Arterial Microvessels: An Early or Late Sign of Atherosclerosis?

Hypoxia is a strong stimulus for the induction of angiogenesis. In an elegant series of experiments, including in vivo labeling of hypoxic tissues, Sluimer et al. (1) have demonstrated that hypoxia in advanced atherosclerotic plaques colocalized with the expression of hypoxia-induced transcription factors (i.e., HIF1α, HIF2α), growth factors (i.e., vascular endothelial growth factor), and glucose transporters (i.e., GLUT1, GLUT3) and that all these microenvironmental changes were accompanied by neovascularization—the number of microvessels per mm² intima area was significantly greater in advanced than in early atherosclerotic lesions.

We have previously shown that 2 distinctive angiogenic events occur during atherosclerosis in humans (2). In addition to ectopic plaque neovascularization, we found a hyperplastic network of vasa vasorum in the arterial adventitia in early lesions of patients with active, symptomatic disease. However, the arterial adventitia is a physiologically vascularized compartment of the arterial wall and is not expected to harbor a hypoxic microenvironment. Studies based on swine models of hypercholesterolemia showed that adventitial neovascularization is not exclusively related to plaque formation; those animals presented with the highest vasa vasorum count but without any arterial wall thickening (3). The authors suggested that the main stimulus to vessel wall neovascularization might not be local hypoxia but could rather be related to the increased oxidative stress.

However, Sluimer et al. (1) showed that metabolically active macrophages may contribute to tissue hypoxia by oxygen exhaustion (4) and that this mechanism could also contribute to hyperplasia of vasa vasorum in the arterial adventitia. Because contrast-enhanced transcutaneous ultrasound is a bedside procedure that can be used to visualize both plaque (5) and adventitial microvessels (6), the 2 compartments might be accessible for the diagnosis of early and late stages of preclinical atherosclerosis. A common pathogenic mechanism might eventually be targeted therapeutically.

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In their letter, Dr. Biedermann and colleagues point to the existence of distinct angiogenic events in the intima and adventitia in human atherosclerosis. They also suggest that adventitial angiogenesis might not be driven by local hypoxia, whereas the intima is hypoxic and may drive intimal angiogenesis, as we have shown in our recent paper (1).

In that study, we were not able to analyze the existence of hypoxia in the adventitia because our analysis was restricted to carotid endarterectomy specimen that only contained the intima and small parts of the media. It is known that the adventitia does contain macrophages, which does increase the quest for oxygen, and adventitial microvessels are present. As suggested recently, one reason for adventitial hypoxia might be insufficient perfusion, because the adventitial vessels are very thin walled (J.C. Sluimer et al., unpublished data, March 2008) and may collapse at least in part during the cardiac cycle (2). The true value of this suggestion, however, needs to be determined by the actual quantification of adventitial microvessel flow during the cardiac cycle.

Plaque macrophage hypoxic stress is indeed suggested to be a strong driver of plaque angiogenesis. Although adventitial and plaque angiogenesis may have another driving stimulus, there is a close connection between plaque and adventitial microvessels, because the vast majority of plaque vessels seem to sprout from adventitial microvessels that penetrate through the media, as demonstrated by Virmani et al. (3). This close anatomic connection between adventitial and plaque microvessels might therefore also stimulate angiogenesis in the adventitia, albeit indirectly. We agree with Dr. Biedermann and colleagues that this does not imply that the reverse—increased adventitial angiogenesis causes increased plaque angiogenesis—is also true. We do support the call and need for adequate visualization technologies able to quantify plaque and adventitial angiogenesis. In