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

ORIGINAL ARTICLE
Imaging

Association of Epicardial and Abdominal Visceral Adipose Tissue With Coronary Atherosclerosis in Patients With a Coronary Artery Calcium Score of Zero

Hiroshi Tsushima, MD; Hideya Yamamoto, MD, PhD; Toshiro Kitagawa, MD, PhD; Yoji Urabe, MD, PhD; Fuminari Tatsugami, MD, PhD; Kazuo Awai, MD, PhD; Yasuki Kihara, MD, PhD

Background: We sought to examine whether epicardial and abdominal visceral adipose tissue distribution is associated with coronary atherosclerosis in patients with a coronary artery calcium (CAC) score of zero, assessed by coronary computed tomography angiography (CCTA).

Methods and Results: We studied 352 patients with suspected coronary artery disease (mean age 61±11 years, 57% male) with a CAC score of zero who had undergone CCTA. Non-calcified coronary plaques (NCPs) were detected in 102 patients (29%); those causing ≥50% stenosis were found in 15 patients (4%). Patients were divided into 4 groups on the basis of CT-based epicardial adipose tissue (EAT) volume and abdominal visceral adipose tissue (VAT) area using the sex-specific median value. Multivariate analysis showed that the adjusted odds ratios for the presence of NCPs in the high VAT area/low EAT volume group, and the high VAT area/high EAT volume group were 2.80 (95% confidence interval [95% CI]: 1.25–6.35, P=0.01) and 2.68 (95% CI: 1.36–5.45, P=0.004), respectively. Interestingly, the low VAT area/high EAT volume group showed an equivalent adjusted odds ratio of 3.02 (95% CI: 1.33–6.90, P=0.008).

Conclusions: EAT volume is eligible as a marker to be evaluated in addition to VAT area in patients with a CAC score of zero. (*Circ J* 2015; **79:** 1084–1091)

Key Words: Atherosclerosis; Metabolic syndrome; Multidetector computed tomography (MDCT); Obesity; Plaque

Visceral adipose tissue (VAT) is reported to produce pro-inflammatory cytokines that contribute to coronary atherosclerosis.[1,2] Recent studies have suggested that there is also a relationship between epicardial adipose tissue (EAT), coronary artery calcium (CAC) score, and coronary artery disease (CAD).[3,4] EAT shares a common embryological origin with VAT, and adipocytokines from EAT might be local contributors to the pathogenesis of coronary atherosclerosis.[5–7]

Editorial p 969

The role of the CAC score as an indicator of coronary atherosclerosis is well established.[8,9] The absence of coronary artery calcification is associated with a low prevalence of obstructive CAD and a very low risk of future cardiovascular events.[10,11] Nonetheless, a CAC score of zero does not completely exclude either coronary atherosclerosis or coronary arterial obstruction by non-calcified coronary plaques (NCPs).[12,13] The factors that determine the distribution of epicardial and visceral abdominal adipose tissue and their ramification in patients at low risk for CAD are not fully understood.

We hypothesized that the distribution of epicardial and abdominal visceral adipose tissue influences coronary atherosclerosis in patients with a CAC score of zero. We sought to establish whether there is a relationship between epicardial and abdominal visceral adipose tissue distributions and the incidence of NCPs detected by coronary computed tomography angiography (CCTA) in patients with a CAC score of zero.

Methods

Study Population

Between January 2008 and April 2013, 2,320 consecutive patients underwent 64-slice CCTA and of them, we retrospectively examined 381 patients with a CAC score of zero who were not diagnosed with CAD. We excluded 7 patients in whom motion artifact or inadequate contrast concentration impaired image quality, 9 with arrhythmia such as chronic atrial fibril-

Received October 26, 2014; revised manuscript received January 9, 2015; accepted January 14, 2015; released online February 24, 2015
Time for primary review: 29 days

Department of Cardiovascular Medicine (H.T., H.Y., T.K., Y.U., Y.K.), Department of Diagnostic Radiology (F.T., K.A.), Hiroshima University Graduate School of Biomedical and Health Sciences, Hiroshima, Japan

Mailing address: Hideya Yamamoto, MD, PhD, Department of Cardiovascular Medicine, Hiroshima University Graduate School of Biomedical and Health Sciences, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan. E-mail: hideyayama@hiroshima-u.ac.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-14-1169

Table 1. Patients Characteristics According to the Presence or Absence of NCPs

Variable	All patients (n=352)	NCPs (+) (n=102)	NCPs (–) (n=250)	P value
Age (years)	61±11	63±10	59±11	0.01
Male, n (%)	199 (57)	73 (72)	126 (50)	<0.001
Hypertension, n (%)	187 (53)	54 (53)	133 (53)	0.96
Hypercholesterolemia, n (%)	187 (53)	57 (56)	130 (52)	0.51
Diabetes mellitus, n (%)	62 (18)	20 (20)	42 (17)	0.53
Current smoking, n (%)	54 (15)	18 (18)	36 (14)	0.45
BMI (kg/m^2)	23.7±3.7	24.1±3.6	23.5±3.7	0.21
Obesity (BMI ≥25 kg/m^2), n (%)	124 (35)	39 (38)	85 (34)	0.45
MetS, n (%)	111 (32)	43 (42)	68 (27)	0.006
Medications				
Statins, n (%)	81 (23)	18 (18)	63 (25)	0.13
Renin-angiotensin system inhibitors, n (%)	91 (26)	31 (30)	60 (24)	0.21
Hypoglycemic agents, n (%)	36 (10)	15 (15)	21 (8)	0.08
Framingham risk score category				
Low risk (<10%), n (%)	240 (68)	52 (51)	188 (75)	<0.001
Intermediate (10–20%), n (%)	100 (29)	43 (42)	57 (23)	<0.001
High risk (>20%), n (%)	12 (3)	7 (7)	5 (2)	0.02
Total cholesterol (mg/dl)	200±34	205±32	198±35	0.06
LDL cholesterol (mg/dl)	119±31	126±28	115±32	<0.001
HDL cholesterol (mg/dl)	62±17	59±15	63±17	0.007
Triglycerides (mg/dl)	137±92	143±79	135±97	0.09
Hemoglobin A_{1c} (%)	6.1±1.1	6.1±1.0	6.1±1.2	0.71
CRP (mg/L)	0.9±1.3	1.0±0.15	0.8±1.2	0.001
EAT volume (ml)	121±46	114±48	88±54	<0.001
VAT area (cm^2)	96±53	132±39	117±49	<0.001

Data are presented as mean±standard deviation or number (%). BMI, body mass index; CRP, C-reactive protein; EAT, epicardial adipose tissue; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MetS, metabolic syndrome; NCP, non-calcified coronary plaques; VAT, visceral adipose tissue.

lation, and 13 with missing data concerning 1 or more of the traditional CAD risk factors. Consequently, the data of 352 patients were analyzed. The Ethics Committee of Hiroshima University Hospital gave approval for the conduct of the study.

Risk Factor Assessments

Hypertension was defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or active treatment with an antihypertensive agent. Hypercholesterolemia was defined as a serum low-density lipoprotein (LDL) level ≥140 mg/dl on direct measurement, a total cholesterol ≥220 mg/dl, or current use of lipid-lowering drugs. Diabetes mellitus was defined by a glycosylated hemoglobin level ≥6.5%,[14] or current use of oral hypoglycemic drugs or insulin. Current smoking was defined as smoking regularly or having quit in the past 30 days. Metabolic syndrome (MetS) was diagnosed according to the Japanese criteria[15] and the Framingham risk score was calculated.[16] Obesity was defined as a body mass index (BMI) ≥25 kg/m^2.[17]

CT Angiography and Image Analysis

Imaging examinations were performed using a 64-slice CT scanner (LightSpeed VCT; GE Healthcare, Little Chalfont, Buckinghamshire, UK). Patients with a resting heart rate ≥60 beats/min were administered metoprolol 20–40 mg orally 60 min before the scan. All patients were administered nitroglycerin 0.3 mg sublingually just before scanning. An unenhanced scan with prospective ECG triggering was performed to measure the CAC score, followed by CTA. We calculated CAC scores using dedicated software (Smartscore, version 3.5; GE Healthcare).[18] During an inspiratory breath hold, contrast-enhanced scanning was performed by a retrospective ECG-gated scan using the helical mode or prospective ECG-triggered CTA (with the center of the imaging window corresponding to 75% of the R-R interval) based on our previous report.[19,20] A body weight-adjusted volume (0.6 ml/kg) of iodine-based contrast medium was injected into the antecubital vein over the course of 10s, followed by a 25-ml 0.9% NaCl solution flush over 5s. Reconstructed images were transferred to a computer workstation (Advantage Workstation Ver.4.4; GE Healthcare) for post-processing and subsequent image analysis.

Measurement of VAT Area and EAT Volume on CT

Abdominal scans were performed simultaneously at the level of the 4th and 5th lumbar vertebrae in the spiral position, and 12 slices of 5-mm thickness were obtained during a breath hold after normal expiration. The VAT area was defined as the intraperitoneal adipose tissue area with a CT density between −150 and −50 Hounsfield units (HU) on a slice at the level of the umbilicus, which was measured using dedicated software (Virtual Place, AZE Inc, Tokyo, Japan).[18,21]

EAT was defined as that seen surrounding the myocardium but limited by the epicardium on plain CT images acquired for calcium scoring. The EAT area was defined that with a density between −250 and −30 HU, which was manually traced and automatically quantified using the same software as for the

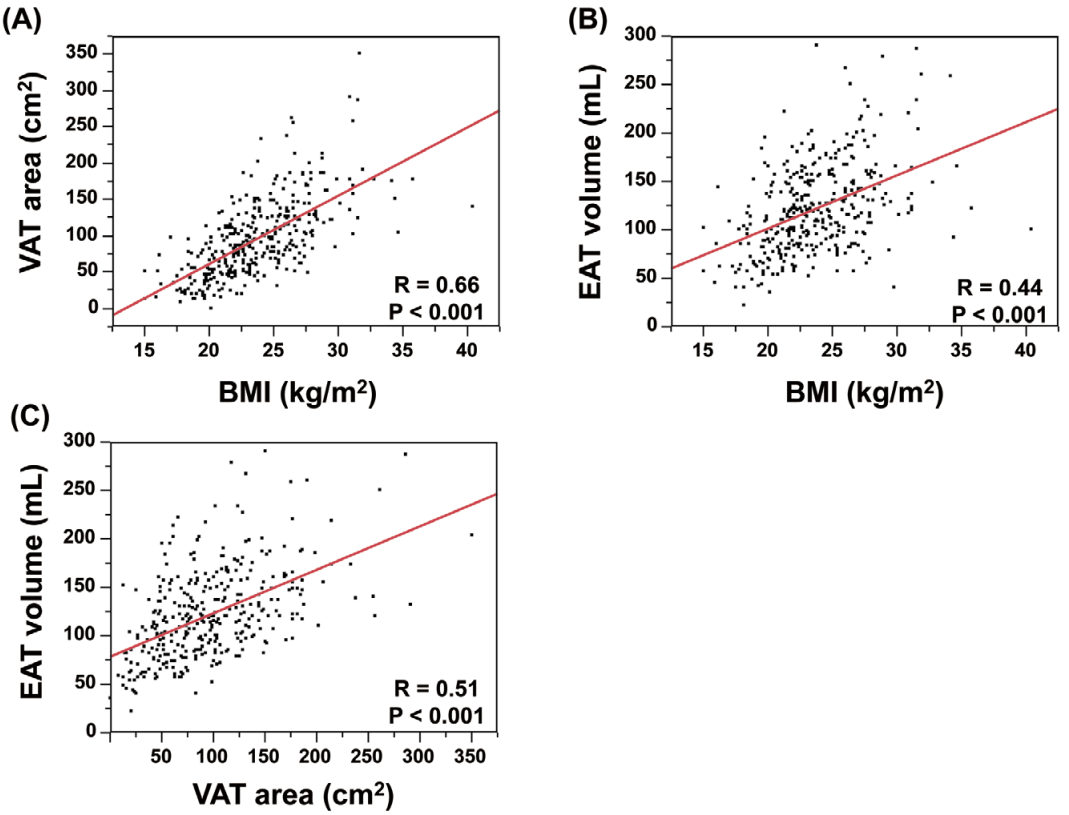

Figure 1. Correlation of abdominal visceral adipose tissue (VAT) area (**A**) and epicardial adipose tissue (EAT) volume (**B**) with body mass index (BMI), and that between VAT area and EAT volume (**C**).

VAT area. As previously described,[22] EAT volume was measured by calculating the sum of the EAT areas measured from 1 cm above the left main coronary artery to the left ventricular apex at 1-cm intervals.

Evaluation of CCTA Findings

We defined NCP as a structure >1 mm² in an area with a CT density ≤130 HU, located within the vessel wall and clearly distinguishable from the contrast-enhanced coronary lumen and surrounding pericardial tissue.[19,20] Independent observers assessed the presence of NCPs on cross-sectional and multiplanar CCTA image reconstructions in all coronary segments >2 mm in diameter according to the Society of Cardiovascular Computed Tomography 18-segment model.[23] The proportion of lumen stenosis was determined by measuring the luminal diameter at the narrowest site and comparing it with the diameter of the normal proximal site: ≥50% stenosis was considered clinically significant. Plaque volume was calculated by summating all the contiguous cross-sectional plaque areas along a vessel centerline using a slice thickness of 1.0 mm.[24]

Statistical Analysis

Continuous variables are presented as mean±standard deviation, and categorical variables are presented as numbers of patients (proportion). We compared the characteristics and CT findings of the patients allocated to 1 of 4 groups on the basis of CT-based EAT volume and VAT area measurements using the median value for each sex. Analysis of variance or the Kruskal-Wallis test was used for group comparisons of continuous variables. Tukey's test was used for analysis of variables that were normally distributed, and the Steel-Dwass method for those that were not. The Pearson's chi-squared test was used for categorical variables. The presence of NCPs was assessed as a binary outcome. We calculated the odds ratio (OR) with 95% confidence intervals (95% CIs) for the presence of NCPs stratified by a combination of VAT area and EAT volume (VAT/EAT) using a univariate model, a multivariate age-adjusted model, and a multivariate model adjusted for age, sex, Framingham risk score category, and serum levels of LDL cholesterol, high-density lipoprotein (HDL) cholesterol and C-reactive protein (CRP), which were significantly different between the patients with and without NCPs. ORs stratified by a combination of MetS and EAT volume (MetS/EAT) or of BMI and EAT volume (BMI/EAT) were also calculated to assess whether these different measures of obesity are useful as a substitute for VAT area to avoid unnecessary exposure to ionizing radiation. P values <0.05 were considered statistically significant. All statistical analyses were performed with JMP 10 statistical software (SAS Institute Inc, Cary, NC, USA).

Results

Patients Characteristics and CT Findings

The mean age of the analyzed cohort was 61±11 years; 57% were male. More than half had hypertension (53%), the same proportion had hypercholesterolemia (53%), 18% had been

Table 2. Patients Characteristics in 4 Groups Defined by VAT Area and EAT Volume

Variable	Low VAT area (n=175)		High VAT area (n=177)		P value
	Low EAT volume (n=123)	High EAT volume (n=52)	Low EAT volume (n=54)	High EAT volume (n=123)	
Age (years)	58±12	61±11	59±10	64±10*	<0.001
Male, n (%)	66 (54)	32 (62)	33 (61)	68 (55)	0.69
Hypertension, n (%)	43 (35)	27 (52)*	34 (63)*	83 (67)*	<0.001
Hypercholesterolemia, n (%)	52 (42)	26 (50)	33 (61)*	76 (62)*	0.01
Diabetes mellitus, n (%)	9 (7)	7 (13)	16 (30)*	30 (24)*	<0.001
Current smoking, n (%)	16 (13)	9 (17)	6 (11)	23 (19)	0.48
BMI (kg/m^2)	21.3±2.9	22.9±2.3*	24.7±3.6*	25.9±3.4*	<0.001
Obesity (BMI ≥25 kg/m^2), n (%)	15 (12)	12 (23)	25 (46)*	72 (59)*	<0.001
MetS, n (%)	7 (6)	9 (17)*	25 (46)*	70 (57)*	<0.001
Medications					
Statin use, n (%)	19 (15)	10 (19)	15 (28)	37 (30)*	0.04
Renin-angiotensin system inhibitors, n (%)	18 (15)	13 (25)	15 (28)*	45 (37)*	0.001
Hypoglycemic agents, n (%)	7 (6)	4 (8)	9 (17)*	16 (13)*	0.08
Framingham risk score category					
Low risk (<10%), n (%)	100 (81)	32 (62)*	40 (74)	68 (55)*	<0.001
Intermediate (10–20%), n (%)	22 (18)	19 (37)*	13 (24)	46 (37)*	0.003
High risk (>20%), n (%)	1 (1)	1 (2)	1 (2)	9 (7)*	0.03
Total cholesterol (mg/dl)	196±35	200±34	202±35	203±32	0.32
LDL cholesterol (mg/dl)	113±32	118±31	121±28*	123±31*	0.03
HDL cholesterol (mg/dl)	67±18	65±7	57±13*	58±15*	<0.001
Triglyceride (mg/dl)	106±65	111±96	175±122*	163±86*	<0.001
Hemoglobin A_{1c} (%)	5.9±1.0	6.0±1.3	6.4±1.1*	6.3±1.1*	0.009
CRP (mg/L)	0.6±1.2	0.9±1.3*	0.9±1.3*	1.1±1.4*	0.02
Presence of NCPs, n (%)	17 (14)	19 (37)*	19 (35)*	47 (38)*	<0.001
1	12 (10)	15 (29)*	12 (22)*	33 (27)*	0.003
≥2	5 (4)	4 (8)	7 (13)*	14 (11)*	0.12
NCPs with ≥50% stenosis, n (%)	1 (1)	6 (12)*	2 (4)	6 (5)*	0.01
≥2	5 (4)	4 (8)	8 (15)	13 (11)	0.09
Maximum luminal stenosis (%)	4±12	12±21*	10±16*	12±19*	0.001
Total plaque volume (mm^3)	9±30	26±68*	25±44*	28±49*	0.01

Data are presented as mean±standard deviation or number (%). *P<0.05 compared with the low VAT area low EAT volume reference group. Abbreviations as in Table 1.

diagnosed with diabetes mellitus, and 15% were current smokers. The majority of the study population had low to intermediate risk according to their Framingham risk scores (68% low, 29% intermediate, and 3% high risk). Of the 352 patients in the cohort, 102 (29%) had at least 1 NCP, and 15 (4%) had significant stenosis. The mean EAT volume and VAT area were 121±46 ml and 96±53 cm^2, respectively. Patients with NCPs were mostly male, significantly older and had higher percentages of MetS, and intermediate and high risk categories of Framingham risk scores. The serum levels of LDL cholesterol and CRP, and VAT area and EAT volume were significantly higher in patients with NCPs (Table 1).

The median VAT areas of men and women were 102 cm^2 (interquartile range [IQR]: 74–136 cm^2) and 69 cm^2 (IQR: 46–105 cm^2), respectively, and the median EAT volumes were 119 ml (IQR: 91–150 ml) and 114 ml (IQR: 82–148 ml), respectively. The VAT area and EAT volume had moderate correlations with BMI (R=0.66 and R=0.44, respectively; both P<0.001), and VAT area and EAT volume also moderately correlated with each other (R=0.51, P<0.001; Figure 1).

Association of VAT Area and EAT Volume With the Presence of NCPs

Table 2 shows the characteristics and CT findings of the 4 patient groups classified by VAT area and EAT volume according to the median VAT area (men, 102 cm^2; women, 69 cm^2) and the median EAT volume (men, 119 ml; women, 114 ml). Most of patient characteristics were significantly different among the 4 groups. Furthermore, the prevalence of NCPs, total plaque volume, and maximum proportion of luminal stenosis were significantly higher in the high EAT volume/low VAT group and the 2 high VAT groups compared with the low EAT volume/low VAT reference group.

ORs for the Presence of NCPs Stratified by EAT Volume and Other Adipose Factors

Univariate and multivariate ORs for the presence of NCPs were significantly increased in all the high EAT volume groups, whether also defined by VAT or MetS, when compared with the low EAT reference groups (Table 3). Figure 2 shows the ORs for the presence of NCPs stratified by EAT volume combined with VAT area (VAT/EAT), presence of MetS (MetS/EAT), and BMI (BMI/EAT) compared with the low VAT area/low EAT volume reference group after adjusting for age, sex,

Table 3. Univariate and Multivariate Models Examining the Presence of Non-Calcified Plaques Stratified by EAT Volume and VAT Area, MetS or BMI

	Univariate		Age-adjusted		Multivariate*	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
VAT area and EAT volume						
Low VAT and low EAT (n=123)	1 (ref)	–	1 (ref)	–	1 (ref)	–
Low VAT and high EAT (n=52)	3.59 (1.70–7.77)	0.001	3.41 (1.59–7.43)	0.002	3.02 (1.33–6.90)	0.008
High VAT and low EAT (n=54)	3.38 (1.59–7.29)	0.002	3.32 (1.55–7.20)	0.002	2.80 (1.25–6.35)	0.01
High VAT and high EAT (n=123)	3.86 (2.09–7.39)	<0.001	3.39 (1.82–6.57)	<0.001	2.68 (1.36–5.45)	0.004
MetS and EAT volume						
Non-MetS and low EAT (n=147)	1 (ref)	–	1 (ref)	–	1 (ref)	–
Non-MetS and high EAT (n=96)	2.94 (1.62–5.43)	<0.001	2.67 (1.46–4.98)	0.002	2.47 (1.29–4.80)	0.007
MetS and low EAT (n=30)	3.42 (1.44–7.99)	0.006	3.80 (1.58–9.03)	0.003	2.81 (1.10–7.09)	0.03
MetS and high EAT (n=79)	3.31 (1.77–6.26)	<0.001	3.02 (1.61–5.76)	<0.001	2.20 (1.10–4.45)	0.03
BMI and EAT volume						
Non-obese and low EAT (n=137)	1 (ref)	–	1 (ref)	–	1 (ref)	–
Non-obese and high EAT (n=91)	2.93 (1.62–5.36)	<0.001	2.66 (1.13–3.98)	0.02	2.42 (1.26–4.71)	0.008
Obese and low EAT (n=40)	1.42 (0.60–3.21)	0.41	1.61 (0.67–3.68)	0.28	1.25 (0.49–3.04)	0.62
Obese and high EAT (n=84)	2.25 (1.21–4.21)	0.01	1.77 (1.13–3.98)	0.02	1.53 (0.77–3.02)	0.22

*Adjusted for age, sex, Framingham risk score category, and serum LDL cholesterol, serum HDL cholesterol and serum CRP levels. Obesity was defined as BMI ≥25 kg/m^2. CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

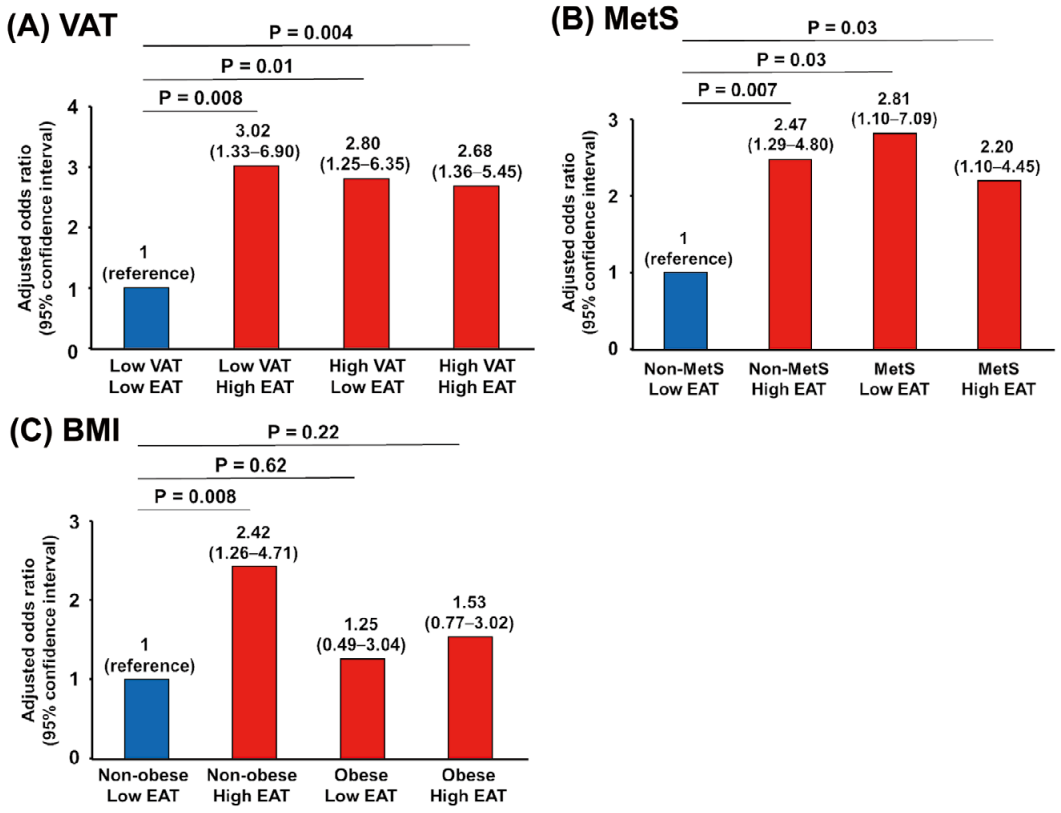

Figure 2. Odds ratios for the presence of non-calcified coronary plaques stratified by epicardial adipose tissue (EAT) volume and (**A**) abdominal visceral adipose tissue (VAT) area, (**B**) metabolic syndrome (MetS), and (**C**) body mass index (BMI) adjusted for age, sex, Framingham risk score category, and serum levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and C-reactive protein.

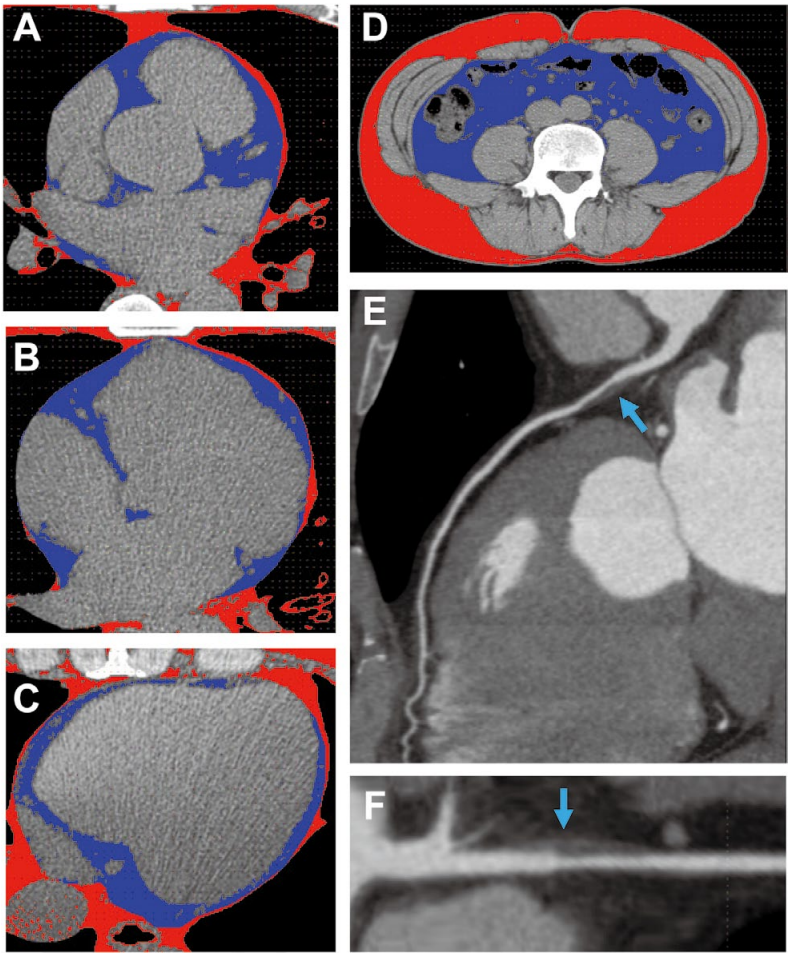

Figure 3. Coronary computed tomography angiography images from a 45-year-old man with a coronary artery calcium score of zero. Epicardial adipose tissue volume was elevated (150 ml) (**A**–**C**) but abdominal visceral adipose tissue area was low (92 cm^2) (**D**). The multiplanar reconstructed image shows a non-obstructive atherosclerotic lesion with non-calcified plaque in the proximal portion of the left anterior descending artery (**E**,**F**; arrows). The total plaque volume was 143 mm^3.

Framingham risk score category, and serum levels of LDL cholesterol, HDL cholesterol and CRP. The ORs of the high VAT area/low EAT volume group and the high VAT area/high EAT volume group were 2.80 (95% CI: 1.25–6.35, P=0.01) and 2.68 (95% CI: 1.36–5.45, P=0.004), respectively. Interestingly, the OR of the low VAT area/high EAT volume group was similar (OR 3.02, 95% CI: 1.33–6.90, P=0.008; **Figure 2A**). Broadly comparable findings were observed in the analysis stratified by MetS/EAT volume. Compared with the non-MetS/low EAT volume reference group, the ORs for the presence of NCPs in the non-MetS/high EAT volume group, the MetS/low EAT group, and the MetS/high EAT volume group were 2.47 (95% CI: 1.29–4.80, P=0.007), 2.81 (95% CI 1.10–7.09, P=0.03), and 2.20 (95% CI: 1.10–4.45, P=0.03), respectively (**Figure 2B**). In contrast, when obesity was defined by BMI, the only OR for the presence of NCPs that was significantly elevated compared with the low BMI/low EAT volume reference group was in the low BMI/high EAT volume group (2.42, 95% CI 1.26–4.71, P=0.008; **Figure 2C**).

Figure 3 shows a representative case of a patient with high EAT volume, low VAT area, and NCPs.

Discussion

We found an association between epicardial and visceral abdominal adipose tissue distribution and the presence of NCPs detected by CCTA in patients with a CAC score of zero, suggesting that both high VAT area and high EAT volume are implicated in the pathophysiology of NCP formation. Consequently, we believe that combined assessment of VAT area and EAT volume may be a useful means of more accurately stratifying cardiac risk in this group of patients. Notably, an increased EAT volume identified patients with NCPs even when the VAT area was low, implying that accumulation of EAT contributes to coronary plaque formation, even in patients without abdominal obesity. This relationship was observed whether or not obesity was stratified by the presence of MetS.

Association of VAT and EAT With Coronary Atherosclerosis

It is increasingly recognized that EAT is a risk factor for coronary atherosclerosis.[25] Nevertheless, there have been few studies that have examined the combined contributions of EAT and VAT. In most cases, BMI, presence of MetS, or waist circumference are used as a substitute for VAT area. We have also studied the association between EAT volume and the presence and characteristics of NCPs, and proposed that VAT and EAT may work synergistically to accelerate coronary atherosclerosis from within and from outside the vessel wall, respectively.[22] Additionally, the subjects of the studies of EAT are patients with suspected CAD and with various levels of coronary atherosclerosis risk. In the present study, we targeted patients with a CAC score of zero, which is regarded as a marker

of low risk for CAD.[10,11] To our knowledge, no other reports have examined both VAT area and EAT volume in patients with a CAC score of zero. Konishi et al reported that accumulation of pericardial fat, rather than abdominal obesity, could be implicated in the early development of CAD in their study of subjects with suspected CAD.[26] Our data from patients with fewer CAD risk factors are consistent with the findings for various levels of coronary atherosclerosis.

Cutoff Levels of VAT Area

The importance of EAT volume even in the absence of abdominal visceral obesity (low VAT area) or MetS does not help to establish whether abdominal visceral adiposity is an independent risk factor for cardiovascular disease, although VAT area is a criterion for diagnosing MetS in Japanese patients.[15] According to our previous report, the cutoff levels of VAT area to identify coronary artery calcification were 116 cm^2 and 82 cm^2 in men and women, respectively.[18] Furthermore, our other report also showed that when median VAT areas of 126 cm^2 for men and 91 cm^2 for women were used as cutoffs to define high and low VAT area groups, high VAT area was significantly associated with NCP burden.[21] In the present study, we used median VAT areas of 102 cm^2 for men and 69 cm^2 as the cutoffs for the high and low groups.

NCPs With a CAC Score of Zero

A CAC score of zero indicates a low prevalence of CAD and subsequent cardiovascular events in both symptomatic and asymptomatic patients.[10,11] However, in our cohort of patients with a CAC score of zero, the prevalence of NCPs was 29%. Previous studies have identified a prevalence of NCPs of 7–39% in patients with a CAC score of zero.[27–29] It is suggested that risk stratification using the combination of VAT area and EAT volume is useful for identifying CAD in patients with a CAC score of zero.

A recent population-based, prospective cohort study found that EAT is also associated with the progression of coronary artery calcification, especially in younger subjects (age <55 years) and those with an existing low CAC score (≤100), suggesting that EAT may drive early atherosclerosis.[30] The results of this study[30] support our previous findings that high EAT volume is associated with an increased likelihood of NCPs in patients with a CAC score of zero.

EAT Volume and Detection of Plaques in Patients Without Abdominal Obesity

We used CCTA to show that high EAT volume was associated with increased ORs for the presence of NCPs in non-obese patients, which is consistent with the findings of previous studies of patients with various levels of coronary atherosclerosis. Pericardial fat is reportedly more abundant in non-obese patients with coronary atherosclerosis compared with those without,[31] and Okada et al reported a significant correlation between EAT volume and the severity of CAD or plaque components in non-obese patients.[32] Detection of plaques is thought to be clinically important, even if the plaques are non-obstructive, as the presence of both obstructive and non-obstructive CAD on CCTA reportedly predicts a worse prognosis.[33]

Clinical Implications

Although a CAC score of zero indicates a low risk of CAD and future cardiovascular events, the existence of NCPs cannot be ignored. Our findings suggest that patients with high EAT volume are at greater risk of coronary atherosclerosis, even in the absence of abdominal obesity. A simultaneous assessment of VAT area and EAT volume may be a more accurate means of stratifying risk in patients with a CAC score of zero. Taken together, we judge that surveillance CCTA would be an effective strategy for managing long-term risk in those found to have higher VAT area and/or a higher EAT volume on initial screening.

In this study, we studied whether different measures of obesity are useful as a substitute for VAT area. ORs for the presence of NCPs in combination with EAT volume were similar between MetS and VAT. Therefore, MetS status could be used as a surrogate marker of VAT area to avoid unnecessary exposure to ionizing radiation. In contrast, the OR in the low BMI/high EAT volume group was significantly higher, but the high BMI groups was not significantly different compared with the reference group. One reason to explain this difference is that many of the patients with low VAT area may be included in the high BMI group.

Study Limitations

This was a cross-sectional study in which cardiovascular mortality and morbidity were not assessed; rather, an alternate endpoint of the presence of plaques on CCTA was used. Nevertheless, our findings support those of recent longitudinal studies. We recently described the relationship between high EAT volume (>107 ml) and increased rates of coronary events, even in a subgroup of patients with CAC score <100,[34] and the results of a large population study support the hypothesis that high EAT volume promotes early atherosclerosis, as EAT volume is reportedly associated with progression of coronary artery calcification, especially in subjects with low CAC scores.[30] We elected to use the presence of NCPs as the dependent variable, but had too few data to undertake a meaningful analysis of other variables such as the presence of obstructive stenosis or the number or volume of plaques.

We are also unable to identify the precise mechanism by which VAT and EAT accumulation could contribute to coronary plaque formation. However, our observation that serum lipid and glycosylated hemoglobin levels were more elevated in the high VAT than low VAT groups, but did not differ between the low EAT groups (Table 2) is worthy of further study. Interestingly, serum CRP levels were also higher in both the low VAT/high EAT group and the high VAT group when compared with the low VAT/low EAT reference group, suggesting that systemic inflammation may also play a role in the onset of coronary atherosclerosis, in addition to direct effects on the vascular wall.

Conclusions

In patients with a CAC score of zero, high EAT volume is associated with the presence of NCPs on CCTA, even in those with low VAT area. EAT volume is eligible as a marker to be evaluated in addition to VAT area in patients with a CAC score of zero. We propose that accumulation of EAT may contribute to coronary plaque formation in patients without abdominal obesity or MetS.

Acknowledgments

H.Y. received a Grant-in Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (Tokyo, Japan, No. 23591044).

Disclosures

Conflict of Interest: None of the authors has any conflict of interest to disclose.

References

1. Nicklas BJ, Penninx BW, Cesari M, Kritchevsky SB, Newman AB, Kanaya AM, et al. Association of visceral adipose tissue with incident myocardial infarction in older men and women: The Health, Aging and Body Composition Study. *Am J Epidemiol* 2004; **160:** 741–749.
2. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature* 2006; **444:** 875–880.
3. 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.
4. 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.
5. 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.
6. Sacks HS, Fain JN. Human epicardial adipose tissue: A review. *Am Heart J* 2007; **153:** 907–917.
7. Iacobellis G, Malavazos AE, Corsi MM. Epicardial fat: From the biomolecular aspects to the clinical practice. *Int J Biochem Cell Biol* 2011; **43:** 1651–1654.
8. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008; **358:** 1336–1345.
9. Yamamoto H, Ohashi N, Ishibashi K, Utsunomiya H, Kunita E, Oka T, et al. Coronary calcium score as a predictor for coronary artery disease and cardiac events in Japanese high-risk patients. *Circ J* 2011; **75:** 2424–2431.
10. Blaha M, Budoff MJ, Shaw LJ, Khosa F, Rumberger JA, Berman D, et al. Absence of coronary artery calcification and all-cause mortality. *JACC Cardiovasc Imaging* 2009; **2:** 692–700.
11. Sarwar A, Shaw LJ, Shapiro MD, Blankstein R, Hoffmann U, Cury RC, et al. Diagnostic and prognostic value of absence of coronary artery calcification. *JACC Cardiovasc Imaging* 2009; **2:** 675–688.
12. Gottlieb I, Miller JM, Arbab-Zadeh A, Dewey M, Clouse ME, Sara L, et al. The absence of coronary calcification does not exclude obstructive coronary artery disease or the need for revascularization in patients referred for conventional coronary angiography. *J Am Coll Cardiol* 2010; **55:** 627–634.
13. Morita H, Fujimoto S, Kondo T, Arai T, Sekine T, Matsutani H, et al. Prevalence of computed tomographic angiography-verified high-risk plaques and significant luminal stenosis in patients with zero coronary calcium score. *Int J Cardiol* 2012; **158:** 272–278.
14. International Expert Committee report on the role of the A1c assay in the diagnosis of diabetes. *Diabetes Care* 2009; **32:** 1327–1334.
15. Tajima M, Lee JS, Watanabe E, Park JS, Tsuchiya R, Fukahori A, et al. Association between changes in 12 lifestyle behaviors and the development of metabolic syndrome during 1 year among workers in the Tokyo metropolitan area. *Circ J* 2014; **78:** 1152–1159.
16. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel Ⅲ). *JAMA* 2001; **285:** 2486–2497.
17. Yatsuya H, Li Y, Hilawe EH, Ota A, Wang C, Chiang C, et al. Global trend in overweight and obesity and its association with cardiovascular disease incidence. *Circ J* 2014; **78:** 2807–2818.
18. Ohashi N, Yamamoto H, Horiguchi J, Kitagawa T, Hirai N, Ito K, et al. Visceral fat accumulation as a predictor of coronary artery calcium as assessed by multislice computed tomography in Japanese patients. *Atherosclerosis* 2009; **202:** 192–199.
19. Kunita E, Yamamoto H, Kitagawa T, Ohashi N, Utsunomiya H, Oka T, et al. Association between plasma high-molecular-weight adiponectin and coronary plaque characteristics assessed by computed tomography angiography in conditions of visceral adipose accumulation. *Circ J* 2012; **76:** 1687–1696.
20. Urabe Y, Yamamoto H, Kitagawa T, Utsunomiya H, Tsushima H, Tatsugami F, et al. Association between serum levels of n-3 polyunsaturated fatty acids and coronary plaque detected by coronary computed tomography angiography in patients receiving statin therapy. *Circ J* 2013; **77:** 2578–2585.
21. Ohashi N, Yamamoto H, Horiguchi J, Kitagawa T, Kunita E, Utsunomiya H, et al. Association between visceral adipose tissue area and coronary plaque morphology assessed by CT angiography. *JACC Cardiovasc Imaging* 2010; **3:** 908–917.
22. 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* 2012; **161:** 45–49.
23. Raff GL, Abidov A, Achenbach S, Berman DS, Boxt LM, Budoff MJ, et al. SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. *J Cardiovasc Comput Tomogr* 2009; **3:** 122–136.
24. Tardif JC, L'Allier PL, Ibrahim R, Gregoire JC, Nozza A, Cossette M, et al. Treatment with 5-lipoxygenase inhibitor VIA-2291 (Atreleuton) in patients with recent acute coronary syndrome. *Circ Cardiovasc Imaging* 2010; **3:** 298–307.
25. Yerramasu A, Dey D, Venuraju S, Anand DV, Atwal S, Corder R, et al. Increased volume of epicardial fat is an independent risk factor for accelerated progression of sub-clinical coronary atherosclerosis. *Atherosclerosis* 2012; **220:** 223–230.
26. Konishi M, Sugiyama S, Sugamura K, Nozaki T, Ohba K, Matsubara J, et al. Association of pericardial fat accumulation rather than abdominal obesity with coronary atherosclerotic plaque formation in patients with suspected coronary artery disease. *Atherosclerosis* 2010; **209:** 573–578.
27. Henneman MM, Schuijf JD, Pundziute G, van Werkhoven JM, van der Wall EE, Jukema JW, et al. Noninvasive evaluation with multislice computed tomography in suspected acute coronary syndrome: Plaque morphology on multislice computed tomography versus coronary calcium score. *J Am Coll Cardiol* 2008; **52:** 216–222.
28. Uretsky S, Rozanski A, Singh P, Supariwala A, Atluri P, Bangalore S, et al. The presence, characterization and prognosis of coronary plaques among patients with zero coronary calcium scores. *Int J Cardiovasc Imaging* 2011; **27:** 805–812.
29. Ito T, Suzuki Y, Ehara M, Matsuo H, Teramoto T, Terashima M, et al. Impact of epicardial fat volume on coronary artery disease in symptomatic patients with a zero calcium score. *Int J Cardiol* 2013; **167:** 2852–2858.
30. Mahabadi AA, Lehmann N, Kalsch H, Robens T, Bauer M, Dykun I, et al. Association of epicardial adipose tissue with progression of coronary artery calcification is more pronounced in the early phase of atherosclerosis: Results from the Heinz Nixdorf Recall Study. *JACC Cardiovasc Imaging* 2014; **7:** 909–916.
31. Yong HS, Kim EJ, Seo HS, Kang EY, Kim YK, Woo OH, et al. Pericardial fat is more abundant in patients with coronary atherosclerosis and even in the non-obese patients: Evaluation with cardiac CT angiography. *Int J Cardiovasc Imaging* 2010; **26**(Suppl 1)**:** 53–62.
32. Okada K, Ohshima S, Isobe S, Harada K, Hirashiki A, Funahashi H, et al. Epicardial fat volume correlates with severity of coronary artery disease in nonobese patients. *J Cardiovasc Med (Hagerstown)* 2014; **15:** 384–390.
33. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. *J Am Coll Cardiol* 2011; **58:** 849–860.
34. Kunita E, Yamamoto H, Kitagawa T, Ohashi N, Oka T, Utsunomiya H, et al. Prognostic value of coronary artery calcium and epicardial adipose tissue assessed by non-contrast cardiac computed tomography. *Atherosclerosis* 2014; **233:** 447–453.