Impaired Cerebrovascular Reactivity With Steal Phenomenon Is Associated With Increased Diffusion in White Matter of Patients With Moyamoya Disease

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Background and Purpose—Reduced cerebrovascular reactivity (CVR) with steal phenomenon is an independent predictor for stroke and may indicate tissue exposed to episodic low-grade ischemia. The apparent diffusion coefficient (ADC) calculated using diffusion-weighted MRI is effective in characterizing focal brain ischemia and subtle structural changes in normal-appearing white matter (WM). We hypothesized that regions of steal phenomenon are associated with increased ADC in normal-appearing WM of patients with Moyamoya disease.

Methods—Twenty-two patients with unilateral CVR impairment secondary to Moyamoya disease and 12 healthy control subjects underwent diffusion-weighted MRI and functional MRI mapping of the cerebrovascular response to hypercapnia. Parametric maps of ADC and CVR were calculated, coregistered, and segmented using automated image processing methods. ADC of normal-appearing WM was compared between hemispheres, and between WM with negative CVR (ie, steal phenomenon) and WM with positive CVR.

Results—In patients, ADC of normal-appearing WM was elevated in the hemisphere ipsilateral to the CVR impairment compared with the contralateral hemisphere (P<0.005) and in WM with negative CVR compared with WM with positive CVR (P<0.001). WM in regions of steal phenomenon within the affected hemisphere had higher ADC than homologous contralateral WM (P<0.005). In control subjects, negative CVR in WM was not associated with elevated ADC.

Conclusions—Regions of steal phenomenon are spatially correlated with elevated ADC in normal-appearing WM of patients with Moyamoya disease. This structural abnormality may reflect low-grade ischemic injury after exhaustion of the cerebrovascular reserve capacity. (Stroke. 2010;41:1610-1616.)

Key Words: hemodynamics ▪ magnetic resonance imaging, diffusion-weighted ▪ magnetic resonance imaging, functional ▪ Moyamoya disease

Cerebrovascular reactivity (CVR) can be defined as the increase in cerebral blood flow in response to a vasodilatory stimulus. Negative CVR, also known as steal phenomenon, occurs when a stimulus results in the redistribution of blood flow from regions of exhausted cerebrovascular reserve to areas with preserved vasodilatory capacity. Steal phenomenon is a risk factor for future ischemic stroke. In patients with Moyamoya disease, a progressive narrowing of the supraclinoid internal carotid artery (ICA) and its proximal branches, negative or severely reduced CVR has been used to identify patients who may benefit from surgical revascularization. However, the impact of steal phenomenon on normal-appearing brain tissue (ie, in the absence of overt infarction) has not been previously investigated.

Diffusion-weighted MRI is useful in characterizing focal brain ischemia in the acute and chronic stages, diffuse and focal leukoaraiotic changes, and normal brain structures. In chronic hypoperfusion, ischemic injury to white matter (WM) is associated with axonal destruction and glial proliferation, resulting in the hyperintense lesions on T2-weighted MRI referred to as leukoaraiosis. These lesions are associated with an increase in the apparent diffusion coefficient (ADC), likely reflecting increased water diffusivity due to axonal loss. ADC changes are not confined to ischemic lesions, however, and may occur in WM that appears normal on conventional MRI. Increased ADC in otherwise normal-appearing WM occurs, for example, in patients with extracranial ICA stenosis, previous stroke, and to some extent in normal aging.

In the present study, we sought to determine whether regions of steal phenomenon are associated with ADC changes in normal-appearing WM of patients with Moyamoya disease. We assessed CVR by measuring changes in the...
Figure 1. Maps of CVR obtained from (A–C) 3 patients with unilateral CVR deficits of varying anatomic location and severity, and (D–F) 3 healthy control subjects. Units of the CVR color scale are percent BOLD signal change per mm Hg change in \( P_{\text{etco2}} \). CVR maps are overlaid on coregistered anatomic images.

Methods

Subjects

Subjects were participants in an ongoing study of CVR in cerebrovascular disease, for which institutional ethics review board approval and informed patient consent had been obtained. Images from 252 patients who underwent CVR studies between June 2005 and December 2009 were screened by an experienced neuroradiologist using the following inclusion criteria: (1) angiographically confirmed diagnosis of Moyamoya disease or Moyamoya syndrome; (2) a CVR map showing impaired reactivity within 1 hemisphere (Figure 1A–C) and normal reactivity within the contralateral hemisphere (a minimum 30% mean CVR reduction in the affected hemisphere compared with the contralateral hemisphere was required for inclusion); and (3) no evidence of cerebral infarction or intracranial hemorrhage on anatomic MR images (T1-weighted images, T2-weighted fluid-attenuated inversion recovery [FLAIR] images, and diffusion-weighted images). The presence of focal white matter hyperintensities (WMHs) on FLAIR images was permitted. Patients with obvious motion artifacts on any image series were excluded. Twenty-two patients (age 30–12 years) met the inclusion criteria and were considered in subsequent analysis (Table 1). Twelve healthy control subjects (age 31±7 years) with no history of any neurological or systemic disease underwent an identical imaging protocol.

MRI Acquisition

Imaging was performed using a Signa HDx 3.0 T scanner with an 8-channel phased array head coil (GE Healthcare, Milwaukee, Wis).

Vasodilatory Stimulus

An automated gas blender adjusted the composition and flow to a sequential gas delivery mask and breathing circuit according to the method described by Slessarev et al.17 This apparatus enables prospective control of the patient’s end-tidal \( P_{\text{co2}} \) (\( P_{\text{etco2}} \)) and \( P_{\text{o2}} \) (\( P_{\text{eto2}} \)) independently of each other and of minute ventilation. During the BOLD MRI acquisition, a vasodilatory stimulus was provided by alternating between iso-oxic states of normocapnia and hypercapnia (Table 2). \( P_{\text{etco2}} \) values were selected as the maxima of the continuously sampled \( P_{\text{co2}} \) waveform during exhalation.

Image Reconstruction

MRI and \( P_{\text{etco2}} \) data were imported to AFNI18 for analysis. BOLD images were slice time-corrected and volume-registered. BOLD images and diffusion-weighted images were then aligned to the anatomic data set using the local Pearson correlation cost functional.19 CVR maps were constructed as follows. To compensate for temporal error resulting from the pulmonary to cerebral circulation time, the \( P_{\text{etco2}} \) waveform was time-shifted to the point of maximum correlation with the whole brain average BOLD signal. To minimize the effect of task-correlated motion (ie, head motion correlated to the \( P_{\text{etco2}} \) waveform), the BOLD time series at each voxel was orthogonalized to the 6 motion parameters estimated by the volume registration. A voxelwise linear least-squares fit of the BOLD time series to the PET waveform was then performed. CVR was defined as the percent BOLD signal change per unit change in \( P_{\text{etco2}} \).

ADC maps were constructed by computing the ADC along 3 orthogonal directions using the equation:

\[
\text{ADC} = \frac{1}{\lambda} \frac{b}{b_0} \left[ 1 - \exp\left(-\frac{b}{\lambda}\right) \right]
\]

where \( b \) is the diffusion gradient strength (in \( s/mm^2 \)), \( b_0 \) is the diffusion gradient strength without diffusion weighting (in \( s/mm^2 \)), and \( \lambda \) is the apparent diffusion coefficient (in \( mm^2/s \)).

blood oxygen level-dependent (BOLD) MRI response to hypercapnia.12 This semiquantitative approach to CVR mapping is reproducible,13 provides high spatial resolution, and has been validated against alternative methods of CVR assessment.14–16 We hypothesized that the ADC of WM in regions of steal phenomenon would be elevated compared to WM with normal reactivity. This hypothesis was tested in a group of patients with unilateral CVR impairment, allowing comparison between regions of steal phenomenon in the affected hemisphere and homologous WM in the contralateral hemisphere.
ADC is the ADC along direction $i$, $S_{i}^{b=1000}$ is the signal intensity in the diffusion-weighted image with diffusion gradient along direction $i$, $S_{i}^{b=0}$ is the signal intensity in the image without diffusion gradients, and $\Delta b=1000$ mm$^2$/s. The average ADC ($\text{ADC}_{av}$) was calculated as the mean of the ADC values along the 3 principal axes.

Anatomic images as well as coregistered CVR and ADC maps were transformed to Talairach space and resampled to a 1-mm isotropic grid to facilitate subsequent analysis.

Regions of Interest
Foci of WMH were identified on T2-weighted FLAIR images by a neuroradiologist and manually traced onto the T2-weighted ($b=0$) diffusion images.

Next, a tissue probability map for WM was generated from the anatomic data set (SPM5; Wellcome Department of Imaging Neuroscience, University College, London, UK) and thresholded at a probability of 0.9 to produce an initial WM region of interest (ROI). The initial ROI was then masked to exclude regions of WMH as well as any voxels with $\text{ADC}_{av}>1.5 \times 10^{-3}$ mm$^2$/s (threshold selected between the ADC of cerebrospinal fluid and normal brain tissue). To minimize contamination with gray matter or cerebrospinal fluid, the WM ROI underwent binary erosion using a spherical structuring element of 4-mm diameter (Matlab, Image Processing Toolbox; Mathworks, Natick, Mass). The result was a conservative WM ROI that appeared well separated from gray matter and cerebrospinal fluid when overlaid on the coregistered ADC map (Figure 2B).

The WM ROI was divided into left and right hemispheres, and a categorical CVR mask was used to subdivide the WM within each hemisphere into regions of positive and negative CVR (Figure 2C).

Lastly, we defined a set of homologous WM ROIs to allow interhemispheric ADC comparison while controlling for within-
hemisphere ADC variation. For WM with negative CVR in the affected hemisphere, a homologous contralateral ROI was defined by reflecting the categorical CVR mask about the midsagittal plane and then combining the negative CVR region with the WM mask of the contralateral hemisphere using a logical “and” operation (Figure 2D). For WM with positive CVR in the affected hemisphere, a similar procedure was used to generate a homologous contralateral ROI (Figure 2E).

Statistical Analysis

The following comparisons were performed using a Student t test for dependent or independent samples as appropriate. ADCav values in patients were compared between: affected hemisphere versus unaffected hemisphere (all WM); negative CVR versus positive CVR (all WM); negative CVR versus positive CVR (affected hemisphere only); negative CVR versus positive CVR (unaffected hemisphere only); negative CVR (affected hemisphere) versus homologous contralateral WM; and positive CVR (affected hemisphere) versus homologous contralateral WM. ADCav was also compared between positive CVR and negative CVR in control subjects (all WM). For patients with WMHs detected on FLAIR images, mean CVR was compared between WMHs and the mean CVR for all WM. Finally, mean WM CVR in the patient’s affected hemisphere was compared with that of the contralateral hemisphere and with that of healthy control subjects. Results were considered significant if the per-comparison P value was <0.05/10 comparisons = 0.005, that is, Bonferroni correction for multiple comparisons.

Results

All CVR values are given in units of percent BOLD signal change per mm Hg change in Pco2 (mean±SD). Figure 1 shows sample control and patient CVR maps. Mean WM CVR in patients was 0.027±0.032 in the affected hemisphere compared with 0.064±0.031 in the unaffected hemisphere (P<10−6 between hemispheres) and 0.062±0.038 in control subjects (P<0.005 versus patient’s affected hemisphere).

Sample ADCav maps and ROIs are shown in Figure 2. ADCav values for each ROI are provided in Table 3. ADCav was higher in the affected hemisphere than the unaffected hemisphere (P<0.005) and higher in all WM with negative CVR than all WM with positive CVR (P<0.001). Within the affected hemisphere, ADCav was higher in WM with negative CVR compared with WM with positive CVR (P<0.001; Figure 3, right). Within the unaffected hemisphere, there was no significant difference in ADCav between WM with negative and positive CVR, although there was a trend toward increased ADCav in WM with negative CVR (Figure 3, middle). ADCav was increased in WM with negative CVR in the affected hemisphere compared with homologous con-
Figure 3. Comparison of ADC_{av} between regions of positive and negative CVR in WM of patients and control subjects. Left, ADC_{av} of WM in healthy control subjects (both hemispheres included). Middle, ADC_{av} of WM in the hemisphere contralateral to the patient’s CVR impairment. Right, ADC_{av} of WM in the hemisphere ipsilateral to the patient’s CVR impairment. Square and diamond markers indicate the mean ADC_{av} computed across subjects for tissue with positive and negative CVR, respectively. Error bars indicate the 95% CI for the mean.

Discussion

Our results demonstrate that steal phenomenon is associated with increased ADC in normal-appearing WM of patients with Moyamoya disease. Although diffusion-weighted imaging has been used to monitor progression of focal ischemic lesions in patients with Moyamoya disease, increased ADC within the normal-appearing WM has not been previously reported. Soinne et al studied patients with unilateral extracranial ICA stenosis and reported increased ADC of ipsilateral WM compared with contralateral WM. However, Moyamoya disease differs from extracranial ICA stenosis in the development of numerous parenchymal, leptomeningeal, and transdural collateral vessels supplying the hemodynamic compound brain parenchyma. Thus, the results reported by Soinne et al cannot be generalized to this population. Furthermore, 14 of 45 patients in the study by Soinne et al had lacunar infarcts, whereas we excluded patients with cortical or lacunar infarction to minimize the reported influence of such pathology on the ADC of normal-appearing WM. Even in the absence of focal infarction, we found an ADC increase in ipsilateral WM compared with contralateral WM. The use of a high-resolution CVR mapping method allowed us to further localize the increased ADC to regions of negative CVR.

Elevated ADC is consistent with structural damage to tissue, resulting in increased water diffusivity. In experimental models of chronic hypoperfusion, WM appears particularly vulnerable, undergoing rarefaction with demyelination, axonal loss, and gliosis. Our results suggest that subtle ischemic changes may be present in regions of steal phenomenon in the normal-appearing WM of patients with Moyamoya disease, leading to increased ADC in these areas. We also found increased ADC within foci of WMH on FLAIR images, in agreement with previous studies. Mean CVR within these WMHs was negative and significantly lower than the mean CVR of normal-appearing WM, supporting the hypothesis that CVR impairment plays a role in the pathogenesis of these lesions.

Steal phenomenon was also observed both in control subjects and in the hemisphere of normal reactivity in patients (Figure 1), suggesting that CVR impairment cannot be the sole determinant of ADC elevation. Negative CVR in the WM of healthy young adults has been previously documented in the centrum semiovale, corpus callosum, and periventricular WM. This raises the following question: how might steal phenomenon be a normal physiological response in some brain areas and yet lead to ischemic injury in others? One explanation for our findings would be a spatial variation in vulnerability to CVR impairment within the WM. The aforementioned areas that are chronically exposed to physiological steal may be better able to tolerate negative CVR, whereas WM that normally exhibits robust positive CVR (e.g., subcortical WM) may be more adversely affected when exposed to pathological negative reactivity and more likely to undergo ischemic changes with concomitant ADC elevation. Although negative CVR in control subjects was not associated with increased ADC, it may not be an entirely benign phenomenon. The distribution of steal phenomenon in healthy young adults is spatially concordant with the development of age-related WM disease, which is in turn associated with ADC elevation and cognitive decline.

Regional variation in normal WM ADC has also been reported, although not all studies found such variation to be statistically significant. Nonetheless, it is possible that increased ADC in regions of steal phenomenon could reflect a tendency for steal to occur in areas that naturally have higher ADC. We took 2 steps to rule out this possibility. First, we compared the ADC of WM with negative CVR in the affected hemisphere with the ADC of homologous contralateral WM. ADC was significantly elevated in the ipsilateral WM compared with contralateral WM. The use of a high-resolution CVR mapping method allowed us to further localize the increased ADC to regions of negative CVR.
1.7 \times 10^{-5} \text{ mm}^2/\text{s} \) (using Eq. 2 in Wittes$^{24}$ with \( \alpha=0.05, \beta=0.2, n=12, \) and \( \sigma^2 \) estimated from the control subjects). However, ADC of WM in control subjects was virtually identical when compared between regions of positive and negative CVR (Figure 3, left).

We constructed CVR maps using the BOLD MRI response to hypercapnia and must consider the limitations of this technique. First, BOLD signal changes do not directly reflect changes in cerebral blood flow, but rather a complex interaction of cerebral blood flow, cerebral blood volume, arterial Po2, hematocrit, and cerebral metabolic rate of oxygen consumption.$^{25}$ However, empirical evidence suggests that the BOLD response to hypercapnia is dominated by cerebral blood flow effects in healthy subjects$^{14,15}$ and in patients with steno-occlusive cerebrovascular disease.$^{16}$

Second, the echoplanar imaging readouts typically used for BOLD MRI are associated with signal loss and geometric distortion near the interfaces of aerated sinuses and adjacent tissue. These artifacts had little effect on our measurements because we excluded cortical gray matter and eroded the underlying WM by approximately 1 full BOLD voxel (Figure 2B), leaving a WM ROI sufficiently distant from regions of signal loss and distortion. However, these artifacts may impede the future comparison of ADC and CVR within the cortex.

Our study is also limited by the relatively small number of patients. Unilateral CVR impairment was found to be rare among patients with Moyamoya disease, particularly in the complete absence of infarction. Despite the small sample size, the ADC differences reported in Table 3 were highly significant and similar in magnitude to ADC increases in the normal-appearing WM of patients with previous lacunar strokes.$^{5,10}$ In that context, ADC has been correlated with cognitive dysfunction, suggesting that ADC elevation may in part reflect a neurodegenerative process induced by chronic hypoperfusion (see Costantino$^{26}$ for a review of the relationship between vascular insufficiency and neurodegeneration). The discovery that ADC increases are localized to regions of negative CVR may prove useful for future investigations of cognitive function in patients with Moyamoya disease. For example, CVR maps could be used to automatically identify WM regions where increased ADC would be expected due to negative CVR. ADC of these ROIs may correlate more closely with cognitive dysfunction than ADC of ROIs chosen without knowledge of the spatial distribution of CVR impairment.$^{5,10}$

In summary, we compared parametric maps of CVR and ADC in patients with unilateral CVR impairment secondary to Moyamoya disease. ADC of normal-appearing WM was increased in the hemisphere ipsilateral to the CVR deficit, and in WM with negative CVR compared with WM with positive CVR. ADC changes were present despite the complete absence of cortical or lacunar infarction. These findings suggest that in addition to its prognostic implications for stroke, steal phenomenon is associated with subtle abnormalities in WM structure, consistent with low-grade ischemic injury. Further study is recommended to extend this analysis to patients with bilateral CVR impairment and to determine the relationship between WM ADC and cognitive function before and after surgical revascularization.

### Sources of Funding

Financial support from the Canadian Stroke Network and the Ontario Research Fund is gratefully acknowledged. D.M.M. received support from the Radiologist-Scientist Training Program, Department of Medical Imaging, University of Toronto. J.C. received support from the Comprehensive Research Experience for Medical Students (CREMS) Program, Faculty of Medicine, University of Toronto.

### Disclosures

J.A.F. and D.J.M. contributed to the development of the RespirAct, a device used in this study. These authors stand to benefit financially if this device is successfully commercialized by Thornhill Research Inc, a University of Toronto/University Health Network-related company.

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Stroke. 2010;41:1610-1616; originally published online June 24, 2010; doi: 10.1161/STROKEAHA.110.579540

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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