Advanced Contrast-Enhanced MRI for Looking Beyond the Lumen to Predict Stroke
Building a Risk Profile for Carotid Plaque
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Abstract—Carotid plaque MRI can identify components indicative of stroke risk, including the thin/ruptured fibrous cap and lipid core. Gadolinium contrast, typically administered for routine MR angiography acquisitions, can be used to improve plaque characterization, extending risk assessment beyond the plaque’s hemodynamic impact on the lumen. Gadolinium preferentially enhances the cap, improves reliability of vessel wall measurements, and highlights neovessels, improving stroke risk stratification. Additionally, the precontrast series from the contrast-enhanced MR angiography can help identify intraplaque hemorrhage, another important risk marker. Prospective validation of these features is needed to develop a carotid plaque risk profile for clinical implementation. (Stroke. 2010;41[suppl 1]:S12-S16.)

Key Words: atherosclerosis ■ carotid artery ■ carotid plaque ■ carotid stenosis ■ imaging ■ magnetic resonance ■ MRI ■ risk factors ■ stroke risk

A milestone in our ability to determine stroke risk has been our understanding that a plaque’s composition may provide greater insight than just its hemodynamic effect on the lumen.1 MRI has a unique ability to characterize soft tissue components of plaque. It has focused on targets defined by pathological studies as indicators of stroke risk such as fibrous cap thickness, lipid core size, and, more recently, intraplaque hemorrhage (IPH). These targets have evolved as MRI techniques have advanced to achieve the most clinically relevant and reliable measures.

Fibrous Cap and Lipid Core
The thickness of the fibrous cap and size of the lipid core were early targets by MRI because of their strong correlation with thrombosis and disruption established by pathological studies.2 MRI can identify the lipid core with high accuracy, sensitivity, and specificity3 and can identify unstable (thin and/or ruptured) caps.4 MRI-identified fibrous cap rupture is strongly associated with having had a recent ischemic attack or stroke.5

Intraplaque Hemorrhage
Pathological evidence indicates that IPH plays an essential role in the development of the lipid core through free cholesterol and phospholipids derived from erythrocyte membranes and leads to macrophage accumulation and enlargement of the necrotic core.6 The role of IPH as a marker of vulnerability is highlighted by its predominance in symptomatic compared with asymptomatic plaque specimens.7 MRI has emerged as a reliable and highly accurate tool for detecting IPH in vivo.8 It is capable of in vivo stratification of plaques into stable and previously symptomatic categories.9

Contrast-Enhanced MRI Imaging of Plaque
Detecting Plaque Components After Contrast Administration
Intravenous administration of gadolinium contrast during plaque MRI has advanced our ability to overcome signal intensity limitations. Gadolinium is routinely administered for contrast-enhanced MR angiography (CEMRA), and postcontrast black blood images can then be acquired to characterize carotid plaque based on enhancement properties. This has improved the reliability of vessel wall and plaque size measurements and strengthened our ability to resolve small structures, in particular, the fibrous cap. Compared with in vivo noncontrast MRI images, in vivo postcontrast images of the carotid wall more closely approximate corresponding specimen measurements of the wall area and volume.10 Our group has shown the preferential enhancement of fibrocellular tissue within carotid atheroma on MRI after gadolinium administration11 (Figure 1). This optimized contrast between the cap and core is maintained over at least 30 minutes after gadolinium injection,12 facilitating a thorough postcontrast MRI evaluation of plaque composition. Contrast-enhanced MRI is capable of quantifying intact fibrous cap length and area and lipid core sizes when compared with histology13 and it can distinguish intact and thick fibrous caps from thin and/or ruptured caps with good interreader and excellent agreement.
intrareader agreement. Lipid core size also can be measured with better reproducibility after contrast administration.

Our group reported mean cap thickness measurements in a population-based study using contrast-enhanced MRI and revealed them to be greater than those reported based on histological analysis of symptomatic plaque specimens, although the difference seemed largely accounted for by specimen shrinkage and our mostly asymptomatic cohort. Repeat-scan and repeat-reading reliability estimates of plaque component and vessel wall size measurements by contrast-enhanced MRI mostly ranged from good to excellent. Reliability was primarily related to reader variability rather than scan acquisition error, and reliability estimates for smaller structures (ie, cap thickness) were lowest because of the structure’s size relative to scan resolution. This highlights the importance of techniques that minimize the effect of these resolution constraints for cap measurements such as by high-field MRI to increase the acquired resolution or the administration of contrast to enhance the signal of small structures.

Revealing IPH on CEMRA Images

Use of CEMRA for carotid stenosis measurements requires the acquisition of a highly T1-weighted gradient-echo sequence before and after contrast administration. This technique is highly sensitive for identifying IPH as hyperintense signal, particularly on the precontrast (mask) sequence before intraluminal signal might obscure its visualization (Figure 2). Our group demonstrated that the mask sequence acquired in vivo on a 3-T MRI scanner is accurate (94%) with a sensitivity and specificity of 87% and 99%, respectively, for detecting IPH based on correlation with endarterectomy specimen analysis. These values are comparable or superior to those reported in the literature using dedicated IPH-detection sequences. Furthermore, intra- and interobserver agreements for IPH detection by 2 readers were excellent ($\kappa=0.94$ [95% CI, 0.87 to 1] and $\kappa=0.91$ [95% CI, 0.84 to 0.98], respectively). The advantage of this technique for IPH detection is that it is part of a standard MR angiographic sequence and requires no additional scan time but is at least comparable in its diagnostic value to dedicated sequences for IPH detection.

Neovascularity

Background

Intimal neovessels are thought to arise primarily from abundant pre-existing vasa vasorum in the adventitia. These newly formed microvessels appear to grow into the intima through breaks in the medial wall and are characterized by leaky, immature imperfect linings due to the harsh atherosclerotic environment. These thin-walled microvessels are thought to be a primary source of IPH, ultimately leading to a sudden increase in plaque volume and the development of plaque instability. This is supported by specimen studies that have observed an association between IPH and areas of increased microvessel density and between neovessel development and consequent events.

Adventitial Enhancement

Given the importance of neovascularity, our ability to image it has gained much recent attention. The adventitia is a logical target because it serves as the main source of the new vessels. One approach to imaging neovessels in carotid plaque is contrast-enhanced ultrasound, which relies on the intravenous...
administration of gas-filled microspheres detectable by ultrasound. Contrast-enhanced ultrasound enhancement correlates with intraplaque neovascularization in carotid endarterectomy specimens. Staub et al showed that adventitial vasa vasorum detected by contrast-enhanced ultrasound correlated with cardiovascular disease and intraplaque neovascularization by contrast-enhanced ultrasound correlated with prior transient ischemic attacks or strokes. Romero et al used CT angiography to identify carotid wall enhancement as a marker of adventitial vasa vasorum and showed it to be significantly more common in symptomatic than in asymptomatic patients with ≥70% stenosis. Using dynamic contrast-enhanced MRI, Kerwin et al showed that adventitial perfusion by gadolinium measured by its transfer constant correlated with the amount of neovascularity and macrophages in the corresponding plaque specimen. These studies support the notion that plaque neovascularization can be imaged and the adventitia is an important target.

Adventitial Enhancement, IPH, and Recent Events

To explore the clinical implication of plaque neovascularization, we reviewed contrast-enhanced MRI examinations done on 58 consecutive patients (45 male, mean age 73 ± 8.4 years) for carotid atherosclerosis. Examinations consisted of 3-dimensional time-of-flight and CEMRAs and 2-dimensional transverse pre- and postcontrast black blood MRI (BBMRI) images acquired through carotid plaque on both 1.5-T and 3-T scanners. Two readers categorized neovascularity based on degree of outer wall (adventitial) circumferential enhancement (0, absent; 1, <50%; 2, ≥50%) on postcontrast BBMRI at the slice revealing the thickest plaque (Figure 3). Intra- and interreader agreement were good (κ = 0.74 [95% CI, 0.44 to 1] and κ = 0.73 [95% CI, 0.49 to 0.97], respectively). The readers never disagreed by >1 category. IPH was detected in 32 (55%) patients using the mask (CEMRA) sequence as de-
scribed previously. Thirty patients (52%) were symptomatic defined by ipsilateral carotid-territory stroke or transient ischemic attack. Mean interval between the event and contrast-enhanced MRI examination was 49±24 days (range, 3 to 79 days). Mean stenosis was 61%.

As expected, these events were more prevalent in patients with IPH (74% versus 22%; \( P=0.003 \)). We observed an association between adventitial enhancement (AE) category and events (13%, 39%, and 75% for categories 0, 1, and 2, respectively; \( P=0.001 \)). Even in the absence of IPH, this association remained (Figure 4). The highest prevalence of events (nearly 80%) was seen when both IPH and category 2 AE were present. The independent associations of IPH, AE category, age, sex, and cardiovascular risk factors with events based on a multivariable logistic regression model are shown in the Table. Events were associated with presence of AE and with IPH, but not with any other markers, including stenosis. This highlights the added value of gadolinium for identifying plaque vulnerability beyond its routine application for CEMRA stenosis measurements.

### Identifying Risk for Future Events: Prospective Studies

These MRI investigations have related vulnerable features to preceding cerebrovascular events. Associations with future events would be more convincing; however, it is noteworthy that the risk of stroke in the territory of a previously ruptured plaque is increased. Inzitari et al.\(^25\) demonstrated that stroke risk in the territory of a symptomatic carotid is substantially higher than the risk in the territory of an asymptomatic carotid causing similar stenosis.

The few limited prospective MRI studies available have shown that IPH predicts future events.\(^{26,27}\) and leads to increased wall and lipid-rich necrotic core volumes.\(^{28}\) Large lipid-rich necrotic cores and thin or ruptured caps have been shown to independently predict future events.\(^{27}\)

### Summary

Contrast-enhanced MRI is capable of reliably identifying several carotid plaque features associated with events. Future carotid MRI protocols could include a CEMRA sequence from which stenosis measurements are derived with IPH information extracted from mask images followed by post-contrast BBMRI to identify thin or ruptured caps, large lipid cores, and neovascularization. These features might be used to establish a “risk profile” for carotid plaque and select the appropriate treatment. Large prospective studies are now needed to validate these features and determine the effectiveness of management strategies for varying profiles.

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### References


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![Figure 4. Association of AE and IPH with previous events (combined data from 2 readers). Stroke/transient ischemic attack prevalence increases with increasing AE category for those cases without \( P=0.004 \) and with \( P=0.241 \) IPH.](image-url)


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