Arterial Spin-Labeling MRI Can Identify the Presence and Intensity of Collateral Perfusion in Patients With Moyamoya Disease

Greg Zaharchuk, PhD, MD; Huy M. Do, MD; Michael P. Marks, MD; Jarrett Rosenberg, PhD; Michael E. Moseley, PhD; Gary K. Steinberg, MD, PhD

Background and Purpose—Determining the presence and adequacy of collateral blood flow is important in cerebrovascular disease. Therefore, we explored whether a noninvasive imaging modality, arterial spin labeling (ASL) MRI, could be used to detect the presence and intensity of collateral flow using digital subtraction angiography (DSA) and stable xenon CT cerebral blood flow as gold standards for collaterals and cerebral blood flow, respectively.

Methods—ASL and DSA were obtained within 4 days of each other in 18 patients with Moyamoya disease. Two neurointerventionalists scored DSA images using a collateral grading scale in regions of interest corresponding to ASPECTS methodology. Two neuroradiologists similarly scored ASL images based on the presence of arterial transit artifact. Agreement of ASL and DSA consensus scores was determined, including kappa statistics. In 15 patients, additional quantitative xenon CT cerebral blood flow measurements were performed and compared with collateral grades.

Results—The agreement between ASL and DSA consensus readings was moderate to strong, with a weighted kappa value of 0.58 (95% confidence interval, 0.52–0.64), but there was better agreement between readers for ASL compared with DSA. Sensitivity and specificity for identifying collaterals with ASL were 0.83 (95% confidence interval, 0.77–0.88) and 0.82 (95% confidence interval, 0.76–0.87), respectively. Xenon CT cerebral blood flow increased with increasing DSA and ASL collateral grade (P<0.05).

Conclusions—ASL can noninvasively predict the presence and intensity of collateral flow in patients with Moyamoya disease using DSA as a gold standard. Further study of other cerebrovascular diseases, including acute ischemic stroke, is warranted. (Stroke. 2011;42:2485-2491.)

Key Words: angiography ■ arterial spin labeling ■ cerebral blood flow ■ cerebral hemodynamics ■ cerebrovascular disease ■ collateral flow ■ neuroradiology ■ perfusion

Moyamoya disease is characterized by progressive stenosis of the supraclinoid anterior circulation.1 By the time of diagnosis, these patients have extensively developed collateral vessels. Cerebral collateral flow is poorly understood despite its importance in maintaining the cerebral circulation during acute stroke and chronic hypoperfusion.2,3 In acute stroke, the presence of collaterals is associated with better outcomes after thrombolytics4–5 and appears to decrease the rate of hemorrhagic transformation.6 A commonly accepted method of judging the presence of collateral vessels is digital subtraction angiography (DSA), which is relatively time-consuming, invasive, and costly. DSA-based grading systems described in the literature are qualitative, relying on the visual inspection of contrast transit to an ischemic region.7–9 Other methodologies, including bolus contrast methods such as CT perfusion and MRI-based perfusion-weighted imaging, may permit evaluation of the adequacy of flow related to collaterals, although they do require the use of exogenous contrast agents. It would be helpful to have information about the collateral networks using a truly noninvasive, noncontrast tomographic approach.

Arterial spin-labeling (ASL) is a noncontrast MRI perfusion method whose greatest flaw is its exquisite sensitivity to arterial arrival delays.10–15 However, the bright intravascular signal known as arterial transit artifact (ATA) actually contains important information about late-arriving flow. However, this complicates the calculation of quantitative cerebral blood flow (CBF),16,17 which can be circumvented by the use of gold standard diffusible tracer methods such as stable xenon (Xe) CT.18,19 The goal of the current study was to test
whether ASL using a single postlabel delay (PLD) time could be used to reliably identify the presence of angiographic collaterals using DSA as a gold standard. Additionally, we sought to understand whether quantitative CBF measurements using stable Xe CT correlated with either DSA-based or ASL-based measures of collateral flow.

Materials and Methods
The study was approved by our institution’s Committee on Human Research. DSA and ASL imaging was performed in 18 patients with newly diagnosed Moyamoya disease (5 men, 13 women; mean age, 43 years; range, 19–65 years; 11 unilateral disease, 7 bilateral disease) as part of their preoperative assessment for possible superficial temporal artery to middle cerebral artery bypass. All patients were symptomatic, with the most common symptoms including transient ischemic attacks, small deep white matter infarcts, seizures, and headache. The DSA study was acquired within 4 days of the MRI study in all cases.

DSA was performed using a dedicated biplane cerebral angiographic system (Axiom Artis dBA Twin; Siemens Medical Systems). Images of bilateral internal and external carotid artery and at least 1 vertebral artery injection were acquired and stored. Imaging through the entire arterial and venous phases was performed to evaluate slowly flowing collateral vessels.

All MRI studies were performed at 1.5 T. In addition to the anatomic imaging, which is part of the clinical routine at our institution, we acquired pulsed continuous ASL using a repetition time of 5500 ms, echo time of 2.5 ms, labeling period of 1500 ms, and a PLD of 2000 ms, with a total acquisition time of 6 minutes. Readout was accomplished with a 3-dimensional background-suppressed fast spin-echo method, with in-plane and through-plane spatial resolution of 3 mm and 4 mm, respectively.

In 15 of these patients (83%), stable Xe CT CBF measurements were also performed. CT was performed using a GE Lightspeed 8 detector scanner integrated with a stable Xe enhancer system (Diversified Diagnostic Products). The Xe CT protocol imaged 4 contiguous 10-mm slices (80 kVp, 240 mA), with the lowest slice at the level of the basal ganglia. Eight sets of images were acquired at 45-second intervals. The first 2 time points were acquired during room air inhalation, whereas the remaining 6 time points were acquired during 28% Xe gas inhalation. End-tidal Xe concentration was assumed equal to arterial Xe concentration, a reasonable approximation except in patients with severe respiratory disease. CBF was calculated using the Kety autorigraphic method by the manufacturer’s commercial software, yielding CBF maps with a 1-mm nominal and 2 to 3 mm true in-plane spatial resolution. Rigid body rotation based on mutual information using SPMS (University College of London, available at www.fil.ion.ucl.ac.uk/spm/software/spm5) was used to coregister the ASL CBF images to the Xe CT images.

Two interventional neuroradiologists (M.P.M. and H.Y.D.) separately evaluated the DSA studies using a 4-point collateral grading scale describing the intensity of collateral flow.7 It incorporates specific comparison locations between regions identified on DSA and tomographic images based on 2 slices corresponding with the Alberta Stroke Programme Early Computed Tomography Score (ASPECTS) locations. This scale is as follows: 0, no collaterals visible (absence of any capillary blush); 1, mild to moderate collaterals; 2, robust collateral flow; and 3, normal antegrade flow. This grading was performed in 20 regions in each patient, as described in Figure 1. We chose to focus only on cortical regions because of the difficulties in visualizing capillary blush on DSA and signal on ASL imaging in the white matter. Disagreements were resolved by consensus. ASL images were evaluated by 2 additional neuroradiologists (G.Z. and N.J.F.) blinded to the DSA studies and grading results. These were scored in the same regions of interests using a similar 4-point scale (0, no or minimal ASL signal; 1, moderate ASL signal with ATA; 2, high ASL signal with ATA; and 3, normal perfusion without ATA). To improve the robustness of this score, several slices immediately above and below the precise ASPECTS slice were mentally summed to be more comparable with the DSA measurement.21 An example of the ASL collateral grading scale is shown in Figure 2. Disagreements were resolved by consensus.

Agreement, linear-weighted $\kappa$ values, Kendall $\tau$-b measure of correlation, and the exact Bowker test of symmetry (to determine any tendency for disagreements to be predominantly in 1 direction) were calculated for both the individual inter-reader scores and intermodality consensus scores. Also, the scores were dichotomized between 0 and 2 (collateral flow) and 3 (antegrade flow) and were compared using unweighted $\kappa$, the Kruskal-Goodman $\gamma$ measure of correlation, and the exact Bowker test of symmetry. The consensus DSA reading was considered the gold standard and, based on this, specificity, positive predictive value, and negative predictive value of ASL for identifying collateral flow were determined.

Quantitative Xe CT CBF was measured in the same regions-of-interest in which collaterals were assessed, using the two 10-mm slices most closely aligned with the ASPECTS system. After coregistering and reslicing the ASL CBF images to the same slice thickness and locations as the Xe CT slices (10-mm-thick), quantitative CBF values were also obtained in the same regions; the ASL measurements cannot be considered quantitative, considering the unknown effects of arterial arrival time, and are shown only for comparative purposes. The Jonckheere-Terpstra test was used to evaluate whether there was a trend for increasing CBF based on either the consensus DSA or the ASL collateral scores. All statistical analyses were performed with Stata Release 9.2.

Results
An example of a DSA image in the late venous phase and corresponding ASL images at the relevant levels in a patient with unilateral Moyamoya disease is shown as Figure 3. Note the clear depiction of arterial transit artifact on the ASL images in the right middle cerebral artery territory that also demonstrates delayed collateral flow on the DSA study. Although most cases showed good correlation, we present in
Figure 4 an example of a case in which there was a discrepancy between the DSA and ASL collateral scores in which an area was deemed to be fed by collaterals on ASL but was called normal antegrade flow on DSA. Interestingly, it was later deemed that this patient had early bilateral Moya-moya disease and underwent bilateral superficial temporal artery to middle cerebral artery bypass.

Overall, there was good agreement between the 2 readers for each modality as shown in the Table. It was more common for the ASL readers to agree regarding the exact
score as compared with the DSA readers (83% versus 65%, respectively). This is also reflected in a higher-weighted $\kappa$ for the ASL readers ($\kappa=0.79$; 95% CI, 0.74–0.84) compared with the DSA readers ($\kappa=0.52$; 95% CI, 0.47–0.56). Weighted $\kappa$ for the agreement between the consensus DSA and ASL scores was 0.58 (95% CI, 0.52–0.64). Using a dichotomized scale (ie, collateral flow [score, 0–2] versus normal flow [score 3]), the $\kappa$ value was even higher (0.65; 95% CI, 0.56–0.72), which can be considered as substantial agreement.22 Based on DSA consensus scores, 46% of the regions assessed where deemed to be fed by collaterals. For the consensus ASL and DSA collateral scores, sensitivity, specificity, positive predictive value, and negative predictive value were 0.83 (95% CI, 0.77–0.88), 0.82 (95% CI, 0.76–0.87), 0.80 (95% CI, 0.73–0.86), and 0.85 (95% CI, 0.79–0.90), respectively. The nonsignificant exact Bowker test ($P=0.45$) indicated that was no tendency toward false-positive results over false-negative results. Supplemental Table I (http://stroke.ahajournals.org) shows the breakdown of the various collateral scores using the entire 4-point scale.

Figure 5 shows the results of the Xe CT and ASL CBF measurements as a function of either increasing DSA or increasing ASL collateral scores. The Xe CT CBF measurements increase with increasing collateral score, regardless of the method used, but the trend is more pronounced for the ASL collateral score compared with the DSA collateral score (ASL collateral score: $J^*=8.00$; for DSA collateral score: $J^*=6.16$; Supplemental Table II). ASL CBF shows that the regions with robust collaterals (score $\geq 2$) had higher apparent CBF than those with anterograde perfusion (score $=3$). This is likely attributable to artifacts associated with delayed arterial arrival and high ASL signal in the feeding arteries that perfuse more distal tissue.

### Table. Inter-Reader and Intermodality Agreement of Collateral Scores

<table>
<thead>
<tr>
<th></th>
<th>Full 4-Point Score</th>
<th>Weighted $\kappa$</th>
<th>95% CI</th>
<th>Kendall $\tau$-b</th>
<th>Symmetry Test $P$</th>
<th>DSAc vs DSA2 reflects that the average scores for reader 1 were higher than those of reader 2.</th>
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<tbody>
<tr>
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<td>DSA1 vs DSA2 0.52 0.47–0.56 0.78 &lt;0.0001 DSA1&gt;DSA2</td>
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<td>ASL1 vs ASL2 0.79 0.74–0.84 0.85 &lt;0.0001 ASL2&gt;ALSL</td>
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<td>ASLc vs DSAc 0.58 0.52–0.64 0.67 0.0013 DSAc&gt;ASLc</td>
</tr>
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</table>

### Dichotomized Scores (Collateral vs Antegrade Perfusion)

<table>
<thead>
<tr>
<th></th>
<th>$\kappa$</th>
<th>95% CI</th>
<th>Kruskal $\gamma$</th>
<th>Symmetry Test $P$</th>
<th>DSAc vs DSA2 reflects that the average scores for reader 1 were higher than those of reader 2.</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
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<td>DSA1 vs DSA2 0.86 0.80–0.91 0.99 0.009 DSA1&gt;DSA2</td>
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<td>ASLc vs DSAc 0.65 0.56–0.72 0.91 0.450</td>
</tr>
</tbody>
</table>

ASA indicates arterial spin-labeling; CI, confidence interval; DSA, digital subtraction angiography.

DSA1: DSA scored by reader 1.

DSA2: DSA scored by reader 2.

DSAc: DSA score based on consensus read of readers 1 and 2.

ASL1: ASL scored by reader 1.

ASL2: ASL scored by reader 2.

ASLc: ASL score based on consensus read of readers 1 and 2.

Figure 5 shows the results of the Xe CT and ASL CBF measurements as a function of either increasing DSA or increasing ASL collateral scores. The Xe CT CBF measurements increase with increasing collateral score, regardless of the method used, but the trend is more pronounced for the ASL collateral score compared with the DSA collateral score (ASL collateral score: $J^*=8.00$; for DSA collateral score: $J^*=6.16$; Supplemental Table II). ASL CBF shows that the regions with robust collaterals (score $\geq 2$) had higher apparent CBF than those with anterograde perfusion (score $=3$). This is likely attributable to artifacts associated with delayed arterial arrival and high ASL signal in the feeding arteries that perfuse more distal tissue.

![Figure 5. Mixed-cortical cerebral blood flow (CBF) measured with a gold standard method (xenon CT [Xe CT]) and arterial spin-labeling (ASL) in the same regions assessed for collaterals, as a function of either (A) digital subtraction angiography (DSA)-based consensus collateral score or (B) ASL-based consensus collateral score. Xe CT CBF increased with both DSA-based and ASL-based collateral scores, but the trend was more pronounced for the ASL-based collateral score. Data shown are from the 15 patients who had both Xe CT and ASL performed. The number of regions in which the measurements were made is shown under the data points. Error bars represent standard deviation of the respective method. These are shown only on the upper half of the Xe CT and the lower half of the ASL data for clarity. No significant difference between the CBF measurement types for any of the collateral scores was present.](http://stroke.ahajournals.org)
Discussion

Collateral blood flow plays a critical role in supporting the cerebral circulation in the setting of acute and chronic cerebral ischemia.\(^3,23,24\) In response to a decrease in local perfusion pressure, there is recruitment of flow from both circle of Willis and leptomeningeal anastomoses, which compensate for the lack of antegrade flow.\(^3\) Patients with the same vascular occlusion may have significantly different outcomes based on their ability to recruit collateral pathways to restore flow to the ischemic region during the minutes and hours after an acute event.\(^25,26\) The eventual failure of collateral pathways is thought to lead to infarct growth and is ultimately responsible for the decreasing efficacy of stroke therapy with time.\(^27\) Timely knowledge about the status of collaterals affects the decision-making process regarding acute therapy in individual patients with ischemic stroke.\(^23,27\) For example, Kucinski et al\(^25\) demonstrated that the best predictor of favorable outcome in the retrospective series of patients undergoing intra-arterial thrombolysis was the presence of good collateral flow as judged by the initial DSA study. For all these reasons, having the ability to assess the location and amount of collateral perfusion using a noninvasive test such as MRI would be desirable.

Given its sensitivity to arrival time and its ability to quantify CBF, ASL combines features of both angiography and perfusion. Previous studies have shown good correlation with gold standard CBF imaging of gray matter in healthy subjects,\(^28\) but it is likely that it underestimates CBF in regions with delayed arterial arrival times. This is because the label decays with the blood T1, which is on the same order as known long arterial arrival delays. This likely explains why the ASL CBF measurements are highest in regions rated to have robust collaterals (score \(= 2\)). Also, patients with chronic hyperperfusion and ATA had poor cerebrovascular reserve in response to acetazolamide.\(^11\) ATA is dependent on several sequence parameters, particularly the labeling time and the PLD. Only a single PLD was used in this study; ASL sequences with a range of PLD times exist and can be helpful for quantifying CBF\(^32-34\) but require longer imaging times for equivalent signal-to-noise ratio. There is some evidence that choosing a single PLD in a range that is highly sensitive to delay can increase the sensitivity for identifying pathology.\(^12,35\)

This study shows that an ASL sequence with a single moderately long PLD can identify regions with collateral flow and can differentiate between poor and robust collateral flow, as determined using a DSA-based collateral grading scale. In particular, the agreement between consensus ASL and DSA scores for the distinction of normal perfusion versus collateral flow was quite good. Also, there was no evidence of a systematic bias in the ASL scoring compared with the consensus DSA. These findings are consistent with a previous study\(^36\) that used a high-field (3-T) multiple PLD ASL method that also used perfusion territory imaging, an ASL method that can separate flow contributions from different cerebral arteries. These investigators examined a population of patients with a variety of cerebrovascular disease, some of whom had Moyamoya disease, and found a \(\kappa\) value of 0.72 for distinguishing collateral from antegrade perfusion, similar to that in the current study (\(\kappa\)=0.65). In addition to validating these general results, the current study also examines how well different readers agree on both the DSA and ASL grading scales, showing that agreement is higher with the ASL method. Furthermore, we suggest that high-field imaging, perfusion territory imaging, and multiple PLD ASL imaging are not required to identify collateral flow with a similar degree of accuracy. This is important because these modifications to the ASL experiment required additional imaging time (10 minutes for the ASL and 4 minutes for the 3-dimensional time-of-flight angiogram that is required to plan the ASL sequence). The current study demonstrates good performance using a faster ASL imaging protocol (6 minutes), making it more feasible in the clinical setting.

We also undertook understanding the relationship between collateral scores and CBF. Previous reports have suggested that identification of collaterals on DSA was not a good predictor of the adequacy of cerebral perfusion based on oxygen extraction fraction measurements using positron emission tomography.\(^37,38\) Our findings show that gold standard Xe CT-based CBF increases as collateral score increases for both DSA-based and ASL-based consensus collateral scores. This effect was more pronounced with the ASL-based scores than the DSA-based scores (Supplemental Table II). Interestingly, the highest correlation was for Xe CT CBF based on ASL collateral score. ASL CBF also increased with increasing collateral score but is unreliable in the presence of known long arterial arrival delays. This likely explains why the ASL CBF measurements are highest in regions rated to have robust collaterals (score \(= 2\)), because this flow is destined for more distal slices. Bolus perfusion-weighted imaging, using either CT or MRI, also can be used to estimate CBF, cerebral blood volume, mean transit time, and normalized bolus arrival time and could be used for this application. However, it is challenging to acquire quantitative CBF measurements using such nondiffusible intravascular tracers, particularly in patients with Moyamoya disease.\(^29,39\) Delay-corrected algorithms\(^40\) may mitigate problems associated with pure delays, but not with dispersion.\(^41\) We performed perfusion-weighted imaging measurements in a subset of these patients, but we do not present these data because the acquisition parameters were not standardized, and the imaging planes did not completely cover the regions of interest interrogated in the remainder of the study. To our knowledge, few methods using bolus perfusion-weighted imaging to distinguish normal from collateral flow have been reported,\(^42\) and we hope to explore this more thoroughly in a prospectively recruited study. This ASL method may be particularly amenable for use in patients who cannot receive gadolinium-containing contrast agents or who may need multiple studies (either in a single or consecutive sessions) to assess either cerebrovascular reserve or effects of treatment.

The limitations of this study include the difficulties of applying the DSA collateral grading system,\(^2\) initially developed for acute ischemic stroke as part of the PROACT 2
study, to a chronic cerebrovascular disease such as Moyamoya disease. Also, perfusion territory imaging using vessel-selective ASL was not used,6,43,44 which may further help identify regions fed via collateral pathways. Such a method would allow one to distinguish slow antegrade flow attributable to a high-grade stenosis from leptomeningeal or other retrograde-type collateral flow, which was not possible with the current study. Historically, such methods have required additional scan time, but newer techniques have been described that achieve vessel selectivity without the scan time penalties.45 It is probable that such methods would prove even more accurate. Also, we do not report quantitative CBF using the ASL method. Given the long arterial arrival delays in Moyamoya patients,29 it is likely that some degree of CBF underestimation occurs in the regions perfused by collaterals. Finally, we recognize that the use of a consensus reading from 2 separate readers for each modality allows only a limited evaluation of the variability related to multiple readers, which is reported in the Table.

Conclusions
This study shows that ASL can noninvasively evaluate the presence and intensity of collateral flow in patients with Moyamoya disease when compared to DSA. Further study of other cerebrovascular diseases, including acute ischemic stroke, is warranted.

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Disclosures
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References


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### Supplemental Table 1: Comparison of Consensus DSA and ASL Collateral Scores

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### Supplemental Table 2: CBF Trend with Collateral Score

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<th>CBF Method</th>
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<td>xeCT CBF</td>
<td>ASL CBF</td>
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<tr>
<td></td>
<td>J* / p</td>
<td>J* / p</td>
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<td>ASL</td>
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<td>3.81/0.0001</td>
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J* = Jonckheere-Terpstra statistic
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