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 cm³, 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 coronary artery.
visceral layer of the pericardium.\textsuperscript{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).\textsuperscript{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.\textsuperscript{10} The areas of the PVAT\textsubscript{RCA}, PVAT\textsubscript{LAD} and PVAT\textsubscript{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).\textsuperscript{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\textsuperscript{3}/m\textsuperscript{2}).\textsuperscript{12} The extent of coronary vasomotion was evaluated at segment 7 according to the AHA classification.\textsuperscript{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).\textsuperscript{7} Coronary vasodilating responses to intracoronary ISDN from baseline diameter were evaluated as basal coronary tone.\textsuperscript{7}

**Results**

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

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). Notably, a recent study has shown that biological factors released from coronary PVAT potentiate coronary vasoconstriction. Importantly, we have previously demonstrated that adventitial inflammation induced by chronic treatment with IL-1β induces coronary spasm in porcine models. In addition, we recently demonstrated that adventitial VV formation is enhanced at the spastic coronary segment in both the porcine model and VSA patients. Taken together, inflammatory cytokines derived from increased coronary PVAT and VV formation may impair coronary vaso-motor 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

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). Notably, a recent study has shown that biological factors released from coronary PVAT potentiate coronary vasoconstriction. Importantly, we have previously demonstrated that adventitial inflammation induced by chronic treatment with IL-1β induces coronary spasm in porcine models. In addition, we recently demonstrated that adventitial VV formation is enhanced at the spastic coronary segment in both the porcine model and VSA patients. Taken together, inflammatory cytokines derived from increased coronary PVAT and VV formation may impair coronary vaso-motor 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

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.
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**

K.O. was awarded the 2015 Cardiovascular Radiology & Intervention Early Career Investigator Travel Stipend of the American Heart Association, 2015.

**References**


**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); http://dx.doi.org/10.1253/circj.CJ-16-0213