Magnetic Resonance Perfusion Imaging in Acute Ischemic Stroke Using Continuous Arterial Spin Labeling

Julio A. Chalela, MD; David C. Alsop, PhD; Julio B. Gonzalez-Atavales, PhD; Joseph A. Maldjian, MD; Scott E. Kasner, MD; John A. Detre, MD

Background and Purpose—Continuous arterial spin-labeled perfusion MRI (CASL-PI) uses electromagnetically labeled arterial blood water as a diffusible tracer to noninvasively measure cerebral blood flow (CBF). We hypothesized that CASL-PI could detect perfusion deficits and perfusion/diffusion mismatches and predict outcome in acute ischemic stroke.

Methods—We studied 15 patients with acute ischemic stroke within 24 hours of symptom onset. With the use of a 6-minute imaging protocol, CASL-PI was measured at 1.5 T in 8-mm contiguous supratentorial slices with a 3.75-mm in-plane resolution. Diffusion-weighted images were also obtained. Visual inspection for perfusion deficits, perfusion/diffusion mismatches, and effects of delayed arterial transit was performed. CBF in predetermined vascular territories was quantified by transformation into Talairach space. Regional CBF values were correlated with National Institutes of Health Stroke Scale (NIHSS) score on admission and Rankin Scale (RS) score at 30 days.

Results—Interpretable CASL-PI images were obtained in all patients. Perfusion deficits were consistent with symptoms and/or diffusion-weighted imaging abnormalities. Eleven patients had hypoperfusion, 3 had normal perfusion, and 1 had relative hyperperfusion. Perfusion/diffusion mismatches were present in 8 patients. Delayed arterial transit effect was present in 7 patients; serial imaging in 2 of them showed that the delayed arterial transit area did not succumb to infarction. CBF in the affected hemisphere correlated with NIHSS and RS scores ($P=0.037$ and $P=0.003$, Spearman rank correlation). The interhemispheric percent difference in middle cerebral artery CBF correlated with NIHSS and RS scores ($P=0.007$ and $P=0.0002$, respectively).

Conclusions—CASL-PI provides rapid noninvasive multislice imaging in acute ischemic stroke. It depicts perfusion deficits and perfusion/diffusion mismatches and quantifies regional CBF. CASL-PI CBF asymmetries correlate with severity and outcome. Delayed arterial transit effects may indicate collateral flow. (Stroke. 2000;31:680-687.)

Key Words: magnetic resonance imaging ■ perfusion ■ stroke, ischemic

Compromised cerebral blood flow (CBF) is cardinal to the development of acute cerebral ischemia, and perfusion imaging (PI) may be a useful diagnostic tool in acute ischemic stroke. Imaging in acute stroke has focused primarily on the structural evidence of ischemia rather than on CBF. This is largely due to the unavailability of the CBF measurement techniques used in the acute period. Positron emission tomography provides a noninvasive means of measuring metabolism and perfusion of the human brain.1,2 Although extensively studied in cerebrovascular disease, it is a costly technique that is not widely available.

More recently, several groups have performed perfusion-weighted MRI (PWI) using bolus infusion of gadolinium diethylenetriaminepentaacetic acid (GdDTPA).3,4 PWI readily provides relative regional cerebral blood volumes and bolus peak arrival times, but specifically quantifying relative regional CBF requires complex calculations based on models that are still under development, and absolute quantification of CBF is not possible. Few studies of PWI in acute stroke have reported quantitative CBF results. The quality of PWI data is greatly influenced by the duration of the intravenous contrast bolus, which is ideally given with a power injector.4 Furthermore, because the dynamic contrast changes imaged in PWI occur over only 30 to 60 seconds and must be sampled with high temporal resolution, the number of slices that can be acquired is generally limited to approximately 7. This may be a significant limitation when the location of the stroke is unknown. Xenon-enhanced CT (Xe-CT) is an alternative technique that allows determination of CBF with the use of an inhaled radiodense gas.5 While Xe-CT shows excellent promise in the evaluation of AIS, Xe-CT quantifies CBF but does not depict cytotoxic injury in the posterior fossa as well as diffusion-weighted MRI (DWI) does. Additionally, some patients experience sensory symptoms, altered sensorium,
and depressed respiration as a result of the anesthetic properties of xenon.5

In this study we explored the role of PI using MRI with continuous arterial spin labeling (CASL-PI) in acute ischemic stroke. CASL-PI is a noninvasive technique for measuring cerebral perfusion with electromagnetically labeled endogenous arterial water as a freely diffusible tracer.6-8 Arterial water is labeled proximal to the brain, and the effects of cerebral perfusion are assessed by comparing images obtained with and without arterial spin labeling. The effects of arterial tagging on distal images can be quantified in terms of tissue perfusion because the regional changes in signal intensity are determined by blood flow and T1 relaxation. This allows for quantification of regional perfusion without the administration of exogenous tracers or arterial blood sampling. CASL-PI is entirely noninvasive and has been extended to a multislice modality, greatly increasing its potential clinical utility.8

A unique feature of CASL-PI is the extremely short half-life of the perfusion tracer, approximately 1 second for the T1 of blood at 1.5 T. This renders CASL-PI very sensitive to variations in arterial transit time, since accurate quantification of CBF requires knowledge or assumptions about the delay from the location of arterial spin labeling to the imaging slice. This sensitivity has been greatly reduced through the introduction of a postlabeling delay.9 With this approach, clinically meaningful perfusion data have been acquired from patients with chronic cerebrovascular disease at rest10 and during flow augmentation.9,11 While residual sensitivity to arterial transit delays may in itself have diagnostic value, the question remained of whether CASL-PI could provide interpretable data in the setting of acute stroke when perfusion levels are lowest and arterial transit delays longest. In this study we describe the successful use of CASL-PI in 15 patients with acute cerebral ischemia.

Subjects and Methods

Patient Population

Institutional review board approval was obtained before initiation of the study. Informed consent was obtained from all patients before enrollment. Fifteen patients admitted to our hospital with acute ischemic stroke were studied prospectively. A baseline CT of the head was obtained to rule out intracerebral hemorrhage. Patients were eligible if they had symptoms compatible with an anterior circulation ischemic stroke and were excluded if they had symptoms for >24 hours, brain stem syndromes, or contraindications for an MRI study or if they were medically unstable. Admission National Institutes of Health Stroke Scale (NIHSS) and 30-day Rankin Scale (RS) were measured in all patients.

Perfusion MRI

All MRI studies were performed in a GE Horizon Echospeed 1.5-T scanner. Fluid-attenuation inversion recovery (FLAIR) images and DWI were obtained concurrently. The CASL-PI technique previously described was used.8 For measurements of perfusion, gradient echo-planar images were obtained with a field of view of 24 cm along the frequency-encoding direction and 15 cm for the phase direction and an acquisition matrix of 64×40. An acquisition bandwidth of ±62.5 kHz allowed an effective echo time of 22 ms and an image acquisition time of 45 ms. Multislice image acquisition was performed without pausing between slices so that 8 slices could be acquired in <400 ms. A slice thickness of 8 mm was used, and interslice gaps of 2 mm were used to minimize interference between slices. Slice locations were chosen to include supratentorial structures.

Perfusion data were saved as raw echo amplitudes and transferred to a workstation for processing. Custom software written in the Interactive Data Language (IDL; Research Systems) environment was used to reconstruct the images. The 45 pairs of labeled and control images were first corrected for motion11 and then averaged to produce a single set of perfusion-sensitive images. These images were quantified with a modification of the approach we described previously.9

The CASL signal depends on the efficiency with which the inflowing blood is labeled, the rate at which the spin label decays, and the sensitivity of the scanner to the label. We have previously estimated the efficiency of our labeling of blood water spins13 to be 96% and directly measured the additional inefficiency of the amplitude-modulated control technique.8 On the basis of these results, a total labeling efficiency of 71% for the parameters of this study was assumed for quantification. The spin label decays exponentially with T1, the MR longitudinal relaxation rate. T1 can be different in the arterial blood and tissue, and uncertainty regarding the time at which the label enters the tissue can cause uncertainty in the quantification,8 but T1 is similar in normal gray matter and blood and therefore the uncertainty is minimal. The T1 of tissue can be measured, but our existing T1 measurement technique9 was much more prone to motion artifact than the perfusion-sensitive images. Because of the relatively poor quality of our T1 images and the uncertainty regarding the time the label enters the tissue, we chose to use a literature value of the T1 of blood, 1100 ms,14 for quantification. This is equivalent to assuming that all of the label is in the arterial microvasculature and never reaches the tissue. When the extremely short decay rate of the spin label is considered, this assumption seems justified, particularly in patients with cerebrovascular disease in whom arterial transit times are likely prolonged. Failure of this assumption will lead to an underestimation of flow in short T1 tissues, such as white matter, and an overestimation of flow in long T1 tissues, such as an edematous lesion in the gray matter.

In previous studies,8,9,15 the sensitivity of the MRI scanner to water spins was calibrated at each pixel by dividing the perfusion-sensitive image by the control image intensity. Quantification of absolute blood flow then requires a map of the brain-blood partition coefficient,15,16 which can be estimated by segmenting tissue into gray and white matter or can be directly measured with a series of T1 and T2 sensitive images. Either of these procedures also tends to degrade the quality and reliability of perfusion images. For this study we instead chose to use the intensity of cerebrospinal fluid (CSF) as a calibration standard. For each subject, a region in the lateral ventricle containing only CSF was manually defined, and the average intensity in the control image within this region was calculated. This intensity was then corrected for partial saturation because of the 4-second repetition time and used as an intensity reference for pure water. CASL difference images were corrected for the T2 decay during the echo time using the T2 of arterial blood, in keeping with our assumption that the label is predominantly in arterial blood, and corrected for partial saturation because of the 4-second repetition time and used as an intensity reference for pure water. CASL difference images were corrected for the T2 decay during the echo time using the T2 of arterial blood, in keeping with our assumption that the label is predominantly located in the arterial microvasculature.

The modified equation for flow as a function of the measured signals is therefore as follows:

\[
    f = \frac{\text{SignalCASL} \left[ 1 - \exp \left( \frac{TR \cdot C_{sf}}{T1a} \right) \right] \exp \left( \frac{w}{T1a} \right) \exp \left( \frac{TE}{T2a} \right)}{\text{SignalCSF} \cdot p} \]

where \( f \) is the flow in milliliters per gram per second, \( \text{SignalCASL} \) is the difference between the control and labeled image intensities, \( \text{SignalCSF} \) is the average intensity of the control image in the manually defined ventricular region, \( TR \) is the sequence repetition time (4 seconds), \( T1c_{sf} \) is the relaxation rate of CSF (4.2 seconds),17 \( w \) is the postlabeling delay (1.5 seconds), \( T1a \) is the T1 of blood (1.1 seconds), \( TE \) is the echo time (22 ms), \( T2a \) is the T2 of arterial blood (240 ms),14 \( \alpha \) is the labeling efficiency (71%), \( \lambda_b \) is the milliliter of water per milliliter of arterial blood (0.76),15 and \( p \) is the density of brain tissue (1.05 g/mL).

Postacquisition analysis included visual inspection of CASL-PI and concurrently acquired DWI and FLAIR images. These data were assessed for perfusion deficits (PDs), delayed arterial transit, and...
perfusion/diffusion mismatches (PD > DWI or DWI > PD). Perfusion in both middle cerebral arteries (MCAs) as well as other major vascular territories was quantified by a region of interest analysis based on published templates after manual transformation of CASL-PI data into Talairach space based on anatomic images obtained concurrently (Figure 1). Regional CBF was quantified in both hemispheres, and the percent difference when compared with the unaffected hemisphere was determined in each vascular territory. The Spearman correlation coefficient was used to determine whether the regional CBF and interhemispheric CBF differences correlated with stroke severity and neurological outcome as determined by the admission NIHSS and RS at 30 days.

Results

The age of the 15 patients ranged from 42 to 76 years (median age, 62 years). Ten men and 5 women were studied. All patients had clinical symptom of supratentorial ischemia. The time between symptom onset and MRI examination ranged from 3 to 24 hours, with a median of 10 hours. The stroke severity ranged from 4 to 24 points on the NIHSS, with a median score of 8. One patient (patient 7) received intravenous thrombolysis before being imaged. Table 1 summarizes

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex</th>
<th>Clinical Presentation</th>
<th>Stroke Mechanism</th>
<th>Time to Scan, h</th>
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</thead>
<tbody>
<tr>
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<td>Atrial fibrillation</td>
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</tr>
<tr>
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<td>58/M</td>
<td>Motor aphasia</td>
<td>Stroke during angiogram</td>
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<td>Cardioembolic</td>
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<tr>
<td>4</td>
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<td>Cardioembolic</td>
<td>5</td>
</tr>
<tr>
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<td>56/M</td>
<td>Aphasia, R hemiparesis</td>
<td>Carotid dissection</td>
<td>6</td>
</tr>
<tr>
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<td>66/F</td>
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<td>Cryptogenic stroke</td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td>71/M</td>
<td>L hemiparesis, neglect</td>
<td>Cardioembolic</td>
<td>10</td>
</tr>
<tr>
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<td>Global aphasia</td>
<td>Cryptogenic</td>
<td>24</td>
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<td>9</td>
<td>76/M</td>
<td>Aphasia, R hemiparesis</td>
<td>Large-vessel atherosclerosis</td>
<td>19</td>
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<tr>
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<td>Fluent aphasia</td>
<td>Cardioembolic</td>
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</tr>
<tr>
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<td>Carotid dissection</td>
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<td>Small-vessel disease</td>
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<tr>
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<td>68/M</td>
<td>L hemiparesis, neglect</td>
<td>Cardioembolic</td>
<td>12</td>
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</tbody>
</table>

R indicates right; L, left.
Figure 2. Selective representative images of multislice CASL-PI data acquired in all 15 patients. All images are displayed in radiological orientation with a gray scale of 0 to 150 mL/100 g per minute. In normal regions, increased perfusion is evident in cortical gyri and subcortical gray matter structures, while regions of focal hypoperfusion indicate ischemia.
the clinical and demographic information for the patients studied.

Technically adequate images allowing visual interpretation of perfusion maps were obtained in all patients (Figure 2). PDs were present in 11 patients, in those imaged as early as 3 hours and as late as 24 hours. In each case the location of the PD correlated with the clinical localization on the basis of the patients' symptoms. Normal perfusion was present in 2 patients with thalamic infarcts and in 1 patient with a superficial MCA infarct. DWI abnormalities were present in the 3 patients with normal perfusion. One of the patients with normal perfusion had received intravenous thrombolysis. Relative hyperperfusion (perfusion in affected hemisphere > unaffected hemisphere) was present in 1 patient with a MCA branch infarct. Coexistent DWI abnormalities were found in 10 patients with PD.

PD > DWI was detected in 7 patients, and DWI > PD was present in 1 patient. One of the patients with PD > DWI had a large PD without an associated DWI abnormality. In 3 patients the PD matched the DWI abnormality. Figure 3 illustrates several patterns of perfusion/diffusion mismatching encountered in our series. The extent of perfusion/diffusion mismatching ranged from complete hypoperfusion without associated DWI lesion in patient 14 to a large DWI lesion with a small PD in patient 15.

Delayed arterial transit was present in 7 patients. These delayed arterial transit effects did not significantly affect our ability to qualitatively interpret the CASL-PI results. Subsequent structural imaging studies were available in 2 patients with delayed arterial transit; in both patients the follow-up MRI showed sparing of the area where delayed arterial transit artifact had been present. This is illustrated for 1 patient who underwent serial CASL-PI in Figure 4.

Table 2 provides the results of quantitative regional CBF obtained by template analysis. The CBF values correlated well with the findings by visual inspection; lower values were obtained in areas with hypoperfusion evident on visual inspection of perfusion maps. Despite a broad range of infarcts and clinical deficits, there was a significant difference between CBF in affected and unaffected MCA territories ($P = 0.011$, paired $t$ test). CBF in the MCA territory of the affected hemisphere correlated with the NIHSS score on admission and the Rankin score at 30 days ($P = 0.037$ and $P = 0.003$, respectively, Spearman rank correlation). In contrast, CBF values in the unaffected hemisphere did not correlate with either the admission NIHSS scores or RS scores at 30 days ($P = 0.337$ and $P = 0.088$, respectively). The interhemispheric percent difference in MCA CBF correlated with the NIHSS and RS scores ($P = 0.007$ and $P = 0.0002$, respectively). Percent differences in CBF for the MCA were > 50% in 3 patients with severe strokes and NIHSS scores of > 20 points. All 3 patients had poor functional outcome, with RS scores of > 4 at 30 days. In 1 patient relative hyperperfusion in the affected hemisphere was evident on both visual inspection and automated analysis.

Discussion

We previously used CASL-PI to successfully assess CBF and cerebrovascular hemodynamic reserve in patients with chronic cerebrovascular disease, but its use in acute ischemic stroke had not been validated. In this series CASL-PI in acute stroke successfully depicted PDs, restored perfusion, hyperperfusion, perfusion/diffusion mismatches, and delayed arterial transit in addition to providing quantitative CBF determination. While absolute quantification of CBF in acute stroke may have been affected by limitations in the assumptions used in its calculation, the CBF values obtained are in agreement with values in the literature. These findings have potential diagnostic, therapeutic, and prognostic implications for the management of acute cerebral ischemia.
Determining the presence of a PD in acute stroke is of great significance, since PDs always precede structural MRI ischemic lesions. Furthermore, the relation between the PD and the associated DWI abnormality may indicate the presence of an ischemic penumbra (PD > DWI). Traditionally the ischemic penumbra has been characterized with the use of electroencephalography or evoked potentials, which are disturbed at flow rates higher than the potassium gradient across the plasma cell membranes. CASL-PI provided indirect evidence of an ischemic penumbra in 7 of our patients. In such patients a PD exceeding the DWI abnormality was present, signaling additional tissue at risk. In patient 14 a large PD was observed in the absence of any DWI lesion 6 hours after the onset of symptoms, well beyond the demonstrated time interval for intravenous thrombolytic therapy. Ay and colleagues used the term “penumbra without core” to describe this finding. Such areas almost invariably evolve to infarction, and that was the case in our patient. This raises the intriguing possibility that in some patients the time window for recanalization therapy may be prolonged, and selecting patients for thrombolysis based only on the time of onset of symptoms may be inappropriate. In addition, without the information obtained from the perfusion map and in light of a normal DWI, it is conceivable that patients with penumbra without a core could be diagnosed as having a nonvascular disorder. DWI may be normal in early infarction and may be abnormal in nonischemic lesions; in such circumstances CASL-PI can be used to differentiate stroke mimics from true ischemic lesions. The presence of a focal PD in an area that is clinically symptomatic attests to the ischemic nature of the symptoms.

Prior studies using PWI have found that when the PD exceeds the DWI lesion, the ultimate infarct volume will exceed the original DWI area, and this mismatching has been proposed to represent the ischemic penumbra. This may not represent the ischemic penumbra with complete accuracy since hypoperfused areas may retain viability, DWI lesions are potentially reversible, and information about the metabolic milieu in the ischemic area is not available. Establishing the type and quantity of metabolic by-products accumulated in the ischemic zone may determine the potential reversible nature of the lesion. Such information could potentially be obtained with MR spectroscopy. A multimodal MRI approach using CASL-PI or PWI, MR spectroscopy, and MR angiography could establish the presence of an ischemic zone, map the ischemic penumbra, determine the potential reversibility of the lesion, and establish the occluded vessel.

Determining the presence of hyperperfusion or relative hyperperfusion in an ischemic area may have prognostic implica-
ions. Positron emission tomography studies have suggested that hyperperfused areas in acute ischemic stroke exhibit hemodynamic and metabolic abnormalities consistent with postrecanalization hyperperfusion, vasodilatation, and luxury perfusion. An underlying increased oxidative metabolism reflecting increased protein synthesis is frequently associated. This finding has been correlated with better outcome after acute stroke. We were able to demonstrate relative hyperperfusion (CBF higher in the affected hemisphere) using CASL-PI in a patient with a posterior division MCA stroke. Hyperperfusion was evident on visual inspection of perfusion maps, and relative hyperperfusion was present on automated CBF detection, with CBF values higher in the affected hemisphere. This patient made a dramatic recovery despite a significant DWI lesion. Further studies using CASL-PI are needed to validate the significance of this finding.

PDs determined by CASL-PI could potentially be used in guiding acute stroke treatment and in predicting outcome. The absence of a PD in a patient with stroke suggests spontaneous reperfusion, which has both prognostic and therapeutic implications. Tong and colleagues found that persistent PDs correlated better than DWI with NIHSS score at 24 hours. In our series PDs correlated strongly with RS score at 30 days and with NIHSS score at 24 hours. In our series, a PD as assessed by GdDTPA bolus tracking and NIHSS score in patients with delayed arterial transit may aid in selecting patients for thrombolytic therapy and in assessing the success of therapy. In our series we encountered 3 patients with PD>DWI imaged within 3 to 6 hours of symptom onset. Conceivably such findings could be used to select them as candidates for intra-arterial thrombolysis or for neuroprotective therapies. Since CASL-PI can be combined with any imaging sequence, the sensitivity to local susceptibility effects can be greatly reduced. This may be particularly useful for measuring perfusion in the presence of hemorrhage.

Although the effects of CASL on brain tissue are small, the effects of CASL in the intravascular space can be relatively large. This effect can lead to bright intraluminal signal in patients with delayed arterial transit. We observed delayed arterial transit in 7 patients and were able to obtain serial imaging in 2 patients. The specific cortical areas where delayed arterial transit initially appeared did not evolve into an infarct as judged by subsequent DWI and FLAIR imaging. We hypothesize that superficial delayed arterial transit may represent the presence of collateral circulation through leptomeningeal vessels, a finding that could convey a better prognosis. Thus, while transit effects were previously considered a hindrance of CASL-PI, the presence of delayed arterial transit may actually be a useful element for assessing collateral flow to hyperperfused areas. While delayed arterial transit primarily appears as distinct linear hyperintensities in CASL-PI images, distinguishing it from hyperperfusion remains a significant potential source of artifact, particularly for perfusion quantification. Acquisition and analysis methods to separately quantify perfusion and arterial transit times are under development in our laboratory.

Tong and coworkers previously found a relation between PDs as assessed by GdDTPA bolus tracking and NIHSS score in acute stroke. In our series, a >50% difference in CBF between the affected and the unaffected territory in the MCA region was correlated with stroke severity (NIHSS score >20) and poor outcome (RS score >4). Three patients had CBF asymmetries >50%; all 3 had RS scores >4. Hemispheric CBF asymmetries

<table>
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<tr>
<th>Patient No.</th>
<th>Affected Hemisphere</th>
<th>CBF*</th>
<th>% Difference</th>
<th>NIHSS Score</th>
<th>RS Score (30 d)</th>
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<td>50.6</td>
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<tr>
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<td>42.7</td>
<td>12.6</td>
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<td>32.1</td>
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<tr>
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<td>44.8</td>
<td>1</td>
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<td>4.4</td>
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</table>

*CBF in milliliters per 100 g per minute in MCA territory.
and MCA CBF in the affected hemisphere correlated strongly with stroke severity and functional outcome. Table 2 illustrates the relation between CBF, stroke severity, and functional outcome. Although we did not perform serial imaging in most of our patients, other authors have described enlargement of DWI lesions when large PDs were present in the first 6 hours. Three of our patients with severe strokes (NIHSS score > 20) had large initial PDs and poor functional outcome. We corroborated subsequent enlargement of the DWI lesion in 1 case, supporting the hypothesis that large initial PDs are associated with large infarcts and poor outcome. We suspect that enlargement of the ischemic lesion accounts for the poor outcome seen in the other patients.

Although cerebral perfusion can be evaluated by other MRI techniques such as PWI, CASL-PI offers some unique advantages. CASL-PI does not require administration of exogenous paramagnetic contrast material or the use of a power injector. In addition, CASL-PI may be repeated indefinitely, quantifies CBF as opposed to cerebral blood volume, and may be rendered insensitive to susceptibility-induced signal dropout because any imaging sequence may be used to measure the effects of CASL. Since CASL-PI is measured in a pseudo–steady state, an additional signal averaging time may be used to improve signal to noise ratio, slice coverage, or spatial resolution. We recently reported a 3-dimensional CASL-PI scheme providing 4-mm isotropic voxels.29

In this series CASL-PI provided interpretable information on perfusion status in patients with acute ischemic stroke; depicted perfusion/diffusion mismatches, PDs, areas of relative hyperperfusion, and cortical transit artifacts; and provided quantitative information on CBF. CASL-PI could be used to guide thrombolysis, monitor reperfusion, and assess prognosis. CBF interhemispheric differences, as depicted by CASL-PI, are correlated with stroke severity and functional outcome. Further studies involving larger series of patients and serial imaging are necessary to validate our preliminary findings.

Acknowledgments

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References

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