EDITORIAL COMMENT

Visualizing Coronary Atherosclerosis In Vivo: Thinking Big, Imaging Small*

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Over the past decade, a keen interest has developed in the imaging of atherosclerosis in patients in vivo. One approach is the direct intracoronary visualization with ultrasound, angioscopy, or more recently, magnetic resonance imaging (MRI). Another, more practical approach is non-invasive imaging with ultrasound, MRI, or radionuclide tracers. In this issue of the Journal, Hamilton et al. (1) have reported using the former approach in conjunction with liposomes targeted to endothelial cell adhesion molecules and thrombus mediators in a model of aggravated vascular injury. This study highlights both the potential and current limitations of atherosclerosis imaging in vivo.

See page 453

Atherosclerosis starts with vascular injury, which initiates a sequence of inflammatory responses that involve cellular activation, migration, proliferation, and differentiation (2). These events lead to plaque formation, vascular remodeling, and eventually plaque encroachment into the vascular lumen and resulting luminal stenosis. Finally, plaque rupture or superficial erosion leads to thrombosis and acute coronary syndrome. Early forms of imaging using intracoronary devices were able to assess atherosclerosis at the later stage when the vascular morphology had changed. The newer methods, such as the one reported by Hamilton et al. (1), are geared toward imaging vessel wall injury, cellular trafficking, and molecular alterations in the early and intermediate stages of atherosclerosis.

Noninvasive imaging for the detection of early atherosclerosis will depend on the development of tracers that are targeted to early molecular changes observed in this process and that can easily be administered intravenously. For this approach to succeed, the imaging tracer (microbubbles, paramagnetic agents, or radionuclide tracers) should be present in high enough concentrations at the disease site to be easily imaged over background signal. Certain conditions related to the imaging tracer must be met for this to occur: 1) it must be targeted to a ligand that is selective for the disease process; 2) it must have adequate access to the ligand; 3) it must be retained long enough at the site of interest for image acquisition; 4) it must clear rapidly from the blood pool; and 5) it must be safe.

SIGNAL-TO-NOISE RATIO

In the study by Hamilton et al. (1), the segments that were “positive” on intravascular imaging generally had signal enhancement of 25% to 50% over background despite upstream direct arterial injection of 8 mg of liposomes. There are several reasons why the backscatter was relatively low for a direct intracoronary imaging device. For ultrasound imaging, the signal-to-noise ratio is influenced by tracer size and compressibility and by ultrasound power and frequency. Liposomes are relatively small in size (several hundred nanometers in diameter). Because signal from a scatterer is related to the sixth power of the radius (3), if microbubbles (several micrometers in diameter) instead of liposomes with the same ligand affinity were used, the signal would be much higher. Liposomes are also mostly filled with fluid (4), making them less compressible than gas-filled microbubbles. A further marked increase in signal is possible by oscillating compressible microbubbles at high acoustic power and/or lower ultrasound frequency. Therefore, the use of intravenous microbubbles and state-of-the-art imaging (harmonic, ultraharmonic, or power Doppler) (5) would make it possible to get similar if not better results from transthoracic echocardiography compared with those obtained using intravascular ultrasound and intracoronary-delivered liposomes.

SITE-SPECIFIC TARGETING

As stated previously, the signal-to-noise ratio for targeted agents is partially determined by the site specificity and affinity for the targeted molecule. It is also desirable to have a relatively high density of the tracer at the disease site. For the purposes of imaging inflammation, tracers can be targeted to adhesion molecules expressed on the endothelial surface, such as intercellular adhesion molecules (ICAMs), vascular cell adhesion molecule-1, and selectins (6,7). This approach was initially validated in vitro by Villanueva et al. (8) with ICAM and used successfully by Hamilton et al. (1) to define injury-induced atherosclerosis in coronary arteries in vivo. It has also been used by us and by others for assessing microvascular changes that occur early in inflammation and angiogenesis (9–11). The potential advantage of this approach is the ability to characterize very early disease when endothelial injury or alteration has just begun. The main limitation of this strategy is the potential lack of specificity due to constitutive expression of these molecules, especially ICAM-1 (6,7). Unfortunately, whether targeted liposomes attach to non-diseased vessels was not evaluated.

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by Hamilton et al. (1). The duration of adhesion molecule expression may also be transitory and, for the immunoglobulin family of receptors (ICAMs, vascular cell adhesion molecule-1), may shift from endothelial to non-endothelial locations (6).

Ultrasound imaging of targeted microbubbles in the microcirculation has been possible because of the sensitivity of the imaging techniques used (harmonic, ultra-harmonic, and power Doppler) (5) and the relatively high number of microbubbles retained. The hydrodynamic forces in the great vessels and the larger segments of coronary arteries are much higher, often exceeding 5 dynes cm⁻². Whether spherical bubbles can withstand these high rates despite relatively high bond strength is not known. One way to increase the binding of microbubbles is to make their shapes more flexible and create crenations on their surfaces so that they more closely resemble leukocytes (12). Another approach is to use various bubble populations that bind to different adhesion molecules and potentially increase the binding surface area and the range of binding affinities. This approach was used successfully by Hamilton et al. (1). Furthermore, because the vessel wall is echogenic, tissue suppression techniques (such as ultraharmonic and power Doppler) would be very useful in providing good signals from the microbubbles.

THE ROLE OF VASO VASORUM

Whereas cell trafficking into the potential site of an atherosclerotic plaque occurs via the luminal surface of the vessel early after injury, it occurs via the vasa vasorum in a maturing plaque (13). Neovascularization from the vasa vasorum is seen in atherosclerosis both on the vessel adventitia and within the plaque. These conduits facilitate cell trafficking into the plaque and are therefore partly responsible for the plaque “activity” (14). The hydrodynamic forces are also more conducive to cell adhesion and migration compared with larger vessels with higher velocity flows. Hamilton et al. (1) noted ultrasound signal not only from the plaque but also from the surrounding adventitia, part of which could have come from the vasa vasorum and other newly formed vessels. In this regard it may also be valuable to target molecules expressed during angiogenesis (9,10).

IMAGING PLAQUE CONTENT

Another approach could be targeting active cellular plaque components, such as monocyte/macrophages or T-lymphocytes. Microbubbles can be targeted to activated leukocytes within the microcirculation (15); however, imaging leukocytes within the vessel wall is more likely to succeed with diffusible tracers. Paramagnetic tracers, such as iron oxide particles, have been found inside plaque macrophages on MRI (16).

Products released by leukocytes and activated smooth muscle cells, such as cytokines, metalloproteinases, and tissue factor, could also be targeted for imaging. It may also be possible to assess plaque “activity” by measuring oxidative changes within atherosclerotic lesions, such as the presence of modified low-density lipoprotein (17), or other metabolic alterations (18). Unlike imaging of plaque morphology using earlier intracoronary approaches, imaging these targets could assist in determining plaque “activity” and possibly identify lesions likely to rupture. These non-invasive approaches would be more practical than others that assess thermal and metabolic plaque activity using intracardiac devices.

CLINICAL IMPLICATIONS

Imaging atherosclerosis is now feasible as shown by Hamilton et al. (1) and others (8,17,18). The techniques for this purpose need further development before they can be used noninvasively in humans. Whether characterization of coronary atherosclerosis will provide incremental value in individual patients over standard risk factor assessment in conjunction with currently available biomarkers (such as high-sensitivity C-reactive protein) or those likely to emerge from proteomic profiling of blood from large patient population remains to be determined. These non-invasive imaging approaches could, however, be used to understand the pathobiology of atherosclerosis in humans. They could also be valuable in measuring the efficacy of different therapeutic interventions. Precise quantification of the effect of interventions on plaque “activity” rather than measurement of clinical outcomes alone could decrease the number of patients required in clinical trials that contribute to the high cost of drug development and thus health care, something that even this country can ill afford in the long run.

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REFERENCES


