International Journal of Cardiology 324 (2021) 8–12

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Relationship between epicardial adipose tissue volume and coronary artery spasm

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ARTICLE INFO

Article history:
Received 4 July 2020
Received in revised form 15 August 2020
Accepted 30 September 2020
Available online 2 October 2020

Keywords:
Epicardial adipose tissue
Coronary artery spasm
Abdominal adipose tissue

ABSTRACT

Background: Epicardial adipose tissue (EAT) is considered to play a critical role in vascular endothelial function. Coronary artery spasm has been postulated to be a causal factor in vascular endothelial abnormalities and atherosclerosis. This study aimed to investigate the relationship between coronary artery spasm and EAT volume, total abdominal adipose tissue (AAT) area, and abdominal visceral adipose tissue (AVAT) area.

Method: Among patients undergoing coronary computed tomography (CT) to evaluate coronary artery disease, we identified 110 patients who did not have significant coronary artery stenosis and underwent a coronary spasm provocation test with cardiac catheterization. They were divided into two groups according to the results of the spasm provocation test: spasm-positive and spasm-negative. EAT volume, total AAT area, and AVAT area were evaluated using CT images.

Results: Seventy-seven patients were included in the spasm-positive group and 33 patients in the spasm-negative group. There were no significant differences in baseline clinical characteristics between the two groups, except for the prevalence of current smoking (48% vs. 27%, $p = 0.04$). EAT volume was significantly higher in the spasm-positive group (108 ± 38 mL vs. 87 ± 34 mL, $p = 0.007$), while no significant difference was seen in total AAT area (280 ± 113 cm^2 vs. 254 ± 128 cm^2, $p = 0.32$) or AVAT area (112 ± 54 cm^2 vs. 98 ± 55 cm^2, $p = 0.27$). Multivariate logistic analysis indicated that EAT volume (per 10 cm^3) (odds ratio, 1.198; 95% confidence interval, 1.035–1.388; $p = 0.016$) was a significant predictor of coronary artery spasm.

Conclusion: Our results suggest that EAT has a strong association with coronary artery spasm, while AAT may not.

1. Introduction

Previous studies have shown that increased epicardial adipose tissue (EAT) and abdominal adipose tissue (AAT) are risk factors for cardiovascular disease [1–6]. Adipose tissues produce adipokines, including cytokines and chemokines, which can have systemic effects and cause vascular endothelial function disorders [7].

Coronary spasm has shown to be caused by vascular endothelial abnormality and arteriosclerosis [8]. Acetylcholine (Ach), serotonin, ergonovine, and histamine induce vasodilation by causing the release of nitric oxide from the healthy endothelium [9], whereas such substances can cause vasoconstriction in the coronary artery when endothelial dysfunction exists [10]. Thus, there is a hypothesis that various adipose tissues contribute to coronary artery spasm; however, the difference between EAT and other adipose tissue regarding their effect on the occurrence of coronary artery spasm has not been elucidated. This study aimed to investigate the relationship between coronary artery spasm and various adipose tissues by analyzing the EAT volume, total AAT area, and abdominal visceral adipose tissue (AVAT) area.

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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ijcard.2020.09.074
0167-5273/

2. Patients and methods

2.1. Subjects

We examined patients with chest discomfort who underwent cardiac computed tomography (CT) owing to suspicion of coronary artery disease from January 2008 to July 2015 at Chubu Rosai Hospital. After excluding patients with coronary artery stenoses (≥50% narrowing of at least one major epicardial coronary artery), we finally identified 110 patients who were suspected of coronary artery spastic angina and underwent coronary angiography with a spasm provocation test using intra-coronary Ach. These patients were divided into spasm-positive and spasm-negative groups. This study was performed in accordance with the guidelines of the Declaration of Helsinki and was approved by the institutional ethics review boards.

2.2. Coronary angiography, Ach provocation test

All enrolled patients underwent angiography and a coronary spasm provocation test. The coronary provocation test was performed using Ach according to the guidelines of the Japanese Circulation Society [11]. 1) Insertion of a temporary pacing electrode in the right ventricle for protecting severe bradycardia. 2) Control angiography of left and right coronary arteries. 3) Injection of Ach into the right coronary artery; 20 or 50 μg (each in 5 mL solution) over a period of 20 s, followed by coronary angiography after 1 min. 4) Injection of Ach into the left coronary artery; 20, 50, or 100 μg (each in 5 mL solution) over a period of 20 s, followed by coronary angiography after 1 min. 5) Right and left coronary angiography after administration of nitrate.

Coronary spasm provocation test was diagnosed positive when transient, total, or sub-total occlusion (>90% stenosis) was observed in a right coronary artery or left coronary artery, or 90% stenosis with signs/symptoms of myocardial ischemia (anginal pain and ischemic ST change). If provocation test was positive in the right coronary artery, injection of Ach into the left coronary artery was not performed.

2.3. Computer tomography analysis

Evaluation of EAT volume, total AAT area, and AVAT area were performed using a 64-multislice CT scanner. The CT datasets were transferred to a workstation for image analysis. As previously published [12], the volume of EAT was determined on the basis of cardiac non-contrast CT scanning. EAT was defined as the total amount of adipose tissue between the surface of the heart and the visceral layer of the pericardium. Epicardial areas were measured by tracing a region manually on all sections with contiguous 5-mm-thick axial images [2]. The computer software automatically constructed the epicardial image. A density range of −190 to −30 Hounsfield units (HU) was used to isolate the adipose tissue [13]. The EAT volume was the sum of EAT areas obtained from these procedures. These analyses were performed by two experienced physicians.

Total AAT and AVAT areas were obtained at the level of umbilicus (approximately the level of L4 and L5), as substitutes for total volume [14]. The AAT window width was defined as a range of −150 to −50 HU [15]. The total AAT area was calculated in the region outlining the circumference of the abdominal wall. The abdominal muscular wall separating the visceral and subcutaneous compartments was traced manually. The AVAT area was calculated as the region inside the abdominal muscular wall.

2.4. Statistical analysis

Continuous variables are described as mean ± standard deviation or as median (interquartile range: IQR). Categorical variables are described as numbers and percentages. Continuous variables were compared using Student's *t*-test or Mann-Whitney *U* test, and categorical variables were compared using chi-square or Fisher's exact tests. Univariate and multivariate logistic regression analyses were performed to identify potential predictors related to coronary artery spasm. Variables with a *p*-value <0.20 in the univariate model were used in the multivariate model. A *p*-value <0.05 was considered statistically significant. All statistical analysis was performed using SPSS Statistics 25.

3. Results

Among all enrolled patients, 77 were included in the spasm-positive group and 33 in the spasm-negative group.

The baseline characteristics are presented in Table 1. The prevalence of current smoking was significantly higher in the spasm-positive group (48.1% vs 27.1%, $p = 0.04$). There were no significant differences between the two groups in terms of other comorbidities or laboratory data.

The intra- and inter-observer variabilities of EAT volume in CT images were well correlated (intra-: $r = 0.991$, $p < 0.01$, inter-: $r = 0.994$, $p < 0.01$). CT measurement results are shown in Fig. 1. The EAT volume was larger in the spasm-positive group than that in the spasm-negative group (108 ± 38 cm^3 vs. 87 ± 34 cm^3, $p < 0.01$). There were no significant differences in total AAT or AVAT areas between the two groups (280 ± 113 cm^2 vs. 254 ± 128 cm^2, $p = 0.32$ and 112 ± 54 cm^2 vs. 98 ± 55 cm^2, $p = 0.27$, respectively). Fig. 2 shows representative cases in both groups.

On logistic regression multivariate analysis, EAT volume was found to be a significant predictor of coronary artery spasm, while the total AAT and AVAT areas were not (Table 2).

The receiver operating characteristic curve discriminating patients in the spasm-positive group and those in the spasm-negative group with regard to EAT volume had an area under the curve of 0.667 (95% confidence interval, 0.557 to 0.778; $p < 0.01$) and the cut-off value was 96.5 mL with a sensitivity of 63.6% and specificity of 66.7%.

4. Discussion

The main findings of this study are as follows:

1) EAT volume was significantly higher in patients with coronary artery spasm than in those without, whereas there were no significant differences in total AAT area or AVAT area.

2) Increased EAT volume was a significant predictor of coronary artery spasm.

Adipose tissue has various functions not merely as a lipid store, but as an endocrine and paracrine organ [16]. Adipose tissue produces anti-inflammatory and metabotropic adipokines (e.g., adiponectin, IL-1), pro-inflammatory adipokines (e.g., leptin, IL-6, TNFα, CRP), vasodilators (e.g., NO, adiponectin, adrenomedullin), and vasoconstrictors

Table 1
Baseline patient characteristics.

	Spasm group	Non-Spasm group	*p*-value
	$n = 77$	$n = 33$	
Age, y	64 ± 112	66 ± 12	0.25
Sex female, n (%)	32 (42%)	16 (48.5%)	0.50
Body mass index, kg/m^2	24.5 ± 3.3	23.4 ± 4.0	0.16
Hypertension, n (%)	40 (52%)	16 (49%)	0.74
Diabetes mellitus, n (%)	14 (18%)	8 (24%)	0.47
Dyslipidemia, n (%)	26 (34%)	14 (42%)	0.39
Current smoking, n (%)	37 (48%)	9 (27%)	0.04
HDL-cholesterol, mg/dL	54 ± 15	54 ± 13	0.99
Triglyceride, mg/dL	154 ± 88	127 ± 66	0.12
LDL-cholesterol, mg/dL	111 ± 29	111 ± 31	0.92
HbA1c, %	5.9 ± 1.0	5.9 ± 0.9	0.88
eGFR, ml/min/1.73m^2	73 ± 21	75 ± 16	0.56

HDL = high-density lipoprotein; LDL = low-density lipoprotein; eGFR = estimated glomerular filtration rate.

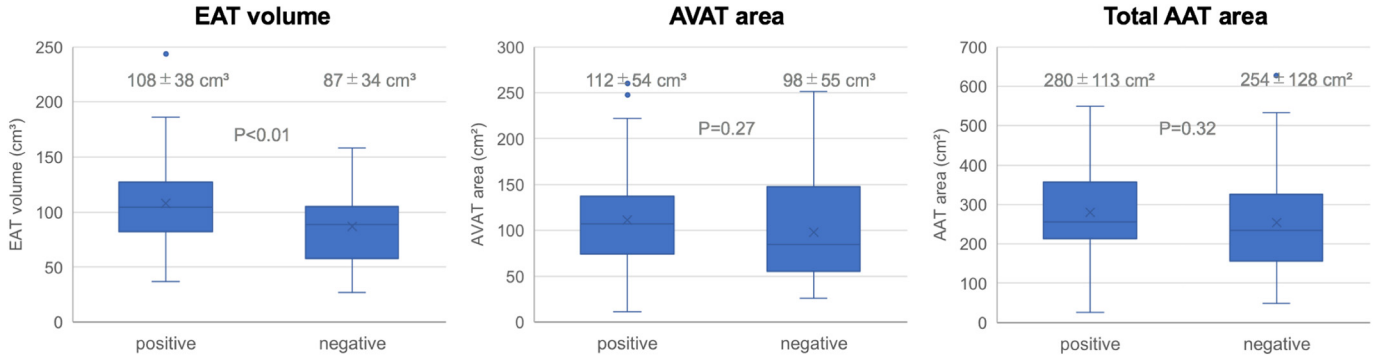

Fig. 1. Comparison of EAT volume, AVAT area and total AAT area between spasm positive group and spasm negative group. Tops and bottoms of boxes show the third and first quartile, respectively. Horizontal lines in the boxes represent median values. Tops and bottoms of bars show the maximum and minimum values without outliers.

(e.g., angiotensin 2, endothelin-1) [1,17,18]. These adipokines can cause endothelial dysfunction and atherosclerotic plaques [19].

EAT is ectopic visceral fat surrounding the heart, which is reported to exhibit significantly higher levels of a chemokine (MCP-1) and several inflammatory cytokines (IL-1β, IL-6, IL-6sR, and TNF-α) than subcutaneous fat [20]. Prior studies have shown the correlation between EAT and cardiovascular disease [21]. Moreover, some clinical studies reported that EAT can cause coronary artery spasm [22–25]. Some reports assessed EAT anterior interventricular groove thickness using transthoracic echocardiography and demonstrated its association with coronary artery spasm as evaluated using the provocation test [22,23]. Another study measured EAT volume using cardiac CT and showed its association with coronary artery spasm using the provocation test [24,25]. Our results were in line with those of previous reports.

As described above, various adipose tissues other than EAT may also contribute to the development of endothelial dysfunction. However, to the best of our knowledge, there have been no studies that compared the effect of AAT and EAT on coronary spasm. In this study, EAT volume had a stronger association with coronary spasm than the total AAT area and AVAT area did. These results suggest that adipose tissue surrounding the coronary arteries may have a larger effect. This might be explained by EAT additionally having a direct effect on the coronary artery endothelial cells through the paracrine and vaso-vasorum pathways [8], and stronger local inflammation in EAT than in other adipose tissues in coronary artery disease patients [21]. A recent study showed the association between coronary spasm and inflammation of coronary adventitia and perivascular adipose tissue, although percent body fat were comparable between the patients with and without coronary spasm [26]. Other studies have demonstrated an importance of inflammation in EAT and vasa-vasorum formation in the spastic coronary segments [27–29]. Our results might support their conclusions, and vice versa.

There are many risk factors for coronary artery spasm including age, low-density lipoprotein-cholesterol, hypertension, diabetes mellitus, and smoking [30]. Increased EAT volume may have some association with these other risk factors, but it also can be considered an independent risk factor for coronary artery spasm. Although further investigations with a larger number of unselected patients are required to establish the role and cut-off values, measurement of EAT could be a supplemental tool to diagnose coronary artery spasm with cardiac CT.

Our study has several limitations. First, this was a single center study with a relatively small number of subjects. Second, provocation test was performed using Ach. The sensitivities of Ach and ergonovine for coronary vasospasm might be different [24,31]. Third, EAT was assessed based on volume, while AAT and AVAT were assessed based on area. However, several studies reported that AVAT area from a single scan obtained at the level of the umbilicus (approximately at the level of L4 and

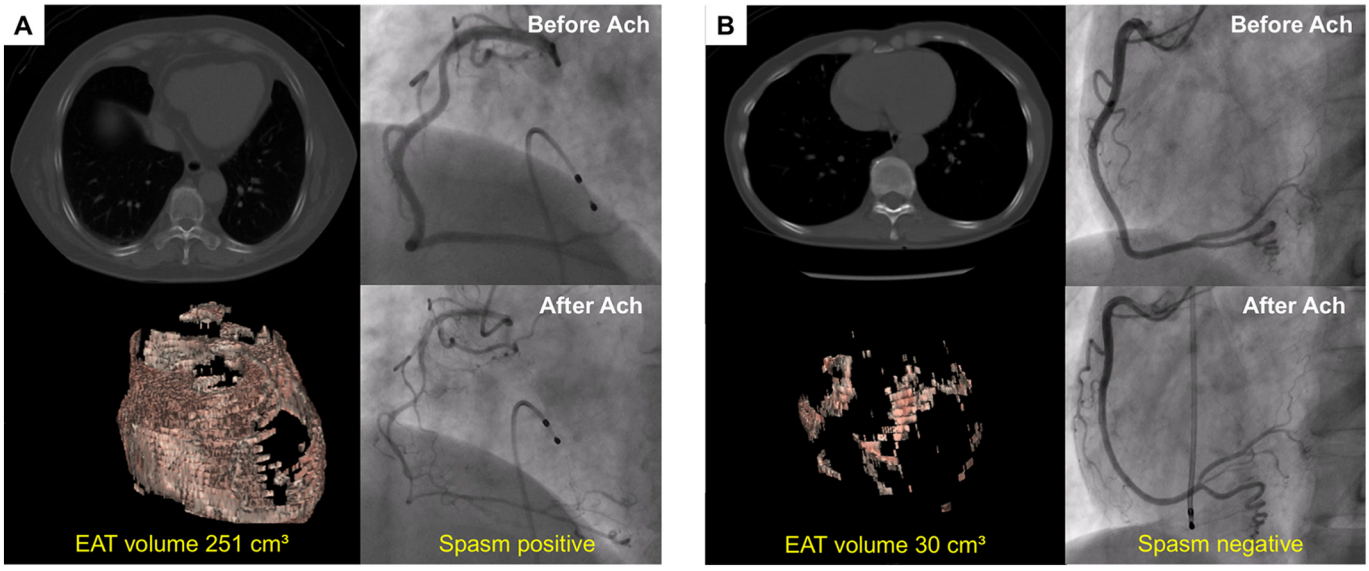

Fig. 2. Representative cases in both groups. A: A 67-year-old woman with chest pain had a large amount of EAT volume (251 cm^3). This patient had no significant stenosis and Ach provocation test was positive. B: A 59-year-old woman with chest pain who had a small amount of EAT volume (30 cm^3). This patient has no significant stenosis and Ach provocation test was negative.

Table 2
Univariate and multivariate logistic regression analysis for coronary artery spasm.

	Univariate		Multivariate	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	0.978 (0.943–1.015)	0.248		
Sex female	0.756 (0.333–1.715)	0.503		
Body mass index	1.092 (0.965–1.236)	0.164	1.003 (0.874–1.150)	0.97
Hypertension	1.149 (0.508–2.598)	0.739		
Diabetes	0.694 (0.259–1.859)	0.468		
Dyslipidemia	0.692 (0.300–1.597)	0.388		
Current smoking	2.467 (1.016–5.989)	0.046	2.021 (0.797–5.127)	0.139
eGFR	0.993 (0.972–1.015)	0.552		
EAT volume (per 10 cm^2)	1.190 (1.045–1.356)	0.009	1.198 (1.035–1.388)	0.016
AVAT area	1.005 (0.996–1.013)	0.271		
Total AAT area	1.002 (0.998–1.006)	0.314		

CI = confidence interval; OR = odds ratio; eGFR = estimated glomerular filtration rate; EAT = epicardial adipose tissue; AVAT = abdominal visceral adipose tissue; AAT = abdominal adipose tissue.

L5) highly correlated with the total AVAT volume [32]. Therefore, we used total AAT and AVAT area as substitutes for total AAT and AVAT volume. Fourth, this study only included patients who underwent the spasm provocation test. Therefore, cut-off values of EAT might be different among different populations. Fifth, if provocation test was positive in the right coronary artery, injection of Ach into the left coronary artery was not performed. Therefore, the relationship between the responsible coronary artery where spasm induced and the localization of EAT could not be assessed. Sixth, data regarding cytokines were not obtained, therefore the relationship between EAT volume and cytokines could not be evaluated.

In conclusion, our results suggest that EAT has a strong association with coronary artery spasm, while AAT and AVAT may not.

Declaration of Competing Interest

H·I received lecture fees from Astellas Pharma Inc., Astrazeneca Inc., Daiichi-Sankyo Pharma Inc., and MSD K. K. T.A. received lecture fees from Astellas Pharma, AstraZeneca, Bayer, Daiichi Sankyo, and Bristol-Myers Squibb. T.M received lecture fees from Bayel Pharmaceutical Co., Ltd., Daiichi-Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Kowa Co., Ltd., MSD K. K., Mitsubishi Tanabe Pharma Co., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K. K., Pfizer Japan Inc., Sanofi-aventis K. K., and Takeda Pharmaceutical Co., Ltd. T.M received unrestricted research grant for Department of Cardiology, Nagoya University Graduate School of Medicine from Astellas Pharma Inc., Daiichi-Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Kowa Co., Ltd., MSD K. K., Mitsubishi Tanabe Pharma Co., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K. K., Otsuka Pharma Ltd., Pfizer Japan Inc., Sanofi-aventis K. K., Takeda Pharmaceutical Co., Ltd., and Teijin Pharma Ltd. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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