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RAPID COMMUNICATION

Increased Coronary Perivascular Adipose Tissue Volume in Patients With Vasospastic Angina

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Background: Recent studies have suggested that coronary perivascular adipose tissue (PVAT) impairs coronary vasomotion, so we examined whether PVAT is increased at the spastic coronary segment in patients with vasospastic angina (VSA).

Methods and Results: PVAT volume in the left anterior descending (LAD) coronary arteries on CT coronary angiography was significantly increased in 48 VSA patients with LAD spasm compared with 18 controls (30.7±2.0 vs. 21.0±3.2 cm^3, P=0.01), whereas that of total epicardial adipose tissue was comparable between the 2 groups.

Conclusions: The results suggested an important role of PVAT in the pathogenesis of coronary spasm. (*Circ J* 2016; **80:** 1653–1656)

Key Words: Adipose tissue; Computed tomography; Coronary spasm

Coronary artery spasm plays an important role in the pathogenesis of a wide range of ischemic heart disease.[1] The adventitial components, such as perivascular adipose tissue (PVAT) and vasa vasorum (VV), have recently attracted much attention as sources of inflammation.[2] Indeed, enhanced PVAT inflammation has been shown to promote atherosclerosis.[3] Notably, epicardial adipose tissue volume (EATV) measured by cardiac computed tomography (CT) is related to coronary plaque burden,[4] and is also significantly associated with cardiovascular events.[5,6] Importantly, we recently demonstrated that adventitial inflammatory changes (eg, VV formation) are enhanced at the spastic coronary segment in patients with vasospastic angina (VSA), with a positive correlation with the extent of coronary vasoconstrictive responses.[7] Indeed, recent studies have suggested that coronary PVAT impairs coronary vasomotion,[8] but it remains to be elucidated whether coronary PVAT is altered in VSA patients. In the present study, we used CT coronary angiography (CTCA) to examine whether coronary PVAT volume (PVATV) is increased at the spastic coronary segment in VSA patients.

Methods

The present study was approved by the ethical committee of the Tohoku University (2015-1-710). From March 2011 to April 2015, a total of 76 consecutive patients with suspected VSA without luminal narrowing ≥75% underwent both coronary angiography and CTCA. Following the guidelines of the Japanese Circulation Society, coronary spasm provocation test was performed with intracoronary acetylcholine (ACh),[9] and the diagnosis of VSA was made when a total or subtotal (>90%) coronary artery narrowing with chest-pain and/or ischemic ECG changes was induced. Among the 76 patients tested, 58 had a positive ACh provocation test, from among whom those with focal spasm alone (n=4), spasm in the left circumflex (LCX) alone (n=1) or the right coronary arteries (RCA) alone (n=5) were excluded. Finally, 48 patients with diffuse spasm in the left anterior descending (LAD) coronary arteries and 18 controls without the spasm were enrolled. For EATV and PVATV measurements, ECG-gated CTCA was acquired with 1 of the following multidetector CT scanners: dual-source 2×64 detector-row CT (Somatom Definition, Siemens Medical, Forchheim, Germany), dual-source 2×128 detector-row CT scanner (Somatom Definition) or a 320 detector-row CT scanner (Aquilion One, Toshiba Medical Systems Co, Tokyo, Japan). Axial images were reconstructed with a 1.0 mm-thickness slice at 1.0 mm intervals. EAT was defined as the adipose tissue between the surface of the heart and the

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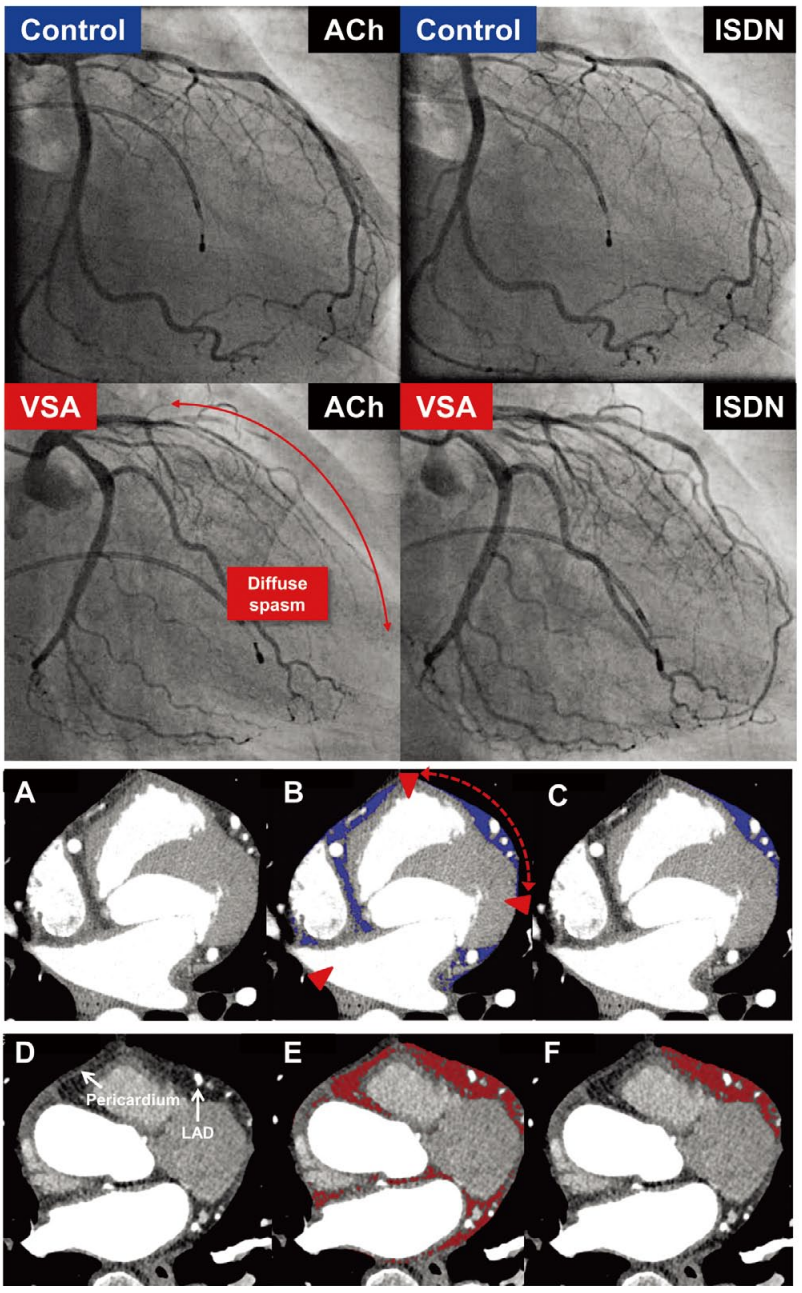

Figure 1. Coronary angiograms and CTCA images. Coronary angiograms after intracoronary acetylcholine (Ach) and isosorbide dinitrate (ISDN), and cross-sectional CTCA images of a control subject (**A**–**C**) and those of a VSA patient (**D**–**F**). EATV (**B**,**E**) and $PVATV_{LAD}$ (**C**,**F**) are shown in blue (control) and red (VSA), respectively. $PVATV_{LAD}$ was larger in a VSA patient compared with a control subject. Red arrows (**B**) at the midpoints between each coronary artery show the boundary lines between each coronary PVAT. CTCA, CT coronary angiography; EATV, epicardial adipose tissue volume; LAD, left anterior descending [coronary artery]; PVAT, perivascular adipose tissue; PVATV, PVAT volume; VSA, vasospastic angina.

visceral layer of the pericardium.[5] EAT area was determined as the adipose tissue with a density between −195 and −45 Hounsfield units, using a standalone workstation (Ziostation2, Ziosoft Inc, Tokyo, Japan).[5] EAT volume was measured by calculating the sum of the EAT areas measured from the right pulmonary artery to the diaphragm with 1.0 cm intervals.[10] The areas of the $PVAT_{RCA}$, $PVAT_{LAD}$ and $PVAT_{LCX}$ were defined as the adipose tissue surrounding the main coronary arteries (RCA, LAD and LCX), respectively (**Figure 1B**). In cases of PVAT covering both the LAD and the RCA or LCX region, the region of interest was extended halfway between both regions (**Figure 1B**).[11] The volumetric measurement of coronary PVATV was performed the same way as for EAT volume. Finally, EATV and coronary PVATV were calculated as the EATV and PVATV indexes (EATV/body surface area [BSA], PVATV/BSA, cm^3/m^2).[12] The extent of coronary vasomotion was evaluated at segment 7 according to the AHA classification.[7] Coronary vasomotor responses to intracoronary ACh were quantified as per cent change in luminal diameter compared with that after intracoronary isosorbide dinitrate (ISDN: 2 mg).[7] Coronary vasodilating responses to intracoronary ISDN from baseline diameter were evaluated as basal coronary tone.[7]

Results

Patient characteristics were comparable between the control and VSA groups in terms of sex (male, 66.7 vs. 47.9 %), age

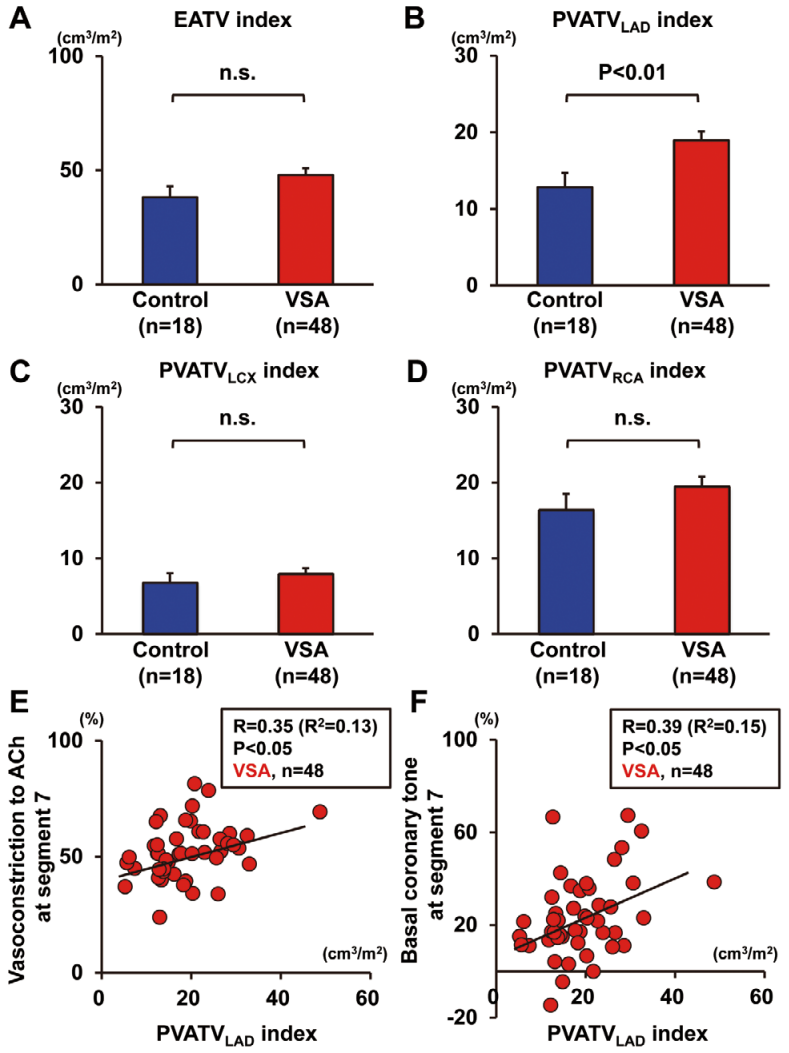

Figure 2. Quantitative volumetric analysis showing increased PVATV of the LAD on CTCA associated with vasoconstrictive responses in VSA patients. Quantitative volumetric analysis shows EATV index (**A**), PVATV$_{LAD}$ index (**B**), PVATV$_{LCX}$ index (**C**) and PVATV$_{RCA}$ index (**D**). PVATV$_{LAD}$ index was significantly increased in the VSA group as compared with the control group (**B**), whereas the other 2 indices were comparable (**A**,**C**,**D**). There were significant positive correlations between the PVATV$_{LAD}$ index and the extent of vasoconstrictive responses to intracoronary acetylcholine (**E**) and basal coronary tone (**F**). CTCA, CT coronary angiography; EATV, epicardial adipose tissue volume; LAD, left anterior descending [coronary artery]; LCX, left circumflex artery; PVAT, perivascular adipose tissue; PVATV, PVAT volume; RCA, right coronary artery; VSA, vasospastic angina.

(57.1±16.3 vs. 63.0±10.5 years), body weight (60.2±12.9 vs. 61.9±10.9 kg), body mass index (22.9±3.7 vs. 24.1±3.1 kg/m^2), other cardiovascular risks and medications (**Tables S1–S3**). Although the EATV index was comparable between the control and VSA groups (38.2±4.9 vs. 47.9±3.0 cm^3/m^2, P=0.09), the PVATV$_{LAD}$ index was significantly increased in the VSA group compared with the control group (19.0±1.2 vs. 12.8±1.9 cm^3/m^2, P=0.007). In contrast, the PVATV$_{RCA}$ index (16.4±2.1 vs. 19.5±1.3 cm^3/m^2, P=0.21) and PVATV$_{LCX}$ index (6.8±1.2 vs. 7.9±0.8 cm^3/m^2, P=0.43) were comparable between the 2 groups (**Figures 1,2A–D**). Furthermore, in the VSA group, there were significant positive correlations between the PVATV$_{LAD}$ index and the extent of coronary vasoconstrictive responses to ACh and that of basal coronary tone (P=0.007 and 0.015, respectively) (**Figures 2E,F**).

Discussion

The major findings of the present study were that the PVATV$_{LAD}$ index was significantly increased in the VSA group compared with the control group, whereas the EATV index was comparable between the 2 groups and the PVATV$_{LAD}$ index was significantly associated with the extent of coronary vasoconstrictive response to intracoronary ACh. To the best of our knowledge, this study provides the first evidence that coronary PVATV is increased at the spastic coronary segments of VSA patients, suggesting the important role of PVAT in the pathogenesis of coronary spasm. PVAT is regarded as an active endocrine and paracrine organ that produces a variety of cytokines (eg, interleukin [IL]-1β, IL-6, and monocyte chemotactic protein-1).[2] Notably, a recent study has shown that biological factors released from coronary PVAT potentiate coronary vasoconstriction.[8] Importantly, we have previously demonstrated that adventitial inflammation induced by chronic treatment with IL-1β induces coronary spasm in porcine models.[1,13] In addition, we recently demonstrated that adventitial VV formation is enhanced at the spastic coronary segment in both the porcine model and VSA patients.[7,14,15] Taken together, inflammatory cytokines derived from increased coronary PVAT and VV formation may impair coronary vasomotor function in VSA patients. Although the PVATV$_{LAD}$ index was significantly larger than the PVATV$_{LCX}$ index, the PVATV$_{LAD}$ index was similar to the PVATV$_{RCA}$ index in the VSA group (**Figure S1**). As patients with LAD spasm followed

by intracoronary ISDN administration did not undergo spasm provocation test in the RCA, the role of adipose tissue in the RCA remains to be examined in future studies. Although we observed volumetric enlargement of the coronary PVAT in the VSA patients in the present study, it remains to be elucidated whether coronary PVAT is functionally and/or metabolically altered. Thus, the relationship between coronary spasm and functional changes in the coronary PVAT needs to be examined in future studies using PET/CT.

In conclusion, the present study demonstrated for the first time that the coronary PVATV is increased at the spastic coronary segment of VSA patients, suggesting the involvement of coronary PVAT in the pathogenesis of coronary spasm.

Disclosure

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References

1. Shimokawa H. 2014 Williams Harvey Lecture: Importance of coronary vasomotion abnormalities: From bench to bedside. *Eur Heart J* 2014; **35:** 3180–3193.
2. 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.
3. Manka D, Chatterjee TK, Stoll LL, Basford JE, Konaniah ES, Srinivasan R, et al. Transplanted perivascular adipose tissue accelerates injury-induced neointimal hyperplasia: Role of monocyte chemoattractant protein-1. *Arterioscler Thromb Vasc Biol* 2014; **34:** 1723–1730.
4. Alexopoulos N, McLean DS, Janik M, Arepalli CD, Stillman AE, Raggi P. Epicardial adipose tissue and coronary artery plaque characteristics. *Atherosclerosis* 2010; **210:** 150–154.
5. Rosito GA, Massaro JM, Hoffmann U, Ruberg FL, Mahabadi AA, Vasan RS, et al. Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: The Framingham Heart Study. *Circulation* 2008; **117:** 605–613.
6. Cheng VY, Dey D, Tamarappoo B, Nakazato R, Gransar H, Miranda-Peats R, et al. Pericardial fat burden on ECG-gated noncontrast CT in asymptomatic patients who subsequently experience adverse cardiovascular events. *JACC Cardiovasc Imaging* 2010; **3:** 352–360.
7. Nishimiya K, Matsumoto Y, Takahashi J, Uzuka H, Hongxin W, Tsuburaya R, et al. Enhanced adventitial vasa vasorum formation in patients with vasospastic angina: Assessment with OFDI. *J Am Coll Cardiol* 2016; **67:** 598–600.
8. Owen MK, Witzmann FA, McKenney ML, Lai X, Berwick ZC, Moberly SP, et al. Perivascular adipose tissue potentiates contraction of coronary vascular smooth muscle: Influence of obesity. *Circulation* 2013; **128:** 9–18.
9. JCS Joint Working Group. Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina): Digest version. *Circ J* 2014; **78:** 2779–2801.
10. Mahabadi AA, Berg MH, Lehmann N, Kälsch H, Bauer M, Kara K, et al. Association of epicardial fat with cardiovascular risk factors and incident myocardial infarction in the general population: The Heinz Nixdorf Recall Study. *J Am Coll Cardiol* 2013; **61:** 1388–1395.
11. Gorter PM, van Lindert AS, de Vos AM, Meijs MF, van der Graaf Y, Doevendans PA, et al. Quantification of epicardial and peri-coronary fat using cardiac computed tomography; reproducibility and relation with obesity and metabolic syndrome in patients suspected of coronary artery disease. *Atherosclerosis* 2008; **197:** 896–903.
12. Shimabukuro M, Hirata Y, Tabata M, Dagvasumberel M, Sato H, Kurobe H, et al. Epicardial adipose tissue volume and adipocytokine imbalance are strongly linked to human coronary atherosclerosis. *Arterioscler Thromb Vasc Biol* 2013; **33:** 1077–1084.
13. Kandabashi T, Shimokawa H, Miyata K, Kunihiro I, Kawano Y, Fukata Y, et al. Inhibiton of myosin phosphatase by upregulated Rho-kinase plays a key role for coronary artery spasm in a porcine model with interleukin-1β. *Circulation* 2000; **101:** 1319–1323.
14. Nishimiya K, Matsumoto Y, Shindo T, Hanawa K, Hasebe Y, Tsuburaya R, et al. Association of adventitial vasa vasorum and inflammation with coronary hyperconstriction after drug-eluting stent implantation in pigs in vivo. *Circ J* 2015; **79:** 1787–1798.
15. Nishimiya K, Matsumoto Y, Uzuka H, Ohyama K, Tanaka A, Taruya A, et al. Accuracy of optical frequency domain imaging for evaluation of coronary adventitial vasa vasorum formation after stent implantation in pigs and humans: A validation study. *Circ J* 2015; **79:** 1323–1331.

Supplementary Files

Supplementary File 1

Table S1. Clinical characteristics and treatments of the control and VSA groups

Table S2. Laboratory data of the control and VSA groups

Table S3. Coronary angiographic findings of the control and VSA groups

Figure S1. Quantitative volumetric analysis of PVAT between the LAD, LCX, and RCA in VSA patients.

Please find supplementary file(s);
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