

# Novel Noninvasive Magnetic Resonance Imaging Methods in Cerebrovascular Disease

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## Abstract

Neuroimaging is a critical component of patient care in multiple stages of cerebrovascular disease. Most imaging focuses on measurements of tissue or vascular structure, with comparatively less emphasis on function. Furthermore, imaging approaches that rely on exogenous contrast agents or ionizing radiation are common and provide crucial information regarding treatment decisions; however, they are suboptimal for monitoring patients longitudinally or in response to therapy due to dose restrictions and related health concerns. We review the state of noninvasive magnetic resonance imaging (MRI) approaches that have demonstrated clinical potential in patients with cerebrovascular disease, yet have not been incorporated into routine radiologic protocols at most hospitals. These approaches include blood oxygenation level-dependent (BOLD) for cerebrovascular reactivity, arterial spin labeling (ASL) for cerebral blood flow quantification, chemical exchange saturation transfer (CEST) for macromolecule, and pH determination and arterial vessel wall imaging for plaque visualization. The strengths and limitations of these approaches are presented, as well as a summary of their implementation in stroke.

## Keywords

Stroke, BOLD, ASL, CEST, reactivity, neurovascular imaging

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Stroke is the leading cause of adult disability and the second leading cause of death in developed countries.<sup>1</sup> Despite progress in stroke treatment, 20–30 % of strokes result in death within 1 month and 70–80 % result in significant long-term disability.<sup>2–4</sup> Improved preventative and acute management of cerebrovascular disease has reduced stroke-related mortality;<sup>5</sup> however, many stroke survivors remain impaired with nearly 33 % institutionalized after stroke.<sup>6–9</sup>

Neuroimaging is a critical component of patient care in all stages of cerebrovascular disease: from identification of stroke risk factors to stratifying acute and chronic stroke patients to the most effective revascularization and rehabilitation treatments. Evaluation of management decisions and post-stroke therapy strategies would be accelerated with an improved understanding of the complex interplay between vascular, neurochemical, and tissue-level hemodynamic impairment.

Characterization of soft-tissue structure using fluid attenuated inversion recovery (FLAIR) and T1-weighted magnetic resonance imaging (MRI)

is central to most standard MRI protocols and extensive work has documented the relevance of these techniques.<sup>10–12</sup> In more specialized protocols, diffusion weighted imaging (DWI) or diffusion tensor imaging (DTI) can be applied to characterize membrane integrity and fiber tract directionality, respectively,<sup>13</sup> and neurochemical tissue signatures can be assessed using principles of magnetic resonance spectroscopy.<sup>14</sup> These relatively well-known approaches have been implemented in patients with cerebrovascular disease for more than 2 decades. However, newer approaches are continuously being developed that hold potential for further expanding our understanding of the functional and structural sequela of tissue changes during and following ischemia.

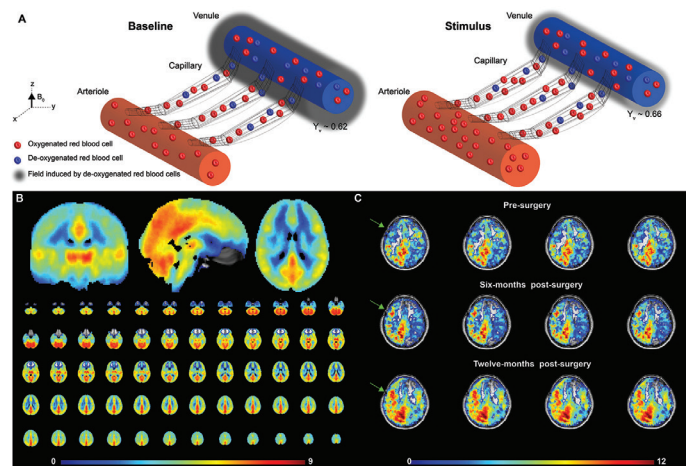
Here, we review the state of novel, noninvasive MRI approaches capable of complementing the existing stroke imaging infrastructure for more comprehensive evaluation of cerebrovascular disease. As each method is in a different stage of development, with varying timelines for routine clinical implementation, the purpose of this article is to review these emerging methods in the context of their strengths and limitations for

**Table 1: Noninvasive Magnetic Resonance Imaging Approaches with Demonstrated Clinical Potential in Cerebrovascular Disease, Listed in Order of Decreasing Clinical Feasibility Testing**

Technique	Primary Parameter(s) Measured	Other Parameters Measured	Duration	Spatial Resolution	Clinical Stroke Reference	Methodological Reference
BOLD Reactivity	CBF and CBV reactivity	CMRO <sub>2</sub>	5–12 minutes	3–4 mm	Mandell et al. <sup>90</sup> Donahue et al. <sup>37</sup>	Buxton et al. <sup>91</sup> van Zijl et al. <sup>26</sup>
ASL	CBF	Arterial arrival time	3–8 minutes	3–5 mm	Tancredi et al. <sup>92</sup> Chalela et al. <sup>93</sup>	Detre et al. <sup>94</sup> Okell et al. <sup>95</sup>
AWI	Vessel wall thickness	Plaque	6–11 minutes	0.5–1 mm	van der Kolk et al. <sup>96</sup> Mandell et al. <sup>97</sup>	van der Kolk et al. <sup>98</sup> Li et al. <sup>87</sup>
CEST	pH	Macro-molecules with labile protons	3–7 minutes	1–3 mm	Sun et al. <sup>99</sup> Tietze et al. <sup>100</sup>	van Zijl et al. <sup>101</sup> Ward et al. <sup>59</sup>

ASL = arterial spin labeling; AWI = arterial wall imaging; BOLD = blood oxygenation level-dependent; CBF = cerebral blood flow; CBV = cerebral blood volume; CEST = chemical exchange saturation transfer; CMRO<sub>2</sub> = cerebral metabolic rate of oxygen consumption.

## Figure 1: Blood Oxygenation Level-dependent Cerebrovascular Reactivity



**A:** Physiology underlying the blood oxygenation level-dependent (BOLD) effect. During either neuronal (e.g., cognitive processing) or vascular (e.g., hypercarbic CO<sub>2</sub>-induced) stimulation, cerebral blood flow (CBF) increases by much more than the cerebral metabolic rate of oxygen consumption (CMRO<sub>2</sub>), leading to increased oxygenated red blood cells (carrying HbO<sub>2</sub>) in capillaries and veins. As deoxy-hemoglobin (Hb) is paramagnetic (counteracts main magnetic field, B<sub>0</sub> of the scanner), the relative increase in oxyhemoglobin (HbO<sub>2</sub>) leads to a more homogenous field in and around capillaries and veins, leading to a lengthening of the magnetic resonance image (MRI) relaxation time T2\* and therefore increased MRI water signal. This effect is reduced primarily by increases in CMRO<sub>2</sub> and small increases in venous cerebral blood volume (CBV) (which are much smaller than arterial CBV changes). This leads to an overall positive water signal increase in healthy tissue. **B:** Mean hypercarbic BOLD reactivity maps in patients (n=50) with varying degrees of ischemic disease reveal relatively symmetric reactivity patterns in average. **C:** Example of a patient with Moyamoya disease before and after surgical revascularization demonstrates abilities for BOLD to serially monitor changes in cerebrovascular reactivity and reserve capacity. Colour bar denotes z-score with stimulus.

evaluating cerebrovascular disease and to provide references relevant for further evaluation of their existing impact on stroke imaging (see Table 1).

## Magnetic Resonance Imaging

MRI has been routinely used clinically for more than 20 years, with a primary purpose for visualizing structural soft-tissue contrast. The main signal source in MRI is water and the contrast derives from how the magnetic properties (longitudinal and transverse relaxation times: T1 and T2, respectively) of water protons in different environments adjust in the presence of a static magnetic field (B<sub>0</sub>; generally 1.5–3.0 Tesla) following perturbation by additional radiofrequency (B1) and gradient (G) fields. Water protons in

different environments have unique relaxation properties and therefore can exhibit exquisite contrast between different healthy tissue types and between healthy and diseased tissue. Importantly and unlike contrast derived from positron emission tomography (PET), single-photon emission computed tomography (SPECT), or computed tomography (CT), different contrasts in MRI can be generated simply by adjusting scan parameters (e.g., B1 and G). This accelerates innovation and clinical implementation in MRI, as testing or approval that may be required from new exogenous tracers is irrelevant. However, a valid concern with MRI is that our ability to validate new techniques may be outpaced by diverging technical innovations. When this occurs, the clinical feasibility of new MR approaches and their true prognostic potential may be unclear. Here, we present an overview of several cerebrovascular imaging methods that have tested clinical potential and which deserve interest for implementation into large-scale clinical trials.

## Blood Oxygenation Level-dependent Cerebrovascular Reactivity

Blood oxygenation level-dependent (BOLD) MR neuroimaging with predominately T2\*-weighted contrast<sup>15,16</sup> and less commonly T2-weighted contrast,<sup>17</sup> has been widely applied to map brain activity<sup>18–21</sup> noninvasively, transforming the field of cognitive neuroscience. BOLD contrast arises owing to the mismatch in cerebral blood flow (CBF), cerebral blood volume (CBV), and cerebral metabolic rate of oxygen (CMRO<sub>2</sub>) increases secondary to both vascular and neuronal stimulation in healthy parenchyma.<sup>22</sup> Specifically, CBF increases by generally 20–100 % (depending on task), whereas CMRO<sub>2</sub> increases only marginally by 0–20 %.<sup>23,24</sup> This leads to an increase in oxyhemoglobin (HbO<sub>2</sub>) relative to deoxyhemoglobin (Hb) in capillaries and veins. As HbO<sub>2</sub> is diamagnetic whereas Hb is paramagnetic, the relative reduction of fractional Hb in the vasculature will increase surrounding water T2 and T2\*, thereby increasing MR signal. Additional dephasing arises from CBV increases in vasculature containing Hb, which will reduce the surrounding water signal.<sup>25,26</sup>

BOLD MR was initially developed to assess changes in blood flow as a surrogate for neuronal activity, allowing functional localization. BOLD signals are indirect markers of neuronal or vascular activity that arise consequential to modulations in hemodynamics and metabolism,<sup>20,21,27–34</sup> In healthy tissue, coupling between these parameters are frequently preserved and therefore it is possible to make inferences regarding both hemodynamics and metabolism from ensemble BOLD signal under certain assumptions. However, when imaging diseased tissue, uncoupling

between flow and metabolism, together with autoregulation complicates interpretation of the BOLD signal.<sup>22,35</sup>

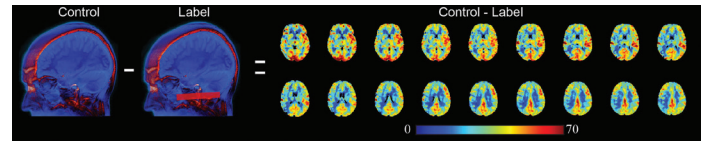
Recently, BOLD imaging has been utilized in studies of cerebrovascular disease in conjunction with primarily isometabolic hypercarbic gas stimulation.<sup>36,37</sup> Here, hypercarbia (generally ~5 % CO<sub>2</sub>) is administered either with a balance of atmospheric air or O<sub>2</sub>.<sup>38</sup> The hypercarbic stimulus elicits relaxation of arterial smooth muscle and correspondingly increases in CBF and CBV. Therefore, the hypercarbic-induced BOLD signal is a marker of cerebrovascular reactivity (CVR) and the degree of increases in BOLD signal can be used to infer how near vasculature is to reserve capacity. This method has been used clinically in a range of patients with cervical and intracranial steno-occlusive disease<sup>39-41</sup> and BOLD-measured CVR has been shown to correlate with angiographic and clinical measures of impairment,<sup>40</sup> inversely with cortical thickness<sup>42</sup> and variably with prognosis and stroke risk.<sup>43,44</sup> Figure 1 shows an example of how BOLD CVR can be used clinically to provide additional information regarding parenchyma response to surgical revascularization.

The advantages of BOLD CVR measurements are (i) a large existing literature demonstrating clinical feasibility, (ii) the noninvasive nature of the MRI protocol, which does not require intravenous contrast, and (iii) simplicity of the imaging sequence (most commonly a whole-brain long echo time single-shot echo planar imaging acquisition). The disadvantages are (i) susceptibility artefacts around regions of air/tissue interface in lower frontal lobe, (ii) contraindications in patients with severe pulmonary disease, and (iii) necessity to monitor basic physiologic changes including heart rate, blood pressure, end-tidal CO<sub>2</sub> (EtCO<sub>2</sub>), and, preferably, fraction-inspired O<sub>2</sub>. Hypercarbic BOLD has been implemented with good success using standard nonrebreathing gas masks and commercial gas mixtures, although more elaborate and controlled gas delivery equipment using end-tidal forcing and similar procedures are also utilized.<sup>45</sup>

### Cerebral Blood Flow-weighted Arterial Spin Labeling

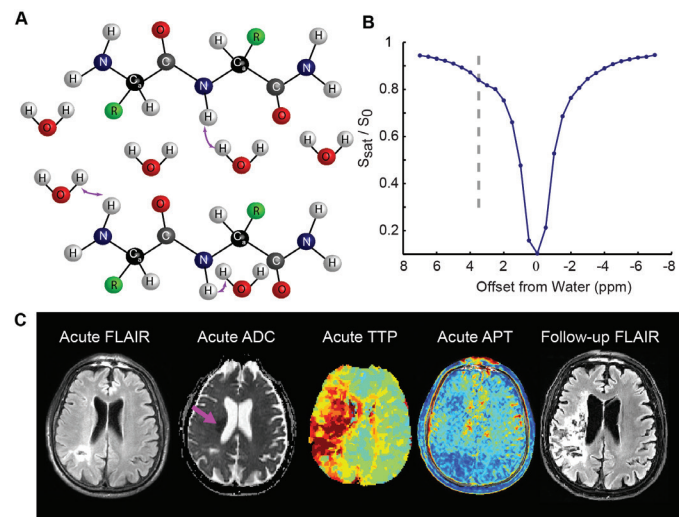
Though arterial spin labeling (ASL) MRI is nearly as old as BOLD MRI,<sup>46</sup> it is less widely used owing to greater technical hurdles related to acquisition. Contrary to BOLD, which provides a qualitative indirect marker for brain neurovascular function, ASL is primarily CBF-weighted, and with appropriate care can be used to quantify CBF in absolute units (millilitres blood/100 g tissue/minute), analogous to PET or CT perfusion imaging. In ASL, arterial blood water magnetization is altered using either a single or more recently a string of radiofrequency pulses; this inverts the magnetization of inflowing blood water relative to static tissue water. This inversion acts as an endogenous bolus. Blood water labeled in carotid and vertebra-basilar arteries travels through the large vasculature, enters the capillaries, and exchanges with tissue water. Tissue signal is imaged after an adequate post-labeling delay time (inversion time, TI) for this capillary exchange. The labeled blood water attenuates the tissue water signal very slightly (less than 1 % of the static tissue signal) and therefore ASL generally requires a separate reference image to be acquired in which the blood water is not labeled. The difference between the label and reference image produces a CBF-weighted image and absolute quantification of CBF is possible upon application of the solution to the flow-modified Bloch equation for one (blood) or two (blood and tissue) compartments.<sup>47</sup>

### Figure 2: Arterial Spin Labeling Magnetic Resonance Imaging for Measuring Cerebral Blood Flow



A: In arterial spin labeling (ASL), blood water is magnetically labeled through inversion of the arterial blood water magnetization. The labeled bolus flows into the imaging slice and exchanges with tissue water, thereby slightly reducing the tissue water signal. This reduction in tissue water signal is better visualized when compared with a separate image in which the inflowing blood water is not labeled (e.g., 'control') and the difference between the label and control image provides a cerebral blood flow (CBF)-weighted map. The CBF can be quantified in absolute units upon application of the flow-modified Bloch equation or tracer kinetic models. Here, the CBF maps correspond to average maps from eight patients with asymmetric right-sided intracranial stenosis.

### Figure 3: Chemical Exchange Saturation Transfer Amide Proton Transfer Magnetic Resonance Imaging for Measuring pH and Macromolecule Content

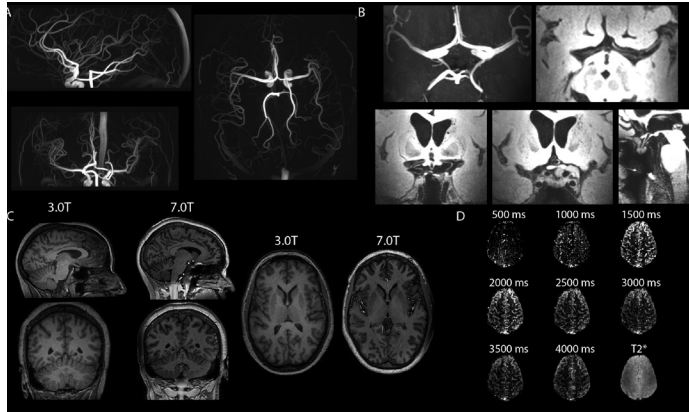


A: Amide protons (N-H) resonate at a unique frequency 3.5 ppm from water protons. Therefore, prior to detection of the water signal, if an off-resonant radiofrequency pulse is applied at the amide resonance, the amide magnetization will be altered. On the timescale of the magnetic resonance imaging (MRI) measurement, the amide protons will exchange with water protons, which are detectable with standard imaging readouts. The signal reduction that is observed in the water signal following amide proton saturation and exchange varies with the amount of the amide protons in the voxel and the exchange rate, which is base-catalyzed over a physiologic range. B: In practice, radiofrequency irradiation is applied at different offsets relative to water. Attenuation is observed at all offsets owing to multiple exchanging species, imperfect pulse performance and so-called 'spillover' effects; however, additional attenuation is observed at the amide proton transfer (APT) resonance (3.5 ppm). By measuring the magnitude of this attenuation in different tissue types, it is possible to obtain information regarding exchange rate, pH, and amide proton content. C: MRI performed 2-4 hours after acute onset of right middle cerebral artery stroke due to a middle cerebral artery occlusion in 58-year-old male: fluid attenuated inversion recovery (FLAIR) demonstrates encephalomalacia from remote stroke with mild hyperintense signal from edema in the acute stroke in the centrum semiovale. The infarct core is identified on the apparent diffusion co-efficient (ADC) map by restricted diffusion (pink arrow) and is surrounded by a large penumbra, identified by delayed time to peak (TTP). Extensive decreased APT effect predicts final infarct volume on a follow-up MRI after 30 days more accurately than the ADC map, in this patient.

Several variants of the original ASL approach have been implemented. First, labeling can be performed using special radiofrequency transmit coils and a single, long pulse for highest SNR in the continuous ASL (CASL) method, or ASL can be performed using pulsed (PASL)



## Figure 4: Ultra-high Field Relevance



**A:** An example of 0.5 mm phase contrast angiography acquired at 7.0T in approximately 4 mm, along with **(B)** arterial vessel wall imaging (0.8 mm) acquired in about 10 minutes. The vessel wall image shows clear vessel wall thickening in anterior cerebral artery and basilar artery. **C:** Standard T1-weighted imaging acquired at 3.0T (1 mm) and 7.0T (0.7 mm) in the same volunteer in near-identical scan times of approximately 5 minutes. **D:** Arterial spin labeling (ASL) acquired at different post-labeling delays demonstrates potential for measuring cerebral blood flow (CBF) at very long arterial arrival times (3–4 s), which are common in stroke. This phenomena is possible owing to the longer blood water T1 at 7.0T (2–2.5 s) relative to 3.0T (1.4–1.7 seconds).

or pseudo-continuous (pCASL) methods whereby a single or string of pulses are applied for labeling. Both PASL and pCASL can be performed using standard body coils for radiofrequency transmission, with pCASL providing nearly the same SNR as CASL.<sup>48</sup> For these reasons, pCASL has recently emerged as the most popular ASL variant. Second, ASL applied at multiple post-labeling delays allows for simultaneous quantification of both CBF and arterial arrival time. When this method is repeated in the presence of bipolar gradients to dephase intravascular blood water signal, or alternatively with modeling procedures, it is additionally possible to quantify arterial CBV.<sup>49–51</sup> Finally, one can label blood water in different feeding arteries using vessel-encoded ASL to visualize perfusion territories.<sup>52</sup> *Figure 2* outlines the ASL principles and shows an example of ASL in patients with ischemic cerebrovascular disease. Reviews of ASL application studies<sup>53</sup> and validation with invasive techniques<sup>57</sup> have recently been presented and principles of spin labeling have been extended to monitor CSF<sup>54</sup> and lymphatic flow.<sup>55</sup>

The advantages of ASL are that it is safe (not requiring intravenous contrast) and quantitative, allowing longitudinal comparison of CBF during treatment. Furthermore, when performed in tandem with BOLD MRI, it possible to enhance quantitative interpretability of functional responses by independently measuring CBF contributions to BOLD contrast, and, under appropriate modeling assumptions, infer changes in the remaining sources to BOLD contrast (e.g., CBV or CMRO<sub>2</sub>). Disadvantages of ASL are the low SNR (generally 10–20-fold lower than BOLD owing to the small effect of the blood water label) and reduced sensitivity to CBF in tissue with delayed arterial arrival times, including white matter or ischemic tissue. The latter confound arises owing to the endogenous label decaying with the T1 of blood water, which is approximately 1.2 s at 1.5T but grows to 1.6 s at 3.0T.<sup>56,57</sup> Arterial arrival times are generally reported in the range of 0.7–1.1 s, with an additional 1 s required for blood water to traverse the capillary bed. Therefore, ASL is more reliable at higher field strength where the blood water T1 (and in turn effective half-life of the tracer) is on the order of the blood-to-tissue transit time.

## pH-weighted Chemical Exchange Saturation Transfer

While the MRI signal is almost always derived from protons on water molecules, it is also possible to indirectly image labile protons that exchange with water. One of the most popular methods for this is with amide proton transfer (APT) imaging.<sup>58,59</sup> Whole-brain APT MRI can be obtained using standard equipment available at most hospitals and using commonplace imaging readouts optimized for structural and functional MRI. Chemical information is obtained through saturation transfer of magnetization between amide protons (primarily on the peptide backbone; *in vivo* concentration = 70–100 mM) and the imaged water protons (concentration = 110 M). In APT, the labile protons originate from amide groups resonating at 8.3 ppm in the proton spectrum (+3.5 ppm from water).<sup>60</sup> Importantly, over a physiologic pH (pH >5), the exchange rate is base-catalyzed and therefore the APT effect-size on the water signal reduces with decreasing pH, or tissue acidosis. As anerobic metabolism during ischemia leads to considerable tissue acidosis, APT may permit insight into the energy status of ischemic parenchyma by indirect pH imaging. Sun and colleagues have demonstrated potential for this method by monitoring the evolution of pH changes following middle cerebral artery occlusion in anesthetized rats at 4.7T.<sup>61,62</sup>

Variables predicting functional outcome following stroke include patient age, the National Institutes of Health Stroke Scale (NIHSS),<sup>63,64</sup> the size of the infarct core,<sup>65,66</sup> and (more controversially) the presence of penumbra.<sup>67</sup> Acute stroke intervention requires a judgment regarding the balance between revascularization benefits and risks. Intravenous or intra-arterial thrombolysis and clot retrieval endovascular procedures have been shown to increase reperfusion rates and reduce final infarct size when administered within the first hours of symptom onset.<sup>68–70</sup> However, reperfusing infarcted tissue increases the risk for hemorrhagic transformation, which occurs in approximately 6 % of treated patients.<sup>71</sup> Much work has been performed to develop fast imaging tools that accurately identify both the ischemic penumbra and the infarcted core of irreversibly damaged tissue. Clinically, this is most-often performed using perfusion CT or perfusion- and diffusion-weighted MRI (PWI and DWI). However, decreased perfusion may represent infarct core, penumbra, and/or benign oligemia.<sup>72–77</sup> Imaging tissue acidosis may provide an additional method for characterizing at risk and infarcted tissue in acute stroke.<sup>78</sup> *Figure 3* shows an example of an acute stroke patient imaged using pH-weighted APT CEST imaging.

The advantages of CEST imaging are that it is noninvasive and provides information regarding pH and macromolecular environment using typical imaging readouts already optimized from other modalities. This is in contrast to MR spectroscopy, which has been widely used for assessment of similar parameters, yet has extremely poor spatial coverage (generally one voxel) and is also time-intensive (5–15 minutes). A disadvantage of CEST imaging is that the nature of the contrast mechanism, including contributions from all exchanging species, has not been well summarized yet and therefore much development work is ongoing. Additionally, methodologic CEST studies are frequently conducted at high field (>3.0T) where contrast is largest and it remains unclear how well this approach will perform at clinically available field strengths.

## Arterial Vessel Wall Imaging

Cervical vascular stenosis is a well-known risk factor for stroke and much progress has been made in preventing strokes in this population. Following the North American Symptomatic Carotid Endarterectomy Trial (NASCET), patients with symptomatic high-grade cervical internal carotid artery (ICA) stenosis have been surgically revascularized with carotid endarterectomy, or more controversially, carotid stenting,<sup>79</sup> reducing stroke incidence. Recently it has been shown that patients with IC stenosis are also at high risk for stroke,<sup>80</sup> but the appropriate treatment for IC stenosis is less clear in the wake of the recently halted Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) study.<sup>81,82</sup> In this prospective trial, 14 % of patients treated with angioplasty combined with stenting and medical management experienced a stroke or died within the first 30 days following treatment compared with 5.8 % of patients who received medical management alone.

Arterial wall imaging of intracranial vessels is important for defining vulnerable plaque features, which have not been characterized for intracranial atherosclerotic disease and for improving management decisions. Much more is known about coronary and carotid bifurcation risk factors. For instance, nearly 70 % of acute coronary events are caused by lesions that are not hemodynamically significant or flow limiting prior to the event.<sup>83</sup> Carotid bifurcation studies have reported morphologic plaque features are more predictive of stroke risk than luminal stenosis.<sup>84</sup> Vulnerable extracranial plaque features, which have been validated in prospective studies and correlate with histopathologic findings following carotid endarterectomy, include lipid-rich necrotic cores, intra-plaque hemorrhage, and torn fibrous caps. Improved understanding of the longitudinal progression of atherosclerosis has shown that early plaque is accommodated by external remodeling without luminal compromise, presumably in an attempt to preserve hemodynamic flow. Studies have demonstrated plaque burden and composition is a dynamic process, which can increase or decrease with time.<sup>85</sup> Results from the recently completed Trial of Cilostazol in Symptomatic intracranial Stenosis 2 (TOSS-2) suggest MR may be sensitive to plaque changes in response to treatment.<sup>86</sup> Preliminary findings of vulnerable intracranial plaque features on MRI include eccentric wall enhancement and intraplaque heterogeneity, which appears to correlate with embolic infarct patterns and ipsilateral stroke.

Once vulnerable plaque features are validated, the effects of current treatments, including anti-platelet therapy and statins, on plaque morphology could be monitored longitudinally with arterial wall imaging, which has recently been developed and studied in healthy volunteers and patients with cerebrovascular disease, utilizing ultra-high spatial resolution methods.<sup>67-70</sup> The general strategy in these methods is to null intravascular signal and CSF signal, revealing contrast between the vessel wall and the surrounding nulled regions.<sup>67</sup> This can be achieved using a long turbo spin echo readout that will poorly refocus flowing spins through the region of interest, together with an inversion pre-pulse to null the longitudinal component of the blood water magnetization. Other methods with similar goals exploit pulse trains in combination with a train of spoiler gradients.<sup>67</sup> *Figure 4* shows an example of vessel wall imaging in a patient with intracranial stenosis. The disadvantage of vessel wall imaging without contrast agents is that such protocols require sub-millimetre imaging of 0.5–0.8 mm to resolve vessel walls. Due to inherently low SNR at clinically available field strengths, this can necessitate

7–12 minutes of scan time. While feasible at a clinical field strength of 3.0T, the improved noninvasive vessel wall contrast has been reported at ultra-high field.

## Ultra-high Field Relevance

Clinical magnetic field strengths are now common at both 1.5T and 3.0T, and approximately 50 research centers worldwide have 7.0T scanners. SNR increases linearly with field strength<sup>88</sup> and thus identical spatial resolution is available in approximately half the scan time if the identical scan is performed at 3.0T compared with 1.5T. While SNR improvements are the most common impetus for moving to higher field (see *Figure 4*), additional beneficial changes in contrast occur as well. For instance, BOLD MRI contrast is extremely sensitive to draining veins, which carry elevated HbO<sub>2</sub> during periods of neuronal and vascular stimulus. These cortical veins cause large susceptibility changes and therefore measurable increases in the T2(\*)-weighted signal, which is not derived from vascular reactivity and may not co-localize with the functional area of interest. However, as magnetic field strength increases, the intravascular blood water T2(\*) reduces relative to the extravascular tissue water T2(\*), which should reduce artifactual contamination from draining veins when BOLD is performed at higher field. At 1.5T, 3.0T, and 7.0T the fraction of the BOLD effect that is extravascular is 0.54, 0.78, and 0.92, respectively.<sup>89</sup>

Unlike T2(\*), blood water T1 will increase with increasing magnetic field strength.<sup>57</sup> This phenomena is particularly important for ASL, as the duration of the blood water label is proportional to the T1. Mean blood water (arterial and venous) T1 is approximately 1.2 s, 1.6 s, and 2.3 s at 1.5T, 3.0T, and 7.0T. Therefore, at 3.0T or higher ASL has increased potential for measuring CBF and arterial arrival times in tissue with reduced velocity and delayed arrival times, as is frequently the case in patients with vascular occlusion or severe stenosis (see *Figure 4*).

High field is particularly well-suited for APT imaging as water relaxation time lengthening, increased SNR, and spectral dispersion at high field facilitates increased sensitivity to the chemical exchange effect at the time of imaging. There are very few drawbacks to performing clinical MRI at 3.0T relative to 1.5T, with the exception of implanted medical devices that may be contraindicated at higher field. However, this limitation is becoming less burdensome as more devices have been tested and approved at 3.0T. At 7.0T, very few medical devices have been tested and at many research centers, medical implanted devices of any kind are contraindicated. This substantially reduces the clinical relevance of 7.0T in the short term. Related to this concern, the specific absorption rate (SAR), defined as the RF power absorbed per unit mass, increases with increasing B0. This occurrence leads to increased heating and related safety concerns at high field, imposing limitations on pulse sequences that require short TR and high RF duty cycle (e.g., pCASL or pulse train CEST). More efforts are underway to evaluate the safety of implanted devices at 7.0T and the range of acceptable SAR constraints, however aside from promising reports of 7.0T feasibility, utilizing 7.0T as a meaningful clinical tool has not yet been achieved in most centers.

## Conclusions and Summary

Multiple noninvasive MRI approaches for evaluating tissue- and vascular hemodynamic impairment have been tested clinically. These include BOLD

MRI for cerebrovascular reactivity evaluation, ASL for CBF quantification, CEST for pH-weighted contrast, and AWI for vessel wall and plaque characterization. The most advanced of these approaches in terms of clinical implementation are BOLD CVR and ASL CBF, with primarily feasibility

testing having been performed in the remaining approaches. Finally, as all methods benefit greatly with increased magnetic field, 3.0T is essentially required and 7.0T even more promising once technical obstacles of ultra-high field imaging are addressed. ■

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