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., HIF-1α, HIF-2α), 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 implicate 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
vivo imaging of angiogenesis with the use of contrast-enhanced transcutaneous ultrasound sound is promising, as elegantly shown by Shah et al. (4). However, trials with an extended number of human subjects and validation of histological angiogenesis are required. These technologies may then help to elucidate the close pathophysiological connection between intimal and adventitial angiogenesis in human atherosclerosis. Whether or not these technologies are going to be useful to detect specific plaque stages remains to be investigated.

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Streit et al. (2) had demonstrated earlier that alcohol septal ablation has arrhythmogenic potential due to myocardial fibrosis that can increase the frequency of ventricular arrhythmias. These fibrotic areas in the myocardium caused by septal ablation can potentially give rise DE on CMR. Therefore, history of prior myocardial septostomy or percutaneous interventions (i.e., ethanol injection) for the relief of left ventricular outflow obstruction could be an important confounding variable that can cause both DE on CMR and ventricular arrhythmias. Adabag et al. (1) did not provide any information on this issue that may potentially affect the results. It would be helpful to know how many of the patients in the study had procedures done for the relief of left ventricular obstructions and whether excluding such patients will provide the same results.

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Reply

We appreciate the interest of Dr. Dhoble and colleagues in our paper (1). Of our reported 177 hypertrophic cardiomyopathy patients, none had undergone alcohol septal ablation before the cardiac magnetic resonance study and 24-h ambulatory Holter electrocardiogram were performed. Nonetheless, Dr. Dhoble and colleagues raise an important point. Percutaneous alcohol septal ablation, pioneered in the last decade as a nonsurgical alternative to surgical myectomy for reduction of left ventricular outflow tract obstruction and heart failure symptoms in hypertrophic cardiomyopathy, intentionally creates a sizable transmural scar in the septum (2). Indeed, there is some evidence that alcohol ablation increases the arrhythmia burden in this disease for which some patients already harbor increased arrhythmogenicity (3). Consequently, alcohol septal ablation is recommended only as a selective alternative to patients for whom the gold standard surgical septal myectomy is undesirable (4).

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