Imaging Intracranial Vessel Wall Pathology With Magnetic Resonance Imaging
Current Prospects and Future Directions

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To date, the probable cause of ischemic stroke is often inferred from the size and location of the infarct, in combination with an evaluation of the heart and the presence of extracranial arterial occlusion or high-grade stenosis.1 Currently used conventional lumenography-based methods such as digital subtraction angiography, computed tomography angiography, and magnetic resonance (MR) angiography are used to determine the presence of such an acute occlusion or high-grade arterial stenosis. From extracranial studies, it is known that luminal narrowing may be absent in patients with severe atherosclerosis owing to arterial remodeling.2–4 Therefore, these methods do not provide information about the underlying pathological processes, which most often involve the vessel wall.5 Vessel wall changes such as vessel wall thickening, enhancement, or the presence of vulnerable atherosclerotic plaques without luminal stenosis are therefore often missed but might be of importance for a better understanding of ischemic stroke.5 Furthermore, intracranial atherosclerosis is an important cause of ischemic stroke6 and often involves the vessel wall. Patients with intracranial atherosclerosis have high recurrent stroke rates,5 and increasingly more attention is being directed to the assessment of the intracranial vessel wall, necessitating an imaging technique directly assessing the intracranial vessel wall. MR imaging (MRI) seems the most promising technique to reliably image intracranial vessel wall pathologies because of its superior soft tissue contrast. Recent advances in MRI7 have made it possible to obtain information about these abnormalities within the intracranial vessel wall, which provides an imaging tool to investigate the role of intracranial vessel wall abnormalities in the diagnosis of stroke.

In this review, we discuss the current status of intracranial vessel wall MRI and its potential to identify different intracranial vessel wall pathologies. First, we present the state-of-the-art MRI methods to visualize the intracranial vessel wall and its pathology and we provide the technical background of these imaging methods. This part also focuses on imaging at different field strengths and on healthy vessel wall and different wall pathologies. Then, we give an overview of intracranial vessel wall abnormalities that may be expected for each ischemic stroke subtype. Finally, given the clinical needs and technical possibilities, we review the future clinical and technical directions of intracranial vessel wall imaging and provide a tentative recommendation for use in daily clinical practice.

MRI of Intracranial Vessel Wall Pathology
Technical Requirements

To successfully image the intracranial vessel wall, MRI methods have been developed and optimized that suppress the intracranial arterial blood signal and, in some cases, combine this with suppression of the cerebrospinal fluid (CSF) signal around the circle of Willis9–22 Obtaining black-blood signal for all intracranial arteries is essential for sufficient image contrast to assess the vessel wall and its pathology. The distal intracranial carotid arteries, distal vertebral arteries, and basilar artery have a predominant caudal-cranial course, which may be beneficial when the outflow of blood is used together with a transverse imaging plane perpendicular to the arteries proximally of the circle of Willis. The basilar artery especially has been shown to be well suited for vessel wall imaging because of its relative large size and straight course.20 On the other hand, compared with the arteries in the neck, the anterior, middle, and posterior branches of the circle of Willis all have a different course, and black-blood imaging based on outflow may be more difficult. Some of the black-blood imaging methods that have been developed for the neck may also be applied and optimized for intracranial vessel wall imaging. These black-blood techniques include double inversion recovery23 and techniques that are based on motion-sensitizing prepulses.24,25 A disadvantage might be that slow flow next to the vessel wall results in incomplete blood suppression, thereby overestimating vessel wall thickness.26

For the detection of focal thickening of the intracranial vessel walls, signal suppression on the outside of intracranial vessel walls is a prerequisite. Most of the intracranial arteries are surrounded by CSF. In elderly patients, this amount of

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<th>FOV, Minimum–Maximum, mm</th>
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<td>800–100/8.4</td>
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<td>TSE</td>
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<td>100×100×100</td>
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<td>n.g.</td>
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<td>Chung et al&lt;sup&gt;44&lt;/sup&gt;</td>
<td>100×100×1.0</td>
<td>0.5×0.5×1.0</td>
<td>2000/100</td>
<td>TSE</td>
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<td>Li et al&lt;sup&gt;50&lt;/sup&gt;</td>
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<td></td>
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<td>Ma et al&lt;sup&gt;51&lt;/sup&gt;</td>
<td>160×160×2.0</td>
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<td></td>
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<td>0.2×0.5×2.0</td>
<td>2800/50.8</td>
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<td>3000/80</td>
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<td>Shi et al&lt;sup&gt;54&lt;/sup&gt;</td>
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<td>0.6×0.6×0.6</td>
<td>2500/67</td>
<td>TSE</td>
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CSF surrounding the intracranial arteries increases as a result of brain atrophy. With MRI methods that provide dark CSF signal or suppress the CSF signal, the outer walls will become visible (Table 1). A combination of intracranial methods that suppress the blood and the CSF will result in the visualization of both the inner and outer arterial vessel wall. However, suppressing the CSF will cost signal-to-noise ratio (SNR) within the vessel wall, and there may be a time penalty for the optimization of MRI methods. Especially when these methods are combined with high-spatial-resolution imaging, scan times may become too long.

Because the diameter of the intracranial arteries is very small, ranging from 2 to 3 mm proximally to <1 mm more distally, sufficient SNR and, concordant to that, submillimeter spatial resolution are required to allow the detection of vessel wall changes such as plaques, vessel wall thickening, and focal enhancement. Especially for vessel wall imaging of the arteries distal to the circle of Willis, a high spatial resolution is needed. To obtain such a high resolution within clinically reasonable scan times, scan coverage has to be reduced (Table 1). Most current intracranial vessel wall imaging methods therefore visualize only a relatively small portion of the intracranial arteries and focus on arteries at the level of the circle of Willis and just proximal to it. Smaller distal intracranial arterial vessel walls are beyond the scope of these sequences. However, a relatively low spatial resolution may well be sufficient to detect enhancement of a lesion or more generalized enhancement of the intracranial vasculature as a result of an increase in contrast-to-noise ratio caused by the contrast uptake (Table 1).

### Magnetic Field Strength

To image the thin intracranial vessel wall at a high resolution, high SNR is essential. To obtain acceptable SNR, one can...
move to higher field strengths because SNR scales linearly with field strength.9,56 The gain in SNR can, in principle, be used for either a shorter scan time or a higher spatial resolution compared with lower field strengths.52 Because this will allow higher spatial resolution within a reasonable scan time, intracranial vessel wall imaging is performed mainly at higher field strengths nowadays (Table 1). The first studies of intracranial vessel wall imaging were performed at a field strength of 1.5 T (Table 1). Because of the lower achievable spatial resolution of these scanners for sufficient SNR, most interest was paid to intracranial vessel wall lesions with a high contrast-to-noise ratio (Table 1) such as vividly enhancing lesions of intracranial arterial walls caused by cerebral vasculitis. With the availability of clinical 3 T MRI scanners, smaller lesions that were typically below the detection limit of 1.5 T MRI became detectable. At 3 T, intracranial vessel wall imaging showed the presence of intracranial plaques and enhancement of intracranial lesions.10–14,21,35–37,40,44–46 Most of these lesions were first described in the posterior circulation (distal vertebral and basilar artery).10–12,16,29,34,38 whereas more recent studies also showed these abnormalities in the middle cerebral arteries.13–15,17,21,29,31,35,36,40,44,45–49 In the last decade, 7 T MRI scanners have become available in a number of research centers and hospitals worldwide. With the even higher attainable SNR at 7 T, it became possible to perform isotropic vessel wall imaging with a larger coverage both in vivo9 and ex vivo53 (Table 1). This made it possible to reconstruct each artery with a different course in different orientations without the loss of detail (Figure 1).9 Pulse sequence optimization at the various field strengths may even allow more detail, for instance, characterization of vessel wall lesions and visualization of more peripherally located arteries. The developments and optimization of vessel wall imaging protocols at higher field strengths (7 and 3 T) may teach us disease-specific key imaging findings of the intracranial arterial walls at high resolution. Head-to-head comparison studies are currently not available but should be performed in the future to examine the appropriate imaging method and MRI field strength for the detection and characterization of intracranial vessel wall lesions.

Healthy Vessel Wall

Imaging vessel wall pathology has been shown to be easier than imaging the thinner, normal, healthy vessel wall. The latter clearly requires a higher resolution and good contrast both between the inner side of the arterial vessel wall and the blood and between the outer vessel wall and the CSF (Figure 2).5 In young patients with limited brain atrophy, the outer vessel wall of the more distal intracranial arteries may be located next to the brain parenchyma, and CSF suppression alone might not be sufficient to show the outer wall of these arteries.9 Visualization of the thicker vessel walls of the intracranial vessels proximal to the circle of Willis and the proximal middle cerebral artery may be easier compared with more distal, very thin vessel walls of small vessels such as the distal middle cerebral artery and the posterior and anterior cerebral arteries. In clinical practice, the healthy vessel wall was shown to be rather difficult to depict with the currently available imaging methods.9,20,21,27,42,44,45,48 However, visualization of the healthy intracranial vessel wall may be important for several reasons. First, pathological changes in the vessel wall, especially when nonfocal pathology is concerned, may be discovered only when a comparison is made between the possible pathological vessel wall and its healthy contralateral side. Second, similar to the intima-media thickness measurements of the carotid artery,56 clear visualization of the intracranial arterial walls may allow thickness measurements of these vessel walls, even when no pathological process is present. Thickness measurements of the intracranial vessel walls may serve as a general parameter or biomarker for the status of these intracranial arteries, as for the carotid artery.59 At this moment, however, this is not yet feasible; at least 2 voxels within the vessel wall are needed for dedicated measurements; therefore, an in-plane resolution of ≤0.2 mm is required. Third, clear visualization of the arterial vessel walls, together with the presence of atherosclerotic changes and focal plaques, may allow the assessment of possible arterial remodeling with a widening of the arterial diameter at the location of the plaque.4 On the other hand, the resolution and contrast-to-noise ratio required to visualize the healthy vessel wall may increase the scan time for the vessel wall imaging sequence to a degree that this method cannot be easily added to a standard clinical MRI examination. On the basis of the indication of intracranial vessel wall imaging, the methods may be optimized to focus on visualization of focal plaques and enhancement of vessel walls rather than clear visualization of the healthy vessel walls.

Nonenhancing Vessel Wall Lesions

When intracranial vessel wall lesions are evident, they may be visualized with intracranial vessel wall

![Image](http://circ.ahajournals.org/)

**Figure 1.** A 58-year-old man presented with transient hemiparesis of the left arm and leg caused by transient ischemic attack of the right middle cerebral artery. The 7 T 3-dimensional magnetization preparation inversion recovery turbo spin-echo transverse images before (A) and after (B) contrast administration show a focal atherosclerotic lesion of the right M1 branch just after its bifurcation and a lesion in the distal basilar artery, both enhancing after contrast administration (arrowheads). C and D, Sagittal and coronal reconstructions of the contrast-enhanced focal lesion of the right M1 branch.
Vessel Wall (Lesion) Enhancement

With improvement of intracranial vessel wall imaging methods, recent studies have shown enhancement of smaller atherosclerotic plaques in intracranial vessels (Table 1). MRI methods for contrast enhancement typically rely on the use of T1-weighted sequences. Contrast-enhanced sequences benefit from a strong effect of the gadolinium-based contrast agents as a result of T1 shortening caused by the contrast uptake. This will result in higher signal intensity on T1-weighted sequences. Contrast-enhanced sequences are used to assess the presence of contrast uptake. Whether or not contrast uptake is present, and if so, the degree of enhancement, an additional T1-weighted MRI sequence without contrast (precontrast) is used to compare with the contrast-enhanced sequence (postcontrast). Still, the added value of both precontrast and postcontrast T1-weighted sequences for the detection of intracranial vessel wall enhancement has not yet been established. When the enhancement is very clear such as with vasculitis, a postcontrast scan may be sufficient (Figures 3 and 4). However, the contrast enhancement can also be modest, or intracranial vessel wall lesions may already have a hyperintense signal before the administration of contrast (precontrast). In these more difficult cases, precontrast and postcontrast MRI vessel wall imaging is required to establish the presence of contrast uptake. Whether there is an optimal time point between contrast administration and peak enhancement needs to be determined. Preliminary results from 7 T MRI examinations show a contrast-to-noise ratio peak after 20 minutes of contrast administration (Figure 4). However, this needs to be established in a larger group of patients and might vary between individual cases and pathologies. Finally, the exact pathophysiological mechanisms of contrast uptake in the intracranial arterial walls and atherosclerotic plaques need to be established. These mechanisms may differ on the basis of the kind of pathology (eg, vasculitis, atherosclerotic plaque) imaged. Contrast enhancement may occur with more generalized or focal inflammation of the vessel wall, together with neovascularization and endothelial contrast leakage, or as a result of vasa vasmorum in atherosclerotic plaques. For instance, pathological enhancement of a plaque in a vessel supplying a stroke territory has been observed within 4 weeks of ischemic stroke, and the strength and presence of enhancement are closely related to the time between stroke and vessel wall assessment. The degree of enhancement is thought to be closely correlated with the level of inflammatory activity, presumably as a result of neovascularization and increased endothelial permeability.
Vulnerable Plaques
Enhancing and nonenhancing plaques are classifications based on overt imaging characteristics, but a characteristic that is probably clinically more relevant is whether the plaque can be described as vulnerable. Vulnerable plaques, that is, atherosclerotic “active” plaques at risk for rupture, are associated with a high risk of (recurrent) ischemic events. Similar to the characterization of carotid plaques, MRI might be used for the characterization of intracranial atherosclerotic plaques to assess the vulnerability of these plaques. For carotid plaques, plaque content differentiation includes the presence of calcifications, fibrin, lipid, vasa vasorum (plaque vascularization), and intraplaque hemorrhage. Detection of intraplaque hemorrhage in particular was found to be related to a higher recurrent stroke risk. In addition to plaque content, the presence of ulceration and the size of the atherosclerotic plaque were found to be correlated with prognosis. With further development of intracranial plaque imaging methods, we expect that characterization of the intracranial arterial plaque will also become possible in the next decade. Detection of intracranial plaque hemorrhage has already been shown to be possible intracranially with an MR direct thrombus imaging sequence for the middle cerebral artery (Table 1). In addition, several studies have investigated plaque vulnerability by means of contrast-enhanced sequences or used multiple contrast weightings (Figure 5). Similar to black-blood techniques, the most successful MRI sequences for the detection of vulnerable plaque in the carotid arteries, for instance, MR direct thrombus imaging combined with several image contrast weightings, should be optimized and tested for intracranial plaque characterization.

Clinical Implementation
In current clinical practice, it can be difficult to establish the cause of ischemic stroke in an individual patient, and differentiation between stroke subtypes is still an important issue.
A method used to define the subtype of ischemic stroke is the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system. Stroke subtypes defined by this system are strokes with a large-artery atherosclerotic cause, cardioembolic strokes, small-artery strokes, strokes with a determined cause, and strokes with an undetermined cause. This classification system has limitations, with many stroke patients being diagnosed with an undetermined cause of stroke. Furthermore, in patients with a presumed cause of stroke, the certainty of the diagnosis often remains elusive. With the use of intracranial vessel wall imaging techniques, small changes within the vessel wall may be revealed, and the certainty of the diagnosis may become better established, enabling better therapeutic management.

In patients with ischemic stroke caused by large-artery atherosclerosis, intracranial vessel wall imaging may show more generalized atherosclerosis of the intracranial and extracranial vasculature, including the carotid arteries (Figure 6), vertebral arteries, and basilar artery. Furthermore, although lumenoGRAPHY may show complete recanalization, it can be hypothesized that small, flat nonstenotic remnants will still be present. In addition, it can also be hypothesized that an occlusive thromboembolus will give a local inflammatory reaction of the vessel wall at the point of occlusion, which may be visible on follow-up as a small area of scar tissue, which may decrease over time.

In the small-vessel occlusion group, intracranial vessel wall MR sequences may be able to differentiate between different causes of small subcortical infarcts by the visualization of the location of the occlusion, the severity of atherosclerosis, or the visualization of a possible thrombus in the trajectory of a probable occluded perforating artery. On the other hand, small-artery atherosclerosis of the perforating artery itself may be difficult to assess if a thrombus is absent, although indirect characteristics such as small hemorrhagic changes in the penetrating artery may prove to be of additional value.

For ischemic strokes of other determined cause, intracranial vessel wall imaging may be of value by reducing the number of (sometimes very invasive) diagnostic studies needed to establish the diagnosis. In patients with vasculitis, for instance, the presence and severity of enhancement of the intracranial vessel wall may help establish the diagnosis without the need of an elaborate diagnostic process and provide targeted treatment. It may also show early signs of the disease process and changes at follow-up, which enables fast treatment before serious ischemic events occur. In the remaining patients (≈40%), the cause of cerebral ischemia is unknown. Recent developments in intracranial vessel wall imaging may help to unravel their cause by showing the presence of vessel wall thickening and plaques and enhancement of plaques or vessel wall. In younger patients, uncommon causes of stroke such as dissections, vasculitis, and transient cerebral arteriopathy may be found to be the cause of stroke. Furthermore, the absence of atherosclerotic changes may favor a cardioembolic cause. In the acute phase, characterization of different underlying components of the plaque, embolic material, and thrombus material may give possibilities to guide and differentiate between stroke subtypes in this early stage. Intracranial vessel wall imaging may thus be a useful tool for identifying the causes of stroke. Moreover, for the therapeutic management of the individual patient, it is essential to determine the underlying cause of ischemic stroke. Antithrombotic medication or oral anticoagulants and lipid-lowering medication are standard treatment for the majority of ischemic stroke patients and are based on lowering the chance of developing subsequent (thrombo)emboli.

Common, more cause-specific treatment options include, among others, oral antiarrhythmic medication and atherosclerotic plaque removal (endarterectomy) or endovascular stenting for carotid artery stenosis. Inflammatory vasculopathies such as vasculitis require intensive monitoring and aggressive treatment with immunosuppressive agents or, in the case of an infective cause, with antibiotics. Furthermore, recent results of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial showed that aggressive medical management, including dual antiplatelets, and lifestyle changes reduced future stroke risk in patients with intracranial stenosis compared with previous studies in similar populations. With the use of intracranial vessel wall imaging, the best treatment option may be determined earlier, preventing unnecessary treatment or wrong treatment, which might even jeopardize a patient’s life. It would therefore be ideal to include a vessel wall sequence in the clinical scan protocol besides the regular clinical scans for ischemic stroke.

The following recommendations are made. First, if intracranial atherosclerosis is considered, a precontrast and postcontrast T1-weighted vessel wall sequence is recommended for investigating vulnerable plaques. Second, a postcontrast T1-weighted sequence can be used to detect diffuse vessel wall enhancement when acute cerebral vasculitis is expected. Third, for patients with transient ischemic attacks, a protocol including a T1-weighted vessel wall sequence before and after contrast administration for the identification of smaller lesions is recommended. Fourth, for plaque...
characterization, multiple contrast weightings improve the detection of plaque components.

An overview of expected vessel wall abnormalities for different causes of ischemic stroke can be found in Table 2.

**Future Directions**

We are still in the early days of intracranial vessel wall imaging. We expect that the developments and applications of intracranial vessel wall imaging will follow a route similar to that for extracranial vessel wall and plaque imaging of the carotid artery. Ideally, MRI of the intracranial vessel wall should be able to describe the presence of both large and small (atherosclerotic) lesions and to characterize the lesions with respect to enhancement, plaque content, and vulnerability. However, at this moment, the lack of validation of MRI with histology to demonstrate the feasibility of intracranial vessel wall MRI in characterizing plaque components makes it difficult to establish the origin of the lesion on the basis of in vivo data only. For the extracranial arteries, histological validation is already widely available because carotid specimens are obtained with endarterectomy and the in vivo MRI can be performed before surgery. For intracranial arteries, however, only a few studies addressed this issue. The reason is that histological validations are difficult to perform because there are no current treatment options such as endarterectomy for the intracranial arteries. This histological validation is important for further development of in vivo imaging; therefore, future research should also focus on pathological validation of intracranial vessel wall imaging with, for instance, postmortem specimens of the circle of Willis. The complete assessment of the intracranial vasculature for atherosclerotic lesions may allow the identification and classification of culprit lesions. The detection and characterization of intracranial atherosclerotic lesions may further enhance our knowledge about intracranial atherosclerosis. In patients with an unknown cause of stroke (≈40%), intracranial vessel wall and plaque imaging may help to establish the cause of stroke. In patients with a probable or possible cause of stroke, information about the intracranial vessel wall, plaque, and other vascular fingerprints may further confirm the cause of stroke or might change the stroke classification. In addition to ischemic stroke, intracranial vessel wall imaging might also be used for other indications such as patients with a hemorrhagic stroke or patients with expected vascular dementia. For example, in patients with a subarachnoid hemorrhagic stroke and multiple aneurysms, enhancement detected with vessel wall imaging was found to be capable of identifying the symptomatic aneurysm. In patients suspected to have vascular dementia, intracranial vessel wall imaging might contribute to a better understanding of the underlying vessel wall pathology, which may lead to better-tailored therapy for these patients. In general, a detailed and robust assessment of the intracranial vessel walls and plaque status might be used in follow-up studies to assess the progression over time and the potential effect of this progression on new medication.

**Conclusions**

MR intracranial vessel wall imaging is a fast growing area of clinical and scientific interest. With intracranial atherosclerosis being an important cause of stroke, intracranial vessel wall imaging will become more important despite the fact that the methodology requires further development. In the next decade, technical innovations and clinical applications within this field will result in new insights into the cause of stroke in individual patients, which might ultimately translate into better and more individualized stroke treatment.

**Search Strategy and Selection Criteria**

References for this review were identified through a search of PubMed between March 1968 and January 2014 and references from relevant articles. The search terms brain diseases, intracranial ischemia, stroke, intracranial arterial arteriosclerosis, cerebral arteries, intracranial vessel wall, and MRI were used. Only articles in English were reviewed. The final reference list was generated on the basis of relevance to the topics covered in this review.

**Disclosures**

None.

**References**


Imaging Intracranial Vessel Wall Pathology With Magnetic Resonance Imaging: Current Prospects and Future Directions
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