From the Microscope to the Clinic
MR Assessment of Atherosclerotic Plaque

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Magnetic resonance is the newest of the clinical imaging technologies to evaluate the cardiovascular system. The ability to image the aorta and the iliofemoral and carotid arteries is now a clinical reality. Imaging of the large epicardial coronary arteries is rapidly developing as a clinical tool. The next step will be to characterize atherosclerotic plaque in vivo in larger vessels and then, potentially, in human coronary arteries. In this issue of Circulation, Fayad et al1 take a step forward in the imaging of atherosclerotic plaque by MR. They report on their experience with high-field MRI of “magnetic resonance microscopy” in small mice, some of which were “wild-type” controls and others genetically engineered to produce severe atherosclerosis (apolipoprotein E knockout). Using commonly available NMR hardware, the investigators were able to visualize aortas with a total area of 0.3 mm² in wild-type controls and others genetically engineered to produce severe atherosclerosis (apolipoprotein E knockout). Using common available NMR hardware, the investigators were able to visualize aortas with a total area of 0.3 mm² in wild-type mice and 0.6 mm² in the apolipoprotein E–knockout mice. To image such small structures, they achieved a spatial resolution of 47 μm per pixel. MR measurements of wall area versus histopathology correlated well (slope = 1, r = 0.86). In addition, the grading of lesion shape and type from MR images also correlated well with that by histopathology (r = 0.91 and r = 0.90, respectively). Correlations of linear regression analysis of MR and histopathology gradings of atherosclerotic severity also were good (slope = 0.64, r = 0.90, n = 58).

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Of course, the ideal model for human atherosclerosis is Homo sapiens, and the versatility of NMR methods allows such studies to be performed in humans. Thus, the importance of the present work is not only that it sets the stage for clinical studies but also that it demonstrates the usefulness of MR microscopy in the “in vivo” setting. Unfortunately, the term in vivo in this context cannot be extrapolated to clinical work. The mice were effectively immobilized by the small radiofrequency coil, and anesthesia was used; as a result, there were fewer of the difficulties (body, respiratory, and cardiac motion) that are present clinically. In addition, the imaging procedure resulted in a 23% mortality rate. Although image quality in humans would be improved under these circumstances, such a method would not survive in clinical practice.

Previous experience with MR in small animals has demonstrated its usefulness in true in vivo imaging. MRI has detected herpes simplex virus–associated changes in the brains of mice2 and bromobenzene-induced liver toxicity in rats.3 Rehwald and colleagues4 described techniques that can be used for high-speed, high-resolution cardiac MRI in rats and rabbits. Summers et al5 described the use of implanted imaging coils in rats to follow balloon-induced carotid injury in vivo, with good correlation between images and histopathology. Wehr and coworkers6 used MR to serially image transplanted segments of carotid arteries in rats as a model of transplant vasculopathy. Franco and colleagues7 successfully measured in vivo myocardial mass in a transgenic mouse model of hypertrophy, using gated multislice, multiphase MRI. Larger animals, like rabbits,8–10 pigs,11 and primates,12 have also been studied. Imaging of small arteries, such as the distal coronary arteries and branch vessels, in humans has been progressing, but with a set of obstacles somewhat different from those in the Fayad study. Both cardiac and respiratory motion combined are the principal difficulties to be overcome in MR coronary angiography. As technology has improved, so has image acquisition speed and image quality. New and innovative gating methods have also been used to reduce the effects of cardiac and respiratory motion. There is little doubt that MR coronary angiography will evolve into an effective clinical tool.

Plaque research in humans has already been demonstrated to be well suited to the strengths of MRI. Toussaint et al13,14 used MR techniques to demonstrate plaque in human carotid arteries and to characterize certain components of plaque, including the fibrous cap and lipid core, by measuring T2 changes. Furthermore, this same group identified alterations in diffusion properties of human plaque in vitro.15 Pan and colleagues16 demonstrated a good correlation between MR imaged carotid artery lumen area and pathological specimens from patients undergoing endarterectomy. Development and application of new intravascular (IV) coils also holds promise for future work on plaque characterization by MRI.17–19 Although it lacks the attractive noninvasive aspect of MRI, IV MRI may have the ability to truly characterize plaque, not just by morphological criteria but also by applying spectroscopy to the plaque and vessel wall. Currently, attempts at using standard NMR spectroscopy to characterize in vivo plaque have been hampered by the limitation of depth accessibility with small surface coils and the distance from the surface of most large arteries. In vitro characterization of human atherosclerotic plaque components has been shown to...
be feasible with MR, so there is promise that more than justifies the ongoing studies.

Oshinski and colleagues also studied plaque indirectly in humans by use of phase velocity mapping (PVM) techniques. These techniques emphasize the inherent sensitivity of MRI to blood velocity and turbulence. PVM was used to measure the wall shear stress of different segments of aorta, with the finding of higher wall shear stress in the supraprenal aorta and lower wall shear stress in the infrarenal aorta. Because plaque is more commonly found in the infrarenal aorta, wall shear-stress measurements by PVM appear to provide insight into a mechanism associated with plaque formation.

Accordingly, the study by Fayad et al complements the existing literature on the application of MR to the study of atherosclerotic plaque. It successfully extends the use of MR to a model that allows the researcher more flexibility in a number of areas. The use of mice allows more control, because the mouse genome is well characterized, can be easily manipulated, and allows the researcher to take advantage of using small laboratory animals. As the authors mention, the study suggests the potential for the serial evaluation of therapies for atherosclerosis in genetically engineered laboratory animals. The study applied hardware that is found in many laboratories, so that researchers at many centers would be able to apply such methods to their own experiments.

The study did not incorporate one of the most important aspects of MR technology that could be of great value for biochemical characterization, namely spectroscopy. In future work, it would seem appropriate to use MR spectroscopy to assess plaque lipid, for example. This might require IV MRI methods. The combination of T2-weighted imaging and 1H spectroscopy could have even more potential than either one alone. However, many hurdles need to be overcome before spectroscopy can be applied appropriately to plaque characterization. The interesting finding of Cassells et al that active plaque may be detectable by differences in temperature also paves the way for in vivo evaluation by MR diffusion-weighted echo-planar imaging.

In summary, MRI has a number of unique characteristics that make it especially useful for the study of atherosclerosis. As a high-resolution, nondestructive technique, it is ideal for serial study. It is noninvasive, allowing study of atherosclerosis without the need for potentially confounding catheter manipulation (except for the possibility of IV MRI) or ionizing radiation. It has the theoretical ability to characterize plaque constituents with NMR spectroscopy and to a lesser extent T2 imaging and to provide real insight into plaque formation, rupture, and stabilization. MRI is an excellent tool for plaque research, whether the bearer of the plaque be large or small.

References

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