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· Magnetic Resonance Imaging of the High-Risk Atherosclerotic Plaque

Professor of Surgery

FUNDING

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Introduction

Cardiovascular disease (CVD) is the number one cause of death worldwide and is a leading cause of long-term disability. It is estimated that the annual cost for the care of victims of CVD is over $390 billion per year in the United States alone. Most CVD events, such as heart attack and stroke, are atherosclerosis-related. Traditionally, the degree of vessel lumen narrowing has been used to identify the high-risk atherosclerotic plaque. However, there is increasing evidence that the structure, composition, and inflammatory activity of the atherosclerotic lesion are more important markers of the vulnerable plaque. Progress in understanding how vulnerable plaques develop has been hindered by our inability to serially examine these critical characteristics of the diseased vessel wall in a non-invasive fashion.

The mission of our research group is to advance high-resolution magnetic resonance imaging (MRI) technology for accurate, non-invasive examination of atherosclerosis. Our laboratory is organized along five core functions: 1) Imaging Physics: develop novel image acquisition techniques; 2) Histology: provide the histological gold-standard for validation of MRI findings; 3) Imaging Software: build custom-designed tools that permit more efficient, reproducible, quantitative image analysis; 4) Clinical Studies: apply MR imaging techniques to understand mechanisms leading to development of the vulnerable plaque; and 5) Reading Center: provide training, quality control, and image analysis for multi-center clinical trials using MRI.

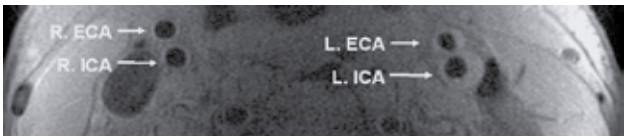

Figure 1: MRI of right and left internal and external carotid arteries demonstrating good suppression of flow artifact and clear delineation of the lumen and outer boundary of normal (right) and diseased (left) carotid arteries. Note evidence of compensatory (expansive) enlargement on the left side. The cross-sectional area of the lumen is similar on both sides, yet there is significantly greater plaque burden on the left. ICA = internal carotid artery; ECA = external carotid artery.

Validation

Significant improvements in MR image quality have been made possible by a combination of hardware development and novel image acquisition sequences (Figure 1). The accuracy of this high-resolution MRI technique has been extensively validated by comparing pre-operative carotid MRI findings to matched histological sections of the excised plaque. We have shown that MRI can categorize carotid plaque types according to established American Heart Association histological classification criteria (Table 1), with a weighted Kappa of 0.79, indicating very good agreement between MRI and histology (*Circulation* 2002; 106:1368). Furthermore, we have shown that MRI can accurately identify the presence and precisely quantify the size of critical features of the vulnerable plaque, as defined by an expert panel (*Circulation* 2003; 108:1664). These features include the degree of lumen narrowing and overall plaque burden (*Circulation* 1998; 98:2666 and *Magnetic Resonance in Medicine* 2000; 44:968), fibrous cap thinning and rupture (Figure 2; *Circulation* 2000; 102:959),

Over 16.7 million people die of cardiovascular disease (CVD) each year — one person every 2 seconds. Our primary goal is to develop and validate high-resolution imaging methods that will improve our ability to identify individuals at highest risk. Furthermore, by allowing us to non-invasively visualize the diseased vessel wall, these imaging tools will enable us to assess the effectiveness of novel therapies for CVD.

the lipid-rich necrotic core and intraplaque hemorrhage (Figure 3; *Arteriosclerosis, Thrombosis and Vascular Biology* 2005; 25:234), and the degree of neovasculature and inflammatory cellular infiltration of the plaque (Figure 4; *Circulation* 2003; 107:851 and *Radiology* 2006; 241:459).

Automated Quantitative Image Analysis

Analysis of the MR images is a time-consuming process, with approximately 70 high-resolution images generated for each artery. In order to perform large-scale clinical studies, automated, quantitative image analysis tools are needed, which would improve reproducibility and efficiency. Our lab has developed a probability based segmentation method that utilizes morphological information, such as local wall thickness, coupled with active contours to limit the impact from noise and artifacts associated with *in vivo* imaging (Figure 5). In experiments involving 142 sets of multi-contrast images from 26 subjects undergoing carotid endarterectomy, segmented areas of the lipid-rich necrotic core, calcification, loose matrix and fibrous tissue on MRI agreed with areas on the corresponding histological section with correlations (R^2) of 0.78, 0.83, 0.41 and 0.82, respectively. In comparison, areas outlined by expert MRI readers blinded to histology yielded correlations of 0.71, 0.76, 0.33 and 0.78, respectively (*Magnetic Resonance in Medicine* 2006; 55:659).

Clinical Studies

With funding from the National Institutes of Health, we have enrolled over 300 individuals over the past seven years in a prospective study, where participants undergo high-resolution MRI examination of their carotid arteries every 18 months. This study has demonstrated that arteries with intraplaque hemorrhage are associated with more rapid progression in overall plaque and lipid-rich necrotic core size (Figure 6; *Circulation* 2005; 111:2768). The percent change in wall volume over 18 months was 6.8% among those with intraplaque hemorrhage, compared with –0.15% for those without hemorrhage (p =

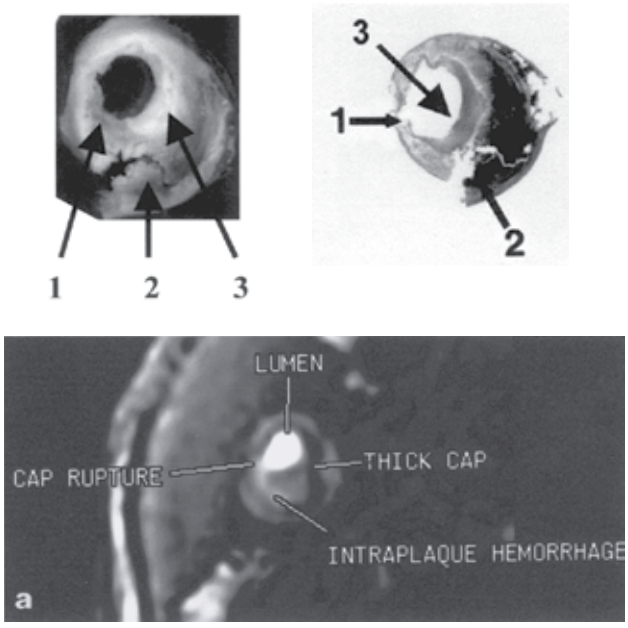

Figure 2: Example of a common carotid plaque with fibrous cap rupture and intraplaque hemorrhage. Photo of gross section of common carotid artery (left panel), trichrome stained histological section (right panel), and corresponding TOF MR image (bottom panel). Arrow 1 indicates an area of cap rupture, arrow 2 = intraplaque hemorrhage, and arrow 3 = area of thick, collagen-rich fibrous cap. The thick cap appears as a dark band adjacent to the lumen on MRI. The dark band is absent, and there is adjacent hyperintense signal in the region of cap rupture.

Lesion Type	Definition
I–II	Isolated foam cells or small foam cell layers
III	Pre-atheroma: small extracellular lipid pools
IV–V	Atheroma/Fibroatheroma: confluent lipid core with surrounding fibrous tissue
VI	Complicated lesion: surface defect, hemorrhage or thrombus
VII (Vb)	Predominantly calcified plaque
VIII (Vc)	Predominantly fibrotic plaque

Table I: Modified American Heart Association (AHA) classification scheme for describing atherosclerosis lesion types.

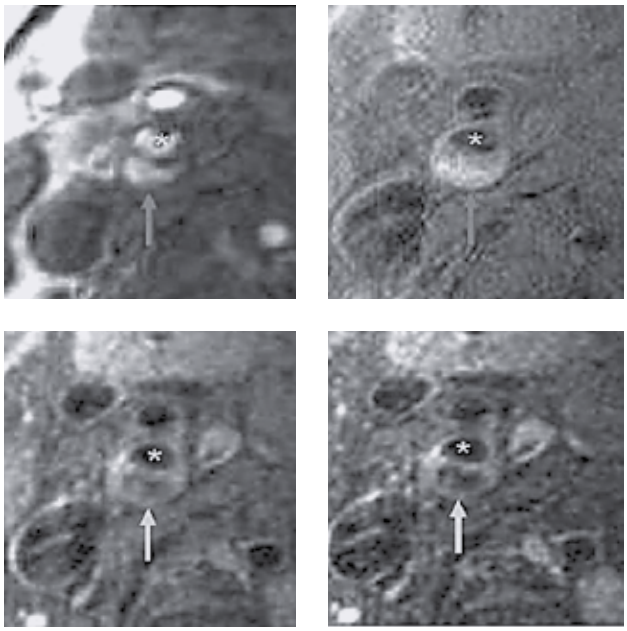

Figure 3: Example of an AHA Type VI (complicated) lesion with acute hemorrhage into the lipid-rich necrotic core. The asterisks indicate the lumen of the internal carotid artery. Early intraplaque hemorrhage, seen on the corresponding histological cross-section on the right, is identified by a hyperintense (bright) signal on time-of-flight (TOF) and T1-weighted (T1W) MR images, and relatively hypointense (dark) on the proton density- (PDW) and T2-weighted (T2W) images.

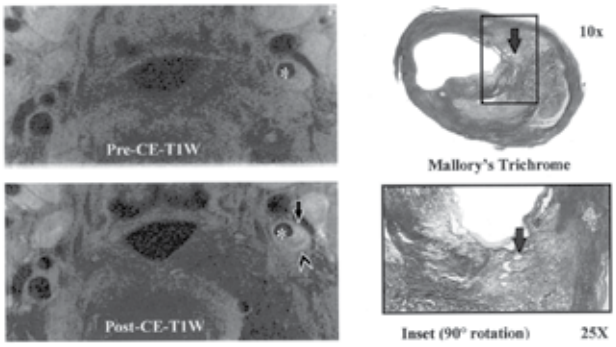

Figure 4: Pre-gadolinium contrast enhanced T1-weighted image of common carotid artery in left upper panel, post-contrast enhanced T1W image in left lower panel, and corresponding 10X and 25X trichrome stained histological sections. Note the enhancement seen in the shoulder region (arrow) in the post-contrast enhanced image. This enhancing region demonstrates abundant development of neovasculature and inflammatory cell infiltration on the corresponding histological section.

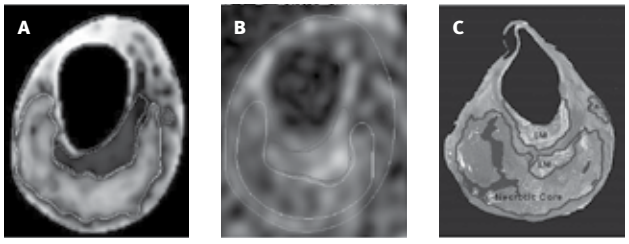

Figure 5: Segmentation results showing (a) automated quantitative image analysis tool; (b) manual outline by expert reviewer; and (c) corresponding histology section demonstrating a large necrotic core, loose matrix (LM) and a small area of calcification (CA). The dark regions within the necrotic core on the histology specimen are artifacts due to sectioning.

0.009). The lipid-rich necrotic core increased by 28.4% in plaques with hemorrhage, compared with –5.2% in those without hemorrhage (p = 0.001). Furthermore, those with intraplaque at baseline were much more likely to develop *new* plaque hemorrhages during follow-up, compared with controls (43% versus 0%, p = 0.006).

In a prospective MRI study to test the hypothesis that specific carotid plaque features are associated with a higher risk of subsequent ipsilateral TIA or stroke, 154 participants underwent a baseline carotid MRI examination, and were called every 3 months to identify symptoms of new-onset transient ischemic attack (TIA) or stroke. Twelve cerebrovascular events that were judged to be carotid-related occurred during a mean follow-up period of 38.2 months. Cox regression analysis demonstrated significant associations between ischemic events and presence of a thin or ruptured fibrous cap (hazard ratio, 17.0; $p < 0.001$), intraplaque hemorrhage (hazard ratio, 5.2; p = 0.005), and larger mean necrotic core area (hazard ratio for 10 mm^2 increase, 1.6; p = 0.01) in the carotid plaque. Figures 7 and 8 demonstrate Kaplan-Meier survival estimates for ipsilateral event-free-survival among patients with and without intraplaque hemorrhage and thin/ruptured fibrous cap, respectively (*Stroke* 2006; 37:818).

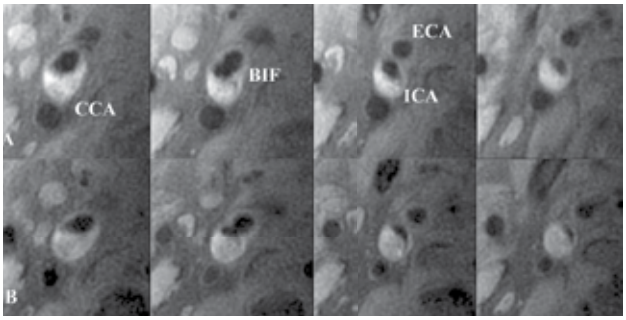

Figure 6: T1-weighted images of progression of atherosclerosis associated with intraplaque hemorrhage in the right carotid artery. Each column presents matched cross-sectional locations in carotid artery from baseline MRI (A) and MRI obtained 18 months later (B). Lumen area was decreased, and wall area was increased in each location on the second examination. CCA = common carotid artery; BIF = common carotid bifurcation; ICA = internal carotid artery; and ECA = external carotid artery.

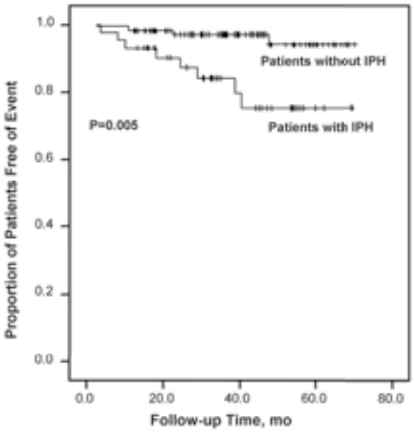

Figure 7: Kaplan-Meier survival estimates of the proportion of subjects remaining free of ipsilateral TIA or stroke with (lower curve) and without (upper curve) IPH. IPH = intraplaque hemorrhage.

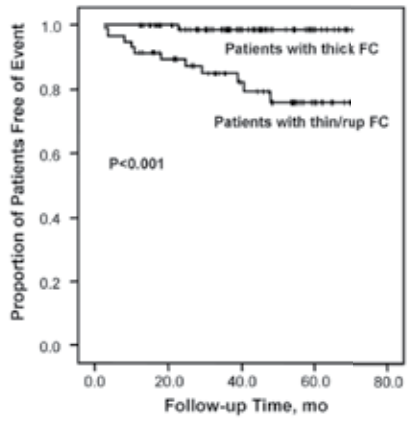

Figure 8: Kaplan-Meier survival estimates of the proportion of subjects remaining free of ipsilateral TIA or stroke with (lower curve) and without (upper curve) thin/ruptured fibrous cap. FC = fibrous cap.

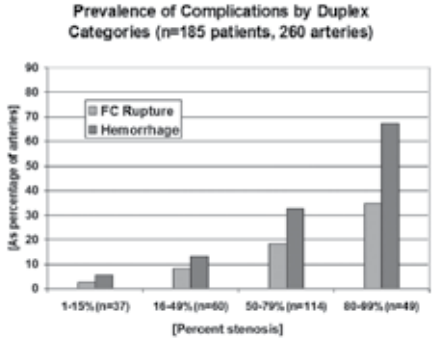

Figure 9: Prevalence of MRI-identified fibrous cap (FC) rupture and intraplaque hemorrhage by degree of stenosis in carotid plaques (n = 260) of asymptomatic volunteers. The degree of stenosis was determined by duplex ultrasound.

In a recent review of 260 carotid MRI examinations performed in asymptomatic subjects, the prevalence of arteries with intraplaque hemorrhage or fibrous cap rupture was assessed across a range of luminal stenoses. The findings shown in Figure 9 indicate that up to a third of subjects with asymptomatic 50–79% stenosis have evidence of plaque disruption or intraplaque hemorrhage. Surprisingly, disruption or hemorrhage was noted in approximately 10% of asymptomatic individuals with only 16–49% carotid stenosis.

Conclusions

Magnetic resonance imaging is a promising tool for studying the pathophysiology of human atherosclerosis progression and regression *in vivo*. In addition to precisely assessing plaque burden, MRI is capable of accurately classifying disease according to established AHA criteria, and identifying critical plaque features such as the fibrous cap and neovasculature. A better understanding of disease mechanisms and factors leading to more rapid progression will permit identification of high-risk individuals for more aggressive treatment, and potentially lead to the development of novel methods for therapeutic intervention.

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