Arterial Spin Labeling Perfusion Magnetic Resonance Imaging Performed in Acute Perinatal Stroke Reveals Hyperperfusion Associated With Ischemic Injury

Christopher G. Watson, ScB; Mathieu Dehaes, PhD; Borjan A. Gagoski, PhD; P. Ellen Grant, MD*; Michael J. Rivkin, MD*

Background and Purpose—Perfusion-weighted imaging in adults with acute stroke often reveals hypoperfusion in the ischemic core and in a surrounding area of nondiffusion-restricted penumbral tissue. Perinatal stroke is common, but the perfusion pattern is rarely documented. We aimed to describe the perfusion pattern in newborns with perinatal stroke.

Methods—Neonates with clinical features of acute stroke underwent magnetic resonance imaging. Perfusion data were obtained using pseudocontinuous arterial spin labeling. Strokes were classified as arterial, venous, or both. Core infarction was determined by the presence of restricted diffusion on diffusion-weighted imaging. Perfusion-weighted imaging and susceptibility-weighted imaging signal in the ischemic area were visually compared with the homologous region in the contralateral hemisphere. Electroencephalogram data were evaluated for seizure activity.

Results—In 25 neonates with acute stroke, 8 of 11 (73%) with arterial ischemic stroke demonstrated hyperperfusion, 1 of 9 (11%) with venous stroke, and 4 of 5 (80%) with both. Hypoperfusion was observed in 3 of 9 (33%) with venous and none with arterial ischemic stroke. Perfusion was normal in 4 of 9 (45%) with venous and 1 of 5 (20%) with both. Twenty-one of 24 patients (88%) with electroencephalogram data had either electrographic seizures or focal sharp waves in the ipsilesional hemisphere (11/11 arterial ischemic stroke, 6/9 venous, and 4/5 both).

Conclusions—Perfusion-weighted imaging can be obtained in neonates with acute stroke and often reveals hyperperfusion in the infarct core. Penumbra in arterial ischemic stroke is seldom found. Hyperperfusion may be caused by poststroke reperfusion or to neuronal hyperexcitability of stroke-associated seizure. Its identification may be useful for consideration of therapy for acute neonatal stroke. (Stroke. 2016;47:1514-1519. DOI: 10.1161/STROKEAHA.115.011936.)

Key Words: cerebral blood flow • infant, newborn • magnetic resonance imaging • perfusion • stroke

Stroke occurs in the perinatal period more frequently than at any other period in childhood, with an incidence as high as 1 in 1600 live births per year. Although mortality is low, greater than half of survivors have permanent motor or cognitive impairment. Magnetic resonance imaging (MRI) enables rapid diagnosis in neonates who raise concern for this cerebral injury. Currently, treatment is supportive, and interventional therapy has not been identified.

Thrombolysis and endovascular retrieval have been used to treat acute stroke in adults, aided through definition of the ischemic core with diffusion-weighted imaging (DWI) and at-risk tissue surrounding the core—the penumbra. Perfusion study of neonates with acute stroke may further elucidate the pathophysiology of this early-life cerebral insult. Furthermore, the existence of a penumbra in neonates with acute stroke has yet to be demonstrated. Existence of penumbral tissue surrounding the core infarct in neonatal stroke might inform and direct new therapy for tissue salvage in these patients.

The penumbra has been defined largely through bolus perfusion imaging in adults. The use of intravascular contrast in neonates is impractical, particularly if repeated imaging studies are needed. Arterial spin labeling (ASL) is a noninvasive MRI method that provides a measure of regional cerebral perfusion. The noninvasive quality of this imaging modality makes it particularly attractive for the use in neonates with stroke. ASL has been successfully used in children with acute stroke.
and in both healthy neonates and neonates with hypoxic-ischemic encephalopathy.\textsuperscript{15–19} Although results of perfusion-weighted imaging (PWI) in patients with perinatal stroke have been reported, in aggregate these studies comprised only 10 neonates with arterial ischemic stroke (AIS).\textsuperscript{20–22} We aimed to study a cohort of neonates with acute stroke to ascertain the perfusion characteristics not only in the ischemic core of the acute infarct but also in the tissue surrounding it.

### Methods

#### Subjects

We included patients receiving ASL imaging at Boston Children’s Hospital between May 2010 and December 2013. Patients were referred for neuroimaging if they presented with symptoms indicative of perinatal stroke, including seizures, apneas, encephalopathy, or bradycardia. We included only patients <28 days old at the time of diagnosis. Patients were excluded if it was determined that they did not have a stroke based on MRI and on other clinical examinations. Because it is not possible to determine the time of insult in perinatal stroke, we used age at symptom onset as a surrogate.

#### MRI Acquisition

Imaging was performed on a 3T Siemens Trio scanner with a 32-channel head coil. Perfusion MRI was acquired using a pseudocontinuous ASL (PCASL) sequence with multislice echo-planar readouts at a resolution of 3×3×5 mm\(^3\), repetition time/echo time=3500/12 ms, labeling time of 1.6 s, and postlabeling delay of 1.5 s. Nine axial slices were acquired in each of 40 label/control image pairs. Acquisition time was 5 minutes. The label/control images were subtracted and averaged to obtain contrast maps proportional to cerebral blood flow (CBF). In addition, DWI, susceptibility-weighted imaging (SWI), and T2-weighted series were obtained using standard protocols.

#### Stroke Classification

Strokes were classified as arterial, venous, or both by consensus opinion of a pediatric neuroradiologist (P.E.G.) and pediatric neurologist (M.J.R.). Classification of arterial infarction was based on evidence of acute ischemic injury indicated by acute diffusion change on DWI in an arterial distribution, affecting both gray and white matter. Venous stroke was diagnosed by evidence on MRI of hemorrhage or infarction in a nonarterial distribution with or without venous or sinus thrombosis. Core infarction was considered to lie in regions of hypointensity on apparent diffusion coefficient (ADC) maps.

Regional perfusion signal on ASL imaging was evaluated by comparing the ischemic core identified by DWI with the homologous uninvolved region in the contralateral hemisphere. In the case of stroke with bilateral involvement, we assessed perfusion by comparison with the contralateral normal hemisphere without ADC abnormality. We categorized perfusion signal as hyperperfusion (increased perfusion signal on ASL or reduced venous deoxyhemoglobin signal on SWI when compared with the control region), hypoperfusion (decreased perfusion signal compared with the control region), mixed (hyper- and hypoperfusion present in the infarcted region), or normal (compared with the control region). We also tabulated data on seizure occurrence, electroencephalogram characteristics, and presence of hemorrhage in addition to stroke. Statistically significant differences in perfusion pattern, presence of clinical seizures, and presence of hemorrhage among stroke subtypes were determined using Fisher exact test (\(P<0.05\)).

### Results

#### Subjects

Perfusion imaging was collected for 33 neonates with acute stroke. Eight patients were excluded because of artifact caused by excessive patient movement, leaving 25 neonates for further analysis. Two of 25 patients had ASL data somewhat corrupted by motion but acceptable SWI data; perfusion in these patients was assessed by SWI. The sample comprised 16 men (64%). Median gestational age at birth was 38.7 weeks (range, 35.7–41.9 weeks), median (estimated) age at stroke was 1 day (ie, second day of life; range, 0–8), and median age at MRI was 3 days (range, 0–16 days). The median time from symptom onset to MRI acquisition was 2 days (range, 0–8 days).

#### Clinical Presentation

Clinical data are shown in Table 1. Among those with AIS, 5 of 11 neonates were born by C-section. The remainder was born by spontaneous vaginal delivery. All had normal Apgar scores. All neonates with venous infarcts were born by spontaneous vaginal delivery, had normal Apgar scores, whereas 2 of 9 had meconium stained fluid. All 5 with both arterial and venous infarcts were born by spontaneous vaginal delivery, but 1 had meconium aspiration. Apgar scores were normal.

The most common initial presenting symptom suggesting stroke and leading to diagnostic MRI was seizure (n=16; 64%). Other symptoms included apneic events (n=11; 44%), bradycardia (n=2; 8%), and encephalopathy (n=2; 8%). Patients presenting with seizures came to attention at a median age of 1 day (interquartile range, 0–1; maximum, 8), and patients presenting with apnea came to attention at a median age of 1 day (interquartile range, 0–1; maximum, 4). Clinical seizures occurred in 21 (84%) neonates; all 11 with AIS had seizures, compared with 6 (67%) with venous stroke and 4 (80%) with both (\(P=0.11\)). Continuous electroencephalogram data were available for 24 (96%) neonates; of those patients, 22 (92%) had either electrographic seizures or focal sharp waves located in the ipsilesional hemisphere (10/11 with AIS, 7/9 with venous stroke, and 5/5 with both). The presence of abnormality on electroencephalogram did not vary with stroke type (\(P=0.16\)). At the time of MRI, 18 (72%) patients were on anticonvulsants (8/11 with AIS, 6/9 with venous stroke, and 4/5 with both). There was no difference in patients receiving anticonvulsants for either stroke type (\(P=1\)) or perfusion signal pattern (\(P=0.27\)).

#### MRI Findings

AIS was present in 11 (44%), whereas venous infarction was found in 9 (36%). Five patients (20%) had both arterial and venous stroke. Fifteen patients (60%) had left hemisphere strokes and 5 (20%) had right hemisphere strokes, whereas 5 (20%) had bitemporal involvement.

<table>
<thead>
<tr>
<th>Stroke Type</th>
<th>Arterial (n=11), n (%)</th>
<th>Venous (n=9), n (%)</th>
<th>Both (n=5), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>11 (100)</td>
<td>6 (67)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>EEG</td>
<td>10 (91)</td>
<td>9 (100)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Abnormal EEG</td>
<td>10 (91)</td>
<td>7 (78)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1 (9)</td>
<td>8 (89)</td>
<td>3 (60)</td>
</tr>
</tbody>
</table>

EEG indicates electroencephalogram.
AIS was distinguished by diffusion imaging characteristics to indicate acute stroke in an arterial distribution (Figure 1A and 1B). Associated hyperperfusion in the field of infarct by DWI was often found (Figure 1C) that also demonstrated decreased susceptibility on SWI (Figure 1D).

Neonates with venous stroke harbored subcortical infarction of white matter or gray matter often with associated hemorrhage (Figure 2A and 2B). Hemorrhage was present in 9 (39%) patients, 8 of whom had venous infarct and only 1 had AIS (P=0.001). Associated hyperperfusion often was found in and beyond the region of infarction by DWI and was matched by the finding of decreased susceptibility on SWI (Figure 2C and 2D).

Hyperperfusion, in all, was found in 13 patients (52%) as demonstrated by PWI or SWI. Only 3 (12%) had hypoperfusion, 4 (16%) had mixed hyper- and hypoperfusion, and 5 (20%) had normal perfusion patterns (Table 2). Hyperperfusion appeared most commonly in patients with AIS (72% versus 11% of venous cases). Four (80%) neonates with both arterial and venous involvement also had hyperperfusion; the increased perfusion was exclusively in the territories of arterial involvement.

Hypoperfusion, on the contrary, was absent in AIS, and present in 3 (33%) neonates with venous stroke. A mixed pattern was present in 3 patients (27%) with arterial stroke and 1 (11%) with venous stroke (Figure 3). Normal perfusion was noted in 4 (44%) neonates with venous infarction and 1 (20%) with both venous and AISs. The distribution of perfusion signal type was significantly different across stroke types (P=0.003; Table 2). None of the 4 patients who did not have clinical seizures had evidence of hyperperfusion.

A stacked bar plot of perfusion signal pattern and estimated time from stroke onset to MRI, with different colors for each stroke type, is provided in Figure I in the online-only Data Supplement. There was a significant difference in perfusion

Table 2. Perfusion Signal Patterns

<table>
<thead>
<tr>
<th>Perfusion Signal</th>
<th>Arterial (n=11)</th>
<th>Venous (n=9)</th>
<th>Both (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperperfusion</td>
<td>8 (73)</td>
<td>1 (11)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Hypoperfusion</td>
<td>0 (0)</td>
<td>3 (33)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mixed</td>
<td>3 (27)</td>
<td>1 (11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Normal</td>
<td>0 (0)</td>
<td>4 (44)</td>
<td>1 (20)</td>
</tr>
</tbody>
</table>

Figure 1. Magnetic resonance imaging of a patient with arterial ischemic stroke and hyperperfusion on perfusion-weighted imaging (PWI). A, Axial diffusion-weighted imaging (DWI) trace image; arrows show the edges of the diffusion abnormality. B, Corresponding DWI apparent diffusion coefficient image to A; arrows show edges of the low-intensity abnormality. C, Axial PWI image; arrows indicate the area of abnormally high signal indicating hyperperfusion. D, Corresponding axial susceptibility-weighted imaging image; arrows indicate area of susceptibility wash-out that matches area of hyperintense signal area found in PWI (C).

Figure 2. Magnetic resonance imaging of a patient with venous stroke and hyperperfusion on pseudocontinuous arterial spin labeling. A, Axial diffusion-weighted imaging (DWI) trace image; arrows show edges of the high intensity abnormality in gray matter. B, Corresponding DWI apparent diffusion coefficient image to A; arrows show edges of the low-intensity abnormality. C, Axial perfusion-weighted imaging (PWI); arrows indicate the area of abnormally high signal indicating hyperperfusion. D, Corresponding axial susceptibility-weighted imaging image; arrows indicate area of susceptibility wash-out that matches area of hyperintense signal area found in PWI (C).
signal type associated with time between symptom onset and MRI \( (P=0.05) \). Hyperperfusion was more likely to be present when MRI was performed within 2 days of symptom presentation.

Signal on SWI corroborated the PWI categorization in nearly all patients. In 12 (92%) infants with hyperperfusion on PWI, SWI signal in the peri-infarct area was attenuated, indicating reduced deoxyhemoglobin content. There were no cases in which increased susceptibility on SWI associated with hyperperfusion on PWI. There were no cases in which attenuated signal on SWI (wash-out) was associated with hypoperfusion.

**Discussion**

In this case series, we demonstrate feasibility of obtaining brain perfusion data using a PCASL sequence in neonates with acute stroke. We confirm that neonates often demonstrate hyperperfusion relative to the unaffected hemisphere within the region of decreased ADC and little evidence of hypoperfusion beyond it, in contrast to the core and penumbral hypoperfusion seen in adults with stroke. The majority of cases with hyperperfusion were AISs, whereas most cases with hypoperfusion occurred in venous stroke. In addition, in nearly all patients presenting with clinical or electrographic seizures, electroencephalogram abnormalities were present in the same hemisphere as the stroke; this clinical feature did not differ by stroke type. Finally, hemorrhage was present almost exclusively in neonates with venous stroke.

We speculate that the increased signal found on ASL represents regional hyperperfusion in neonates with acute stroke. Seizure is the most common presenting sign of perinatal stroke. It is possible that the hyperperfusion found on PCASL imaging is a reflection of seizure-related increase in CBF. All neonates with either hyperperfusion or a mixture of hyperperfusion on PCASL had history of clinical or electroencephalogram seizures. Increased oxygen consumption was associated with increased cerebral blood volume in 11 of 12 acute neonatal brain injuries, including 1 stroke, using Frequency Domain Near Infrared Spectroscopy, supporting the hypothesis of neuronal activity-related increases in perfusion. Thus, increased perfusion in perinatal stroke may therefore be related to increased neuronal activity.

Alternatively, hyperperfusion could arise from PCASL acquisition during the reperfusion phase of acute stroke following vessel recanalization. The temporal relationship between stroke onset and symptom presentation is not clear. In nearly one third of adults with AIS of the middle cerebral artery territory, the occlusion clears spontaneously within 24 hours. Using positron emission tomography to determine CBF and metabolism, Hakim et al found increased ipsilesional CBF with associated increase in glucose metabolism within 48 hours of stroke onset in one third of patients. In our sample, patients with normal or low perfusion in the infarct tended to have a longer delay between stroke onset and ASL acquisition.

Increased signal intensity on PCASL can be secondary to delayed arterial transit time and because of intra-arterial location of label. However, the hyperintensities we have found on PCASL were not intra-arterial, but rather parenchymal and colocalized with regions in which the usual pattern of susceptibility signal caused by normal venous flow was diminished or washed out (SWI; Figure 1D). It is possible that tissue edema existed within the ischemic regions in these patients at the time of imaging acquisition that might be expected to cause venous compression and reduction in susceptibility signal. However, previous studies in patients with prominent edema secondary to tumor have demonstrated preservation of venous susceptibility signal. Consequently, we think that the reduced prominence of susceptibility signal on SWI supports our interpretation that these regions are hyperperfused relative to the nonlesioned hemisphere.

Neonates with acute stroke have been incompletely studied using perfusion imaging. Van der Aa et al used MR angiography to measure CBF in the internal carotid arteries in neonates with AIS. They found that, 2 to 10 days post stroke, ipsilesional CBF was significantly higher than contrallesional CBF in the internal carotid arteries. Pienaar et al included 2 neonates with AIS. Using an automated method to select regions of DWI and ASL signal abnormality, they found perfusion significantly higher within the region of interest than with the rest of the brain, corresponding to areas of reduced ADC values indicative of ischemic infarct in the hyperperfused regions. In both stroke patients, the volume of
hyperperfusion was 2.5 times larger than the volume of ADC abnormality. Two other reports provided evidence in 3 of 4 and 4 of 4 patients, respectively, of hyperperfusion in the infarcted region, with hyperperfusion in surrounding regions.\textsuperscript{20,22}

Here, we report a pattern of perfusion in perinatal stroke similar to that reported by Pienaar et al.,\textsuperscript{21} but expand to 25 patients, confirming that the majority of neonates with AIS have evidence of hyperperfusion. The discrepancy with Winterrmark and Warfield\textsuperscript{22} and de Vis et al.\textsuperscript{20} may be related to low subject numbers or a difference in timing of image acquisition: most of our patients underwent MRI within 2 days of symptom presentation, whereas de Vis et al.\textsuperscript{20} imaged their patients 4 to 5 days after symptom presentation. In addition, both Winterrmark and Warfield\textsuperscript{22} and de Vis et al.\textsuperscript{20} used a pulsed ASL sequence.

In adults with acute stroke, hyperperfusion on ASL correlates with better outcome several months post stroke.\textsuperscript{30,37} In addition, early hyperperfusion predicted greater improvement of National Institutes of Health Stroke Scale scores in the acute stage. Whereas adults with stroke often come to attention immediately, in perinatal stroke, the time of stroke onset is indeterminate.\textsuperscript{38} Infarct-associated hyper- and hyperperfusion reported here adds to the data to consider when treating neonates with acute stroke with maneuvers such as blood pressure regulation. Furthermore, the presence of reperfusion phase-related hyperperfusion suggests that neuroprotective agents such as erythropoietin and other molecules—which reduce neuronal apoptosis, enhance oligodendrocyte differentiation, and exert anti-inflammatory effects—merit further study as potentially important treatments for perinatal stroke. Future studies—with MRI performed at multiple time points before discharge and at follow-up—are required to determine the association between MRI measures including PWI, DWI, and volumetric MRI, and infarct location and neurological outcome in neonates with stroke. A limitation of this study is the lack of quantitative CBF data. Neonates were not sedated and may have moved between prescription of the tagging plane and PCASL acquisition, reducing tagging efficiency. Future work should use a standardized acquisition protocol to account for patient motion.

Conclusions

Acquisition of PCASL in neonates with acute stroke provides clinicians with a fast and safe source of qualitative indication of cerebral perfusion. The presence of early hyperintensity on PCASL may be a biomarker for neuronal hyperexcitability or cerebral reperfusion and could help inform acute treatment development for this important patient group.

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Disclosures

None.

References


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Supplemental Figure I: Relationship between perfusion signal pattern and time between stroke symptom onset and MRI. The four facets each represent the four perfusion signal pattern categories. The time between stroke symptom onset and MRI are separated into quartiles (< 1 day; 1 day; 2-3 days; 4-8 days) along the horizontal axis of each facet. The number of cases is represented on the vertical axis. Neonates with hyperperfusion in the peri-infarct region (High).
tended to have a shorter time from stroke symptom onset to MRI acquisition. A: arterial ischemic stroke; V: venous stroke; B: both (arterial and venous)