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. 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. 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. 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. It is believed that inflammatory cells as well as adipocytokines secreted from the perivascular adipose tissue are delivered into the plaque via the VV. Hence, atherosclerotic process extends not only ‘inside-out’ but also ‘outside-in’ (Figure). 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. 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.
cholesterolemia, atherosclerotic plaque progression was accompa-
nied by an increased number of adventitial VV. It was also
reported that inhibition of the growth of the VV with anti-
angiogenic factors, such as endostatin, angiotatin, and a truncated
plasminogen activator inhibitor-1 (rPAI-1), resulted in reduc-
tion of atherosclerotic lesion progression. Moreover, histo-
logical studies of human advanced plaques revealed that plaque
neovascularization is increased in ruptured atherosclerotic
lesions.8,9 Taken together, these studies suggested a patho-
logical role of the VV in the progression and destabilization
of atherosclerotic lesions. In this regards, intraplaque and advent-
titial microvessel growth appears to be a promising target to
determine plaque vulnerability and to find a therapeutic strat-
egy against atherosclerotic diseases. However, in vivo visual-
ization of the VV in humans has been technically challenging.

Several modalities such as CT angiography,10 contrast-
enhanced ultrasound imaging,11 and contrast-enhanced magnetic
resonance imaging12 have been used to evaluate VV growth in
the human carotid artery in vivo. VV proliferation has a rela-
tionship with the onset of neurological symptoms of brain
ischemia32 and cardiovascular events. Vavaranakis et al13 per-
formed intravascular ultrasound (IVUS) imaging before,
during, and after intracoronary injection of a microbubble con-
trast agent. They evaluated the density of the VV in human coro-
nary 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.14

Optical coherence tomography (OCT) provides higher res-
olution 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 of OCT, match intravascular neoangiogenesis
formation in histology.33 Nishiyama et al also demonstrated that
OFDI clearly visualized adventitial VV in human coronary
lesions in vivo.15 Uemura et al showed that the presence of
microchannels as detected by OCT was an independent pre-
dictor of subsequent progression of coronary plaque with
nonsignificant luminal stenosis.16 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 impor-
tance of intraplaque microchannels as a marker for plaque
vulnerability.17 However, it remains to be validated whether the
OCT or OFDI really enables us to accurately evaluate coron-
ary adventitial VV growth in animals and humans.

In this issue of the Journal, Nishimiya et al18 use OFDI to
visualize the VV in the stent edge portions in pig coronary arter-
es 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 impor-
tant information about the characteristics of coronary plaques
and evaluate the role of the VV in the pathogenesis of athero-
sclerosis and re-stenosis after percutaneous coronary interven-
tions. 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 pathologi-
ical role of plaque neovascularization in the progression and
destabilization of human coronary atherosclerosis.

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