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## **Arterial Spin-Labeling in Routine Clinical Practice, Part 2: Hypoperfusion Patterns**

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# REVIEW ARTICLE

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## Arterial Spin-Labeling in Routine Clinical Practice, Part 2: Hypoperfusion Patterns

**SUMMARY:** Arterial spin-labeling (ASL) is a powerful perfusion imaging technique capable of quickly demonstrating both hypo- and hyperperfusion on a global or localized scale in a wide range of disease states. Knowledge of pathophysiologic changes in blood flow and common artifacts inherent to the sequence allows accurate interpretation of ASL when performed as part of a routine clinical imaging protocol. Patterns of hypoperfusion encountered during routine application of ASL perfusion imaging in a large clinical population have not been described. The objective of this review article is to illustrate our experience with a heterogeneous collection of ASL perfusion cases and describe patterns of hypoperfusion. During a period of 1 year, more than 3000 pulsed ASL procedures were performed as a component of routine clinical brain MR imaging evaluation at both 1.5 and 3T. These images were reviewed with respect to image quality and patterns of hypoperfusion in various normal and disease states.

Arterial spin-labeling (ASL), when applied in a diverse clinical population, is capable of accurately depicting various states of hypo- and hyperperfusion. In Part 1 of this series, we described the technique, artifacts, and pitfalls related to the application of ASL in a routine clinical neuroimaging protocol.<sup>1</sup> Part 3 will focus on patterns of focal and global hyperperfusion on ASL cerebral blood flow (CBF) maps. Here we describe various causes of focal and global hypoperfusion, including acute and chronic cerebral ischemia, seizure, hydrocephalus, vasculitis, aging, and exogenous drugs (Table). The methods for data acquisition and analysis are described in detail in Part 1 of this series. We identified common patterns of hypoperfusion on the basis of a retrospective analysis of 3000 clinical pulsed ASL (PASL) cases acquired consecutively during a 12-month period.

Much of the value of ASL or any other brain perfusion technique is derived from its ability to image tissue at risk for ischemia or infarction and regions that are potentially salvageable with timely intervention. Diffusion-weighted imaging (DWI) is now the mainstay of stroke evaluation but is limited in that it generally indicates only the core of severe ischemia. Detection of regions of mild or moderate ischemia—the ischemic penumbra—requires assessment of CBF, cerebral blood volume (CBV), or mean transit time (MTT). Currently only CBF is measured in our protocol, but CBV and arterial transit time can be theoretically assessed with spin-tag techniques.<sup>2</sup> ASL can also evaluate asymptomatic carotid stenosis by showing asymmetric regions of modestly reduced blood flow. Chronic microvascular ischemia, or leukoaraiosis, may be demonstrated by focally reduced or patchy CBF in the white matter with preserved gray matter flow. Finally, remote infarcts with resultant encephalomalacia correspond to regions of focally low signal intensity on the CBF map.

Localized reductions in ASL signal intensity may also be related to factors other than reduced flow or ischemia. Knowledge of artifacts and physical parameters of the perfusion sequence permits accurate analysis of the cause of locally diminished signal intensity, and these are discussed in detail in Part 1 of this series.<sup>1</sup> The inversion label applied to inflowing spins in the neck, for example, decays on the order of seconds during image acquisition and results in an overall decrease in signal intensity on the more superior sections. In patients with delayed MTT, this effect is particularly pronounced (though, paradoxically, high signal intensity may also be observed, as discussed in later sections). Susceptibility artifacts due to intracranial blood products, calcification, surgical hardware, and air-bone interfaces are common causes of focally reduced signal intensity and may adversely affect image quality or mask underlying regions of hyperperfusion. These artifactual causes of signal-intensity loss on clinical ASL studies are described in detail in Part 1 of this series.<sup>1</sup>

### Discussion

#### *Hypoperfusion Patterns Encountered at Clinical Spin-Tag Perfusion Imaging*

##### *Focally Decreased Signal Intensity*

**Ischemic Core.** In acute stroke, a central region of severely ischemic tissue is present, which has been shown to represent

**Patterns of hypoperfusion encountered at clinical spin-tag perfusion imaging**

Hypoperfusion Pattern	Causes
Focal	Ischemic core
	Ischemic penumbra
	At-risk tissue
	Leukoaraiosis
	Remote insult
	Seizure activity (interictal)
Global	Ventriculomegaly
	Poor cardiac output
	Vasospasm
	Brain death
	Cerebral atrophy
	Exogenous drugs

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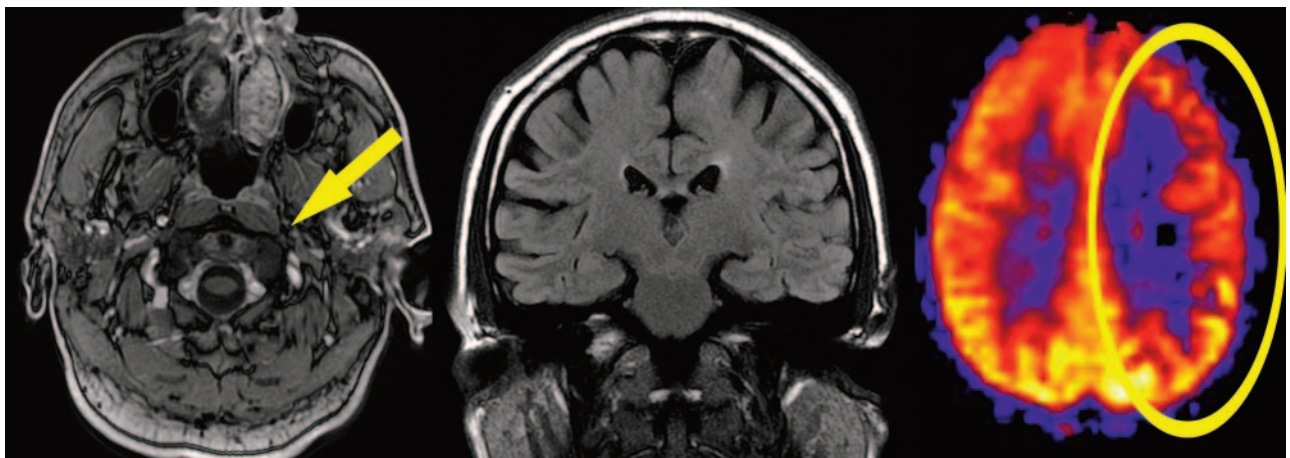
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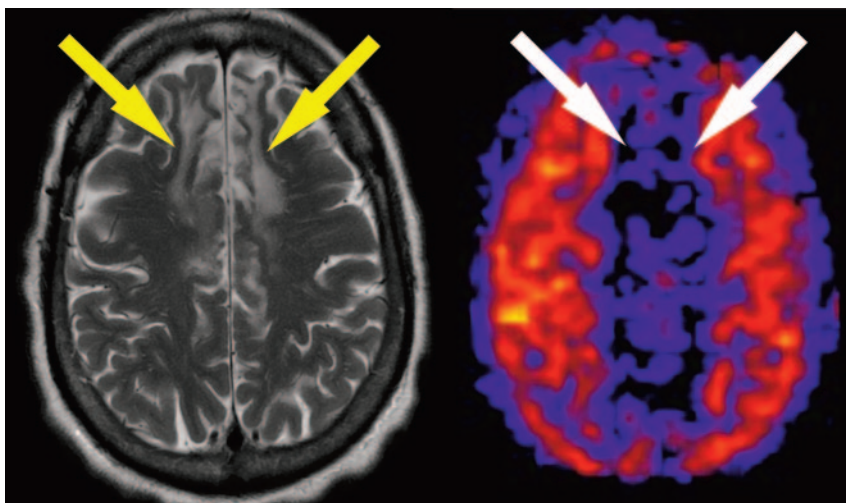
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**Fig 1.** Ischemic penumbra. DWI reveals multiple borderzone infarcts in the left cerebral hemisphere (arrow). MR angiogram (center) demonstrates a left internal carotid artery occlusion. ASL map shows the left ischemic penumbra, corresponding to the perfusion > DWI mismatch.



**Fig 2.** Carotid occlusion and tissue at risk. Axial contrast-enhanced spoiled gradient-recalled-echo image (left) shows chronic occlusion of the left internal carotid artery (arrow). FLAIR (center) shows no evidence of ischemia. Flow asymmetry on the ASL CBF map (ellipse) represents tissue at risk in the left cerebral hemisphere.



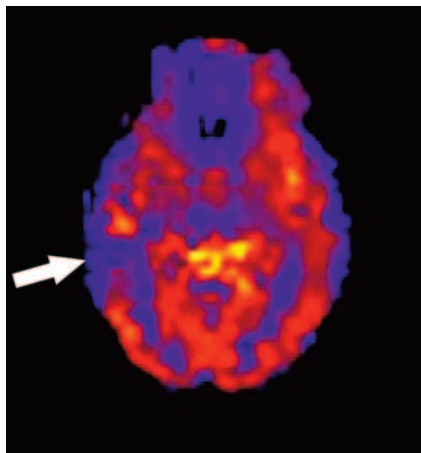
**Fig 3.** Encephalomalacia. Axial T2-weighted image shows high signal intensity in the frontal lobes representing the remote bilateral anterior cerebral artery (ACA) territory infarcts (yellow arrows). ASL CBF map reveals corresponding focal decrease in flow in the ACA territories (white arrows).

a local decrease in blood flow to 10%–25% of normal levels.<sup>3</sup> Flow in the core ischemic lesion is 10–12 mL/100 g per minute or less and generally has an operational definition as the area of restricted diffusion on apparent diffusion coefficient maps. This reduction in blood flow can be easily identified on CBF maps and is frequently surrounded by a region of relatively

higher but still abnormal perfusion, known as the ischemic penumbra.

**Ischemic Penumbra.** The territory surrounding the ischemic core represents tissue with mild or moderate reductions in blood flow, typically to 50%–75% of normal levels.<sup>3,4</sup> This ischemic penumbra is of variable size, depending on the de-





**Fig 4.** Localized hypoperfusion in temporal lobe epilepsy. Interictal ASL CBF map in a 37-year-old woman demonstrates low signal intensity in the right lateral temporal lobe (arrow) and right hippocampus. Electroencephalography confirmed a right temporal seizure focus.

gree of collateral flow from unaffected territories and the length of time from stroke onset. The penumbra is generally accepted as the volume of brain showing a perfusion  $>$  DWI mismatch. ASL CBF maps show this area as a larger region of diminished signal intensity (Fig 1). It is the ischemic penumbra that may benefit most from thrombolytic strategies if identified in a timely fashion.

**Chronic Cerebrovascular Occlusive Disease.** In patients with carotid or other proximal arterial stenosis, tissue at risk for subsequent ischemia and infarction can be identified with spin-tag perfusion, though a current limitation of most versions of ASL is the inability to assess CBV, a sensitive metric for at-risk tissue. However, transit time maps can be generated with ASL by imaging at additional inversion times.<sup>2</sup> If CBF is relatively decreased with a compensatory increase in CBV, a side-to-side flow asymmetry can be appreciated representing at-risk tissue that may benefit from stent placement, endarterectomy, or bypass (Fig 2). A focal decrease in signal intensity of compromised CBF can be seen most commonly in the anterior or posterior watershed zones. A common feature also seen is linear high signal intensity representing slow flow or collateral flow in cortical vessels. Depending on the implementation of

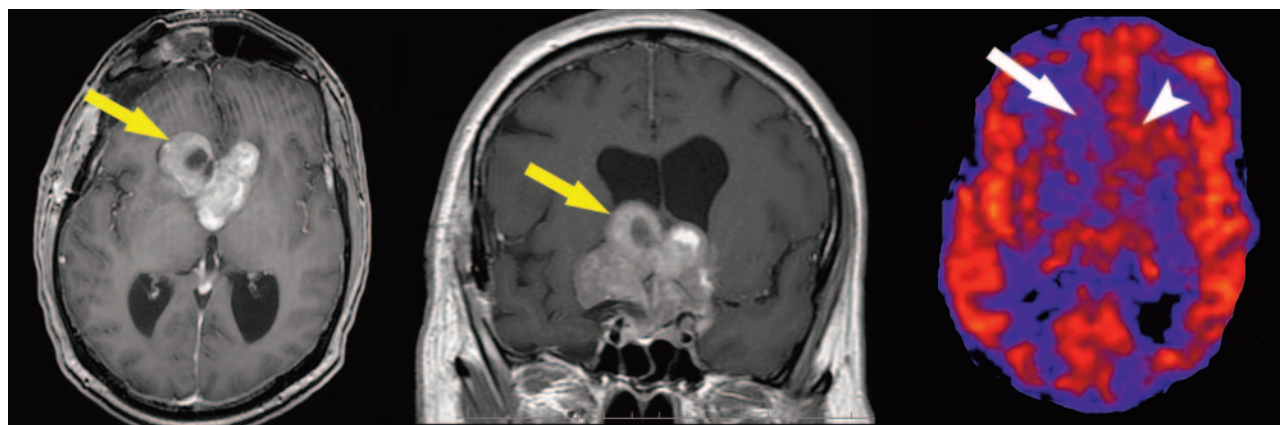
the ASL sequence, crusher gradients can be used to suppress this slow flow in cortical vessels. Because of its repeatability, ASL is particularly capable of assessing cerebrovascular reserve in these patients by obtaining CBF maps before and after an acetazolamide or hypercapnia challenge. Finally, serial assessment following revascularization or confirmation of the post-endarterectomy hyperperfusion syndrome is feasible with ASL.<sup>5</sup>

**Chronic Microvascular Ischemia.** Focally decreased or patchy CBF in the hemispheric white matter may occasionally be seen on ASL maps and usually corresponds with T2 and fluid-attenuated inversion recovery (FLAIR) hyperintensities on conventional MR imaging. Patients with a history of diabetes mellitus or hypertension may have patchy signal intensity in the centrum semiovale, despite preservation of symmetric gray matter CBF. However, ASL in general is not commonly used to evaluate quantitative white matter blood flow because it is known to overestimate low-flow states and because of low white matter perfusion signal-to-noise ratio.

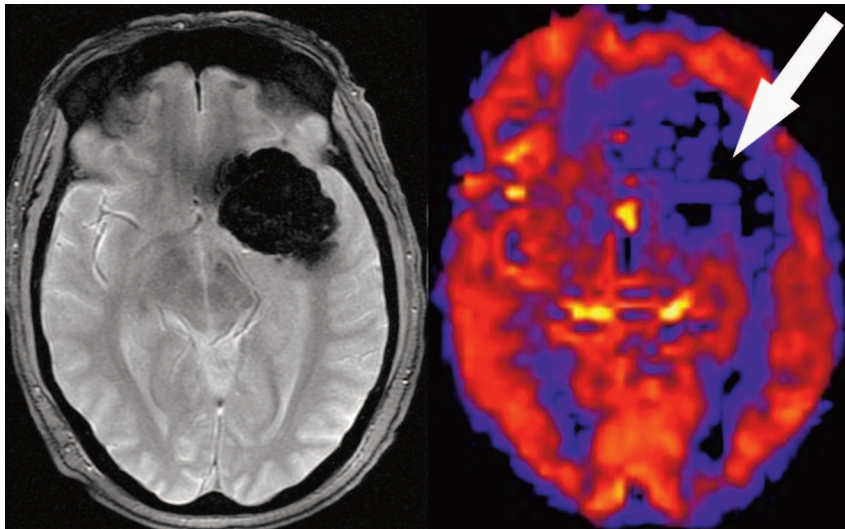
**Encephalomalacia and Ventriculomegaly.** Predictably, regions of encephalomalacia as a result of remote insult, surgical resection cavity, and so forth are devoid of perfused tissue and are represented as focal areas of low signal intensity on the CBF map (Fig 3). Similarly, enlargement of the lateral ventricles may result in large central areas of signal-intensity void on the ASL CBF maps.

**Seizure Activity.** Decreased perfusion is commonly observed in epileptogenic zones on perfusion imaging in the interictal phase. Figure 4 demonstrates asymmetrically low-perfusion signal intensity in the right temporal lobe in a patient with intractable epilepsy. Extensive literature based on interictal single-photon emission CT (SPECT) has established that seizure foci and adjacent territories often have relative hypoperfusion, though controversy exists as to whether the interictal hypoperfused region or the ictal hyperperfused region is more sensitive in predicting the seizure focus.<sup>6</sup> Nevertheless, diminished ASL signal intensity in a patient with epilepsy and without risk factors for cerebral ischemia is suggestive of an epileptogenic territory in the interictal phase.

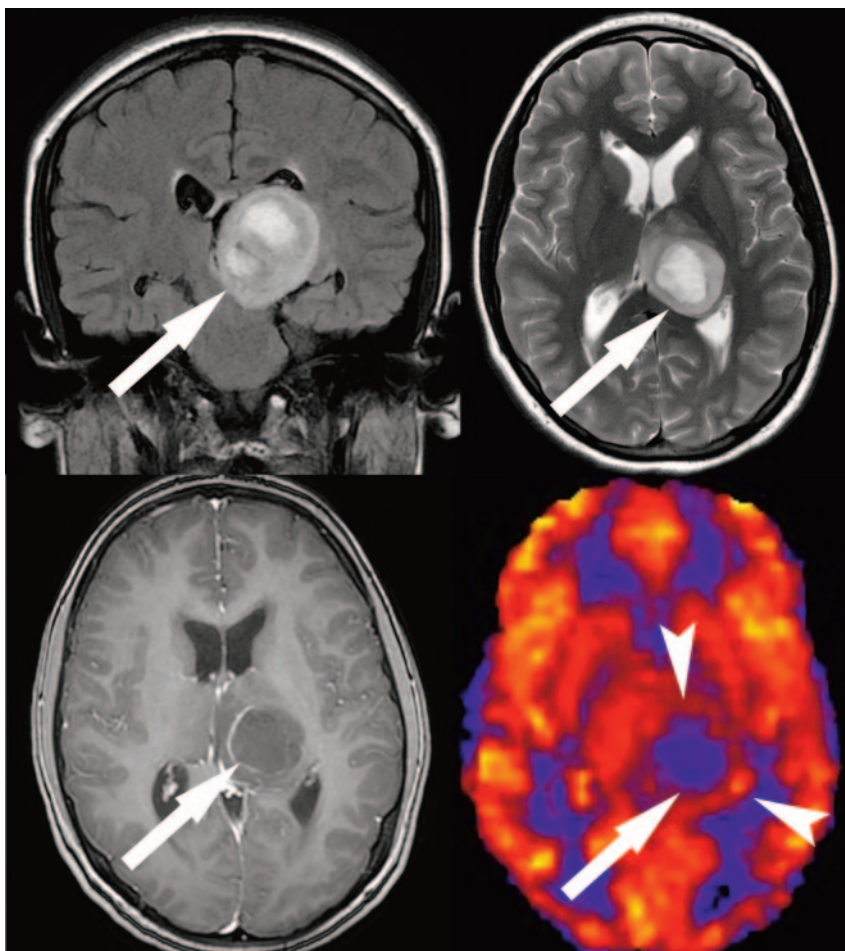
An advantage of using ASL to assess cerebral perfusion in epilepsy is that it can be performed at multiple times before,



**Fig 5.** Hyperperfused tumor on ASL. Axial (left) and coronal (center) gadolinium-enhanced T1-weighted images demonstrate a heterogeneously enhancing mass invading the third and lateral ventricles (yellow arrows). ASL (right) shows regional hypoperfusion within the more cystic portion of the tumor (white arrow). The solid portions show hyperperfusion on ASL (arrowhead). The tumor proved to be a pituitary macroadenoma at surgery.



**Fig 6.** Paradoxically low signal intensity on ASL. T2\*-weighted gradient-recall image reveals a calcified mass arising from the left sphenoid wing. The mass showed avid contrast enhancement (not shown) consistent with meningioma. Despite the enhancement, ASL CBF map shows no increased flow within the tumor (*arrow*). Underlying hyperperfusion may be masked by competing susceptibility effects.

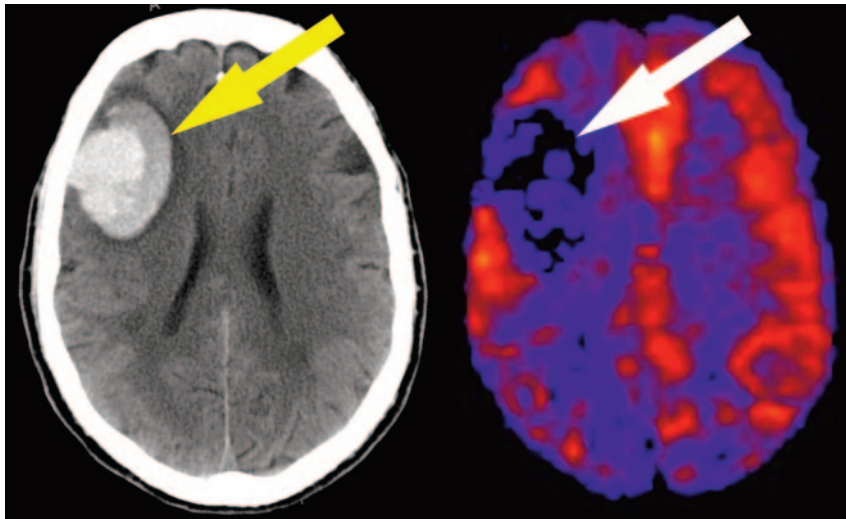


**Fig 7.** Hypoperfused glioma on ASL. Coronal FLAIR (upper left) and axial T2 (upper right) images demonstrate a high-signal-intensity mass in the left thalamus (*white arrows*). Minimal enhancement is seen after contrast (lower left), with corresponding low perfusion on the CBF map (*white arrow*, bottom right). The rim of normal perfusion (*arrowheads*) corresponds to the residual normal tissue in the adjacent thalamus.

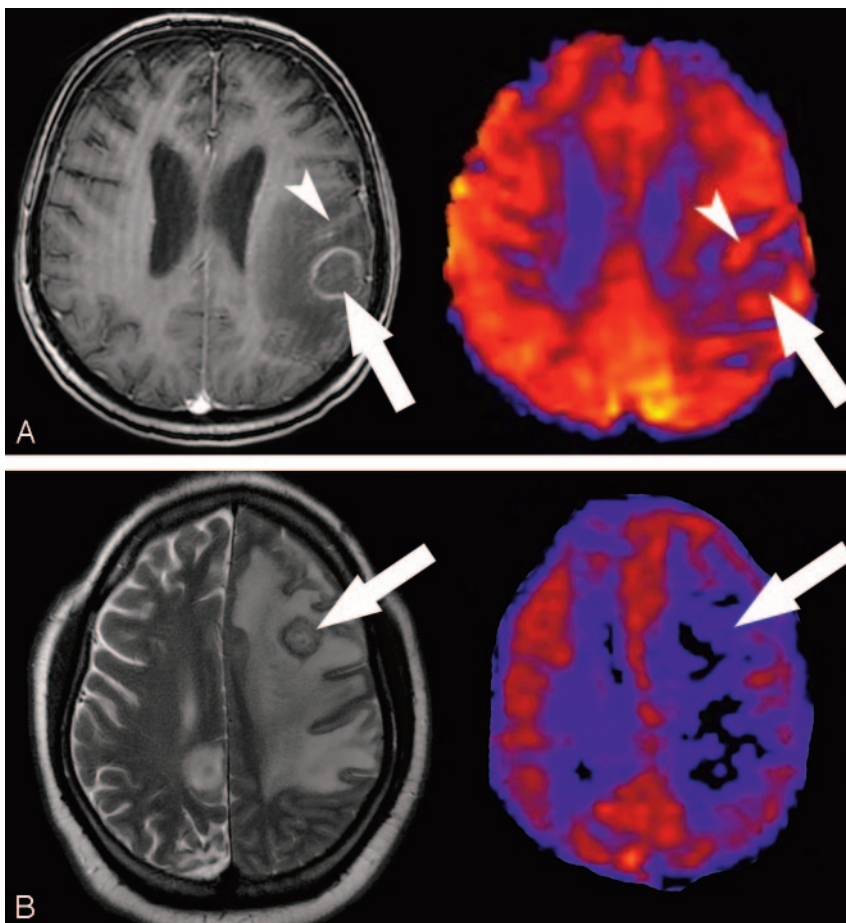
during, and after the ictal event and provides superior temporal resolution to SPECT due to the very short half-life of the spin tag. Another clear advantage of ASL is the consolidated imaging work-up it can provide in combination with structural MR imaging for mesial temporal sclerosis and neocortical epilepsies. Seizure activity can also be associated with focal or regional hyperperfusion, a pattern that is described in further detail in Part 3 of this series.

**Neoplasms.** Brain tumors can demonstrate patterns of hypo- or hyperperfusion. In general, enhancement in the tumor does not correlate with the perfusion pattern. Figure 5 illustrates a lack of significant hyperperfusion despite avid enhancement within the tumor. A heterogeneously enhancing meningioma with a focal perfusion deficit is shown in Fig 6. Calcification associated within the mass likely contributes to this apparent hypoperfusion. Low-grade gliomas typically





**Fig 8.** Blood products on ASL. Axial unenhanced CT scan reveals acute parenchymal hemorrhage in the right frontal lobe (*yellow arrow*). Focal loss of signal intensity on the ASL CBF map (*white arrow*) corresponds to the area of hemorrhage. Note flow asymmetry with decreased signal intensity throughout the right hemisphere.



**Fig 9.** A, Toxoplasmosis on ASL. Decreased perfusion to a toxoplasmosis abscess. Ring-enhancing lesion is demonstrated on corresponding postgadolinium T1-weighted image (*arrow*). The edema surrounding the abscess decreases the perfusion of the white matter, accentuating the normal perfusion of the adjacent gyri. The area of high signal intensity on ASL surrounding the abscess (*arrowhead*) represents the normal adjacent gray matter. B, Toxoplasmosis on ASL. Axial T2-weighted image (left) shows a mass with vasogenic edema in the left frontal lobe (*arrow*). Corresponding ASL image (right) shows diffusely decreased perfusion in the lesion and adjacent white matter (*arrow*).

demonstrate hypoperfusion patterns (Fig 7).<sup>7</sup> In our experience, metastases can also demonstrate patterns of hypo- or hyperperfusion.

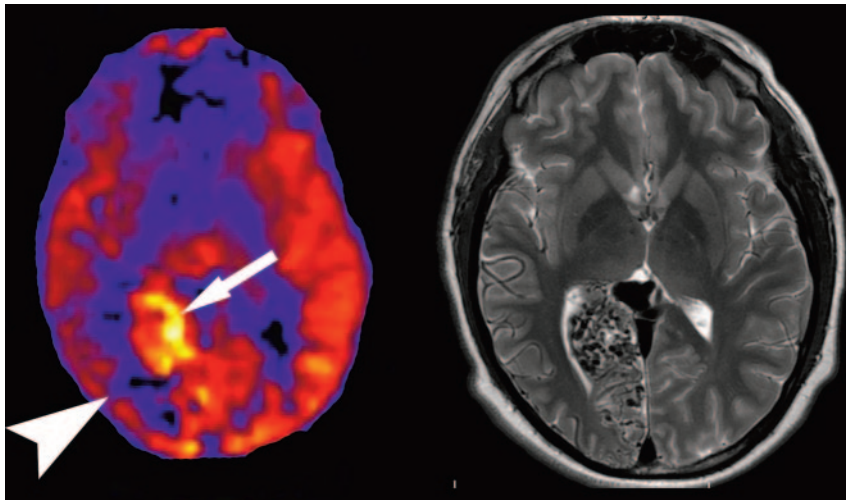
**Hematomas.** Hematomas demonstrate focal areas of hypoperfusion (Fig 8). This can result from a lack of both vascularity and susceptibility effects associated with the blood products.

**Infection.** Cerebral abscesses are characterized by focal areas of decreased perfusion to the lesions as well as decreased perfusion in surrounding edema. The enhancing rim can demonstrate some increased perfusion signal intensity (Fig 9A, -B).

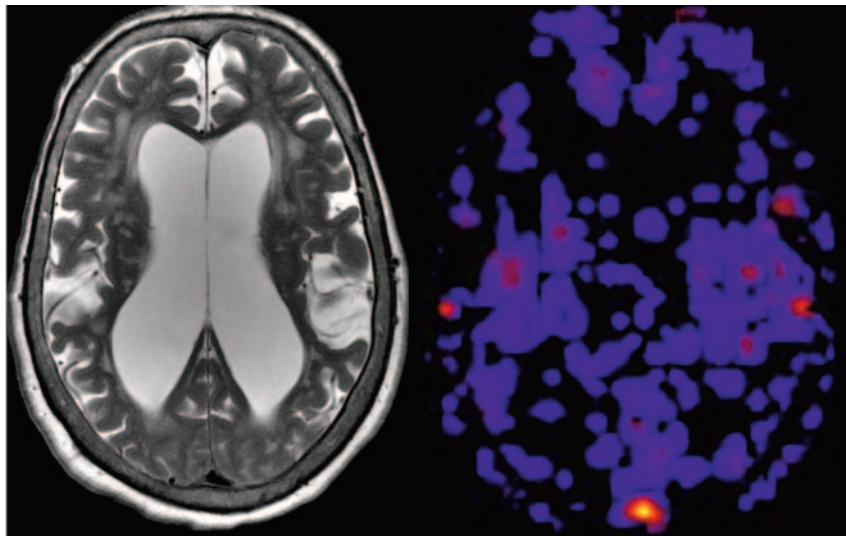
**Arteriovenous Malformation Steal.** Arteriovenous malformations (AVM) characteristically show marked hyperperfusion on PASL. The high-flow state in the AVM can cause a steal phenomenon and result in hypoperfusion in the adjacent parenchyma (Fig 10).

#### **Globally Decreased Signal Intensity**

Global decreases in perfusion signal intensity are commonly found in clinical ASL. Low-flow states, decreased brain volume, vasospasm, and exogenous drugs may result in decreased perfusion. Gadolinium-based contrast agents represent an ar-



**Fig 10.** Steal phenomenon associated with AVM. ASL CBF map shows characteristic hyperperfusion corresponding to the AVM (arrow). Also seen is a regional zone of hypoperfusion representing the associated steal phenomenon (arrowhead).



**Fig 11.** Cerebral atrophy as a cause of globally decreased ASL signal intensity. T2-weighted image (left) reveals advanced cerebral volume loss, ex vacuo ventricular enlargement, and white matter hyperintensities. ASL map demonstrates poor perfusion signal intensity throughout.

tifactual cause of severely reduced global ASL signal intensity (described in Part 1<sup>1</sup>).

**Poor Cardiac Output.** A major uncertainty in the absolute quantification of CBF in clinical ASL arises from the widely variable transit times of the magnetic tag applied to inflowing spins. A typical clinical patient mix includes individuals with decreased cardiac output, arrhythmias, and other instabilities that magnify the bulk flow effects inherent in nonzero delay time ASL imaging. Luh et al<sup>8</sup> have demonstrated, by using cardiac gating during ASL, that even in healthy volunteers, T1-saturation efficiency is reduced when tagging below the brain. Thus the effects of possible hemodynamic compromise, even in the absence of flow-limiting stenoses, should be considered when one is confronted with global reductions in ASL signal intensity. Tagging planes immediately proximal to the imaging slab or velocity-selective tagging may lessen these effects due to bulk flow.<sup>9</sup> Further investigations are needed to evaluate the effects of heart rate variation and diminished cardiac output on clinical ASL.

**Aging and Cerebral Atrophy.** Enlargement of the CSF-containing spaces due to age-related or neurodegenerative cerebral atrophy is a common cause of globally decreased signal intensity on ASL maps in a typical clinical population (Fig 11). In fact, higher than expected global signal intensity in a patient

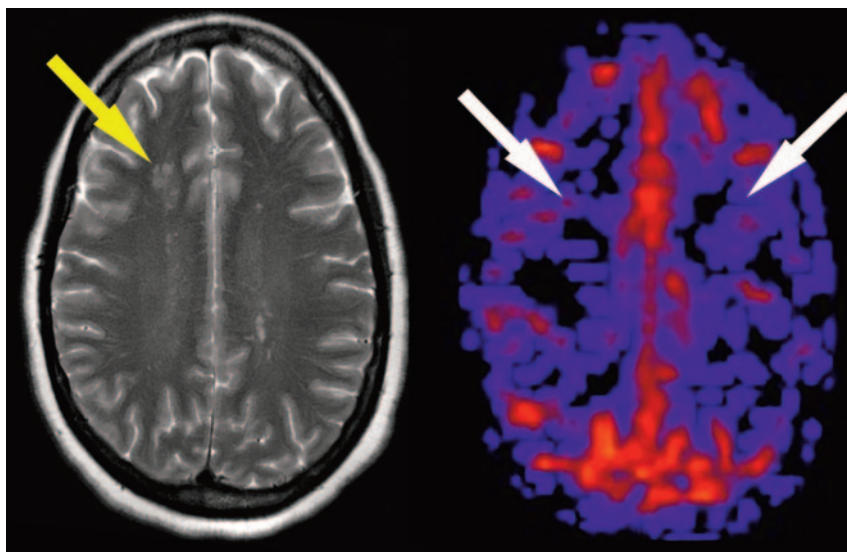
with atrophic changes on conventional MR images should prompt a search for possible causes of underlying hyperperfusion, such as hypercapnia or a recent anoxic insult. Age-dependent decreases in perfusion signal intensity are well-documented and must be accounted for when interpreting ASL in older patients.<sup>10</sup>

**Vasculitis and Cerebral Vasospasm.** Clinical spin-tag perfusion imaging may be useful in demonstrating the effects of central nervous system (CNS) vasculitis and may aid in the diagnosis and serial posttreatment follow-up of these patients. Figure 12 demonstrates low signal intensity in bilateral cerebral hemispheres in a young patient diagnosed with cannabinoid-induced CNS vasculitis.

Following subarachnoid hemorrhage, delayed cerebral vasospasm occurs in up to one third of patients and is particularly prevalent in cases with cisternal accumulation of blood. In a study by Leclerc et al,<sup>11</sup> brain SPECT demonstrated focal or diffuse hypoperfusion in 10 of 11 patients with vasospasm and was more sensitive than dynamic susceptibility contrast MR imaging to states of hypoperfusion. A consolidated MR imaging approach to assessing vasospasm can be incorporated by using ASL because timely diagnosis is critical.

**Exogenous Agents.** Another effect to be considered when confronted with lower than expected global CBF is that pro-





**Fig 12.** Bilateral hypoperfusion in CNS vasculitis. Multiple white matter lesions are shown on the T2-weighted image (yellow arrow). ASL CBF map demonstrates symmetrically decreased signal intensity in the bilateral cerebral hemispheres (white arrows) in a 38-year-old woman with CNS vasculitis.

duced by exogenous agents such as caffeine, known to reduce resting perfusion through its blockade of adenosine receptors in brain microvasculature. A growing volume of data supports the need to control for caffeine use in perfusion-sensitive sequences such as blood oxygen level–dependent functional MR imaging and ASL.<sup>12–14</sup> Certain antihypertensive agents and cocaine have also been shown to decrease resting cerebral perfusion, though recent studies have demonstrated preservation of CBF during short- and long-term treatment of moderate hypertension.<sup>15,16</sup>

**Brain Death.** ASL is sensitive in demonstrating states of hypoperfusion. However, despite its potential for providing a convenient alternative to other more invasive brain death studies, small system instabilities such as motion or incomplete tissue saturation, which might mimic true regions of perfusion, limit the use of ASL for this indication. Suggestion of brain death due to globally decreased signal intensity on ASL CBF maps should be correlated with the clinical scenario and other available imaging tests.<sup>17</sup>

## Conclusion

ASL is an emerging MR perfusion technique, which has promising potential when used in a clinical population. Clinical ASL data can be classified into distinct patterns on the basis of the distribution of high- and low-perfusion signal intensity. These patterns can represent increases or decreases in signal intensity on a global or localized scale. When signal intensity decreases are identified on ASL CBF maps, recognition of such patterns and their causes can lead to improved diagnostic accuracy.

## Acknowledgment

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