Territorial Arterial Spin Labeling in the Assessment of Collateral Circulation
Comparison With Digital Subtraction Angiography

Soke Miang Chng, MD; Esben Thade Petersen, MSc; Ivan Zimine, PhD; Yih-Yian Sitoh, MD; C.C. Tchoyoson Lim, MD; Xavier Golay, PhD

Background and Purpose—Collateral circulation plays a vital role in patients with steno-occlusive disease, in particular for predicting stroke outcome. Digital subtraction angiography (DSA) is the gold standard for the assessment of collateral circulation, despite its invasive nature. Recently, the development of a new class of arterial spin labeling (ASL) methods allowed independent measurement of territorial flow information without the need for contrast media injection. Here, we compared combined territorial ASL (TASL) and MR angiography (MRA) against DSA in the assessment of collateral circulation.

Methods—Eighteen patients presenting with extra- or intracranial arterial steno-occlusive disease were recruited. All DSA studies were performed using a biplane angiography unit. MR imaging consisted of time-of-flight MRA and TASL, performed at 3T. Collateral circulation on both modalities was evaluated in consensus in a double-blinded manner by 3 neuroradiologists.

Results—Good agreement was found between DSA and TASL in the assessment of collateral flow: Cramer coefficient, V = 0.53 (P < 0.0001) and Contingency coefficient, C = 0.67, with kappa = 0.70 and kappa = 0.72 in the assessment of flow and collaterals, respectively. TASL and DSA successfully evaluated 89% and 98% of the vessels, respectfully. Failure was linked to motion-related artifacts in TASL, and highly tortuous vessels in DSA. Generally, combined MRA–TASL was comparable to DSA in diagnostic quality.

Conclusions—TASL provided radiological information comparable to DSA on collateral flow, with the advantage that it could be performed during routine MRI studies. TASL may provide insight on collateral perfusion in patients who may not otherwise be candidates for DSA, and may potentially replace it. (Stroke. 2008;39:3248-3254.)

Key Words: magnetic resonance imaging ■ arterial spin labeling ■ territorial ASL ■ digital subtraction angiography ■ atherosclerosis ■ cerebrovascular accident ■ collateral circulation

In patients with cerebrovascular steno-occlusive disease, the presence of collateral circulation is essential to maintain cerebral perfusion, metabolism, and function. Many studies have shown the importance of an adequate hemodynamic compensation via collaterals in patients with cerebral arterial stenosis, and correlated collateral flow with infarct volume in predicting stroke outcome.1–4 Intraarterial digital subtraction angiography (DSA) is considered the gold standard in the assessment of collateral circulation by the direct visualization of collateral vessels. This has so far been the only modality giving both temporal as well as spatial cerebral blood circulation information. The procedure, however, is invasive and entails certain perioperative risks. Although the overall procedural complication rate is less than 1% when performed by experienced operators,5 the procedure also requires the use of ionizing radiation as well as the injection of iodinated contrast media (with the attendant risks of allergic and other adverse reactions). Technical difficulties may also arise in patients with highly tortuous vessels that may prevent access with the angiography catheter.

In the past decade, magnetic resonance angiography (MRA) has made rapid technological advances in the non-invasive visualization of cerebral blood vessels, without the need for injection of intravenous contrast media. The main problem of MRA is that it does not provide any information on the timing of vessel filling, which can be particularly important in the assessment of collateral flow. This gap can be filled by a recently-developed series of arterial spin labeling (ASL) sequences, based on the rapid acquisition of multiple volumes after a single labeling pulse.6–8 ASL is a

Received March 28, 2008; final revision received May 6, 2008; accepted May 20, 2008.
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Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.108.520593

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Materials and Methods

Subjects

The ethics committee of our institution approved the study protocol, and written informed consent was obtained from all patients. A total of 18 patients (9 men and 9 women, age range of 21 to 85, median age of 59.5 years) presenting with extra or intracranial arterial stenosis or occlusion, and with prior DSA studies, were recruited over a period of 2 years from 2004 to 2006. All patients, except 1 Indian male, were of Chinese origin. Of the 18 patients, 11 presented with unilateral internal carotid artery (ICA) stenoses or occlusions, 3 with bilateral ICA stenoses or occlusions, 3 with Moya Moya disease of which 1 had left ICA occlusion, and finally 1 patient had multiple intracranial stenoses. All patients had symptoms related to the territory supplied by the diseased vessel(s), of which 13 had infarcts confirmed on MRI, whereas 5 patients had transient ischemic attacks (TIA) only with no infarct seen on imaging.

Digital Subtraction Angiography

All DSA studies were performed using a biplane angiography unit (Advantx, GE Medical Systems). Both the carotid and vertebrobasilar systems were studied at the level of the neck and intracranially. Each vessel angiogram was obtained in 2 projections (frontal and lateral projections), using similar contrast volume and injection rate. The majority of the patients had both DSA and TASL performed within the same month (13 of 18 patients). The maximum time between the 2 studies was 4 months (3 of 18 patients).

MR Angiography and TASL

All MRI studies were performed on a 3.0 T Philips Achieva System (Philips Medical Systems). Images were acquired using the quadrature body coil for transmission and an 8-element phased-array head coil for MR signal reception. The scan protocol for each patient, including conventional MR localizer and SENSE reference scan, consisted of a time-of-flight (TOF) MRA followed by TASL scans for consecutive labeling of the three vascular territories of the left-and right-ICA as well as the posterior circulation. For ASL perfusion MRI we used the recently developed QUASAR pulse sequence (QUAntitative STAR labeling of Arterial Regions). This sequence is capable of acquiring images at multiple inversion times after labeling at a high temporal resolution and therefore provides dynamic information about the bolus and its arrival to the tissue. The readout is performed using a conventional multi-slice single-shot gradient echo-planar imaging with a small flip angle. This resulted in the following scan parameters for the QUASAR TASL pulse sequence: 6 to 9 slices; thickness = 8 mm; gap = 2 mm; matrix = 64 × 64; FOV = 240 mm; α = 35°; TR/TE = 4000/23 ms; T1/ΔT1 = 100/300 ms; time points = 12; SENSE = 3; 50 averages; scan time: 3:20 minutes per perfusion territory. The planning of the labeling volume for the vascular territories was performed according to Hendrikse et al on the basis of the MIPs and native data from the TOF-MRA covering an area spanning from the carotid bifurcation to the circle of Willis (Figure 1). The size of the oblique labeling slab can be adjusted in one direction and is infinite in the other two directions. Labeling slabs covering the ICAs were planned on basis of the axial and coronal MIPs and aligned such that each ICA was labeled independently. Signal contribution from the contralateral ICA, as well as the basilar and vertebral arteries, was avoided by appropriate angulations. The posterior circulation was planned using both axial and sagittal MIPs of the circle of Willis. The planning for all territories was verified on the native TOF images to minimize the amount of contamination attributable to mislabeling of adjacent vessels, although it was not always completely avoidable. The scan parameters for the TOF-MRA were: 180 slices, thickness = 2 mm (reconstructed 1.0 mm); matrix = 400 × 253; FOV = 200 × 180 × 190 mm; α = 20°; TR/TE = 18/3.4 ms; SENSE = 3; scan time: 3:45 minutes.

ASL Postprocessing

All images were exported on a Windows PC running IDL 6.1 (Research Systems Inc.). The labeled and nonlabeled ASL images were first subtracted to produce ΔM images, one for each of the individual territories. These images were subsequently combined into a red-green-blue (RGB) frame to demonstrate the spatial distribution of the three perfusion territories. The left ICA territory is visualized in green, the right ICA territory in red, and the posterior circulation in blue (Figure 1b). Areas demonstrating mixing of perfusion from more than one vessel will show a combined color, eg, perfusion contributed by both ICAs may be visualized as yellow (= red + green). The color ΔM images from the multiple inversion time points were then saved as a movie file to visualize the dynamic aspects of the bolus, such as time of arrival and the duration of the bolus, which can differ between regions attributable to, for example, collateral perfusion.
Collateral flow assessment and DSA-TASL comparison

Collateral flow assessment on both DSA and MRI were evaluated using a grading system similar to Kim et al.\textsuperscript{15} at 13 anatomic sites based on regional vascular territories (Figure 2). These 13 sites included 10 segments of the main intracranial arteries (A1–2; M1–6; P1,2) as well as 3 perforator territories (insula, basal ganglia and corona radiata). Flow was graded using a scale from 0 to 3: 0=no visible collaterals to the ischemic site; 1=collaterals to the periphery of the ischemic site; 2=complete irrigation of the ischemic bed via collateral flow; and 3=normal antegrade flow. Each study was also separately graded for the presence or absence of Willisian and pial collaterals. The DSA data were graded on both anterior and posterior views for each of the two internal carotids and vertebral artery angiograms. As shown in Figure 2c and 2d, collateral flow was evaluated for TASL on the basis of the Alberta Stroke Programme Early CT Score (ASPECTS) system,\textsuperscript{15} in which the presence of flow was assessed in the corresponding marked anatomic locations on the TASL-MR images. All DSA and TASL data sets were evaluated in consensus in a double-blinded manner by 3 neuroradiologists (S.M.C., Y.Y.S., T.C.C.L.), and the corresponding measurements were tabulated for further statistical analysis.

Statistical analysis

Statistical analysis on the diagnostic information of TASL compared with DSA was performed using various contingency tests, as a simple correlation analysis is often not good enough to assess the equivalence of two measurement methods. In particular, both contingency (C) and Cramer’s (V) coefficients were calculated from a $\chi^2$ statistics. Corresponding estimated probability values were derived from the $\chi^2$ analysis. These statistical analyses were performed using the Statview\textsuperscript{TM} version 5.0.1 (SAS Institute Inc). In addition, Fleiss’ kappa coefficient was also calculated as a measure of agreement between both methods\textsuperscript{16} using Microsoft Excel.

Results

The DSA studies on all 18 patients were of adequate diagnostic quality, whereas one examination of the 18 TASL studies was nondiagnostic because of heavy motion artifacts. Part of the TASL data in another 2 patients was excluded, also because of motion artifacts. Finally, motion in 1 patient resulted in mislabeling of one perfusion territory, but could still be evaluated for collateral perfusion. Conversely, in 1 of the DSA studies, the vertebrobasilar system could not be evaluated because of problems with accessing the highly tortuous vessels. This gave a total of 316 anatomic sites that were assessed for flow (Table 1). The presence of Willisian and pial collaterals were assessed on 126 sites (Table 2).

Tables 1 and 2 show the contingency tables for the categorical variables used for the assessment of collateral perfusion and presence or absence of collateral flow, respectively. A significant contingency was found between DSA and TASL (Contingency coefficient, C=0.67; Cramer coefficient, V=0.53, estimated $P<0.0001$). This contingency remained unchanged after separation between proximal and distal perfusion sites (C=0.67, V=0.52, est. $P<0.0001$ and $P<0.0001$ respectively).

Table 1. Contingency Table Representing the Categorical Variable Grading Flow in All 13 Segments Described in Figure 2

<table>
<thead>
<tr>
<th>DSA</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>TASL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>10</td>
<td>2</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>12</td>
<td>36</td>
<td>12</td>
<td>61</td>
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<tr>
<td>3</td>
<td>5</td>
<td>5</td>
<td>12</td>
<td>183</td>
<td>205</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>53</td>
<td>58</td>
<td>197</td>
<td>316</td>
</tr>
</tbody>
</table>

0, no visible collaterals to the ischemic site; 1, collaterals to the periphery of the ischemic site; 2, complete irrigation of the ischemic bed via collateral flow; and 3, normal antegrade flow.
C=0.70, V=0.56, est. P<0.0001, respectively), and when considering gray matter territories alone, excluding the perforators territories (C=0.67, V=0.53, est. P<0.0001). Furthermore, Cramer's coefficient was V=0.58 for the presence of collaterals (est. P<0.0001). Finally, a weighted kappa 0.70 was found for the presence of flow and kappa=0.72 for the presence of collaterals, both of which can be considered as "substantial agreement" after Landis and Koch.17

One case example was a patient who presented with right ICA occlusion (Figure 3). The DSA study showed complete occlusion of the right ICA (Figure 3d). Collateral flow to the right anterior cerebral artery (ACA) territory was supplied by the contralateral ICA via the anterior communicating artery (ACommA; Figure 3e), whereas collateral flow to the right middle cerebral artery (MCA) territory was derived mainly from the posterior circulation via the right posterior communicating artery (PCommA; Figure 3f). The TOF MRA of the patient showed corresponding anatomic information on the collateral flow pattern at the level of the circle of Willis (Figure 3c), whereas the TASL data of the patient showed corresponding territorial perfusion pattern (Figure 3a and 3b).

Table 2. Contingency Table Representing the Categorical Variable Assessing the Presence (1) of or Absence (0) of Willisian and Pial Collaterals

<table>
<thead>
<tr>
<th></th>
<th>DSA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>TASL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>40</td>
<td>6</td>
</tr>
<tr>
<td>1</td>
<td>11</td>
<td>69</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
<td>75</td>
</tr>
</tbody>
</table>

Figure 3. Patient with right ICA occlusion. a and b, TASL of the patient with posterior circulation coded in blue, left ICA in green and right ICA in red, showing collateral flow to the right ACA and right MCA territories from the left ICA and posterior circulation, respectively. c, TOF MRA of the same patient gave corresponding anatomic information on the collateral flow pattern. This correlated with the patient’s DSA study in (d) right common carotid angiogram frontal projection which showed occluded right ICA. (e) left ICA angiogram frontal projection showed collateral flow to the right ACA territory via the ACommA, and (f) left vertebral artery collateral flow to the right MCA territory via the PCommA.
Another example was a patient with Moya Moya disease presenting with distal left ICA occlusion (Figure 4). The DSA study showed occlusion of the left ICA distal to the origin of the left PCommA (Figure 4a). Because of congenital hypoplasia/absence of the ipsilateral P1 segment (Figure 4e), the left PCommA provided supply to the left posterior cerebral artery (PCA) territory. Collateral flow to the left MCA territory was, in turn, seen to arise from the left PCA branches via pial anastomoses (Figure 4a). The TASL images of the patient showed this perfusion pattern remarkably, with flow from the proximal left ICA (labeled green), supplying first the left PCA territory via the dominant PCommA in the images acquired at an early time after labeling (Figure 4b), followed by perfusion of part of the left MCA territory (also labeled green) in the images acquired at a later stage (Figure 4c). The TASL images at different time points demonstrated not only the territorial perfusion flow pattern in this patient, but also the temporal information of the collateral flow to the left MCA territory arriving later. In addition, this patient also had stenosis of the right MCA M1 segment (Figure 4d), with the left vertebral angiogram showing some collateral flow to the distal right MCA territory from the right PCA branches via pial anastomoses (Figure 4e). The TASL images showed corresponding flow in the right MCA/PCA watershed territory appearing slightly purple (Figure 4c), possibly representing mixing of collateral flow arising from the PCA (encoded blue) with right MCA antegrade flow (encoded red).

Discussion
Our results show significant agreement between the information obtained from a combined reading from TASL and MRA versus DSA methods for evaluation of collateral perfusion in steno-occlusive diseased patients. Indeed, the $\chi^2$ analysis performed here provides very good confidence in rejecting the hypothesis of independence of both measurement methods ($P<0.0001$). Kappa values of 0.70 and 0.72 for the presence of flow and collateral perfusion, respectively, can both be considered as “substantial agreement” between the two modalities.\textsuperscript{17}

The general diagnostic quality of TASL combined with MRA was good compared with DSA as seen in the example cases of Figures 3 and 4. In both illustrative cases, the combined TASL/MRA study was able to clearly demonstrate normal anatomy, anatomic variants, as well as collateral circulation at the level of the circle of Willis. In the second case in Figure 4, TASL/MRA was even able to demonstrate more complex territorial perfusion pattern related to disease in the presence of variant anatomy.

In the past decade, there have been rapid advances in MRA techniques allowing noninvasive visualization of the cerebral vessels, without the need for intravenous injection of contrast agents.\textsuperscript{18} In particular, the advent of higher field strength scanners in clinical practice has allowed significant improvements in MRA image resolution,\textsuperscript{19} whereas the introduction of parallel imaging techniques has facilitated its clinical application by reducing the scan time required.\textsuperscript{20} As shown in our first case example in Figure 3c, the image resolution of the MRA gave clear anatomic information compared to DSA. Of course, because these noncontrast MRA techniques use either the inflow of prepared blood or the velocity of the blood for image generation, an inherent important limitation of these techniques is the exaggeration of a stenosis due to...
slow flow in the region. The other limitation of MRA is the lack of dynamic and functional information, which is crucial in the assessment of cerebral perfusion in cerebrovascular steno-occlusive disease. However, as has been demonstrated in this study, combining MRA with cerebral perfusion imaging such as multi-time point TASL overcomes this limitation.

Current clinical cerebral perfusion methods, including single photon emission computed tomography and bolus tracking perfusion computed tomography and MRI, require intravenous injection of either radioactive tracers or contrast agents. In contrast, the development of ASL has enabled the measurement of cerebral blood flow without the need for intravenous contrast media. With vessel-selective approaches, it is possible to obtain spatial and dynamic information similar to DSA. Another advantage of ASL includes the possibility of obtaining quantitative perfusion images along with exact anatomic location. The noninvasiveness of the technique also means that it may be repeated without the risk of adverse effects, which is useful in the longitudinal monitoring of disease progression or of patients after vascular by-pass surgery.

Compared to DSA, limitations of ASL include its high sensitivity to motion during the scan. This is related to the intrinsic low signal-to-noise ratio of the modality, and because TASL relies on the subtraction of labeled and non-labeled images. This is a problem particularly in seriously ill patients, which we encountered in 3 of the patients in our study. Motion artifacts in TASL present the additional problem of potential mislabeling of the vessels if the patient moves after the TASL scan has been planned. In one of the study cases, we found that this gave rise to erroneous mixing of colors on the TASL images (data not shown). On the other hand, although the posterior circulation in one of the patients could not be assessed on DSA because of technical difficulty with cannulating the vessels, this information was available on TASL, highlighting one of the advantages of this imaging modality over DSA.

In our study, the labeling of each flow territory was performed sequentially, which is slow and may increase motion artifacts in between territories. This could be a problem in acute stroke patients. A solution to this difficulty would be to plan all 3 territories at the same time and acquire the data in an interleaved fashion. This is being worked on in our laboratory. Furthermore, techniques such as dual-vessel labeling and Hadamard-like encoding schemes may be useful to reduce the sensitivity of TASL to motion. Further development and clinical validation of such techniques will enhance the clinical utility of TASL, particularly in the assessment of patients in the acute setting.

Another disadvantage of ASL is the rather short duration of the bolus and the low signal-to-noise ratio associated with this technique. The bolus is generated by the inversion of blood water and it decays with the T1 relaxation of blood. Loss of this bolus or labeling signal also occurs as a result of exchange of blood water at the tissue level. Despite substantial improvements in signal-to-noise ratio and lengthening of T1 of blood at higher field strength, at 3 Tesla, the T1 of blood is still only 1.6 to 1.7s. Our study did not show any statistically significant difference in the diagnostic quality of TASL compared to DSA after separating for proximal and distal perfusion sites. However, the short duration of the bolus does mean that regions with long transit delays from the labeling region to the tissue of interest may appear dark, giving the false impression of no perfusion to the region. In 4 patients with delayed antegrade flow, apparent territorial perfusion defects demonstrated an ASL signal only in the later images. This emphasizes the importance of obtaining the TASL data at different time points, to demonstrate the arrival of delayed bolus, either attributable to delayed antegrade flow or slower arrival of the bolus via collaterals. Even then, with the loss of labeling signal in TASL, the potential failure to detect severely delayed antegrade or collateral flow remains a problem.

In ASL, the labeled arterial blood flow is exchanged at the level of the capillaries, which allows measurement of quantitative cerebral blood flow (CBF). However, it also means that none or very little of the bolus will reach the venous side of the cerebral circulation, because typical mean transit times (MTT) in the brain will be in the order of minutes for freely diffusible tracers. In contrast, DSA can evaluate all phases of the bolus passage including the arterial, capillary, and venous phase. The venous phase is important in DSA as the time it takes for the injected contrast to appear in the veins gives an idea of the intravascular transit time (different from MTT). Anatomic variants or abnormalities on the venous side may also be detected in the same study on DSA.

Although the information given by combined TASL/MRA was comparable to DSA in our study cohort, we note that most of the cases recruited in our study had proximal large vessel severe stenosis or occlusion rather than intracranial multi-vessel disease. In the patient with multiple intracranial stenoses attributable to Moya Moya disease (Figure 4), we found interpretation of the TASL data more difficult compared to the cases of single large vessel proximal stenosis or occlusion. We felt this was related to the more complex mixing of antegrade and collateral flow at multiple locations in this patient.

Overall, in this study, the success rate for TASL/MRA and DSA were 89% and 98%, respectively. These results suggest that combined MRI-based methods can be an alternative and completely noninvasive way to evaluate collateral perfusion in patients with cerebrovascular steno-occlusive disease. The perioperative risks associated with DSA, as well as the potential long term adverse effects of ionizing radiation, can be eliminated. In addition, a proportion of patients with cerebrovascular atherosclerotic disease will often have comitant conditions such as hypertension or renal artery stenosis, which contribute to the impairment of renal function. Compared with DSA, the fact that TASL/MRA does not require the injection of any contrast media is particularly important in this patient population. Finally, these techniques can easily be added to any MR neuroimaging protocol, to study the collateral flow even in patients otherwise not scheduled for a diagnostic DSA.

Conclusion
The results of our pilot study suggest that TASL provides comparable information on collateral flow as DSA. MRA and
TASL do not involve ionizing radiation or the injection of exogenous contrast media, and may be combined with other conventional MR imaging in the same examination. The possibilities of combining these techniques may greatly enhance our understanding of collateral circulation and potentially supplement or replace DSA in the clinical assessment of patients with cerebrovascular disease.

Acknowledgments
We acknowledge the very good support from our team of technologists and in particular our chief technologist Violet Chua.

Sources of Funding
This work was supported in parts by the following grants from the National Medical Research Council of Singapore # NMRC/0919/2004, NMRC/0855/2004 and the National Healthcare Group Cluster Research Fund # NHGA-RPR/04012.

Disclosures
Drs Y.-Y. Sitoh, T.C.C. Lim, and X. Golay are on the speaker’s bureau of Philips Medical Systems. Dr Ivan Zimine is currently working for Philips Medical Systems (Japan) as a Clinical Scientist.

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Stroke. 2008;39:3248-3254; originally published online October 9, 2008; doi: 10.1161/STROKEAHA.108.520593

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

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