Selective Reduction of Blood Flow to White Matter During Hypercapnia Corresponds With Leukoaraiosis

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Background and Purpose—Age-related white matter disease (leukoaraiosis) clusters in bands in the centrum semiovale, about the occipital and frontal horns of the lateral ventricles, in the corpus callosum, and internal capsule. Cerebrovascular anatomy suggests that some of these locations represent border zones between arterial supply territories. We hypothesized that there are zones of reduced cerebrovascular reserve (susceptible to selective reductions in blood flow, ie, steal phenomenon) in the white matter of young, healthy subjects, the physiological correlate of these anatomically defined border zones. Furthermore, we hypothesized that these zones spatially correspond with the regions where the elderly develop leukoaraiosis.

Methods—Twenty-eight healthy volunteers underwent functional MR mapping of the cerebrovascular response to hypercapnia. We studied 18 subjects by blood oxygen level-dependent MRI and 10 subjects by arterial spin labeling MRI. We controlled both end-tidal pCO2 and pO2. All functional data was registered in Montreal Neurological Institute space and generated composite blood oxygen level-dependent MR and arterial spin labeling MR maps of cerebrovascular reserve. We compared these maps with frequency maps of leukoaraiosis published previously.

Results—Composite maps demonstrated significant (90% CI excluding the value zero) steal phenomenon in the white matter. This steal was induced by relatively small changes in end-tidal pCO2. It occurred precisely in those locations where elderly patients develop leukoaraiosis.

Conclusions—This steal phenomenon likely represents the physiological correlate of the previously anatomically defined internal border zones. Spatial concordance with white matter changes in the elderly raises the possibility that this steal phenomenon may have a pathogenetic role. (Stroke. 2008;39:1993-1998.)

Key Words: cerebrovascular accident ■ cerebrovascular disorders ■ magnetic resonance imaging

Since the advent of CT, physicians and researchers have noted the prevalence of abnormality in the white matter of elderly human brain. Characterized by patchy or diffuse low density on CT images, and corresponding hyperintensity on T2-weighted MRIs, this abnormality histopathologically represents rarefaction of myelin, loss of axons and oligodendrocytes, dilatation of perivascular spaces, and mild gliosis.1 It is simply called white matter disease, or leukoaraiosis,2 literally meaning diminution of white matter density. Leukoaraiosis clusters in several locations: cigar-shaped bands in the deep white matter of the centrum semiovale,3,4 in the white matter about the occipital and frontal horns of the lateral ventricles,3–5 in the genu and splenium of the corpus callosum,3,5 and in the posterior limb of the internal capsule.4 Prevalence increases with age with some degree of leukoaraiosis in more than half of those older than 60 years of age.5 It was initially considered a benign age-related change, but more recent studies suggest it may be associated with cognitive dysfunction7 and the development of dementia.8

Despite growing appreciation of its clinical significance, the pathogenesis of leukoaraiosis is poorly understood.9 Evidence suggests an ischemic process,10 but what causes the ischemia?

One theory is based on a concept of “internal border zones.” Studying the patterns of white matter injury in gross pathological specimens of the human brain, Zulch11 hypothesized that the borders between arterial supply territories are particularly vulnerable to injury. He described a border zone in the deep white matter of the centrum semiovale and one in the deep white matter of the corpus callosum. Later studies12 added a third border zone, in the periventricular white matter. Supplied by the longest arteries and arterioles, these zones may have relatively low perfusion pressure, yielding vulnerability to episodic reduction in systemic arterial blood pres-
sure. An argument against this theory is that, by autoregulation of arterial and arteriole smooth muscle tone, the brain is able to maintain relatively constant cerebral blood flow (CBF) over a wide range of blood pressures (mean arterial blood pressure 50 to 150 mm Hg). A more widely accepted theory is that ischemia occurs secondary to (that is, requires) disease of the arterioles supplying the white matter, so-called "small vessel disease." This theory is based on an observed association between leukoaraiosis and small vessel disease. It was initially hypothesized that arteriole stenosis causes chronic underperfusion of downstream parenchyma, resulting in white matter injury. More recent studies suggest that pathological stiffening of arterioles reduces their capacity for autoregulatory vasodilatation, making the brain vulnerable to episodic reductions in systemic arterial blood pressure. It is unknown whether small vessel disease temporally precedes leukoaraiosis. Also, only the minority of white matter lesions has spatially concordant small vessel disease.

Although it is true that the brain can autoregulate to keep flow constant despite reduction of blood pressure, autoregulatory capacity is not infinite. Once the cerebrovascular reserve is exhausted, further lowering of arterial blood pressure leads to a reduction of blood flow and risk of ischemia. In normal subjects, if the arterial border zones of the white matter are continuously compensating for low perfusion pressure, then one might expect these regions to have reduced or exhausted cerebrovascular reserve. Furthermore, even complete exhaustion of the cerebrovascular reserve is not the most hemodynamically vulnerable condition. Spatial heterogeneity of cerebrovascular reserve adds yet additional risk; an episode of hypotension will cause not only a direct reduction of blood flow in the region of exhausted reserve, but also autoregulatory vasodilatation in those parts of the brain with preserved reserve will cause redistribution of blood flow away from the region of exhausted reserve. This is aptly called a steal phenomenon.

We hypothesized that there are regions of reduced cerebrovascular reserve, susceptible to steal phenomenon, in the white matter of young, healthy subjects, the physiological correlate of the anatomically defined internal border zones. Furthermore, we hypothesized that these zones spatially correspond with the regions where the elderly develop leukoaraiosis. We assessed cerebrovascular reserve by imaging the CBF response to a vasodilatory stimulus. We used blood oxygen level-dependent (BOLD) MR and arterial spin labeling MR to image blood flow and inhaled carbon dioxide (CO₂) as a vasodilatory stimulus. This approach has been described elsewhere.

Subjects and Methods

Experiment 1

Subjects
We studied 18 healthy volunteers. In particular, we screened for history of cardiovascular or neurological disease. Age range was 22 to 42 years. There were 10 males and 8 females. The study was approved by our Institutional Review Board, and subjects consented to participating.

MRI
MRI was performed on a GE Sigma 1.5 T scanner (GE Healthcare, Milwaukee, Wis) with a single-channel head coil. We acquired T1-weighted anatomic images through the entire brain using a 3-dimensional spoiled gradient echo pulse sequence (slice thickness 2.2 mm, matrix size 256×256), then acquired BOLD MR cerebrovascular reactivity data for the entire brain using a T2*-weighted single shot gradient echo sequence with spiral readout (TR 2240 ms, TE 40 ms, flip angle 85°, slice thickness 4.5 mm, field of view 20×20 cm, matrix size 64×64, 320 frames). Four identical BOLD MR acquisitions were performed for each subject.

End-Tidal pCO₂ and pO₂ Manipulation
During the BOLD MR acquisitions, we alternated between high and low end-tidal partial pressure of carbon dioxide (pETCO₂) states using an automated gas sequencer (Gas Flow Sequencer Model GS01; Volitek Enterprises, Toronto, Canada), rebreathing circuit, mouthpiece, and nose clip. The gas sequence was: 8 periods of hypercapnia (45 seconds at pETCO₂=45 mm Hg, SD=1 mm Hg) interspersed with 8 periods of hypocapnia (45 seconds at pETCO₂=35 mm Hg, SD=1 mm Hg). Tidal pCO₂ was monitored continuously (Capnomac Ultima; Datex Corporation, Madison, Wis), digitized, and recorded (LabView; National Instruments Corporation, Austin, Texas). The apparatus and technique are described in detail elsewhere.

Data Analysis
We imported the MR and pETCO₂ data into the software AFNI. We viewed the first raw image of each BOLD MR acquisition and excluded those acquisitions (9 of 72) in which there was appreciable change in head position between the anatomic acquisition and the BOLD MR acquisition. Each BOLD MR acquisition was then temporally shifted to the point of maximum correlation with the subject’s pETCO₂ waveform. One can define a parameter called "cerebrovascular reactivity" as the change in CBF per unit change in vasodilatory stimulus. We performed least squares fitting of the BOLD MR signal waveform to the pETCO₂ waveform on a voxel-by-voxel basis, and from the fitted data, we calculated percentage MR signal change per mm Hg pETCO₂ change on a voxel-by-voxel basis, that is, cerebrovascular reactivity. We then segmented the anatomic images into gray matter and white matter (SPM5; Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College, London, UK), generated cerebrovascular reactivity maps containing only the brain parenchyma, and transformed these maps into Montreal Neurological Institute space. We generated mean intrasubject maps of reactivity, then calculated the mean and SD of cerebrovascular reactivity across all 18 subjects on a voxelwise basis. Using a t-distribution, we generated a 90% CI for the mean on a voxelwise basis. Voxels with a 90% CI that did not include the value zero were deemed statistically significant for the directionality of BOLD MR signal change, that is, steal versus no steal. We plotted these composite maps of significant reactivity as well as composite maps showing all voxels. We also calculated mean cerebrovascular reactivity for all gray matter and for all white matter.

Experiment 2
Theoretically, a negative BOLD MR signal response to hypercapnia could arise from decreased CBF, increased cerebral blood volume, increased cerebral metabolic rate of oxygen consumption, decreased arterial pO₂, or spatial heterogeneity in the arrival of a pCO₂ change at the brain. Although empirical evidence suggests that the BOLD MR signal response to changes in pETCO₂ is dominated by the CBF effect, we felt it prudent to confirm our findings using a technique that is independent of these confounders. We excluded cerebral blood volume and cerebral metabolic rate of oxygen consumption as confounders by using a MR arterial spin labeling pulse sequence. Arterial spin labeling MR signal changes are more directly related to blood flow than are BOLD MR signal changes. The specific arterial spin labeling pulse sequence we used was flow-sensitive alternating inversion recovery (FAIR). FAIR has been validated both for measuring cerebral perfusion and for measuring cerebrovascular reactivity.
We excluded arterial pO2 as a confounder by using a gas sequencer that can prospectively target and control pETO2 within a very narrow range (100 mm Hg, SD=2 mm Hg).34 The time delay between change in pCO2 in the pulmonary capillaries and arrival of this change in the cerebral circulation is spatially heterogeneous.35 If this relative difference in delay was large enough, then theoretically, the changes in arterial pCO2 in one region of the brain could be 180° out of phase with the changes elsewhere, mimicking a steal phenomenon.26 We overcame this potential confounder by using nonperiodic oscillation of the carbon dioxide stimulus (Figure 1).

Subjects
We studied an additional 10 healthy volunteers (age range, 29 to 40 years; 9 males).

MRI
MRI was performed on a Signa 3.0-T scanner (GE Healthcare) with an 8-channel phased array head coil. We acquired anatomic images as for the first experiment and then acquired cerebrovascular reactivity data using an arterial spin labeling MR pulse sequence, specifically, a 2-dimensional spin echo FAIR sequence30 with echoplanar readout (TR 2000 ms, TE 22.7 ms, TI 1000 ms, 5 axial slices, slice thickness 5.0 mm with 2.0-mm inter slice gap, field of view 24x24 cm, matrix size 64x64, 345 frames). The FAIR technique has limited z-axis spatial coverage. We chose to acquire the FAIR slices through the centrum semiovale.

Gas Manipulation
During the FAIR MR acquisitions, we alternated between high and low pETCO2 states using a more advanced version of the breathing apparatus used in the first experiment. Specifically, we used a computer-controlled gas blender (RespirAct; Thornhill Research, Toronto, Canada), sequential gas delivery mask (Hi-Ox-80 Viasys HealthCare, Yorba Linda, Calif), and rebreathing circuit. The gas sequence was: normocapnia normoxia (60 seconds at pETCO2=40 mm Hg, SD=1 mm; pETO2=100 mm Hg, SD=2 mm), hypercapnia normoxia (60 seconds at pETCO2=50 mm Hg, SD=1 mm; pETO2=100 mm Hg, SD=2 mm), normocapnia normoxia (100 seconds), hypercapnia normoxia (180 seconds), and normocapnia normoxia (110 seconds). Tidal pCO2 and pO2 were monitored continuously (RespirAct), digitized, and recorded (LabView; National Instruments Corporation). The apparatus and technique are described in detail elsewhere.34

Data Analysis
Data analysis was identical to that for the first experiment with one exception: FAIR MR raw images underwent a preprocessing step, specifically, we calculated the difference between each pair of FAIR MRIs on a voxelwise basis and fit the resultant difference maps to the pETCO2 waveform to calculate cerebrovascular reactivity.30 One subject was excluded because of head motion.

Results
Experiment 1
The composite BOLD MR cerebrovascular reactivity map (Figure 2A) showed several bilaterally symmetrical regions of negative reactivity (depicted in blue). There was negative reactivity in cigar-shaped bands in the deep white matter of the centrum semiovale, in the white matter about the occipital horns of the lateral ventricles and to a lesser extent frontal horns, in the genu and splenium of the corpus callosum, and in the posterior limb of the internal capsule. Mean reactivity for all gray matter was positive: 0.12% SD 0.03% (percentage change in BOLD MR signal intensity per mm Hg change in pETCO2). Mean reactivity for all white matter was positive: 0.05% SD 0.01% (units as previously). The composite map of only significant reactivity (Figure 1B) showed persisting, although less marked, negative reactivity in the centrum semiovale, periventricular white matter, corpus callosum, and internal capsule (Figure 2B).

Experiment 2
The composite arterial spin labeling MR cerebrovascular reactivity map (Figure 3A) showed negative reactivity in the
centrum semiovale, periventricular white matter, and corpus callosum—the same distribution as seen in the first experiment. The internal capsule could not be assessed because the arterial spin labeling MR pulse sequence has limited coverage in the craniocaudal dimension. Mean gray matter and white matter reactivity were both positive: 1.5% (SD, 0.4%) and 0.5% (SD, 0.2%), respectively (percentage change in CBF per mm Hg change in pETCO2). The composite map of only significant reactivity (Figure 3B) showed much less dramatic negative reactivity but still small foci of persisting negative reactivity in the centrum semiovale, periventricular white matter, and corpus callosum (Figure 3B).

**Discussion**

Our results provide several new insights. First, we have identified regions of hemodynamic vulnerability in the white matter of young, healthy human subjects. The cerebrovascular response to hypercapnia (or potentially hypotension) may reduce blood flow to these regions in its attempt to maintain flow elsewhere in the brain. Second, we have shown that the observed steal phenomenon occurs with changes in pCO2 and total CBF that are well within the range of total CBF autoregulation. That is, hemodynamic vulnerability may exist even within the range of blood pressure and arterial pCO2 that is typically considered harmless. Third, we have shown that this steal phenomenon is clustered in those regions where elderly patients most frequently develop leukoaraiosis. Figure 4 compares our observed steal phenomenon (Figure 4A) with a composite map of leukoaraiosis published by Sachdev et al4 (Figure 4B). The map of leukoaraiosis was generated by imaging 55 community-dwelling elderly volunteers at an initial time and 3 years later and plotting regions that show significant increase in white matter hyperintensity over time.

Our results strengthen the idea that repeated episodes of mild hypercapnia, or potentially hypotension, may have a role in the pathogenesis of leukoaraiosis. Although we have used inhaled carbon dioxide as a research tool, hypercapnia occurs naturally as well. Arterial pCO2 of healthy subjects varies by approximately 4 mm Hg during waking hours37 and mild hypercapnia occurs during sleep.39 Among healthy adults, lower respiratory function in midlife is associated with greater leukoaraiosis in later life.40 Similarly, the blood pressure of healthy subjects varies throughout the day40; and postprandial hypotension,41 orthostatic hypotension,42 and greater nocturnal fall in blood pressure41 are each associated with greater leukoaraiosis.

As well, hypercapnia and reduction of blood pressure are features of several disease states. Chronic obstructive pulmonary disease results in chronic elevation of pCO2. It is associated with leukoaraiosis39 and with cognitive deficit.43 Hypertensive disease deserves particular mention. Large randomized trials on the prevention of stroke, myocardial infarction, and other vascular events have led to a widespread view that blood pressure should be kept as low as possible. However, some have cautioned that antihypertensive medication may reduce CBF and lead to cognitive impairment.44 This has led to hundreds of studies on the effects of antihypertensive medications on CBF. Notably, only a few of these studies report a medication-induced decrease in CBF.45 However, our results suggest that this lack of evidence may reflect methodology rather than physiology. The majority of these studies assess total CBF. Some assess particular regions of brain, but these regions are nearly always large and contain both gray matter and white matter. Our results define specific, relatively focal regions of white matter where one would expect to observe an antihypertensive medication-induced decrease in CBF.

Our results also have implications for BOLD MR mapping of cerebrovascular reactivity as a diagnostic tool. The trans-
cranial Doppler, Xe-CT, single photon emission CT, and positron emission tomography literature shows that reduced cerebrovascular reserve, and especially steal phenomenon, is a strong and independent risk factor for ischemic stroke. Most of the stroke risk studies calculate mean cerebrovascular reactivity for the entire middle cerebral artery territory (transcranial Doppler) or for each hemisphere (Xe-CT, single photon emission CT, positron emission tomography). The greater spatial resolution of BOLD MR offers the potential to identify more focal regions of steal phenomenon, but this also introduces the difficulty of differentiating normal white matter steal phenomenon from pathological steal.

Our results might be criticized on the grounds that both experiments demonstrated striking negative reactivity in the white matter, but the spatial extent of statistically significant negative reactivity was limited. This is a reasonable observation, but it should not affect our conclusions. First, the statistically significant negative reactivity was specifically clustered in those regions hypothesized to be negative a priori. Second, although we do transform all MR data into a standardized coordinate space, there is intersubject variability in vascular anatomy and arterial border zones,46 for which we did not account. This would tend to blur relatively smaller regions of negative reactivity into the more abundant positive reactivity. It is thus likely that any observed common focus of regions of negative reactivity is an underestimation of the true spatial extent.

To date, there are only a few reports related to a white matter steal phenomenon. In 1977, a group studying the CBF response to hypotension in dogs unexpectedly observed a selective reduction of blood flow in their single white matter region of interest located in the centrum semiovale.47 Five years later, a similar study revealed selective reduction of blood flow in 3 of 5 white matter regions assessed: a periventricular region, a deep white matter region, and a visual radiation region.48 There is one study26 that provides evidence of a steal phenomenon in the white matter of normal human subjects. Measuring the CBF response to hyperventilation in several regions of interest in 6 normal subjects, the authors observed a selective increase in blood flow in their centrum semiovale region of interest. Given that hyperventilation is a vasoconstrictive rather than vasodilatory stimulus, one may consider their result a “reverse” steal phenomenon.

In conclusion, we have mapped a selective reduction of blood flow to white matter during mild hypercapnia in young, healthy human subjects. This steal phenomenon was induced by relatively small changes in $D_0^2$. It occurred precisely in those locations where elderly patients develop leukoaraiosis. These results strengthen the evidence for a mechanism whereby repeated episodes of mild hypercapnia or hypotension may have a role in the pathogenesis of leukoaraiosis.

Acknowledgments
We thank the Toronto Western Hospital magnetic resonance imaging technologists, particularly Garry Detzler, Eugen Hlasny, David Johnstone, and Keith Ta, for their contributions to the data acquisition. We thank Marat Slessarev and Alex Vesely for their contributions to the development of the apparatus used in the second experiment. We would also like to acknowledge the support of the Radiologist Scientist Training Program, Department of Medical Imaging, University of Toronto.

Disclosures
Two of the study authors (JAF, DJM) contributed to the development of the RespirAct, a device used in the second experiment of the study. These authors stand to gain financially if the device is successfully commercialized by Thornhill Research Inc, a University of Toronto/University Health Network-related company.

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Stroke. 2008;39:1993-1998; originally published online May 1, 2008; doi: 10.1161/STROKEAHA.107.501692

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