Assessing Reperfusion With Whole-Brain Arterial Spin Labeling
A Noninvasive Alternative to Gadolinium

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Background and Purpose—Arterial spin labeling (ASL) is a perfusion imaging technique that does not require gadolinium. The study aimed to assess the reliability of ASL for evaluating reperfusion in acute ischemic stroke in comparison with dynamic susceptibility contrast (DSC) imaging.

Methods—The study included 24 patients with acute ischemic stroke on admission and 24-hour follow-up ASL and DSC scans. Two readers rated images for interpretability and evidence of reperfusion. Cohen unweighted κ was used to assess (1) inter-rater reliability between readers for determining interpretability and the presence of reperfusion, (2) agreement between ASL and DSC for determining reperfusion for individual raters, and (3) agreement between ASL and DSC for determining reperfusion after consensus.

Results—Inter-rater reliability for both ASL and DSC was moderate to good (κ of 0.67 versus 0.55, respectively). Reader 1 rated 16 patients as having interpretable ASL and DSC when compared with 15 patients for reader 2. The κ between ASL and DSC for determining reperfusion was 0.50 for reader 1 and 0.595 for reader 2. After consensus, 18 ASL and 17 DSC image sets were rated interpretable for reperfusion and 13 had both interpretable ASL and DSC scans, yielding a κ for assessment of reperfusion of 0.8.

Conclusions—Inter-rater reliability of ASL and DSC was moderate to good. Agreement between ASL and DSC for determining reperfusion was moderate for each individual rater and increased substantially after consensus. ASL is a noninvasive and practical alternative to DSC for reperfusion assessments in patients with confirmed acute ischemic stroke. (Stroke. 2014;45:456-461.)

Key Words: magnetic resonance imaging ▪ perfusion imaging

ARTERIAL SPIN LABELING (ASL), a noninvasive MR perfusion imaging technique, does not require the administration of potentially toxic exogenous contrast agents.1–3 Mainly used for research, advances in labeling and image readout make ASL easily applicable to routine clinical use. ASL identifies perfusion defects and, therefore, aids in identifying areas of penumbra in patients with acute ischemic stroke (AIS).4,6 This study sought to determine the reliability of ASL in comparison with dynamic susceptibility contrast (DSC) imaging for reperfusion evaluation in patients with AIS.

Materials and Methods

Patients
The data were prospectively collected and analyzed from patients with AIS at Medstar Washington Hospital Center in Washington, DC, during 8 months. The analysis was performed as part of an ongoing quality improvement initiative to provide perfusion imaging to patients with renal failure. This research study was conducted in compliance with National Institutes of Health and study site institutional ethics requirements. Patients were included in the study if they had (1) an admission MRI scan with interpretable ASL and DSC, (2) a 24-hour follow-up MRI with interpretable ASL and DSC, and (3) a perfusion defect on mean transit time (MTT) or time to peak (TTP) maps derived from admission DSC sequences. Patients admitted to Washington Hospital Center after evaluation and tissue-type plasminogen activator (tPA) administration at an outside hospital also received ASL and DSC perfusion-weighted imaging (PWI) on admission and, if they met inclusion criteria, were included in the analysis. We administered intravenous tPA according to standard guidelines.7,8 A stroke neurologist scored the National Institutes of Health Stroke Scale (NIHSS) at approximately the same time as the admission MRI. In 18 patients, the follow-up NIHSS was scored at ≥24 hours after last known well.

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Imaging
The MRI acquisitions were performed on a clinical 3 Tesla MRI scanner (Achieva; Philips Medical Systems, Best, The Netherlands) equipped with an 8-channel coil and locally developed software to perform ASL perfusion imaging. The standard imaging protocol used to screen all patients with stroke was part of a quality improvement initiative and included diffusion-weighted imaging (DWI), T2-fluid attenuated inversion recovery, bolus tracking DSC PWI and ASL PWI. Patients with a glomerular filtration rate <30 mL/min did not undergo DSC bolus tracking PWI because of the increased risk of developing nephrogenic systemic fibrosis.

ASL was acquired using a pseudocontinuous labeling technique. Labeling of the arterial blood was performed by applying a train of 18°, 0.5 ms, Hanning-shaped radio frequency pulses at an interval of 1 ms, for a duration of 1650 ms, with a balanced gradient scheme.9,10 The control images were acquired by adding 180° to the phase of all even radio frequency pulses. Twenty slices were acquired in ascending fashion with an in-plane resolution of 3x3 mm² with single shot echo planar imaging in combination with background suppression and parallel imaging (SENSE factor 2.5). 1525 ms after the labeling stopped. Background suppression consists of a saturation pulse immediately before labeling and inversion pulses at 1680 and 2830 ms after the saturation pulse.11 Other ASL parameters were repetition time, 4000 ms; echo time, 14 ms; pairs of control/label, 38; field of view, 240x240x119 mm; matrix, 80x79; scan time 2½ minutes. The ASL data were analyzed with Matlab (version 7.5; The MathWorks, Natick, MA) and SPM8 (Wellcome Trust Center for Neuroimaging, Oxford, United Kingdom). Cerebral blood flow (CBF) images in mL×100 mL⁻¹×min⁻¹ were calculated from the ASL images according to a previously published model.12 The T²* transversal relaxation rate and T1 of arterial blood at 3T were assumed to be, respectively, 50 and 1680 ms.13,14 The water content of blood was assumed to be 0.76.

DSC PWI was acquired with the vendor’s standard commercially available gradient echo sequence and software. The PWI was a DSC series using a single dose of 0.1 mmol/kg of gadolinium (gadolinium-DTPA; Magnevist; Bayer Schering Pharma). MTT and TTP maps were generated and used for evaluation. Briefly, the sequence was 1.43 minute (3x3x7-mm resolution) echo time, 25.0 ms; repetition time, 1000.0 ms; field of view, 256x256; slice thickness, 7.0 mm for a total of 20 slices performed with a single dose of gadolinium at an injection rate of 5 mL/s.

Qualitative and Quantitative Reperfusion Evaluation
Two stroke neurologists (S.W. and J.G.M), blinded to patient identifiers and clinical information and aided by corresponding DWI images, independently evaluated sets of admission and 24-hour ASL relative CBF (rCBF) maps and DSC MTT/TTP maps presented in random order using publicly available software (MIPAV version 4.4.1; National Institutes of Health, Bethesda, MD). The authors could choose to view the images in either color or grayscale and were allowed to adjust for window and leveling. Aided by DWI maps to localize the site of acute ischemia, they read and classified the ASL and DSC perfusion scans from admission to 24 hours as showing reperfusion, no reperfusion, or uninterpretable. Reperfusion was defined as a visually conspicuous decrease in size of perfusion defect on the 24 hours when compared with the admission scan. In a separate session, any discrepant reads between the 2 neurologists were subject to tie-breaking reads performed by a third reader (L.L.L.). The majority (2 of 3) was used as the consensus read.

For patients found on consensus to have interpretable ASL and DSC scans, a separate rater (M.L.) with extensive experience and established reliability statistics measured lesion volumes on MTT using a semiautomated quantitative, planimetric method in Cheshire (Perceptive Informatics).13 The MTT was calculated in Cheshire from the PWI as the first moment of the time concentration curves divided by the zero moment. Deconvolution and arterial input functions were not used in the MTT calculation. Planimetric measurements of MTT volume have been validated as highly consistent and repeatable. Lesion areas were segmented slice-by-slice with user-selected seed points followed by user-driven editing. Reperfusion volume percentage was calculated by subtracting admission MTT volume from 24-hour MTT volume and dividing by admission MTT volume.

Statistical Analysis
Agreement was assessed in this study using Cohen unweighted κ. The agreement was assessed (1) between the 2 neurologists for determining interpretability and the presence of reperfusion, (2) between ASL and DSC for each reader using scans noted to be mutually interpretable (ie, scans that were interpretable at admission and on follow-up for both ASL and DSC), and (3) between ASL and DSC in scans noted to be mutually interpretable after consensus. Difference in admission and follow-up NIHSS scores between the group of patients with mutually interpretable scans and the group of patients with ≥1 uninterpretable scan after consensus were compared using the Mann–Whitney U test. Values are reported as median and interquartile range unless otherwise indicated.

Results
During 8 months, 160 patients had an admission MRI for stroke evaluation. Thirty-one patients who did not receive an admission DSC scan and 1 patient who did not receive an admission ASL scan were excluded. Ninety-six additional patients were excluded because they did not receive a 1-day follow-up MRI scan. Of the remaining 32 patients, 8 did not have a follow-up ASL scan. Twenty-four patients (14 women) met the inclusion criteria (Tables 1 and 2). Their mean age was 63 years (SD±18), and median admission NIHSS was 12 (interquartile range, 4–20 [IQR, 25–75]). The median time from last known well to the admission scan for all patients was 3.2 hours (IQR, 1.5–5.5), and to the 24-hour scan was 25.6 hours (IQR, 23.8–30.1). Standard intravenous tPA was initiated at the study center in 10 patients and at an outside hospital in 10 others. In the 10 patients treated at an outside hospital, perfusion imaging was performed on admission after intravenous tPA. The postintravenous tPA admission scans were read for reperfusion with the 24-hour scans. For the 10 patients who received intravenous tPA at an outside hospital, received endovascular therapy as their initial treatment or (2) untreated, the median time to admission imaging was 5.2 hours (IQR, 3.5–5.7).

In these 24 patients, agreement between the 2 neurologists for categorizing scans as reperfusion, no reperfusion, or uninterpretable was moderate to good for ASL and DSC (κ=0.672 and 0.551, respectively). Reader 1 rated 16 of 24 patients (67%) as having mutually interpretable ASL and DSC scans. The κ for agreement between ASL and DSC for detecting reperfusion was 0.50. Reader 2 rated 15 patients (62%) as having mutually interpretable ASL and DSC scans, and agreement for detecting reperfusion was 0.595. Eighteen ASL and 17 DSC scan sets were interpretable for reperfusion after tie-breaking reads and consensus, but only 13 patients (54%) had both interpretable ASL and DSC perfusion scans (Table 2). The κ for agreement between ASL and DSC after consensus was 0.8.

Median admission NIHSS for patients with mutually interpretable ASL and DSC on consensus was 10 (IQR, 4–15), and
for patients with ≥1 uninterpretable scan was 14 (IQR, 8–21). Follow-up NIHSS at 24 hours was performed in 9 of the 13 patients (69%) with mutually interpretable ASL and DSC scans (median NIHSS, 2; IQR, 1–16). It was performed in 9 of the 11 patients (82%) with ≥1 uninterpretable scan (median NIHSS, 16; IQR, 1–29). No difference was detected in admission or 24-hour NIHSS between these 2 groups (P=0.1 and 0.09 by Mann–Whitney U test for admission and 24-hour NIHSS, respectively).

Table 1. Excluded Patients With ≥1 Uninterpretable Scan

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Sex</th>
<th>Hours From Onset to Initial/Follow-Up Scan</th>
<th>Treatment</th>
<th>Stroke Vascular Territory</th>
<th>Consensus ASL Reads</th>
<th>Consensus DSC Reads</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>M</td>
<td>4.9/27.6</td>
<td>IV tPA (OH)</td>
<td>Left MCA</td>
<td>Uninterpretable</td>
<td>Uninterpretable</td>
</tr>
<tr>
<td>76</td>
<td>M</td>
<td>1.9/27.3</td>
<td>IV tPA (AH)</td>
<td>Left PCA</td>
<td>Uninterpretable</td>
<td>Uninterpretable</td>
</tr>
<tr>
<td>41</td>
<td>F</td>
<td>1.3/23.3</td>
<td>IA tPA* (AH)</td>
<td>Left MCA</td>
<td>No reperfusion</td>
<td>Uninterpretable</td>
</tr>
<tr>
<td>75</td>
<td>F</td>
<td>6.2/25.6</td>
<td>IV tPA (OH)</td>
<td>Left MCA</td>
<td>No reperfusion</td>
<td>Uninterpretable</td>
</tr>
<tr>
<td>79</td>
<td>F</td>
<td>3.0/24.1</td>
<td>None* (AH)</td>
<td>Left MCA</td>
<td>Reperfusion</td>
<td>Uninterpretable</td>
</tr>
<tr>
<td>51</td>
<td>M</td>
<td>5.5/23.0</td>
<td>IV tPA (OH)</td>
<td>Left anterior choroidal</td>
<td>No reperfusion</td>
<td>Uninterpretable</td>
</tr>
<tr>
<td>53</td>
<td>F</td>
<td>1.3/23.8</td>
<td>IV tPA (AH)</td>
<td>Right MCA</td>
<td>Reperfusion</td>
<td>Uninterpretable</td>
</tr>
<tr>
<td>61</td>
<td>M</td>
<td>4.2/24.3</td>
<td>IV tPA (OH)</td>
<td>Right MCA</td>
<td>Uninterpretable</td>
<td>No reperfusion</td>
</tr>
<tr>
<td>42</td>
<td>M</td>
<td>5.5/24.6</td>
<td>IV tPA (OH)</td>
<td>Right MCA</td>
<td>Uninterpretable</td>
<td>Reperfusion</td>
</tr>
<tr>
<td>77</td>
<td>F</td>
<td>1.2/21.1</td>
<td>IV tPA (AH)</td>
<td>Left MCA</td>
<td>Uninterpretable</td>
<td>Reperfusion</td>
</tr>
<tr>
<td>89</td>
<td>F</td>
<td>2.6/23.5</td>
<td>IV tPA (AH)</td>
<td>Left MCA</td>
<td>Uninterpretable</td>
<td>Reperfusion</td>
</tr>
</tbody>
</table>

AH indicates admission hospital; F, female; IV, intravenous; M, male; MCA, middle cerebral artery; OH, outside hospital; PCA, posterior cerebral artery; and tPA, tissue-type plasminogen activator.

*Relative contraindication to IV tPA: satellite lesions.
†Patient on Coumadin.

In the 13 patients with mutually interpretable scans, the median initial lesion volume on MTT was 115 mL (IQR, 24–259 mL). Classification of reperfusion consistently favored large reperfusion volume changes on MTT: median volume increase of –91% (IQR, –100% to –35%) for ASL and increase of 92% (IQR, –100% to –43%) for DSC. Conversely, no reperfusion volume changes were consistently small: median volume change of –9% (IQR, –26% to –2%) and of –9% (IQR, –19% to –2%) for ASL and DSC, respectively.

Discussion

Our study found moderate agreement between ASL and DSC on admission and 24-hour perfusion maps, which further increased with the consensus reads.

Table 2. Included Patients With Mutually Interpretable Perfusion Scans

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Sex</th>
<th>Hours From Onset to Initial/Follow-Up Scan</th>
<th>Treatment</th>
<th>Stroke Vascular Territory</th>
<th>Consensus ASL Reads</th>
<th>Consensus DSC Reads</th>
<th>Perfusion Volume Change, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>M</td>
<td>2.9/23.6</td>
<td>IV tPA (OH)</td>
<td>Left MCA</td>
<td>No reperfusion</td>
<td>No reperfusion</td>
<td>25</td>
</tr>
<tr>
<td>44</td>
<td>M</td>
<td>5.7/28.2</td>
<td>IV tPA (OH)</td>
<td>Left MCA, left lenticulostricate</td>
<td>No reperfusion</td>
<td>No reperfusion</td>
<td>–9</td>
</tr>
<tr>
<td>36</td>
<td>M</td>
<td>1.5/27.5</td>
<td>IV tPA (AH)</td>
<td>Right MCA</td>
<td>No reperfusion</td>
<td>No reperfusion</td>
<td>–10</td>
</tr>
<tr>
<td>36</td>
<td>F</td>
<td>3.5/30.0</td>
<td>IA tPA, Reapro* (AH)</td>
<td>Left MCA</td>
<td>No reperfusion</td>
<td>No reperfusion</td>
<td>–2</td>
</tr>
<tr>
<td>66</td>
<td>M</td>
<td>6.2/36.0</td>
<td>IV tPA (OH)</td>
<td>Left MCA</td>
<td>No reperfusion</td>
<td>No reperfusion</td>
<td>–26</td>
</tr>
<tr>
<td>75</td>
<td>F</td>
<td>1.1/28.1</td>
<td>IV tPA (AH)</td>
<td>Left MCA</td>
<td>Reperfusion</td>
<td>No reperfusion</td>
<td>–19</td>
</tr>
<tr>
<td>88</td>
<td>F</td>
<td>3.6/24.6</td>
<td>IV tPA (OH)</td>
<td>Right MCA</td>
<td>Reperfusion</td>
<td>Reperfusion</td>
<td>–100</td>
</tr>
<tr>
<td>75</td>
<td>F</td>
<td>1.6/25.4</td>
<td>IV tPA, IA tPA (AH)</td>
<td>Left MCA</td>
<td>Reperfusion</td>
<td>Reperfusion</td>
<td>–92</td>
</tr>
<tr>
<td>48</td>
<td>F</td>
<td>3.4/33.6</td>
<td>IV tPA (AH)</td>
<td>Right PCA</td>
<td>Reperfusion</td>
<td>Reperfusion</td>
<td>–100</td>
</tr>
<tr>
<td>49</td>
<td>F</td>
<td>1.1/25.7</td>
<td>IV tPA (AH)</td>
<td>Right MCA</td>
<td>Reperfusion</td>
<td>Reperfusion</td>
<td>–100</td>
</tr>
<tr>
<td>78</td>
<td>F</td>
<td>6.9/30.1</td>
<td>None* (AH)</td>
<td>Left MCA</td>
<td>Reperfusion</td>
<td>Reperfusion</td>
<td>–43</td>
</tr>
<tr>
<td>70</td>
<td>M</td>
<td>1.7/37.4</td>
<td>IV tPA (AH)</td>
<td>Left PCA</td>
<td>Reperfusion</td>
<td>Reperfusion</td>
<td>–35</td>
</tr>
<tr>
<td>35</td>
<td>F</td>
<td>5.6/34.1</td>
<td>IV tPA (OH)</td>
<td>Right MCA</td>
<td>Reperfusion</td>
<td>Reperfusion</td>
<td>–90</td>
</tr>
</tbody>
</table>

AH indicates admission hospital; F, female; IA, intra-arterial; IV, intravenous; M, male; MCA, middle cerebral artery; OH, outside hospital; PCA, posterior cerebral artery; and tPA, tissue-type plasminogen activator.

*Patient presented beyond therapeutic time window for IV tPA or IA tPA.
The median time to admission imaging was 1.6 hours in patients receiving pretreatment scans, which is early in the patient’s clinical course. The moderate agreement between ASL and DSC among individual readers indicates that ASL can be used reliably to determine reperfusion even when evaluated by a single reader. There was a substantial agreement after consensus between both imaging techniques in the 13 patients with mutually interpretable ASL and DSC scans, which could be the result of selecting patients with less ambiguous scan interpretability. Alternatively, the high level of agreement after consensus may indicate that increasing the individual readers’ practice with interpreting ASL images may yield a more uniform reperfusion interpretation among raters, resulting in reperfusion assessments that are more consistent with those of DSC.

After consensus, we encountered only a single discrepancy between ASL and DSC for detecting reperfusion. Although larger patient numbers would be needed to perform a thorough evaluation for sources of discrepancy, it is interesting that the measured volume of reperfusion in this patient was only 19%, a percentage of change thought to be borderline visually detectable by any technique. This is consistent with the common challenge in the visual detection of changes of defects, including reperfusion in patients with borderline quantitative changes. Regardless, the high degree of agreement of reperfusion reads between techniques after consensus underscores the use of ASL as an alternative to DSC for reperfusion evaluation, particularly in cases where gadolinium is contraindicated.

Our scanning protocol included ASL before DSC, eliminating degradation of the ASL signal by T1 shortening because of residual gadolinium from DSC in the same imaging scan. Interestingly, our ASL protocol also allowed us to identify 2 patients with hyperperfusion on 24-hour perfusion imaging—thought to represent hyperemia. Increased rCBF values and decreases in lesion size measured by ASL and DSC have been reported in patients after angiographically confirmed endovascular recanalization. However, with ASL, reliable quantification of rCBF in the infarction core and hypoperfused territories may be dependent on the chosen postlabeling delay. The dependence of ASL on postlabeling delay is thought to hinder identification of perfusion defects that are otherwise identifiable on DSC. However, the feasibility of using ASL with multiple inversion times and continuous monitoring of patient perfusion status opens the possibility not only to improve perfusion measurements, but also to determine the precise timing of reperfusion in patients with AIS.

Our study has a number of limitations. First, it is limited by a small sample size, with only 24 of the original 160 patients with admission MRI scans meeting the inclusion criteria. The majority of patients excluded (136) lacked imaging to be used
for reperfusion evaluation at either admission or follow-up. The remainder of excluded patients had perfusion imaging that was not interpretable for reperfusion. Reader 1 rated only 67% of the patients as having mutually interpretable ASL and DSC scans, whereas reader 2 rated only 62%. After consensus, only 13 patients were noted to have interpretable ASL and DSC perfusion scan sets. In a study population of 105 patients, our group found that the number of interpretable admission ASL scans produced was 97%, similar to that of DSC (96%). To be included in the analysis for comparison in the current study, patients were required to have 4 interpretable perfusion maps (admission scan and 24-hour scan for both ASL and DSC). Unfortunately, quality control data were not collected during the perfusion imaging to determine why the scans were uninterpretable. It is possible that a decay in neurological status might lead to excessive patient motion within the scanner, resulting in uninterpretable perfusion maps. Although median NIHSS at 24 hours after last known well was higher in patients with ≥1 uninterpretable scan, no significant difference could be detected between those patients and patients with mutually interpretable scans. For DSC perfusion imaging, it is possible for an experienced reader to determine the presence, location, and, potentially, relative size of a perfusion defect from the unprocessed gradient echo acquisition even in the presence of significant patient motion. Future studies might allow readers to view the unprocessed images to aid in identifying perfusion defects, in case the processed perfusion maps are unreadable because of motion. For ASL, methods for improving signal:noise ratio and for motion correction are areas of active research interest. It is interesting to note that in our study the number of interpretable ASL scan sets produced was comparable with the number of DSC sets produced, with 18 ASL and 17 DSC sets rated interpretable. This further supports comparability between techniques for reperfusion assessment.

Second, 10 of the 24 patients received their admission scan after tPA treatment at an outside hospital, indicating that partial reperfusion may have occurred in these 10 patients before admission perfusion imaging. However, all patients in this study had perfusion defects on admission DSC scan, and thus could still be read for the presence of reperfusion at 24 hours. Third, we did not derive lesion volume measurements from ASL scans. Delineation of lesion contours is challenging on ASL because the intrinsically low white matter signal can be difficult to distinguish from areas of ischemia. For this reason, we chose instead to derive our volume measurements by validated methods using MTT maps.

Finally, for assessing reperfusion by DSC the readers evaluated only MTT and TTP maps, where perfusion defects seem as hyperintensities in contrast to the hypointensity on ASL rCBF maps. At the time, MTT and TTP maps were routinely used for reperfusion evaluation at the study center. However, automated threshold methods using Tmax now exist for quantification of perfusion defects. Their reliability in reflecting clinical stroke severity, however, is not established. CBF maps derived from DSC images might have been used for comparison with ASL rCBF maps. However, because MTT and TTP maps were more routinely used clinically for evaluation of reperfusion, they were thought more suitable for use in visual determination of reperfusion.

In conclusion, we found moderate inter-rater agreement for ASL and for DSC among individual readers and strong agreement for detecting reperfusion after consensus reads. ASL represents a powerful imaging technique for assessing reperfusion in patients with confirmed AIS.

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Disclosures

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References


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