vasospasm with angina

distinguish VSA. Recent studies have suggested that EAT has been associated with many manifestations of vasoconstrictor-vasodilator imbalance and impaired coronary vasomotion.[7] However, the relationship between EAT and VSA is not well established. We hypothesized that echocardiographic EAT-AIG thickness can be a marker for the detection of VSA in patients without obstructive coronary artery disease. Our study aim was to assess the utility of EAT-AIG thickness by echocardiography in differentiating between patients with and without VSA.

METHODS

Study Population

We consecutively enrolled 792 patients who underwent their first coronary angiographic examinations from May 1, 2012, to November 1, 2014, at Tokushima University Hospital. In the present study, the analyzed population was patients who had no significant coronary artery stenosis but were suspected to have VSA (chest pain or chest discomfort at rest). Therefore, patients who demonstrated ≥50% stenosis on coronary angiography ($n = 482$) or lacked typical VSA symptoms ($n = 212$) were excluded. Subjects were also excluded if they refused to undergo the intracoronary acetylcholine (ACh) stress test ($n = 33$). After these exclusions, 65 patients remained for the final analysis (Figure 1). They were scheduled to undergo intracoronary ACh stress testing to diagnosis VSA. We also enrolled 30 age- and gender-matched healthy control subjects who were selected from our healthy volunteer database on the basis of a comprehensive history and physical examination, to determine the normal value of EAT. The study was approved by the institutional review board of Tokushima University Hospital (no. 2183-1), and written informed consent was obtained from all subjects.

All subjects were classified into either the VSA group or the non-VSA group. The VSA group was defined as patients who had coronary spasm in any coronary artery during the intracoronary ACh stress test. Hypertension was defined as systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg or current treatment with antihypertensive medication. Diabetes mellitus was defined as fasting blood glucose 126 mg/dL, glycated hemoglobin ≥ 6.5%, and/or the need for oral hypoglycemic agents. Dyslipidemia was defined as plasma total cholesterol > 220 mg/dL or the use of lipid-lowering therapy. Smoking was defined as current or previous use of cigarettes.

Echocardiographic Examination

Echocardiography was performed using commercially available ultrasound machines (Vivid E9 [GE Healthcare, Milwaukee, WI], iE33 [Philips Healthcare, Best, The Netherlands]; Aplio 500 [Toshiba Medical Systems, Tochigi, Japan]; or α10, Preirus [Hitachi, Tokyo, Japan]) 1 day before coronary angiography. The details of EAT thickness measurements have already been described in our previous report.[4] Using a high-frequency linear probe (7.5–11 MHz), EAT thickness was measured at end-systole in two locations: in the AIG, where the left anterior descending coronary artery (LAD) runs, and on the free wall of the RV, away from any major epicardial artery. While assessing EAT-AIG thickness, we searched for the distal portion of the LAD and carefully rotated the probe until a longitudinal section was identified. EAT-AIG thickness was measured as the distance from the outer wall of the myocardium to the visceral layer of the epicardium. EAT-RV thickness was measured using the method previously reported by Iacobellis and Willens.[8] The thickness of pericardial adipose tissue over the free wall of the RV outside of the parietal pericardium was also measured at end-systole from the same image used to measure EAT-RV thickness. Measurements were performed during three cardiac cycles for each parameter, and the mean for each parameter was used for analysis. The reproducibility of EAT-AIG thickness, expressed as the intraclass correlation coefficient, has been described in detail by our group as 0.98 and 0.91 for intraobserver and interobserver variation.[4]

Provocation Testing of VSA

The intracoronary infusion of ACh was performed according to the guidelines for diagnosis and treatment of patients with vasospastic angina.[9] The administration of vasoactive drugs, including calcium channel blockers, nitrates, β-adrenergic blockers, and other vasodilators, was stopped for ≥2 days before angiography. Before performing vasospasm provocation testing with ACh, controlled coronary angiography was performed. ACh was injected from the same angle over a period of 20 sec into the right coronary artery (RCA; at a dose of 20 or 50 μg) and the left coronary artery (LCA; at a dose of 20, 50, or 100 μg) according to the clinical condition. Angiography was subsequently performed 1 min after the start of each injection. Angiography was also performed after presentation of ischemic changes on electrocardiography or chest pain. Coronary spasm was defined as total or subtotal occlusion (≥90% stenosis) accompanied by episodes of chest pain or ischemic ST-segment changes on electrocardiography (Figure 2).

Statistical Analysis

Data are presented as mean ± SD. Student's t test was used to compare continuous variables between the two groups (VSA and non-VSA). When comparing between three groups (VSA, non-VSA, and normal), we added the control group to use the analysis of variance with the Bonferroni method. Logistic regression was used to calculate odds ratios and 95% CIs after adjustment for potential confounders. Potential confounders, such as smoking, diabetes mellitus, and dyslipidemia, were entered in multivariate models. The performance of clinical risk factors (smoking, diabetes mellitus, and dyslipidemia) plus various combinations of EAT-AIG thickness was assessed using the area under the curve in receiver operating characteristic analysis. To evaluate the correlation of EAT-AIG thickness and presence of VSA, two models were constructed and compared using receiver operating characteristic analysis. Model 1, the basic model, consisted of clinical risk factors alone. Model 2 included the variables in model 1 plus EAT-AIG thickness. The DeLong method was used to compare the C statistic.[10] We conducted bootstrapping with 2,000 resamples to assess the internal validation. Statistical analysis was performed using standard statistical software packages (SPSS version 21.0 [SPSS, Chicago, IL], MedCalc version 15.8 [MedCalc Software, Mariakerke, Belgium], and R version 3.3.3 [R Foundation for Statistical Computing, Vienna, Austria]). P values $< .05$ were considered to indicate statistical significance.