It is a generally accepted view that the atherosclerosis process is triggered by endothelial damage induced by lifestyle-related diseases such as hypertension, diabetes and dyslipidemia.¹ Thus, it is believed that atherosclerosis progresses ‘inside-out’ from the endothelium to the adventitia. On the other hand, it has been reported that growth of atherosclerotic plaques is accompanied by neovascularization from the vasa vasorum (VV) extending through the tunica media into the base of the plaque.³ The VV consist of small arteries that are distributed to the outer and middle coats of the larger blood vessels. VV invasion can be observed when the vessel wall exceeds a certain thickness, which in mammals is 0.5 mm or 29 lamellar units.³ It is assumed that the VV serve as a conduit for nutrients and oxygen, which can not be supplied to the adventitial and outer medial layers of the larger vessels by diffusion from the luminal side. Resident immune cells are present in the adventitia and macrophages home to that site.⁴ It is believed that inflammatory cells as well as adipocytokines secreted from the perivascular adipose tissue are delivered into the plaque via the VV.⁵ Hence, atherosclerotic process extends not only ‘inside-out’ but also ‘outside-in’ (Figure).³

The role of the VV in the pathogenesis of atherosclerosis has been studied using animal models of atherosclerosis and human autopsy samples. Histological analyses and micro-CT studies of the pig coronary artery have revealed that inflammatory cells accumulate in the adventitia with proliferation of the VV prior to arterial wall thickening.⁶ In a mouse model of hyper-

Figure. Vasa vasorum (VV) in atherosclerosis. In the normal artery, adventitial VV extend in the longitudinal direction of the main lumen. In atherosclerotic plaque, the VV proliferate, form a dense plexus and invade the plaque. Inflammatory cells accumulate inside the plaque, adventitia, and perivascular adipose tissues. The VV serve as a conduit for inflammatory cells, as well as adipocytokines secreted from perivascular adipose tissue, into the plaque.
cholerescleroica, atherosclerotic plaque progression was accompanied by an increased number of adventitial VV. It was also reported that inhibition of the growth of the VV with antiangiogenic factors, such as endostatin, angiostatin, and a truncated plasminogen activator inhibitor-1 (rPAI-1), resulted in reduction of atherosclerotic lesion progression. Moreover, histological studies of human advanced plaques revealed that plaque neovascularization is increased in ruptured atherosclerotic lesions. Taken together, these studies suggested a pathological role of the VV in the progression and destabilization of atherosclerotic lesions. In this regards, intraplaque and adventitial microvessel growth appears to be a promising target to determine plaque vulnerability and to find a therapeutic strategy against atherosclerotic diseases. However, in vivo visualization of the VV in humans has been technically challenging.

Several modalities such as CT angiography, contrast-enhanced ultrasound imaging, and contrast-enhanced magnetic resonance imaging have been used to evaluate VV growth in the human carotid artery in vivo. VV proliferation has a relationship with the onset of neurological symptoms of brain ischemia and cardiovascular events. Vavuranakis et al performed intravascular ultrasound (IVUS) imaging before, during, and after intracoronary injection of a microbubble contrast agent. They evaluated the density of the VV in human coronary plaques as an enhancement in the grey-scale intensity of the intima-media and adventitia after injection. However, the resolution of IVUS is not high enough to visualize the plexus structure of the VV.

Optical coherence tomography (OCT) provides higher resolution than IVUS and is expected to be capable of visualizing plaque neovascularization. Vorpalh et al reported that small black holes in optical frequency-domain imaging (OFDI), a newer generation OCT, match intravascular neangiogenesis formation in histology. Nishiyama et al also demonstrated that OFDI clearly visualized adventitial VV in human coronary lesions in vivo. Uemura et al showed that the presence of microchannels as detected by OCT was an independent predictor of subsequent progression of coronary plaque with nonsignificant luminal stenosis. Those authors assumed that microchannels represent intraplaque neovascularization, which plays a pivotal role in the progression of coronary plaques by increasing the flow of blood, inflammatory cells and cytokines into the lesions. Moreover, Kitabata et al suggested the importance of intraplaque microchannels as a marker for plaque vulnerability. However, it remains to be validated whether the OCT or OFDI really enables us to accurately evaluate coronary adventitial VV growth in animals and humans.

In this issue of the Journal, Nishimiya et al use OFDI to visualize the VV in the stent edge portions in pig coronary arteries ex vivo and they validated the findings with histological analysis. Furthermore, they visualized the VV in the stent edge portions in human in vivo by OFDI. If OCT or OFDI becomes able to evaluate the distribution of the VV more accurately with further technical improvements, we could obtain important information about the characteristics of coronary plaques and evaluate the role of the VV in the pathogenesis of atherosclerosis and re-stenosis after percutaneous coronary interventions. The effects of medical therapy on the VV could also be evaluated with OFDI. The study by Nishiyama et al provides a new perspective to the better understanding of the pathological role of plaque neovascularization in the progression and destabilization of human coronary atherosclerosis.

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