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ORIGINAL ARTICLE
Imaging

Local Thickness of Epicardial Adipose Tissue Surrounding the Left Anterior Descending Artery Is a Simple Predictor of Coronary Artery Disease

— New Prediction Model in Combination With Framingham Risk Score —

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Background: Compared with global cardiac adiposity, the local accumulation of fat surrounding coronary arteries might have a more direct impact on coronary artery disease (CAD). Here, we compared the local epicardial adipose tissue (EAT) thickness and global cardiac adiposity volumes for predicting CAD.

Methods and Results: A total of 197 consecutive subjects underwent 320-slice multi-detector computed tomography coronary angiography and were segregated into CAD (≥1 coronary artery branch stenosis ≥50%) and non-CAD groups. EAT thickness was measured at the right coronary artery (EAT_{RCA}), the left anterior descending artery (EAT_{LAD}), and the left circumflex artery (EAT_{LCX}). Although EAT_{RCA} and EAT_{LCX} were similar between the 2 groups, EAT_{LAD} was larger in the CAD group than in the non-CAD group (5.45±2.16 mm vs. 6.86±2.19 mm, P<0.001). EAT_{LAD}, after correcting for confounding factors, was strongly associated with CAD (r=0.276, P<0.001) and Gensini score (r=0.239, P<0.001). On multiple regression analysis, Framingham risk score combined with EAT_{LAD} was a strong predictor of CAD (adjusted R^2=0.121; P<0.001).

Conclusions: The local fat thickness surrounding the LAD is a simple and useful surrogate marker for estimating the presence, severity, and extent of CAD, independent of classical cardiovascular risk factors.

Key Words: Coronary artery disease; Epicardial adipose tissue; Framingham risk score

Epicardial adipose tissue (EAT) is located below the visceral layer of the pericardium and directly contacts the coronary arteries. The proximity of EAT to the coronary arteries prompted us to consider the pathophysiological consequences associated with this tissue. We and others have shown that EAT is a source of multiple inflammatory cytokines.[1–5] Reportedly, EAT volume (EATV), determined using either multi-detector computed tomography (MDCT) or magnetic resonance imaging and echocardiography, correlates with the presence and severity of coronary artery disease (CAD).[6–8] Prospectively, EAT also predicts the incidence of CAD independent of traditional cardiovascular risk factors.[9]

Compared with global cardiac adiposity, such as EATV, the local accumulation of fat surrounding an artery, which can be assumed using local EAT thickness, might have a more direct impact on regional coronary atherosclerosis and predict CAD more efficiently. This idea, however, has not been fully clarified.

The aim of this study was therefore to measure the local EAT thicknesses surrounding the coronary arteries of patients with or without CAD and determined their clinical

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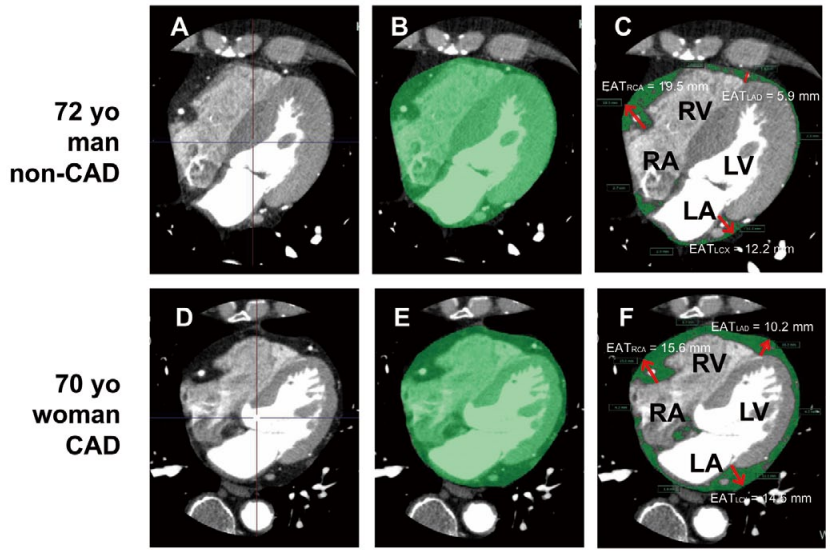


Figure 1. Representative measurements of local epicardial adipose tissue (EAT) thickness in the area surrounding right coronary artery (RCA; EAT_{RCA}), left anterior descending artery (LAD; EAT_{LAD}) and left circumflex artery (LCX; EAT_{LCX}). From (**A**,**D**) plain axial 4-chamber views, a region of interest (ROI) for EAT measurements was manually placed (**B**,**E**) along the visceral pericardium, and (**C**,**F**) the EAT area was automatically acquired as the density range between −190 and −30 Hounsfield units. As compared with (**C**) a 72-year-old man without coronary artery disease (CAD), a (**F**) 70-year-old woman with obstructive CAD had an increase in EAT_{LAD} (5.9 mm vs. 10.2 mm), although similar EAT_{RCA} and EAT_{LCX}. The presence of ≥1 stenosis >50% on luminal diameter in at least 1 major epicardial coronary artery or branches was defined as CAD. Red arrows, measures of EAT thickness. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

utility, compared with the global cardiac EATV, for predicting CAD.

Methods

Patients

A total of 482 consecutive subjects who underwent MDCT between April 2012 and August 2015 at Tokushima University Hospital were enrolled in this study. Of these, 25 were excluded due to lack of data for Framingham risk score (FRS) calculation. Also, 95 subjects who could not have Gensini score calculated due to poor coronary CT angiography (CTA) quality (mainly coronary artery calcification) and lack of follow-up coronary angiography (CAG), and 160 who did not have abdominal CT were excluded. Of 202, 5 were excluded because of insufficient image quality for EAT measurements. Finally, we analyzed CTA datasets of 197 patients. The other exclusion criteria were irregular heartbeat during MDCT; serum creatinine >2.0 mg/dL; class III or IV heart failure; known hypersensitivity to iodine-based contrast agents; acute coronary events, stroke, or coronary revascularization within the preceding 3 months; overt liver disease; and hypothyroidism.[10] The ethics committee of Tokushima University Hospital approved the study.

Covariates, including cardiac disease history and risk factors, were obtained from patient electronic medical records. All participants provided written informed consent after they were advised regarding radiation exposure-related risks and the possible complications associated with iodine-containing contrast agents. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or the current use of antihypertensive medication. Diabetes was defined as glycated hemoglobin concentration ≥6.5%, fasting plasma glucose >126 mg/dL, or the current use of anti-diabetic medications. Dyslipidemia was defined as total serum cholesterol ≥220 mg/dL, low-density lipoprotein cholesterol (LDL-C) ≥140 mg/dL, serum triglyceride (TG) ≥150 mg/dL, and serum high-density lipoprotein cholesterol (HDL-C) <40 mg/dL, and/or current use of anti-hyperlipidemic medications. Smoking was defined as past or current smoking; non-smoking was defined as never having smoked. FRS is a multivariable statistical model that uses age, sex, smoking history, blood pressure, cholesterol and HDL-C, and blood glucose level or history of diabetes to estimate the coronary event risk for individuals without previously diagnosed CAD.[11–13] FRS was used to estimate a 10-year risk of CAD, defined as angina pectoris, recognized and unrecognized myocardial infarction, and death due to CAD. According to this score, patients were stratified as follows: low likelihood of CAD, <10%; intermediate likelihood, 10–20%; and high likelihood, >20%.[14,15]

CTA Data Acquisition

CTA was performed using a 320-slice CT scanner (Aquilion One; Toshiba Medical Systems, Tokyo, Japan) having 0.275-ms rotation and 0.5/320/0.25 collimation as previously described.[16] Briefly, a plain scan was taken to measure the coronary calcium score, using the standard Agatston method (slice thickness, 3 mm; maximum tube current, 170 mA; tube voltage, 120 KV). For CTA, tube voltage was set at 120 KV, with a maximum tube current of 214 mA. All reconstructed CT image data were transferred

Table 1. Subject Characteristics vs. CAD Status

Parameters	Non-CAD (n=84)	CAD (n=113)	P-value†
Age (years)	64±14	70±11	0.002
Male	48 (57)	74 (66)	0.233
Anthropometry			
BMI (kg/m^2)	23.8±4.4	24.4±4.0	0.148
BMI ≥25 kg/m^2	32 (38)	57 (50)	0.085
WC (cm)	85.1±12.0	86.6±11.5	0.358
VFA (cm^2)	102±57	119±66	0.063
SFA (cm^2)	135±88	130±86	0.686
Comorbidities			
T2DM	21 (25)	38 (34)	0.177
Hypertension	60 (71)	94 (83)	0.048
Dyslipidemia	60 (71)	86 (76)	0.459
History of smoking	33 (39)	59 (52)	0.072
FRS (%)	9.6±7.2	12.5±7.2	0.006
EAT measures			
EATV (cm^3)	104±45	124±57	0.006
EATV index (cm^3/m^2)	63±25	75±32	0.004
EAT_{RCA} thickness (mm)	15.49±4.73	16.46±4.76	0.160
EAT_{LAD} thickness (mm)	5.45±2.16	6.86±2.19	<0.001
EAT_{LCX} thickness (mm)	9.80±3.39	10.33±3.61	0.297
Agatston score			
Total	116±328	879±1,333	<0.001
In RCA	45±189	349±743	<0.001
In LAD	53±131	309±437	<0.001
In LCX	8±29	169±369	<0.001
Coronary artery stenosis ≥50%			
RCA	–	69 (61)	–
LAD	–	72 (64)	–
LCX	–	61 (54)	–
1-vessel disease	–	55 (49)	–
2-vessel disease	–	27 (24)	–
3-vessel disease	–	31 (27)	–

Data are given as mean±SD or n (%). †Independent t-test or chi-squared test. BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; EAT, epicardial adipose tissue; EATV, epicardial adipose tissue volume; EATV index, EATV/BSA; FRS, Framingham risk score; LAD, left ascending artery; LCX, left circumflex artery; RCA, right coronary artery; SFA, subcutaneous fat area; T2DM, type 2 diabetes mellitus; VFA, visceral fat area; WC, waist circumference.

to an offline workstation (Synapse Vincent, ver. 4.4, Fuji Film, Tokyo, Japan) for post-processing and image analysis. Contrast agent transmit time, using a bolus tracking technique according to body weight, was measured using a contrast agent (Iopamiron, 370 mg iodine/mL, Bracco Imaging, Milan, Italy) and contrast agent injection syringe (Bracco Imaging) followed by a 50-mL saline flush, both at flow rates of 5 mL/s using a dual-head power injector (Nemoto Kyorindo, Tokyo, Japan). For coronary CTA, 40–50 mL contrast agent was injected into an antecubital vein, directly followed by 40 mL i.v. saline (maximum, 5 mL/s). One nitroglycerine spray (0.3 mg) was given sublingually. If needed, i.v. metoprolol tartrate (12.5 mg) was used to lower heart rate to <60 beats/min. The scan time was 5–8s, and images were collected during an inspiratory breath hold. Measurements were performed during a motionless phase of the cardiac cycle, which was usually a diastolic phase, with retrospective cardiac gating at 70–80% of the RR interval. For image reconstruction, a medium sharp convolution kernel was used, with a 0.5-mm slice thickness and a 0.25-mm increment.

CTA and EAT Volume and Thickness

The presence of stenosis (>50% of the luminal diameter) in at least 1 major epicardial coronary artery or branch was defined as CAD. The coronary tree was further divided into 15 segments, based on the American Heart Association classification.[17] To evaluate atherosclerosis severity, the coronary segments with the most severe luminal diameter stenosis were scored as 0 points, <25% stenosis; 1 point, 25–50%; 2 points, 51–75%; 4 points, 76–90%; 8 points, 91–99%; or 16 points, 100%, as modified from Gensini,[18] and the cumulative score from all segments was recorded as the modified Gensini severity score. We had performed CAG in patients with suspected significant coronary stenosis on MDCT or in whom severity could not be determined because of coronary calcification.

Measurement of EATV was performed as described.[1] Briefly, using Vincent's volume measurement software, both the EAT thickness and cross-sectional EATV were

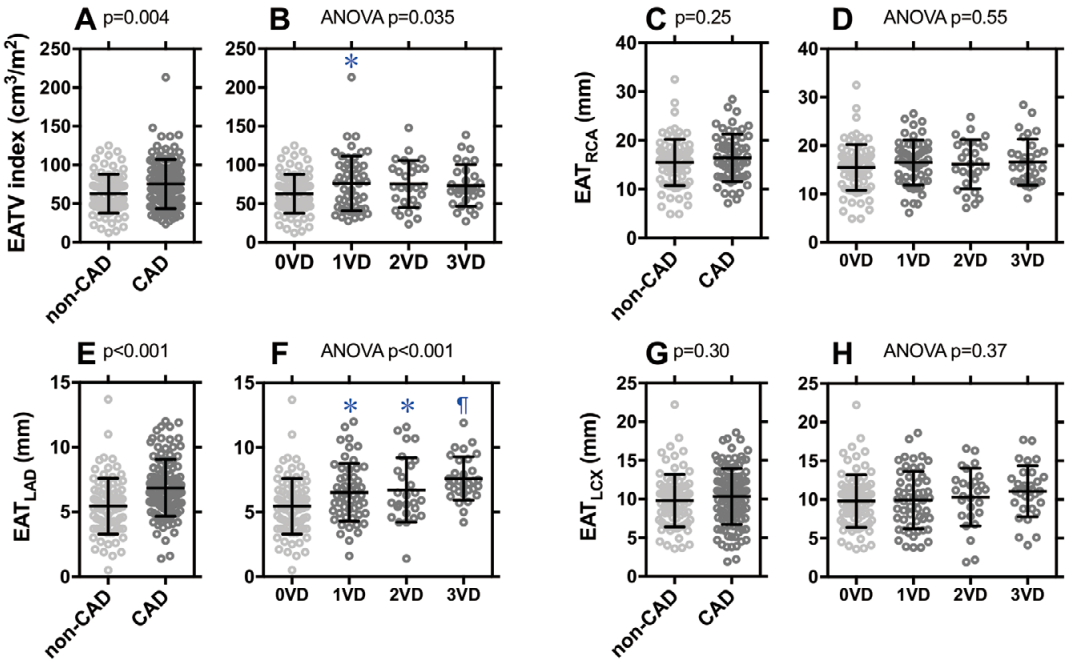


Figure 2. Total EAT volume (EATV) index (EATV/body surface area) and local EAT thickness in the area surrounding the RCA (EAT_{RCA}), LAD (EAT_{LAD}) and LCX (EAT_{LCX}) according to CAD status and number of diseased vessels. 0VD, 0-vessel disease (no CAD); 1–3VD, 1–3-vessel disease (CAD). CAD was defined as ≥1 stenosis >50% on luminal diameter in at least 1 major epicardial coronary artery or branches. Whiskers, mean±SD. Between-group differences for CAD status were analyzed using independent Student's t-test, and those for 0VD vs. 1–3VD were analyzed using 1-way analysis of variance and a linear regression model, followed by post-hoc Dunnet test. Statistical significance for all tests was set at P<0.05. *P<0.05, ¶P<0.001 vs. 0VD. Abbreviations as in Figure 1.

measured using the computer workstation. To calculate EATV, all axial images (approximately 250 per patient) were loaded into the workstation and the epicardium was manually traced on these images. EATV measurements were performed on axial images by manually tracing the parietal pericardium, from the left main pulmonary artery level to the left ventricular apex, as described.[1] The total EATV was calculated on a highlighted fat map, with a threshold of −190 to −30 HU.[20] The EATV index was defined as EATV/body surface area.[1] Local EAT thicknesses were measured on short-axis view (**Figure 1**). Using an axial, 4-chamber view in which all 4 chambers had been observed proportionally, EAT thickness measurements were performed at the following points: (1) surrounding the left anterior descending artery (LAD; EAT_{LAD}); (2) surrounding the right coronary artery (RCA; EAT_{RCA}); and (3) surrounding the left circumflex artery (LCX; EAT_{LCX}). On the highlighted fat map, the length of lines perpendicular to the lines between the heart surface and the visceral epicardium was determined: (1) EAT_{LAD} at the anterior interventricular groove (AIVG); (2) EAT_{RCA} at the right atrioventricular groove (RAVG); and (3) EAT_{LCX} at the left atrioventricular groove (LAVG). The subcutaneous fat area (SFA) and intra-abdominal visceral fat area (VFA) were measured at the level of the umbilicus as previously described.[16]

Preliminary to this study, we had determined the location of the EATT measures. Comparison with curved planar reformation (CPR) images of the coronary arteries was used to determine the appropriate views (axial and coronal) to measure EAT thickness. For all samples we had compared, the coronal views were variable, but the axial views were not. Thus, the axial view was selected. Next, we measured the variation of data according to the height in the view. In 8 non-CAD (61±10 years, 5 men) and 8 CAD patients (69±10 years, 4 men), EAT thickness in the axial 4-chamber view (current protocol) had only small differences in mm and %, and hence this measurement was used as the representative value (**Table S1**).

Statistical Analysis

All statistical analysis was performed using SPSS 21.0 for Windows (SPSS, Chicago, IL, USA). Continuous variables are expressed as mean±SD and were compared using unpaired Student's t-test. Categorical variables are summarized as frequency and percentage and were compared using chi-squared test. Differences in continuous variables between the 2 groups were compared using independent Student's t-test. Comparisons between groups stratified by the number of narrowed coronary arteries were done using 1-way analysis of variance and a linear regression model. Statistical significance for all tests was set at P<0.05; Bonferroni correction was applied when necessary. Correlations between CAD (yes or no), EATV, waist circumference (WC), VFA, and EAT thickness were determined using Pearson's correlation coefficient test. Multivariate regression analysis was used to determine the predictors of CAD, adjusting for clinical risk factors (including age, male sex,

Table 2. Univariate Indicators of CAD and Gensini Score

Parameters	CAD		Gensini score	
	r	P-value	r	P-value
Age (years)	0.236	0.001	0.168	0.018
Male gender (yes or no)	0.085	0.235	0.158	0.026
Anthropometry				
BMI (kg/m^2)	0.070	0.327	0.085	0.235
BMI ≥25 kg/m^2 (yes or no)	0.123	0.086	0.100	0.160
VFA (cm^2)	0.133	0.063	0.163	0.022
SFA (cm^2)	–0.029	0.686	0.012	0.869
WC (cm)	0.066	0.358	0.087	0.226
Comorbidities				
T2DM (yes or no)	0.096	0.179	0.143	0.045
Hypertension (yes or no)	0.141	0.048	0.027	0.710
Dyslipidemia (yes or no)	0.053	0.461	0.123	0.086
History of smoking (yes or no)	0.128	0.073	0.164	0.021
FRS (%)	0.197	0.006	0.200	0.005
EAT measures				
EATV (cm^3)	0.194	0.006	0.100	0.162
EATV index (cm^3/m^2)	0.206	0.004	0.100	0.161
EAT_{RCA} thickness (mm)	0.101	0.160	0.006	0.935
EAT_{LAD} thickness (mm)	0.306	<0.001	0.263	<0.001
EAT_{LCX} thickness (mm)	0.075	0.297	0.065	0.367

Abbreviations as in Table 1.

diabetes mellitus, hypertension, smoking habits, body mass index [BMI], and WC). Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off points for EAT measurements to predict significant CAD, and to assess whether the dichotomously defined EAT thickness measurements provided added predictive value for significant CAD, in addition to traditional risk factors.

Results

General Characteristics

General subject characteristics are listed according to CAD status in **Table 1**. In the CAD group, the mean age and prevalence of hypertension were higher, and the mean VFA and number of patients with BMI ≥25 kg/m^2 tended to be higher. Otherwise, the 2 groups had similar numbers of male patients and similar average BMI, WC, and SFA. The number of patients with type 2 diabetes mellitus, dyslipidemia, and history of smoking was not significantly different between the 2 groups. FRS was higher in the CAD group than in the non-CAD group (9.6±7.2% vs. 12.5±7.2%, P=0.006).

EATV and EAT Thickness

Figure 1 shows the representative EAT thickness measurements in the areas surrounding the RCA, LAD, and LCX. EAT_{LAD}, but not EAT_{RCA} or EAT_{LCX}, was larger in CAD patients (10.2 mm) than in non-CAD patients (5.9 mm). Comparing the group means, EATV, EATV indexes, and EAT_{LAD} were higher in the CAD group (**Table 1**, **Figure 2A**,**C**,**E**,**G**). When patients were further divided into subgroups according to number of diseased vessels, that is, those with 0-vessel disease (0VD; no CAD) or 1–3VD (CAD), $EATV_{LAD}$ increased with the number of diseased vessels, whereas EATV index, EAT_{RCA}, and EAT_{LCX} did not differ across the 4 groups (**Figure 2B**,**D**,**F**,**H**).

Univariate Indicators of CAD and Gensini Score

Univariate regression analysis was used to estimate the presence of CAD and determine the Gensini score (**Table 2**; **Figure 3**). CAD was significantly correlated with age, hypertension, and FRS. Although whole body and abdominal adiposity parameters (BMI, BMI ≥25 kg/m^2, VFA, SFA, and WC) were not correlated with CAD, some EAT measures (EATV, EATV index, and EAT_{LAD}; but not EAT_{RCA} and EAT_{LCX}) were correlated with CAD. EAT_{LAD} (r=0.306, P<0.001) was more strongly correlated with CAD than was EATV or EATV index. Gensini score was significantly correlated with age, male sex, VFA, smoking history, and FRS. EAT_{LAD}, but not EATV, EATV index, EAT_{RCA}, or EAT_{LCX}, was also correlated with the Gensini score (**Table 2**; **Figure 3A**–**D**). On scatter plot analysis between the Gensini score in each coronary artery and the corresponding EAT measures, significant correlation was found only between Gensini score in the LAD and EAT_{LAD}, but not between those in the RCA and LCX (**Figure S1A**).

To minimize the bias of LAD dominance in the severity of coronary atherosclerosis, we subdivided patients into a LAD group (coronary stenosis >50% in LAD; **Figure 3E**–**H**) and a non-LAD group (no coronary stenosis >50% in LAD; **Figure 3I**–**L**). We found that Gensini score was smaller, but a borderline correlation was still observed between EAT_{LAD} and Gensini score even in the non-LAD group (**Figure 3C**,**G**,**K**).

Multivariate Indicators of CAD and Gensini Score

We determined the impact of individual covariates on CAD and Gensini score using multivariate regression models in a standard, sequential (hierarchical) fashion (**Table 3**).

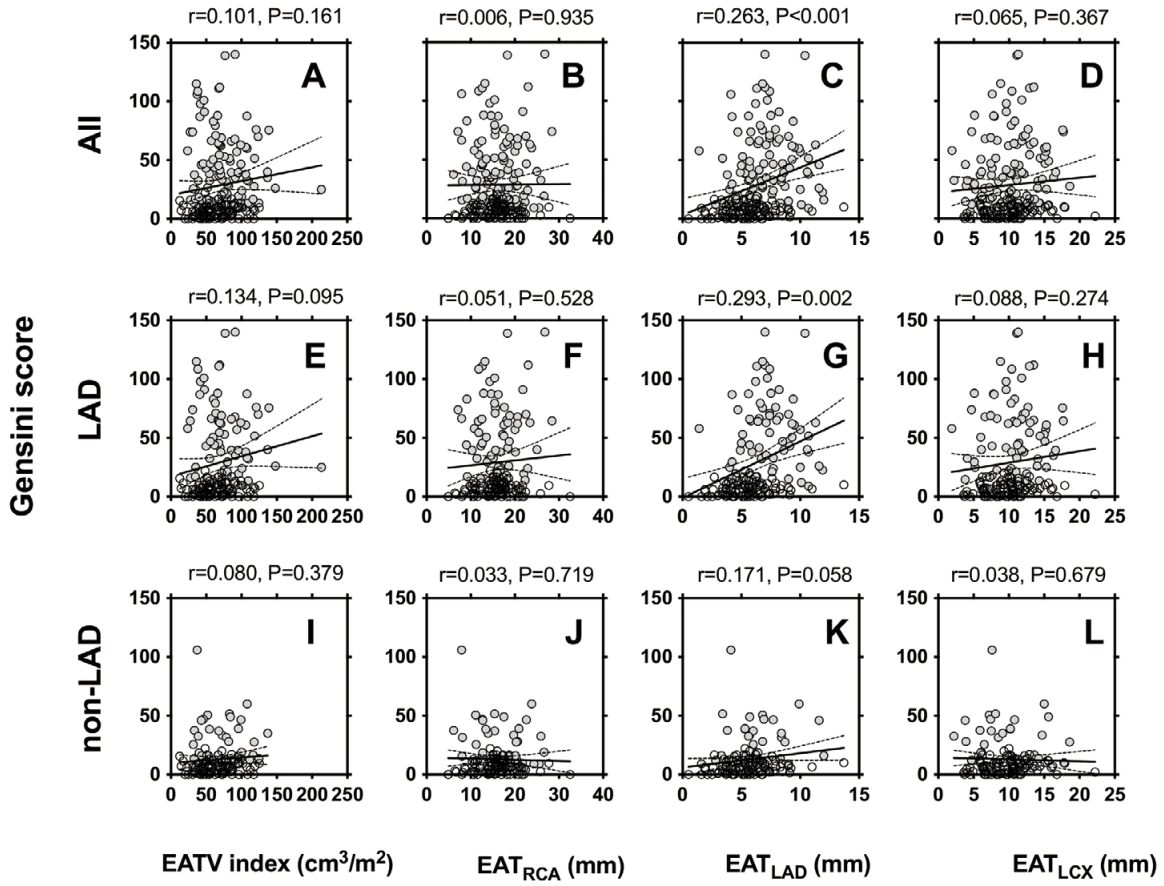


Figure 3. Linear correlation between Gensini score, total EATV index (EATV/body surface area) and local EAT thickness in the area surrounding the RCA (EAT_{RCA}), LAD (EAT_{LAD}) and LCX (EAT_{LCX}) for (**A**–**D**) all patients; (**E**–**H**) the LAD group (coronary stenosis >50% in LAD); and (**I**–**L**) the non-LAD group (no coronary stenosis >50% in LAD). (○) Non-coronary artery disease (non-CAD); (●) CAD. CAD was defined as ≥1 stenosis >50% on luminal diameter in at least 1 major epicardial coronary artery or branches. Linear regression analysis was carried out for the combined group of non-CAD and CAD subjects. Abbreviations as in Figures 1,2.

Age was a determinant of CAD, after correcting for sex and BMI (model 1; **Table 3A**). The addition of smoking history, hypertension, dyslipidemia (LDL-C >140 mg/dL or statin use, TG >150 mg/dL, or HDL-C <40 mg/dL), and type 2 diabetes mellitus did not result in appreciable increases in corrected R^2 (model 2). When added to the combination model using these traditional risk factors (models 1, 2), EATV index (a marker of global cardiac adiposity) did not increase corrected R^2 (model 3), but the addition of EAT_{LAD} increased corrected R^2 (0.135; model 4). The FRS 10-year CAD risk was a weak model for CAD (model 5), but the addition of the EATV index (0.058; model 6) and EAT_{LAD} increased corrected R^2 (0.121; model 7).

Age and male sex (model 1) were determinants of Gensini score (**Table 3B**), after correcting for BMI. The addition of traditional risk factors (smoking history, hypertension, dyslipidemia, and type 2 diabetes mellitus; 0.074; model 2) or EATV index (0.069; model 3) did not result in appreciable increases in corrected R^2, but addition of EAT_{LAD} to the model increased corrected R^2 (0.125; model 4). Compared to only FRS (R^2=0.035; model 5), the addition of EAT_{LAD} also increased corrected R^2 (0.098; model 7).

EAT Measures and Possible Covariates

To determine the clinical features associated with EAT thickness, we performed univariate regression analysis between the EAT measures and their possible covariates (**Table S2**). EATV index was correlated with CAD, age, BMI, WC, SFA, and VFA. EAT_{RCA} and EAT_{LCX} were not correlated with CAD, but were correlated with age, BMI, WC, SFA, and VFA. In contrast, EAT_{LAD} was correlated with CAD and age, but not with BMI, WC, SFA, or VFA.

Combined FRS and EAT Prediction Model for CAD

Optimal cut-off points for predicting CAD on ROC curve analysis are shown in **Figure 4**. FRS, EATV index, and EAT_{LAD} cut-off points for predicting CAD were >8% (sensitivity, 66%; specificity, 54%), >90 cm^3/m^2 (sensitivity, 33%; specificity, 88%), and >5.7 mm (sensitivity, 72%; specificity, 57%), respectively. Compared with only the FRS cut-off (model 1), the addition of the EAT_{LAD} cut-off to the FRS (model 1 vs. model 3: P=0.014) resulted in a stronger predictive value than did the model combining the EATV index cut-off and that for the FRS (model 2 vs. model 3: P=0.042).

Table 3. Multivariate Indicators of CAD (A) and Gensini Score (B)

A. CAD

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7	
Adjusted R^2	0.059		0.065		0.073		0.135		0.034		0.058		0.121	
P-value	0.002		0.006		0.004		<0.001		0.006		0.001		<0.001	
	r	P-value	r	P-value	r	P-value	r	P-value	r	P-value	r	P-value	r	P-value
Age (years)	0.254	<0.001	0.238	0.001	0.202	0.008	0.189	0.008						
Male gender (yes or no)	0.080	0.256	0.044	0.587	0.055	0.500	0.075	0.345						
BMI (kg/m^2)	0.097	0.170	0.067	0.363	0.015	0.852	0.020	0.774						
History of smoking (yes or no)			0.108	0.178	0.103	0.198	0.089	0.25						
Hypertension (yes or no)			0.097	0.177	0.096	0.179	0.114	0.098						
Dyslipidemia (yes or no)			0.064	0.377	0.049	0.499	0.063	0.366						
T2DM (yes or no)			0.054	0.446	0.037	0.603	0.051	0.453						
FRS (%)									0.197	0.006	0.163	0.022	0.191	0.005
EATV index (cm^3/m^2)					0.127	0.117					0.175	0.014		
EAT_{LAD} thickness (mm)							0.276	<0.001					0.303	<0.001

B. Gensini score

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7	
Adjusted R^2	0.049		0.074		0.069		0.125		0.035		0.034		0.098	
P-value	0.005		0.003		0.006		<0.001		0.005		0.013		<0.001	
	r	P-value	r	P-value	r	P-value	r	P-value	r	P-value	r	P-value	r	P-value
Age (years)	0.187	0.009	0.198	0.006	0.201	0.009	0.156	0.029						
Male gender (yes or no)	0.152	0.033	0.120	0.142	0.119	0.148	0.146	0.067						
BMI (kg/m^2)	0.092	0.200	0.046	0.525	0.051	0.527	0.006	0.929						
History of smoking (yes or no)			0.105	0.191	0.105	0.19	0.088	0.258						
Hypertension (yes or no)			−0.014	0.843	−0.014	0.844	0.001	0.987						
Dyslipidemia (yes or no)			0.151	0.037	0.152	0.038	0.15	0.033						
T2DM (yes or no)			0.11	0.120	0.111	0.12	0.107	0.118						
FRS (%)									0.200	0.005	0.188	0.009	0.196	0.004
EATV index (cm^3/m^2)					−0.011	0.894					0.064	0.374		
EAT_{LAD} thickness (mm)							0.239	<0.001					0.260	<0.001

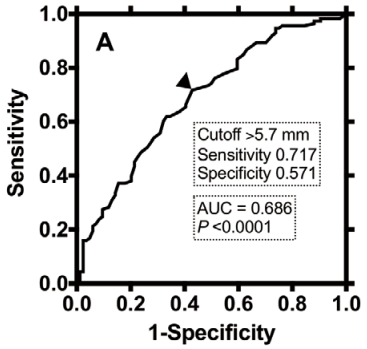
Abbreviations as in Table 1.

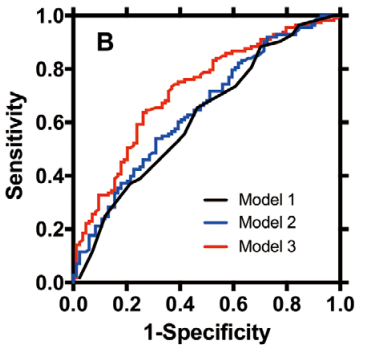
Discussion

There major observations were noted in the present study. First, after correcting for possible confounding factors, EAT_{LAD}, but not whole cardiac adiposity (EATV index), was independently associated with CAD and with the severity and extent of coronary atherosclerosis (Gensini score; **Tables 2**,**3**). Second, along with the unequal distributions of EAT, we compared local variation in the strength of associations between EAT thickness and coronary atherosclerosis. Of all EAT measurements, EAT_{LAD} was most significantly increased (**Table 1**) and associated with CAD and Gensini score (**Table 2**). Third, EAT_{LAD}, but no other EATV measures, provided additional prognostic value for predicting CAD, in combination with FRS. Thus, the simple measurement of EAT_{LAD} can be a useful surrogate clinical marker of CAD.

Local EAT Thickness and Global Cardiac Adiposity

A growing body of evidence suggests that local fat distribution, compared with global cardiac adiposity, plays an important role in the development of an unfavorable metabolic and cardiovascular risk profile.[7,20–22] When added to models using traditional risk factors for CAD and Gensini scores (models 1, 2), EATV index, a marker of global cardiac adiposity, did not increase corrected R^2 (model 3). Addition of EAT_{LAD}, however, increased corrected R^2 (0.135; model 4). Thus, we suggest that only modest associations are seen between global EATV and coronary atherosclerosis, but strong associations are





ROC curve analysis

Variables	AUC	95% CI	P
Model 1 FRS	0.621	0.539 - 0.696	0.007
Model 2 FRS + EATV index	0.647	0.566 - 0.720	0.0007
Model 3 FRS + EAT_{LAD}	0.719	0.642 - 0.785	<0.0001

Comparisons	P
Model 1 vs Model 2	0.377
Model 1 vs Model 3	0.014
Model 2 vs Model 3	0.042

Figure 4. Receiver operating characteristic (ROC) curve analysis of the predictive accuracy of (**A**) EAT thickness in the area surrounding the left anterior descending artery (LAD; EAT_{LAD}) and (**B**) multivariate models combining EAT measures and Framingham risk score (FRS), for significant CAD. (**B**) Cut-offs of FRS and total EATV index (EATV/body surface area) for predicting CAD were >8% (sensitivity, 66%; specificity, 54%) and >90 cm^3/m^2 (sensitivity, 33%; specificity, 88%), respectively. Between-model comparison was done using C statistics, and statistical significance was set at P<0.05. AUC, area under the curve. Other abbreviations as in Figures 1,2.

observed between local EAT thicknesses and the presence, severity, and extent of CAD. Of the studies examining the relationship between EAT measures and atherosclerosis of the adjacent arteries, the majority have shown that increases either in EATV or in the local thickness of the coronary perivascular adipose tissue were significantly correlated with obstructive CAD.[7]

The correlation of global EAT adiposity and local EAT thicknesses with regard to prognostic impact has not fully been evaluated. In the present study, local EAT thickness, as compared with EATV, was a sensitive and prognostic measure of CAD. Global cardiac adiposity is well known to be strongly associated with whole-body adiposity.[24,25] In the current study, EATV index correlated well with CAD, as well as with age, BMI, WC, SFA, and VFA (**Table S2**). In contrast, EAT_{RCA} and EAT_{LCX} correlated with age, BMI, WC, SFA, and VFA, but not with CAD; EAT_{LAD} correlated with CAD and age, but not with BMI, WC, SFA, or VFA. Therefore, EAT_{LAD} independently reflects local circumstances, relative to whole-body adiposity. EAT, mainly consisting of adipocytes and tissue macrophages, can be a source of endocrine and paracrine cytokines, substrates, and adipokines. Thus, if EAT becomes "sick fat", it directly contributes to atherosclerosis through an outside-to-inside inflammatory atherogenic signal conveyed through the vasa vasorum.[25–27] In contrast, the progression of atherosclerotic plaque[28] and the presence of an oxygen-insufficient microenvironment, the inner layers may provide an inside-to-outside signal, similar to hypoxic conditions, resulting in EAT accumulation.[29] This may be supported by our previous observation that pro-inflammatory cytokine profiles are more prominently enhanced in locations where severe atherosclerosis is observed.[1,30]

Location-Specific EAT Thickness and CAD

EAT_{LAD}, but not EAT_{RCA} or EAT_{LCX}, was greater in the CAD group. When patients were divided into 0VD or 1–3VD (CAD) subgroups, EAT_{LAD} increased across the groups, whereas EATV index, EAT_{RCA}, and EAT_{LCX} were similar across the 4 groups (**Figure 2**). Previous reports have described associations between location-specific EAT thickness and obstructive CAD.[20–22] Wang et al showed that EAT thickness in the LAVG, but not EATV, was significantly associated with coronary atherosclerosis;[20] also, a meta-analysis confirmed that increases in location-specific EAT thicknesses at the LAVG are associated with obstructive CAD.[21] Our previous study found that EAT_{LAD} was greater in the CAD group than in the non-CAD group, and that it had added diagnostic value over other conventional risk factors.[22] Ohyama et al reported that the local EATV around the LAD, but not around the RCA or LCX, was significantly increased in patients with LAD spasms, suggesting the involvement of coronary EAT in the pathogenesis of coronary spasms, a form of atherosclerosis.[31,32]

Thus, location-specific EAT thickness is more closely associated with the presence of coronary atherosclerosis than is global cardiac adiposity, but the EAT thickness location with the greatest CAD prognostic value remains controversial. Combining data from current and previous studies,[20–22] there are 2 possible explanations for the different impacts of location-specific EAT thicknesses. First, there are deeper gaps in atrioventricular grooves than in the AIVG. The paracrine effects of cytokines from EAT may be small in the RAVG and LAVG. Second, measurement of AIVG may be more accurate than for RAVG and LAVG because of anatomical characteristics, and thus its changes may sensitively reflect the presence of atherosclerosis. On ROC curve analysis for estimating CAD, of the EAT thicknesses at the RCA, LAD and LCX (**Figure S1B**), EAT_{LAD} had the largest area under the curve compared with EAT_{RCA} or EAT_{LCX}, further supporting this notion. The finding of significant correlation only between Gensini score in the LAD and EAT_{LAD}, but not between those in RCA and LCX (**Figure S1A**), may also explain the close association of EAT_{LAD} with the severity of CAD. Even in the non-LAD group, a borderline correlation was still observed between EAT_{LAD} and Gensini score (**Figure 3I–L**). We cannot denote a causality that EAT thickness of LAD

affects to atherosclerosis of other 2 branches, however could suggest an interaction.

CAD Prediction Model

In the current study, cut-offs for predicting CAD were determined for FRS (>8%; sensitivity, 66%; specificity, 54%), EATV index (>90 cm^3/m^2; sensitivity, 33%; specificity, 88%), and EAT_{LAD} (>5.7 mm; sensitivity, 72%; specificity, 57%). Compared with only FRS >8% (model 1), the addition of EAT_{LAD} produced a stronger predictive value than the model combining EATV index and FRS (model 1 vs. model 3, P=0.014; model 2 vs. model 3, P=0.042). Therefore, we can assume that EAT_{LAD}, but not EATV index, provides additional prognostic value for predicting CAD, in combination with FRS. We first showed that the simple measurement of EAT_{LAD} is a useful surrogate marker of CAD in the clinical setting. Although FRS is a standard prediction model for CAD, its predictive power is limited. By adding EAT_{LAD}, simply measured on either echocardiography[22] or CT (the present study), the model gains satisfactory prognostic power for predicting the presence of CAD.

Study Limitations

This study has potential limitations. First, the design of this clinical study was cross-sectional, and it was conducted at a single center with a relatively small number of subjects. Second, the subjects consisted entirely of Japanese patients, therefore the relevance of this study to other ethnic backgrounds awaits further research. Third, the ROC results cannot be applied broadly to patients with suspected CAD, and the sensitivity and specificity of EAT_{LAD} for diagnosing CAD need to be confirmed in a future, larger study. Fourth, we did not consider the impact of medication[33–35] or lifestyle[36] on EAT.

Conclusions

Local fat thickness in the area surrounding the LAD is a simple and useful measure for estimating the presence, severity, and extent of CAD, independent of classical coronary risk factors. Further investigation, involving a large-scale study, is warranted to confirm the clinical efficacy of EAT thickness in patients with suspected coronary atherosclerosis.

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Disclosures

The authors declare no conflicts of interest.

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Supplementary Files

Supplementary File 1

Figure S1. (**A**) Linear correlation between Gensini score in coronary vessels and EAT thickness in the area surrounding the RCA (EAT_{RCA}), LAD (EAT_{LAD}) and LCX (EAT_{LCX}) in patients with (○) non-CAD or (●) CAD.

Table S1. Differences in EAT parameters vs. CAD status

Table S2. EAT measures and possible covariates

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-17-1289