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Focal Vasa Vasorum Formation in Patients With Focal Coronary Vasospasm

– An Optical Frequency Domain Imaging Study –

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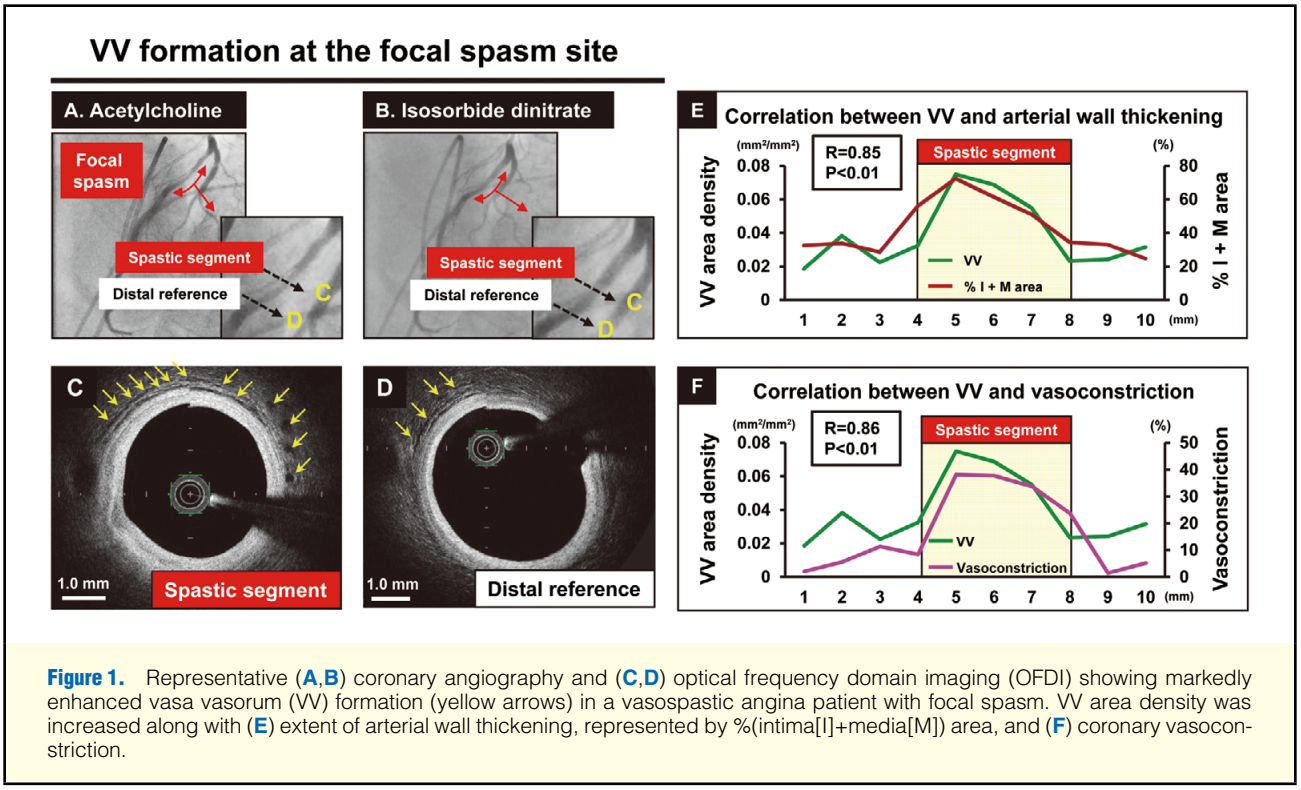

Figure 1. Representative (**A**,**B**) coronary angiography and (**C**,**D**) optical frequency domain imaging (OFDI) showing markedly enhanced vasa vasorum (VV) formation (yellow arrows) in a vasospastic angina patient with focal spasm. VV area density was increased along with (**E**) extent of arterial wall thickening, represented by %(intima[I]+media[M]) area, and (**F**) coronary vasoconstriction.

Coronary artery spasm plays important roles in the pathogenesis of a wide range of ischemic heart disease, not only in vasospastic angina (VSA) but also in other forms of ischemic heart disease.[1] Although VSA is believed to be more prevalent in Asian compared with Caucasian subjects,[2] it has been recently suggested that the prevalence of VSA could be similar in both populations.[3] Thus, coronary spasm is an emerging issue in the world. Furthermore, given that 14% of VSA patients treated with appropriate medications have refractory angina,[4] novel therapeutic strategies are warranted.

Editorial p????

Coronary adventitia has attracted much attention as a source of inflammation because it harbors nutrient blood vessels,

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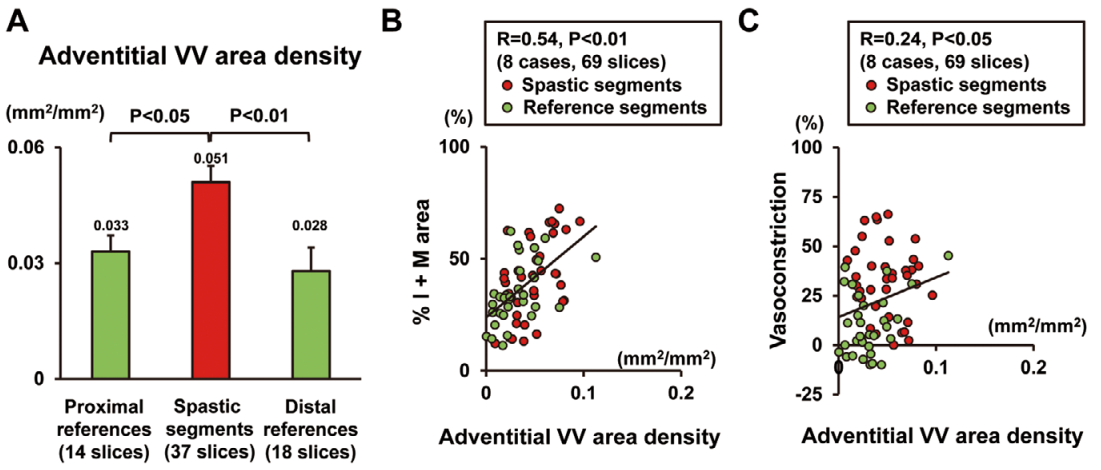

Figure 2. (**A**) Adventitial vasa vasorum (VV) area density was significantly greater at the spastic segment compared with the proximal or distal reference segment. There were significant positive correlations between VV area density and (**B**) % (I+M) area or (**C**) coronary vasoconstriction.

termed "vasa vasorum" (VV).[5] Indeed, we have recently shown that optical frequency domain imaging (OFDI) can visualize adventitial VV in pigs[6] and humans[7] and that adventitial VV formation is diffusely enhanced in VSA patients with diffuse spasm.[8] Adventitial VV formation at the focal spasm site, however, remains to be examined. We previously demonstrated that coronary focal spasm can be induced at the inflammatory coronary segment in pigs.[1,9] In the present study, we thus examined adventitial VV in patients with focal spasm using OFDI.

The study protocol was approved by the ethics committee of Tohoku University Graduate School of Medicine (2014-1-640). From March 2014 to February 2015, we performed coronary spam provocation test with i.c. acetylcholine (ACh) in 115 consecutive patients with suspected VSA without coronary stenosis ≥75% on coronary angiography. The diagnosis of VSA was made in accordance with the guidelines of the Japanese Circulation Society.[4] Focal spasm was defined as discrete luminal narrowing localized in the major coronary artery. Finally, we examined 8 patients (age, mean±SEM, 66.8±5.0 years; male, 38%) with focal spasm in the left anterior descending (LAD) coronary arteries (**Tables S1–S3**). Among them, one patient had 50–75% organic stenosis in the focal spasm site of the LAD (**Table S3**). Intracoronary OFDI (LUNAWAVE, Terumo, Tokyo, Japan) was performed over the entire length of the LAD after i.c. isosorbide dinitrate (ISDN; 2 mg). For both the spastic segments and for the 5-mm proximal/distal reference segments adjacent to the spastic segments, we performed morphometric analysis with OFDI (**Table S4**) every 1 mm (**Figure S1**). Coronary vasomotor responses to ACh were quantified as percent change in lumen diameter compared with that after ISDN.[10] OFDI data analysis and statistical analysis are given in the **Online Supplemental Methods**.

In a VSA patient with focal spasm, adventitial VV formation was enhanced at the spastic segment compared with the distal reference segment, corresponding to the extent of arterial wall thickening and that of coronary vasoconstriction response (**Figure 1**). In all of the patients, adventitial VV formation was significantly increased at the spastic focal segments compared with the proximal or distal reference segments (**Figure 2A**). Furthermore, there were significant positive correlations between the extent of adventitial VV formation and that of arterial wall thickening or coronary vasoconstriction response (**Figures 2B,C**). Similar correlation was also noted between the extent of adventitial VV formation and that of arterial wall thickening at the reference segments (P<0.01, R=0.47).

To the best of our knowledge, this is the first report showing that adventitial focal VV formation coincides with the focal spastic segments in VSA patients. We have previously demonstrated in pigs that coronary hyperconstriction can be induced by adventitial inflammatory changes[1,9] and after drug-eluting stent implantation,[10,11] through Rho-kinase activation in the vascular smooth muscle. It was previously reported that adventitial VV formation precedes manifestation of coronary vasomotion abnormalities in hypercholesterolemic pigs.[12] Thus, it is possible that enhanced adventitial VV formation initiates adventitial inflammatory changes with resultant coronary spasm.

In the present study, coronary vasospastic responses were noted at atherosclerotic lesions with focal spasm. We have previously demonstrated that coronary spasm can be induced at the atherosclerotic lesion in porcine models involving balloon injury and high-cholesterol diet.[1,13] The extent of adventitial VV formation through hypoxia-induced angiogenesis was positively correlated with the severity of atherosclerotic changes in pigs.[5] Indeed, in the present study, such positive correlations were noted between the extent of adventitial VV formation and that of arterial wall thickening at both the spastic and reference segments. No significant correlation was noted, however, between the extent of arterial wall thickening and that of the spasm (P=0.09, R=–0.28). Thus, it remains to be examined in future studies whether atherosclerotic changes are involved in the enhanced VV formation at the focal spasm site. In this regard, a previous intravascular ultrasound study showed that arterial wall thickening is more prominent at the focal spasm site compared with the diffuse spasm site.[14] We

have recently demonstrated that atherosclerotic changes may not be correlated with adventitial VV formation at the diffuse spasm site.[8] Thus, it is possible that the underlying mechanisms of VV formation are different between focal and diffuse spasm.

In the pathogenesis of VSA, the roles of other adventitial components remain to be elucidated. Indeed, we have recently demonstrated that coronary perivascular adipose tissue is also increased in VSA patients.[15]

In conclusion, adventitial focal VV formation coincides with focal spasm in VSA patients, for which atherosclerotic changes may be involved.

Disclosure

None.

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Supplementary Files

Supplementary File 1

Table S1. Demographic characteristics and treatment

Table S2. Laboratory data

Table S3. Coronary angiography findings

Table S4. Morphometric analysis of OFDI

Figure S1. (**A**) Morphometric parameters, including lumen diameter, intimal (I)+medial (M) thickness, lumen area, vessel area and I+M area, were manually measured in off-line manner, at every 1 mm along the spastic segments and the proximal/distal references within 5 mm adjacent to the spastic segments.

Methods

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-16-0580