Imaging Inflammation in Cerebrovascular Disease

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Currently, diagnosis of intracranial large vessel pathologies is based on luminal appearance using angiographic studies either noninvasively with magnetic resonance (MR) or computed tomography or invasively with catheter angiography. However, exciting new methodologies are in development that allow imaging beyond the lumen to characterize the disease process of the vessel wall. Inflammation has been implicated in large artery cerebrovascular lesions, having a role in the progression of symptomatic intracranial atherosclerosis, growth and rupture of brain aneurysms, delayed cerebral ischemia after subarachnoid hemorrhage, and rupture risk of brain arteriovenous malformations. Imaging the spatial distribution, severity, and temporal changes in cerebrovascular inflammation may offer insight into the clinical diagnosis and treatment decisions in the near future. Substantial challenges remain for the development of high-resolution, specific, and sensitive techniques to quantify patterns of inflammation in large intracranial arteries. This review serves to highlight developments in vascular wall imaging and molecular imaging techniques to better elucidate the predictive value of vascular inflammation in the progression of cerebrovascular disease.

Methods
We conducted searches using PubMed and Google Scholar for relevant articles published since 1980 in English. We used search words, such as cerebral arteries or cerebrovasculature, inflammation, or imaging, combined with subject heading search words representing different pathological conditions or imaging modalities, such as magnetic resonance imaging (MRI), molecular imaging, positron emission tomography (PET), ultrasound, vessel wall imaging, intracranial atherosclerosis, intracranial aneurysm, angitis, vasculitis, Moyamoya disease, giant cell arteritis, or ultrasmall superparamagnetic iron oxide (USPIO). The first search was performed in January 2015 and the last in May 2015. Articles were screened by title and abstract, and if relevant, the article was reviewed in its entirety. Because of restrictions in Stroke on the publication of Topical Reviews, final discretion of selected references was determined by the authors.

Vessel Wall Imaging
Black blood MRI is the workhorse of vessel wall examinations in vivo. Suppression of signals from the blood is fundamental to generate contrast between the lumen and the vessel wall. Adequate wall visualization is further dependent on careful compensation for residual blood signals arising from slow and laminar flow. Additional sensitivity for detection of intracranial arterial wall irregularities related to inflammatory processes is provided by gadolinium contrast-enhanced T1-weighted MRI. Selective gadolinium uptake in diseased arterial wall segments—in part because of increased density of intracranial arterial vasa vasorum (Figure A and B)—has been shown to be associated with the progression of cerebrovascular diseases, such as intracranial atherosclerosis or brain aneurysms. Initial examinations at 1.5 T revealed age-related increases in intracranial arterial wall enhancement that could result from neovascularity seen with atherosclerotic disease, whereas at 3 T, patterns of focal eccentric wall enhancement in atherosclerotic disease patients could be distinguished from smooth and concentric enhancement patterns in patients with inflammatory diseases, such as vasculitis and arteritis.

However, translation of pulse sequence techniques that were developed for vessel wall imaging of the extracranial carotid artery to the intracranial circulation is not straightforward. Intracranial arterial wall imaging is particularly challenging because of anatomic variability, tortuous geometry, and much smaller vessel diameters and wall thicknesses in branches distal to the circle of Willis. These factors heighten the requirements for spatial resolution, especially because thick-slice anisotropic acquisition geometries can lead to wall thickness measurement errors in curved vessels. Moreover, wall thickness measurements in healthy and diseased vessels and detection of focal abnormalities are hampered by insufficient contrast to discriminate the vessel wall from surrounding brain parenchyma and cerebrospinal fluid (CSF). Because smaller voxels and CSF suppression come at the cost of signal-to-noise ratio, many studies use fast spin echo techniques at 3 T and higher field strengths. To further limit acquisition times in clinical settings, brain coverage is often reduced, thus necessitating precise targeting of the vessel of interest. As a result, most studies are limited to a small subset of the intracranial vasculature and focus mainly on the larger arteries comprising the circle of Willis.

Received June 1, 2015; final revision received June 1, 2015; accepted August 7, 2015.


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Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.115.008229

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Several techniques have been proposed to overcome the limitations specific to imaging of the intracranial arterial wall. Because the effectiveness of double inversion recovery for blood suppression is reduced in 3-dimensional imaging, novel techniques, such as motion-sensitized driven-equilibrium magnetization preparation and nonselective delay alternating with nutation for tailored excitation pulse trains, have been optimized for high-resolution black blood MRI. In combination with a contrast-enhanced 3-dimensional fast spin echo sequence, improved blood suppression with motion-sensitized driven-equilibrium enabled visualization of wall enhancement in saccular, mostly ruptured aneurysms, argueably related to wall inflammation.

Black blood MRI with additional CSF suppression was achieved at 7 T with inversion recovery magnetization preparation and a fast spin echo sequence, which was further improved to enable whole brain coverage. Similarly, a carefully optimized delay alternating with nutation for tailored excitation prepulse was described for improved suppression of signals from blood while jointly nulling CSF signal, which could be used in combination with a proton density–weighted fast spin echo technique. Still, even with suppression of CSF, similar signal intensities in surrounding brain parenchyma reportedly precluded complete arterial wall visualization in ≈50% of the intracranial arterial segments. In a multicontrast vessel wall imaging approach, these techniques can be implemented alongside T1-weighted acquisitions in proton density– and T2-weighted sequences, which could provide valuable information to discriminate inflammatory diseases from other intracranial vasculopathies.

Vessel Wall Imaging in Intracranial Atherosclerosis

Despite efforts to suppress potentially misleading signals from laminar blood flow and improve visibility of the vessel wall by reducing perivascular CSF signals, a standard of reference to quantify the sensitivity and specificity of measurements in healthy and diseased vessel walls is currently not available. Recently, studies have correlated high-resolution MRI findings with intracranial atherosclerotic disease (ICAD). Turan et al collected the postmortem ICAD specimens 4 days after 3 T MRI examination and processed the specimens for histology. Different image signal characteristics were found to be consistent with various atherosclerotic components, namely lipid and loose matrix, fibrous tissue, and calcium. Similar findings were noted in van der Kolk’s study that used vessel wall imaging at 7 T to successfully distinguished different plaque components. These studies provided valuable insight into the ICAD pathology. However, the characterization of ICAD was limited to postmortem evaluation because intracranial atherosclerotic plaques are not removed from living patients during clinical interventions.

Currently, there is no standard protocol for MRI of ICAD, nor is there a gold standard phantom to compare MRI pulse sequences and imaging platforms. A small batch manufacturing technique was developed to create a hydrogel plaque phantom that provided a platform for establishing a uniform imaging method for diagnosis of ICAD. The phantom was scanned on different 3 T systems, and preliminary data showed that variations in signal intensity between the fibrous cap, lipid core, and vessel wall were observed on the T2 images. Thus, additional work is needed for standardization of ICAD MRI techniques to allow for multicenter studies.

Imaging of Cerebral Vasculitis

Primary angitis of the central nervous system shares with ICAD, Moyamoya disease, and reversible cerebral vasospasm the same pattern on 3-dimensional time-of-flight MR angiography: focal arterial stenoses of medium-sized intracranial arteries. The accurate positive diagnosis is often difficult to reach even with digital subtraction angiography and cerebral/meningeal biopsy. 3 T contrast-enhanced high-resolution MR acquisitions may be reliable to distinguish these diseases. Indeed, some authors have described an absence of vessel wall enhancement on high-resolution MRI in reversible cerebral vasospasm syndrome as compared with primary angitis of the central nervous system. Different patterns of wall thickening have been reported, such as a diffuse and uniform wall thickening in reversible cerebral vasospasm syndrome, whereas a focal thickening with concentric (70%) or eccentric (30%) vessel wall enhancement in vasculitis was more frequently observed. Mossa-Basha et al have shown that a high-resolution MR protocol combining pre- and postcontrast T1 and T2 sequences can increase the sensitivity in differentiating ICAD from other vasculopathies to more than 96%. In young adults (<55 years) with unilateral M1 segment stenosis, 3 T high-resolution MRI protocol, including T1 pre- and postcontrast and proton density acquisitions perpendicular to the M1 segment, may help to distinguish ICAD (eccentric wall thickening and enhancement) from vasculitis (circumferential wall thickening and enhancement), from intracranial dissection (dissecting flap, pseudolumen, and mural hematoma), or from Moyamoya disease (concentric wall enhancement without wall thickening and fine meshwork of basal collateral vessels). High-resolution fat-saturated T1-weighted MRI (3 T) before and after IV gadolinium administration may also help to reach the positive diagnosis of giant cell arteritis, in which arterial stenoses may be absent. Indeed, wall enhancement of the extracranial arteries (mainly the superficial temporal and occipital arteries) is depicted on high-resolution fat-saturated T1-weighted MRI with a sensitivity of 0.80 and a specificity of 0.80. In addition, intradural artery enhancement (mainly the internal carotid artery) is observed in more than half cases in giant cell arteritis patients. It should also be mentioned that an animal study on a mouse model of Kawasaki disease has demonstrated the advantage of myeloperoxidase-gadolinium (Gd) because it increased the vessel wall intensity 2.5-fold higher than that in regular gadolinium contrast–enhanced high-resolution T1-weighted MRI at 7 T. However, vessel wall enhancement should be interpreted carefully, especially in the pediatric population (<18 years) because normal intracranial parietal enhancement is frequently seen in both cavernous and petrous internal carotid artery, as well as in M1 segment on high-resolution fat-saturated contrast-enhanced MRI. High-field (7 T) 3-dimensional time-of-flight MR angiography has shown its benefits in detecting small-size vessels.
Role of Intravascular Imaging

Although our review is mostly focused on noninvasive vessel wall imaging techniques, advances in catheter-based technology for the minimally invasive treatment of cerebrovascular disease is also enabling the development of high-resolution intravascular imaging technology.\textsuperscript{35-37} Albeit invasive, with resolution approaching microscopy, these technologies have secured an important role in characterization of lesions in the peripheral and coronary circulations to support endovascular treatments. The cerebrovascular system presents significant challenges for intravascular imaging, with fragile, thin-walled vessels that have a tortuous path. Dedicated ongoing research to optimize optical coherence intravascular imaging systems specifically for brain arteries presents an exciting paradigm not only for accurate diagnosis, but also for guiding ideal endovascular treatments.

Molecular Imaging of Cerebrovascular Inflammation

Neuroinflammation Imaging in Stroke

Major pathophysiology caused by vascular dysfunction and morphological manifestation of damage to the brain can be investigated using an emerging hybrid imaging technique, which combines PET and MRI. This technique enables regional quantification of physiological parameters and assesses the distribution of molecular markers in the brain while providing an excellent view of the anatomy in ischemic brain. Cerebral ischemia induces hypoxia, and the resultant neuronal injury leads to the activation of the inflammatory cascade, in which migratory microglial cells initially play the central role. These cells (10% of the total brain cells) are activated and exhibit phagocytic activity in response to neuronal dysfunction because of cell stress and apoptosis after an ischemic stroke. The upregulation of mitochondrial translocator protein 18 kDa in microglia has been explored as a potential biomarker for imaging of microglial activation in neuroinflammation.\textsuperscript{38} In humans, the appearance of activated microglia occurs early in the ischemic core, whereas at later time points, activated cells appear on the periphery of brain infarct. Both PET and MRI use molecular imaging probes and sensors to visualize inflammation. The postchentic PET imaging using \textsuperscript{11}C-labeled PK11195 translocator protein 18 kDa ligand (based on isoquinoline carboxamide) enabled time-dependent imaging of neuroinflammation that showed binding along the outer border of ischemic lesions, as well as in regions distal to the primary lesion.\textsuperscript{39} After several days, the areas populated by activated microglia proximal to the infarct colocalize with an increased fluodeoxyglucose uptake. Findings from PET studies suggest neuroinflammation around the infarct correlates with negative outcomes. More recently, several longer half-life \textsuperscript{18}F-labeled ligands of translocator protein 18 kDa were reported (eg, dimethylpyrazolopyrimidine \textsuperscript{18}F-DPA-714\textsuperscript{40} and imidazopyridines \textsuperscript{18}F-PBR102 and \textsuperscript{18}F-PBR111\textsuperscript{41}) that, in direct comparative imaging experiments in animals, showed better imaging characteristics than PK11195. Innate immune system cells, that is, neutrophils and monocyte/macrophages originating from brain blood supply, are also actively engaged in the neuroinflammatory cascade, and neutrophil infiltration correlates positively with ischemic damage. It has been reported that myeloperoxidase, a specific enzymatic marker of terminal differentiation of neutrophils, was consistently found peaking early at 3 days after infarct and widely distributed in ischemic tissues, correlating with the size of the lesions.\textsuperscript{42} Neutrophil-derived ectopic myeloperoxidase activity in ischemic regions is responsible for enzymatic chlorination and nitrosylation of proteins with potential deleterious effect on brain cells. MRI of myeloperoxidase enzymatic activity after an intravenous injection of a small molecular weight paramagnetic myeloperoxidase substrate DTPA(Gd)-bis-hydroxyindolamide (bis-5HT-DTPA(Gd)) or myeloperoxidase-Gd\textsuperscript{43} enabled detection of inflammation on the periphery of infarcted zone in animal models. The infiltration of leukocytes into the ischemic brain areas results in oxidative damage and resultant neuronal degeneration. PET is capable of providing quantitative assessment of such areas by delineating microenvironments that experienced oxidative stress. Copper-64 or -62 radioisotope–labeled diacetyl-bis(N4-methylthiosemicarbazone (64Cu-ATSM) is one of the most promising candidates for imaging oxidative stress in the brain using PET, which can be used in combination with fluorine-18 fluorodeoxyglucose imaging.\textsuperscript{44,45} In addition, \textsuperscript{62}Cu-ATSM–assisted PET in the brain allows for initial evaluation of cerebral blood flow, and the regional uptake at 20 minutes (delayed phase) reflects over-reduction of ATSM that serves as an imaging signature of oxidative stress displayed as a result of mitochondrial dysfunction.\textsuperscript{44}

Imaging of Endothelial Activation in Stroke

The expression of endothelial leukocyte adhesion molecules P- and E-selectin is transcriptionally activated in brain ischemia\textsuperscript{46} supposedly by proinflammatory cytokines. It has been reported that inducible E-selectin expression can be visualized in vivo using antibody-targeted MR iron oxide (IO)–based agents.\textsuperscript{47} The IO-assisted MRI approach has been applied to imaging of early (several hours) or late (24 hours) endothelial activation in stroke using the sialyl LewisX–decorated IO nanoparticles that serve as multivalent ligands of endothelial selectins.\textsuperscript{48} In endothelin-induced stroke, these targeted nanoparticles resulted in hypointense signals on T2*-weighted MR images at 3 hours after the injury but only 24 hours after transient artery occlusion in mice. Paramagnetic Gd-DTPA derivatives functionalized with a sialyl LewisX mimetics rather than superparamagnetic IO can potentially serve as alternatives to
selectin-targeted IO in stroke imaging.\textsuperscript{49} The importance of MRI of activated endothelial lining of brain blood vessels is that it allows the delineation of the area of potentially salvageable penumbra, in contrast to diffusion-weighted MRI, which detects primarily the smaller infarct area.

Molecular Imaging of Intracranial Aneurysms

The pathophysiology of symptomatic unruptured intracranial aneurysms (IA) resembles that of ruptured aneurysms, generally showing significant endothelial cell damage, structural changes of the wall, and inflammatory cell infiltration.\textsuperscript{50,51} Early reports that investigated inflammation-induced antigen (vascular cell adhesion protein-1, C3b) expression in aneurysmal tissues also established the elevated presence of CD68 and CD3+ cells in unruptured IA (versus normal basilar arteries), pointing to an existing link between IA progression and inflammation.\textsuperscript{52} Both hemodynamic stress and inflammation promote vascular smooth muscle cell death and activate their migration, resulting in thin and dilated areas of the cerebral vasculature.\textsuperscript{53} Proinflammatory cytokines (tumor necrosis factor-\(\alpha\), interferon-\(\gamma\), interleukin-6) secreted by brain-resident mast cells, recruited neutrophils, and macrophages potentially upregulate the expression of adhesion molecules in endothelium, resulting in leukocyte recruitment essential to the pathogenesis of vascular inflammation.\textsuperscript{54} Network-based gene expression analysis showed major histocompatibility complex class II gene overexpression in IA, pointing to the definite role of professional antigen-presenting and interferon-\(\gamma\)-activated cells in IA formation.\textsuperscript{55} Another important pathway that may be altered because of genetic factors is endothelin signaling via type A endothelin receptors. These receptors are situated on smooth muscle cells, and their activation results in vasoconstriction.\textsuperscript{56} Therefore, the abundant evidence already gathered by several independent research groups suggests that imaging of molecules associated with local inflammation would greatly assist in determining active remodeling and progression of IA to rupture.\textsuperscript{57} Such imaging can be accomplished either by molecular imaging or by cell imaging, that is, the former aimed at imaging molecular target expression and distribution in vivo, whereas the latter designed to track myeloid cells of interest. Molecular imaging of cerebral arteries is challenging because of their specific morphology, that is, thin walls (0.06–0.25 mm\textsuperscript{57,58}) located in the intradural space and surrounded by CSF and widened peri-vascular spaces, resulting in a compartment that could nonspecifically trap imaging probes.

MRI of Myeloperoxidase in Aneurysms

Recently, we noticed a correlation between neutrophil myeloperoxidase presence in human surgically excised unruptured aneurysms and rupture risk predicted by the PHASES score model,\textsuperscript{59} suggesting the importance of myeloperoxidase detection in aneurysmal wall as a predictor of instability (Figure). We have observed in human aneurysm specimens both adventitial vascularization as a pathway for neutrophilic myeloperoxidase infiltration (Figure A and B) and mural presence of myeloperoxidase in the absence of vasa vasorum (Figure C and D). We have

Figure. A and B, Histology sections of an unruptured, 9 mm pericallosal artery aneurysm resected after surgical clipping. This aneurysm in a 71-year-old female was surveilled for a period of 10 years and underwent treatment because of imaging evidence of growth. Structure of the wall of the aneurysm (A, Masson trichrome stain, 10\times) shows a large vessel (vasa vasorum [VV]; coursing on the adventitial surface (A). Frozen, nonconsecutive section of the same aneurysm (B, 10\times) shows myeloperoxidase (MPO; anti-human MPO mAb staining, green fluorescence) in the vasculature of the aneurysm wall, demonstrating an outside-in pathway for migration of inflammatory cells. In B, blue fluorescence indicates nuclei (DAPI); and red fluorescence, endothelial (anti-human CD31 mAb). C and D, Sections of an unruptured, 7 mm, irregular middle cerebral artery bifurcation aneurysm resected from a 54-year-old female (C, MPO stain, 4\times) with dense staining for MPO presence (D, top, 20\times) and activity (D, bottom, 20\times) in the layers of smooth muscle cells, indicating an inside-out pathway for sustained local inflammation. In D, bottom, blue fluorescence indicates nuclei (DAPI); and red fluorescence, MPO activity staining using Cy3-(5-hydroxytryptamine) substrate. L indicates vessel lumen.
previously explored the use of myeloperoxidase-specific MR signal enhancement for imaging inflammation in an animal model of saccular aneurysm. Noninvasive imaging of myeloperoxidase activity in blood vessel was performed by using high-resolution MRI combined with IV administration of bis-5HT-DTPAGd myeloperoxidase substrate. To induce local intramural inflammation of the vessel wall in a model aneurysm, we used image-guided intramural injection of the Escherichia coli lipopolysaccharide solution into the vessel and compared these animals with noninjected controls. The procedure leads to infiltration of myeloperoxidase-positive neutrophils and myeloperoxidase-negative macrophages at the site of injection. After injecting bis-5HT-DTPAGd, we observed a visible and lasting T1-weighted MR signal enhancement in lipopolysaccharide-injected aneurysms. Future clinical translation of this MRI technique requires an optimization of the pulse sequence, enabling a specific imaging of vascular wall in aneurysms that have nonlinear blood flow. We optimized a motion-sensitized driven-equilibrium-prepared turbo spin echo MRI approach for the detection of a myeloperoxidase-specific imaging probe in experimental aneurysm models and further applied it for imaging realistic in vivo rabbit aneurysm models. Blood signal within the lumen of the aneurysm was sufficiently suppressed in combination with fat saturation and inversion pulse specific for aneurysm wall imaging. The optimized imaging protocol in the rabbit model of saccular aneurysms revealed a significant increase in the change of signal-to-noise ratio from pre-contrast to postcontrast imaging in the inflamed aneurysms as compared with naïve aneurysms and the adjacent carotid artery (P<0.0001). 61

Ultrasmall Superparamagnetic IO Contrast in MRI of Aneurysmal Inflammation

Despite early concerns about the safety of using USPIO particles, MRI with these contrast agents has continued to gain acceptance as a feasible means of detection and risk assessment of aneurysms and other vascular pathologies. The power of this technique lies in high level of USPIO uptake into inflammatory cells (monocytes, macrophages, and microglia), which has now been firmly established as both structural components and biological mediators of lesion progression in vascular disease. 62 Uptake of USPIOs in lesions induces localized magnetic susceptibility, which primarily shorten T2 and T2* relaxation times, and thus are detected as hypointense areas in corresponding MR images. The localization of USPIOs in infiltrated macrophages associated with carotid plaques has been verified repeatedly through histology, and a clear connection between amount of inflammatory cell burden and disease severity and outcome has been established. 63,64 However, although the majority of animal studies show USPIO-laden macrophage accumulation several days after insult, 64–66 there is growing evidence showing early (within hours) accumulation of particles not associated with inflammatory cells, 67–69 which may reflect other sources of USPIO accumulation, such as the extravasation of free USPIOs. In some cases, this pattern overlaps that of increased vascular permeability as detected by Gd-DTPA, suggesting that USPIOs may cross the leaky vascular wall via passive diffusion 60,71; however, in other cases, a mismatch between the 2 contrast mechanisms may indicate entrapment or nonpassive transport into tissue. 71–73 In some animal models, the time course of USPIO contrast enhancement follows more closely with the appearance and remission of clinical signs than other sources of MR contrast. 74 Trials of USPIO-enhanced detection of human aneurysms have yielded promising results. In patients imaged 72 hours after USPIO administration, 7 out of 9 aneurysms (78%) showed USPIO-mediated contrast in the lesion wall, and moreover, aneurysm tissue harvested from these patients stained positive for macrophages (CD68+) and iron stain. 74 In a follow-up study, USPIO-induced signal changes in aneurysm wall of 5 patients could be partly ameliorated after patients were given a regimen of daily aspirin. 75 Related larger clinical studies are now underway, 76 which should provide general validation of USPIO-mediated MR contrast imaging for rupture risk assessment of human aneurysms.

Summary

Imaging inflammation in large intracranial artery pathology may play an important role in the diagnosis of and risk stratification for a variety of cerebrovascular diseases. Looking beyond the lumen has already generated widespread excitement in the stroke community, and the potential to unveil molecular processes in the vessel wall is a natural evolution to develop a more comprehensive understanding of the pathogenesis of diseases, such as ICAD and brain aneurysms.

Disclosures

Dr Gounis received research grants/fee-for-service research (money paid to institution) from Blockade Medical, CereVasc LLC, Codman Neurovascular, Cook Medical, eV3 Neurovascular/Covidien, InNeuroCo Inc, Neuronal Protection System LLC, National Institutes of Health, Philips Healthcare, Spineology Inc, Silk Road, and Stryker Neurovascular; consultation/fee-per-hour (money paid to individual) from Stryker Neurovascular; and investment/stocks from InNeuroCo Inc. Dr Puri received research grants/fee-for-service research (money paid to institution) from eV3 Neurovascular/Covidien and Stryker Neurovascular; and consultation/fee-per-hour (money paid to individual) from eV3 Neurovascular and Codman Neurovascular. Dr Bogdanov received support from National Institutes of Health. The other authors report no conflicts.

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Stroke. 2015;46:2991-2997; originally published online September 8, 2015;
doi: 10.1161/STROKEAHA.115.008229

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/46/10/2991