Whole-Brain Arterial Spin Labeling Perfusion MRI in Patients With Acute Stroke

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Background and Purpose—Perfusion MRI can be used to identify patients with acute ischemic stroke who may benefit from reperfusion therapies. The risk of nephrogenic systemic fibrosis, however, limits the use of contrast agents. Our objective was to evaluate the ability of arterial spin labeling (ASL), an alternative noninvasive perfusion technique, to detect perfusion deficits compared with dynamic susceptibility contrast (DSC) perfusion imaging.

Methods—Consecutive patients referred for emergency assessment of suspected acute stroke within a 7-month period were imaged with both ASL and DSC perfusion MRI. Images were interpreted in a random order by 2 experts blinded to clinical information for image quality, presence of perfusion deficits, and diffusion–perfusion mismatches.

Results—One hundred fifty-six patients were scanned with a median time of 5.6 hours (range, 3.0–17.7 hours) from last seen normal. Stroke diagnosis was clinically confirmed in 78 patients. ASL and DSC imaging were available in 64 of these patients. A perfusion deficit was detected with DSC in 39 of these patients; ASL detected 32 of these index perfusion deficits, missing 7 lesions. The median volume of the perfusion deficits as determined with DSC was smaller in patients who were evaluated as normal with ASL than in those with a deficit (median [interquartile range], 56 [10–116] versus 114 [41–225] mL; P=0.01).

Conclusions—ASL can depict large perfusion deficits and perfusion–diffusion mismatches in correspondence with DSC. Our findings show that a fast 2½-minute ASL perfusion scan may be adequate for screening patients with acute stroke with contraindications to gadolinium-based contrast agents. (*Stroke. 2012;43:1290-1294.*)

Key Words: acute stroke □ cerebral hemodynamics □ imaging □ MRI □ stroke management

In patients presenting with stroke-like symptoms, MRI can be used to identify ischemic brain tissue and evaluate the amount of tissue at risk for infarction. Perfusion imaging identifies brain tissue that has reduced blood flow, the potential target for reperfusion therapies. In patients who present to the emergency department beyond the standard time window for intravenous tissue-type plasminogen activator, MRI has been postulated as a tool to identify individuals with salvageable brain tissue by detecting whether hypoperfused tissue has developed irreversible ischemic injury.

Perfusion is assessed in routine clinical practice with dynamic susceptibility contrast (DSC) imaging. In DSC MRI, a gadolinium contrast agent is injected and a time series of fast T2*-weighted images is acquired. The use of gadolinium-based contrast agents is however limited because of the risk of inducing nephrogenic systemic fibrosis in patients with poor renal function. Gadolinium is therefore contraindicated in patients with an estimated glomerular filtration rate <30 mL/min and in those on hemodialysis.

Arterial spin labeling (ASL) is an alternative noninvasive MR technique for visualizing perfusion and quantifying cerebral blood flow. ASL perfusion imaging uses blood as an endogenous contrast agent by magnetically labeling it with radiofrequency pulses and does not require gadolinium-based contrast agents. The perfusion contrast is given by the difference in magnetization induced by the exchange of these labeled spins at the brain tissue level and a nonlabeled control image. Limited by its low intrinsic signal-to-noise ratio, ASL perfusion measurements generally take several minutes for an accurate perfusion measurement. An improved pseudo-continuous labeling scheme, however, has increased the signal-to-noise ratio because it has a higher labeling efficiency and enables the combined use of the body transmit coil with the multidetector coils. By combining it with background suppression, the signal-to-noise ratio is increased...
Further, by almost 2-fold, allowing for shorter imaging time and increased spatial resolution.13

Previous studies have shown that ASL can detect perfusion deficits in patients with acute and subacute stroke.14–16 The aims of our study were to test the feasibility of using ASL in the clinical setting for evaluating hypertensive patients with stroke and to evaluate the ability of ASL to detect perfusion deficits and perfusion–diffusion mismatch of varying volumes compared with DSC perfusion imaging.

Materials and Methods

Patients

This prospective study was conducted in compliance with human subjects protection requirements. All patients who had an acute MRI for the assessment of suspected ischemic stroke at the Washington Hospital Center in Washington, DC, over a 7-month period were considered. At this hospital, MRI is the initial imaging modality for the evaluation of acute stroke. Patients with a suspected stroke who were ≥18 years of age were included and patients who had a contraindication to MRI or were pregnant were excluded. A vascular neurologist or stroke fellow evaluated all patients and scored the National Institutes of Health Stroke Scale. Patients who met standard eligibility criteria and were within 4.5 hours of symptom onset were treated with intravenous tissue-type plasminogen activator.17

Imaging Protocol

Imaging was performed on a clinical 3-T MRI scanner (Achieva; Philips Medical Systems, Best, The Netherlands) equipped with an 8-channel coil and locally developed software to enable ASL perfusion imaging. The imaging protocol was the standard imaging protocol used to screen all patients with stroke and was part of a quality improvement study. It included diffusion-weighted imaging (DWI), T2*-weighted fluid attenuation inversion recovery imaging, DSC, and ASL perfusion-weighted imaging. DSC images were not acquired in patients with a glomerular filtration rate <60 mL/min.15

The DSC perfusion-weighted images were acquired with the vendor's standard commercially available gradient echo sequence. A single dose of 0.1 mmol/kg of gadolinium (gadolinium-DTPA; Magnevist; Bayer Schering Pharma) was administered at 5 mL/s. The scan parameters were: repetition time, 1000 ms; echo time, 25 ms; field of view, 256×256 mm; 20 slices of 7 mm; scan time 1.43 minutes. ASL perfusion-weighted images were acquired using a pseudocontinuous labeling technique according to a previously published protocol.19 In short, ASL was performed by using a train of 180°, 0.5 ms, Hanning-shaped radiofrequency pulses at an interval of 1 ms, for a duration of 1650 ms, with a balanced gradient scheme.12,13 The control images were acquired by adding 180° to the phase of all even radiofrequency pulses. After a 1525-ms delay, 20 slices were acquired in ascending fashion with an in-plane resolution of 3×3 mm² with single-shot gradient echo imaging in combination with background suppression and parallel imaging (SENSE factor 2.5). Background suppression consisted of a saturation pulse immediately before labeling and inversion pulses at 1680 and 2830 ms after the saturation pulse.20 The other ASL MRI parameters were: repetition time, 4000 ms; echo time, 14 ms; pairs of control/label, 12; 20 slices with a 3×3×7 mm resolution; scan time 2.5 minutes.

Fluid attenuation inversion recovery and DWI images were acquired with the vendor's standard commercially available sequences. The fluid attenuation inversion recovery imaging were balanced (roughly) across field strength for conspicuity of chronic ischemic parenchyma with the following parameters: repetition time/echo time, 9000/120 ms and TI, 2600 ms; 40 slices with 1×1×4 mm resolution (SENSE factor 1.75); scan time 2.27 minutes. For DWI, the parameters were: repetition time/echo time =4500/62.1 ms; 40 slices with 1×1×3.5 mm resolution (SENSE factor 1.75); scan time 3.05 minutes.

Perfusion-Weighted Image Analyses

DSC perfusion-weighted images were calculated from the acquired series of T2*-weighted images with the vendor's standard available perfusion software (Advanced Brain Perfusion; Philips Healthcare, Cleveland, OH) on the MRI console. The time-to-peak (TTP) images were used for perfusion deficit analyses. ASL perfusion-weighted images were generated according to a previously published model that corrects for T1 decay, T2* decay, and the different delay times of the imaging slices.21 In patients with motion artifacts, in-plane motion was first corrected for by coregistering all dynamic pairs with SPM5 (Wellcome Trust Centre for Neuroimaging, Oxford, UK) using the normalized mutual information and a rigid body transformation.

Quantitative Perfusion Deficit and Mismatch

The acute cerebral and diffusion ischemic volumes were measured from DWI and the DSC TTP series using a semiautomated quantitative method in Cheshire (Perceptive Informatics, Waltham, MA) by a core laboratory rater who has extensive experience and established rater reliability statistics.22 Lesion areas were segmented on a slice-by-slice basis with user-selected seed points followed by user-driven editing. DWI lesions were identified on affected brain areas with maximal signal drop in intensity areas visible from the b=1000 mm²/s trace or isotropic images. The rater was careful not to include bilateral artifacts, chronic lesions, and, if necessary, reviewed apparent diffusion coefficient maps to isolate acute lesions. Perfusion-weighted imaging lesions on the TTP maps were identified as hypodense areas, excluding susceptibility artifacts adjacent to the paranasal sinuses. The volumes were automatically calculated by multiplying the total lesion area by the slice thickness.

Qualitative Image Evaluation

Unaware of the patient's identity, clinical information, and diagnosis, 2 experienced readers (S.W., J.G.M.) reviewed the DSC and ASL perfusion-weighted images. The images were viewed independently in random order. The readers also had access to the DWI and fluid attenuation inversion recovery imaging. They rated image quality, presence/absence of perfusion deficits, DWI lesions, perfusion–diffusion mismatch, and significance of the mismatch. Image quality was scored as excellent, good, fair, poor, and uninterpretable. A perfusion deficit was defined as an area with visually significant increased TTP on DSC and with decreased perfusion signal on ASL when compared with the surrounding brain tissue and contralateral hemisphere.

When there was a discrepancy in the evaluation of a perfusion deficit between both readers, they looked at the images together and reached a consensus. The readers used commercially available software to view the images (MIPAV, Version 4.4.1; National Institutes of Health, Bethesda, MD) and were able to adjust for contrast, color scheme, and size of the images.

Statistical Analyses

To compare acute DWI ischemic lesion volume, acute perfusion lesion volume on TTP, and diffusion–perfusion mismatch, logarithmic transformation was applied to correct for normality and comparison was performed with an independent t test. Values are expressed as mean±SD or median (first interquartile to third interquartile) unless otherwise specified. A probability value <0.05 was considered statistically significant. Interreader reliability analyses were performed using the κ statistic to determine consistency among raters.23 Statistical analysis was performed using SPSS (Version 15.01; SPSS Inc, Chicago, IL) for Windows.

Results

One hundred fifty-six consecutive patients (83 women, 73 men; 62±17 years) had an MRI as part of the initial evaluation of stroke at Washington Hospital Center between June 2009 and January 2010. The median time from symptom onset to imaging was 5.6 hours (range, 3.0–17.7 hours). Of the 156 patients, 30 patients were excluded because they could
not receive contrast due to glomerular filtration rate <30 mL/min and 21 patients were excluded because of incomplete imaging data. A total of 105 patients underwent both ASL and DSC perfusion imaging. Of the 31 patients in whom DSC was contraindicated, 14 had a stroke.

The quality of the DSC and ASL images was variable. Ninety-six percent of all DSC images were interpretable (100 of 105 patients): in 75 patients, the DSC images were judged as good to excellent (71%); in 15, they were fair (14%); in 10, they were poor (10%); and in 5, they were uninterpretable (5%). Ninety-seven percent of all ASL images were interpretable (100 of 105 patients): in 76 patients, the ASL images were judged as good to excellent (76%); in 17, they were fair (16%); in 9, they were poor (9%); and in 3, they were uninterpretable (3%).

Of the 105 patients with both ASL and DSC perfusion imaging, 64 (61%) had a clinically confirmed stroke. The median baseline National Institutes of Health Stroke Scale score was 6 (range, 0–33). The median time between symptom onset and imaging was 6.5 hours (range, 3.0–23.2 hours). Twenty-nine (45%) of the 64 patients with confirmed stroke received intravenous tissue-type plasminogen activator. In these patients, the median time to imaging was 3.0 hours (range, 1.7–4.0 hours).

Figures 1 and 2 illustrate 2 examples of ASL and DSC perfusion imaging in patients with acute stroke. A perfusion deficit was detected with DSC in 39 (61%) of the 64 patients with confirmed stroke (Table 1). ASL identified a perfusion deficit in 32 (82%) of the 39 patients with a deficit on DSC.

In the 7 patients with stroke with a deficit depicted on DSC but not on ASL, 5 of these patients had a cortical gray matter deficit and 2 a deficit in the basal ganglia (Figure 3). The ASL image quality was scored as poor to uninterpretable in 4 of the 7 patients, all with a cortical perfusion deficit. Four of the 25 patients with stroke who were classified as having normal perfusion by DSC were classified as having a perfusion deficit with ASL. The quality of the DSC images in 3 of these 4 patients was poor. A perfusion deficit was depicted in 1 of these 4 patients in the basal ganglia with ASL but not with DSC. The interrater agreement for detecting perfusion deficits with DSC and ASL perfusion imaging was, respectively, 0.64 and 0.6.

Table 2 lists how many patients were identified as having a significant perfusion–diffusion mismatch on ASL and DSC perfusion imaging. Twenty (31%) of the 64 patients with a confirmed stroke had a significant mismatch on DSC, and of these, 18 (90%) were also determined to have a mismatch on ASL. The 2 patients who had a mismatch on DSC but not on ASL had cortical lesions; 1 had an uninterpretable ASL. In 6

### Table 1. Agreement Between the Perfusion Deficits Depicted With ASL and DSC Perfusion Imaging

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<tr>
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<th>DSC (n=64)</th>
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<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>ASL Yes</td>
<td>32</td>
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<td>No</td>
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ASL indicates arterial spin labeling; DSC, dynamic susceptibility contrast.
Mismatched Depicted With ASL and DSC Perfusion Imaging

Patients with stroke in a clinical setting is feasible with ASL. This study demonstrates that fast evaluation of hyperacute deficit (on DSC) in patients who did not have a defect present on the DSC images were too poor of quality. The median volume of the perfusion deficit on DSC for all patients with stroke was 110 mL (range, 35–215 mL). The median volume of the perfusion deficit (on DSC) in patients who did not have a defect present on ASL was 56 mL (range, 10–116 mL). This was significantly smaller than the median volume of 114 mL (range, 41–225 mL) in patients that did have a defect on ASL ($P=0.01$ $t$ test performed on log transformation of volumes).

### Discussion

This study demonstrates that fast evaluation of hyperacute patients with stroke in a clinical setting is feasible with ASL perfusion imaging. Detection of large perfusion deficits and the presence of a perfusion–diffusion mismatch with ASL is comparable to that of DSC perfusion imaging. In the patients in whom a perfusion deficit was detected with DSC but evaluated as normal with ASL, the perfusion deficit volume was smaller.

Our findings that perfusion deficits are detectable with ASL correspond with previous studies in small groups of pediatric and adult patients with both acute and subacute stroke. Using a prototype single-slice pulsed ASL sequence, Siewert et al showed that ASL could detect perfusion abnormalities in a group of 18 subacute patients with stroke in comparison to gadolinium-enhanced DSC imaging. With a more recent pulsed ASL scan that uses a FAIR alternating labeling scheme combined with a QUIPS2 bolus cutoff, Viallon et al showed similar results in a group of 41 patients with acute stroke within 2 weeks of symptom onset. Their results showed that ASL can identify territorial hypoperfusion in correspondence with DSC, however, for lacunar infarctions, the spatial resolution of ASL was not sufficient to predict local perfusion deficits. This is in line with our findings that in those patients in whom ASL did not detect a perfusion deficit, the lesion volume as defined with TTP DSC was smaller, indicating that ASL is relatively insensitive for small perfusion deficits.

There are important differences between both perfusion imaging techniques used in this study. The ASL perfusion-weighted images are based on cerebral blood flow and ischemic tissue is reflected by loss of signal. This is substantially different to DSC, in which the measured mean transit times are predominantly used for lesion detection in stroke. This hemodynamic parameter derived through deconvolution reflects the transit time of the administered contrast bolus through the brain parenchyma. Ischemia will lead to increased transit times and a lesion is reflected by increased signal or hypointensity. When comparing both techniques, this is an important difference, because the contrast-to-noise of the ASL perfusion-weighted maps is lower and ischemic lesions are less clearly delineated. Although our study shows correspondence, the ischemic lesions that were not detected with ASL were of smaller volume. By using an ASL technique with image acquisition at multiple delay times after the initial labeling, it is also possible to measure the arterial arrival times with ASL. In a recent study of 15 patients with acute minor stroke and transient ischemic attack, MacIntosh et al demonstrated that a whole-brain 3-dimensional GRASE pulsed ASL sequence with prolonged arrival times values can be measured within the affected hemisphere. With further research, this potentially may be a valuable additive to the currently acquired perfusion-weighted images, because small inconspicuous lesions, for instance in the basal ganglia, may be easier to detect.

Recent acute ischemic stroke imaging guidelines recommend MRI for detection of ischemic changes and to exclude potential intracerebral hemorrhage. Currently, there is increasing evidence supporting that perfusion imaging may play an important role in the selection of patients beyond the strict 3-hour window who could benefit from thrombolysis treatment. In our study, however, DSC imaging was not performed in 20% of the patients presenting with stroke-like symptoms due to increased risk of developing nephrogenic systemic fibrosis. This significant amount of patients illus-
trates the importance of having an alternative noninvasive method for perfusion imaging. Because ASL uses radiofrequency pulses and does not require injection of gadolinium-based contrast agents, it may potentially be a viable alternative for those patients with a poor glomerular filtration rate or on hemodialysis. A relatively long 2½-minute ASL sequence was used in this study. Fernández-Seara et al showed, however, that perfusion maps can be acquired in <1 minute by combining pseudocontinuous ASL with background suppression and a single-shot 3-dimensional GRASE readout.11 A potential limitation of our study may be that an ASL perfusion sequence was used that acquires the images after a fixed time point after the labeling. In patients with delayed inflow, for instance caused by collateralization, this may lead to an underestimation of cerebral perfusion. The perfusion deficit in ASL imaging is a result different from that reflected by prolonged transit times in DSC because the perfusion signal drop may be explained by both decreased cerebral blood flow and delayed arrival of the blood bolus. However, with the sequence, the effective delay time from beginning of labeling to the readout is 3 seconds and should allow appropriate inflow time. An additional limitation is that ASL is predominantly sensitive to gray matter perfusion. Due to the limited signal-to-noise ratio, it is therefore difficult to detect small cerebral blood flow changes in white matter with ASL. For the evaluation of perfusion deficit presence on DSC, no threshold other than visual assessment was used. Areas with benign oligemia may have therefore been erroneously evaluated to be at risk for infarction and potentially have led to discrepancies when compared with ASL.

Conclusions

ASL can depict large perfusion deficits and perfusion–diffusion mismatches in correspondence with DSC. Our findings show that a fast 2½-minute ASL perfusion scan can be used as a fast noninvasive method to image for screening patients suspected of ischemic stroke in a clinical setting.

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Disclosures

None.

References

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