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Enhanced Adventitial Vasa Vasorum Formation in Patients With Vasospastic Angina

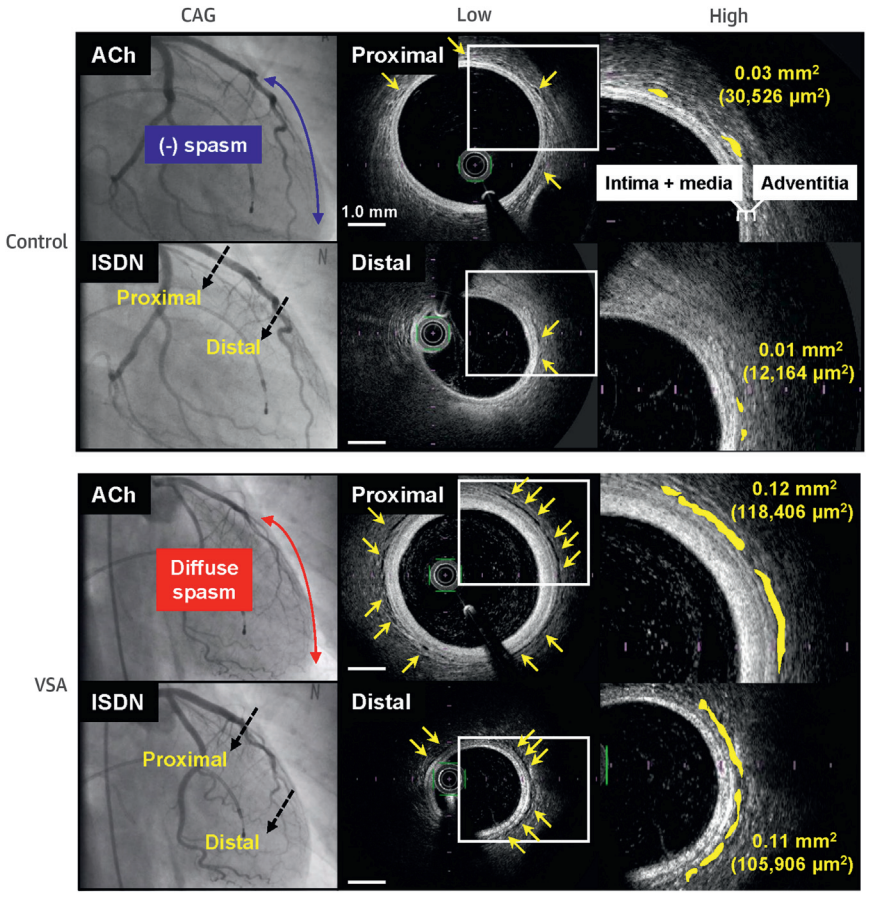
Assessment With OFDI

Coronary artery spasm plays important roles in the pathogenesis of a wide range of ischemic heart disease. Recent studies have demonstrated that coronary spasm is frequently noted in Caucasians as in Asians (1). We previously demonstrated that vascular smooth muscle cell hypercontraction through Rho-kinase activation is the key mechanism of the spasm, for which adventitial inflammatory changes may be involved (1). The adventitia has recently attracted much attention as a source of inflammation as it harbors nutrient blood vessels called vasa vasorum (VV). Indeed, VV plays an important role as a supply route of vascular inflammation in the progression of coronary atherosclerotic plaque (2). We recently demonstrated that enhanced VV formation after drug-eluting stents (DES) implantation is associated with coronary hyperconstricting responses through Rho-kinase activation in pigs in vivo (3). We also confirmed the accuracy of optical frequency domain imaging (OFDI) to evaluate VV formation in humans in vivo (4). However, it remains to be elucidated whether the extent of VV is enhanced in patients with vasospastic angina (VSA). In the present study, we thus examined whether VV formation is enhanced in VSA patients by using the OFDI system, and, if so, whether there is any correlation between the extent of VV and that of coronary vasoconstriction.

From April 2013 to February 2015, a total of 115 consecutive patients with suspected VSA symptoms without coronary stenosis ≥75% on coronary angiography (CAG) were enrolled. After control CAG, a coronary spasm provocation test with intracoronary acetylcholine (ACh) was performed. Finally, 63 patients with the diffuse spasm in the left anterior descending coronary artery (LAD) and 26 controls without the spasm were enrolled. Clinical characteristics were comparable between the VSA and the control groups.

Intracoronary OFDI (Lunawave, Terumo, Japan) was performed along the LAD, after administration of intracoronary isosorbide dinitrate (ISDN) (2 mg) after the spasm provocation test. Morphometric analysis of OFDI was performed at every 10-mm by 2 independent investigators. Although the percentage of intimal + medial area tended to be greater in the VSA group compared with the control group, all morphometric parameters were statistically comparable between the 2 groups. Importantly, representative OFDI examination showed that VV formation was markedly enhanced at the spastic LAD in a patient with VSA compared with a control subject (**Figure 1**). VV area density was calculated by following formula: [VV area/(area outside external elastic lamina within a distance of the thickness of intima plus media − vessel area)] and was significantly greater in the VSA group compared with the control group (control, 0.036 ± 0.004 mm^2/mm^2 vs. VSA, 0.088 ± 0.004 mm^2/mm^2;

FIGURE 1 Enhanced Adventitial VV Formation on OFDI in VSA Patients



Representative CAG and OFDI images showing that VV formation **(yellow arrows)** were markedly enhanced in a VSA patient with diffuse spasm in the left anterior descending artery compared with a control subject without the spasm. ACh = acetylcholine; CAG = coronary angiography; ISDN = isosorbide dinitrate; OFDI = optical frequency domain imaging; VSA = vasospastic angina; VV = vasa vasorum.

$p < 0.001$). In the VSA group, there was a significant positive correlation between VV area density and the extent of coronary vasoconstricting responses to ACh ($R = 0.553$, $p < 0.001$). Similarly, a significant positive correlation was noted between VV area density and Rho-kinase activity in circulating leukocytes (1) ($R = 0.370$, $p < 0.001$).

The major findings of the present study were that VV formation was enhanced at the spastic coronary segments in VSA patients and the extent of VV formation was positively correlated with Rho-kinase activity. We previously demonstrated that the Rho-kinase pathway plays a key role in the pathogenesis of coronary arteriosclerosis and that up-regulation of Rho-kinase is involved in VV formation in pigs after DES implantation (1,3). A similar mechanism may also be involved in VV enhancement in VSA patients. However, the causal relationship between VV formation and coronary spasm remains to be examined in future studies.

In conclusion, the present study demonstrates for the first time that adventitial VV formation is enhanced at the spastic coronary segment in VSA patients with a positive correlation with the extent of coronary vasospastic responses, suggesting the involvement of adventitial VV formation in the pathogenesis of the spasm.

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Survival Differences in Clinical Trials With Long-Term Follow-Up

We would like comment on the results and implications of the recent publication by Henderson et al. (1) on the 10-year mortality after routine invasive versus selective invasive strategies for the management of non-ST-segment elevation acute coronary syndrome (NSTEACS) and the accompanying editorial by Patel and Ohman (2). Based on the absence of differences in all-cause and cardiovascular mortality between the routine invasive and selective invasive groups, Henderson and colleagues conclude that "the advantage of reduced mortality of routine early invasive strategy seen at 5 years was attenuated during later follow-up, with no evidence of a difference in outcome at 10 years" and recommend "further trials of contemporary intervention strategies in patients with NSTEACS." Discussing the strengths and limitations and possible explanations of the RITA-3 (Third Randomised Intervention Treatment of Angina) 10-year data, Patel and Ohman (2) question whether guidelines should be revised.

In our opinion, the 10-year RITA-3 report does not support a change in the recommendation of the American College of Cardiology/American Heart Association (or European) guidelines for routine invasive strategy (3). This is related to the interpretation of the findings of clinical trials with long duration of follow-up. In these instances, the difference in survival (or mortality) between groups may attenuate over time as more patients die in each group. Evaluation of the benefit of an intervention (compared with control) is better performed by estimating the difference in average survival in each group or by estimating the area between the survival (or mortality) curves of the active and control groups. Such techniques were used, for example, to assess the benefit of angiotensin-converting enzyme inhibitors in the CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) heart failure trial (4) and of treatment of isolated systolic hypertension in the long-term extension of the SHEP (Systolic Hypertension in the Elderly Program) trial (5).

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