Radiology

Symptomatic Carotid Artery Stenosis: Impairment of Cerebral Autoregulation Measured at the Brain Tissue Level with Arterial Spin-labeling MR Imaging[1]

Reinoud P. H. Bokkers, MD
Matthias J. P. van Osch, PhD
H. Bart van der Worp, MD, PhD
Gert J. de Borst, MD, PhD
Willem P. T. M. Mali, MD, PhD
Jeroen Hendrikse, MD, PhD

Purpose: To measure the cerebral autoregulatory status of the brain tissue supplied by the individual brain-feeding arteries in patients with symptomatic stenosis of the internal carotid artery (ICA) by using arterial spin-labeling (ASL) magnetic resonance (MR) imaging and to compare this status with that in healthy controls.

Materials and Methods: Institutional review board approval and informed consent were obtained. Twenty-three patients (mean age, 69.3 years ± 8.0 [standard deviation]) with unilateral symptomatic stenosis of the ICA and 20 healthy controls (mean age, 66.8 years ± 6.3 [standard deviation]) underwent perfusion and flow territory–selective ASL MR imaging before and after intravenous administration of acetazolamide. Cerebrovascular reactivity was measured throughout the brain in the gray matter that is supplied by the individual ICAs and the basilar artery. Data were analyzed with paired and unpaired t tests.

Results: In patients with symptomatic stenosis of the ICA, the flow territory of the symptomatic ICA was smaller than that of the asymptomatic ICA. After administration of acetazolamide, a significant increase in cerebral blood flow at the brain tissue level was measured in both control subjects and patients in all perfusion territories. Mean cerebrovascular reactivity values were 35.9% ± 3.0% (standard error) and 44.6% ± 3.5% (standard error) in the flow territories of the patients with symptomatic ICAs and those with asymptomatic ICAs, respectively, and 47.9% ± 3.1% (standard error) in the control subjects. Cerebrovascular reactivity was lower in the flow territory of the symptomatic ICA than in the arteries of control participants (mean difference, −12.0%; 95% confidence interval: −20.7%, −3.3%).

Conclusion: In patients with symptomatic stenosis of the ICA, vasodilatory capacity in the flow territories of the major cerebral arteries can be visualized and quantified at the brain tissue level with ASL MR imaging.

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Radiology

Patients with symptomatic stenoses of the carotid artery have a high risk for ischemic stroke (1,2). In these patients, impairment of the vasodilatory capacity of the cerebral vasculature is an important measure of the degree of hemodynamic compromise (3). Autoregulatory vasodilatation of the terminal arterioles sustains normal perfusion by reducing the vascular resistance to arterial inflow (4,5). In patients with a recent cerebral ischemic event, the vasodilatory capacity, or cerebrovascular reactivity, is reduced compared with that in patients without symptoms (6). Ischemic events occur more frequently in patients with both high-grade stenoses and impaired cerebrovascular reactivity than in those with high-grade stenosis but normal reactivity (7–11).

There are two basic strategies for measuring cerebral vasodilatory capacity. In the first strategy, flow velocity in a major cerebral artery is measured before and after administration of a vasodilatory stimulus. The increase in blood flow reflects the dilatory capacity of the vasculature distal to the artery (12). The second strategy measures cerebral perfusion at the brain tissue level before and after a vasodilatory challenge with techniques such as positron emission tomography (PET), computed tomography, single photon emission computed tomography, or dynamic susceptibility contrast–enhanced magnetic resonance (MR) imaging (13,14). A disadvantage of these imaging methods is that they are invasive and require ionizing radiation or contrast agents. Furthermore, a steno-occlusive lesion in one of the brain-feeding arteries may lead to a shift in the perfusion territories of these arteries (15,16); such a shift would make it difficult to measure vasodilatory capacity in the complete territory of an individual artery.

Arterial spin labeling (ASL) is an MR imaging technique for measuring cerebral blood flow (CBF) at the brain tissue level. It uses radiofrequency pulses to noninvasively label water protons in blood (17–19). In conjunction with a vascular challenge, ASL MR imaging can be used to measure the vasodilatory capacity throughout the brain at high spatial resolution (20,21). Furthermore, with the recent introduction of flow territory–selective ASL techniques, it is also possible to visualize the perfusion territories of the individual brain-feeding arteries (22,23). By combining quantitative perfusion with flow territory–selective ASL, it is possible to simultaneously assess both the cerebral hemodynamic status at the brain tissue level and the flow territories of the major brain-feeding arteries.

The aim of our study was to measure the cerebral autoregulatory status of the brain tissue supplied by the individual brain-feeding arteries in patients with symptomatic stenosis of the internal carotid artery (ICA) by using ASL MR imaging and to compare this status with that in healthy controls.

Materials and Methods

The study was approved by the institutional ethical review board, and written informed consent was obtained from all participants.

Subjects

Twenty-three patients (13 men and 10 women; mean age, 69.3 years ± 8.0 [standard deviation]) with recently symptomatic unilateral stenosis of the ICA (≥50% blockage) referred to the Department of Radiology at the University Medical Center Utrecht for diagnosis and grading of the stenosis were prospectively included in our study between January 2008 and February 2009. All patients had sustained a transient ischemic attack or nondisabling ischemic stroke ipsilateral to the stenosis of the ICA. Patients were excluded from the study if they had diabetes mellitus ($n = 7$), had severe renal ($n = 3$) or hepatic ($n = 2$) dysfunction, or had experienced a severe stroke causing major disability (score of 3–5 on the modified Rankin scale; $n = 6$) (24). Stenosis of the ICA was graded with duplex ultrasonography. The control group consisted of 20 healthy volunteers (12 men and 8 women; mean age, 66.8 years ± 6.3 [standard deviation]). All control participants were recruited through local media advertisements and had no history of neurologic disease or vascular abnormality at MR imaging or MR angiography of the brain.

MR Imaging

All MR imaging investigations were performed with a 3-T MR imager (Achieva; Philips Medical Systems, Best, the Netherlands) equipped with an eight-channel head coil and locally developed software to enable ASL MR imaging.

Advances in Knowledge

- In patients with symptomatic stenosis of the internal carotid artery (ICA), decreased vasodilatory capacity was measured with arterial spin-labeling (ASL) MR imaging in the brain tissue supplied by the symptomatic ICA.
- The flow territory of the symptomatic ICA was smaller than that of the contralateral asymptomatic ICA.

Implication for Patient Care

- With further testing and validation, reactivity measurements with ASL MR imaging may be used as a diagnostic tool in patients with symptomatic stenosis of the ICA to evaluate cerebral autoregulation.

Both patients and volunteers underwent ASL perfusion MR imaging before and 15 minutes after intravenous administration of 14 mg per kilogram of body weight of acetazolamide (Goldshield Pharmaceuticals, Croydon Surrey, United Kingdom). A T1-weighted spin-echo sequence was obtained in the sagittal plane for positioning of the imaging section. Perfusion imaging was performed with a pseudocontinuous ASL sequence (25). Labeling was performed by using a train of 18°, 0.5 msec, Hanning-shaped radiofrequency pulses at an interpulse pause of 0.5 msec, for a duration of 1650 msec, in combination with a balanced gradient scheme (26,27). The control studies, which were done without labeling of arterial blood, were achieved by adding 180° to the phase of all even radiofrequency pulses.

Imaging was performed with single-shot echo planar imaging in combination with parallel imaging (MR imaging with sensitivity encoding factor, 2.5) 1525 msec after the labeling stopped. ASL MR imaging was performed in combination with background suppression, which consisted of a saturation pulse immediately before labeling and inversion pulses at 1680 and 2830 msec after the saturation pulse (28). The perfusion images, consisting of 17 7-mm sections aligned parallel to the orbitomeatal angle, were acquired in ascending fashion with an in-plane resolution of 3 × 3 mm. The other ASL MR imaging variables were as follows: repetition time msec/echo time msec, 4000/14; pairs of control per label, 38; field of view, 240 × 240 × 119 mm; matrix, 80 × 79; and scanning time, 5 minutes.

To determine the flow territories of the ICAs and the basilar artery, flow territory–specific perfusion images were acquired with selective ASL according to a previously published protocol (29,30). Selective labeling was accomplished by spatial manipulation of the labeling efficiency within the labeling plane by applying additional gradients between the labeling pulses in sets of five dynamics: no labeling applied (control), nonselective labeling applied (globally perfusion weighted),

labeling varied in right-to-left direction (distance of 50 mm between full label and control situation), labeling varied in anteroposterior direction (distance of 18 mm between full label and control situation), and labeling varied in a different anteroposterior direction (shifted 9 mm in posterior direction compared with the previous dynamic). The flow territories of the left ICA, the right ICA, and the basilar artery were identified with k-means clustering (31). An inversion-recovery sequence was acquired to measure the magnetization of arterial blood and for segmentation purposes. Both the flow territory–selective ASL and inversion-recovery images were acquired with the same geometric variables and resolution as the quantitative perfusion ASL images. T2-weighted fluid-attenuated inversion-recovery images were acquired for detecting areas with tissue infarction by using the following variables: 11000/125; inversion time, 2800 msec; matrix size, 240 × 240 with 24 sections; and section thickness, 2 mm.

Data Analysis

Data were analyzed with Matlab (version 7.5; MathWorks, Natick, Mass), and SPM5 (Wellcome Trust Centre for Neuroimaging, Oxford, England).

CBF (with units of mL · 100 mL^{-1} · min^{-1}) was calculated from the ASL MR images according to a previously published model (32). The T2* of arterial blood and T1 of blood were assumed to be 50 and 1680 msec, respectively (33,34). The water content of blood was assumed to be 0.76 mL per milliliter of arterial blood (35). The mean resting magnetization of the blood in all volunteers was determined by selecting a region of interest in the cerebrospinal fluid and iteratively fitting the inversion-recovery data according to a previously outlined procedure (35).

Cerebrovascular reactivity was defined as the percentage of increase in CBF after administration of acetazolamide. The CBF of the white and the gray matter of the individual perfusion territories of the ICAs and basilar artery were measured before and after acetazolamide administration. For the

placement of the regions of interest throughout all sections, three preprocessing steps were performed (Fig 1). First, a surrogate T1-weighted image was calculated from the inversion-recovery sequence by calculating the reciprocal of the quantitative T1 and subsequently segmented with SPM5 software into gray and white matter probability maps. Thresholding was applied to avoid partial voluming of white and gray matter. Second, the flow territories of the participants' ICAs and basilar artery were defined. This was done by manually segmenting the perfusion territories of the individual arteries, as determined with the flow territory–selective ASL sequence with the clustering algorithm. On all 17 sections, the flow territory border of the regional perfusion image was delineated by one observer (R.P.B., with 4 years of MR imaging experience), as shown in Figure 1. The final step was to combine the gray matter mask and flow territory masks. Areas of hyperintensity on the fluid-attenuated inversion-recovery MR images, depicting areas of infarction, were manually excluded from the region of interest. To correct for motion, all images obtained before and after administration of acetazolamide were coregistered with the SPM5 software to the baseline CBF map by using a least-squares approach and a six-parameter (rigid body) spatial transformation.

Flow territory maps of the individual brain-feeding arteries in the patients with stenosis of the ICA and healthy control participants were produced by normalizing the selective ASL images with SPM5 software to a standardized PET brain template. The segmentations of the flow territories were then pooled and projected onto a standardized T1-weighted anatomic image. The combined flow territory maps were color-coded to produce probability maps: 100% indicated that all participants demonstrated perfusion in that area of the brain and 0% indicated that no participant demonstrated perfusion in that region. The flow territory maps of patients with stenosis of the right ICA were mirrored in the midline, whereas flow
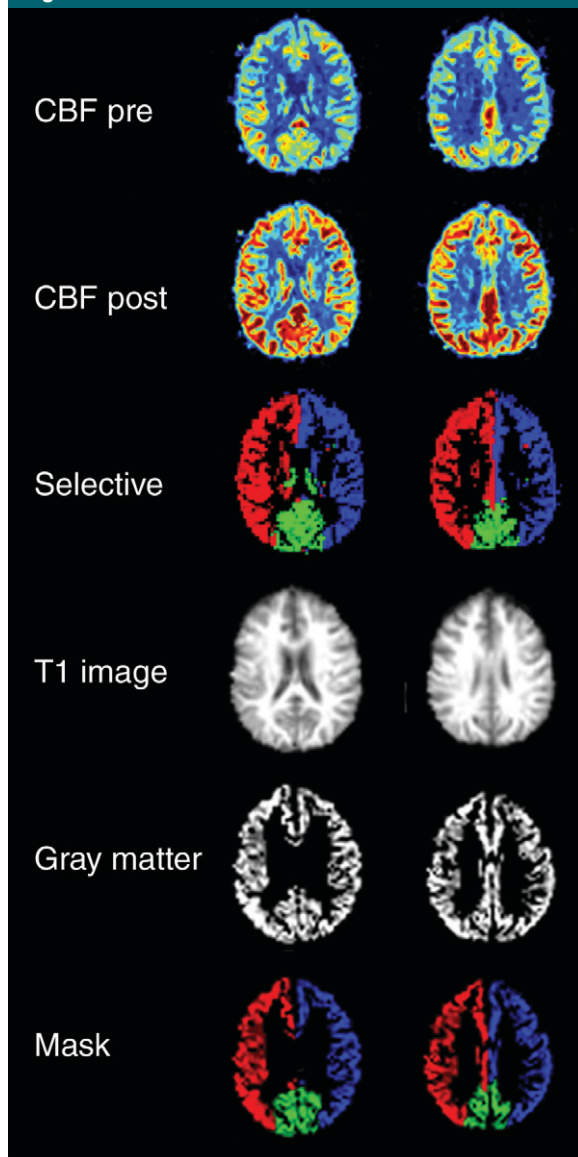
Figure 1

Figure 1: Pictorial description of postprocessing steps shows two of 17 sections obtained in a 56-year-old woman. First shown are transverse CBF maps before *(CBF pre)* and after *(CBF post)* administration of acetazolamide, respectively (4000/14; flip angle, 90°; 7-mm sections). Selective ASL images *(Selective)* show perfusion territory of right ICA (red), left ICA (blue), and basilar artery (green). T1-weighted image (2600/14; flip angle, 90°; 7-mm sections) was segmented into a gray matter probability map. By combining the gray matter map with cerebral flow territory information from the selective ASL image, a gray matter mask was obtained of both ICAs and the basilar artery.

territory maps of patients with left-sided stenosis remained unchanged. All images were displayed in radiologic coordinates.

We used SPSS (version 15.0.1; SPSS, Chicago, Ill) and Matlab software for statistical analysis. Descriptive statistical analyses were performed to summarize patient characteristics. Differences between measurements of CBF obtained before and after administration of acetazolamide and between the measurements of cerebrovascular reactivity of the flow territory of the symptomatic and of the contralateral asymptomatic ICA were assessed by using a paired t test. To compare the CBF and cerebrovascular reactivity measurements in the hemispheres ipsilateral and contralateral to the stenosis of the ICA with those values in the control group, an unpaired t test was used. Values were considered significantly different if the 95% confidence interval (CI) did not include zero (36). Because no differences were found in CBF or cerebrovascular reactivity between the left and right ICAs in the control group

(paired t test), values for both arteries were averaged for analysis. When patients were compared with controls, the data for controls were represented for each participant as the average between the hemispheres. Voxel-based χ^2 testing with Bonferroni correction (corrected for the number of brain voxels in the flow territory sections) was performed to analyze differences in the extent of the flow territories between the symptomatic and asymptomatic ICA in patients and control participants. Values are expressed as means ± standard errors unless otherwise specified.

Results

The demographic and clinical characteristics of the participants are outlined in Table 1. Figure 2 shows CBF maps before and after acetazolamide administration in a 69-year-old man with symptomatic stenosis of the right ICA. Figure 3 shows the segmented flow territory maps of the ICAs and the basilar artery, projected on a standardized brain template, for all patients with symptomatic stenosis of the ICA and for the healthy control participants. The flow territory of the stenosed ICA was significantly smaller than that in the healthy control participants. No changes in flow territory, indicative of intracranial steal, were observed after administration of acetazolamide in the patients with symptomatic stenosis of the ICA.

The flow territories of the symptomatic ICAs were significantly smaller than those of the asymptomatic ICAs and of the ICAs in control participants. Table 2 summarizes the CBF values before and after administration of acetazolamide in the flow territories of the ICAs ipsilateral and contralateral to the symptomatic stenosis and of the basilar artery. There was a significant ($P < .01$) increase in CBF at the brain tissue level in all perfusion territories in both healthy control participants and patients. In all flow territories, CBF was lower in patients than in the control group, but reduced cerebrovascular reactivity as compared with controls was observed only in the territory of the symptomatic ICA (mean

Table 1

Demographic and Clinical Characteristics of the Study Population

Characteristic	Healthy Control Subjects ($n = 20$)	Patients ($n = 23$)
Male*	12 (60)	13 (57)
Age (y)†	66.8 ± 6.3	69.3 ± 8.0
Men (y)†	67.6 ± 6.2	69.1 ± 7.5
Women (y)†	66.9 ± 6.3	69.6 ± 9.0
Degree of symptomatic ICA stenosis		
0%–49%	20	0
50%–69%	0	2
70%–99%	0	21
Occluded	0	0
Reason for presentation		
Transient ischemic attack	0	13
Ischemic stroke	0	6
Amaurosis fugax	0	4

Note.—Unless otherwise specified, data are numbers of patients.

* Data in parentheses are percentages.

† Data are means ± standard deviations.

Figure 2

Figure 2: Axial CBF maps (scale units of mL · 100 mL^{-1} · min^{-1}) (4000/14; flip angle, 90°; 7-mm sections) before *(CBF pre)* and after *(CBF post)* administration of acetazolamide in a 69-year-old man with symptomatic stenosis of the right ICA. Decreased CBF and decreased cerebrovascular reactivity (scale units of percentage CBF increase) can be appreciated, especially in the top sections, in the flow territory of the affected right ICA. For selective ASL image, green = right ICA territory, blue = left ICA territory, red = basilar artery territory; *FLAIR image* = fluid-attenuated inversion-recovery MR image.

difference, −12.0%; 95% CI: −20.7%, −3.3%). In the perfusion territory of the symptomatic ICA, the cerebrovascular reactivity was nonsignificantly lower in the six patients who had experienced stroke (34.8% ± 15.5) than in the 13 patients who had experienced a transient ischemic attack (36.6% ± 15.8; mean difference, 1.8% [95% CI: −14.6%, 18.2%]) or the four patients with amaurosis fugax (35.3% ± 10.0; mean difference, 0.5% [95% CI: −20.0%, 20.9%). Cerebrovascular reactivity was lower ($P < .01$) in the flow territory of the symptomatic ICA than in the contralateral asymptomatic ICA (mean difference, −8.7%; 95% CI: −12.5%, −4.8%). No difference in reactivity was observed between the asymptomatic ICA and the arteries of the healthy control participants (mean difference, 4.7%; 95% CI: −12.9%, 6.3%).

Discussion
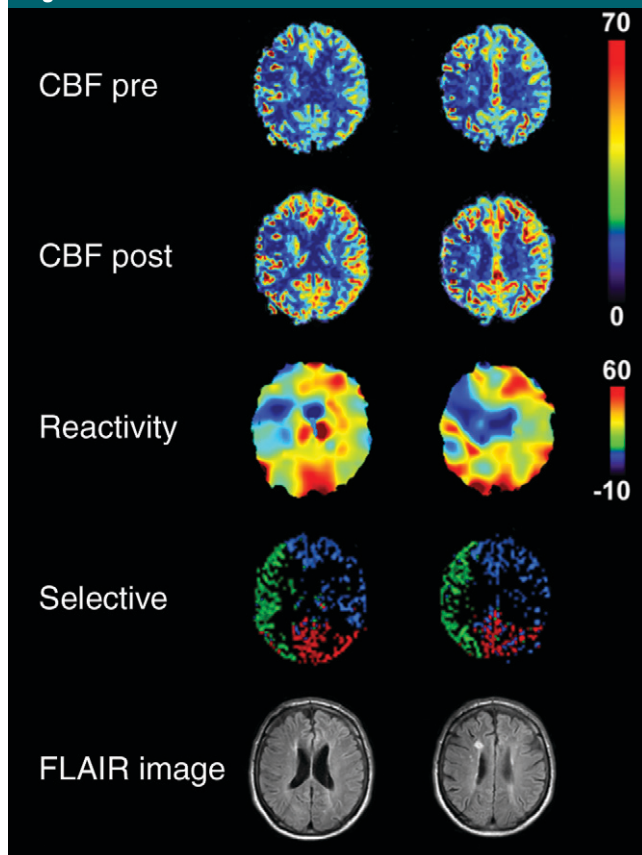
In the present study, we were able to assess the hemodynamic status in the individual flow territories of the major brain-feeding arteries. Patients with symptomatic stenosis of the ICA had decreased cerebral vasodilatory capacity, as measured with ASL MR imaging in the brain tissue supplied by the symptomatic ICA, when compared with the contralateral ICA and arteries in healthy control participants. We also found that the flow territory of the symptomatic ICA was smaller than that of the asymptomatic contralateral ICA.

Our results are in line with those of studies that have investigated reactivity by measuring the increase in flow velocity with transcranial Doppler in the major cerebral arteries (37–39) and with studies that assessed reactivity at the brain tissue level in patients with symptomatic stenosis of the carotid artery (40–42). In those studies, regions of interest were selected on the basis of traditional flow territory maps. However, a steno-occlusive lesion in the ICA can lead to a considerable shift in the flow territories of the brain-feeding arteries (43). This shift affects the reliability of these maps. The only cerebrovascular reactivity
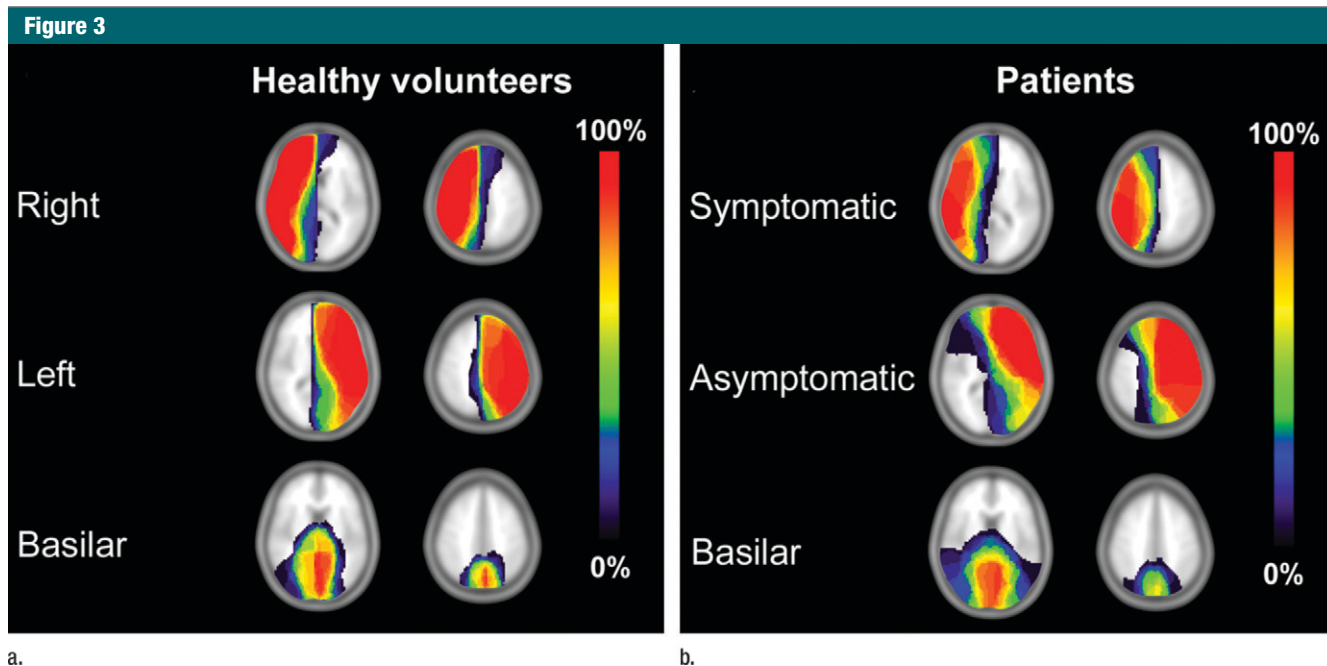
Figure 3

Figure 3: Axial perfusion territory maps projected on a standardized brain template for right ICA, left ICA, and basilar artery in **(a)** healthy control participants ($n = 20$) and **(b)** patients with symptomatic ICA stenosis ($n = 23$). Scale indicates percentage of individuals in that group who had perfusion in that area.

Table 2

CBF before and after Acetazolamide Administration and Reactivity

Group and Artery	CBF (mL · 100 mL^{-1} · min^{-1})		Reactivity (%)
	Before Acetazolamide	After Acetazolamide	
Healthy control subjects			
ICA	52.2 ± 1.8	77.4 ± 3.2*	47.9 ± 3.1
Basilar artery	48.7 ± 2.6	82.6 ± 4.8*	69.9 ± 4.8
Patients			
Symptomatic ICA	44.7 ± 1.9	60.9 ± 3.0*	35.9 ± 3.0†‡
Asymptomatic ICA	43.1 ± 2.4	61.5 ± 3.1*	44.6 ± 3.5
Basilar artery	42.9 ± 2.5	66.5 ± 3.7*	56.7 ± 3.9

Note.—Data are means ± standard errors.

* Significant increase in CBF after administration of acetazolamide (paired t test).

† Significant difference in cerebrovascular reactivity between patients and control subjects (paired t test).

‡ Significant difference in cerebrovascular reactivity between symptomatic and asymptomatic ICA flow territories (paired t test).

studies that have assessed the autoregulatory status of the efferent vasculature of the stenosed carotid are those with transcranial Doppler imaging (37–39). A disadvantage of this technique is that it measures the global increase in blood flow velocity in a major cerebral artery and does not assess perfusion changes at the tissue level. By combining quantitative perfusion with flow territory–selective ASL, we were able to noninvasively assess the hemodynamic status

at the brain tissue level and simultaneously visualize the perfusion territories of the major brain-feeding arteries. Our finding of a smaller flow territory of the ICA that is ipsilateral to the stenosis indicates that the affected hemisphere is supplied with blood through collaterals from the contralateral ICA and vertebrobasilar arteries.

One study has assessed cerebrovascular reactivity with ASL MR imaging in patients with cerebrovascular disease

(20). In 12 patients with a symptomatic, anterior circulation, large artery stenosis, cerebrovascular reactivity was measured by using a continuous ASL approach at 1.5 T. Changes in CBF after administration of acetazolamide varied from focal and diffuse vasodilatory failure to normal autoregulation. In the present study, we included a healthy control group to avoid potential effects of generalized atherosclerosis. Furthermore, at 3 T, ASL MR imaging benefits from an increased T1 decay and higher signal-to-noise ratio relative to 1.5-T imaging. With the introduction of pseudocontinuous labeling schemes and background suppression, the quality of ASL images has improved substantially. This improvement is of special importance for reactivity measurements when differences in perfusion before and after a challenge are measured.

The decision to perform carotid endarterectomy or stenting in patients with carotid artery stenosis does not depend on the presence and severity of cerebral hemodynamic impairment (44). Guidelines for the treatment of carotid stenosis are based primarily on large randomized clinical trials in which

cerebral perfusion and hemodynamic reserve capacity were not considered. However, observational studies have strongly suggested that the risk for ischemic stroke is higher in patients with impaired cerebrovascular reactivity in the hemisphere ipsilateral to symptomatic or asymptomatic carotid stenosis than in those with normal perfusion (11,45). Assessment of the cerebrovascular reactivity at the brain tissue level with ASL MR imaging may therefore be used in future studies to noninvasively select patients at the highest risk for stroke who may benefit most from revascularization.

A limitation of the pulsed continuous ASL technique used in the present study is that the labeling of the arterial water spins is flow dependent. With an increase in flow velocity in the brain-feeding arteries as a result of administration of acetazolamide, the efficiency of labeling may decrease, leading to a reduction in the amount of blood that is labeled and, subsequently, to a lower CBF and vascular reactivity. However, this effect will be present in all arteries. Furthermore, with this ASL technique, the images are made 1525 msec after labeling. It is possible that because of the increase in blood flow after administration of acetazolamide, the blood flows faster from the supplying arteries to the brain tissue, leading to an earlier arrival of the magnetic bolus at the brain tissue and, therefore, to an earlier washout of the labeled blood. However, the parameters for the pulsed continuous ASL sequence were chosen such that this effect was minimized. Because only a single perfusion measurement was made after administration of acetazolamide, it is possible that variation in the time-response curve may have prevented the maximal response of CBF from being reached. However, perfusion measurements were obtained after 15 minutes, which previous studies have indicated to be within the plateau phase of maximal response (46,47). Both an advantage and a limitation of the present study is that the mean cerebrovascular reactivity of the complete flow territory was measured, possibly resulting in the dilution of the effects

of small areas with severely decreased reactivity. Furthermore, hemodynamic steal may have caused a shift of the flow territories of the brain-feeding arteries in individual patients.

In this study, we used quantitative perfusion and flow territory–selective ASL to measure vasodilatory capacity. The results show that, in patients with symptomatic stenosis of the ICA, the vasodilatory capacity in the flow territories of the major cerebral arteries can be visualized and quantified at the brain tissue level with ASL MR imaging.

References

1. The European Stroke Prevention Study (ESPS). Principal end-points. The ESPS Group. Lancet 1987;2(8572):1351–1354.

2. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1998;339(20):1415–1425.

3. Derdeyn CP, Videen TO, Yundt KD, et al. Variability of cerebral blood volume and oxygen extraction: stages of cerebral haemodynamic impairment revisited. Brain 2002;125(pt 3):595–607.

4. Lassen NA. Cerebral blood flow and oxygen consumption in man. Physiol Rev 1959;39(2):183–238.

5. MacKenzie ET, Farrar JK, Fitch W, Graham DI, Gregory PC, Harper AM. Effects of hemorrhagic hypotension on the cerebral circulation. I. Cerebral blood flow and pial arteriolar caliber. Stroke 1979;10(6):711–718.

6. Kleiser B, Widder B. Course of carotid artery occlusions with impaired cerebrovascular reactivity. Stroke 1992;23(2):171–174.

7. Silvestrini M, Vernieri F, Pasqualetti P, et al. Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. JAMA 2000;283(16):2122–2127.

8. Powers WJ. Cerebral hemodynamics in ischemic cerebrovascular disease. Ann Neurol 1991;29(3):231–240.

9. Yonas H, Smith HA, Durham SR, Pentheny SL, Johnson DW. Increased stroke risk predicted by compromised cerebral blood flow reactivity. J Neurosurg 1993;79(4):483–489.

10. Gur AY, Bova I, Bornstein NM. Is impaired cerebral vasomotor reactivity a predictive

factor of stroke in asymptomatic patients? Stroke 1996;27(12):2188–2190.

11. Markus H, Cullinane M. Severely impaired cerebrovascular reactivity predicts stroke and TIA risk in patients with carotid artery stenosis and occlusion. Brain 2001;124 (pt 3):457–467.

12. Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg 1982;57(6):769–774.

13. Eskey CJ, Sanelli PC. Perfusion imaging of cerebrovascular reserve. Neuroimaging Clin N Am 2005;15(2):367–381, xi.

14. Derdeyn CP, Grubb RLJ Jr, Powers WJ. Cerebral hemodynamic impairment: methods of measurement and association with stroke risk. Neurology 1999;53(2):251–259.

15. van der Zwan A, Hillen B, Tulleken CAF, Dujovny M, Dragovic L. Variability of the territories of the major cerebral arteries. J Neurosurg 1992;77(6):927–940.

16. van Laar PJ, Hendrikse J, Golay X, Lu H, van Osch MJ, van der Grond J. In vivo flow territory mapping of major brain feeding arteries. Neuroimage 2006;29(1):136–144.

17. Williams DS, Detre JA, Leigh JS, Koretsky AP. Magnetic resonance imaging of perfusion using spin inversion of arterial water. Proc Natl Acad Sci U S A 1992;89(1):212–216. [Published correction appears in Proc Natl Acad Sci U S A 1992;89(9):4220.]

18. Detre JA, Leigh JS, Williams DS, Koretsky AP. Perfusion imaging. Magn Reson Med 1992;23(1):37–45.

19. Edelman RR, Siewert B, Darby DG, et al. Qualitative mapping of cerebral blood flow and functional localization with echo-planar MR imaging and signal targeting with alternating radio frequency. Radiology 1994; 192(2):513–520.

20. Detre JA, Samuels OB, Alsop DC, Gonzalez-At JB, Kasner SE, Raps EC. Noninvasive magnetic resonance imaging evaluation of cerebral blood flow with acetazolamide challenge in patients with cerebrovascular stenosis. J Magn Reson Imaging 1999;10(5):870–875.

21. Zhao P, Alsop DC, Abduljalil A, et al. Vasoreactivity and peri-infarct hyperintensities in stroke. Neurology 2009;72(7):643–649.

22. Paiva FF, Tannús A, Silva AC. Measurement of cerebral perfusion territories using arterial spin labelling. NMR Biomed 2007;20(7):633–642.

23. van Laar PJ, van der Grond J, Hendrikse J. Brain perfusion territory imaging: methods and clinical applications of selective arterial

spin-labeling MR imaging. Radiology 2008;246(2):354–364.

24. Bamford JM, Sandercock PA, Warlow CP, Slattery J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1989;20(6):828.

25. Dai W, Garcia D, de Bazelaire C, Alsop DC. Continuous flow-driven inversion for arterial spin labeling using pulsed radio frequency and gradient fields. Magn Reson Med 2008;60(6):1488–1497.

26. Garcia DM, Bazelaire CM, Alsop DC. Pseudocontinuous flow driven adiabatic inversion for arterial spin labeling [abstr]. In: Proceedings of the 13th meeting of the International Society for Magnetic Resonance in Medicine. Berkeley, Calif: International Society for Magnetic Resonance in Medicine, 2005; 37.

27. Wu WC, Fernández-Seara M, Detre JA, Wehrli FW, Wang J. A theoretical and experimental investigation of the tagging efficiency of pseudocontinuous arterial spin labeling. Magn Reson Med 2007;58(5):1020–1027.

28. Ye FQ, Frank JA, Weinberger DR, McLaughlin AC. Noise reduction in 3D perfusion imaging by attenuating the static signal in arterial spin tagging (ASSIST). Magn Reson Med 2000;44(1):92–100.

29. Gevers S, Nederveen A, Bokkers RP, et al. Reproducibility of flow territories defined by plannings-free vessel encoded pseudocontinuous arterial spin labeling [abstr]. In: Proceedings of the 17th meeting of the International Society for Magnetic Resonance in Medicine. Berkeley, Calif: International Society for Magnetic Resonance in Medicine, 2009; 1524.

30. Wong EC. Vessel-encoded arterial spinlabeling using pseudocontinuous tagging. Magn Reson Med 2007;58(6):1086–1091.

31. Wong EC, Kansagra AP. Mapping middle cerebral artery branch territories with vessel encoded pseudo-continuous ASL: sine/cosine tag modulation and data clustering in tagging efficiency space [abstr]. In: Proceedings of the 16th meeting of the International Society for Magnetic Resonance in Medicine. Berkeley, Calif: International Society for Magnetic Resonance in Medicine, 2008; 182.

32. Alsop DC, Detre JA. Reduced transit-time sensitivity in noninvasive magnetic resonance imaging of human cerebral blood flow. J Cereb Blood Flow Metab 1996;16(6):1236–1249.

33. Golay X, Petersen ET, Hui F. Pulsed star labeling of arterial regions (PULSAR): a robust regional perfusion technique for high field imaging. Magn Reson Med 2005;53(1):15–21.

34. St Lawrence KS, Wang J. Effects of the apparent transverse relaxation time on cerebral blood flow measurements obtained by arterial spin labeling. Magn Reson Med 2005;53(2):425–433.

35. Chalela JA, Alsop DC, Gonzalez-Atavales JB, Maldjian JA, Kasner SE, Detre JA. Magnetic resonance perfusion imaging in acute ischemic stroke using continuous arterial spin labeling. Stroke 2000;31(3):680–687.

36. Gardner MJ, Altman DG. Confidence intervals rather than P values: estimation rather than hypothesis testing. Br Med J (Clin Res Ed) 1986;292(6522):746–750.

37. Silvestrini M, Troisi E, Matteis M, Cupini LM, Caltagirone C. Transcranial Doppler assessment of cerebrovascular reactivity in symptomatic and asymptomatic severe carotid stenosis. Stroke 1996;27(11):1970–1973.

38. Soinne L, Helenius J, Tatlisumak T, et al. Cerebral hemodynamics in asymptomatic and symptomatic patients with high-grade carotid stenosis undergoing carotid endarterectomy. Stroke 2003;34(7):1655–1661.

39. Telman G, Kouperberg E, Nitecki S, et al. Cerebral hemodynamics in symptomatic and asymptomatic patients with severe unilateral carotid stenosis before and after carotid endarterectomy. Eur J Vasc Endovasc Surg 2006;32(4):375–378.

40. Chen A, Shyr MH, Chen TY, Lai HY, Lin CC, Yen PS. Dynamic CT perfusion imaging with acetazolamide challenge for evaluation of patients with unilateral cerebrovascular steno-occlusive disease. AJNR Am J Neuroradiol 2006;27(9):1876–1881.

41. Bisdas S, Nemitz O, Berding G, et al. Correlative assessment of cerebral blood flow obtained with perfusion CT and positron emission tomography in symptomatic stenotic carotid disease. Eur Radiol 2006;16(10):2220–2228.

42. Hasegawa Y, Yamaguchi T, Tsuchiya T, Minematsu K, Nishimura T. Sequential change of hemodynamic reserve in patients with major cerebral artery occlusion or severe stenosis. Neuroradiology 1992;34(1):15–21.

43. van Laar PJ, Hendrikse J, Mali WP, et al. Altered flow territories after carotid stenting and carotid endarterectomy. J Vasc Surg 2007;45(6):1155–1161.

44. Sacco RL, Adams R, Albers G, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: cosponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Stroke 2006;37(2):577–617.

45. Blaser T, Hofmann K, Buerger T, Effenberger O, Wallesch CW, Goertler M. Risk of stroke, transient ischemic attack, and vessel occlusion before endarterectomy in patients with symptomatic severe carotid stenosis. Stroke 2002;33(4):1057–1062.

46. Dahl A, Russell D, Rootwelt K, Nyberg-Hansen R, Kerty E. Cerebral vasoreactivity assessed with transcranial Doppler and regional cerebral blood flow measurements. Dose, serum concentration, and time course of the response to acetazolamide. Stroke 1995;26(12):2302–2306.

47. Grossmann WM, Koeberle B. The dose-response relationship of acetazolamide on the cerebral blood flow in normal subjects. Cerebrovasc Dis 2000;10(1):65–69.