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Coronary Adventitial and Perivascular Adipose Tissue Inflammation in Patients With Vasospastic Angina

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ABSTRACT

BACKGROUND Recent studies suggested that perivascular components, such as perivascular adipose tissue (PVAT) and adventitial vasa vasorum (VV), play an important role as a source of various inflammatory mediators in cardiovascular disease.

OBJECTIVES The authors tested their hypothesis that coronary artery spasm is associated with perivascular inflammation in patients with vasospastic angina (VSA) using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT).

METHODS This study prospectively examined 27 consecutive VSA patients with acetylcholine-induced diffuse spasm in the left anterior descending artery (LAD) and 13 subjects with suspected angina but without organic coronary lesions or coronary spasm. Using CT coronary angiography and electrocardiogram-gated ^{18}F-FDG PET/CT, coronary PVAT volume and coronary perivascular FDG uptake in the LAD were examined. In addition, adventitial VV formation in the LAD was examined with optical coherence tomography, and Rho-kinase activity was measured in circulating leukocytes.

RESULTS Patient characteristics were comparable between the 2 groups. CT coronary angiography and ECG-gated ^{18}F-FDG PET/CT showed that coronary PVAT volume and coronary perivascular FDG uptake significantly increased in the VSA group compared with the non-VSA group. Furthermore, optical coherence tomography showed that adventitial VV formation significantly increased in the VSA group compared with the non-VSA group, as did Rho-kinase activity. Importantly, during the follow-up period with medical treatment, both coronary perivascular FDG uptake and Rho-kinase activity significantly decreased in the VSA group.

CONCLUSIONS These results provide the first evidence that coronary spasm is associated with inflammation of coronary adventitia and PVAT, where ^{18}F-FDG PET/CT could be useful for disease activity assessment. (Morphological and Functional Change of Coronary Perivascular Adipose Tissue in Vasospastic Angina [ADIPO-VSA Trial]; UMIN000016675) (J Am Coll Cardiol 2018;71:414–25) © 2018 by the American College of Cardiology Foundation.

Coronary artery spasm plays an important role in the pathogenesis of a wide range of ischemic heart disease, not only in variant angina but also in other forms of angina pectoris and myocardial infarction (1,2). Recent studies have demonstrated that coronary spasm is also frequently noted in Caucasians and in Asians (3). We have previously demonstrated that activation of Rho-kinase,

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a molecular switch for vascular smooth muscle contraction, is a central mechanism of coronary spasm in animals and humans (1,4,5). We also have recently demonstrated that optical coherence tomography (OCT) enables the precise measurement of vasa vasorum (VV) area and that adventitial inflammatory changes, including VV formation, play important roles in the pathogenesis of coronary spasm in pigs and humans (6–8).

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The perivascular components, such as VV and perivascular adipose tissue (PVAT), have attracted much attention as sources of vascular inflammation (9). Indeed, PVAT is regarded as an active endocrine and paracrine organ that produces a variety of cytokines (e.g., interleukin [IL]-1β) (9). Epicardial adipose tissue volume measured by cardiac computed tomography (CT) is also significantly associated with cardiovascular events (10,11). However, it remains to be fully elucidated whether coronary artery spasm is associated with perivascular inflammation including coronary adventitia and PVAT in patients with vasospastic angina (VSA).

Functional alternations of the coronary artery are associated with PVAT inflammation (9–11). We have recently demonstrated that coronary PVAT volume is increased at the spastic coronary segment of VSA patients by CT coronary angiography (CTCA) (12), which suggests involvement of PVAT inflammation in the pathogenesis of the spasm. Currently, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT is widely used to detect inflammation because it reflects the metabolic activity of glucose, which is known to be enhanced in inflamed tissue (13,14). Indeed, we have recently demonstrated that ^{18}F-FDG PET/CT is useful for the assessment of coronary perivascular inflammation in pigs in vivo (15). However, it remains to be examined whether ^{18}F-FDG PET/CT is also useful to assess disease activity and functional changes in the coronary adventitia and PVAT in VSA patients.

In the present study, we thus prospectively examined whether coronary artery spasm was associated with perivascular inflammation in VSA patients using ^{18}F-FDG PET/CT, and if so, whether imaging modalities (CTCA and OCT) were useful for detecting morphological alternations of coronary adventitia and PVAT and whether ^{18}F-FDG PET/CT was also useful to assess disease activity after medical treatment.

METHODS

The ethics committee of Tohoku University Graduate School of Medicine (No. 2014-1-720) approved the study protocol, which was performed in compliance with the Declaration of Helsinki (UMIN000016675). Written informed consent was obtained from all patients before study entry. The detailed methods are available in the Online Appendix.

STUDY PATIENTS. The details of patient enrollment are provided in the Online Appendix. From March 2015 to September 2016, we prospectively enrolled a total of 54 consecutive eligible patients, from whom written informed consent was obtained at our Tohoku University Hospital (**Figure 1**). Inclusion criteria included age 20 years or older and rest angina due to suspected VSA. Exclusion criteria included acute coronary syndrome, left ventricular ejection fraction of 50% or less, serum creatinine level of 1.2 mg/dl or higher, history of an adverse reaction to contrast media, history of cardiac surgery, severe asthma, diabetes mellitus with insulin therapy, inflammatory or autoimmune diseases with steroid therapy, stent implantation in the left anterior descending coronary artery (LAD), organic coronary stenosis, focal spasm alone, spasm that occurred in the left circumflex artery (LCx)/right coronary artery (RCA) alone, and insufficient quality of ^{18}F-FDG PET/CT. We performed electrocardiogram (ECG)-gated CTCA and control coronary angiography and excluded 5 patients with luminal narrowing ≥75%. After control coronary angiography, we performed a coronary spasm provocation test with intracoronary acetylcholine (ACh). Diffuse spasm was diagnosed when luminal narrowing was noted from the proximal to the distal segment of the coronary artery, whereas focal spasm was defined as a discrete luminal narrowing (>90%) localized in the major coronary artery (16). In addition, we performed ECG-gated ^{18}F-FDG PET/CT. Among 36 patients with a positive provocation test, 9 were excluded, including 2 with focal spasm alone, 5 with spasm in the LCx or RCA alone, and 2 with insufficient quality of ^{18}F-FDG PET/CT. Finally, 27 VSA patients and 13 subjects with suspected angina but without organic coronary lesions or coronary spasm were enrolled in the VSA group and the non-VSA group, respectively. Of the VSA group, 15 patients were followed up and underwent ^{18}F-FDG PET/CT after a median follow-up of 23 months.

CORONARY SPASM PROVOCATION TEST WITH ACh AND QUANTITATIVE CORONARY ANGIOGRAPHY. We performed a provocation test of coronary spasm with ACh in accordance with the Japanese Circulation

ABBREVIATIONS AND ACRONYMS

ACh = acetylcholine
CT = computed tomography
CTCA = computed tomography coronary angiography
ECG = electrocardiogram
FDG = fluorodeoxyglucose
IL = interleukin
LAD = left anterior descending coronary artery
LCx = left circumflex artery
OCT = optical coherence tomography
PET = positron emission tomography
PVAT = perivascular adipose tissue
RCA = right coronary artery
ROI = region of interest
SUV = standardized uptake value
TBR = target-to-background ratio
VSA = vasospastic angina
VV = vasa vasorum