Noninvasive Imaging of Coronary Artery Disease
– Myth or Reality? –

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Atherosclerosis and its thrombotic complications are the major cause of mobility and mortality in the modern world. Identification of the severity and vulnerability of the culprit atherosclerotic lesion by clinical imaging renders the development of intervention strategies to prevent acute cardiovascular events such as myocardial infarction. An ideal clinical imaging modality for atherosclerotic vascular disease should be safe, cost-effective, noninvasive or minimally invasive, accurate, and reproducible, and the results should correlate with the extent of atherosclerotic disease. Coronary plaque and its vulnerability can be examined by intravascular ultrasonography or optical coherence tomography, but both techniques are invasive and may not be feasible for routine clinical application. Noninvasive computed tomography and high-resolution magnetic resonance imaging allow not only visualization of coronary artery stenosis but also characterization of plaque composition. Nevertheless, cardiac and respiratory motion currently restricts their effectiveness in the coronary tree. Ultrasound imaging is widely available, inexpensive, and well-suited for high-throughput screening in populations that are at risk for atherosclerosis. The carotid intima-media thickness (CIMT), assessed by B-mode ultrasonography as a simple test assessing structural changes in the arterial wall, has been suggested as a surrogate maker for atherosclerotic disease. However, the accuracy of CIMT as a marker of atherosclerosis has recently been questioned by the fact that the main predictors of medial hypertrophy or intimal thickening of the common carotid artery are age and hypertension, which do not necessarily reflect the atherosclerotic process.

In this issue of the Journal, Deyama and colleagues provide elegant prospective clinical evidence that contrast-enhanced ultrasound assessment of carotid plaque neovascularization may predict the severity and instability of coronary artery disease. Their working hypothesis is based on the following rationale. First, atherosclerotic lesions are systemic and a continuum. Patients with symptomatic disease in 1 vascular bed are at increased risk of disease in other beds. Second, angiogenesis in an atherosclerotic plaque may contribute to the plaque’s progression and rupture. Phylogenetically, the primary functions of the neovessels are to deliver nutrients to the vessel wall and to remove waste or noxious products. By contrast, uncontrolled formation of intraplaque or adventitial neovessels appears to contribute to the progression and destabilization of atherosclerotic plaque. Moreover, some of the neovessels are immature and prone to destruction, which may subsequently contribute to the development of intraplaque hemorrhage and plaque instability. Third, contrast-enhanced ultrasound has shown advantages in real-time visualizing of intraplaque neovascularization. Indeed, data collected by Deyama et al indicate that neovascularization in the carotid artery as assessed by contrast-enhanced ultrasound is strongly associated with the severity of coronary artery lesions and may be used to predict regression by anti-atherosclerotic treatment such as statins. In addition, they show that extensive neovascularization is independently associated with acute coronary syndrome. Overall, their study, although with limited patient numbers, suggests a promising strategy for risk stratification and treatment evaluation of patients with coronary artery disease. A longitudinal, prospective study with long-term follow-up in a large number of patients is required to assess the precise prognostic value of carotid plaque contrast-enhancement ultrasound in determining future coronary events.

However, we still need to confront substantial challenges to make clinical imaging of the rupture-prone coronary plaque a reality. First, although there is a clear relationship between disease in the coronary and carotid arteries, there are several differences in the disease’s appearance in these 2 arteries. For example, carotid plaques appear by histology to be more advanced and present a more mixed pathology, and although the degree of stenosis in the coronary artery has little ability to predict acute coronary syndrome, severe carotid stenosis causing hypoperfusion is highly predictive of stroke, although this effect may be time-limited. As well, although the 2 arteries share similar risk factors for atherosclerosis, the effect of these risk factors may be artery-specific. Further studies are warranted to better understand the exact similarities and differences of atherosclerotic disease in the coronary and carotid arteries. Second, the adventitial and intraplaque vasa vasorum are distinct microvascular nutrients networks intimately associated with vessel wall disease and plaque vulnerability. In their study, the current authors only observed that intraplaque neovascularization may lead to overlooking of the overall angiogenesis in the carotid vessels. Currently, preclinical studies...
have shown that both detection and characterization of adventitial neovascularization is technically feasible. The further development of these imaging techniques relies on the successful implementation of contrast microspheres capable of enhancing microvascular structures and being targeted to specific tissues. Third, state-of-art techniques are needed to overcome the limitations of contrast-enhanced ultrasound, including the short half-life of the bubbles in vivo, their restriction to the intravascular compartment, and the low contrast-to-noise. Molecular imaging of vascular phenotype changes at the subcellular level is emerging and under clinical trial. Undoubtedly, the rapid development of cost-effective ultrasound will bring noninvasive monitoring of plaque rupture and regression out of the realms of myth and into reality.

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None.

References