Introduction

Intracranial atherosclerotic disease (ICAD) is one of the leading causes of stroke world-wide (1). Despite intensive vascular risk factor control and optimal antiplatelet therapy, risk of recurrent strokes is as high as 25–30% after the initial event in patients with symptomatic ICAD (2). Furthermore, ICAD has been shown to be associated with long term sequelae such as cognitive decline and vascular dementia that can have a huge economic burden (3-5). Given its high risk of recurrent subclinical and clinical ischemic events as well as its association with dementia, investigations studying the development and progression of ICAD have become a priority in cardiovascular research.

Imaging studies report a prevalence of 3.5% to 12.9% of ICAD in asymptomatic populations. These estimates are derived from luminal imaging exams, such as magnetic resonance angiography (MRA) (6) and transcranial Doppler ultrasound (7,8), which use stenosis as a surrogate for ICAD. However, autopsy studies suggest luminal exams may underestimate true prevalence. Pathological evidence of intimal lesions in a study of 193 cases acquired from the Brain Arterial Remodeling Study reported a prevalence of greater than 40% at age 60 and above (9). In a French study,
among 259 patients who had fatal brain infarctions, the prevalence of intracranial plaques was as high as 62.2% (10). Differences in these prevalence rates between neuroimaging and autopsy studies may be due to methods of plaque detection by these lumen-based imaging techniques. A need for more sensitive methods of *in vivo* plaque detection are needed.

High resolution vessel wall MR imaging (VW-MR) permits visualization of the vessel wall enabling direct imaging of plaque, including angiographically occult plaque that has not yet led to detectible stenosis. In the population-based Atherosclerosis Risk in Communities (ARIC) study, the prevalence of ICAD representative of a US community-based population was 34.4% using VW-MR (11,12). These results suggest ICAD prevalence rates in asymptomatic populations using VW-MR more closely approximate estimates reported from autopsy studies (9,10,12). As intracranial VW-MR becomes a technique that is increasingly used among investigators, it is important to be aware of the diagnostic utility and limitations of the technique. In this review, we provide an update on the imaging technique, imaging features of ICAD by VW-MR, technical considerations and interpretive pitfalls. We also describe how studying ICAD with VW-MR may improve the diagnostic work-up of ischemic stroke. Finally, we discuss future directions and how multiparametric investigations may be used to develop methods for automatic lesion detection and assessment of radiomic features may aid patient risk-stratification for large scale assessments.

**Intracranial VW-MR**

Our ability to image beyond the lumen with VW-MR has allowed us to address diagnostic dilemmas in differentiating steno-occlusive vasculopathies, including ICAD (13). Previously, neuroimaging has largely been limited to lumen-based techniques such as computed tomography angiography (CTA) and MRA. These angiographic methods lack the ability to resolve intracranial vasculopathies as they only detail secondary luminal changes (13). Digital subtraction angiography (DSA) presents luminal and hemodynamic information with high spatial resolution but is invasive with risks of neurologic complications and radiation exposure (14). CTA is noninvasive, widely available, and fast but requires intravenous contrast administration and also exposes the patient to ionizing radiation. Time-of-flight MRA (TOF-MRA) addresses the limitations of DSA and CTA with no ionizing radiation or intravenous contrast administration but is susceptible to flow-artifacts, can overestimate stenosis measurements, and may be limited in detecting vascular pathology in the absence of luminal stenosis (15-17). With optimized contrast and spatial resolution, VW-MR imaging permits visualization of the vessel wall at the site of vascular injury. Studies comparing VW-MR with other angiographic techniques are shown in *Table 1*. Stenosis measurements by VW-MR have been shown to be comparable to measurements by DSA and have stronger correlations with DSA than measurements between DSA and CTA (19,21). Also, compared to 3D TOF-MRA, VW-MR sources images and VW-MR black blood luminal angiography show higher agreement with CTA for measuring degree of stenosis (22). As a noninvasive imaging technique that does not necessitate ionizing radiation, VW-MR may offer improved stenosis measurements that could complement conventional luminal techniques.

Intracranial applications of VW-MR followed technical developments of VW-MR for carotid arteries. Carotid VW-MR was used to characterize atherosclerotic plaque, efforts of which were partly driven by endarterectomy specimen availability (24). Atherosclerotic plaque features from carotid arteries could be identified with histopathologic confirmation and related to stroke risk (25). Extrapolating what we have learned from carotid plaque imaging, investigators have applied these concepts to interpreting VW-MR of intracranial arteries (26,27).

Intracranial VW-MR is a valuable diagnostic adjunct to conventional angiographic imaging to help distinguish intracranial vasculopathies. Studies report on its use for identifying cerebral vasculitis, reversible cerebral vasoconstriction syndrome (RCVS), arterial dissection, and ICAD (13,17,28-32). These studies describe imaging features of the vessel wall that improve the specificity of conventional angiographic imaging. For example, vasculitis is typically characterized by smooth, homogeneous, concentric wall thickening and enhancement in contrast with eccentric, and often heterogeneous wall thickening and enhancement with ICAD. Distinguishing vasculitis and RCVS can be challenging based on clinical and angiographic presentations but is especially important as management strategies differ (31). While both diseases can result in wall thickening, the vessel wall often shows no or only mild enhancement with RCVS, in contrast to avid wall...
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Enhancement seen with inflammatory vasculopathies (31). Intracranial VW-MR has also been shown to distinguish arterial dissections from other steno-occlusive vasculopathies by visualization of an intimal flap separating the true and false lumens and the presence of an intramural hematoma (33). These imaging features can differ from atherosclerotic plaque, which has a tendency to show focal, eccentric wall thickening. Given histologic verification of intracranial vasculopathies is largely unavailable, VW-MR imaging offers the most accurate assessment of in vivo vessel wall pathology available in the clinical domain.

**VW-MR of ICAD**

The advent of intracranial VW-MR has enabled a shift from studying luminal stenosis to intracranial vessel wall and plaque characteristics as predictors of plaque rupture and ischemic stroke. Qualitative and quantitative imaging features of ICAD include, but are not limited to, degrees and patterns of vessel wall thickening and enhancement, wall remodeling and eccentricity indices, signal intensities of plaque on pre-contrast T1- and T2-weighted acquisitions, plaque distribution/quadrant, and metrics of plaque length,
volume, and per-patient burden. Which features are most strongly associated with symptomatic plaque is still poorly understood and the focus of recent meta-analyses (34,35). One such study evaluating VW-MR imaging features of culprit plaque and ischemic stroke reported plaque enhancement (OR, 10.09; 95% CI, 5.38–18.93), positive wall remodeling (OR, 6.19; 95% CI, 3.22–11.92), and plaque surface irregularity (OR, 3.94; 95% CI, 1.90–8.16) to be strongly associated with stroke events (34). Limitations of this meta-analysis, however, included methodological heterogeneity among studies in design, patient selection, and reporting outcomes. For example, patient selection was based on either lesion, symptom, or both among the 20 included articles (34) and the inclusion criterion for stenosis varied from any stenosis (36), >30% stenosis (37), ≥50% stenosis (38), to >70% stenosis (39). Also, among the 11 studies pooled to estimate the effect of degrees in plaque enhancement characteristics, the intravenous contrast injection-to-scan interval time ranged from 1.3 minutes (40) to “within 20 minutes” (41). Better understanding symptomatic plaque features to use as imaging biomarkers of ICAD would be helpful to increase diagnostic confidence in image interpretation and also provide guidelines for future trials.

**Imaging biomarkers of ICAD**

**Vessel wall enhancement**

Intracranial plaque enhancement has been shown to strongly correlate with ischemic stroke independent of the degree of stenosis (34,35,42,43). Both degree and persistence of enhancement at follow-up imaging strengthen diagnostic confidence in identifying culprit plaque and future risk for stroke recurrence (42,44). If plaque at baseline shows no enhancement or a decrease in the degree of enhancement at follow-up imaging, the plaque is unlikely to be a culprit lesion (42). Though likely multifactorial, mechanisms thought to underlie vessel wall enhancement in symptomatic plaque include neovascularization and inflammation, similar to unstable carotid plaque (45). An ultrastructural study of ruptured coronary plaques also showed increased density of thin-walled microvessels with compromised endothelial cell junctions extending from the adventitia, which can be extrapolated to gadolinium leakage in plaque (46). While mechanisms of intracranial plaque enhancement may be similar, enhancement may be a stronger biomarker of disease in intracranial arteries, considering their relative lack of vasa vasorum, compared with coronary and carotid arteries (47). This paucity of vasa vasorum in normal intracranial arteries is thought to be a consequence of surrounding cerebrospinal fluid (CSF) from which nutrients are thought to diffuse (48). Thus, vessel wall enhancement in healthy intracranial arteries is not expected though there are noteworthy exceptions. The intracranial internal carotid arteries and vertebral arteries, at the site of dural penetration, may show mild enhancement as vasa vasorum extend from the extracranial segments of the arteries (47,49). Thus, a mild degree of wall enhancement in these segments may be a normal finding. Moreover, mild vessel wall enhancement has been reported as part of aging, further limiting its specificity as an imaging marker (50). Autopsy studies support this finding and show vasa vasorum in more likely to be found in intracranial arteries with advancing age.

**Arterial wall remodeling**

The adaptability of arteries to disease makes VW-MR particularly advantageous to study ICAD. To compensate for atherosclerotic wall thickening, the vessel can remodel outwardly, preserving the lumen and blood flow, until this mechanism is overcome leading to angiographically detectable stenosis (51,52). Notably, in the population-based ARIC study, up to 10.8% of identified lesions by VW-MR were nonstenotic (12). The threshold for stenosis of intracranial vessels in response to atherosclerotic plaque accumulation has been estimated at approximately 55.3%, and the posterior circulation seems to have a greater ability to accommodate plaque formation (52). Possible explanations for this include differences in sympathetic innervation and flow dynamics. While investigations strive to better understand differences between the anterior and posterior circulations, having a higher index of suspicion may be warranted in patients with posterior circulation strokes when angiographic exams are negative. This is especially important given nearly 20–25% of ischemic strokes involve the posterior circulation (53–55) and there is a 33% 90-day risk of stroke after a first event from a vertebrobasilar stenosis (56).

Vessels may also show inward remodeling in which there is contraction of the outer wall with plaque development. A number of studies have reported associations between outward remodeling of intracranial arteries and increased plaque vulnerability (57–60). A possible explanation for this is the higher content of lipids and inflammatory cells (61).
These inflammatory cells are often concentrated at the plaque shoulders (e.g., margins) where the fibrous cap is most prone to rupture (62). Understanding arterial wall remodeling is an important step to establish the biologic underpinnings of disease progression. VW-MR may play an important role in helping to characterize this mechanism.

Vessel wall thickening

Morphologic features of concentric and eccentric wall thickening and enhancement have been described to distinguish between plaque and other vasculopathies. While earlier studies have used eccentric vessel wall thickening patterns to identify intracranial plaque, an increasing number of studies report an overlap of eccentric and concentric wall thickening as plaque features (63-65). A meta-analysis pooling 7 studies to assess eccentric versus concentric features to identify culprit plaque also did not identify eccentricity to be significantly associated with culprit lesions (OR, 1.22; 95% CI, 0.51–2.91) (34). Histology also supports both eccentric and concentric wall thickening for atherosclerotic plaque features (66,67), suggesting a lack of specificity of this morphologic imaging biomarker. For example, one histologic study reported that while 69% of middle cerebral artery (MCA) plaques were eccentric, 75% of vertebral and 62% of basilar artery (BA) plaques were concentric (67). Another histology study showed concentric plaques in 63.9% and eccentric plaques in 26.1% of MCAs (66). T2-weighted imaging, which can show eccentric heterogeneous or hyperintense T2 signal in plaque, may also be a useful adjunct for identifying these lesions (28,68,69). However, T2-weighted imaging can require lengthy acquisition times considering its relatively low signal profile and this may be prohibitive especially for stroke patients.

Components of intracranial atherosclerosis

Although much of our understanding of the clinical implications of intracranial atherosclerotic plaque components detected by VW-MR originated from investigations of carotid plaque, the extent of the similarity between carotid and intracranial plaques is unclear. This is partly because histological correlation of in vivo VW-MR of ICAD is difficult to obtain with only a few case reports available (70,71). Moreover, adequate spatial resolution to image ICAD components in vivo is difficult to achieve. Intravascular ultrasound (IVUS) of in vitro circle of Willis (COW) specimens has been reported to have a 73.5% and 96.6% sensitivity and specificity, respectively, for plaque detection using histopathology as a reference standard. However, IVUS underestimated quantitative estimates of necrotic core and fibrofatty areas of plaque. In comparison, in vitro imaging showed 7 Tesla (7T) MR to have a positive predictive value of 88% and 93% for detecting fibrous and attenuated calcium deposits, respectively (72). In another study, T1, T2, T2*, and proton density signal characteristics of ex vivo intracranial plaque specimens were measured on ultra-high resolution 7T MR to identify lipid, fibrous tissue, fibrous cap, and calcifications (73). However, distinguishing these components in vivo using VW-MR at 3T poses a greater challenge given acquisition time and spatial resolution constraints relevant to the size of these structures. Several studies have used intrinsic T1 hyperintensity on VW-MR as a surrogate imaging biomarker for intraplaque hemorrhage (72,73). Xu and colleagues reported the prevalence of intraplaque hemorrhage in ICAD to be 19.6% in symptomatic and 3.2% in asymptomatic MCA plaque (39). Yu and colleagues reported a prevalence of 80.0% vs. 48.8% of VW-MR-identified intraplaque hemorrhage in symptomatic versus asymptomatic BA stenoses, respectively (74). However, autopsy studies suggest a far lower prevalence of intraplaque hemorrhage in intracranial plaque (67,75). One autopsy study reported a prevalence of 12% among middle cerebral arteries, vertebral arteries, and basilar arteries (67). This is in contrast to an 81% prevalence of intraplaque hemorrhage reported in a histologic study of carotid endarterectomy specimens (76), questioning our ability to directly extrapolate prevalence rates from extracranial carotid studies to ICAD.

Multiple patterns of intracranial plaque by VW-MR have been reported. As seen with extracranial carotid plaques, intracranial plaque can present with a thin rim of enhancement overlying a hypoenhancing core with hypointense foci of calcification (Figure 1A). However, more often intracranial plaques are too small to identify these distinct features and instead show eccentric wall thickening and enhancement on T1-weighted imaging due to spatial resolution constraints (Figure 1B) (13).

Technical considerations for VW-MR

The small size of intracranial arteries challenges spatial resolution constraints to resolve vessel wall changes and plaque components by VW-MR. First, adequate spatial resolution is important for discriminating pathologic wall
thickening. Prior work in carotid artery imaging showed wall thickening can be greatly exaggerated with seemingly small changes in spatial resolution (27,77). This artifactual thickening can mimic ICAD. Recognizing this pitfall, the Vessel Wall Imaging Study Group of the American Society of Neuroradiology issued an expert consensus recommending 0.5 mm isotropic resolution for intracranial VW-MR (13). This recommendation considered what was felt to be achievable at most institutions at reasonable acquisition times for in vivo imaging. However, vessel walls of the COW can vary in both healthy and diseased segments and may be below the acquired spatial resolution of 0.5 mm. COW specimens imaged using 7T VW-MR showed mean vessel wall thicknesses ranging between 0.45 to 0.66 mm with slightly thicker measurements in patients with symptomatic cerebrovascular disease (78). Thus, one should be wary of partial volume effects when interpreting these exams.

Also contributing to misidentifying ICAD is artifactual eccentric wall thickening due to an oblique orientation of a 2D image slice or reconstruction relative to the vessel wall, which is frequently encountered when imaging the tortuous intracranial arteries. Vessel segments should be viewed in orthogonal planes to distinguish circumferential and eccentric thickening. Acquiring 3D isotropic sequences and creating multiplanar reformats with thin slice thicknesses oriented orthogonal to the vessel axis can help minimize these volume-averaging effects. 3D isotropic resolution sequences also enable imaging of large fields of view within a reasonable scan time (79). Specifically, 3D variable flip angle turbo spin echo (VFA-TSE) pulse sequences have been increasingly used for intracranial VW-MR due to its scan efficiency compared to 2D TSE techniques (80). Vendor labels for single-slab 3D VFA-TSE pulse sequences include Sampling Perfection with Application optimized Contrasts by using different flip angle Evolutions (SPACE, Siemens Healthcare), Volumetric Isotropic TSE Acquisition (VISTA, Philips Healthcare), and CUBE (GE Healthcare); however, these sequences are not optimized for intracranial VW-MR and are not recommended without appropriate modifications.

Incomplete CSF and blood suppression artifacts are important to be aware of as these can be mistaken for wall thickening or enhancement on postcontrast imaging (81). Slow flow artifacts are particularly common near the vessel walls and in veins due to slower laminar flow along the walls. CSF suppression is particularly challenging since CSF flow is slow and nulling slow CSF flow signal which has a long T1 is particularly challenging. Acquiring imaging of the vessel segment in at least 2 planes may help confirm whether there is true wall enhancement though this is not always practical. Another strategy to avoid this artifact is to shorten the echo train (>60 turbo factor) to minimize larger free induction decay artifacts that can grow with longer echo train lengths (82). To minimize CSF and blood suppression artifacts, preparation pulses such as delayed alternating with nutation for tailored excitation, improved motion-sensitized driven-equilibrium, trailing magnetization flip-down, and

Figure 1 VW-MR of intracranial atherosclerotic plaque. (A) Contrast-enhanced coronal 3D VW-MR acquired through the short axis of the cavernous segment of the left internal carotid artery reveals an enhancing fibrous cap (long white arrow) separating the lumen (short white arrow) from the hypoenhancing lipid rich necrotic core (black arrow); (B) contrast-enhanced 3D VW-MR reconstructed through the short axis of the M1 MCA shows eccentric wall thickening and homogeneous enhancement (short white arrow). MCA, middle cerebral artery; VW-MR, vessel wall MR.
anti-DRIVE preparations have been used (83-86). However, these preparation pulses may reduce vessel wall signal-to-noise (87) and further development to optimize vessel wall conspicuity would be advantageous.

Considering the lengthy acquisition time needed for the high spatial resolution of intracranial VW-MR imaging, poor image quality due to motion degradation is often reported. Up to 17% of cases are reported to be excluded due to motion degradation, highlighting a need for improved scan efficiency (80). Some sites perform only postcontrast imaging to minimize the burden of a lengthy exam (88-90). However, reports on intrinsic T1 hyperintense signal in plaque as a risk feature suggest pre-contrast imaging may be of value (74,91). Technical developments to improve scan efficiency while maintaining a high spatial resolution are ongoing with techniques such as compressed sensing (92,93).

ICAD and ischemic stroke

There are several mechanisms of ischemic stroke that result from ICAD. A primary mechanism is plaque rupture, which leads to occlusion of small penetrating arteries and hypoperfusion. Plaque rupture exposes the thrombogenic core and results in an in-situ thrombus, which can either occlude the artery locally or embolize distally. A second mechanism includes the development and growth of plaque over penetrating artery origins known as branch atheromatous disease. Third, severe stenosis or occlusion of the lumen may lead to hemodynamic impairment and hypoperfusion. These mechanisms can be inferred by infarct patterns on imaging (94) and combining information from both infarct patterns and intracranial plaque features by VW-MR may improve diagnostic specificity and patient selection for interventions (Figure 2).

The use of VW-MR to identify patients with plaques who will benefit from stenting versus medical management may be an important application in future clinical trials. The Stenting versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Arterial Stenosis (SAMMPRIS) trial concluded that patients with transient ischemic attacks or ischemic strokes due to 70–99% intracranial arterial stenosis have increased stroke or death outcomes within 30 days after treatment with percutaneous angioplasty and stenting compared to medical therapy alone (14.7% vs. 5.8%, P=0.06) (95). This led to a

Figure 2 Culprit atherosclerotic plaque in the MCA. (A) Axial diffusion weighted imaging shows acute infarcts in the right MCA territory; (B) CTA MIP of the right MCA shows focal stenosis of the distal M1 segment (arrow); (C) high resolution 2D black blood T2-weighted image through the long axis of the right M1 segment shows T2 hyperintense eccentric atherosclerotic plaque at the site of luminal narrowing (arrow). Inset shows an orthogonal view of the artery; (D,E) pre- (D) and post-contrast (E) 3D VW-MR reconstructions through the long axis of the right M1 segment show enhancing atherosclerotic plaque at the site of luminal narrowing (arrows). Insets show short axis reconstructions at the level of the arrows. MCA, middle cerebral artery; CTA, computed tomography angiography; MIP, maximum intensity projection; VW-MR, vessel wall MR.
revision of the 2014 American Heart Association guidelines for managing patients with stroke due to severe intracranial arterial stenosis. Yet even with aggressive medical therapy, the SAMMPRIS trial reported a 12.2% annual risk of stroke recurrence though there were ensuing concerns about the study’s design and conclusions, including patient selection. The use of VW-MR to help stratify treatment groups has yet to be tested in interventional trials, but its ability to identify risk features beyond luminal narrowing supports its role in personalizing treatment strategies and improving outcomes particularly in this era of precision medicine.

Intracranial VW-MR may also have a role in managing patients with cryptogenic strokes. Up to 30–40% of strokes have no identifiable cause despite a comprehensive work-up (96-98). The work-up for these patients is often long and costly, including multiple imaging exams of the brain and heart and outpatient care with Holter monitoring. Nonstenotic intracranial plaque, given the possibility of outward remodeling, remains a potential explanation for cryptogenic strokes. The potential diagnostic value of VW-MR for assessing cryptogenic stroke has not been fully established but has shown promise for identifying culprit lesions not detectible by conventional imaging techniques.

Future directions

The clinical implementation of VW-MR for risk stratification and treatment of ICAD depends not only on availability of optimized sequences across different scanner platforms, but also on accurate and reliable interpretation of the images. Reliability estimates for qualitative assessment of intracranial VW-MR for plaque presence and stenosis degree have been shown to range from fair to good on non-contrast exams acquired on 3T MR scanners (12). Notably, reliability estimates for quantitative feature assessments generally range from good to excellent with semi-automated processing tools (12). Measures such as remodeling index, wall thickness measures, plaque area and wall area are well suited to support data-driven methods for lesion detection through semi-automated methods. Innovative investigations exploring these possibilities include automated intracranial vessel wall segmentation methods using convolutional neural networks and radiomic texture analysis of plaque (99,100). These techniques are heavily reliant on the quality of the provided data and interpretations. Future investigations to improve scan efficiency and studies on diagnostic accuracy are needed to facilitate clinical adoption. Image refinement and standardization of radiomic feature definitions and extraction methods are also needed in this era of increasing digitization. With the accumulation of large amounts of multiparametric data, artificial intelligence will facilitate maximizing diagnostic and prognostic yield from these acquired images. Analysis of large population-based studies will be able to leverage these innovative methods to acquire robust data on intracranial atherosclerosis and stroke-risk assessments.

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